

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination of U.S. 5,843,780

Art Unit: 3991

Inventor: Thomson, J.

Examiner: Padmashri Ponnaluri

Control No.: 90/008,102

RESPONSE TO FIRST OFFICE ACTION

Attn: MAILSTOP: *EX PARTE* REEXAM

Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the first Office Action received in the matter of Reexamination No. 90/008,102 for U.S. Pat. 5,843,780 (“the ‘780 patent”). This Response is being filed within the two-month period for response set in the Office Action, which was mailed March 30, 2007. No fees are believed to be due.

Claims 1-11 are under reexamination. There are no amendments to the specification or drawings submitted in this response.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper. Claims 12-14 are newly added.

The Patent Owner’s response to the Office Action commences on page 4.

A Declaration of Colin Stewart, D. Phil., is submitted with this Response and is incorporated herein in its entirety.

Attachment A is a collection of publications evidencing the acclaim accorded Dr. Thomson as a direct result of his invention relating to the culturing and characterization of primate/human embryonic stem cells.

Attachment B is a collection of the documents referenced in this Response and in the accompanying Stewart Declaration.

The following is a complete listing of the claims and replaces all prior claim listings:

1. (Currently amended) A purified preparation of primate embryonic stem cells derived from a pre-implantation embryo which (i) is capable of proliferation in an in vitro culture for over one year, (ii) maintains a karyotype in which all the chromosomes characteristic of the primate species are present and not noticeably altered through prolonged culture, (iii) maintains the potential to differentiate into derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) will not differentiate when cultured on a fibroblast feeder layer.

2. (Previously presented) The preparation of claim 1 wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. (Previously presented) A purified preparation of primate embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-3 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have karyotypes which includes the presence of all of the chromosomes characteristic of the primate species and in which none of the chromosomes are noticeably altered.

4. (Previously presented) The preparation of claim 3 wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. (Previously presented) The preparation of claim 3 wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. (Previously presented) The preparation of claim 3 wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. (Previously presented) The preparation of claim 3 wherein the cells remain euploid for more than one year of continuous culture.

8. (Previously presented) The preparation of claim 3 wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

9. (Currently amended) A method of isolating a primate embryonic stem cell line, the method comprising the steps of:

- (a) isolating a primate blastocyst;
- (b) isolating cells from the inner cell mass of the blastocyst of (a);
- (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;
- (d) dissociating the mass into dissociated cells;

(e) replating the dissociated cells on embryonic feeder cells;
(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and
(g) culturing the cells of the selected colonies to produce an isolated primate embryonic stem cell line that is capable of proliferation as undifferentiated cells for over one year.

10. (Previously presented) A method as claimed in claim 9 further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. (Currently amended) A cell line that is capable of proliferation for over one year developed by the method of [step] claim 9.

12. (Newly added) A method of isolating a primate embryonic stem cell line, the method comprising the steps of:

(a) isolating a primate blastocyst;
(b) isolating cells from the inner cell mass of the blastocyst of (a);
(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;
(d) dissociating the mass into dissociated cells;
(e) replating the dissociated cells on embryonic feeder cells;
(f) selecting colonies that have compact morphologies that are flatter than mouse embryonic stem cell colonies, wherein the cells have high nucleus to cytoplasm ratios and prominent nucleoli; and
(g) culturing the cells of the selected colonies to produce an isolated primate embryonic stem cell line that is capable of proliferation as undifferentiated cells for over one year.

13. (Newly added) A method as claimed in claim 12, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

14. (Newly added) A cell line that is capable of proliferating for over one year as undifferentiated cells developed by the method of claim 12.

REMARKS

Claims 1-11 are pending in the reexamination of the instant patent and stand rejected. Claims 1, 9 and 11 have been amended and claims 12-14 are newly added herein. Reconsideration and withdrawal of the rejection of claims 1-11, entry of new claims 12-14 and issuance of claims 1-14 are respectfully requested.

Claim Amendment Summary

Claim 1 has been amended to recite that the cells are derived from a pre-implantation embryo. Support for this amendment is found in the specification at least at column 8, lines 19-26 and column 9, lines 15-16.

Claims 9 and 11 have been amended to recite that the cell line produced is capable of proliferation for over one year. Support for the phrase “capable of proliferation for over one year” is found at least in column 12, lines 25-29, and in present claim 1 of the patent. Claim 11 has also been amended to correct an obvious typographical error, where the term “step” has been replaced by the term “claim.” This amendment does not constitute new matter.

New claim 12 is similar to originally issued claim 9 and is directed to a method of isolating a primate embryonic stem cell line that is capable of proliferation for over one year, where, in step (f), colonies are selected that are flatter than mouse ES cell colonies. Support for the type of colony selection is found at least in column 14, lines 24-29 of the patent. No new matter has been added by way of the addition of claim 12. New claims 13 and 14 depend from claim 12 and are supported at least in original claims 10-11. No new matter has been added by way of the additions of claims 13 and 14.

The Invention

Dr. James A. Thomson (Dr. Thomson) invented a novel purified preparation of primate/human embryonic stem cells and a method of isolating a primate/human embryonic stem cell line. There is no dispute that prior to Dr. Thomson’s landmark invention, mouse ES cells were known as were methods of making them. There is no dispute that Hogan reported the isolation of embryonic germ (EG) cells in U.S. Patent

No. 5,690,926. Nonetheless, mouse ES cells and Hogan's EG cells are not Dr. Thomson's claimed primate/human ES cells.

Dr. Thomson's primate/human ES cells differ from mouse ES and Hogan's EG cells by source of sample, marker expression and by function. For example:

- Primate/human ES cells are SSEA-1 negative, while mouse ES and Hogan's EG cells are SSEA-1 positive;
- Dr. Thomson's cells are derived from pre-implantation embryos; Hogan's EG cells are derived from post-implantation embryos;
- When primate/human ES cells are cultured in leukemia inhibitory factor (LIF) in the absence of a feeder layer, they differentiate; in contrast, mouse ES cells can be propagated in an undifferentiated state in the presence of (LIF) in the absence of feeder layers;
- Primate/human ES cells can differentiate into trophoblast that produces chorionic gonadotropin; in contrast, neither mouse ES nor Hogan's EG cells can differentiate into trophoblast;
- Colonies of primate/human ES cells are more compact and distinctly flatter than mouse ES cell colonies.

Further, at the time of Dr. Thomson's invention, there was no reasonable expectation of success that mouse ES cell derivation protocols could be used to isolate primate/human ES cells based on the experience in the field at the time of Dr. Thomson's invention. It was long recognized that the techniques used to isolate mouse ES cells were unpredictable and were not universally applicable to the isolation of ES cells from other species, or even from different strains of mice. Further, for nearly two decades from the discovery of mouse ES cells, others repeatedly tried and failed to isolate non-murine ES cells, particularly primate/human ES cell lines. See Declaration of Colin Stewart, D. Phil. (hereafter, "Stewart, ¶ #).

The level of acclaim in the art for Dr. Thomson's invention bears witness to the fact that the isolation of primate/human ES cells represented true innovation that was not simply a small step in embryonic stem cell research. Examples abound (See Attachment A):

- In 2005, the American Association for the Advancement of Science (AAAS), founded in 1848, identified as one of the most significant “Milestones of Science” the work of Dr. Thomson, specifically, growing embryonic stem cells that may be used to create other types of cells.
- In 2001, Dr. Thomson was profiled in TIME magazine as one of the doctors “who are changing our world.” Calling him “The man who brought you stem cells,” TIME – like so many others – recognized Dr. Thomson as the scientist who had first isolated human embryonic stem cells.
- Dr. Thomson was a recipient of the Golden Plate Award presented by the American Academy of Achievement in 1999, whose honorees have included – in the scientific fields alone – famed explorer Robert Ballard, oral polio vaccine inventor Dr. Jonas Salk, Nobel Prize Chemist Dr. Linus Pauling, astronaut Dr. Sally Ride, and renowned physicist Dr. Edward Teller. Dr. Thomson was cited for his “recent breakthrough in culturing human embryonic stem cells outside the body.”
- Dr. Thomson was inducted into the Biotech Hall of Fame in 2001, which noted that Dr. Thomson had “successfully isolated and cultured human embryonic stem cells” and that the work had “set the stage for a revolution in medicine and science.”
- In 2003, Dr. Thomson was named a winner of a World Technology Summit Award in Health & Medicine, sponsored by the World Technology Network, which comprises leading corporations and individuals in technology-related fields. The World Technology Awards “are presented each year to the outstanding innovators from each sector within the technology arena.”
- In 2002, Dr. Thomson was selected to receive a \$100,000 research grant to continue his work on stem cells. The announcement of the award recognized Dr. Thomson as “the first person to isolate stem cells from human embryos.” The LIFE International Research Award “is presented to internationally renowned scientists whose research has led to clinical applications.”
- The Christopher Columbus Fellowship Foundation awarded its Frank Annunzio Award Columbus Scholar accolade to Dr. Thomson in 2003, together with a

\$50,000 research grant. The award announcement cites Dr. Thomson as “the first to isolate and culture nonhuman primate embryonic stem cells in 1995 and human ES cells in 1998.” It noted that Dr. Thomson’s research “has encouraged scientists around the world” about the possibilities for human stem cells.

- The American College of Veterinary Pathologists honored Dr. Thomson in 2004 with its Outstanding Achievement Award, which is presented to a member who “performs extraordinary acts or makes an extraordinary contribution that brings great credit to themselves and the discipline of veterinary pathology.” (Dr. Thomson was trained as a doctor of veterinary medicine.) Again he was cited for his work with embryonic stem cells.
- The American Association for Laboratory Animal Science bestowed its Nathan R. Brewer Scientific Achievement Award on Dr. Thomson in 2006 for his discoveries in the field of embryonic stem cells.

It cannot be denied that Dr. Thomson made a landmark invention that was unknown, unpredictable and long overdue in the art. Dr. Thomson’s invention embodies the very definition of a new and useful, novel, and non-obvious invention. Dr. Thomson alone has laid out the groundwork for a plethora of studies on primate/human ES cells that are rapidly driving the field toward remarkable clinical application and Dr. Thomson is entitled to a patent on his invention.

Claim Interpretations and Relevant Case Law

The Patent Owner disagrees with several of the Examiner’s statements made on page 4 et seq. of the Office Action, and does not accept the Examiner’s view as an accurate interpretation of the relationship of the claims to the art under the present law.

Primate ES cells, let alone a purified preparation of the same, were not known in the art prior to the landmark invention of Dr. Thomson. According to *In re Best*, 562 F.2d 1252, 1254-55, 195 U.S.P.Q. 430 (C.C.P.A 1977) (a case cited by the Examiner in support of her argument on inherent anticipation), where *In re Best* cites *In re Swinehart*, 439 F. 2d 210 (1971),

“[I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by *things* in the prior art, does not cause a claim drawn to those *things* to distinguish over the prior art. Additionally, where the

Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Swinehart, 439 F.2d at 212-213. [Emphasis added.]

Here, this standard for inherent anticipation does not apply. The *things* claimed by Dr. Thomson, namely, a purified preparation of primate ES cells, *were not in the prior art*. Nor does the applied prior art either explicitly or inherently teach a purified preparation of primate ES cells. Simply stated, the purified primate and human ES cells disclosed in the present patent did not previously exist. They differ markedly from prior art murine ES cells (Williams '065) and Hogan's EG cells (Hogan '926) and the cells of the other prior art references which cells do not share the claimed features. There is no composition in the cited prior art that is a purified preparation of primate ES cells. Because *In re Best* applies only where the composition (or method) already exists in the prior art, it is inapplicable here.

The Examiner also asserts that "the primate or human ES cells inherently produce chorionic gonadotropin when differentiated into trophoblast." The Examiner misses the point. There is no prior art purified preparation of primate ES cells where the ES cells differentiate into trophoblast. Dr. Thomson invented a purified preparation of primate ES cells that is novel over prior art preparations of cells, because Dr. Thomson's cells can and do differentiate into trophoblast, which trophoblast produce chorionic gonadotropin. Until Dr. Thomson's invention and patent application, the art did not know that primate ES cells could be differentiated into trophoblast. The art did know that murine ES cells would *not* differentiate into trophoblast; but the art did not know that a purified preparation of primate ES cells could differentiate into trophoblast because such cells were not yet in the art.

The Examiner further asserts that the cell surface marker profile identified on the claimed primate ES cells is an inherent characteristic of the cells. The Examiner alleges that because other primate cells express some of the markers discovered to be expressed by Dr. Thomson's cells, that Dr. Thomson's cells were in the art. The Examiner's argument flows in the wrong direction. A purified preparation of primate ES cells was

nowhere in the art. The Examiner admits that human ES cells differ from mouse ES cells (see four lines from bottom of page 5 of the Office Action). The Examiner incorrectly concludes that because human EC cells and the ES cells share some of the same markers, that EC cells and the presently claimed ES cells are the same. But they are not the same cells, as documented in the patent at column 10, lines 61-64 - the presently claimed purified ES cell line has a normal karyotype and the human EC cell line is aneuploid. Again, the Examiner's attempt to apply inherency to the novel ES cells of the invention fails.

