Citation : Astellas Institute for Regenerative Medicine, 2023 CACP 26
Commissioner's Decision #1659
Décision du commissaire nº 1659
Date: 2023-11-29

TOPIC:	A11	Application for Patent - Amendment to - New Matter
	C00	Disclosure - Adequacy or Deficiency of Description
	G00	Utility
SUJET:	A11	Demande de brevet - Modification - Nouvelle matière
	C00	Divulgation - Caractère adéquat ou inadéquat de la description
	G00	Utilité

Application No. : 2,596,227
Demande nº 2 596 227

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,596,227 having been rejected under subsection 199(1) of the *Patent Rules*, has consequently been reviewed in accordance with paragraph 86(7)(c) of the *Patent Rules*. The recommendation of the Patent Appeal Board and the decision of the Commissioner are that the application be refused unless necessary amendments are made.

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INTRODUCTION

[1] This recommendation concerns the review of rejected Canadian patent application number 2,596,227 which is entitled “Improved modalities for the treatment of degenerative diseases of the retina”. Astellas Institute for Regenerative Medicine is the sole Applicant. A review of the rejected application has been conducted by a Panel of the Patent Appeal Board pursuant to paragraph 86(7)(c) of the *Patent Rules*.

[2] As explained in more detail below, our recommendation is that the Commissioner of Patents inform the Applicant by notice pursuant to subsection 86(11) of the *Patent Rules* that certain amendments to the claims are necessary to make the application allowable.

BACKGROUND

The Application

[3] The present application was filed under the Patent Cooperation Treaty and has an effective filing date in Canada of July 20, 2005. It was laid open to public inspection on August 3, 2006.

[4] The rejected application describes and claims methods for differentiating human embryonic stem cells and human pluripotent stem cells into retinal pigment epithelium cells for use in the treatment of degenerative diseases of the retina.

[5] The application has 18 claims on file that were received at the Patent Office on December 16, 2021.

Prosecution History

[6] On September 29, 2022, a Final Action was written under subsection 86(5) of the *Patent Rules*. The Final Action indicates that claims 1 to 18 on file encompass subject-matter that lacks utility and is not fully supported by the description contrary to section 2 and subsection 27(3) of the *Patent Act* and section 60 of the *Patent Rules*. In addition, the Final Action indicates that page 11 of the description contains new matter contrary to section 38.2 of the *Patent Act* and that dependent

claim 3 does not comply with subsection 63(1) for failing to state additional features.

[7] The Response to the Final Action dated August January 30, 2023 disagrees that the claims on file are not fully supported by the description and that the description contains new matter but nevertheless proposes amendments to the claims and description solely to advance prosecution.

[8] On May 2, 2023 the application was forwarded to the Patent Appeal Board for review under paragraph 86(7)(c) of the *Patent Rules* along with a Summary of Reasons explaining that the rejection is maintained as the arguments presented in the Response to the Final Action are not persuasive and the proposed amendments presented in the Response to the Final Action do not overcome all of the defects identified in the Final Action.

[9] In a letter dated May 4, 2023, the Patent Appeal Board forwarded a copy of the Summary of Reasons to the Applicant and requested that they confirm their continued interest in having the application reviewed.

[10] In a letter dated December August 3, 2023, the Applicant confirmed their interest in having the review proceed.

[11] The present Panel was formed to review the rejected application under paragraph 86(7)(c) of the *Patent Rules* and to make a recommendation to the Commissioner as to its disposition. Given our recommendation that the proposed amendments to the claims and description presented in the Response to the Final Action are allowable, no further written or oral submissions from the Applicant are necessary.

Issues

[12] In view of the above, the following issues are considered in this review:

- whether the claims on file lack utility contrary to section 2 of the *Patent Act;*
- whether the specification, insofar as it relates to the claims on file, is insufficient contrary to subsection 27(3) of the *Patent Act*;
- whether the claims on file lack support contrary to section 60 of the *Patent Rules*;

- whether the description contains new matter contrary to section 38.2 of the *Patent Act*; and

- whether claim 3 fails to state additional features contrary to subsection 63(1) of the *Patent Rules*.

[13] In addition, the proposed claims and the proposed amendments to the description submitted with the Response to the Final Action have also been considered.

PURPOSIVE CONSTRUCTION

Legal Background

[14] According to Free World Trust v Électro Santé Inc, 2000 SCC 66 [Free World Trust] and Whirlpool Corp v Camco Inc, 2000 SCC 67, a purposive construction of the claims is performed from the point of view of the person skilled in the art in light of the relevant common general knowledge and considers the specification and drawings. In addition to interpreting the meaning of the terms of a claim, purposive construction distinguishes the essential elements of the claim from the non-essential elements. Whether or not an element is essential depends on the intent expressed in or inferred from the claim, and on whether it would have been obvious to the person skilled in the art that a variant has a material effect upon the way the invention works.

[15] In carrying out the identification of essential and non-essential elements, all elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language.

Analysis

The person skilled in the art and the relevant common general knowledge

[16] Neither the Final Action nor the Response to the Final Action identify the person skilled in the art. As indicated above, purposive construction is performed from the perspective of the person skilled in the art. We therefore present our view regarding the identity of the person skilled in the art and the relevant common

general knowledge.

