Commissioner’s Decision #1405

Décision du commissaire #1405

TOPIC: GOO (Utility); B22 (not supported by disclosure); C00 (adequacy or deficiency of description)

SUJET: GOO (Utilité); B22 (portée excessive); C00 (caractère adéquat ou inadéquat de la description)

Application No.: 2,388,497

Demande n°.: 2,388,497

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,388,497 having been rejected under subsection 30(3) of the *Patent Rules*, has subsequently been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules*. The recommendation of the Board and the decision are as follows:

Agent for the Applicant:

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## INTRODUCTION

[1] Patent application number 2,388,497, entitled "METHOD OF PRODUCING DIFFERENTIATED PROGENITOR CELLS BY CULTURING MORULA OR INNER CELL MASS CELLS", is owned by Advanced Cell Technology, Inc. and stands rejected after the Applicant's response to a Final Action as the Applicant's response did not overcome the rejection. A review of the rejected application has therefore been conducted by the Patent Appeal Board pursuant to paragraph 30(6)(*c*) of the *Patent Rules*. For the reasons set out below, our recommendation is that the application be refused.

## BACKGROUND

Basics concepts

[2] The instant application relates to the fields of applied reproductive biology, and regenerative medicine. More specifically, the application discusses methods that are derived from the prior studies of the mammalian development of the embryo and we consider helpful to describe some uncontroversial basic concepts underlying the claimed invention.

[3] Mammalian development starts with the fertilization of an egg. This fertilized egg is totipotent, meaning it has the potential to generate all the specialized cells that make up an adult animal and that support its development *in utero*.

[4] As development continues, cells of the early embryo proliferate and form a solid mass, which is termed the morula. Following one further day of development, the morula becomes a blastocyst, which is the result of the first observable sign of cellular differentiation. The blastocyst contains two cell types: inner cell mass (ICM) cells growing on the interior of the blastocyst and trophoblast cells growing on the exterior.

[5] ICM cells are said to be pluripotent because they have the potential to develop into any type of cells *in vivo*, excepting those of the extraembryonic tissues. Pluripotent cells can be derived from isolated ICM cells and propagated indefinitely *in vitro* in an undifferentiated state. Such cells existing *in vitro* are referred to as embryonic stem (ES) cells.

[6] Most of the cells of the developing embryo will completely differentiate and acquire structures and functions to become specialized cells (e.g., neuron, epithelial cell, muscle cell, etc.). Other cells will only partly differentiate into multipotent progenitor cells and, in principle, their differentiation potential is limited to cells of a specific tissue (e.g., muscle, nervous, epithelial and connective tissues).

The application

[7] The specification describes procedures for making differentiated progenitor cells that can be used for cell therapy or as a source of cells to provide tissues and organs for transplantation. More specifically, the description discloses that morula or ICM cells can be directly differentiated into progenitor cells in the presence of a differentiation-inducing agent or environment.

[8] According to the background section of the description, prior research efforts to find a source of cells for cell therapies or transplantations were principally directed to producing ES cells that have the potential to differentiate into derivatives of all three embryonic germ layers (i.e., endoderm, ectoderm and mesoderm) when induced to do so (see the disclosures of Thomson et al, Science, 282:1145-1147 (1998) [*Thomson*] and U.S. Patent No. 5,843,780, both cited on page 4).

[9] However, as of the filing date, reliable methods of directing the differentiation of ES cells toward a desired type of differentiated cells were not available:

> A potential application of embryonic stem cells is to use those cells as a source to produce differentiated cells for cell therapy and for the generation of tissues and organs for transplantation. However, stable embryonic stem cell lines and reliable methods for expansion of those cells into differentiated cells/tissues/organs are not yet available. [Emphasis added] (page 5, lines 5-10)

[10] The specification also refers to known methods of producing ES cells. Their production requires the long-term culture of ICM cells on a layer of feeder cells:

> Methods for deriving embryonic stem (ES) cell lines in vitro from early preimplantation mouse embryos are well known. (*See*, e.g., Evans et al, Nature, 29:154-156 (1981); Martin, *Proc. Natl. Acad. Sci., USA*, 78:7634-7638 (1981)). ES cells can be passaged in an undifferentiated state, provided that a feeder layer of fibroblast cells (Evans et al, *Id*.) or a differentiation inhibiting source (Smith et al., *Dev. Biol.*, 121:1-9 (1987)) is present.

[11] According to the Applicant, the claimed invention would bypass the step of producing ES cells and allow the direct production of differentiated progenitor cells of a particular embryonic lineage from morula or ICM cells.

> By the present invention, the production of embryonic stem cells is bypassed, i.e., morula-derived cells or inner cell mass cells are induced to differentiate directly into differentiated progenitor cells which are then used for cell therapy and for the generation of tissues and organs for transplantation. (page 8, lines 13-15)

[12] The description describes the contemplated differentiated progenitor cells as follows:

> Thus, the differentiated progenitor cells of the present invention are not pluripotent and are, in essence, tissue-specific stem cells. The differentiated progenitor cells may give rise to cells from all three embryonic germ layers, i.e., endoderm, mesoderm and ectoderm. [Emphasis added] (page 8, lines 27-30)

[13] The description further recites, on pages 10-13, a list of hundreds of putative differentiation-inducing agents, environments and combination thereof said to induce the morula or ICM cells to differentiate directly into progenitor cells. The list of differentiation agents includes numerous representatives of each of the following broad categories of compounds: growth factors, cytokines, extracellular matrix components, hormones, hormone antagonists and antibodies to various growth factors or growth factor receptors.

[14] However, the description does not provide evidence that a single agent or environment exhibits the contemplated differentiation-inducing activity toward morula or ICM cells. To the extent that there is any disclosure as to which agent(s) or environment(s) should be used to obtain differentiated progenitor cells of a given type, it comes in the form of a disclosure of a screening test that is preferably used to identify those agents and/or environments that might induce the differentiation of morula or ICM cells into desired differentiated progenitor cell types:

> Preferably, a screening test is used to detect agents that induce the differentiation of morula-derived cells or inner cell mass cells into desired differentiated cell types. (page 10, lines 30-31)

[15] Consistent with the statement noted above that reliable methods of directing the differentiation of ES cells toward a desired type of differentiated cells were not available, the description does not teach or suggest to the skilled reader that any of the listed agents and environments are commonly known to directly differentiate ES cells into progenitor cells of a desired type.