No Joint Inventors

In Item 3 of the section entitled Claim Rejections, on page 9 of the Office Action, there appears a statement that the application currently names joint inventors. This is incorrect. There is only one named inventor of this patent, Dr. James A. Thomson.

Rejection of claims 9-10 under 35 U.S.C. § 102(b) over Williams

Claims 9-10 have been rejected under 35 U.S.C. §102(b) as being anticipated by Williams (U.S. Patent No. 5,166,065; hereinafter "Williams"). The Examiner asserts that Williams teaches the currently claimed method for the isolation of embryonic stem (ES) cells from human (primate) blastocysts. Further, the Examiner states, on page 10 of the Office Action, that Williams discloses the use of leukemia inhibitory factor (LIF) to the fibroblast feeder layer in the maintenance of the ES cells in culture, and the removal of LIF from the culture medium resulted in differentiation of ES cells. Therefore, the Examiner concludes that Williams meets the limitations of claims 9-10. The Patent Owner respectfully traverses this rejection.

Anticipation Requires that all Claim Elements be Present

Williams lacks all of the claimed elements. Williams neither discloses a method of making primate/human ES cells, nor discloses the isolation of the cells themselves.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. " MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as

complete detail as is contained in the . . . claim.” *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Williams must describe each and every element of claims 9-10 in order to anticipate these claims under 35 U.S.C. §102(b). The Williams reference does not satisfy this requirement.

Even the Examiner’s efforts to string together a disclosure in Williams that includes all of the elements of the present claims fails. The Examiner makes reference to specific disclosures in Williams that are simply incorrect. For example:

- On page 9 of the Office Action, the Examiner cites Williams column 2, lines 30-32; column 3, lines 6-7; column 3, lines 35-40; column 5, lines 25-26 as teaching “the method for the isolation of ES cells from human (primate) blastocyst. However, the Examiner does not cite the full sentence in column 2, lines 30-37, which actually recites the following: “Accordingly, a first aspect of the present invention relates to a method for the isolation of embryonic stem (ES) cells from animal embryos in vitro which method comprises deriving ES cells from said embryos in culture medium, **said culture medium containing an effective amount of leukaemia inhibitory factor (LIF)**, for a time and under conditions sufficient for the development of said ES cells.” [Emphasis added.]
- On page 9 of the Office Action, the Examiner cites Williams column 5, lines 26-29 and lines 52-55, as disclosing “plating the inner cell mass on embryonic feeder layer.” Column 5, lines 26-29 and lines 52-55 in Williams disclose maintenance of D3 cells, an already established mouse cell line that is NOT inner mass cells.
- On page 9 of the Office Action, the Examiner notes Williams column 6, lines 2-5 as “selecting colonies with markers, which recognizes stem cell-specific surface antigens.” Once again, this section of Williams refers to immunofluorescence of D3 cells, NOT colonies grown from inner mass cells.

Williams simply does not disclose what the Examiner says Williams discloses. Even if one looks elsewhere in Williams, one cannot find what the Examiner says Williams discloses. More importantly, there is a critical difference in what Dr. Thomson did, and what the Examiner implies Dr. Thomson did. Dr. Thomson did not select his cells based on their marker expression profile, but rather tested the cells he had already

selected for their marker expression profile. This distinction goes to the heart of the Examiner's inherency argument which fails under the correct interpretation of the facts. All of the elements of claims 9 and 10 are not found in Williams, claims 9 and 10 are not anticipated by Williams.

Newly added claim 12 is also not anticipated by Williams. Claim 12 recites that colonies that are flatter than mouse cell colonies are selected. Williams does not disclose a method of isolating primate ES cells where colonies that are flatter than mouse ES cell colonies are selected, because at the time Williams was filed, flatter ES cell colonies were simply not known (Stewart, ¶ 19). The only known ES cell colonies were mouse ES cell colonies, which have an uneven and clumpy morphology. Dr. Stewart, an expert in mouse ES cell technology, states that if now, as could not have been the case then, a skilled artisan were to have before him a culture plate of ES cell colonies where some of the colonies were mouse ES cell colonies and other colonies were primate ES cell colonies, the artisan, following the invention of Dr. Thomson, would be able to distinguish each cell type by the colony morphology. However, prior to Dr. Thomson's invention, it would not have been possible to distinguish between the two cell types because the skilled artisan would not have known the morphology of the primate ES cell colonies (Stewart, ¶ 19). Dr. Thomson alone invented primate ES cell colonies, and Williams cannot be held to teach a method of isolating primate ES cell colonies, because neither Williams, nor any other cited reference, nor any other artisan skilled in stem cell technology at the time of the present application, knew what they were.

Anticipation Requires Enablement

Williams does not enable claims 9 and 10 (or newly added claims 12-13). In a recent case, the Federal Circuit has reaffirmed that "to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art." *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006). The legal standard for an enabling anticipatory reference requires that the prior art reference teach one of ordinary skill in the art to make or carry out the claimed invention *without undue experimentation*. [Italics added.] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 (Fed.Cir. 2006); *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F.3d 1051, 1053 (Fed.Cir. 2003).

Enablement is a question of law based on underlying facts. *Minnesota Mining & Mfg. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed.Cir. 2002). Enablement is clearly a necessity for anticipation and Williams is not an enabling reference for primate ES cells.

An anticipatory reference must place the public in possession of the invention. *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985). It is not enough for a reference to simply suggest that the disclosure contained therein can be used in a different way that is neither described nor enabled in the prior art reference, and be effective as an anticipatory reference for the unsupported suggestion.

The Examiner applies Williams as anticipating the isolation of primate/human ES cells based only on the suggestion that the methods disclosed therein for murine cells would be applicable to primate ES cells. It is not enough to simply note that Williams states that his method would “extend to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish...” (col. 3 lines 6-8), without more. Williams does not disclose any means for derivation of ES cells from any mammal other than mouse, and if the skilled artisan followed Williams and applied the methods disclosed therein to primate ES cell isolation, the artisan would fail (Stewart, ¶ 24). Even Williams himself could not extend his methods to the isolation of ES cells from other mammals (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75: “[t]he murine model for totipotential stem cell isolation is yet to prove applicable to domestic animals”, page 574; and Stewart, ¶ 22).

In addressing method claims, the court in *In re Best* states that

"appellants need only have shown that the cool-down rate for a typical laboratory-scale sample when employed in Hansford's process, would not yield a cooled zeolite with the x-ray diffraction pattern of claims 3. Appellants failed to do even that." *In re Best*, 562 F.2d 1252, 1255 (Fed.Cir. 1977).

Here, if the Williams method was followed, according to Williams in *Cherny/Williams Id*), ES cells would not be isolated from any non-murine species.

Some considerations that aid in determining the enabling character of a reference are: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented [in the reference], (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those

in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 838 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir. 1988).

Williams fails as an enabling anticipatory reference for the claimed invention under the *Wands* analysis for the following reasons: (1) the quantity of experimentation necessary was great as evidenced by how many others tried and failed to isolate non-murine ES cells (Stewart, ¶¶ 22, 27, 28, 30, 31, 32); (2) there is simply no guidance for isolating primate ES cells in the Williams reference (Stewart, ¶¶ 22-25); (3) there are no working examples of the isolation of primate ES cells in the reference; (4) the nature of the invention by Dr. Thomson is the first isolation and culture of primate ES cells, for which he is widely acclaimed (See Attachment A); (5) there were no examples of methods for isolating primate ES cells in the art; in light of Williams' own subsequent statements, the skilled artisan would conclude that Williams' method cannot be used to isolate a primate ES cell line, (6) even where the relative skill level of those skilled in the art is very high (Ph.D. level) (Stewart, ¶ 12); (7) in a very difficult and unpredictable art. Further (8), the claims specifically recite a "purified preparation of primate embryonic stem cells and method of making the same," thus are not overly broad and do not read on mouse ES cells. A practitioner reading the cited references could not arrive at the presently claimed invention. Williams does not place the public in possession of the claimed invention.

Williams does not teach an all-purpose recipe for isolating and culturing embryonic stem cells from all species. Williams requires undue experimentation in order to practice the present invention and does not place the public in possession of the claimed invention as evidenced by Williams in Cherny/Williams, *Reprod. Fertil. Dev.* 6: 569-75 (1994).

Consistent with the state of the art and what Cherny and Williams published, even the Patent Office viewed the disclosure of Williams as not being enabled for anything more than murine ES cells and methods of isolating/culturing them. Throughout the file history of the Williams patent (and related patent applications), Williams was never able to overcome the Examiner's enablement rejection of claims encompassing non-murine ES cell culture. Since the application that matured into U.S. patent number 5,166,065 was filed in 1990, the consistent position of the U.S. Patent and Trademark Office and of

the Examiners handling the Williams' patent applications over 17 years is that Williams *et al.* enabled only murine ES cell isolation and culture. The Patent Owner finds no basis in the Examiner's comments for a change in the Patent Office's position now and respectfully maintains that Williams does not enable human embryonic stem cell isolation and, as such, cannot anticipate the present claims.

The failure by Williams eviscerates the "teaching" in his patent reference - and relied on by the Examiner - that his mouse ES cell method was equally applicable to a list of animals (cows, pigs, sheep, etc.) when, in fact, it was not. Its application to primates/humans was never shown either. This failure further evidences the unpredictability of this art. (Stewart, ¶¶ 31, 32).

Failure of Others is Evidence of Non-Enablement

Besides Williams, many others failed to isolate ES cells from any non-murine species prior to Dr. Thomson's invention. In fact, Dr. Stewart recites a long list of publications that disclose clear failure by others to isolate ES cell lines from non-murine species including rat, hamster, sheep, pig and even human (Stewart, ¶ 12-15).

Evidence of failure by others is found in:

- Brook and Gardner, 1997, PNAS 94:5709-5712, Brook et al., 2003, Diabetes 52:205-208 – methods used to isolate mouse ES cells are not universally predictable across different strains of mice
- Brenin et al., 1997, Transplant Proc. 29:1761-1765 – rat ES cells were not isolated by Iannaccone et al., 1994, Dev. Biol. 163:288-292, rather Iannaccone's cells were contaminating mouse ES cells; and Ouhibi et al., 1995, Mol. Reprod. & Dev. 40:311-324 – rat ES cells that can be passaged beyond passage four could not be isolated
- Doetschman et al., 1988, Dev. Biol. 127:224-227 – failure to isolate hamster ES cells capable of long term proliferation
- Piedrahita et al., 1990, Theriogenology 34:879-901 – failure to isolate ovine ES cells and doubtful isolation of porcine ES cells; and a later publication by Moore et al. (including Piedrahita), 1997, In Vitro Cell Dev Biol 33:62-71 showing porcine ES cells were not in fact isolated in the earlier publication

- Talbot et al., 1995, Mol. Repord. & Dev. 42:35-52 – failure to isolate bovine ES cells
- Bongso, 1994, Human Reprod. 9:2110 – failure to isolate long term cultures of human ES cells; and Rubinoff et al. (including Bongso), 2000, Nature Biotech. 18:399-404 – acknowledgment of the earlier failure and Dr. Thomson’s success.

If others skilled in the art, having the requisite level of knowledge of the art, failed, in repeated attempts, to isolate non-murine ES cells, that failure is strong evidence that the cited references are *not* enabling for anticipation purposes. “Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.” *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985).

The overreaching statement by the Examiner that ES cell lines can be isolated from the embryos of other animals is not enabled, not even for Williams himself. Williams cannot anticipate and the rejection of claims 9-10 under 35 U.S.C. § 102(b) should be reconsidered and withdrawn.

Rejection of claims 1-8 and 11 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over Williams

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-8 and 11 under 35 U.S.C. §102(b) as being anticipated by Williams. The Examiner asserts that the ES cells disclosed by Williams contain, either expressly or inherently, all of the characteristics of the primate ES cells as encompassed in the pending claims. Williams does not anticipate the present invention because Williams does not contain all the elements of the present claims.

Williams does not disclose primate/human ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, ’780 patent (Stewart , ¶ 20), that proliferate in the absence of LIF for over one year (Stewart , ¶ 23), that form trophoblast (Stewart , ¶ 20).

The Examiner's mischaracterization of Williams, already discussed above though not repeated here, is equally applicable evidence that Williams does not disclose what the Examiner says Williams discloses.

Referring to the Examiner's specific assertions in the Office Action, on page 10, section 5 first paragraph, the Examiner asserts that Williams teaches isolation of ES cells from animal embryos (blastocyst), and maintenance of ES in vitro culture medium containing LIF. Williams' method is only applicable to mouse ES cells by Williams' own admission (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75 and Williams file history). The Examiner's assertion holds no weight in view of the contradictions from both Williams himself and the PTO's own record in the Williams file history.

