Commissioner’s Decision #1278
Décision du Commissaire #1278

TOPIC: F01, O00, B22
SUJET: F01, O00, B22

Application No. : 583,049
Demande no. : 583,049

COMMISSIONER'S DECISION SUMMARY

C.D. 1278 Application No. 583,049

Anticipation (F01)
Obviousness (O00)
Lack of Support (B22)

The application related to compositions comprising cryopreserved hematopoietic stem cells derived from human neonatal or fetal blood, therapeutic uses of such compositions for effecting hematopoietic reconstitution (*e.g.* in bone marrow replacement therapy) and methods of obtaining such compositions. In other aspects, the application related to human neonatal or fetal hematopoietic stem cells into which a heterologous gene sequence had been stably incorporated and similar therapeutic uses of compositions comprising such cells. All of the claims in the application were rejected by the examiner. Certain claims were held to be anticipated by the prior art, certain claims were considered obvious in view of the prior art, and the remaining claims were found to lack support in the description. The Board agreed with the examiner on the questions of anticipation and support, but disagreed on the question of obviousness. The Board therefore recommended that the applicant be given the opportunity to delete the claims considered to be anticipated and lacking support -- a recommendation which was accepted by the Commissioner -- failing which it was the Board's recommendation that the entire application be refused.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 583,049 having been rejected under Subsection 30(4) of the *Patent Rules*, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has consequently been considered by the Patent Appeal Board and the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application 583,049.

[2] The Applicant and successor in title is PharmaStem Therapeutics Inc. The inventors are Edward A. Boyse, Hal E. Broxmeyer and Gordon W. Douglas and the invention is entitled "Isolation and Preservation of Fetal and Neonatal Hematopoietic Stem and Progenitor Cells of the Blood."

[3] The application relates to compositions comprising cryopreserved hematopoietic stem cells derived from human neonatal or fetal blood, therapeutic uses of such compositions for effecting hematopoietic reconstitution (*e.g.* in bone marrow replacement therapy) and methods of obtaining such compositions. In other aspects, the application relates to human neonatal or fetal hematopoietic stem cells into which a heterologous gene sequence has been stably incorporated and similar therapeutic uses of compositions comprising such cells.

BACKGROUND

[4] By way of background information, the application teaches that hematopoietic stem cells are very primitive pluripotent cells that can give rise to hematopoietic progenitor cells. Progenitor cells are more committed than stem cells and are themselves capable of generating precursor cells which ultimately differentiate into the morphologically and functionally distinct specialized cells found in whole blood, *e.g.* red blood cells and various types of white blood cells. Stem and progenitor cells are morphologically indistinguishable and their definitions include functional attributes. Stem cells have extensive capacity for self-renewal so as to provide a constant pool of cells whereas progenitor cells have limited, or no, self-renewal capacity.

[5] As an alternative to other sources, such as bone marrow and peripheral blood, the application teaches that human fetal and neonatal blood (*i.e.* umbilical cord blood) are rich sources of hematopoietic progenitor and stem cells which may be harvested, cryopreserved and then used in the future to treat a variety of diseases and disorders, *e.g.* leukemias and anemias, through reconstitution of a subject's hematopoietic/immune system.

PROSECUTION HISTORY

[6] The subject application was filed on November 14, 1988 and the Applicant was informed on November 29, 1994 that the application had been approved for allowance. However, in a letter dated January 20, 1995, the Applicant was informed by the Acting Commissioner of Patents that the application was not allowable and that the approval for allowance had been withdrawn.

[7] Prosecution of the application resumed and the Examiner in charge of the application issued a Final Action on June 21, 2002 in which all 82 claims then pending in the application were rejected. Claims 1-5 and 12-20 were rejected for lack of novelty and claims 21-45 and 57-66 were rejected on the grounds of obviousness; both grounds for rejection were based on a prior disclosure made in a medical journal in 1983 by Dr. Kenichi Koike. Claims 6-11, 46-56 and 67-82 were rejected for lack of support.

[8] On December 23, 2002, the Applicant replied to the Final Action and submitted a new set of 81

claims. The submission of the new claims resulted in the cancellation of claim 44 and the removal of the term "progenitor" from claims 6-11, 57, 62, 67 and 79. Claim numbering and dependencies were also adjusted accordingly. The Applicant argued the newly submitted claims addressed the objections raised in the Final Action and requested favourable reconsideration.

[9] In the Examiner's estimation, the Applicant's reply to the Final Action did not overcome the objections raised in the Final Action. Accordingly, the Applicant requested an oral hearing before the Patent Appeal Board and a review by the Commissioner of Patents. The oral hearing was held on January 5, 2005. At the hearing, the Applicant was represented by Mr. David Aitken and Dr. Stephanie White of the firm Osler, Hoskin & Harcourt. Also appearing were representatives of the Applicant's United States counsel: Dr. Adriane Antler and Mr. Bill Thomann, both of the firm Jones Day. Dr. Axel Zander, a hematologist and oncologist, appeared as an expert on behalf of the Applicant. The Patent Office was represented by Mr. Daniel Bégin, the Examiner in charge of the application.

[10] At the hearing the Board heard additional oral submissions from the Applicant's representative, Mr. David Aitken, as well as from the Applicant's subject matter expert, Dr. Axel Zander. Mr. Aitken provided an overview of the essence of the invention, a review of the independent claims, commentary on proceedings in other jurisdictions and a discussion of, in his view, the relevant Canadian case law. Noteworthy is the attention paid by Mr. Aitken and Dr. Zander to a decision from a Technical Board of Appeals in the European Patent Office upholding a decision by the Opposition Division to revoke the corresponding European Patent.

[11] Mr. John Cavar was a member of the Board at the hearing but he retired from the Public Service before the Board's recommendations to the Commissioner were finalized so he was not available to sign them. However, he is aware of these recommendations and agrees with them.

THE ISSUES

[12] Having regard to the claims submitted in response to the Final Action, the Board is faced with three questions:

(1) Are claims 1-5 and 12-20 anticipated?
(2) Are claims 21-44 and 56-65 obvious?
(3) Do claims 6-11, 45-55 and 66-81 lack support?

FINDINGS

[13] For the reasons set out below, the Board finds as follows:

(1) claims 1-5 and 12-20 lack novelty;
(2) claims 21-44 and 56-65 are not obvious; and
(3) claims 6-11, 45-55 and 66-81 lack support.

REASONING

QUESTION 1: ANTICIPATION

[14] The first question before the Board is whether or not claims 1-5 and 12-20 are anticipated. Claim 1 reads as follows:

> 1. A cryopreserved, therapeutic composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells.

The Position of the Examiner

[15] In rejecting claims 1- 5 and 12-20 for lack of novelty the Examiner relied upon a prior publication in a medical journal by Dr. Kenichi Koike (Acta. Paediatr. Japan, vol. 25, pp. 275-283, 1983 - henceforth “Koike”). In the Final Action the Examiner stated the following:

> Koike discloses the collection of cord blood, the isolation of cord blood mononuclear fraction by Ficoll-hypaque gradient centrifugation, its washing in McCoy's 5A medium, the mixing of one ml of a cellular suspension with 10% DMSO and 10 % FBS. Applicant's attention is more specifically drawn to page 281 where it is stated that "the results that cord blood cells contain many pluripotent and nearby progenitor cells comparable to marrow cells, indicate that fetal hemopoietic cells or organs may be useful as one of the sources of hemopoietic progenitor cells for marrow transplantation".
>
> The subject matter of claims 1-5 and 12-20 [Formerly claims 1, 16 and 28] is disclosed by Koike.
>
> Applicant has argued that Koike's citation should be withdrawn because the disclosed isolation method does not inevitably result in a composition comprising viable blood-derived human neonatal or fetal hematopoietic stem cells in an amount sufficient to effect hematopoietic reconstitution of a human. Applicant has referred to his own data i.e. CB-90 (p.69- 73 of Table III) and to a lesser degree CB-12, CB-25, CB-28, CB-30, CB-38 in order to demonstrate that recovery of viable stem cells after Ficoll-hypaque gradient centrifugation was not inevitable. Applicant has then extrapolated from his own data to the experiment published by Koike and concluded that since Koike was also using Ficoll-hypaque separation his method would not inevitably be a useful method giving a useful composition.
>
> The examiner respectfully disagrees with applicant's premise that a citation, to be valid, must demonstrate that all the compositions disclosed must be encompassed by applicant's claim. It is the examiner's view that if it is deemed scientifically sound that a given process would result in a composition having the claimed attributes such citation is valid. The examiner would like to stress that in about 100 samples provided by the instant application (i.e. more that 95% of the samples), recovery of viable stem cells was deemed successful even after Ficoll-hypaque separation. The examiner's objection is therefore maintained.