[17] Based on the teachings of the description, the references cited therein and the subject-matter of the claims, our view is that the person skilled in the art is a clinical ophthalmologist. In addition, they would have experience in the use of retinal pigment epithelium in the treatment of retinal degeneration and other visual disorders.

[18] With regard to the common general knowledge of the person skilled in the art, based on the description, in our view the common general knowledge of this team would include the following:

- Retinal pigment epithelium (RPE) plays an important role in photoreceptor maintenance and regulation of angiogenesis, and various retinal pigment epithelium malfunctions are associated with vision altering ailments, such as retinitis pigmentosa, retinal pigment epithelium detachment, dysplasia, atrophy, retinopathy, macular dystrophy, including age-related macular degeneration (pages 2 to 3);

- RPE has wound healing abilities and has been extensively studied in application to transplant therapy where it has been shown in several animal models and humans that transplantation has a good potential for vision restoration. However, problems with graft rejection hinder the progress of this approach if allogenic transplantation is used (page 3);

- Therapies using ectopic RPE cells have been shown to behave like fibroblasts and have been associated with a number of destructive retinal complications including axonal loss and proliferative vitreoretinopathy with retinal detachment (page 4);

- RPE delivered as loose sheets tends to scroll up resulting in poor effective coverage of photoreceptors as well as multilayer RPE with incorrect polarity (page 4);

- Neural retinal grafts typically do not functionally integrate with the host retina (page 4);

- The RPE is a densely pigmented epithelial monolayer between the choroid and neural retina that serves as a part of a barrier between the

blood stream and retina and is easily recognized by its cobblestone cellular morphology of black pigmented cells (page 8);

- There are several known markers for RPE, including cellular retinaldehyde-binding protein (CRALBP), RPE65, bestrophin, and pigment epithelium derived factor (PEDF) (page 8);

- An unusual feature about RPE is its apparent plasticity, cells are normally mitotically quiescent but can began to divide in response to injury or coagulation. RPE cells adjacent to the injury flatten and proliferate forming a new monolayer. Several studies have indicated that the monolayer can produce cells of fibroblast appearance that can later revert to their original RPE morphology (page 8);

- *In vitro*, depending on the combination of growth factors and substratum, RPE can be maintained as an epithelium or rapidly dedifferentiate and become proliferative. The epithelial phenotype can be re-established in long-term quiescent cultures (pages 8 to 9); and

- In mammals, RPE shares the same progenitor with neural retina. Under certain conditions, it has been suggested that RPE can transdifferentiate into neuronal progenitors, neurons and lens epithelium. One of the factors that can stimulate the change of RPE into neurons is bFGF, a process that is associated with the expression of transcriptional activators normally required for eye development, including mitf, pax 6 (pages 8 to 9).

The claims on file

[19] There are 18 claims on file. Claims 1 and 10 are the independent claims and read as follows:

> 1. A method of generating an expanded retinal pigment epithelium (RPE) cell preparation, the method comprising:
>
> (a) obtaining RPE cells that have a cobblestone polygonal epithelial-like cellular morphology and pigmentation, which expresses RPE65 and bestrophin, wherein the RPE cells are obtained by *in vitro* differentiation of human embryonic stem (ES) cells;

(b) dispersing the RPE cells and culturing the dispersed RPE cells under adherent conditions in the presence of basic FGF, wherein the cultured RPE cells dedifferentiate and proliferate, losing pigmentation and epithelial-like morphology;

(c) culturing the dedifferentiated cells in the absence of basic FGF, wherein the cells form an RPE cell monolayer, become quiescent, and regain pigmentation and epithelial-like morphology, and wherein the RPE cell monolayer includes cells that express RPE65 and bestrophin; and

(d) expanding the RPE cells by repeating steps (b) and (c) through multiple passages.

10. A method of culturing a human retinal pigment epithelium (RPE) cell population comprising:

(a) culturing human RPE cells under adherent conditions and in the presence of basic FGF, wherein the human RPE cells are derived from *in vitro* differentiation of human pluripotent stem cells;

(b) obtaining from the culture of (a) cells that have lost pigmentation and epithelial morphology, and

(c) culturing the cells that have lost pigmentation and epithelial morphology to obtain a cell monolayer, wherein the cell monolayer comprises RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation.

[20] The dependent claims 2, 4 to 9 and 11 to 18 define further limitations regarding the number of passages (claim 2), the markers characterizing the dedifferentiated cells (claim 4), markers characterizing the RPE monolayer (claims 5, 6, 11 and 12), isolating a pure preparation of human RPE cells (claims 7 to 9 and 13 to 15) and culturing the monolayer (claims 16 to 18). With regard to dependent claim 3, it appears that there are no further limitations over claim 1 upon which it depends.

Essential elements

[21] As stated above, all of the elements set out in a claim are presumed essential unless it is established otherwise or where such a presumption is contrary to the claim language. Further, a claim element is essential when it would have been

obvious to the person skilled in the art that its omission or substitution would have a material effect on the way the invention works: Free World Trust at para 55.