The Examiner next asserts that Williams teaches that the ES cells are maintained in culture medium, containing an effective amount of LIF for 20 weeks. The Examiner interprets this to mean that the ES cells taught by Williams are capable of proliferation in in vitro culture for over one year. The Examiner stretches the point in two regards. First, if primate ES cells were grown in LIF in the absence of a feeder layer as is taught in Williams, they would not proliferate at all, because primate ES cells are LIF independent and they would differentiate instead of proliferating if grown in LIF (Thomson et al., 1995, *PNAS* 92:7844-7848; Thomson et al., 1996 *Biol. Reprod.* 55:254-259 and Stewart, ¶ 23). Second, twenty (20) weeks is simply not over one year. Williams does not even teach undifferentiated proliferation of *mouse* ES cells for over one year let alone teach proliferation of primate ES cells for over one year. What Williams teaches is that the artisan should isolate and grow non-mouse ES cells in LIF in order to accomplish proliferation of those cells in an undifferentiated state for 20 weeks. This teaching is inoperable, as Williams later admits (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75).

Next the Examiner asserts that the ES cells taught by Williams "maintain karyotype in which all chromosomes are characteristics of the primate species and noticeably altered through culture." This is simply not true. The words "karyotype" and "chromosome" nowhere appear in Williams and primate ES cells that maintain karyotype for over one year cannot be gleaned out of a reference that does not teach or enable

primate ES cells at all. Even when the reference is held to enable the cells it does disclose, namely mouse ES cells, properties are ascribed to those cells by the Examiner that are nowhere taught in the reference.

On page 12 of the Office Action, the Examiner relies on a claim interpretation that primate ES cells inherently differentiate into trophoblast that produce chorionic gonadotropin. As noted by Dr. Stewart in his Declaration, a primate embryo contains a multitude of cells. (Stewart, ¶ 21) There would be no way of knowing from Williams which primate cells to pick to establish primate ES cell lines that when differentiated, would form trophoblast that produce chorionic gonadotropin. The art did not know that primate ES cell lines could be differentiated into trophoblast until the present invention. The art did know that murine ES cells would *not* differentiate into trophoblast; but the art did not know that a purified preparation of primate ES cells could differentiate into trophoblast because such cells were not yet in the art (Stewart , ¶ 20).

Williams is not an enabling reference for a purified preparation of primate ES cells. To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. To “anticipate,” the identical subject matter must not only be previously known, but the knowledge must be sufficiently enabling to place the information in the possession of the public. This is simply not the case with Williams. Nowhere in Williams is there any guidance as to how to isolate a purified preparation of primate ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, ’780 patent (Stewart , ¶ 20), that proliferate in the absence of LIF for over one year (Stewart , ¶ 23), that form trophoblast (Stewart , ¶ 20).

Failure by others in the art, as discussed above and incorporated herein in its entirety, further evidences the unpredictability in the art and the lack of enablement by Williams.

For at least the above reasons, the rejection of claims 1-8 and 11 under 35 U.S.C. § 102(b) over Williams should be reconsidered and be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-8 and 11 under 35 U.S.C. §103(a) as being obvious over Williams. Specifically, the Examiner asserts that Williams discloses ES

cells and methods to isolate these cells, and therefore it would have been obvious to one of skill in the art to use the teachings of Williams to arrive at the presently claimed invention. The Patent Owner respectfully traverses this rejection for the following reasons.

Williams does not disclose primate/human ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, '780 patent (Stewart , ¶ 20), that proliferate in the absence of LIF for over one year (Stewart , ¶ 23), that form trophoblast (Stewart , ¶ 20).

According to the U.S. Supreme Court ruling in *Graham v. John Deere*, 383 U.S. 1 (1960), in making a case for obviousness, the Examiner must 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. These principles have just been reconfirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350 (Slip Op. April 30, 2007).

In *KSR Int'l Co.*, the US Supreme Court restated the requirements for a finding of obviousness. Encouraging the application of common knowledge and common sense, the Court took care to guard against hindsight bias and *ex post* reasoning and to distinguish the predictable from the unpredictable arts ("If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." [Emphasis added]). The field of stem cell culture can only be viewed as a highly unpredictable art (in contrast to the throttle pedals of KSR). Because the skilled person in this art understands the significant unpredictability associated with primate/human ES cell isolation, the rejection of the claims under §103 could only have been made with hindsight bias and *ex post* reasoning in the face of Dr. Thomson's success.

When applying 35 U.S.C. § 103, the following tenets of patent law must be followed: 1) the claimed invention must be considered as a whole; 2) the references must be considered as a whole; 3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and 4) reasonable expectation of success is the standard with which obviousness is determined (MPEP § 2141 II).

The deficiencies in Williams discussed elsewhere herein, although not repeated here, are equally applicable to the rejection of claims 1-8 and 11 under 35 U.S.C. §103(a) over Williams. Nowhere does Williams teach, enable or otherwise disclose a purified preparation of primate/human ES cells as encompassed by the claims. Williams does not disclose any cell that proliferates for over one year in an undifferentiated state that maintains a normal karyotype. Williams does not teach the skilled artisan even how to arrive at such a cell. Rather, Williams defines long term maintenance as being twenty two passages (approximately 100 cell generations or 10 weeks of culture). Williams suggests that the mouse ES cells can be maintained for up to 20 weeks. Maintaining cells in culture for twenty weeks is not even close to the over one year time period achieved by Dr. Thomson's cells. Williams does not address karyotype or even chromosomal structure in his cells.

When viewed as a whole, a skilled artisan would understand that Williams is directed to the advantages of LIF in isolating and maintaining ES cells obtained from mice. In fact, the first line of the Williams specification states:

“This invention relates to the use of a previously discovered and characterized molecule, leukaemia inhibitory factor (LIF), in the isolation and propagation of embryonic stem cells in vitro.”

Williams then states in column 3, lines 6-16

“Thus, the invention extends to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish This invention also includes the use of LIF in culture media to modulate the survival and growth of human and other animal species”

But this is simply not true as Williams himself declares in Cherny (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75), along with others (Piedrahita et al., 1990, *Theriogenology* 34: 879-901, and Stewart, ¶¶ 22, 23, 30-32). Williams' own publication and those of others recited herein, evidences the enormous unpredictability in this art.

How can Williams be considered to render the present claims obvious when Williams himself admits that his technology would not suffice to isolate ES cells from other species? A major point of the Cherny/Williams reference is to provide a review of

the ES cell field and how the successful methodology of isolating murine ES cells can be applied (or otherwise cannot be applied) to domestic animals. Cherny/Williams states

“initial research into the isolation of domestic animal ES cells in our and other laboratories attempted to repeat the work carried out in mice by isolating cell lines directly from cultured preimplanted embryos. Published reports of such studies in pigs, cattle and sheep, together with our own research, indicated that cells which display some ES cell characteristics could be identified but the isolation of proven, pluripotential ES cell lines remained elusive.”

Even Hogan (U.S. Patent No. 5,690,926; hereafter “Hogan”) also cited by the Examiner against the present claims, admits in the file history of her patent that the generation of human ES cells from pre-implantation embryos was unpredictable (see reference to Hogan ‘926 below).

There can be no reasonable expectation of success here. It would have been unreasonable for a skilled artisan to apply the murine model disclosed in Williams or other references, to primates or humans in light of the many failures by others in doing so. (Stewart, ¶¶ 12, 22, 27, 28, 30, 32).

This rejection is the first of several based on § 103 in this Action. Even if the Examiner had successfully made a *prima facie* case for an obviousness rejection, that case would be rebutted by the objective indicia of nonobviousness that are recounted earlier in this Response and accumulated in Attachment A. The inventor, Dr. Thomson, has received – and continues to receive – wide acclaim for his invention - isolation and cultivation of human/primate ES cells. Were the invention obvious, others would not have repeatedly failed to accomplish it and such scientific and professional acclaim would not have been ascribed to its discoverer.

The subject art is complicated and unpredictable. (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences

between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-8 under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103 as being obvious over Hogan (U.S. Patent 5,690,926)

Rejection under 35 U.S.C. §102(e)

Claims 1-8 and 11 were rejected under 35 U.S.C. §102(e) as being anticipated by Hogan. Specifically, the Examiner asserts that Hogan discloses non-mouse pluripotential stem cells and therefore meets the limitations of the claims 1-8 and 11. Hogan cannot anticipate the present invention because Hogan fails to disclose each and every element of the claims, either inherently or expressly. Hogan does not show the identical invention in as complete detail as is contained in the present claims, rather Hogan shows culture of a different cell type obtained from a different starting source and having a different cell surface marker and therefore Hogan's cells are different cells having characteristics distinct from those claimed by Dr. Thomson.

Hogan's cells are derived from primordial germ cells from post-implantation embryos, and therefore, are not the present embryonic stem cells derived from pre-implantation embryos. Hogan admits as much in the file history of her patent where she states:

“At the time of the applicants invention it was known that other labs had tried very hard to isolate pluripotent embryonic stem cells from rat, pig and sheep without success. What seems to happen is that the inner cell mass cells differentiate very easily into endoderm and they fail to proliferate further as pluripotent embryonic stem cells. (In fact, there have been reports within the last year of success in obtaining cells from Rhesus monkey blastocysts and perhaps one recent success from rat blastocysts.) In view of the perceived problems isolating pluripotent stem cells from blastocysts and the differences between early embryos in divergent species, one skilled in the art would not expect that methods of obtaining stem cells from mice blastocysts would be directly applicable to other species.

Importantly, applicant's claimed invention does not use blastocysts to derive embryonic stem cells. Applicant uses a very different method to derive embryonic stem cells. As disclosed throughout the application and the murine

and human primordial germ cell Examples, applicant's embryonic stems cells are derived from primordial germ cells dissected from post-implantation embryos.”

(See Amendment dated June 4, 1996 responding to the December 4, 1995 Office Action in Application Serial No. 08/217,921, now U.S. Patent No. 5,690,926).

For this reason, Hogan's cells are also known in the art as embryonic germ (EG) cells (Stewart, ¶ 26).

The Patent Owner does not understand how the Examiner can pick and choose some, but not all the characteristics of Hogan's cells to support an anticipation rejection, either inherently or otherwise. Anticipation, inherent or otherwise, cannot rely on picking and choosing some but not all characteristics of a prior art composition.

At the bottom of page 14 of the Office Action, the Examiner states that Hogan's cells are SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 positive, similar to the presently claimed cells. However, the Examiner conveniently ignores the fact that Hogan's cells are SSEA-1 positive, whereas the presently claimed cells are SSEA-1 negative. Table 1, '780 patent; Stewart, ¶ 27. Such picking and choosing cannot be used to support a rejection based on anticipation.

The Examiner is silent on the issue of trophoblast formation by Hogan's cells when induced to differentiate. This is because Hogan's cells cannot form trophoblast when induced to differentiate (Stewart, ¶ 27). Hogan's cells are EG cells, not the ES cells of the present invention. EG and ES cells are not equivalents in how they are created, where they are derived from, and what they can differentiate into. Hogan is inapplicable and irrelevant as an anticipation reference.

Each and every element of the claims is not disclosed in Hogan and therefore the rejection of claims 1-8 and 11 under 35 U.S.C. § 102(e) over Hogan should be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-8 under 35 U.S.C. §103(a) as being obvious over Hogan. The Examiner asserts that Hogan discloses ES cells and methods to isolate these cells, and therefore it would have been obvious to one of skill in the art to use the

teachings of Hogan to arrive at the presently claimed invention. The Patent Owner respectfully traverses this rejection.

The deficiencies of Hogan discussed above are equally applicable to the instant rejection of claims 1-8 under 35 U.S.C. §103(a) over Hogan.

Hogan teaches EG cells derived from primordial germ cells obtained from post-implantation embryos. Hogan's methods for isolating her cells, and the characteristics of those isolated cells cannot render obvious a purified preparation of primate embryonic stem cells obtained from pre-implantation embryos. There is nothing in Hogan that points the skilled artisan to the presently claimed primate ES cells. Following Hogan and without the benefit of hindsight afforded by the present patent, the skilled artisan would expect to isolate EG cell lines that are SSEA-1 positive and that cannot form trophoblast when induced to differentiate. Further, there is no expectation of success that a purified preparation of primate ES cells would be obtained following the teaching of Hogan.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claim 11 under 35 U.S.C. § 102(a) or in the alternative, under 35 U.S.C. § 103(a) as obvious over Bongso

The Examiner rejected claim 11 under 35 U.S.C. §102(a) as being anticipated or in the alternative as being obvious under 35 U.S.C. § 103(a) over Bongso (Human Reproduction, vol. 9, No. 11, 1994). The Examiner asserts that Bongso discloses an ES

cell line from primate/human blastocyst and that Bongso's ES cells are derived from a substantially identical method as recited in claim 9. Therefore the Examiner contends that the subject matter of claim 9 is the same or an obvious variation of the reference teachings.