The Position of the Applicant

[16] The Board notes that in the response to the Final Action, and at the oral hearing, the Applicant emphasized that the presence of viable stem cells can only be reasonably concluded based on functional assays and that one of skill in the art cannot reasonably conclude that viable

stem cells are necessarily present in any sample subjected to *in vitro* manipulations (*e.g.* Ficoll-Hypaque separation).

[17] In the reply dated December 23, 2002, the Applicant put forth, in part, the following argument with respect to the Examiner's rejection of claims 1-5 and 12-20 for lack of novelty:

> Claims 1 -5 and 12 -20 relate to a cryopreserved, therapeutic composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells, and methods for obtaining same. Applicant notes that the term "hematopoietic reconstitution" consistent with its usage in the subject application means long-term, complete multi-lineage hematopoietic repopulation *in vivo* (see instant specification at page 9, lines 17-18, 28-34; page 24, lines 17-22), *i.e.*, engraftment of the hematopoietic stem cells and their growth and differentiation so as to repopulate the blood.
>
> . . .
>
> Koike discloses the testing for viability of several types of progenitor cells in cryopreserved samples of bone marrow and cord blood samples. On page 276, Koike states that cord blood samples were collected, subjected to Ficoll-hypaque separation and then frozen. After thawing, the samples were tested for the presence of certain types of progenitor cells by their ability to form colonies *in vitro*. Koike does not anticipate the instant claims, because the isolation method disclosed does not inevitably result in a composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the blood in an amount sufficient to effect hematopoietic reconstitution of a human, to which an amount of cryopreservative sufficient for cryopreservation of said cells has been added. Furthermore, Koike does not teach or suggest a means for determining whether the neonatal or fetal hematopoietic stem cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult.
>
> As indicated in the Response submitted May 28, 2001, Ficoll-hypaque gradient centrifugation is the separation procedure disclosed by Kioke [*sic*], to which cord blood samples are subjected prior to formulation with cryopreservative. The data in the present specification, as demonstrated for example by the data regarding cord blood sample CB-90 (pages 69-73; Table III), prove that recovery of viable stem cells after Ficoll-hypaque gradient centrifugation is not inevitable. In CB-90, no multipotential progenitor cells (CFU-GEMM) were recovered after Ficoll-hypaque gradient centrifugation, and since stem cells are commonly believed present at lower levels than progenitor cells, one skilled in the art can only conclude that no stem cells were recovered in this sample. In addition to sample CB-90, see, for example sample CB-25 (page 70; Table III), in which, the progenitor cell assay was not even set up due to the too low yield of cells; samples CB-12 and CB-44 (pages 69-70; Table III), in which cell viability and/or cell yield was too low to set up the progenitor assays; samples CB-28 and CB-30 (page 70; Table III), in which no progenitor cells were detected; and sample CB-38 (page 70; Table III), in which cell clumping and hemolysis occurred. As additional evidence in support of the fact that stem cell recovery cannot be deemed inevitably to occur after Ficoll-hypaque centrifugation, a publication by Apperley (August 1994, Bone Marrow Transplantation 14:187-196), discloses at least one cord blood sample in which no BFU-E (BFU-E is a type of erythroid progenitor cell) was detected, even prior to any separation procedures, although over 108 nucleated cells

were present in the sample.

. . .

Moreover, publications in the art provide additional supporting evidence. As described in Paragraph 15 of the Second Declaration of Dr. Hal E. Broxmeyer filed July 20, 1994 in connection with the reexamination of the corresponding United States Patent No. 5,004,681 ("the Second Broxmeyer Declaration"), the publication by Abboud et al., 1992, Exp. Hematol. 20:1043-1047 (affixed to the Second Broxmeyer Declaration as Exhibit C), also indicates that the demonstration of substantial hematopoietic progenitor cell loss upon Ficoll-hypaque centrifugation separation elicits the reasonable expectation that substantial amounts of hematopoietic stem cells are similarly lost. Indeed, three expert declarants, Drs. Boyse, Bernstein and Broxmeyer, as evidenced by their Declarations, deem the extrapolation of progenitor cell loss to stem cell loss as appropriate (see the Boyse Declaration, ¶ 14; the First Bernstein Declaration, ¶ 12; the Second Broxmeyer Declaration, ¶ 26). This evidence proves that use of a Ficoll-hypaque separation method (the method disclosed by Koike) does not inevitably result in recovery of viable stem cells.

The data described above in Table III of the present specification and in Apperley are consistent with additional data in the present specification which show that cell separation and washing steps such as disclosed by Koike are known to cause substantial losses of cord blood progenitor cells (Boyse Declaration, ¶ 15; the First Broxmeyer Declaration, 9, 11-15). The Second Broxmeyer Declaration and the Declaration of Dr. Giao Hangoc filed on July 20, 1994 in connection with the reexamination of the corresponding United States Patent No. 5,004,681 (the "Hangoc Declaration"), present additional evidence of the loss of hematopoietic stem and progenitor cells upon Ficoll-hypaque centrifugation and washing. The evidence presented by way of the Second Broxmeyer Declaration and the Hangoc Declaration demonstrates that Ficoll- hypaque gradient centrifugation and washing causes substantial losses of hematopoietic progenitor cells, regardless of whether centrifugation is performed at 4 °C or at room temperature. Discussed therein as supporting evidence is not only the data in the present specification, but many publications by third parties (see Exhibits C-K to the Second Broxmeyer Declaration and the discussion of the foregoing therein).

Furthermore, the evidence presented by Applicant shows that (1) individual cord blood collections are highly variable in their stem cell content, such that any particular cord blood collection may have low or no stem cells, even prior to cell separation procedures; (2) the sensitivities of cells, and the different sensitivities of different cell types and even of cells from different sources, to cell separation and washing procedures, and losses of cells occurring due to the time elapsing between collection and separation, preclude a conclusion that viable stem cells were necessarily in the blood fraction combined with cryopreservative by the method disclosed by Koike; (3) the sensitivities of cells, and the different sensitivities of different cell types and even of stem cells from different sources, to cryopreservation procedures, preclude a conclusion that viable stem cells were necessarily in the blood fraction cryopreserved by the method disclosed by Koike; and (4) the presence of viable stem cells can only be reasonably concluded based on functional assays; in the absence of such assays, one of ordinary skill in the art cannot reasonably conclude that viable stem cells are necessarily present in any sample subjected to *in vitro* manipulations. In view of the expected high variability in stem cell content and stem cell losses during *in vitro* manipulations, the possibility always exists for any particular cord blood sample subjected to Ficoll-hypaque centrifugation and washing that no stem cells are recovered.

> Also, the vagueness and deficiencies in details in the separation and washing procedures disclosed by Koike also preclude any conclusion that such procedures inevitably yield a plurality of viable stem cells formulated with cryopreservative, and negate any ability to reliably and accurately reproduce these procedures without impermissibly "filling in the blanks" with hindsight knowledge or knowledge lacking from the disclosure of the Koike publication to select procedural variables. [footnotes omitted]

Anticipation: Legal Principles

[18] The subject application was filed before October 1, 1989 and, by virtue of section 78.1 of the *Patent Act*, is governed by the *Patent Act* as it read immediately before that date as well as by Part V of the *Patent Rules* as they read on the date of the Final Action.