[22] With respect to claim language, our preliminary view is that the person skilled in the art reading claims 1 to 18 in the context of the specification as a whole and in view of their common general knowledge would understand that there is no use of language in any of the claims indicating that any of the elements are optional, preferred or were otherwise intended as being non-essential. Therefore, our preliminary view is that the person skilled in the art would consider all of the elements in the claims to be essential.

UTILITY

Legal Background

[23] Utility is required by section 2 of the *Patent Act*:

> 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.

[24] In AstraZeneca Canada Inc v Apotex Inc, 2017 SCC at paras 54 to 55 [AstraZeneca], the Supreme Court of Canada outlines the approach to follow to determine whether a patent discloses an invention with sufficient utility under section 2 of the *Patent Act*:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2, courts should undertake the following analysis. First, courts must identify the subject-matter of the invention as claimed in the patent. Second, courts must ask whether that subject-matter is useful—is it capable of a practical purpose (i.e., an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized—a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (*AZT,* at para 56).

[25] As indicated above, the inventor must either have demonstrated the utility of the invention, or have been capable of soundly predicting its utility as of the filing date. Utility cannot be supported by evidence and knowledge that only became available after this date: Apotex Inc v Wellcome Foundation Ltd, 2002 SCC 77 at para 56 [AZT], cited in the passage above.

[26] In AZT, at paras 70 to 71, the Supreme Court of Canada lists the requirements to be met for a sound prediction of utility:

- there must be a factual basis for the prediction;
- the inventor must have, at the date of the patent, an articulable and sound line of reasoning from which the desired result can be inferred from the factual basis; and
- there must be proper disclosure of the factual basis and line of reasoning.

[27] These requirements are assessed from the perspective of the person skilled in the art to whom the patent is directed, considering the relevant common general knowledge. Further, with the exception of the common general knowledge, the factual basis and sound line of reasoning must be included in the patent application: Bell Helicopter Textron Canada Ltée v Eurocopter SAS, 2013 FCA 219 at paras 152 to 153 [Bell Helicopter].

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

Analysis

What is the subject-matter of the invention as claimed?

[29] In our view the subject-matter of the invention as recited in claims 1 to 9 that must be useful is directed to methods of generating an expanded RPE cell preparation. The RPE cells are obtained by *in vitro* differentiation of human embryonic stem (ES) cells and can be expanded through multiple passages of dispersing and culturing in the presence of bFGF to allow the RPE cells to dedifferentiate and

proliferate followed by culturing in the absence of bFGF to allow the RPE cells to regain their pigmentation and epithelial-like phenotype.

[30] With regard to claims 10 to 18, it is our view that the subject-matter of the invention as recited in these claims that must be useful is directed to methods of culturing a RPE cell population. The RPE cells are derived from *in vitro* differentiation of human pluripotent stem cells and are cultured under adherent conditions in the presence of bFGF, cells which have lost pigmentation and epithelial morphology are cultured to obtain a cell monolayer comprising RPE cells having a cobblestone polygonal epithelial-like morphology and pigmentation.

Is that subject-matter useful?

[31] As indicated above, utility must be established by either demonstration or sound prediction as of the filing date: AZT at para 56.

[32] According to page 2 of the Final Action, the description does not provide full support for the utility of the subject-matter of the claims. Specifically, there is no support by a substantive embodiment or sound prediction in the description as filed for the utility of repeatedly adding and withdrawing bFGF for generating expanded RPE cell preparations, nor applying medium comprising bFGF to differentiated RPE cells.

[33] The Response to the Final Action, on pages 2 to 9, disagrees with this assessment and submits that the description, when read in the context of the specification as a whole, provides both a clear factual basis and sound line of reasoning for the skilled person to soundly predict, *prima facie*, that the claimed method (of claims 1 to 9 on file) would generate an expanded RPE cell preparation and that the claimed method (of claims 10 to 18) would culture a human RPE population to obtain a cell monolayer comprising RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation.

[34] There appears to be agreement that the utility that had to be established for claims 1 to 18 was not demonstrated. Therefore, what must be considered is whether the utility of the claimed subject-matter has been established by sound prediction.

[35] The factual basis, the line of reasoning and the level of disclosure required for a sound prediction are to be assessed as a function of the knowledge that the

person skilled in the art would have to base that prediction on, and as a function of what that person skilled in the art would understand from the specification as a logical line of reasoning leading to the utility of the invention.

[36] With regard to a factual basis supporting the prediction of utility and from which the desired result can be inferred, it is our view that the factual basis found in the instant specification and/or the common general knowledge includes the following:

- hES cell cultures that are overgrown on mouse embryonic fibroblasts in the absence of LIF, FGF and Plasmanate™ can spontaneously differentiate into RPE-like cells which express RPE-specific molecular markers (see Examples 1, 3 and 8 and Figures 1 and 3);

- These RPE-like cells can be isolated by selective picking with a glass capillary to establish primary cultures. Such RPE-like cells can be easily passaged, frozen and thawed, thus allowing their expansion (see paragraph bridging pages 14 to 15 of the description, Examples 2 and 11 and Figure 2);

- *In vitro*, depending on the combination of growth factors and substratum, RPE can be maintained as an epithelium or rapidly dedifferentiate and become proliferative. The epithelial phenotype can be re-established in long-term quiescent cultures (see Example 2, Figure 2 and under common general knowledge listed above);

- In a preferred embodiment bFGF is added to the RPE cultures during proliferation and the cells are cultured without bFGF during differentiation (page 10 of the description); and

- bFGF stimulated proliferation of dissociated embryonic chick RPE cells in culture and caused morphological changes in these cells, including loss of pigmentation. However, no transdifferentiation to neuronal phenotypes was observed. In contrast, when small sheets of RPE were cultured in the presence of bFGF, a large number of retinal progenitor cells were generated (see Zhao et al., International Review of Cytology, vol. 171, pages 225 to 266, 1997, cited in the description).