In the Notice of Allowability dated March 17, 1998, in the file history of the present patent, the Office conceded that Bongso did not teach or fairly suggest primate ES cells which are stable in *in vitro* culture for longer than one year. The Examiner has specifically avoided this feature.

Bongso cannot anticipate claim 11 nor render it obvious. Bongso's cells were only capable of proliferating for two passages (page 2114 in Bongso: "After the second subculture, the cells differentiated into fibroblasts or died."). Dr. Thomson's cells are capable of proliferating undifferentiated for over one year. Bongso's cells are not the presently claimed cells.

Even more importantly, in a subsequent publication by Bongso (Rubinoff et al., 2000, Nature Biotechnology 18:399-404), referring to the presently cited reference and D. Thomson's work, in the background section of this paper (page 399), Bongso states:

"More recently Thomson and colleagues reported the isolation and characterization of diploid rhesus and marmoset monkey ES cells with extensive capacity for differentiation (Thomson et al., 1995, PNAS 92:7844-7848; Thomson et al., 1996 Biol. Reprod. 55:254-259). These monkey ES cells resemble human EC stem cells in their morphology, marker expression, and lack of response to LIF. Earlier we described the characteristics of primary cultures of undifferentiated cells from the human blastocyst that were able to undergo limited replication *in vitro* (Bongso et al., 1994, Hum. Reprod. 9:2110-2117). Since these early studies did not use embryonic feeder cell support (required for proliferation of pluripotent human EC and nonhuman primate ES cells) but relied instead on LIF supplementation of the culture medium, these cells eventually underwent differentiation or death. Therefore, we subsequently employed a culture system incorporating embryonic fibroblast feeder cell layers to derive human ES cells from blastocysts. While this work was in progress, Thomson and coworkers reported the derivation of ES cell lines from the human blastocyst. We confirm these results and extend the characterization of the human ES cell phenotype."

Bongso admits that Dr. Thomson was the first to invent primate/human ES cells. Bongso states that he did not isolate primate/human ES cell lines. The unpredictable nature of the art of embryonic stem cell isolation would not support even a rejection for obviousness, much less anticipation as is alleged here.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

The rejection over Bongso should not stand.

Rejection of claims 1-11 under 35 U.S.C. § 103(a) over either Robertson I, Robertson II, Piedrahita, separately or together in view of Williams ('065) and Hogan ('926)

The Examiner rejected claims 1-11 as being obvious over either Robertson I, Robertson II, Piedrahita, separately or together in view of Williams and Hogan ('926). The Examiner contends that the claimed invention differs from Robertson (I and II) and Piedrahita by claiming primate ES cells. The Examiner states that Williams teaches the exact same method as Robertson I, II and Piedrahita reference and also encompasses primates/human ES cells. Therefore, the Examiner asserts that Williams motivates the skilled artisan to combine the teachings of Robertson I and II and Piedrahita with Williams to isolate ES cells from primates/humans. Further, the Examiner states that Hogan provides additional motivation for the isolation and maintenance of primate/human ES cells in vitro for longer periods. The Patent Owner respectfully traverses this rejection.

Robertson I and II each describe the initiation and culture of what would be considered by those in the field as mouse embryonic stem cells. Neither Robertson reference teaches or suggests that any of their methods or techniques are applicable to

other any other species. Neither reference provides data or suggests that the techniques could be successfully applied to other species. The existence of mouse ES cells is acknowledged in the Background section in the present patent. Robertson I and II do no more than establish the state of the art at the time, that is, that mouse ES cells could be isolated.

The Examiner misreads Piedrahita. Piedrahita does not teach porcine (pig) or ovine (sheep) ES cells capable of culture for more than one year. In fact this reference teaches that the methods used to create and culture mouse ES cells could not be made to work on porcine and ovine systems. While some cell cultures were initiated, ES cells as defined in the art were not in fact created from pig or sheep embryos as reported by Piedrahita. Piedrahita makes this clear in the Abstract section of the article. For example, Piedrahita states that:

“While murine isolated ICM or intact embryos plated on STO or HEF feeders gave rise to cell lines with embryonic stem cell-like (ES-like) morphology, ovine embryos did not,” and “porcine ES-like cells did not undergo observable differentiation in vitro.” (See second sentence of the Abstract)

The main body of Piedrahita explains these conclusions in greater detail – see, for example, page 894 of Piedrahita where it is stated that porcine ES-like cells did not differentiate when induced to do so. Further, in the discussion section of Piedrahita, it is noted that

“differences were observed in the type of colonies that could be isolated from each species.” (Page 896 of Piedrahita)

Only epithelial cells could be derived from ovine embryos and the porcine cell lines created by Piedrahita did not differentiate. In light of these data, Piedrahita writes

“One explanation is that the trigger for induction of differentiation varies with species.” (Page 896 of Piedrahita)

In fact, Piedrahita, in the last sentence of the article on page 897, offers that they do not know why the difficulties with the ovine and porcine systems arose, and do not know if the problems reside in the source materials, the age of the embryos, or the culture conditions.

What Piedrahita actually teaches is that the methodologies used to initiate ES cell cultures in the mouse did not work when applied to other animal systems and, at least at the time of publication of Piedrahita, no methods were known to those skilled in the art for making ES cells in other species. The present patent addresses the difficulties posed by Piedrahita beginning at column 3 line 49.

Citation of Piedrahita by the Examiner adds no new support for an obviousness rejection. When this reference is taken as a whole, Piedrahita teaches that when the methods used to create murine ES cells are applied to pig and sheep, ES cells as encompassed by the present claims *are not made*. In other words, Piedrahita teaches away from applying the murine system to other species and therefore teaches away from the presently claimed invention.

Williams adds nothing to support the Examiner's case, particularly in light of his statements in Cherny/Williams (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75). Further, when taken as a whole, Williams is directed to the use of leukemia inhibitory factor (LIF) to aid in the creation and culture of embryonic stem cell lines in vitro. Williams teaches that the use of LIF substitutes for the use of feeder layers otherwise needed to maintain mouse embryonic stem cell lines in an undifferentiated state (see column 1 lines 51-62 and column 3 lines 62-65). The central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells (Stewart, ¶ 23).

With respect to Hogan, the Examiner contends that Hogan would motivate the maintenance of primate/human cells in vitro for a long period of time. This is incorrect. Hogan's cells are post-implantation embryo derived EG cells, not ES cells and Hogan herself admits in her file history that techniques used on mouse ES cells do not render obvious primate/human ES cell isolation. The skilled artisan, upon reading Hogan, would not be motivated to follow Hogan to arrive at the presently claimed cells.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety. None of the cited references alone or together can support the obviousness rejection in the face of these facts.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Conclusion

For all the reasons stated above, the Patent Owner respectfully requests reconsideration and withdrawal of the rejections of the claims 1-11 as presently presented and allowance of new claims 12-14.

A copy of this response is being served on the Third Party Requester, per the Certificate of Service attached hereto.

WISCONSIN ALUMNI RESEARCH FOUNDATION



Date: May 30, 2007

By:

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ATTACHMENT A

ATTACHMENT B

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of this paper is being served on the Requester, The Foundation for Taxpayer and Consumer Rights, through its counsel:

Daniel B. Ravicher, Esq.
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
New York, NY 10018

via overnight delivery service on the date shown below.

May 30, 2007
Date

Joseph R. DelMaster, Jr.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination of U.S. 6,200,806

Art Unit: 3991

Inventor: Thomson, J.

Examiner: Bennett Celsa

Control No.: 90/008,139

RESPONSE TO FIRST OFFICE ACTION

Attn: MAILSTOP: *EX PARTE* REEXAM

Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a response to the first Office Action received in the matter of Reexamination No. 90/008,139 for U.S. Pat. 6,200,806 (“the ‘806 patent”). The Response is being filed within the two-month period for response set in the Action, which was mailed March 30, 2007. No fees are believed to be due.

Claims 1-11 are under reexamination. There are no amendments to the specification or drawings submitted in this Response.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper. Claims 12-14 are newly added.

The Patent Owner’s response to the Office Action commences on page 4.

A Declaration of Colin Stewart, D. Phil., is submitted with this Response and is incorporated herein in its entirety.

Attachment A is a collection of publications evidencing the acclaim accorded Dr. Thomson as a direct result of his discovery and invention relating to the culturing and characterization of primate/human embryonic stem cells.

Attachment B is a collection of the documents referenced in this Response and in the accompanying Stewart Declaration.

The following is a complete listing of the claims and replaces all prior claim listings:

1. (Currently amended) A purified preparation of pluripotent human embryonic stem cells derived from a pre-implantation embryo which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and are not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

2. (Previously presented) The preparation of claim 1, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. (Previously presented) A purified preparation of pluripotent human embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have euploid karyotypes and in which none of the chromosomes are altered.

4. (Previously presented) The preparation of claim 3, wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. (Previously presented) The preparation of claim 3, wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. (Previously presented) The preparation of claim 3, wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. (Previously presented) The preparation of claim 3, wherein the cells remain euploid for more than one year of continuous culture.

8. (Previously presented) The preparation of claim 3, wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

9. (Currently amended) A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of:

- (a) isolating a human blastocyst;
- (b) isolating cells from the inner cell mass of the blastocyst of (a);
- (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;
- (d) dissociating the mass into dissociated cells;
- (e) replating the dissociated cells on embryonic feeder cells;

(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and

(g) culturing the cells of the selected colonies to [thereby obtain] produce an isolated pluripotent human embryonic stem cell line that is capable of proliferation as undifferentiated cells for over one year.

10. (Previously presented) A method as claimed in claim 9, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. (Currently amended) A cell line that is capable of proliferation for over one year developed by the method of claim 9.

12. (Newly added) A method of isolating a pluripotent human embryonic stem cell line, the method comprising the steps of:

(a) isolating a human blastocyst;

(b) isolating cells from the inner cell mass of the blastocyst of (a);

(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;

(d) dissociating the mass into dissociated cells;

(e) replating the dissociated cells on embryonic feeder cells;

(f) selecting colonies that have compact morphologies that are flatter than mouse embryonic stem cell colonies, wherein the cells have high nucleus to cytoplasm ratios and prominent nucleoli; and

(g) culturing the cells of the selected colonies to produce an isolated human embryonic stem cell line that is capable of proliferation as undifferentiated cells for over one year.

13. (Newly added) A method as claimed in claim 12, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

14. (Newly added) A cell line that is capable of proliferating for over one year as undifferentiated cells developed by the method of claim 12.

REMARKS

Claims 1-11 are pending in the reexamination of the instant patent and stand rejected. Claims 1, 9 and 11 have been amended and claims 12-14 are newly added herein. Reconsideration and withdrawal of the rejection of claims 1-11, entry of new claims 12-14 and issuance of claims 1-14 is respectfully requested.

Claim Amendment Summary

Claim 1 has been amended to recite that the cells are derived from a pre-implantation embryo. Support for this amendment is found in the specification at least at column 8, lines 23-29 and column 9, lines 15-16.

Claims 9 and 11 have been amended to recite that the cell line produced is capable of proliferation for over one year. Support for the phrase “capable of proliferation for over one year” is found at least in column 12, lines 25-29, and in present claim 1 of the patent.

New claim 12 is similar to originally issued claim 9 and is directed to a method of isolating a human embryonic stem cell line that is capable of proliferation for over one year, where, in step (f), colonies are selected that are flatter than mouse ES cell colonies. Support for the type of colony selection is found at least in column 14, lines 24-29 of the patent. No new matter has been added by way of the addition of claim 12. New claims 13 and 14 depend from claim 12 and are supported at least in original claims 10-11. No new matter has been added by way of these claim amendments and additions.

The Invention

Dr. James A. Thomson (Dr. Thomson) invented a novel purified preparation of primate/human embryonic stem cells and a method of isolating a primate/human embryonic stem cell line. There is no dispute that prior to Dr. Thomson’s landmark invention, mouse ES cells were known as were methods of making them. There is no dispute that Hogan reported the isolation of embryonic germ (EG) cells in U.S. Patent No. 5,690,926. Nonetheless, mouse ES cells and Hogan’s EG cells are not Dr. Thomson’s claimed primate/human ES cells.

Dr. Thomson's primate/human ES cells differ from mouse ES and Hogan's EG cells by source of sample, marker expression and by function. For example:

- Primate/human ES cells are SSEA-1 negative, while mouse ES and Hogan's EG cells are SSEA-1 positive;
- Dr. Thomson's cells are derived from pre-implantation embryos; Hogan's EG cells are derived from post-implantation embryos;
- When primate/human ES cells are cultured in leukemia inhibitory factor (LIF) in the absence of a feeder layer, they differentiate; in contrast, mouse ES cells can be propagated in an undifferentiated state in the presence of (LIF) in the absence of feeder layers;
- Primate/human ES cells can differentiate into trophoblast that produces chorionic gonadotropin; in contrast, neither mouse ES nor Hogan's EG cells can differentiate into trophoblast;
- Colonies of primate/human ES cells are more compact and distinctly flatter than mouse ES cell colonies.