[19] The Final Action does not identify the relevant statute under which the claims are said to be anticipated. However, considering the filing date of the subject application and the publication date of the cited art, the relevant statutory provision for assessing anticipation is subsection 27(1)(b) of the *Patent Act* as it read immediately before October 1, 1989; that subsection indicates the following:

> 27.(1) Subject to this section, any inventor or legal representative of an inventor of an invention that was
> (a) . . .
> (b) not described in any patent or in any publication printed in Canada or in any other country more than two years before presentation of the petition hereunder mentioned, and
> (c) . . .
> may, on presentation to the Commissioner of a petition setting out the facts, in this Act termed the filing of the application, and on compliance with all other requirements of this Act, obtain a patent granting him an exclusive property in the invention.

[20] A judicially approved test for anticipation was established in *Beloit Canada Ltd. v. Valmet Oy* (1986), 8 C.P.R. (3d) 289 at 297 (F.C.A.), rev'g (1984), 78 C.P.R. (2d) 1 (F.C.T.D.) wherein Mr. Justice Hugessen indicated the following:

> One must, in effect, be able to look at a prior, single publication and find in it all the information which, for practical purposes, is needed to produce the claimed invention without the exercise of any inventive skill. The prior publication must contain so clear a direction that a skilled person reading and following it would in every case and without possibility of error be led to the claimed invention.

Findings

[21] Considering these legal principles, and for the reasons that follow, the Board finds that claims 1-5 and 12-20 lack novelty since all of the essential features of the claims are either explicitly or implicitly found in Koike. Koike provides all of the information which is needed, for practical purposes, to produce the claimed subject matter, and a person of skill in the art following Koike would, in every case and without possibility for error, be led to the claimed subject matter.

Analysis

[22] The Board must first determine the limits of the claimed invention by comparing certain features found in claim 1 with the teachings of the description; following which the question of teachings of the prior art may then be considered. Bearing in mind the relevant legal principles, if the prior art discloses something which falls within the scope of the claim, then there is anticipation.

[23] Claim 1 reads as follows:

> 1. A cryopreserved, therapeutic composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood of a single human collected at birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells.

[24] In the Board's estimation, the critical features found in claim 1 which demand particular consideration are the following:

(1) the expression "composition comprising viable human neonatal or fetal hematopoietic stem cells derived from the umbilical cord blood or placental blood";

(2) the term "therapeutic"; and

(3) the expression "an amount sufficient to effect hematopoietic reconstitution of a human adult" .

[25] Concerning the first expression, it is apparent that claim 1 can be reasonably understood to encompass whole, or separated, cord blood which comprises stem cells (as well as progenitor cells); the presence of stem cells being indirectly determined through assay for the presence of progenitor cells also found in such compositions. Section 5.1.3 of the description indicates that, while whole cord blood is preferred, compositions which fall within the scope of claim 1 may optionally be enriched for stem and progenitor cells. Section 5.1.3.1 (at page 38, lines 7-14) indicates that one method of enrichment is to separate whole cord blood by Ficoll-Hypaque centrifugation in order to obtain a low density fraction which contains both stem and progenitor cells. Section 5.4.2 (at page 50, lines 16-22) and section 6.2 indicate that *in vitro* assays for progenitor cells were used as a measure of the presence of stem cells in Ficoll-Hypaque separated low density fractions obtained from whole cord blood.

[26] Concerning the term "therapeutic" and the expression "an amount sufficient to effect hematopoietic reconstitution of a human adult", the Board understands that these features are merely functional qualifications, or allusions to inherent properties of the claimed compositions. Therefore, for a composition to fall within the scope of claim 1 there is no strict requirement to find a recognition, or an explicit indication, that there are sufficient stem cells present to effect hematopoietic reconstitution; it is sufficient that a composition simply inherently contain enough stem cells to effect this desired result.

[27] As to the number of stem cells sufficient to effect the desired result, the description indicates that on page 42, lines 11 to 23 that, in theory, only a single stem cell is needed for hematopoietic reconstitution but goes on to indicate that under clinical conditions generally more than a single

cell would be needed. Section 6.8, which is entitled "CALCULATIONS OF THE RECONSTITUTING POTENTIAL OF CORD BLOOD, indicates on page 97, lines 14 to 29 that:

> The following discussion demonstrates that individual collections of cord blood (such as described in Section 6.1) contains sufficient hematopoietic stem and progenitor cells to repopulate the hematopoietic system of an individual.
>
> A survey of published reports indicates that the number of CFU-GM infused for autologous bone marrow reconstitution in human patients, can be relied on as an indicator of the potential for successful hematopoietic reconstitution. By standardizing published data by patient weight, and assuming a patient weight of 150 pounds (67.5 kilograms), the calculated number of CFU-GM needed for successful hematopoietic reconstitution using autologous bone marrow cells ranges from 2-425 x 10^4, with faster recovery noted using greater than 10 x 10^4 CFU-GM.[citations omitted]

[28] Apart from absolute numbers of stem cells, the description in other places refers to volumes of whole neonatal blood that may be used to effect reconstitution. For example, section 5.1.1.1 indicates on page 27, lines 2 to 6 that:

> The following information suggests that as little as 50 ml of cord blood contains enough of the appropriate cells to repopulate the hematopoietic system of an adult, and it is possible that even less cord blood would have the same effect

[29] However, this passage and others like it are of limited use in determining the precise limits of claim 1 as they relate to compositions derived from whole cord blood, *i.e.* a Ficoll-Hypaque separated sample. Thus, while claim 1 generally directs the reader to the desired eventual result, it remains that neither claim 1 nor the specification provides a precise numerical indication of the number of hematopoietic stem cells derived from neonatal or placental blood that are required to effect the desired result.

[30] Importantly, beyond the narrowly focussed discussion above, and beyond the question of whether or not a given composition contains a sufficient number of stem cells to *directly* effect reconstitution -- an interpretation of claim 1 which seems to be consistent with the thrust of all of the Applicant's arguments -- is the broader question of whether claim 1 encompasses compositions which contain a sufficient number of stem cells to *eventually* effect reconstitution; *e.g.* through post-thawing expansion of stem cells in a cryopreserved sample. Consistent with this latter broader interpretation is the reference in the preamble of claim 1 to a "cryopreserved, therapeutic composition" which implies that the claimed composition exists in a frozen state until it is used for therapy; that is to say, the frozen composition of claim 1 is not immediately and directly used to effect reconstitution since it must at least be thawed first.

[31] In this vein, the specification teaches in section 5.1.3.2, which is entitled "IN VITRO CULTURES OF HEMATOPOIETIC STEM AND PROGENITOR CELLS", on page 43, lines 4-6 that: "An optional procedure (either before or after cryopreservation) is to expand the hematopoietic stem and progenitor cells in vitro" (see also section 5.1.3, at page 36, *supra*). Similarly, section 6.9 teaches "IN VITRO CULTURE CONDITIONS FOR HEMATOPOIETIC STEM AND PROGENITOR CELLS".

[32] In view of these teachings, it is apparent that claim 1 encompasses a composition minimally containing a sufficient amount of stem cells to simply allow for *in vitro* expansion of their numbers thereby indirectly allowing for eventual hematopoietic reconstitution. As such, it is

apparent that the numbers of stem cells that need to be present in a composition of claim 1 are much lower than the numbers that would be required if the composition were to be used to directly effect reconstitution. The Board is satisfied that a Ficoll-Hypaque separated cord blood sample contains sufficient numbers of stem cells to allow at least for their *in vitro* expansion and therefore they inherently have therapeutic value.

[33] To summarize its understanding of claim 1, the Board finds that the claim reasonably encompasses a product *per se* which may consist of a Ficoll-Hypaque separated cord blood sample and a cryopreservative.

[34] Turning now to the disclosures of the prior art and the question of whether or not Koike discloses something that falls within the scope of claim 1, it is noted that Koike is concerned with hematopoietic reconstitution in humans and discloses the processing of human cord blood samples (which were known to contain hematopoietic stem cells) by Ficoll-Hypaque purification followed by cryopreservation. *In vitro* assays for viable progenitor cells similar to those of the present application were done both before and after thawing of purified samples and indicated the presence of significant numbers of such cells. Just as in the present application, the presence of viable progenitor cells would therefore be taken by a person skilled in the art as an indirect indicator of the presence of stem cells in the cryopreserved compositions disclosed by Koike. Also, under the heading "Method of Freezing", Koike indicates the presence of an appreciable total number of cord blood mononuclear cells in his cryopreserved samples, and does disclose in table 2 that viable CFU-GM progenitor cells in thawed samples were detected in numbers comparable to those found in similarly processed samples of the present application (see table V).