[37] Regarding the line of reasoning, it is our view that it would have been apparent to

the person skilled in the art that given the results disclosed with chick RPE cells, it would be reasonable to infer that bFGF would also be "capable of a practical purpose" in the context of stimulating proliferation of RPE cells (obtained from the *in vitro* differentiation of hES cells) and causing morphological changes, including loss of pigmentation. Further, the person skilled in the art would understand that culturing the cells that have lost pigmentation in the absence of bFGF is necessary to allow the cells to form a cell monolayer, become quiescent and regain pigmentation and epithelial-like morphology and pigmentation.

[38] Therefore, it is our view that the line of reasoning is sound and that the results disclosed with chick RPE cells constitute a proper factual basis supporting the prediction of utility of repeatedly adding and withdrawing bFGF and from which the desired result can be inferred of generating expanded RPE cell preparations of claims 1 to 9 on file.

[39] However, the Final Action also alleges that there is no support for the utility of applying medium comprising bFGF to differentiated RPE cells. It appears that this defect is meant to apply to the method of culturing a human RPE cell population of claims 10 to 16 on file which refer to culturing human RPE cells in the presence of bFGF in step (a) but do not indicate that cells are cultured in the absence of bFGF in subsequent step (c). Although the Response to the Final Action considers that the cells are indeed cultured in the absence of bFGF in subsequent step (c), dependent claims 17 and 18 on file do not support this interpretation. Specifically, dependent claims 17 and 18 on file refer to culturing the cell monolayer of differentiated RPE cells and the cells that have dedifferentiated and lost pigmentation and epithelial morphology, respectively, in the absence of bFGF. Given this limitation to the culturing conditions in step (c) of dependent claims 17 and 18 on file , it is our view that the person skilled in the art would interpret the scope of claims 10 to 16 on file as encompassing culturing the cells in either the presence or absence of bFGF during this step.

[40] With regard to culturing the cells of step (c) of claim 10 in the presence of bFGF, in our view, the person skilled in the art would consider that given common general knowledge identified above, as well as the results disclosed with chick RPE cells, it would be reasonable to infer that culturing RPE cells in the presence of bFGF would result in transdifferentiation into neuronal phenotypes—a result inconsistent with culturing the dedifferentiated RPE cells that have lost pigmentation and

epithelial morphology to obtain a cell monolayer, wherein the cell monolayer comprises differentiated RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation as required by claims 10 to 16 on file. Therefore, it is our view that there is no factual basis or sound line of reasoning for the utility of culturing dedifferentiated and differentiated RPE cells in the presence of bFGF in the method of culturing a human RPE cell population of claims 10 to 16 on file.

[41] However, in our view, the same line of reasoning and factual basis supporting the utility of claims 1 to 9 on file also applies to dependent claims 17 and 18 on file which specifically refer to a method of culturing a human RPE cell population in which the cell monolayer comprising differentiated RPE cells and dedifferentiated RPE cells are cultured in the absence of bFGF.

[42] The Final Action on page 2 also alleges that claims 1 to 18 on file encompass subject-matter that lacks utility because the description only provides support for obtaining or isolating a RPE cell population by hand-picking pigmented epithelial cells and does not support the utility of using certain RPE markers to immunoselect live RPE cells or any other means of isolating RPE cells from ES cultures.

[43] The Response to the Final Action on page 9 disagrees with this assessment and notes that the claims do not refer to obtaining RPE cells from such cultures. Furthermore, RPE cells could be obtained from a source that is sufficiently pure so as not to require a selection step.

[44] With regard to the means of isolating RPE cells from hES cultures, we agree with the Final Action that the description exemplifies the use of selective picking with a glass capillary to establish primary cultures. However, the description also teaches that the RPE cells can be easily passaged, frozen and thawed, thus allowing their expansion. These hES derived RPE cell lines can also be a source of RPE cells that have been obtained by *in vitro* differentiation of human ES cells or human pluripotent stem cells. With regard to the use of certain RPE markers to immunoselect for RPE cells, it is our view that the person skilled in the art would consider that it would be reasonable to infer that markers of RPE cells would be useful to isolate RPE cells that have been obtained by *in vitro* differentiation of human ES cells or human pluripotent stem cells. Further, we note that there is no indication in the record before us of any means of obtaining RPE cells from ES cell

cultures that would not work. In this view, there is no need to limit the scope of cells that are obtained by *in vitro* differentiation of hES cells to those that have been hand-picked.

[45] In view of the foregoing, it is our view that the utility of the subject-matter of claims 1 to 9, 17 and 18 on file has been established by a sound prediction and therefore these claims comply with section 2 of the *Patent Act*. It is also our view that the utility of the subject-matter of claims 10 to 16 on file has not been established by demonstration or sound prediction over their entire scope and therefore these claims do not comply with section 2 of the *Patent Act*.