Further, at the time of Dr. Thomson's invention, there was no reasonable expectation of success that mouse ES cell derivation protocols could be used to isolate primate/human ES cells based on the experience in the field at the time of Dr. Thomson's invention. It was long recognized that the techniques used to isolate mouse ES cells were unpredictable and were not universally applicable to the isolation of ES cells from other species, or even from different strains of mice. For nearly two decades from the discovery of mouse ES cells, others repeatedly tried and failed to isolate non-murine ES cells, particularly primate/human ES cell lines. See Declaration of Colin Stewart, D. Phil. (hereafter, "Stewart, ¶ #).

The level of acclaim in the art for Dr. Thomson's invention bears witness to the fact that the isolation of primate/human ES cells represented true innovation that was not simply a small step in embryonic stem cell research. Examples abound (See Attachment A):

- In 2005, the American Association for the Advancement of Science (AAAS), founded in 1848, identified as one of the most significant "Milestones of

Science” the work of Dr. Thomson, specifically, growing embryonic stem cells that may be used to create other types of cells.

- In 2001, Dr. Thomson was profiled in TIME magazine as one of the doctors “who are changing our world.” Calling him “The man who brought you stem cells,” TIME – like so many others – recognized Dr. Thomson as the scientist who had first isolated human embryonic stem cells.
- Dr. Thomson was a recipient of the Golden Plate Award presented by the American Academy of Achievement in 1999, whose honorees have included – in the scientific fields alone – famed explorer Robert Ballard, oral polio vaccine inventor Dr. Jonas Salk, Nobel Prize Chemist Dr. Linus Pauling, astronaut Dr. Sally Ride, and renowned physicist Dr. Edward Teller. Dr. Thomson was cited for his “recent breakthrough in culturing human embryonic stem cells outside the body.”
- Dr. Thomson was inducted into the Biotech Hall of Fame in 2001, which noted that Dr. Thomson had “successfully isolated and cultured human embryonic stem cells” and that the work had “set the stage for a revolution in medicine and science.”
- In 2003, Dr. Thomson was named a winner of a World Technology Summit Award in Health & Medicine, sponsored by the World Technology Network, which comprises leading corporations and individuals in technology-related fields. The World Technology Awards “are presented each year to the outstanding innovators from each sector within the technology arena.”
- In 2002, Dr. Thomson was selected to receive a \$100,000 research grant to continue his work on stem cells. The announcement of the award recognized Dr. Thomson as “the first person to isolate stem cells from human embryos.” The LIFE International Research Award “is presented to internationally renowned scientists whose research has led to clinical applications.”
- The Christopher Columbus Fellowship Foundation awarded its Frank Annunzio Award Columbus Scholar accolade to Dr. Thomson in 2003, together with a \$50,000 research grant. The award announcement cites Dr. Thomson as “the first to isolate and culture nonhuman primate embryonic stem cells in 1995 and human

ES cells in 1998.” It noted that Dr. Thomson’s research “has encouraged scientists around the world” about the possibilities for human stem cells.

- The American College of Veterinary Pathologists honored Dr. Thomson in 2004 with its Outstanding Achievement Award, which is presented to a member that “performs extraordinary acts or makes an extraordinary contribution that brings great credit to themselves and the discipline of veterinary pathology.” (Dr. Thomson was trained as a doctor of veterinary medicine.) Again he was cited for his work with embryonic stem cells.
- The American Association for Laboratory Animal Science bestowed its Nathan R. Brewer Scientific Achievement Award on Dr. Thomson in 2006 for his discoveries in the field of embryonic stem cells.

It cannot be denied that Dr. Thomson made a landmark invention that was unknown, unpredictable and long overdue in the art. Dr. Thomson’s invention embodies the very definition of a new and useful, novel, and non-obvious invention. Dr. Thomson alone has laid out the groundwork for a plethora of studies on primate/human ES cells that are rapidly driving the field toward remarkable clinical application and Dr. Thomson is entitled to a patent on his invention.

Claim Interpretations and Relevant Case Law

The Patent Owner disagrees with several of the Examiner’s statements made on page 5 et seq. of the Office Action, and does not accept the Examiner’s view as an accurate interpretation of the relationship of the claims to the art under the present law.

Human ES cells, let alone a purified preparation of the same, were not known in the art prior to the landmark discovery of Dr. Thomson. According to *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A 1977) (a case cited by the Examiner in support of his argument on inherent anticipation), where *In re Best* cites *In re Swinehart*, 439 F. 2d 210 (1971),

“[I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by *things* in the prior art, does not cause a claim drawn to those *things* to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the

applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Swinehart, 439 F.2d at 212-213. [Emphasis added.]

Here, this standard for inherent anticipation does not apply. The *things* claimed by Dr. Thomson, namely, a purified preparation of human ES cells, *were not in the prior art*. Nor does the applied prior art either explicitly or inherently teach a purified preparation of human ES cells. Simply stated, the purified human ES cells disclosed in the present application did not previously exist. They differ markedly from prior art murine ES cells (Williams '065) and Hogan's EG cells (Hogan '357 and '926) and the cells of the other prior art references which do not share the claimed features. There is no composition in the cited prior art that is a purified preparation of human ES cells. Because *In re Best* applies only where the composition (or method) already exists in the prior art, it is inapplicable here.

The Examiner also cites to *Ex parte Novitski*, 26 USPQ 2d 1389 (Bd. App. & Inter. 1993) to support the inherency argument. *Ex Parte Novitski* is equally inapplicable here. In that case, an obviousness rejection was upheld by the Board of Appeals and Interferences because the cited reference disclosed the claimed method. Here, the references cited by the Examiner nowhere disclose the claimed invention. Moreover, the "inherent" characteristics of Dr. Thomson's cells that the Examiner cites from Dr. Thomson's disclosure, are Dr. Thomson's actual discovery, his invention. How can a discovery itself render obvious that which was not known?

When reciting all that Dr. Thomson's cells are as evidence of "inherency," the Examiner misses the point. There is no prior art purified preparation of human ES cells. Dr. Thomson isolated a purified preparation of human ES cells that is novel over prior art preparations of cells, because Dr. Thomson's cells can and do spontaneously differentiate into trophoblast, which trophoblast produces chorionic gonadotropin. Until Dr. Thomson's invention, the art did not know that human ES cells would spontaneously differentiate into trophoblast. The art did know that murine ES cells would *not* differentiate into trophoblast; but the art did not know that a purified preparation of

human ES cells could differentiate into trophoblast because such cells were not yet in the art.

Dr. Thomson's cells have certain new marker expression profiles and other features as documented in Table 1 in the present patent. Dr. Thomson's cell are novel over the prior art and a rejection based on inherent anticipation cannot be sustained.

Rejection of claims 9-10 under 35 U.S.C. § 102(b) over Williams

Claims 9-10 have been rejected under 35 U.S.C. §102(b) as being anticipated by Williams (U.S. Patent No. 5,166,065; hereinafter "Williams").

Anticipation Requires that all Claim Elements be Present

Williams lacks all of the claimed elements. Williams neither discloses a method of making primate/human ES cells, nor discloses the isolation of the cells themselves.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. " MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Williams must describe each and every element of claims 9-10 in order to anticipate these claims under 35 U.S.C. §102(b). The Williams reference does not satisfy this requirement.

Even the Examiner's efforts to string together a disclosure in Williams that includes all of the elements of the present claims fails. The Examiner makes reference to specific disclosures in Williams that are simply incorrect. For example, beginning on page 17 of the Office Action:

- The Examiner notes that Williams at column 2, lines 37-40 and 47-50 are cited as teaching that Williams' method is portable to species other than mouse.

However, the Examiner fails to cite to the beginning of this paragraph in column 2 which states: "Accordingly, a first aspect of the present invention relates to a method for the isolation of embryonic stem (ES) cells from animal embryos in vitro which method comprises deriving ES cells from said embryos in culture

medium, **said culture medium containing an effective amount of leukaemia inhibitory factor (LIF)**, for a time and under conditions sufficient for the development of said ES cells.” [Emphasis added.]

- The Examiner cites to column 6, lines 52-58 and 66-column 7, line 4 as reciting that cells of the inner cell mass were obtained. These two sections of Williams actually refer to two different methods of obtaining the cells, not one continuous method as the Examiner might imply.
- The Examiner cites to Williams column 5, lines 19-34 as standing for the proposition that the inner cell mass cells are cultured on a feeder layer. This is not so. This section teaches culture of established cell lines on feeder layers.
- Column 8, lines 29-31 says that the colonies were plated as described above, and what is described is that the cells were plated in LIF, not feeder layers.
- Column 3, lines 54-55 does not address the pluripotential nature of the cells; column 4, lines 24-27 refers to maintenance of pluripotential phenotype when the cells are maintained in LIF, not on feeder layers; and, column 5, lines 19-34 refers to maintenance of established cell lines, not newly derived cells. These sections of Williams do not separately or collectively, disclose what the Examiner says they disclose.
- The Examiner acknowledges that LIF substitutes for the feeder layer. However, if LIF is used in place of a feeder layer, Dr. Thomson’s cells are not obtained (Stewart, ¶ 23).

Williams simply does not disclose what the Examiner says Williams discloses. Even if one looks elsewhere in Williams, one cannot find what the Examiner says Williams discloses. Importantly, Dr. Thomson did not select his cells based on their marker expression profile, but rather tested the cells he had already selected for their marker expression profile. This goes to the heart of the Examiner’s inherency argument, which fails under the correct interpretation of the facts. All of the elements of claims 9 and 10 are not found in Williams, claims 9 and 10 are not anticipated by Williams.

Newly added claim 12 is also not anticipated by Williams. Claim 12 recites that colonies that are flatter than mouse cell colonies are selected. Williams does not disclose a method of isolating human ES cells where colonies that are flatter than mouse ES cell

colonies are selected, because at the time Williams was filed, flatter ES cell colonies were simply not known (Stewart, ¶ 19). The only known ES cell colonies were mouse ES cell colonies, which have an uneven and clumpy morphology. Dr. Stewart, an expert in mouse ES cell technology, states that if a skilled artisan were to have before him a culture plate of ES cell colonies where some of the colonies were mouse ES cell colonies and other colonies were human ES cell colonies, the artisan, following the invention of Dr. Thomson, would be able to distinguish each cell type by the colony morphology. However, prior to Dr. Thomson's invention, it would not have been possible to distinguish between the two cell types because the skilled artisan would not have known the morphology of the human ES cell colonies (Stewart, ¶ 19). Dr. Thomson alone invented human ES cell colonies, and Williams cannot be held to teach a method of isolating human ES cell colonies, because neither Williams, nor any other cited reference, nor any other artisan skilled in stem cell technology at the time of the present application, knew what they were.

Anticipation Requires Enablement

Williams does not enable claims 9 and 10 (or newly added claims 12-13). In a recent case, the Federal Circuit has reaffirmed that “to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art.” *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366, 1381 (Fed.Cir. 2006). The legal standard for an enabling anticipatory reference requires that the prior art reference teach one of ordinary skill in the art to make or carry out the claimed invention *without undue experimentation*. [Italics added.] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 (Fed.Cir. 2006); *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F.3d 1051, 1053 (Fed.Cir. 2003). Enablement is a question of law based on underlying facts. *Minnesota Mining & Mfg. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed.Cir. 2002). Enablement is clearly a necessity for anticipation and Williams is not an enabling reference for human ES cells.

An anticipatory reference must place the public in possession of the invention. *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985). It is not enough for a reference to simply suggest that the disclosure contained therein can be used in a different way that is

neither described nor enabled in the prior art reference, and be effective as an anticipatory reference for the unsupported suggestion.

The Examiner applies Williams as anticipating the isolation of human ES cells based only on the suggestion that the methods disclosed therein for murine cells would be applicable to human ES cells. It is not enough to simply note that Williams states that his method would “extend to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish...” (col. 3 lines 6-8), without more. Williams does not disclose any means for derivation of ES cells from any mammal other than mouse, and if the skilled artisan followed Williams and applied the methods disclosed therein to human ES cell isolation, the artisan would fail (Stewart, ¶ 24). Even Williams himself could not extend his methods to the isolation of ES cells from other mammals (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75: “[t]he murine model for totipotent stem cell isolation is yet to prove applicable to domestic animals”, page 574; and Stewart, ¶ 22).

In addressing method claims, the court in *In re Best* states that

"appellants need only have shown that the cool-down rate for a typical laboratory-scale sample when employed in Hansford's process, would not yield a cooled zeolite with the x-ray diffraction pattern of claims 3. Appellants failed to do even that." *In re Best*, 562 F.2d 1252, 1255 (Fed.Cir. 1977).