[35] By comparing the scope of claim 1 to the disclosure of Koike, the Board is led to conclude that the claim is so broad so as to include the compositions of Koike which contain stem cells in sufficient numbers to at least allow for indirect hematopoietic reconstitution after thawing and which therefore also inherently have therapeutic value.

[36] In the response to the Final Action, the Applicant has pointed to data for a handful of samples in his own data in table III as support for the notion that recovery of stem cells from a Ficoll-Hypaque preparation is evitable since few viable progenitor cells were found in certain samples. As the Examiner has pointed out, the vast majority of samples in table III were shown to contain viable progenitor cells, and hence presumably viable stem cells also. Remembering that the purpose in both Koike and the present application is to recover viable cells, it is not clear to the Board why a person of skill in the art is *clearly taught*, in either or both disclosures, to generate compositions that are devoid, for practical purposes, of viable cells. Considered as a whole, the present specification *teaches* the recovery of viable progenitor cells and hence the recovery of viable stem cells. By the same token, Koike also *teaches* the recovery of viable progenitor cells and therefore inherently teaches the recovery of viable stem cells. A person of skill in the art is *taught* by Koike, and *led* in each case and without the possibility of error, to generate a composition which will inherently contain stem cells and which will *inevitably* fall within the scope of claim 1.

[37] In the response to the Final Action and at the oral hearing the Applicant has also argued that the presence of viable stem cells can only be reasonably concluded based on functional assays and that one of skill in the art cannot reasonably conclude that viable stem cells are necessarily present in any sample subjected to *in vitro* manipulations (*e.g.* Ficoll-Hypaque separation). However, in light of the Applicant's own teachings, it seems that a person of skill in the art, upon

reading the Applicant's specification, would appreciate that a cord blood sample subjected to Ficoll-Hypaque separation would contain stem cells. By the same token, a person skilled in the art, upon reading Koike, would arrive at the same conclusion. Although it may be argued, as has Applicant based on the several declarations submitted, that a cord blood sample subjected to Ficoll-Hypaque purification and washing would be subject to stem cell loss, there is no valid reason to immediately conclude that there would be a complete loss of stem cells. Although a whole cord blood sample may be a preferred embodiment of claim 1, the claim is not so limited. Further, it is noted that the Applicant has never argued that the cell compositions of Koike do not, as a matter of fact, contain any stem cells.

[38] Thus, the Board is in agreement with the Examiner's assessment that it is a scientifically sound conclusion that the compositions of Koike inherently contain stem cells. It is not reasonable to discount Koike and say that there is a lack of direct and demonstrable proof of the existence of stem cells in Koike since the Applicant has granted himself the liberty of using similar *in vitro* assays as an indirect indicator of the presence of stem cells in his Ficoll-Hypaque preparations. Therefore, the Board finds that Koike did disclose a composition comprising "viable human neonatal or fetal hematopoietic stem cells", *i.e.* a Ficoll-Hypaque separated cord blood preparation, since both Koike and the present specification disclose the same blood source which was known in the art to contain stem cells, the same separation methods, equivalent cryopreservation methods and equivalent assay methods.

[39] Therefore, to conclude on the question of anticipation, the Board finds all of the features of claim 1, either explicitly or implicitly, in the prior publication by Koike. Further, Koike contains all of the information which a person of skill in the art would need, for practical purposes, to generate a cryopreserved composition which falls within the scope of claim 1 and a person skilled in the art following Koike would be led to the claimed subject matter.

[40] The Board notes that dependent claims 2-5 and method claims 12-20 do not recite any features sufficient to distinguish the claimed subject matter over Koike. Therefore, they too are found to be anticipated.

QUESTION 2: OBVIOUSNESS

[41] The next question for the Board's consideration is whether or not claims 21-45 and 57-66 are obvious in view of Koike. Claims 21, 22, 44, 56, 61, 63 and 65 are the independent claims which are said to be obvious in view of Koike:

> 21. A composition comprising viable cryopreserved human neonatal or fetal stem cells obtained from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult, and an amount of cryopreservative sufficient for cryopreservation of said cells <u>for use</u> in a method for hematopoietic or immune reconstitution of a human adult.[emphasis added]
>
> 22. A composition comprising viable cryopreserved human neonatal or fetal stem cells obtained from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult, and an amount of cryopreservative sufficient for cryopreservation of said cells <u>for use</u> in a method for

treatment of a human adult having a disease or disorder.[emphasis added]

44. Use of a composition comprising a plurality of viable human or fetal hematopoietic stem cells derived from the blood for the manufacture of a medicament for hematopoietic or immune reconstitution.[emphasis added]

56. A composition comprising cryopreserved human neonatal or fetal hematopoietic stem cells obtained from the umbilical cord blood or placental blood of a single human collected at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult, and an amount of cryopreservative sufficient for cryopreservation of said cells for use in a method for hematopoietic or immune reconstitution of a human adult.[emphasis added]

61. Use of composition comprising a plurality of viable human neonatal or fetal hematopoietic stem cells derived from the blood for the manufacture of a medicament for hematopoietic or immune reconstitution, in which the cells have been previously cryopreserved.[emphasis added]

63. A composition comprising viable human neonatal or fetal hematopoietic stem cells for use in a method for hematopoietic or immune reconstitution of a human adult, in which the stem cells are progeny of cells obtained by the method of claim 12.[emphasis added]

65. A composition obtained by the method of claim 12 for use in a method for the treatment of a human having a disease or disorder.[emphasis added]

The Position of the Examiner

[42] The Examiner rejected claims 21-44 and 56-65 as obvious in view of Koike and stated the following:

Applicant has argued that Koike only discloses the testing for viability of certain hematopoietic progenitor cells (i.e. early multipotent progenitor cells not hematopoietic stem cells) in cryopreserved samples of bone marrow and cord blood samples. Applicant further asserts (with Dr. Bernstein's declaration) that the cells detected by Koike are progenitor cells not stem cells and that in vitro colony forming assays did not detect the presence of stem cells that are capable of carrying out long term human hematopoietic reconstitution. Secondly, applicant states that Koike has merely speculated that cord blood might be used as a source of hematopoietic stem cells for restoring bone marrow function.

The examiner respectfully disagrees with applicant on that matter. Firstly, the fact that the presence of stem cells was inferred from the presence of progenitor cells is in no way a demonstration that stem cells were not present in the preparation of Koike, in fact such inferrence was common practice at the time of the invention [see page 97 of the instant application which indicates that "A survey of published reports indicates that the number of CFU-GM (hematopoietic progenitor cell) infused for autologous bone marrow reconstitution in human patients, can be relied on as an indicator of the potential for successful hematopoietic reconstitution"]. Secondly, the examiner does not consider that Koike, in the final paragraph on page 281, has merely speculated that cord blood might be used as a source of hematopoietic stem cells for restoring bone marrow function. On the contrary, the examiner believes that Koike's publication should be considered as a whole and that the statement in the final paragraph on page 281 in fact consists in a prediction [that cord blood would be a good source of

hematopoietic stem cells capable restoring bone marrow function] that is sound.

It is therefore deemed that the compositions of Koike do comprise viable human neonatal or fetal hematopoietic stem cells obtained from umbilical cord blood or placental blood and that the use thereof for the treatment of pathologies defined by the above-mentioned claims is a natural extension of the teachings of Koike.