[16] Although the description does not disclose technical details about how the identification and isolation of progenitor cells of different types are to be performed, the description gives the following non-specific guidance on page 11, lines 10-13:

> Differentiated cells are identified by use of differentiation-specific antibodies, morphology, PCR using differentiation-specific primers, or any other applicable technique for identifying specific types of differentiated cells.

and on page 13, lines 21-26:

> Once subjected to the differentiation protocol, primitive cells from a particular embryonic lineage can be isolated from the differentiated inner cell mass derivatives by conventional techniques. If desired, the isolated differentiated progenitor cells can be expanded, for example, by cell culture or other appropriate methods. By the present invention, the differentiated progenitor cells are obtained through differentiated inner cell mass cells without having to generate embryonic stem cells.

[17] The description then discloses two examples, neither of which discloses the direct production of differentiated progenitor cells of a particular embryonic lineage from morula or ICM cells. Instead, the first example shows that only a fraction of the ICM cells cultured on a mouse fibroblast feeder layer are capable of developing into ES-like cells. According to the description, these results indicate that there are pluripotent ICM cells which cannot, or do not, develop into ES cells.

[18] The second example is an example that describes how an experiment which relates to injection of ICM cells and teratoma formation in steers could be conducted.

[19] The specification ends with 25 claims, claiming methods of producing differentiated progenitor cells by directly culturing morula or ICM cells in the presence of a differentiation-inducing agent or environment (claims 1-15) and claiming methods of identifying such a differentiation and environment agent (claims 16-25).

Prosecution history

[20] Patent application 2,388,497 was filed in Canada on October 13, 2000 and published on April 26, 2001. Examination culminated with the issuance of a Final Action (FA) on August 6, 2013. The FA states that dependent claims 1-25 do not comply with section 2 of the *Patent Act* and section 84 of the *Patent Rules*. The FA further states that the specification, insofar as it relates to claims 1-25, does not comply with subsection 27(3) of the *Patent Act*.

[21] According to the FA, these defects were identified because the specification fails to disclose a single agent or environment that has the effect of producing differentiated progenitor cells directly from the morula or ICM cells and therefore:

a) there is no factual basis supporting an articulable and sound line of reasoning for the utility of the claimed methods;
b) the claimed methods are not correctly and fully described; and
c) the skilled person would have to perform undue experimentation to determine if any of the many differentiation agents or environments listed in the description has the ability to produce differentiated progenitor cells directly from morula or ICM cells.

[22] Two passages of the FA that relate to the lack of factual basis in the description supporting an articulable and sound line of reasoning for the utility of the claimed methods encapsulates well the issue before us:

> The application itself does not teach which of the conditions or environments that are known to cause differentiation of ES cells into progenitor lines were capable of also causing differentiation of morula or ICM cells directly into progenitor lines. The application also does not present a factual basis or sound line of reasoning for why this surprising effect should occur.
>
> […]

> As discussed above, the application merely provides the hypothetical possibility that a differentiation-inducing agent or environment known in the art to induce ES cell differentiation could be employed to instead produce differentiated progenitor cells directly from morula or ICM cells. Therefore, the utility of the claimed method for the identification of differentiation agents or environments having the surprising effect of producing differentiated progenitor cells directly from morula or ICM cells has not been established

[23] The FA also addressed the disclosures of the pre- and post-filing scientific publications that, according to the Applicant, provide factual basis for the prediction.

[24] The FA indicated that the post-filing scientific publications cannot be relied upon to provide the factual basis for the prediction:

> Further, the applicant must be in a position to establish the utility of their invention no later than at their filing date, and consequently the factual basis upon which either the demonstration or sound prediction are based must exist as of the filing date, which is October 13, 2000 (see section 12.08.05 of the *Manual of Patent Office Practice*). Consequently, only the teachings of Talbot et al. (1994), Schuldiner et al. (2000) or Thomson et al. (1998) may be relied upon to supply such a basis.

[25] According to the FA, the differentiated cells were not obtained from morula or ICM cells in Talbot et al., "A continuous culture of pluripotent fetal hepatocytes derived from the 8-day epiblast of the pig" (1994) 30A(12) In Vitro Cell Dev Biol Anim [*Talbot*]:

> In the correspondence of February 20, 2012, the applicant argued that Talbot et al. (1994), *In Vitro Cell and Dev Biol Animal*, 30A:843-50 described the spontaneous differentiation of porcine ICM derived cells into hepatocytes. However, according to a later publication by the same authors (Talbot et al. (2002), *In Vitro Cell and Dev Biol Animal*, 38:191 -7), these differentiated cell types were obtained from the culture of totipotent ES cells (see page 191, abstract and first column).

[26] As for Schuldiner et al., "Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells" (2000) 97(21) Proc Natl Acad Sci USA [*Schuldiner*] and Thomson et al., "Embryonic stem cell lines derived from human blastocysts" (1998) 282(5391) Science [*Thomson*], which were published before the filing date, the FA expressed the view that they fail to provide a sufficient factual basis for a sound prediction of utility:

> Neither document provides a factual basis for the prediction that conditions which are known in the art to produce one effect, namely the differentiation of ES cells into progenitor cells, can instead be used to cause ICM cells to bypass the step of forming ES cells and differentiate directly into progenitor cells, as is asserted in the present application.