Here, if the Williams method was followed, according to Williams in *Cherny/Williams Id*), ES cells would not be isolated from any non-murine species.

Some considerations that aid in determining the enabling character of a reference are: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented [in the reference], (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 838 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir. 1988).

Williams fails as an enabling anticipatory reference for the claimed invention under the *Wands* analysis for the following reasons: (1) the quantity of experimentation necessary was great as evidenced by how many others tried and failed to isolate non-murine ES cells (Stewart, ¶¶ 22, 27, 28, 30, 31, 32); (2) there is simply no guidance for isolating human ES cells in the Williams reference (Stewart, ¶¶ 22-25); (3) there are no

working examples of the isolation of human ES cells in the reference; (4) the nature of the invention by Dr. Thomson is the first isolation and culture of human ES cells, for which he is widely acclaimed (See Attachment A); (5) there were no examples of methods for isolating human ES cells in the art; in light of Williams' own subsequent statements, the skilled artisan would conclude that Williams' method cannot be used to isolate a human ES cell line, (6) even where the relative skill level of those skilled in the art is very high (Ph.D. level) (Stewart, ¶ 12); (7) in a very difficult and unpredictable art. Further (8), the claims specifically recite a "purified preparation of human embryonic stem cells and method of making the same," thus are not overly broad and do not read on mouse ES cells. A practitioner reading the cited references could not arrive at the presently claimed invention. Williams does not place the public in possession of the claimed invention.

Williams does not teach an all-purpose recipe for isolating and culturing embryonic stem cells from all species. Williams requires undue experimentation in order to practice the present invention and does not place the public in possession of the claimed invention as evidenced by Williams in Cherny/Williams, *Reprod. Fertil. Dev.* 6: 569-75 (1994).

Consistent with the state of the art and what Cherny and Williams published, even the Patent Office viewed the disclosure of Williams as not being enabled for anything more than murine ES cells and methods of isolating/culturing them. Throughout the file history of the Williams patent (and related patent applications), Williams was never able to overcome the Examiner's enablement rejection of claims encompassing non-murine ES cell culture. Since the application that matured into U.S. patent number 5,166,065 was filed in 1990, the consistent position of the U.S. Patent and Trademark Office and of the Examiners handling the Williams' patent applications over 17 years is that Williams *et al.* enabled only murine ES cell isolation and culture. The Patent Owner finds no basis in the Examiner's comments for a change in the Patent Office's position now and respectfully maintains that Williams does not enable human embryonic stem cell isolation and, as such, cannot anticipate the present claims.

The failure by Williams eviscerates the "teaching" in his patent reference - and relied on by the Examiner - that his mouse ES cell method was equally applicable to a list

of animals (cows, pigs, sheep, etc.) when, in fact, it was not. Its application to humans was never shown either. This failure further evidences the unpredictability of this art. (Stewart, ¶¶ 31, 32).

Failure of Others is Evidence of Non-Enablement

Besides Williams, many others failed to isolate ES cells from any non-murine species prior to Dr. Thomson's invention. In fact, Dr. Stewart recites a long list of publications that disclose clear failure by others to isolate ES cell lines from non-murine species including rat, hamster, sheep, pig and even human (Stewart, ¶¶ 12-15).

Evidence of failure by others is found in:

- Brook and Gardner, 1997, PNAS 94:5709-5712, Brook et al., 2003, Diabetes 52:205-208 – methods used to isolate mouse ES cells are not universally predictable across different strains of mice
- Brenin et al., 1997, Transplant Proc. 29:1761-1765 – rat ES cells were not isolated by Iannaccone et al., 1994, Dev. Biol. 163:288-292, rather Iannaccone's cells were contaminating mouse ES cells; and Ouhibi et al., 1995, Mol. Reprod. & Dev. 40:311-324 – rat ES cells that can be passaged beyond passage four could not be isolated
- Doetschman et al., 1988, Dev. Biol. 127:224-227 – failure to isolate hamster ES cells capable of long term proliferation
- Piedrahita et al., 1990, Theriogenology 34:879-901 – failure to isolate ovine ES cells and doubtful isolation of porcine ES cells; and a later publication by Moore et al. (including Piedrahita), 1997, In Vitro Cell Dev Biol 33:62-71 showing porcine ES cells were not in fact isolated in the earlier publication
- Talbot et al., 1995, Mol. Reprod. & Dev. 42:35-52 – failure to isolate bovine ES cells
- Bongso, 1994, Human Reprod. 9:2110 – failure to isolate long term cultures of human ES cells; and Rubinoff et al. (including Bongso), 2000, Nature Biotech. 18:399-404 – acknowledgment of the earlier failure and Dr. Thomson's success.

If others skilled in the art, having the requisite level of knowledge of the art, failed, in repeated attempts, to isolate non-murine ES cells, that failure is strong evidence that the cited references are *not* enabling for anticipation purposes. “Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.” *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985).

The overreaching statement by the Examiner that ES cell lines can be isolated from the embryos of other animals is not enabled, not even for Williams himself. Williams cannot anticipate and the rejection of claims 9-10 under 35 U.S.C. § 102(b) should be reconsidered and withdrawn.

Rejection of claims 1-8 and 11 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over Williams

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-8 and 11 under 35 U.S.C. §102(b) as being anticipated by Williams. The Examiner asserts that the ES cells disclosed by Williams contain, either expressly or inherently, all of the characteristics of the human ES cells as encompassed in the pending claims. Williams does not anticipate the present invention for the following reasons.

The Examiner’s mischaracterization of Williams, though not repeated here, is equally applicable.

Williams is not an enabling reference for a purified preparation of human ES cells. To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. To “anticipate,” the identical subject matter must not only be previously known, but the knowledge must be sufficiently enabling to place the information in the possession of the public. This is simply not the case with Williams. Nowhere in Williams is there any guidance as to how to isolate a purified preparation of human ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, ’806 patent; (Stewart, ¶ 20), that proliferate in the absence of LIF for over one year (Stewart, ¶ 23), and that can form trophoblast (Stewart, ¶ 20).

Equating derivation and maintenance of mouse ES cells in culture medium containing LIF in place of a feeder layer, the Examiner asserts that Williams teaches isolation of ES cells from animal embryos (blastocyst), and maintenance of ES cells in vitro in culture medium containing LIF. LIF cannot substitute for feeder layers when human ES cells are isolated and Williams' method is only applicable to mouse ES cells by Williams' own admission (Cherny/Williams, *Reprod. Fertil. Dev.* 6: 569-75 (1994), and Williams file history). Therefore, the Examiner's assertion holds no weight.

The Examiner next asserts that Williams teaches that the ES cells are capable of indefinite proliferation in vitro in an undifferentiated state. The Examiner stretches the point in two regards. First, if human ES cells were grown in LIF in the absence of a feeder layer as is taught in Williams, they would not proliferate at all, because human ES cells are LIF independent and they would differentiate instead of proliferating if grown in LIF (Thomson et al., 1995, *PNAS* 92:7844-7848; Thomson et al., 1996 *Biol. Reprod.* 55:254-259 Stewart, ¶ 23). Second, 20 weeks as disclosed in Williams is simply not over one year. Williams does not even teach undifferentiated proliferation of mouse ES cells for over one year let alone teach proliferation of human ES cells for over one year. What Williams teaches is that the artisan should isolate and grow non-mouse ES cells in LIF in order to accomplish proliferation of those cells in an undifferentiated state for 20 weeks. This teaching is inoperable, as Williams later admits (Cherny/Williams, *Reprod. Fertil. Dev.* 6: 569-75 (1994)).

Next the Examiner asserts that the ES cells taught by Williams "maintain karyotype in which all chromosomes are characteristics of the primate species and noticeably altered through culture." This is simply not true. The words "karyotype" and "chromosome" nowhere appear in Williams and human ES cells that maintain karyotype for over one year cannot be gleaned out of a reference that does not teach or enable human ES cells at all. Even when the reference is held to enable the cells it does disclose, namely mouse ES cells, properties are ascribed to those cells by the Examiner that are nowhere taught in the reference.

The Examiner states that there is no structural difference between the pluripotential human ES cells disclosed by Williams and the claimed ES cells (page 20 of the Office Action). There are many structural differences between Dr. Thomson's cells

and the cells of Williams. Williams does not disclose human ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, '806 patent (Stewart , ¶ 20), that proliferate in the absence of LIF for over one year (Stewart , ¶ 23). Further, as noted by Dr. Stewart in his Declaration, the art did not know that human ES cell lines could spontaneously differentiate into trophoblast until the present invention. The art did know that murine ES cells would *not* differentiate into trophoblast; but the art did not know that a purified preparation of human ES cells could differentiate into trophoblast because such cells were not yet in the art (Stewart , ¶¶ 20, 21). There are patentably distinct structural differences between Williams' cells and the presently claimed cells.

For at least the above reasons, the rejection of claims 1-8 and 11 under 35 U.S.C. § 102(b) over Williams should be reconsidered and be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-8 and 11 under 35 U.S.C. §103(a) as being obvious over Williams. The Patent Owner respectfully traverses this rejection for the following reasons.

Williams does not disclose human ES cells that differ from mouse ES cells in the expression of five (5) markers. See Table 1, '806 patent (Stewart , ¶ 20), that proliferate in the absence of LIF for over one year (Stewart , ¶ 23), that form trophoblast (Stewart , ¶ 20).

According to the Supreme Court ruling in *Graham v. John Deere*, 383 U.S. 1 (1960), in making a case for obviousness, the Examiner must 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. These principles have just been reconfirmed in *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350 (Slip Op. April 30, 2007).

In *KSR Int'l Co.*, the US Supreme Court restated the requirements for a finding of obviousness. Encouraging the application of common knowledge and common sense, the Court took care to guard against hindsight bias and *ex post* reasoning and to distinguish the predictable from the unpredictable arts ("If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." [Emphasis added.]). The field

of stem cell culture can only be viewed as a highly unpredictable art (in contrast to the throttle pedals of KSR). Because the skilled person in this art understands the significant unpredictability associated with primate/human ES cell isolation, the rejection of the claims under §103 could only have been made with hindsight bias and *ex post* reasoning in the face of Dr. Thomson's success.

When applying 35 U.S.C. § 103, the following tenets of patent law must be followed: 1) the claimed invention must be considered as a whole; 2) the references must be considered as a whole; 3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and 4) reasonable expectation of success is the standard with which obviousness is determined (MPEP § 2141 II).

The deficiencies in Williams discussed elsewhere herein, although not repeated here, are equally applicable to the rejection of claims 1-8 and 11 under 35 U.S.C. §103(a) over Williams. Nowhere does Williams teach, enable or otherwise disclose a purified preparation of human ES cells as encompassed by the claims. Williams does not disclose any cell that proliferates for over one year in an undifferentiated state that maintains a normal karyotype. Williams does not teach the skilled artisan even how to arrive at such a cell. Rather, Williams defines long term maintenance as being twenty two passages (approximately 100 cell generations or 10 weeks of culture). Williams suggests that the mouse ES cells can be maintained for up to 20 weeks. Maintaining cells in culture for twenty weeks is not even close to the over one year time period achieved by Dr. Thomson's cells. Williams does not address karyotype or even chromosomal structure in his cells.

When viewed as a whole, a skilled artisan would understand that Williams is directed to the advantages of LIF in isolating and maintaining ES cells obtained from mice. In fact, the first line of the Williams specification states:

“This invention relates to the use of a previously discovered and characterized molecule, leukaemia inhibitory factor (LIF), in the isolation and propagation of embryonic stem cells in vitro.”

Williams then states in column 3, lines 6-16:

“Thus, the invention extends to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish This invention also includes the use of LIF in culture media to modulate the survival and growth of human and other animal species”

But this is simply not true as Williams himself declares in Cherny (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75), along with others (Piedrahita et al., 1990, *Theriogenology* 34: 879-901, and Stewart, ¶¶ 22, 23, 30-32). Williams’ own publication and those of others recited herein, evidences the enormous unpredictability in this art.

How can Williams be considered to render the present claims obvious when Williams himself admits that his technology would not suffice to isolate ES cells from other species? A major point of the Cherny/Williams reference is to provide a review of the ES cell field and how the successful methodology of isolating murine ES cells can be applied (or otherwise cannot be applied) to domestic animals. Cherny states:

“initial research into the isolation of domestic animal ES cells in our and other laboratories attempted to repeat the work carried out in mice by isolating cell lines directly from cultured preimplanted embryos. Published reports of such studies in pigs, cattle and sheep, together with our own research, indicated that cells which display some ES cell characteristics could be identified but the isolation of proven, pluripotential ES cell lines remained elusive.”

Even Hogan (U.S. Patent No. 5,690,926; hereafter “Hogan”) also cited by the Examiner against the present claims, admits in the file history of her patent that the generation of human ES cells from pre-implantation embryos was unpredictable (see reference to Hogan ‘926 below).