The Position of the Applicant

[43] In the response of December 23, 2002 the Applicant addressed the issue of obviousness and stated, in part, the following:

> The Applicant respectfully submits that Koike discloses the testing for viability of certain hematopoietic progenitor cells in cryopreserved samples of bone marrow and cord blood samples. The cord blood samples were collected, subjected to Ficoll-hypaque separation and then some samples containing only 2 -5 x 10^6 mononuclear cells were frozen. After thawing, the samples were tested for progenitor cell viability by their ability to form colonies *in vitro*. Koike tested for CFU-GM, BFU-E and CFU-E progenitor cells, which are early multipotent progenitor cells, not hematopoietic stem cells, see specification at page 17, line 7 to page 18, line 9. As is made clear by knowledge of the definitions of stem and progenitor cells set forth in the present application (see the present patent, Section 2.1), the cells detected by Koike are progenitor cells, not stem cells (see also the Second Bernstein Declaration, ¶ 9). Further, Dr. Bernstein in the Second Bernstein Declaration at ¶ 30 states that *in vitro* colony forming assays do not detect the presence of stem cells that are capable of carrying out long term human hematopoietic reconstitution. Koike in the final paragraph on page 281, (paragraph bridging columns 1-2) merely speculates that cord blood might be used as a source of hematopoietic stem cells for restoring bone marrow function.
>
> Applicant respectfully submits that nothing in the disclosure of Koike provides a suggestion or a reasonable expectation of success for achieving the cryopreserved composition comprising viable human neonatal or fetal hematopoietic stem cells derived from umbilical cord blood or placental blood of a single human collect at the birth of said human, in which said cells are present in an amount sufficient to effect hematopoietic reconstitution of a human adult; and an amount of cryopreservative sufficient for cryopreservation of said cells. Further, nothing in Koike provides a reasonable expectation of success in using neonatal or fetal stem and/or progenitor cells in hematopoietic or immune reconstitution or in the treatment of a disease or disorder in a human.
>
> First, there were clear teachings in the art that would lead the skilled artisan to avoid cryopreservation of even a potential fetal or neonatal source of stem cells with the ability to carry out hematopoietic reconstitution (PHSCs). For example, it was known that PHSCs from different sources had different sensitivities to cryopreservation, and that PHSCs from certain sources, *e.g.*, fetal liver and fetal thymus, appeared to be destroyed by cryopreservation.
>
> . . .
>
> Second, the only assay for determining the presence of stem cells from a particular tissue source that are capable of effecting hematopoietic reconstitution of a human in an amount sufficient for effecting such reconstitution, where the stem cells of such source have not previously been demonstrated *in vivo* to carry out hematopoietic

reconstitution, is administering the cells to a patient and determining whether hematopoietic reconstitution occurs. At the time the invention was made, there was no *in vitro* assay for detecting the pluripotential hematopoietic stem cell which can reconstitute the hematopoietic system of a human.

Third, *in vitro* colony forming assays utilized in Koike at the time the invention was made, were not recognized as indicative of the presence of stem cells with the ability to carry out hematopoietic reconstitution (long-term marrow repopulating stem cells; PHSCs). For example, *in vitro* colony-forming cells were known to be distinct from and physically separable from the stem cell that has the ability to effect hematopoietic reconstitution (see, Second Bernstein Declaration, ¶¶ 9-21 to which the Examiner's attention is invited).

Fourth, as explained by Dr. Bernstein in the Second Bernstein Declaration, ¶ 30, knowledge common in the art would, if anything, have led him, as well as one of ordinary skill, to expect that normal human neonatal or fetal blood would not be likely to have utility for hematopoietic reconstitution. As Dr. Bernstein states (¶30):

. . .

There is no hint or suggestion in Koike that stem cells with the ability to carry out hematopoietic reconstitution of a human are even present, much less in any enabling amount, in human neonatal/fetal blood; and there was no reasonable expectation of success in achieving a composition (with exogenous cryopreservative) that contains sufficient stem cells for hematopoietic reconstitution in a human. Moreover, as explained above, Koike did not cryopreserve a sufficient amount of stem cells to effect hematopoietic reconstitution of a human adult.

It is submitted, therefore, that Koike, taken alone or in any combination with any of the other references cited previously by the Examiner, does not render obvious any of the claimed subject matter of the invention.

Furthermore, Applicant proposes to note to the Examiner that the teaching of Koike does not make the claimed compositions obvious since (1) even assuming *arguendo* that the stem cell with hematopoietic reconstituting ability was present, in order for one of ordinary skill in the art at the time the invention was made to have an expectation that the claimed composition would have utility for hematopoietic reconstitution, one of ordinary skill would have believed that amounts sufficient to effect hematopoietic reconstitution, of the stem cells with hematopoietic reconstituting ability, would have to be present in a collection of human neonatal/fetal blood cells from a single human neonate or fetus (and thus be present in a single collection), and there was no expectation or suggestion in the prior art that such amounts were available and/or obtainable in a single collection; and (2) assuming *arguendo* that the idea of the invention was suggested, concerns that there would be maternal cell contamination and graft-versus-host disease would have contributed to preventing an expectation of utility.

. . .

Moreover, the publications discussed on pages 24-31 of Applicant's response filed on December 20, 1996 evidence the initial prior art skepticism and severe doubt among experts in the art after the initial publication by the instant inventors disclosing the presently claimed invention. These references show chronologically the transition in the thinking in the art, from skepticism to uncertainty to an acknowledgment of utility of the claimed invention accompanied by suggestions of its use and copying,

> which transition occurred as publications in the field appeared which gradually demonstrated, irrefutably, by actual successful therapeutic uses *in vivo*, the utility of the claimed compositions for human hematopoietic reconstitution.
>
> These references also further document the reasons set forth above as to why one of ordinary skill in the art would not have reasonably expected or predicted the utility of human neonatal/fetal blood cells for hematopoietic reconstitution, in view of the teaching of Koike. [footnotes omitted]

Obviousness: Legal Principles

[44] The *Patent Act* as it read immediately before October 1, 1989 does not contain an explicit provision requiring that an invention be nonobvious. Nonetheless, the principle of nonobviousness is considered to be implicit in the meaning of the term "invention" and has long been considered by the courts to be a fundamental requirement for patentability.

[45] In *Beloit Canada Ltd. v. Valmet Oy* (*supra* at 294) Mr. Justice Hugessen stated the following test for obviousness:

> The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.

Findings

[46] Having regard to this test, and for the reasons that follow, the Board is of the opinion that claims 21-44 and 56-65 are not obvious in view of Koike.

Analysis

[47] In the Final Action claims 21-44 and 56-65 are not said to be anticipated. Therefore there is an implicit acknowledgment that there is some sort of distinction between Koike and the claimed subject matter. As emphasized above and in a contradistinction to claim 1, it is apparent that the independent claims considered obvious include an explicit, embedded use limitation. Further, in view of the Board's findings on anticipation, it is apparent that a composition (*e.g.* a Ficoll-Hypaque separated cord blood sample or even whole neonatal or placental blood) which falls within the scope of the claims is old. Therefore, the claims in question are considered to relate to the new use of an old product.

[48] In the present case, the claimed utility of the compositions is a clinical or medical utility related principally to hematopoietic or immune reconstitution. The new utility is based, in part, on *in vitro* cryopreservation experiments which validate a method of practical application of the idea of

using a composition comprising hematopoietic stem cells from human cord blood as a clinically useful alternative to bone marrow in order to effect hematopoietic reconstitution. The cryopreservation experiments indicated that viable stem cells could be recovered from cord blood in numbers sufficient to effect hematopoietic reconstitution. Importantly, the present application in section 6.11 also goes on to disclose *in vivo* experiments successfully performed on lethally irradiated mice using neonatal blood in order to provide restorative treatment. The blood volumes used to infuse the mice in these experiments are comparable, based on the mass of a subject, to those that are disclosed to be obtainable from the umbilical cord of a single human. Section 6.12 of the application sets out a therapeutic protocol using cryopreserved cord blood performed on an individual. The protocol is therefore not a hypothetical example and provides meaningful technical guidance to a person of skill in the art, even if successful results of this example are not disclosed.

[49] The claims have been rejected in view of Koike who discloses compositions derived from human cord blood. Much like in the present application, Koike also discloses successful cryopreservation experiments that indicated significant numbers of viable stem cells in thawed samples of the compositions, something that would appear to bode well for therapeutic uses of such compositions. Koike concludes with a suggestion that "fetal hematopoietic cells or organs may be useful as one of the sources of hemopoietic progenitor cells for marrow transplantation", something that is said in the Final Action to be predictive of the claimed use.