[27] With respect to the requirements of section 84 of the Rules and subsection 27(3) of the Act, the FA stated the following with respect to claims 1-15:

> The description only teaches that agents that induce the differentiation of morula-derived or ICM cells into desired differentiated cell types might be identified using a screening test, and lists a large number of possible "differentiation agents" (see page 11, line 1- page 13, line 20) or "environments" (see page 10 lines 11-20). However, the description does not teach which of these "differentiation agents" or "environments", if any, are useful to induce differentiation of cells directly into specific progenitor cell types, since no such results were achieved. Therefore, in order to use the method of claims 1-15, a skilled person would have to perform undue experimentation to determine if any of the many "differentiation agents" or "environments" listed in the description have the ability to produce differentiated progenitor cells directly from morula or ICM cells, contrary to the teachings of the prior art.
>
> In view of the preceding objection, the specification does not comply with subsection 27(3) of the *Patent Act*. The specification does not correctly and fully describe the claimed method of producing differentiated progenitor cells

> comprising obtaining morula-derived cells or ICM cells from a blastocyst and directly culturing said cells in the presence of a differentiation-inducing agent or environment to produce differentiated progenitor cells as recited in claims 1-15, so as to enable any person skilled in the art to practice the invention. The specification does not describe a single differentiation-inducing agent or environment which was useful in the claimed method and which resulted in the production of differentiated progenitor cells directly from morula or ICM cells.

and the following with respect to claims 16-25:

> Claims 16-25 do not comply with section 84 of the *Patent Rules* because there is no support in the present description for the subject matter of these claims. Specifically, a method of identifying a differentiation agent or environment that induces the differentiation of morula or ICM cells to a differentiated progenitor cell type is not present in the description as filed. As acknowledged by the applicant on page 2 of the correspondence of November 30, 2011, the description does not specifically show differentiation assays for ICM or morula-derived cells.
>
> In view of the preceding objection, the specification does not comply with subsection 27(3) of the *Patent Act*. The specification does not correctly and fully describe the claimed method of identifying a differentiation agent or environment that induces the differentiation of morula or ICM cells to a differentiated progenitor cell type as recited in claims 16-25, so as to enable any person skilled in the art to practice the invention. The specification does not correctly and fully describe a method which identified even a single differentiation-inducing agent or environment which resulted in the production of differentiated progenitor cells directly from morula or inner cell mass cells. The application merely provides the hypothetical possibility that using the method of claims 16-25, a differentiation-inducing agent or environment known in the art to induce ES cell differentiation could be identified which instead produces differentiated progenitor cells directly from morula or ICM cells. [Emphasis in the original]

[28] In a response to the FA dated February 5, 2014 (R-FA), the Applicant argued that the contention that the sound prediction is flawed was not supported by sufficient facts and reasoning:

> Pages 11-12 of the present specification disclose numerous known differentiation agents that are suitable to practice the instant method claims. No evidence of record calls into question the suitability of any of the listed differentiation agents. The Examiner has provided neither evidence nor reasoning as to why the utility should be questioned. For this reason alone Applicant believes the objection should fail.

[29] The Applicant also argued that the utility of the claims on file is established by sound prediction and thus the claims comply with section 2 of the *Patent Act*. The Applicant again referred to those scientific publications that it asserts provide the factual basis for the prediction. According to the Applicant, the cited pre-filing publications provide the factual basis for claims 1-25 by disclosing the following:

> Talbot et *al*. (1994) *In Vitro* Cell and Dev Biol Animal 30A:843 describes the spontaneous differentiation of porcine ICM derived cells into hepatocytes (Abstract) (note the cell names "PICM" indicate they are ICM derived).
>
> Schuldiner et *al*. (2000) PNAS 97:11307 report the effects of numerous growth and differentiation factors on hES cells (Fig 3). Like ICM cells, ES cells have the ability to differentiate into progenitor cells (Thomson (1998) Science 282:1145).
>
> The specification also makes clear that cells of the bovine ICM could spontaneously differentiate into epithelial cells (page 3, lines 8-17).

[30] Moreover, in view of the fact that activin is one of the agents disclosed in the specification, the Applicant also introduced an additional group of references (*Activin* references), all of which were published before the filing date, but were not referred to in the specification. According to the Applicant, the *Activin* references

deal with the role of activin in cardiac formation in bird embryos and the expression of activin in murine ICM cells:

> Yatskievych et al. (1987) Development 124:2561 show that activin induced cardiac differentiation in a dose dependent fashion in the posterior avian epiblast (Abstract). Albano et al. (1993) Development 117:711 show that activin is expressed in the mouse ICM of 3.5 day blasotcysts (Abstract). Because activin was shown to induce cardiac formation in the embryo of birds and because it was also shown to be expressed in murine ICM just before the onset of cardiac formation (see Robbins et al. 1990 JBC 265:11905 Abstract regarding murine cardiac development), a skilled artisan would have a factual basis for making a sound prediction that activin could induce cardiac formation from ICM cells. Activin is disclosed as a differentiation agent on page 11, line 21 of the specification.

[31] With regard to the "sound line of reasoning", the Applicant submitted the following with respect to claims 1-15:

> Given that the record establishes 1) that cells derived from the ICM can spontaneously differentiate into progenitor cell lines of varying types; 2) growth factors enhance this effect; and 3) growth factors enhance the differentiation of ES cells. A skilled artisan would have a rational basis to believe that ICM derived cells treated with specific growth factors would demonstrate an enhanced capacity to differentiate into progenitor cells.

and the following with respect to claims 16-25:

> As regards the sound line of reasoning, Applicant submits that given that ICM cells can spontaneously form progenitor cells and given that differentiation and growth factors can enhance this process, a skilled artisan would have sound reason to predict that an assay that screens a test factor could readily determine the effectiveness of a given growth or differentiation factor to enhance the differentiation of the ICM cell into a given progenitor cell.

[32] The Applicant also argued that the claims and description on file comply with section 84 of the *Patent Rules* and subsection 27(3) of the *Patent Act* as the claims find literal support throughout the specification, that numerous differentiation factors are disclosed and that a research article published after the publication date of the application confirms that one of the listed factors enhances the differentiation of ICM derived cells to progenitor cells.

[33] Unconvinced that the Applicant's arguments rendered the application allowable, the Examiner forwarded the file to the Patent Appeal Board (the Board). The file included a Summary of Reasons (SOR) for maintaining that the application did not comply with the *Patent Act* and *Patent Rules*.