SUFFICIENCY OF DISCLOSURE

Legal Background

[46] Subsection 27(3) of the *Patent Ac*t requires, among other things, a specification of a patent to correctly and fully describe an invention, and to enable its practice:

> 27(3) 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.

[47] A determination of whether the specification complies with paragraphs 27(3)(a) and 27(3)(b) of the *Patent Act* requires that three questions be answered: What is the invention? How does it work? Having only the specification, can the person of skill in the art 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 [Teva] and Consolboard v MacMillan Bloedel (Sask) Ltd, [1981] 1 SCR 504 at 520 [Consolboard].

[48] With respect to this third question, “it is necessary that no additional inventive

ingenuity be required in order to make the patent work": Aventis Pharma Inc v Apotex Inc, 2005 FC 1283 at para 172. A patent will not be invalid for insufficient disclosure where routine experimentation is required of the skilled person, but the Supreme Court of Canada has held that a disclosure is insufficient if the specification "necessitates the working out of a problem": Idenix Pharmaceuticals, Inc v Gilead Pharmasset LLC, 2017 FCA 161 at para 19, citing Pioneer Hi-Bred v Canada [1989] 1 SCR 1623 at 1641.

[49] In Consolboard, at page 517, the Supreme Court of Canada referred to the textbook Canadian Law and Practice Relating to Letters Patent for Inventions (1969, 4th edition) from which it quoted H.G. Fox as saying "the inventor must, in return for the grant of a patent, give to the public an adequate description of the invention with sufficiently complete and accurate details as will enable a workman, skilled in the art to which the invention relates, to construct or use that invention when the period of the monopoly has expired".

[50] Further, "it is not enough for the disclosure to teach how to make the preferred embodiment. The disclosure must teach the skilled person to put into practice all embodiments of the invention, and without exercising inventive ingenuity or undue experimentation": Seedlings Life Science Ventures, LLC v Pfizer Canada ULC, 2021 FCA 154, at para 68.

Analysis

[51] The Final Action explains on pages 2 and 3 that in view of the lack of support for the utility of the subject-matter of the claims, the specification does not correctly and fully describe the invention and its operation or use, so as to enable any person skilled in the art to practice the invention.

[52] The Response to the Final Action on page 8 disagrees with this assessment and submits that the application as a whole teaches and enables a method of expanding/culturing RPE cells by culturing with bFGF to stimulate proliferation (losing their pigmentation and cobblestone appearance) followed by differentiation by culturing without bFGF (regaining their pigmentation and cobblestone appearance). In addition, page 9 of the Response the Final Action argues that nowhere in the specification is it ever taught that RPE cells must be obtained by a selection step involving hand-picking cells.

[53] In this view, the Response to the Final Action refers to the Examples section of the present application as describing numerous experiments in which RPE cells are obtained by *in vitro* differentiation of hES cells, and further mentions obtaining expanded RPE cell preparations (e.g. page 10, line 33 to page 11, line 2; page 22, line 5). In addition, multiple passages from the description are identified which provide a repeated and consistent teaching that RPE cells of the disclosure can be passaged, alternating between proliferation and differentiation, and that proliferating RPE cells lose pigmentation while differentiating RPE cells regain pigmentation and become quiescent. Notably, the passage on page 10 lines 11 to 13 is said to fit into this understanding, by teaching that bFGF is added to RPE cultures during proliferation but that the RPE cells differentiate without bFGF.

[54] With regard to the obtaining RPE cells the Response to the Final Action notes that the specification teaches that hand-picking could be used in cultures that contain pigmented and non-pigmented cells, but that claim 1 does not refer to obtaining RPE cells from such cultures. Furthermore, RPE cells could be obtained from a source that is sufficiently pure so as not to require a selection step.

[55] In addition, the Response to the Final Action notes that there is no requirement whatsoever under the *Patent Act*, *Patent Rules*, or the jurisprudence interpreting the *Patent Act* and *Patent Rules* that claimed subject-matter be disclosed with working examples (demonstrating substantive support) in the patent specification.

[56] Having reviewed the specification as a whole from the point of view of the person skilled in the art identified above, we generally agree with the analysis in the Response to the Final Action for the following reasons.

[57] First, there is no language in subsection 27(3) of the *Patent Act* or the relevant jurisprudence that explicitly requires the disclosure of examples of experimental results supported that the inventions works. As indicated above, a determination of whether the specification is sufficient requires that three questions be answered: What is the invention? How does it work? Having only the specification, can the person of skill in the art produce the invention using only the instructions contained in the disclosure?

[58] Second, with respect to the first two questions, in our view the person skilled in the art would understand that the description provides considerable guidance on how to isolate, culture and expand the RPE cells of the invention and teaches in a

preferred embodiment that bFGF is added to RPE cultures during proliferation but that the RPE cells differentiate without bFGF. In addition, the description provides guidance on the use of selective picking with a glass capillary to establish primary cultures and teaches that the RPE cells can be easily passaged, frozen and thawed, thus allowing their expansion. These hES derived RPE cell lines can also be a source of RPE cells that have been obtained by *in vitro* differentiation of human ES cells or human pluripotent stem cells.