[50] However, Koike does not disclose any sort of *in vivo* experiments that would lead a person of skill in the art from the laboratory to the clinic. Further, Koike does not provide any clinical teachings or guidance to a person of skill in the art as to how to go about effecting successful hematopoietic reconstitution. The Board notes that the inventors of the present application adapted known mice model protocols which date to 1977 (see section 6.11) in order to generate some of their *in vivo* data. Such protocols would also presumably have been available to Koike to adopt in order to further extend his laboratory findings. However, it appears that he did not. It is also apparent that at least six years passed between the work of Koike and the filing of the present application. In this time it does not appear to the Board, based on the citation of Koike alone, that anyone else was successful, or even had the inclination, to further Koike's work along the path toward therapeutic uses of compositions derived from human cord blood. This is so despite the fact that there may have been positive indicators in Koike pointing toward therapeutic utility.

[51] In addition to the classical test for obviousness set out in *Beloit Canada Ltd. v. Valmet Oy* (*supra*), the Board is also guided by a number of other relevant decisions.

[52] In *Pope Appliance Corp. v. Spanish River Pulp & Paper Mills Ltd.*, [1929] 1 D.L.R. 209 at 216 (P.C.), rev'g, [1928] 1 D.L.R. 313 (S.C.C.), aff'g, [1926] 3 D.L.R. 902 (Ex. Ct.) Lord Dunedin, speaking for the Privy Council, made the following simple observation concerning an allegedly obvious solution to the problem of finger pinching in paper making machines:

> The first and obvious observation is that if it required no invention it was very odd that people were allowed to go on pinching their fingers for 35 years.

[53] In *Farbwerke Hoechst Aktiengesellschaft Vormals Meister Lucius and Bruning v. Halocarbon (Ontario) Ltd.* (1979), 42 C.P.R. (2d) 145 at 155 (S.C.C.), rev'g (1976), 28 C.P.R. (2d) 63 (F.C.A.), aff'g (1974), 15 C.P.R. (2d) 105 (F.C.T.D.) the Supreme Court stated that:

> Very few inventions are unexpected discoveries. Practically all research work is done by looking in directions where the "state of the art" points. On that basis and with hindsight, it could be said in most cases that there was no inventive ingenuity in the new development because everyone would then see how the previous accomplishments pointed the way.

[54] Finally, the Board takes note of the comments made by Mr. Justice Lederman in *Bayer Aktiengesellschaft v. Apotex Inc.* (1995), 60 C.P.R. (3d) 58 at 80-81 (Ont.Ct.Gen.Div.), aff'd (1998), 82 C.P.R. (3d) 526 (Ont.C.A.):

> Thus, although one would normally imagine that this mythical person's laboratory is filled with mythical test tubes and Petri dishes and that his or her daily life is spent in experimentation, for the purposes of this legal exercise, no research of any kind can be contemplated. So, although it may have been logical to an actual skilled person at the time, based on the state of the art, to conduct certain testing, that is not open to the mythical skilled technician. The mythical researcher cannot have an inquiring or thinking mind which ultimately would lead him or her to the answer but rather he or she is expected to instantly and spontaneously exclaim, without more, "I already know the answer and it is obvious". Nor is it appropriate to say that there were significant telltales which pointed the way for the mythical expert or that there were sufficient clues which made the invention "worth a try".

[55] If the presently claimed subject matter is obvious in view of Koike, then it is not clear to the Board why patients in need of hematopoietic reconstitution, and who might benefit from the advantages of the claimed invention, would be allowed to go on suffering for some six more years, nor is it clear to the Board why a person of skill in the art would be led directly and without difficulty to the claimed subject matter even if the teachings of Koike pointed the way. Although Koike may have pointed the way and made a contribution to the art, it remains that there are significant gaps in the teachings of Koike that a person of skill in the art would not have been able to fill in without doing further undue experimentation.

[56] Accordingly, the Board finds that independent claims 21, 22, 44, 56, 61, 63 and 65 are not obvious in view of Koike alone, and by extension, finds that dependent claims 23-43, 57-60, 62 and 64 are also not obvious.

QUESTION 3: SUPPORT

[57] The final question to be addressed is whether or not claims 6-11, 45-55 and 66-81 lack support contrary to the provisions of subsection 174(2) of the *Patent Rules*.

[58] The claims said to lack support generally relate to hematopoietic stem cells derived from human neonatal or fetal blood having a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder stably incorporated therein. Representative claims are as follows:

> 6. An *in vitro* human neonatal or fetal hematopoietic stem cell derived from the blood in which a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder is stably incorporated, which cell is capable of generating a progeny cell which expresses the heterologous gene sequence.

45. A composition comprising a plurality of viable human or fetal hematopoietic stem cells derived from the blood, which stem cells contain a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder, which heterologous gene sequence is stably incorporated and capable of expression by progeny of the stem cells, for use in a method for the hematopoietic or immune reconstitution of a human.

66. A composition comprising a human neonatal or fetal hematopoietic stem cell derived from the blood in which a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder is stably incorporated, which cell is capable of generating a progeny cell which expresses the heterologous gene sequence, for use in a method for treatment or prevention of a disease or disorder in a human patient.

79. A composition comprising a plurality of viable human neonatal or fetal hematopoietic stem cells derived from the blood, which stem cells contain a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder, which heterologous gene sequence is stably incorporated and capable of expression by progeny of the stem cells.

81. The method of claim 12 further comprising stably transforming the thawed stem cells with a heterologous gene sequence of use in the treatment or prevention of a human disease or disorder, which heterologous gene sequence is capable of expression by progeny of the stem cells.

The Position of the Examiner

[59] On the question of support the Examiner stated the following:

Claims 6-11, 46-56 and 67-82 [formerly claims 10-15, 59-69 and 83-97] do not comply with Subsection 174(2) of the Patent Rules because there is no support in the present description for the subject matter of these claims.

Applicant has argued that in view of the subsequent successes (1995-1996 i.e. 7-8 years after the filing of the instant application) of the claimed methods and the gene therapy approach using human neonatal or fetal hematopoietic stem cells from the blood, the utility of the claimed invention was sound and therefore the above-mentioned claims should not be rejected.

The examiner agrees that the [prospective] utility of genetically modified hematopoietic stem cells was sound at the time of the invention however the rejection of the above-mentioned claims is not based on lack of [prospective] utility but instead for lack of support for the claimed subject matter.

Applicant has not prepared any transformed human neonatal or fetal blood-derived hematopoietic stem or progenitor cells. It is deemed that applicant is, in fact, claiming hoped- for use and hoped-for compositions which have been described only in terms of their desired attributes. The description of a patent application is addressed to one skilled in the art to which the invention relates and must be written such that one skilled in the art would be able to put the invention into practice. Applicant has not shown that he was successful in transforming any of the stem/progenitor cells present in fetal or neonatal blood and was even less capable of demonstrating their capacity to provide an efficient gene therapy. Applicant has therefore failed to provide sufficient support for the above-mentioned claims. Applicant is respectfully referred to

Commissioner's Decision (re Institut Pasteur in Canadian Patent Reporter 76 C.P.R. (3d) pp.206-218) for a further understanding of that matter. Furthermore, It is worth noting that the instant application can be distinguished from the application which resulted in the Monsanto decision (Monsanto Co. v. Commissioner of Patents (1979) 42 C.P.R. (2d) 161) wherein all of the claimed subject matter was disclosed and what was *predicted* was that all of the disclosed subject matter would have *utility* based on structural similarities in view of some of the claimed compounds having been tested and shown to be useful. In the instant application, applicant is attempting to claim compositions containing neonatal or fetal blood- derived transformed stem/progenitor cells and their use while he has not disclosed and cannot explicitly and unambiguously describe any of such transformed stem/progenitor cells. Applicant is basing his claims on a *prediction* that he could obtain these products using well-known techniques and that the products obtained would be useful. However, the Supreme Court did not rule in the Monsanto case that products, that were not disclosed and could not be described, could be claimed.