[34] The SOR disagreed that the *Activin* references cited by the Applicant in the R-FA provided the necessary information to establish the utility of the claims:

> In response to the final action, the applicant maintains the position that the utility of the claims is established by sound prediction, and that the claimed subject matter is fully supported and is correctly and fully described. In addition to reiterating the analysis of several documents previously presented in defence of this position, which were discussed in the final action, the applicant introduces several additional documents to support this position. In particular, the applicant refers to Yatskievych et al. (1997) Development 124:2561-70; Albano et al. (1993) Development 117:711-23; and Robbins et al. (1990) Journal of Biological Chemistry 265:11905-09, to support the argument that activin induced cardiac differentiation in ICM, and therefore serves as a factual basis for making a sound prediction. However, nothing in these references suggests that activin can be used to bypass the normal process of differentiation of morula or ICM cells into stem cells and instead form differentiated cardiac cells directly, as is claimed in the present application.

[35] The SOR concluded that the application stood rejected on the same grounds stated in the FA and noted that a corresponding application was refused by the European Patent Office in 2010.

[36] In a letter dated November 25, 2014 wherein the SOR was enclosed, the Board offered the Applicant an opportunity to make further written submissions and/or attend an oral hearing.

[37] In a letter dated February 11, 2015, the Applicant informed the Board that it did not wish to not participate in a hearing. In addition, the Applicant informed the Board that no additional written submissions would be provided in response to the SOR.

**ISSUES**

[38] Based on our reading of the FA, the SOR and the R-FA, the main issues raised in the FA and SOR are whether the utility of the claimed subject matter has been established by sound prediction and whether the specification complies with subsection 27(3) of the Act. More precisely:

1. Would the person of ordinary skill in the art (POSITA) soundly predict that the agents and environments encompassed by claims 1-15 would directly differentiate cultured morula or ICM cells into the contemplated differentiated progenitor cells?

2. Would the POSITA soundly predict that the methods of claims 16-25 would identify an agent or environment that directly induces the differentiation of cultured morula or ICM cells into differentiated progenitor cells?

3. Does the specification correctly and fully describe a method of identifying differentiation agents or environments that directly induce the

> differentiation of morula or ICM cells into tissue-specific progenitor cells and enable the POSITA to positively identify the differentiation agents or environments that can successfully be used in a method of directly producing differentiated tissue-specific progenitor cells from morula or ICM cells without exercising inventive ingenuity or undertaking undue experimentation?

[39] Given the issues identified above, we consider that addressing the alleged defect that was raised under section 84 of the *Patent Rules* is unnecessary for the purposes of this review as it does not raise an issue not already presented as a failure to comply with subsection 27(3) of the *Patent Act*.

## LEGISLATION AND LEGAL PRINCIPLES

### Purposive construction

[40] In accordance with *Free World Trust v Électro Santé Inc.*, 2000 SCC 66 [*Free World Trust*] essential elements are identified through a purposive construction of the claims done by considering the whole of the disclosure, including the specification and drawings (see also *Whirlpool Corp v Camco Inc.*, 2000 SCC 67 at paras. 49(f) and (g) and 52). In accordance with the *Manual of Patent Office Practice* §13.05 [revised June 2015; MOPOP], the first step of purposive claim construction is to identify the person skilled in the art and their relevant common general knowledge ("CGK"). The next step is to identify the problem addressed by the inventors and the solution disclosed in the application. Essential elements can then be identified as those elements of the claims that are required to achieve the disclosed solution.

### Utility

[41] As noted above, one of the issues before us is whether the utility of the claimed subject matter has been established by sound prediction. Utility is part of the

definition of "invention" in section 2 of the *Patent Act* which states that the claimed subject matter must be "useful":

> ***invention*** means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter

[42] The utility requirement was described by the Supreme Court of Canada in *Consolboard Inc. v MacMillan Bloedel (Saskatchewan) Ltd.*, [1981] SCR 504, at p. 525:

> There is a helpful discussion in Halsbury's Laws of England, (3rd ed.), vol. 29, at p. 59, on the meaning of 'not useful' in patent law. It means "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do". [emphasis added]

[43] The asserted utility is fundamental to the utility analysis and must be ascertained at its outset. In *Pfizer Canada Inc. v Canada (Minister of Health),* 2011 FCA 236 at para 17, the Federal Court of Appeal stated that the determination of the asserted utility of a patent is an aspect of patent construction:

> Like claims construction, the promise of the patent is also a question of law (*Eli Lilly Canada Inc. v. Novopharm Ltd.*, 2010 FCA 197 [*Eli Lilly*]). In this particular case, the Applications Judge, assisted with expert evidence, needed to purposively ascertain the promise of the patent "within the context of the patent as a whole, through the eyes of the person of skill in the art (POSITA) in relation to the science and information available at the time of filing" (*Eli Lilly*, at paragraph 80).

[44] Utility must be established either by demonstration or sound prediction as of the Canadian filing date. Utility cannot be supported by evidence and knowledge that only became available after the filing date (see *Apotex Inc. v Wellcome Foundation Ltd.*, 2002 SCC 77 at para 56 (*AZT*)).

[45] The doctrine of sound prediction allows establishing asserted utility even where that utility had not been fully verified as of the filing date. However, a patent application must provide a "solid teaching" of the claimed invention as opposed to "mere speculation" (*AZT*, at para 69).

[46] The soundness of a prediction is a question of fact (*AZT*, at para 71). A sound prediction has three elements (*AZT*, at para 70):

1) there must be a factual basis for the prediction;
2) the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and
3) there must be proper disclosure of the factual basis and line of reasoning.

[47] These elements are assessed from the perspective of the POSITA to whom the patent application is directed taking into account the common general knowledge that the POSITA would have. Further, with the exception of matters of common general knowledge, the factual basis and the line of reasoning must be included in the patent application (see *Bell Helicopter Textron Canada Limitée v. Eurocopter, société par actions simplifiée*, 2013 FCA 219, at paras 152 and 153).

[48] Although a prediction does not need to amount to a certainty to be sound, there must be a "*prima facie*" reasonable inference of utility (*Mylan Pharmaceuticals ULC v. Eli Lilly Canada Inc.*, 2016 FCA 119, at para 55, *Gilead Sciences, Inc. v. Idenix Pharmaceuticals Inc.*, 2015 FC 1156, at para 251).