[59] With respect to the question of enablement, everything required to perform the claimed subject-matter is found in the description. In our view, there would be no undue burden of experimentation required from the person skilled in the art to expand/culture RPE cells by culturing with bFGF to stimulate proliferation (losing their pigmentation and cobblestone appearance) followed by differentiation by culturing without bFGF (regaining their pigmentation and cobblestone appearance) as defined in claims 1 to 9, 17 and 18 on file. In addition, there would be no undue burden of experimentation required from the person skilled in the art to establish hES derived RPE cell lines that could serve as an alternate means of RPE cells that have been obtained by *in vitro* differentiation of human ES or human pluripotent stem cells.

[60] With regard to claims 10 to 16 on file, as explained above, in our view the person skilled in the art would consider that the scope of these claims encompasses culturing dedifferentiated and differentiated cells in the presence of bFGF. However, as taught in the description, this would result in the transdifferentiation of these RPE cells into neurons—a result inconsistent with culturing the dedifferentiated RPE cells that have lost pigmentation and epithelial morphology to obtain a cell monolayer, wherein the cell monolayer comprises differentiated RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation as required by claims 10 to 16 on file.

[61] In view of the foregoing, it is our view that the specification correctly and fully describes and enables the methods of expanding/culturing RPE cells of claims 1 to 9, 17 and 18 on file and complies with subsection 27(3) of the *Patent Act* in respect of this subject-matter. It is also our view that the specification fails to correctly and fully describe and enable a method of culturing RPE cells as defined in claims 10 to 16 on file and does not comply with subsection 27(3) of the *Patent Act* in respect of this subject-matter.

LACK OF SUPPORT

Legal Background

[62] Section 60 of the *Patent Rules* (equivalent to section 84 of the former *Rules*) requires that the claims be fully supported by the description:

> The claims must be clear and concise and must be fully supported by the description independently of any document referred to in the description.

[63] Section 16.05 of the Manual of Patent Office Practice (Canadian Intellectual Property Office, October 2019) provides the following guidance on the requirements of section 60 of the *Patent Rules*:

> A claim must be fully supported by the description as required by section 60 of the *Patent Rules*. All the characteristics of the embodiment of the invention which are set forth in the claim must be fully set forth in the description (Section 60 of the *Patent Rules*). However, since any claims included in the application at the time of filing are part of the specification (see subsection 27(4) of the *Patent Act* and the definition of "description" in section 2 of the *Patent Rules* subsection 1(1) of the *Patent Rules*), any matter in the originally filed claims that was not included in the description as filed may be added to the description (except for divisional applications which have further requirements regarding new subject-matter see section 20.04 for more details).
>
> A claim is objected to for lack of support by the description if the terms used in the claim are not used in the description and cannot be clearly inferred from the description. Terms used in the claims and in the description must be used in the same sense.

Analysis

[64] According to page 3 of the Final Action, the description only provides full support for generating human RPE cells through the overgrowth of human pluripotent cells that are maintained on mouse embryonic fibroblast cells and cultured in the absence of LIF, FGF, and Plasmanate™.

[65] The Response to the Final Action disagrees with this assessment and explains that claim 1 on file is not directed to methods for generating RPE cells from hES cells,

but instead to a method of expanding RPE cells. Since the claim does not require carrying out a step of differentiation hES cells, the RPE cells could be obtained from a source of hES-derived RPE cells that is sufficiently pure so as to not require a selection step.

[66] As explained in section 16.05 of the Manual of Patent Office Practice, section 60 of the *Patent Rules* requires that all the characteristics of the embodiment of the invention which are set forth in a claim must be fully set forth in the description. Therefore, a claim will lack support in the description if the terms used in the claim are not used in the description and cannot be clearly inferred from the originally filed specification. Having reviewed the originally filed description, it is our view that the claims are fully supported for the purposes of section 60 of the *Patent Rules* by at least the following excerpt from the paragraph bridging pages 14 to 15 of the originally filed description:

> [Emphasis added] Preliminary experiments carried out at Advanced Cell Technology with primate and human ES cell lines who that in specialized culture system these cells differentiate into RPE-like cells that can be isolated and passaged. […] Such RPE-like cells can be easily passaged, frozen and thawed, thus allowing their expansion.

[67] Therefore, in our view the method of generating an expanded RPE cell preparation that has been obtained by *in vitro* differentiation of hES cells of claims 1 to 9 on file and the method of culturing a human RPE cell population wherein the human RPE cells are derived from *in vitro* differentiation of human pluripotent stem cells of claims 10 to 18 on file are fully supported by the originally filed description and the requirements of section 60 of the *Patent Rules* are satisfied.

AMENDMENTS TO SPECIFICATIONS AND DRAWINGS

Legal Background

[68] Section 38.2 of the *Patent Act* sets forth the conditions under which amendments may be made to the specification and drawings of a patent application:

> Amendments to specifications and drawings
>
> 38.2 (1) Subject to subsections (2) to (3.1) and the regulations, the specification and drawings contained in an application for a patent in Canada may be amended before the patent is issued.

> Restriction
>
> (2) The specification and drawings contained in an application, other than a divisional application, may not be amended to add matter that cannot reasonably be inferred from the specification or drawings contained in the application on its filing date.