The Position of the Applicant

[60] The Applicant's response of December 23, 2002 addressed the issue of support. On this matter the Applicant had the following to say:

> The Examiner has suggested that the present description does not provide sufficient support for the claimed subject matter and, in support of this objection, has referred to Commissioner's Decision *re Institut Pasteur* (76 C.P.R. (3d) pp 206-218). The Applicant respectfully submits that, unlike the specification at issue in the *Institut Pasteur* case, the present specification provides a description of the steps that were successfully used to produce the claimed recombinant stem cells and their use, *i.e*. the specification provides sufficient guidance to allow a worker skilled in the art to make and use the claimed invention. In particular, the Applicant respectfully directs the Examiner to Sections 2, 5.6 and 5.6.5 of the present specification, which describe particular methodologies for transforming recombinant nucleic acid molecules into cells, including stem cells and their use in effecting hematopoietic reconstitution and in treating or preventing a disease or disorder in a human.
>
> In Section 2.4 on pages 14-16, references are discussed concerning high-efficiency gene transfer systems for cells, including hematopoietic stem and progenitor cells, including viral vector systems (*e.g.*, retroviral, adenoviral, papovaviral and vaccinia vectors) and DNA mediated gene transfer procedures (*e.g.*, CaPO4 precipitation, DEAE dextran, microinjection, liposomes, chromosome transfer and transfection techniques). Further, recombinant retroviral vectors are discussed as having been widely used experimentally to transduce hematopoietic stem and progenitor cells.
>
> Section 2.4 further discusses that the hypoxanthine phosphoribosyl transferase gene was successfully expressed in mice after retroviral vector mediated transfer of hematopoietic stem cells obtained from the bone marrow, and that both the dihydrofolate reductase and human globin genes were also successfully expressed in mice after CaPO4 transfection of murine hematopoietic stem cells.
>
> Further, Section 5.6.5 on pages 61 -64 teaches hematopoietic reconstitution or treating or preventing a disease or disorder using recombinant hematopoietic stem cells, *i.e.*, stem cells having a stably incorporated heterologous gene capable of expression by the progeny cells. For example, the specification on page 62 discloses that patients who have hematopoietic cells that lack a gene or have a mutant gene can be reconstituted with neonatal stem or progenitor cells that have incorporated a

functional counterpart of the missing or mutant gene.

The specification also teaches on page 62 that patients with infections by pathogenic organisms can also be treated with recombinant hematopoietic stem cells, which recombinant cells contain a heterologous gene that when expressed ameliorates disease symptoms, is toxic to the pathogen, or interferes with the pathogen's life cycle. Further, the specification on page 63 teaches that recombinant hematopoietic stem cells can be used to treat a disease or disorder by constructing recombinant stem or progenitor cells to express a sequence that is anti-sense to the nucleic acid of a hematopoietic cell pathogen. As explained by the specification on page 63, lines 10-23:

Such a sequence, which is complementary to the pathogen's RNA or DNA, can hybridize to and inactivate such RNA or DNA, inhibiting the function or expression of the nucleic acid and disrupting the pathogen's life cycle. As a particular example, recombinant neonatal hematopoietic cells can be used in the treatment of AIDS, a disorder which is caused by HIV, apparently by infection of T4+ lymphocytes (Dagleish et al., 1984, Nature 312:763-766; Klatzmann et al., 1984, Nature 312:767-768). Recombinant neonatal stem and progenitor cells which express an anti-sense nucleic acid that is complementary to a critical region (*e.g*., the long-terminal repeat or polymerase sequence) of the HIV genome (Wain-Hobson et al., 1985, Cell 40:9-17) can be used for hematopoietic reconstitution for the treatment of AIDS.

Moreover, the specification provides in Table II on pages 53-56 a number of exemplary diseases, including genetic diseases and those caused by infection with a pathogen, that could be treated by hematopoietic reconstitution with recombinant hematopoietic stem cells.

Further, the specification teaches in the paragraph bridging pages 63 -64 a number of exemplary methods for the introduction of foreign genes into cells that can be also used to introduce a foreign gene into hematopoietic stem cells for purposes of gene therapy. The techniques that can be used include, but are not limited to, chromosome transfer (*e.g*., cell fusion, chromosome-mediated gene transfer, micro cell-mediated gene transfer), physical methods (*e.g.*, transfection, spheroplast fusion, microinjection, electroporation, liposome carrier), and viral vector transfer (e.g., recombinant DNA viruses, recombinant RNA viruses).

In view of the foregoing, the Applicant respectfully asserts that the present application provides support for the subject matter of claims 6 -11,46 -56 and 67 -82. Withdrawal of this objection is respectfully requested.

Support: Legal Principles

[61] Subsection 174(2) of the *Patent Rules* indicates that “Every claim must be fully supported by the description.”

[62] A
lthough not explicitly mentioned by the Examiner in the Final Action, the question of support also brings into play the requirements of subsection 34(1) of the *Patent Act* as it read immediately before October 1, 1989; that subsection indicates the following:

34. (1) An applicant shall in the specification of his invention

> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
>
> (b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;
>
> . . .
>
> (d) in the case of a process, explain the necessary sequence, if any, of the various steps, so as to distinguish the invention from other inventions;
>
> . . .

[63] On the question of support for claims to biological inventions, the Board is guided by the views of the Patent Appeal Board, as it then was, and by the ensuing decision of the Commissioner of Patents in *re Institut Pasteur* (1995), 76 C.P.R. (3d) 206 [*Pasteur*] which stands for the proposition that the description must provide clear and specific description of the claimed subject matter so as to enable a person of skill in the art to make and use the invention without undue experimentation. At page 215 the decision reads as follows:

> In the present case, the Applicant does not show by examples or broad statements the steps that were successfully used to produce hybridomas secreting monoclonal antibodies which are capable of binding only with the specific antigen. Had any hybridoma and monoclonal antibody for certain antigens been prepared, then it would have been arguable that other hybridomas and monoclonal antibodies, which were claimed but unprepared or prepared but untested, could be allowable in view of the "sound prediction" principle. In this case there is no consideration given by the disclosure to any monoclonal antibody so that there is nothing upon which to base a sound prediction.
>
> The Board finds that there is a lack of guidance in describing the core method to be used and the permissible modifications of that basic method for the specific antigens disclosed. Such deficiencies in guidance cannot be remedied by referring the person skilled in the art to experiment with the "traditional techniques".
>
> In summary, the Board also finds that the description does not include any clear references or description to enable the person skilled in the art to make and use the invention without considerable and protracted experimentation. The Board concludes that the hybridomas and the monoclonal antibodies embraced by the claims 84 and 85 are not described or enabled by the present disclosure as required under Subsection 34(1) of the *Patent Act*.

[64] The Board is also guided by the decision in *Minerals Separation North American Corp. v. Noranda Mines Ltd.*, [1947] Ex.C.R. 306 at 316-317 wherein the general requirements of the description were discussed:

> Two things must be described in the disclosures of a specification, one being the invention, and the other the operation or use of the invention as contemplated by the

> inventor, and with respect to each the description must be correct and full. The purpose underlying this requirement is that when the period of monopoly has expired the public will be able, having only the specification, to make the same successful use of the invention as the inventor could at the time of his application. The description must be correct; this means that it must be both clear and accurate. It must be free from avoidable obscurity or ambiguity and be as simple and distinct as the difficulty of description permits. It must not contain erroneous or misleading statements calculated to deceive or mislead the persons to whom the specification is addressed and render it difficult for them without trial and experiment to comprehend in what manner the invention is to be performed. It must not, for example, direct the use of alternative methods of putting it into effect if only one is practicable, even if persons skilled in the art would be likely to choose the practicable method. The description of the invention must also be full; this means that its ambit must be defined, for nothing that has not been described may be validly claimed. The description must also give all information that is necessary for successful operation or use of the invention, without leaving such result to the chance of successful experiment, and if warnings are required in order to avert failure such warnings must be given. Moreover, the inventor must act *uberrima fide* and give all information known to him that will enable the invention to be carried out to its best effect as contemplated by him.

Findings

[65] Having regard to these decisions, and for the reasons that follow, the Board is of the view that claims 6-11, 45-55 and 66-81 lack support within the meaning of subsection 174(2) of the *Patent Rules*.