Sufficiency of disclosure and enablement

[49] Another issue in the present case is whether the specification satisfies the requirements for sufficiency of disclosure under paragraphs 27(3)(*a*) and (*b*) of the Act, which read:

The specification of an invention must:

(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;

[50] In regards to whether a specification complies with paragraphs 27(3)(*a*) and 27(3)(*b*) of the Act, the courts have identified three relevant questions that must be answered by a reading of the specification: What is the invention? How does it work? Having only the specification, can the POSITA produce the invention using only the instructions contained in the disclosure? (*Teva Canada Ltd. v. Novartis AG*, 2013 FC 141 citing *Teva Canada Ltd. v. Pfizer Canada Inc.*, 2012 SCC 60 and *Consolboard v. MacMillam Bloedel*, [1981] 1 S.C.R. 504 at 526, 56 C.P.R. (2d) 145). These inquiries require fact-specific determinations.

[51] With regard to the third question, the POSITA must not be called upon to display inventive ingenuity or undertake undue experimentation (*Aventis Pharma Inc. v. Apotex Inc.* 2005 FC 1283, *Mobil Oil Corp. v. Hercules Canada Inc*. [1995] F.C.J. No. 1243 and *Merck & Co. v. Apotex Inc.* [1995] 2 F.C. 723).

[52] According to *Novartis Pharmaceuticals Canada Inc. v. Teva Canada Limited*, 2013 FC 283, the relevant date for determining sufficiency of disclosure is the publication date of the application.

**ANALYSIS**

Purposive construction of the claims

*The POSITA and the relevant common general knowledge (CGK) of this person*

[53] In our view, the POSITA is a person practising in the fields of applied reproductive biology, regenerative medicine and cellular therapy.

[54] With respect to the CGK possessed by the POSITA, we consider that the POSITA has CGK in the fields identified above. The POSITA possesses CGK and technical experience that relate to morula and ICM cells, the production of ES cells from different species, the characterization of ES cells, and knowledge of the potential uses of ES cells in regenerative medicine and cellular therapy.

[55] More specifically, we are of the view that CGK includes knowledge that ES cells have the capacity to differentiate, in a spontaneous and unregulated manner, into representatives of all three germ layers either *in vivo* or *in vitro* (see *Thomson* and U.S. Patent No. 5,843,780, both cited on page 4 of the description).

[56] Further, we consider that the POSITA was aware that preliminary experiments of directed differentiation had been conducted with ES cells but that reliable methods for producing a desired type of differentiated cells from ES cells were not available at the filing date (as evidenced by the instant description, on page 5, lines 5-9).

[57] Finally and following the review of the pre-filing publications submitted by the Applicant throughout the prosecution, we are of the view that although these documents may also refer to CGK of the sort identified above, the specific findings disclosed in those publications are not CGK. We note that the publications being put forward are scientific papers rather than, for example, a review article or a textbook. In this regard, the Federal Court has clarified that a piece of particular knowledge as disclosed in a scientific paper does not become CGK merely because it is widely read, and still less because it is widely circulated. Rather, the information in a

scientific paper will only become CGK when there is evidence that it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art (see *Uponor AB v. Heatlink Group Inc.*, 2016 FC 320 at para 48 citing *Eli Lilly & Co. v Apotex Inc.*, 2009 FC 991 at para 97). Applied to the present case, the Applicant did not argue (nor are we otherwise aware) that the specific findings found in the submitted publications are generally known and accepted in the relevant fields, and so we consider that they would not form part of the CGK.

*The problem to be solved and the proposed solution*

[58] Having reviewed the application as a whole, we are of the view that the problem to be solved is a need for improved methods for the production of progenitor cells. The proposed solution is to directly culture the morula or ICM cells in the presence of a differentiation-inducing agent or environment to produce differentiated progenitor cells without going through the production of ES cells.

*The essential elements of the claims that solve the identified problem*

[59] Rejected independent claims 1 and 16 read as follows:

> 1. A method of producing differentiated progenitor cells, comprising:
> (i) obtaining morula or inner cell mass cells from a blastocyst; and
> (ii) directly culturing the morula or inner cell mass cells in the presence of a differentiation-inducing agent or environment to produce differentiated progenitor cells.
>
> 16. A method of identifying a differentiation agent or environment that induces the differentiation of morula or inner cell mass cells to a differentiated progenitor cell type, comprising:

> (i) obtaining morula or inner cell mass cells from a blastocyst;
> (ii) directly culturing said morula or inner cell mass cells in the presence of one or more differentiation agent or environment; and
> (iii) identifying cells in said one or more differentiation agent or environment that have differentiated from said morula or inner cell mass cells into said differentiated progenitor cell type;
> wherein any of said one or more differentiation agent or environment that contains said differentiated progenitor cell type is identified as a differentiation agent or environment that induces the differentiation of morula or inner cell mass cells to said differentiated progenitor cell type.

[60] In light of the proposed solution, we are of the view that the POSITA would consider that: i) a differentiation-inducing agent or environment; ii) morula or ICM cells; and iii) the direct culture of morula or ICM cells with a differentiation-inducing agent or environment to be essential elements that are common to both methods.

[61] The step of identifying a differentiated progenitor cell type is considered an additional essential element of the method of claim 16.

[62] Dependent claims 2-15 further add an isolation step (claim 2), further characterize the blastocyst from which the morula or ICM cells are obtained (claims 3-6), further define the differentiation-inducing environment (claims 7-12) or specify the lineage of the desired differentiated progenitor cells (claims 13-15). We considered that these elements are preferred embodiments.

[63] Dependent claims 17-25 further characterize the blastocyst from which the morula or ICM cells are obtained (claims 17-20), further define the differentiation agent or environment (claim 21), further define the identification step or specify the lineage of the desired differentiated progenitor cell (claims 22-25). We considered that these elements are preferred embodiments.

*Meaning of certain phrases*

[64] In order to determine the scope of the claims 1-25, we will purposively construe the expressions "differentiation-inducing agent or environment", "differentiation agent or environment", "differentiated progenitor cells" and "directly culturing" found in the broadest claims 1 and 16.