[69] The question as to whether matter added to the specification by amendment complies with section 38.2 of the *Patent Act* is considered from the point of view of the person skilled in the art: see Re Uni-Charm Corp's Patent Application 2313707 (2013), CD 1353 (Pat App Bd & Pat Commr) at para 13.

[70] Therefore, assessing whether there is new matter requires a comparison of the pending specification with the originally filed specification and drawings and a determination as to whether the subject-matter of the amendments would have been reasonably inferable from the original specification or drawings by the person skilled in the art.

Analysis

[71] On page 3, the Final Action identifies a new matter defect with the pending description:

> The subject-matter of page 11 of the description as amended by the applicant's correspondence received 2021/12/16, does not comply with section 38.2 of the *Patent Act* because it is not reasonably to be inferred from the specification or drawings as originally filed. Specifically, embodiments relating to dedifferentiating RPE cells in the presence of bFGF, repeated passaging those cells by withdrawing and adding bFGF, or culturing differentiated RPE cells in the presence of bFGF for generating an expanded preparation, are considered to be new matter.

[72] The Response to the Final Action does not dispute this assessment and submits amended description pages 11 and 11a which are said to be reasonably inferable from the application as originally filed.

[73] The amendments to the description that are considered to contain new matter correspond to the language of claim 1 on file:

> (b) dispersing the RPE cells and culturing the dispersed RPE cells under adherent conditions in the presence of basic FGF, wherein

the cultured RPE cells dedifferentiate and proliferate, losing pigmentation and epithelial-like morphology;

(c) culturing the dedifferentiated cells in the absence of basic FGF, wherein the cells form an RPE cell monolayer, become quiescent, and regain pigmentation and epithelial-like morphology, and wherein the RPE cell monolayer includes cells that express RPE65 and bestrophin; and

(d) expanding the RPE cells by repeating steps (b) and (c) through multiple passages.

and the language of claim 10 on file:

(a) culturing human RPE cells under adherent conditions and in the presence of basic FGF, wherein the human RPE cells are derived from in vitro differentiation of human pluripotent stem cells;

(b) obtaining from the culture of (a) cells that have lost pigmentation and epithelial morphology, and

(c) culturing the cells that have lost pigmentation and epithelial morphology to obtain a cell monolayer, wherein the cell monolayer comprises RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation.

[74] The originally filed description, on page 5, refers to the spontaneous differentiation of hES cells into cells with numerous characteristics of RPE. These RPE preparations are capable of phenotypic changes in culture and maintaining RPE characteristics through multiple passages. Notably, this is exemplified in the originally filed description and drawings in Example 2 and Figure 2, respectively.

[75] Further, as explained on pages 8 to 9 of the originally filed description, *in vitro*, depending on the combination of growth factors and substratum, RPE cells can be maintained as an epithelium or rapidly dedifferentiate and become proliferative and that the epithelial phenotype can be re-established in long-term quiescent cultures. More specifically, page 10 of the originally filed description refers to the addition of bFGF to RPE cultures during proliferation and that the cells are cultured without bFGF during differentiation.

[76] In addition, pages 9 and 17 of the originally filed description disclose that differentiated RPE cells can themselves transdifferentiate into cells of neuronal phenotype, neuronal, amacrine and photoreceptor cells, neural retina and to

neuronal progenitors. In this regard, page 9 of the originally filed description explains that bFGF is one of the factors that can stimulate the transdifferentiation of differentiated RPE into neurons.

[77] In view of the above, it is our view that the originally filed description would have led the person skilled in the art with their common general knowledge to reasonably infer that RPE cultures derived from hES cells will dedifferentiate and proliferate and bFGF can be added to RPE cultures during this stage. Further, in our view the person skilled in the art would also reasonably infer that these RPE cultures can regain their epithelial phenotype in long-term quiescent cultures and can be cultured in the absence of bFGF during differentiation. However, if the differentiated RPE cells are cultured in the presence of bFGF, in our view, the person skilled in the art would not reasonably infer that these cells would form a cell monolayer comprising differentiated RPE cells having a cobblestone polygonal epithelial-like cellular morphology and pigmentation. Rather, the person skilled in the art would consider that these cells would transdifferentiate into neurons.

[78] Therefore, in our view the amendments to the description that correspond to the language of claim 1 on file do not encompass new matter, however, the amendments to the description that correspond to the language of claim 10 on file do contain new matter. Consequently, it is our view that the description dated December 2, 2016 encompasses new matter and does not comply with section 38.2 of the *Patent Act*.

DEPENDENT CLAIMS

Legal Principles

[79] Subsection 63(1) of the *Patent Rules* requires that dependent claims state the additional features over the claim to which it refers:

> 63 (1) Subject to subsection (2), a claim that includes all the features of one or more other claims (referred to in this section as a "dependent claim") must refer by number to the other claim or claims and must state the additional features claimed.

Analysis

[80] The Final Action on page 3 identifies the following defect with claim 3:

> Claim 3 does not comply with subsection 63(1) of the *Patent Rules*. This claim does not state any additional features over the claim to which it refers.

[81] The Response to the Final Action does not dispute this characterization and submits proposed claims which cancel claim 3 and render the objection moot.