There can be no reasonable expectation of success here. It would have been unreasonable for a skilled artisan to apply the murine model disclosed in Williams or other references, to humans in light of the many failures by others in doing so. (Stewart, ¶¶ 12, 22, 27, 28, 30, 32.)

This rejection is the first of several based on § 103 in this Action. Even if the Examiner had successfully made a *prima facie* case for an obviousness rejection, that case would be rebutted by the objective indicia of nonobviousness that are recounted earlier in this Response and accumulated in Attachment A. The inventor, Dr. Thomson,

has received – and continues to receive – wide acclaim for his invention - isolation and cultivation of human/primate ES cells. Were the invention obvious, others would not have repeatedly failed to accomplish it and such scientific and professional acclaim would not have been ascribed to its discoverer.

The subject art is complicated and unpredictable. (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-8 under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103 as being obvious over Hogan (U.S. Patent Nos. 5,453,357 and 5,690,926; Hogan ‘357 and Hogan ‘926)

Rejection under 35 U.S.C. §102(e)

Claims 1-8 and 11 were rejected under 35 U.S.C. §102(e) as being anticipated by Hogan ‘357 and Hogan ‘926. The Hogan patents cannot anticipate the present invention because they fail to disclose each and every element of the claims, either inherently or expressly. Hogan does not show the identical invention in as complete detail as is contained in the present claims, rather Hogan shows culture of a different cell type obtained from a different starting source and having a different cell surface marker and therefore Hogan’s cells are different cells having characteristics distinct from those claimed by Dr. Thomson.

Hogan's cells are derived from primordial germ cells from post-implantation embryos, and therefore, are not the present embryonic stem cells derived from pre-implantation embryos. Hogan admits as much in the file history of the ‘956 patent where she states:

“At the time of the applicants invention it was known that other labs had tried very hard to isolate pluripotent embryonic stem cells from rat, pig and sheep without success. What seems to happen is that the inner cell mass cells differentiate very easily into endoderm and they fail to proliferate further as pluripotent embryonic stem cells. (In fact, there have been reports within the last year of success in obtaining cells from Rhesus monkey blastocysts and perhaps one recent success from rat blastocysts.) In view of the perceived problems isolating pluripotent stem cells from blastocysts and the differences between early embryos in divergent species, one skilled in the art would not expect that methods of obtaining stem cells from mice blastocysts would be directly applicable to other species.

Importantly, applicant’s claimed invention does not use blastocysts to derive embryonic stem cells. Applicant uses a very different method to derive embryonic stem cells. As disclosed throughout the application and the murine and human primordial germ cell Examples, applicant’s embryonic stems cells are derived from primordial germ cells dissected from post-implantation embryos.”

(See Amendment dated June 4, 1996 responding to the December 4, 1995 Office Action in Application Serial No. 08/217,921, now U.S. Patent No. 5,690,926).

For this reason, Hogan’s cells are also known in the art as embryonic germ (EG) cells (Stewart, ¶ 26).

The Patent Owner does not understand how the Examiner can pick and choose some, but not all the characteristics of Hogan’s cells to support an anticipation rejection, either inherently or otherwise. Anticipation, inherent or otherwise, cannot rely on picking and choosing some but not all characteristics of a prior art composition. The Examiner conveniently ignores the fact that Hogan’s cells are SSEA-1 positive, whereas the presently claimed cells are SSEA-1 negative. Table 1, ‘806 patent; Stewart, ¶ 27. Such picking and choosing cannot be used to support a rejection based on anticipation.

The Examiner is silent on the issue of trophoblast formation by Hogan’s cells when induced to differentiate. This is because Hogan’s cells cannot form trophoblast when induced to differentiate (Stewart, ¶ 27). Hogan’s cells are EG cells, not the ES cells of the present invention. EG and ES cells are not equivalents in how they are created, where they are derived from, and what they can differentiate into. Hogan is inapplicable and irrelevant as an anticipation reference.

Each and every element of the claims is not disclosed in Hogan and therefore the rejection of claims 1-8 and 11 under 35 U.S.C. § 102(e) over Hogan should be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-8 under 35 U.S.C. §103(a) as being obvious over Hogan '357 and 'Hogan 926. The Examiner asserts that the Hogan patents disclose ES cells and methods to isolate these cells, and therefore it would have been obvious to one of skill in the art to use the teachings of Hogan to arrive at the presently claimed invention. The Patent Owner respectfully traverses this rejection.

The deficiencies of both Hogan patents discussed above are equally applicable to the instant rejection of claims 1-8 under 35 U.S.C. §103(a) over these references.

Hogan teaches EG cells derived from primordial germ cells obtained from post-implantation embryos. Hogan's methods for isolating her cells, and the characteristics of those isolated cells cannot render obvious a purified preparation of human embryonic stem cells obtained from pre-implantation embryos. There is nothing in Hogan that points the skilled artisan to the presently claimed human ES cells. Following Hogan and without the benefit of hindsight afforded by the present patent, the skilled artisan would expect to isolate EG cell lines that are SSEA-1 positive and that cannot form trophoblast when induced to differentiate. Further, there is no expectation of success that a purified preparation of human ES cells would be obtained following the teaching of Hogan.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his discovery. In view of these facts, together with the differences between

the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Neither of the Hogan patents render the present claims obvious and the rejection should be withdrawn.

Rejection of claim 11 under 35 U.S.C. § 102(a) or in the alternative, under 35 U.S.C. § 103(a) as obvious over Bongso

The Examiner rejected claim 11 under 35 U.S.C. §102(a) as being anticipated or in the alternative as being obvious under 35 U.S.C. § 103(a) over Bongso (Human Reproduction, vol. 9, No. 11, 1994). The Examiner asserts that Bongso discloses an ES cell line from primate/human blastocyst and that Bongso's ES cells are derived from a substantially identical method as recited in claim 9. Therefore the Examiner contends that the subject matter of claim 9 is the same or an obvious variation of the reference teachings.

In the Notice of Allowability dated March 17, 1998, in the file history of the present patent, the Office conceded that Bongso did not teach or fairly suggest primate/human ES cells which are stable in *in vitro* culture for longer than one year. The Examiner has specifically avoided this feature.

Bongso cannot anticipate claim 11 nor render it obvious. Bongso's cells were only capable of proliferating for two passages (page 2114 in Bongso: "After the second subculture, the cells differentiated into fibroblasts or died."). Dr. Thomson's cells are capable of proliferating for over one year. Bongso's cells are not the presently claimed cells.

Even more importantly, in a subsequent publication by Bongso (Rubinoff et al., 2000, Nature Biotechnology 18:399-404), referring to the presently cited reference and Dr. Thomson's work, in the background section of this paper (page 399), Bongso states:

"More recently Thomson and colleagues reported the isolation and characterization of diploid rhesus and marmoset monkey ES cells with extensive capacity for differentiation (Thomson et al., 1995, PNAS 92:7844-7848; Thomson et al., 1996 Biol. Reprod. 55:254-259). These monkey ES cells resemble human EC stem cells in their morphology, marker expression, and lack of response to LIF. Earlier we described the characteristics of primary cultures of undifferentiated cells from the human blastocyst that were able to undergo limited

replication in vitro (Bongso et al., 1994, Hum. Reprod. 9:2110-2117). Since these early studies did not use embryonic feeder cell support (required for proliferation of pluripotent human EC and nonhuman primate ES cells) but relied instead on LIF supplementation of the culture medium, these cells eventually underwent differentiation or death. Therefore, we subsequently employed a culture system incorporating embryonic fibroblast feeder cell layers to derive human ES cells from blastocysts. While this work was in progress, Thomson and coworkers reported the derivation of ES cell lines from the human blastocyst. We confirm these results and extend the characterization of the human ES cell phenotype."

Bongso admits that Dr. Thomson was the first to invent primate/human ES cells. Bongso states that he did not isolate primate/human ES cell lines. The unpredictable nature of the art of embryonic stem cell isolation would not support even a rejection for obviousness, much less anticipation as is alleged here.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his discovery. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

The rejection over Bongso should not stand.

Rejection of claims 1-11 under 35 U.S.C. § 103(a) over either Robertson I, Robertson II, Piedrahita, separately or together in view of Williams ('065) and Hogan ('926)

The Examiner rejected claims 1-11 as being obvious either Robertson I, Robertson II, Piedrahita, separately or together in view of Williams and Hogan ('926). The Examiner contends that the Robertson I and II and Piedrahita cells meet all of the

standard criteria for pluripotential ES cells and that this combination teaches mammalian ES cells. The Examiner then states that Williams teaches the same method as Robertson I, II and Piedrahita reference and also encompasses human ES cells. Therefore, the Examiner asserts that Williams motivates the skilled artisan to combine the teachings of Robertson I and II and Piedrahita with Williams to isolate ES cells from primates/humans. Further, the Examiner states that Hogan provides additional motivation for the isolation and maintenance of human ES cells in vitro for longer periods. The Patent Owner respectfully traverses this rejection.

Robertson I and II each describe the initiation and culture of mouse ES cells. Neither Robertson reference teaches or suggests that any of their methods or techniques are applicable to other any other species. Neither reference provides data or suggests that the techniques could be successfully applied to other species. The existence of mouse ES cells is acknowledged in the Background section in the present patent. Robertson I and II do no more than establish the state of the art at the time, that is, that mouse ES cells could be isolated.

The Examiner misreads Piedrahita. Piedrahita does not teach porcine (pig) or ovine (sheep) ES cells capable of culture for more than one year. In fact this reference teaches that the methods used to create and culture mouse ES cells could not be made to work on porcine and ovine systems. While some cell cultures were initiated, ES cells as defined in the art were not in fact created from pig or sheep embryos as reported by Piedrahita. Piedrahita makes this clear in the Abstract section of the article. For example, Piedrahita states that:

“While murine isolated ICM or intact embryos plated on STO or HEF feeders gave rise to cell lines with embryonic stem cell-like (ES-like) morphology, ovine embryos did not,” and “porcine ES-like cells did not undergo observable differentiation in vitro.” (See second sentence of the Abstract)

The main body of Piedrahita explains these conclusions in greater detail – see for example, page 894 of Piedrahita where it is stated that porcine ES-like cells did not differentiate when induced to do so. Further, in the discussion section of Piedrahita, it is noted that: “differences were observed in the type of colonies that could be isolated from each species.” (Page 896 of Piedrahita.) Only epithelial cells could be derived from

ovine embryos and the porcine cell lines created by Piedrahita did not differentiate. In light of these data, Piedrahita writes: “One explanation is that the trigger for induction of differentiation varies with species.” (Page 896 of Piedrahita.) In fact, Piedrahita, in the last sentence of the article on page 897, offers that they do not know why the difficulties with the ovine and porcine systems arose, and do not know if the problems reside in the source materials, the age of the embryos, or the culture conditions.

What Piedrahita actually teaches is that the methodologies used to initiate ES cell cultures in the mouse did not work when applied to other animal systems and, at least at the time of publication of Piedrahita, no methods were known to those skilled in the art for making ES cells in other species. The present patent addresses the difficulties posed by Piedrahita beginning at column 3 line 49.

Thus, citation of Piedrahita by the Examiner adds no new support for an obviousness rejection. When this reference is taken as a whole, Piedrahita teaches that when the methods used to create murine ES cells are applied to pig and sheep, ES cells as encompassed by the present claims, are not made. In other words, Piedrahita teaches away from applying the murine system to other species and therefore teaches away from the presently claimed invention.

Williams adds nothing to support the Examiner’s case, particularly in light of his statements in Cherny/Williams (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75). Further, when taken as a whole, Williams is directed to the use of leukemia inhibitory factor (LIF) to aid in the creation and culture of embryonic stem cell lines in vitro. Williams teaches that the use of LIF substitutes for the use of feeder layers otherwise needed to maintain mouse embryonic stem cell lines in an undifferentiated state (see column 1 lines 51-62 and column 3 lines 62-65). The central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells (Stewart, ¶ 23).

With respect to Hogan, the Examiner contends that Hogan would motivate the maintenance of primate/human cells in vitro for a long period of time. This is incorrect. Hogan’s cells are post-implantation embryo derived EG cells, not ES cells and Hogan herself admits in her file history that techniques used on mouse ES cells do not render

obvious human ES cell isolation. The skilled artisan, upon reading Hogan, would not be motivated to follow Hogan to arrive at the presently claimed cells.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his discovery. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

None of the cited references alone or together can support the obviousness rejection in the face of these facts.

Conclusion

For all the reasons stated above, the Patent Owner respectfully requests reconsideration and withdrawal of the rejections of the claims 1-11 as presently presented and allowance of new claims 12-14.

A copy of this response is being served on the Third Party Requester, per the Certificate of Service attached hereto.