[65] We are of the view that the POSITA would consider the expressions "differentiation-inducing agent or environment" and "differentiation agent or environment" to be equivalent in the context of the instant specification. These expressions define the contemplated agent or environment by a desired functional characteristic and are not limited in any other meaningful manner in the claims. Based on pages 10-13 of the description that recite numerous different agents, environments and combinations thereof as putative differentiation agents or environments, we consider that the POSITA would understand that the above expressions at least include those listed agents and environments. Hence, we are of the view that there is no need to construe the above expressions to encompass anything beyond the listed agents and environments for the purpose of this review.

[66] In view of the noted above passage at para [12], we consider that the expression "differentiated progenitor cells" would be understood by the POSITA as encompassing partly differentiated cells, somewhere between pluripotent cells and terminally differentiated cells, whose differentiation potential is limited to cells of a specific tissue.

[67] Another passage of the description at page 8, lines 22-25 is relevant to the expression "directly culturing" when used in the context of culturing morula and ICM cells:

> By the present invention, <u>the production of embryonic stem cells is bypassed</u>, i.e., morula-derived cells or inner cell mass cells <u>are induced to differentiate directly into differentiated progenitor cells</u> which are then used for cell therapy and for the generation of tissues and organs for transplantation. [Emphasis added]

[68] Accordingly, we construe "directly culturing" to mean that the encompassed agents or environments will directly induce the differentiation of the morula or ICM cells into tissue-specific differentiated progenitor cells (i.e., without producing ES cells from long-term culture of ICM cells as a transitional step).

*The claims, purposively construed*

[69] Based on the above, we are of the view that the POSITA would understand that the method recited in claim 1 bypasses the steps necessary for the production of ES cells. When morula or ICM cells obtained from a blastocyst are directly cultured with a differentiation agent or environment listed on pages 10-13 of the description, any and all tissue-specific differentiated progenitor cell types can be produced. The tissue-specificity obtained is understood to vary according to the differentiation agent(s) or environment(s) used.

[70] With respect to claim 16, we consider that the POSITA would understand that performing the recited method will result in the identification of a differentiation agent or environment that directly induces the differentiation of morula or ICM cells into a tissue-specific differentiated progenitor cell type, wherein the differentiation agent or environment is one or more of the agents or environments listed on pages 10-13 and wherein the production of ES cells is bypassed.

[71] We emphasize that we construe the claimed methods as encompassing the differentiation of morula or ICM cells into a specific differentiation stage (i.e., tissue-specific differentiated progenitor cells).

*Asserted utility of the claims*

[72] As stated above at para [43], the asserted utility of the claims must be construed. After review of the claims, we consider that the claims are certain and unambiguous in stating the asserted utility.

[73] We are of the view that the phrase "of producing differentiated progenitor cells" in claim 1 qualifies the method so claimed and would be understood by the POSITA to mean that performing the method will in fact result in the production of a differentiated progenitor cell.

[74] Likewise, the phrase "of identifying a differentiation agent or environment that induces the differentiation of morula or inner cell mass cells to a differentiated progenitor cell type" in claim 16 would be understood by the POSITA to mean that performing the method will in fact result in the identification of an agent or environment that induces the differentiation of morula or inner cell mass cells to a differentiated progenitor cell type.

[75] Therefore, we consider that the asserted utility of the methods of claims 1-15 is that performing the recited steps will directly induce the differentiation of the morula or ICM cells into tissue-specific differentiated progenitor cells and that all tissue-specific differentiated progenitor cell types can be produced.

[76] With respect to the methods of claims 16-25, the asserted utility is that performing the recited steps will result in the identification of a differentiation agent or environment that directly induces the differentiation of morula or ICM cells into a tissue-specific differentiated progenitor cell type.

Utility of claims 1-15

[77] In the R-FA, the Applicant submits that "[t]he Examiner has provided neither evidence nor reasoning as to why" the Applicant's contention of utility for the claimed subject matter by providing sufficient facts and reasoning that the prediction is not a sound one.

[78] If the Applicant means to suggest that the Examiner was required to provide evidence to support its rejection, we do not see any such obligation arising from the *Patent Act* or *Patent Rules*. Rather, pursuant to s. 30(3) of the *Patent Rules*, an Examiner may reject an application if "the examiner has reasonable grounds to believe that the application still does not comply with the Act or these Rules" with respect to a ground raised in a previous Office requisition.

[79] To the extent that the Applicant is asserting that s. 30(3) of the *Patent Rules* requires the Examiner to provide reasons that justify the basis for a rejection, we are of the view that the FA has clearly done so. In particular, utility is a statutory requirement of patentability and *AZT* explained that utility must be established as of the Canadian filing date and how it could be established, notably by sound prediction. Further, as described above, the FA provided a detailed explanation as to why the Examiner was not convinced by the Applicant's assertions that utility could be established by sound prediction.

[80] In the same letter, the Applicant also submits that the utility of claims 1-15 is established by sound prediction. Accordingly, we will now consider the three elements of a sound prediction in the context of the claimed subject matter, the construed asserted utility, the disclosure found in the instant application and from the point of view of the POSITA.

[81] As stated above, we consider that the asserted utility of the methods of claims 1-15 is that performing the recited steps will directly induce the differentiation of the morula or ICM cells into tissue-specific differentiated progenitor cells and that all tissue-specific differentiated progenitor cell types can be produced.

*Factual basis*

[82] From the outset, we note the absence of any test or preliminary research results supporting that the claimed methods would produce the desired result in the description. Our understanding is that the Applicant does not dispute that finding.

[83] Instead, the Applicant referred to several pre- and post-filing scientific publications that it asserted provide a factual basis for the prediction. As noted above (see para [44]), utility cannot be supported by evidence and knowledge available after the filing date. Accordingly, we agree with the Examiner that it is not necessary to consider the disclosure of the cited references published after October 13, 2000, the filing date of the instant application.

[84] In addition to the *Activin* references introduced above at para [30], four main references that were published before the filing date are relied upon by the Applicant to supply to the factual basis: *Talbot*, *Schuldiner*, *Thomson* and Van Stekelenburg-Hamers et al., "Isolation and characterization of permanent cell lines from inner cell mass cells of bovine blastocysts" (1995) 40(4) Mol Reprod Dev [*Van Stekelenburg-Hamers*].