Analysis

[66] The Board notes that claim 6 is directed to a product *per se, i.e.* a genetically engineered hematopoietic stem cell derived from human neonatal or fetal blood. Claims 45 and 66 are directed to compositions comprising hematopoietic stem cells qualified by an embedded use limitation directed to therapeutic methods; however, the claims do not explicitly indicate the presence of any other components in the compositions. Claim 79 is directed to a composition *per se* which minimally comprises a plurality of genetically engineered hematopoietic stem cells; again no other components of the composition are indicated. Claim 81 is a method claim directed to genetically engineering a thawed hematopoietic stem cell. Importantly, all of these claims indicate that the biological entity carrying the heterologous gene sequence may minimally, essentially and solely consist of hematopoietic stem cells; there are no indications in the claims that the products contain other biological entities, *i.e.* hematopoietic progenitor cells.

[67] Section 5.6.5 of the description represents the Applicant's clearest and most specific description of the claimed subject matter. Throughout this section there are ambiguous references to genetically engineered stem *and* progenitor cells as well as references to genetically engineered stem *or* progenitor cells. There are also descriptions of methods which relate to one step involved in the making a genetically engineered stem cell; that is, the step of inserting the gene sequence into a stem and/or progenitor cell. There are also indications in this subsection that a variety of diseases which "can be" treated by gene therapy with recombinant stem and progenitor cells. However, there is neither a clear and specific description of methods that may be used to isolate only genetically engineered human hematopoietic stem cells nor is there a clear and specific description of the claimed isolated genetically engineered

hematopoietic stem cells themselves which exist apart from other cell types, *i.e.* apart from progenitor cells. It is noted that in section 5.1.3.1 methods of separating stem and progenitor cells are discussed. However, no methods are described that could be used to isolate only hematopoietic stem cells. These defects are not remediable by relying on the common knowledge which might be expected of a person of skill in the art since the genetic engineering of human hematopoietic stem cells derived from neonatal or placental blood was something not routinely done at the time. While the background of the invention discusses in section 2.4 various known methodologies, the state of the art does not extend clearly and specifically to genetically engineered human hematopoietic stem cells alone; at best the prior art at the time of filing describes the genetic engineering of stem/progenitor cells and bone marrow cells, *i.e.* mixtures of cells.

[68] Adding to these problems is the admitted fact that there were no known assays available to a person of skill in the art that he could have used to easily and directly identify a hematopoietic stem cell derived from human neonatal or placental blood. The description also indicates, in section 2.1, that hematopoietic stem and progenitor cells are morphologically indistinguishable and only distinct in terms of functionality.

[69] Finally, there is nothing in the description which indicates that the Applicant, at the time of filing, was in possession of an isolated genetically engineered hematopoietic stem cell derived from human neonatal or placental blood. Accordingly, it does not appear that the Applicant is able to describe the unique and particular features of even one such cell.

[70] In the response to the Final Action the Applicant has suggested that the description is sufficient and that he has successfully produced recombinant stem cells:

> The Applicant respectfully submits that, unlike the specification at issue in the *Institut Pasteur* case, the present specification provides a description of the steps that were successfully used to produce the claimed recombinant stem cells and their use, *i.e.* the specification provides sufficient guidance to allow a worker skilled in the art to make and use the claimed invention. In particular, the Applicant respectfully directs the Examiner to Sections 2, 5.6 and 5.6.5 of the present specification, which describe particular methodologies for transforming recombinant nucleic acid molecules into cells, including stem cells and their use in effecting hematopoietic reconstitution and in treating or preventing a disease or disorder in a human. [emphasis added]

[71] However, it is clear that the description discloses neither the successful preparation of the claimed recombinant stem cells nor any particular methodologies that might be used to transform a population of cells made up exclusively of hematopoietic stem cells derived from human neonatal or placental blood. The response also asserts the following:

> Section 2.4 further discusses that the hypoxanthine phosphoribosyl transferase gene was successfully expressed in mice after retroviral vector mediated transfer of hematopoietic stem cells obtained from the bone marrow, and that both the dihydrofolate reductase and human globin genes were also successfully expressed in mice after CaPO4 transfection of murine hematopoietic stem cells. [emphasis added]

[72] These assertions appear to be based on two references mentioned in subsection 2.4; namely, Miller *et al.* (1984, Science 255:630) and Salser *et al.* (1981, in "Organization and Expression of Globin Genes" Alan R. Liss Inc.,New York, pp. 313-334). The Board notes that Miller *et al.* disclose the transformation of murine bone marrow cells, *i.e.* a mixed population of cells, not a

human hematopoietic stem cell derived from human neonatal or placental blood. The work of Salser *et al.* similarly relates to transformed murine bone marrow cells. Although the murine bone marrow cell populations in both cases may inherently comprise a stem cell, there is nothing in either reference that teaches compositions minimally comprising a transformed stem cell. Accordingly, it seems that these references would be of limited use to a person of skill in the art if he relied upon them to reproduce the claimed subject matter.

[73] The response to the Final Action also refers to section 5.6.5 which is said to disclose a number of diseases that "could be treated" with recombinant hematopoietic stem cells. However, the issues here are firstly, whether or not a person of skill in the art is provided with sufficient information and guidance to initially obtain a recombinant hematopoietic stem cell and, secondly, whether or not the Applicant has provided an adequate description of the cells. What a person of skill in the art might do with such cells, once in hand, is another question.

[74] In view of the foregoing, it would not be clear to a person of skill in the art how he could arrive at the claimed subject matter without undertaking further undue experimentation. The description provides neither sufficient instruction and guidance in terms of methodologies that might be used to generate genetically engineered stem cells alone nor does it provide an adequate description of a genetically engineered hematopoietic stem cell *per se* derived from human neonatal or placental blood.

[75] The present case appears to the Board to provide neither sufficient description of the claimed methodologies nor the claimed products. With respect to the claimed products, the present application, contrary to the Applicant's opinion, is akin to the decision in *Pasteur*. With respect to the claimed methods, the present application, unlike the situation in *Pasteur*, cannot even be said to rely on "traditional techniques."

[76] The Board therefore finds that claims 6-11, 45-55 and 66-81 are not compliant with subsection 174(2) of the *Patent Rules*.

CONCLUSIONS

[77] In summary, the Board concludes that:

(1) claims 1-5 and 12-20 do not comply with subsection 27(1)(b) of the *Patent Act* as it read immediately before October 1, 1989;

(2) claims 21-44 and 56-65 are not obvious; and

(3) claims 6-11, 45-55 and 66-81 lack support and do not comply with subsection 174(2) of the *Patent Rules*.

[78] In respect of claims 63-65, the Board notes that these claims refer to subject matter defined in claim 12. Although the Board has concluded that claim 12 is anticipated and must be deleted, the sole reason for rejecting claims 63-65 has, in the Board's view, successfully been overcome by the Applicant. Therefore, for the sake of clarity, the subject matter defined in claim 12 must be formally incorporated into claims 63-65.

[79] The Board recommends that the Commissioner:

(1) inform the applicant, in accordance with paragraph 31(c) of the *Patent Rules*, that the following amendments of the application are necessary for compliance with the *Patent Act and Rules*:

(a) deletion of claims 1-20, 45-55 and 66-81;

(b) amendment of claims 63-65, which refer to present claim 12, to explicitly and directly incorporate the subject matter defined in present claim 12; and

(c) adjustment of claim numbering and dependencies accordingly;

(2) invite the applicant to make only the above amendments within three months from the date of the Commissioner's decision;

(3) advise the applicant that, if the above amendments, and only the above amendments, are not made within the specified time, the Commissioner intends to refuse the application.

Michael Gillen
Chairman

Murray Wilson
Member

COMMISSIONER'S DECISION

[80] I concur with the findings and recommendation of the Patent Appeal Board. Accordingly, I invite the applicant to make the above amendments, and only the above amendments, within three months from the date of this decision, failing which I intend to refuse the application.

Mary Carman

Commissioner of Patents

Dated at Gatineau, Quebec
this 4th day of September , 2007