[82] Claim 3 depends on the method of claim 1 and states that the RPE preparation is a human RPE preparation. However, the method of claim 1 already states that the RPE cells are obtained by *in vitro* differentiation of human embryonic stem (ES) cells. Therefore, claim 3 fails to state any additional features over claim 1 and does not comply with subsection 63(1) of the *Patent Rules*.

THE PROPOSED CLAIMS REMEDY THE DEFECTS

[83] With the Response to the Final Action the Applicant submitted proposed claims 1 to 8, as well as amended pages 11 and 11a of the description. A review of the proposed claims indicates that claim 1 on file has been amended to indicate that the RPE cells are obtained by *in vitro* differentiation of human embryonic stem (ES) cells and based on their pigmented appearance [Emphasis indicates inserted text]. In addition, claims 3 and 10 to 18 on file have been cancelled and claims 4 to 9 on file have been renumbered as proposed claims 3 to 8. Finally, the proposed amendments to the description correspond to the language of proposed claim 1 and delete the previous amendments corresponding to the language of claims 1 and 10 on file.

[84] Considering that proposed claims 1 to 8 are virtually identical to claims 1, 2 and 4 to 9 on file and given our view that the utility of the subject-matter of claims 1 to 9 on file has been established by a sound prediction and these claims comply with section 2 of the *Patent Act*, that the specification, insofar as it relates to claims 1 to 9 on file is sufficient and complies with subsection 27(3) of the *Patent Act* and that claims 1 to 9 on file are fully supported by the description and comply with section 60 of the *Patent Rules*, it is our view that proposed claims 1 to 8 would also comply with section 2 of the *Patent Act* and section 60 of the *Patent Rules* and that the specification, insofar as it relates to proposed claims 1 to 8, would also comply with

subsection 27(3) of the *Patent Act*. Further, considering the similarities between the proposed amendments to the description and the amendments to the description dated December 2, 2016 and our view that the amendments corresponding to the language of claim 1 on file do not constitute new matter, it is our view that the proposed amendments to pages 11 and 11a of the description would also comply with section 38.2 of the *Patent Act.*

[85] In light of the above, it is our view that the proposed amendments meet the requirements of a necessary amendment under subsection 86(11) of the *Patent Rules*.

CONCLUSIONS

[86] We have determined that the utility of the subject-matter of claims 1 to 9, 17 and 18 on file has been established by a sound prediction and these claims comply with section 2 of the *Patent Act*, that the specification, insofar as it relates to claims 1 to 9, 17 and 18 on file is sufficient and complies with subsection 27(3) of the *Patent Act* and that claims 1 to 18 on file are fully supported by the description and comply with section 60 of the *Patent Rules*. In addition, amended description pages 11 and 11a dated December 2, 2016, insofar as it corresponds to the language of claim 1 on file, do not encompass new matter and comply with section 38.2 of the *Patent Act.*

[87] We have also determined that the utility of the subject-matter of claims 10 to 16 on file has not been established by demonstration or a sound prediction and these claims do not comply with section 2 of the *Patent Act* and that the specification, insofar as it relates to claims 10 to 16 on file is insufficient and does not comply with subsection 27(3) of the *Patent Act*. Further, claim 3 on file fails to state any additional features over claim 1 and does not comply with subsection 63(1) of the *Patent Rules*. In addition, amended description pages 11 and 11a dated December 2, 2016, insofar as it corresponds to the language of claim 10 on file, encompasses new matter and does not comply with section 38.2 of the *Patent Act.*

[88] In our view, proposed claims 1 to 8 submitted with the Response to the Final Action would overcome the lack of utility, insufficiency of disclosure and dependent claim defects. In addition, proposed description pages 11 and 11a would overcome the new matter defect. Therefore, proposed claims 1 to 8 and proposed description

pages 11 and 11a are considered a necessary amendment for compliance with the *Patent Act* and *Patent Rules* as required by subsection 86(11) of the *Patent Rules*.

RECOMMENDATION OF THE BOARD

[89] In view of the above, the Panel recommends that the Applicant be notified, in accordance with subsection 86(11) of the *Patent Rules*, that the replacement of the claims on file with proposed claims 1 to 8, and the replacement of pages 11 and 11a of the description with proposed description pages 11 and 11a, as presented in the Applicant's letter of January 30, 2023, are necessary for compliance with the *Patent Act* and *Patent Rules*.

Christine Teixeira	Marcel Brisebois	Michael O'Hare
Member	Member	Member

DECISION OF THE COMMISSIONER

[90] I concur with the conclusions and recommendation of the Board. In accordance with subsection 86(11) of the *Patent Rules*, I hereby notify the Applicant that the following amendment, and only this amendment, must be made in accordance with paragraph 200(b) of the *Patent Rules* within three (3) months of the date of this decision, failing which I intend to refuse the application:

- replace the claims on file with proposed claims 1 to 8 as presented in the Applicant's letter dated January 30, 2023; and
- replace pages 11 and 11a of the description with proposed description pages 11 and 11a as presented in the Applicant's letter dated January 30, 2023.

Konstantinos Georgaras

Commissioner of Patents
Dated at Gatineau, Quebec
this 29th day of November, 2023.