[85] The *Thomson* and *Van Stekelenburg-Hamers* publications are cited in the description on page 4, line 28 and page 3, line 8 respectively. We did not find any reference to *Talbot* or *Schuldiner* in the instant application.

[86] As discussed below, the factual basis emerging from references relied on by the Applicant is relevant to the differentiation potential of ES cells or ES like cells but not relevant to the differentiation of morula or ICM cells directly into tissue-specific differentiated progenitor cells.

[87] According to the Applicant, the *Van Stekelenburg-Hamers* publication discloses experiments conducted with ICM derived cells that show spontaneous differentiation of ICM cells into different progenitor cell lines. We disagree. We understand that the reported experiments were performed with bovine cell lines produced according to methods similar to the ones used to produce mouse ES cells. The obtained cell lines were the result of long-term culture of ICM cells on a layer of feeder cells, a step that is not encompassed by the construed methods.

[88] We also understand that these long-term cultures of ICM cells in the presence of feeder cells were initiated with the expectation of obtaining bovine ES like cells and that the resulting differentiated cells are not established progenitor cell lines.

[89] With respect to *Thomson*, we are of the view that this reference shows the production of ES cell lines having the potential to differentiate into derivatives of all three embryonic germ layers. We understand that those reported derivatives comprise terminally differentiated cells, but not necessarily progenitor cells. For example, page 1146 of *Thomson* states:

> The human ES cell lines maintained the potential to form derivatives of all three embryonic germ layers. All five cell lines produced teratomas after injection into severe combined immunodeficient (SCID)–beige mice. Each injected mouse formed a teratoma, and all teratomas included gut epithelium (endoderm); cartilage, bone, smooth muscle, and striated muscle (mesoderm); and neural epithelium, embryonic ganglia, and stratified squamous epithelium (ectoderm) (Fig. 4).

[90] Therefore, with respect to the factual basis disclosed in the specification or prior art references cited therein, we are of the view that they establish:

- that ES cells have the capacity to differentiate, in a spontaneous and unregulated manner, essentially into terminally differentiated representatives of all three germ layers either *in vivo* or *in vitro* (*Thomson* and U.S. Patent No. 5,843,780);

- that research on derivation of ES cells and ES like cells from ICM cells had been performed with different species and the commonly used protocols included long-term culture of ICM cells on a layer of feeder cells (*Thomson*, *Van Stekelenburg-Hamers*, U.S. Patent No. 5,843,780 and the instant description); and

- that reliable methods for producing a desired type of differentiated cells from ES cells were not available at the filing date (instant description, on page 5, lines 5-9).

[91] On the other hand, we found no relevant factual basis, in the description or forming part of the CGK, which specifically relates to the production of tissue-specific progenitor cells of any type by directly culturing morula or ICM cells.

[92] Further, we found no factual basis establishing that morula or ICM cells react to a given differentiation signal in a manner identical or substantially similar to ES cells, which acquire their observable characteristics in culture on a layer of feeder cells.

[93] As pointed out in Applicant's response to the FA on page 7 and in the instant description on page 1, lines 14-19, ES cells are the result of long-term culture of ICM cells on a layer of feeder cells. ES cells acquire their observable *in vitro* characteristics in culture, including distinguishing cell surface markers and gene expression profiles (see page 2, line 30 to page 3, line 2 and page 4, lines 22-26). According to the claimed methods, morula and ICM cells would not receive such long-term culture treatment.

[94] Turning to *Talbot*, *Schuldiner* and *Activin* references, those references not referred to in the instant application, we consider that their specific elements of disclosure relied upon by the Applicant are not part of the CGK. As noted above at para [47], Canadian jurisprudence is that, with the exception of matters of CGK, the factual basis and the line of reasoning must be included in the patent application. However, for completeness, we provide the following comments on these references.

[95] Having reviewed the references, we are of the view that the teachings of these documents are not relevant to the production of differentiated progenitor cells by directly culturing morula or ICM cells as recited in the claims.

[96] We consider that the disclosure of *Talbot* publication is very similar to *Van Stekelenburg-Hamers* as the obtained porcine cell lines were also the result of long-term culture of ICM cells on a layer of feeder cells.

[97] We agree with the Applicant that *Schuldiner* reports the effects of different growth and differentiation factors on human ES cells. However, we further observe that *Schuldiner* does not describe the production of tissue-specific differentiated progenitor cells by directly culturing ES cells with growth factors. The ES cells were initially induced to differentiate by deriving embryoid bodies before directing the differentiation with growth factors. *Schuldiner* further discloses that some growth factor receptors are not expressed or expressed at very low levels on undifferentiated human ES cells prior to their derivation into embryoid bodies.

[98] Finally, as for the *Activin* references that were submitted in the R-FA, we agree with the Applicant that these publications report that activin induces cardiac myogenesis in avian pregastrula epiblasts and that activin is expressed in the mouse ICM of 3.5 day blastocyst. However, the observation that activin plays a putative but undefined role in cardiac formation during the embryonic development does not teach what would be the result of the direct culture of isolated morula and ICM cells with activin.

[99] As such, the teachings of *Talbot*, *Schuldiner* and *Activin* references: i) do not specifically relate to the production of tissue-specific progenitor cells by directly culturing morula or ICM cells with one or more of the encompassed agents or environments; ii) do not establish that reliable directed differentiation methods for producing tissue-specific progenitor cells of any type by directly culturing ES cells with one or more of the encompassed agents or environments were available at the filing date; and iii) do not establish that morula and ICM cells will react to a given differentiation signal in a manner identical or substantially similar to ES cells.

[100] Therefore, the disclosure of these additional references would not have altered our view expressed in paras [91] and [92].

*Sound line of reasoning*

[101] The line of reasoning should link the factual basis for the prediction and the prediction itself. The prediction is that directly culturing morula or ICM cells with one or more of the encompassed agents or environments would directly induce the differentiation of the morula or ICM cells into tissue-specific differentiated progenitor cells.

[102] In our view, the gap between the factual basis and the predicted utility is considerable. After having considered the factual basis, the POSITA does not know how isolated morula and ICM cells react when exposed to one or more of the encompassed agents or environments, does not know reliable methods of directing the differentiation of ES cells toward a desired type of tissue-specific differentiated progenitor cells and does not know whether morula or ICM cells react to a given differentiation signal in a manner identical or substantially similar to ES cells. This gap remains even if the non-disclosed teachings of the *Talbot*, *Schuldiner* and *Activin* references are considered to contribute to the factual basis.

[103] We consider that there is no sound line of reasoning in the patent application bridging the gap between the factual basis and the predicted utility and from which the POSITA could make a "*prima facie*" reasonable inference of utility as of the filing date.

*Proper disclosure*

[104] Given our findings with regard to the factual basis and the absence of a sound line of reasoning even if all the cited pre-filing publications are included in the analysis, we consider unnecessary to address the third prong of the test for a sound prediction of

utility. Nevertheless, we reiterate that the *Talbot*, *Schuldiner* and *Activin* publications were not disclosed in the instant patent application, and their specific findings were not considered CGK.

*Conclusion on utility of claims 1-15*

[105] We are of the view that the instant patent application does not provide a "solid teaching" of the claimed invention and we are of the view that the POSITA would not have soundly predicted that directly culturing morula or ICM cells with one or more of the encompassed agents or environments would directly induce the differentiation of the morula or ICM cells into tissue-specific differentiated progenitor cells, let alone that all encompassed tissue-specific differentiated progenitor cell types can be produced.

[106] The utility of the broadest claim 1 has not been established by a sound prediction and we consider that this conclusion also applies to dependent claims 2-15 because their scope (see para [62]) is not limited in a manner that varies our findings with respect to the insufficient factual basis and the absence of a sound line of reasoning for the asserted utility.

Utility of claims 16-25

[107] As stated above, the asserted utility of the claimed methods is that performing the recited steps will result in the identification of a differentiation agent or environment that directly induces the differentiation of morula or ICM cells into a tissue-specific differentiated progenitor cell type.

[108] In the R-FA, the Applicant submits that the factual basis is the same as provided for claims 1-15.

[109] We have already found that the factual basis, even if the undisclosed references are taken into account, is insufficient to support an articulable and sound line of reasoning for the prediction that one or more of the encompassed agents or environments would directly induce the differentiation of the morula or ICM cells into a tissue-specific differentiated progenitor cell type.

[110] Accordingly, we also consider that the asserted utility of claims 16-25 has not been established by a sound prediction as the specification and cited references do not disclose a sufficient factual basis to soundly predict that the claimed methods will result in the identification of a differentiation agent or environment that directly induces the differentiation of morula or ICM cells into a tissue-specific differentiated progenitor cell type.

Sufficiency of disclosure and enablement requirements of subsection 27(3) of the Act

[111] The next issues are whether the specification: i) correctly and fully describes a method of positively identifying differentiation agents or environments that directly induce the differentiation of morula or ICM cells into tissue-specific progenitor cells; and ii) enables the POSITA to positively identify the differentiation agents or environments that can successfully be used in a method of directly producing differentiated tissue-specific progenitor cells from morula or ICM cells without exercising inventive ingenuity or undertaking undue experimentation.

[112] In that regard, the Applicant essentially argues that the specification discloses numerous factors suitable to practice the invention and a screening method to identify those that would work.

[113] Our analysis involves determining how the POSITA is taught by the specification to put the claimed invention into operation.

[114] Having reviewed the specification, we consider that the description: i) does not disclose specific guidance with regard to which agent or environment could be used to obtain all or any of the encompassed type of tissue-specific progenitor cells from ES, morula or ICM cells; and ii) does not provide teaching or evidence suggesting that agents and environments capable of directly inducing the differentiation of morula or ICM cells into any desired tissue-specific progenitor cells are CGK to the POSITA.

[115] Further, we found that the description states that reliable methods for producing a desired type of differentiated cells from ES cells were not available at the filing date and teaches that a screening test should be used to detect agents or environments that induce the differentiation of morula-derived cells or inner mass cells into desired differentiated cell type.

[116] Applying these finding to claims 16 to 25, it is apparent to us that, in the absence of disclosure of a single agent or environment that has the effect of producing differentiated progenitor cells directly from the morula or ICM cells, screening tests are required to positively identify differentiation agents or environments that directly induce the differentiation of morula or ICM cells into tissue-specific progenitor cells according to the methods of claims 16-25.

[117] As for claim 1 and its dependent claims, we also consider that the methods of claims 1-6 and 13-15 can only be practiced by the POSITA once a differentiation agent or environment capable of directly inducing morula or ICM cells to differentiate into any of the tissue-specific progenitor cell types has been identified. However, as claims 7-12 specify a specific environment, we consider that screening tests won't be necessary to perform the methods recited in these claims.

[118] Some routine experimentation is permissible to practise the claimed invention. In the instant case, we are of the view that the POSITA would face extensive and undue experimentation. First, the number of candidate agents, environments and

combinations thereof to test is substantial. Second, each and every screen test requires obtaining freshly isolated morula or ICM cells from a blastocyst. Finally, each and every screen test requires identifying a differentiated progenitor cell type.

[119] In view of the above, we find that the specification is not compliant with the requirements of 27(3) of the *Patent Act*. The specification does not enable the POSITA to practice the invention recited in claims 1-6 and 13-25 without undue experimentation.

Conclusions

[120] Based on our review of the facts of this case, we have found that claims 1-25 lack utility and do not comply with section 2 of the *Patent Act* and the specification, insofar as it relates to claims 1-6 and 13-25, does not comply with subsection 27(3) of the *Patent Act*.

**RECOMMENDATION**

[121] For the reasons set out above, we recommend that the application be refused.

| | | |
|---|---|---|
| Marcel Brisebois | Ryan Jaecques | T. Nessim Abu-Zahra |
| Member | Member | Member |

**DECISION**

[122] I concur with the Patent Appeal Board's findings and its recommendation that the application be refused because claims 1-25 lack utility and do not comply with section 2 of the *Patent Act* and the specification, insofar as it relates to claims 1-6 and 13-25, does not comply with subsection 27(3) of the *Patent Act*.

[123] Accordingly, I refuse to grant a patent on this application. Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Johanne Bélisle
Commissioner of Patents
Dated at Gatineau, Quebec,
this 26th day of July, 2016