WISCONSIN ALUMNI RESEARCH FOUNDATION



Date: May 30, 2007

By:

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ATTACHMENT A

ATTACHMENT B

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of this paper is being served on the Requester, The Foundation for Taxpayer and Consumer Rights, through its counsel:

Daniel B. Ravicher, Esq.
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
New York, NY 10018

via overnight delivery service on the date shown below.

May 30, 2007
Date

Joseph R. DelMaster, Jr.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination of U.S. 7,029,913

Art Unit: 3991

Inventor: Thomson, J.

Examiner: Gary L. Kunz

Control No.: 95/000,154

RESPONSE TO FIRST OFFICE ACTION

Attn: MAILSTOP: *INTER PARTES* REEXAM

Central Reexamination Unit

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

This is a response to the first Office Action received in the matter of *Inter Partes* Reexamination No. 95/000,154 for U.S. Pat. 7,029,913 (“the ‘913 patent”). The response is being filed within the two-month period for response set in the Action, which was mailed March 30, 2007. No fees are believed to be due.

Claims 1-3 are under reexamination and are rejected. There are no amendments to the specification or drawings. Claims 1-3 have been amended.

A list of the claims begins on page 2.

The Patent Owner’s response to the claim rejections in the Office Action commences on page 3.

A Declaration of Colin Stewart, D. Phil., is submitted with this Response and is incorporated herein in its entirety.

Attachment A is a collection of publications evidencing the acclaim accorded Dr. Thomson as a direct result of his invention relating to the culturing and characterization of primate/human embryonic stem cells.

Attachment B is a collection of documents referenced in this Response and in the accompanying Stewart Declaration.

The following is a complete listing of the claims and replaces all prior claim listings:

1. (Currently amended) A replicating in vitro cell culture of human embryonic stem cells derived from a pre-implantation embryo, the culture comprising cells which (i) are capable of proliferation in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor, (ii) maintain a karyotype in which the chromosomes are euploid through prolonged culture, (iii) maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) are inhibited from differentiation when cultured on a fibroblast feeder layer.

2. (Currently amended) The [preparation] in vitro cell culture of claim 1, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. (Currently amended) The [preparation] in vitro cell culture of claim 1 wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, and express alkaline phosphatase.

REMARKS

Claims 1-3 are pending in the reexamination of the instant patent and stand rejected. Claims 1-3 have been amended herein. Reconsideration and withdrawal of the rejection of claims 1-3 is respectfully requested.

Claim Amendment Summary

Claim 1 has been amended to recite that the cells are derived from a pre-implantation embryo. Support for this amendment is found in the specification at least in column 8, lines 34-42, and column 9, lines 29-33.

Claims 2 and 3 have been amended to correct a typographical error and provide antecedent basis from claim 1. No new matter has been added by way of these amendments.

The Invention

Dr. James A. Thomson (Dr. Thomson) invented a novel replicating in vitro cell culture of human embryonic stem cells. There is no dispute that prior to Dr. Thomson's landmark invention, mouse ES cells were known as were methods of making them. There is no dispute that Hogan reported the isolation of embryonic germ (EG) cells in U.S. Patent No. 5,690,926. Nonetheless, mouse ES cells and Hogan's EG cells are not Dr. Thomson's claimed primate/human ES cells.

Dr. Thomson's primate/human ES cells differ from mouse ES and Hogan's EG cells by source of sample, marker expression and by function. For example:

- Primate/human ES cells are SSEA-1 negative, while mouse ES and Hogan's EG cells are SSEA-1 positive;
- Dr. Thomson's cells are derived from pre-implantation embryos; Hogan's EG cells are derived from post-implantation embryos;
- When primate/human ES cells are cultured in leukemia inhibitory factor (LIF) in the absence of a feeder layer, they differentiate; in contrast, mouse ES cells can be propagated in an undifferentiated state in the presence of (LIF) in the absence of feeder layers;

- Primate/human ES cells can differentiate into trophoblast that produce chorionic gonadotrophin; in contrast, neither mouse ES nor Hogan's EG cells can differentiate into trophoblast;
- Colonies of primate/human ES cells are more compact and distinctly flatter than mouse ES cell colonies.

Further, at the time of Dr. Thomson's invention, there was no reasonable expectation of success that mouse ES cell derivation protocols could be used to isolate primate/human ES cells based on the experience in the field at the time of Dr. Thomson's discovery. It was long recognized that the techniques used to isolate mouse ES cells were unpredictable and were not universally applicable to the isolation of ES cells from other species, or even from different strains of mice. Further, for nearly two decades from the discovery of mouse ES cells, others repeatedly tried and failed to isolate non-murine ES cells, particularly primate/human ES cells. See Declaration of Colin Stewart, D. Phil. (hereafter, Stewart, ¶ #).

The level of acclaim in the art for Dr. Thomson's invention bears witness to the fact that the isolation of primate/human ES cells represented true innovation that was not simply a small step in embryonic stem cell research. Examples abound (see Attachment A):

- In 2005, the American Association for the Advancement of Science (AAAS), founded in 1848, identified as one of the most significant "Milestones of Science" the work of Dr. Thomson, specifically, growing embryonic stem cells that may be used to create other types of cells.
- In 2001, Dr. Thomson was profiled in TIME magazine as one of the doctors "who are changing our world." Calling him "The man who brought you stem cells," TIME – like so many others – recognized Dr. Thomson as the scientist who had first isolated human embryonic stem cells.
- Dr. Thomson was a recipient of the Golden Plate Award presented by the American Academy of Achievement in 1999, whose honorees have included – in the scientific fields alone – famed explorer Robert Ballard, oral polio vaccine inventor Dr. Jonas Salk, Nobel Prize Chemist Dr. Linus Pauling, astronaut Dr. Sally Ride, and renowned physicist Dr. Edward Teller. Dr. Thomson was cited

for his “recent breakthrough in culturing human embryonic stem cells outside the body.”

- Dr. Thomson was inducted into the Biotech Hall of Fame in 2001, which noted that Dr. Thomson had “successfully isolated and cultured human embryonic stem cells” and that the work had “set the stage for a revolution in medicine and science.”
- In 2003, Dr. Thomson was named a winner of a World Technology Summit Award in Health & Medicine, sponsored by the World Technology Network, which comprises leading corporations and individuals in technology-related fields. The World Technology Awards “are presented each year to the outstanding innovators from each sector within the technology arena.”
- In 2002, Dr. Thomson was selected to receive a \$100,000 research grant to continue his work on stem cells. The announcement of the award recognized Dr. Thomson as “the first person to isolate stem cells from human embryos.” The LIFE International Research Award “is presented to internationally renowned scientists whose research has led to clinical applications.”
- The Christopher Columbus Fellowship Foundation awarded its Frank Annunzio Award Columbus Scholar accolade to Dr. Thomson in 2003, together with a \$50,000 research grant. The award announcement cites Dr. Thomson as “the first to isolate and culture nonhuman primate embryonic stem cells in 1995 and human ES cells in 1998.” It noted that Dr. Thomson’s research “has encouraged scientists around the world” about the possibilities for human stem cells.
- The American College of Veterinary Pathologists honored Dr. Thomson in 2004 with its Outstanding Achievement Award, which is presented to a member that “performs extraordinary acts or makes an extraordinary contribution that brings great credit to themselves and the discipline of veterinary pathology.” (Dr. Thomson was trained as a doctor of veterinary medicine.) Again he was cited for his work with embryonic stem cells.
- The American Association for Laboratory Animal Science bestowed its Nathan R. Brewer Scientific Achievement Award on Dr. Thomson in 2006 for his discoveries in the field of embryonic stem cells.

It cannot be denied that Dr. Thomson has made a landmark invention that was unknown, unpredictable and long overdue in the art. Dr. Thomson's invention embodies the very definition of a new and useful, novel, and non-obvious invention. Dr. Thomson alone has laid out the groundwork for a plethora of studies on primate/human ES cells that are rapidly driving the field toward remarkable clinical application and Dr. Thomson is entitled to a patent on his discovery.

No Joint Inventors

On page 8 of the Office Action, there appears a statement that the application currently names joint inventors. This is incorrect. There is only one named inventor of this patent, Dr. James A. Thomson.

Rejection of claims 1-3 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being obvious over Williams

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-3 under 35 U.S.C. §102(b) as being anticipated by Williams or further in view of the patent disclosure citing *Ex parte Novitski*. The Examiner asserts that the ES cells disclosed by Williams contain, either expressly or inherently, all of the characteristics of the human ES cells as encompassed in the pending claims. The Patent Owner respectfully traverses this rejection.

Inherent Anticipation Cannot Apply When the Art Does Not Disclose The Invention

Human ES cells, let alone a replicating in vitro cell culture of the same, were not known in the art prior to the landmark invention of Dr. Thomson.

According to *In re Best*, 562 F.2d 1252, 1254-55, 195 U.S.P.Q. 430 (C.C.P.A. 1977), where *In re Best* cites *In re Swinehart*, 439 F. 2d 210 (1971),

“[I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by *things* in the prior art, does not cause a claim drawn to those *things* to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the

applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Swinehart, 439 F.2d at 212-213. [Emphasis added.]

Here, this standard for inherent anticipation does not apply. The *things* claimed by Dr. Thomson, namely, a replicating in vitro cell culture of human ES cells, *were not in the prior art*. The applied prior art neither explicitly nor inherently teach a replicating in vitro cell culture of human ES cells. Simply stated, the replicating in vitro cell culture of human ES cells disclosed in the present patent did not previously exist. They differ markedly from prior art murine ES cells (Williams '065) and Hogan's EG cells (Hogan '926) and the cells of the other prior art references, which cells do not share the claimed features. There is no composition in the cited prior art that is a replicating in vitro cell culture of human ES cells that are capable of proliferation for over one year without the application of exogenous LIF as claimed in present claim 1.

Anticipation Requires that all Claim Elements be Present

Williams lacks all of the claimed elements. Williams does not disclose a replicating in vitro cell culture of human ES cells capable of proliferation without addition of LIF.

Williams' cells require LIF (Stewart, ¶ 23). Williams makes the mere suggestion, later retracted by Williams himself (Cherny et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75: “[t]he murine model for totipotential stem cell isolation is yet to prove applicable to domestic animals”, page 574), that his method is applicable to the isolation of ES cells from other species, including humans. Williams described a method of making mouse ES cells and merely suggested its efficacy for humans, which proved to be wrong in practice. This does not rise to the legal standard for anticipation.

It is hornbook law that “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. “ MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). “The identical invention must be shown in as complete detail as is contained in the . . . claim.” *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore,

Williams must describe each and every element of claims 1-3 in order to anticipate these claims under 35 U.S.C. §102(b). The Williams reference does not satisfy this requirement.

Even the Examiner's efforts to string together a disclosure that includes all of the elements of the present claims fails. The Examiner refers to specific sections in Williams that are simply incorrect. For example:

On page 10 of the Office Action, the Examiner cites Williams column 2, lines 30-40; column 3, lines 35-47; column 4, lines 18-19; and column 6, lines 50-66 as disclosing "human embryonic stem cells...method for preparing such embryonic stem cells which is essentially the same procedure as disclosed by Thomson". This is not correct. At, column 2, lines 30-40, Williams states:

"Accordingly, a first aspect of the present invention relates to a method for the isolation of embryonic stem (ES) cells from animal embryos in vitro which method comprises deriving ES cells from said embryos in culture medium, **said culture medium containing an effective amount of leukaemia inhibitory factor (LIF)**, for a time and under conditions sufficient for the development of said ES cells." (Emphasis added)

Williams does not disclose the same or even the essentially same procedure encompassed by the present claim 1 which explicitly states that the human ES cell culture grows in the absence of LIF.

The Examiner continues on page 10 of the Office Action to cite to sections of Williams that simply do not disclose what the Examiner says Williams discloses. For example:

- (3) column 3 lines 1-3 does not describe plating inner mass cells on embryonic fibroblasts, but does describe plating the cells in LIF;
- (4) column 8, lines 29-31 does not disclose dissociating the mass into dissociated cells, in fact, Williams nowhere discloses dissociation of the cells at all;
- (5) column 8, lines 29-31 does not disclose replating the dissociated cells on embryonic feeder cells (or LIF alone);
- (7) column 6, lines 65-66 does not disclose culturing ES cell colonies on embryonic feeder layers or with LIF alone;

- Last paragraph on page 10 – column 4, line 65 to column 5, line 5 of Williams does not disclose proliferation for over one year without the application of exogenous leukemia inhibitory factor. The only references in this section to propagation of cells discloses that they are propagated in LIF, not in its absence. Moreover, the disclosure of 20 passages in this section is simply not over one year as the Examiner alleges.
- On page 11 of the Office Action, the Examiner states that Williams’s cells maintain karyotype. The words karyotype or chromosome nowhere appear in Williams.

Williams simply does not disclose what the Examiner says Williams discloses. Even if one looks elsewhere in Williams, one cannot find what the Examiner says Williams discloses. This goes to the heart of the Examiner’s inherency argument which fails under the correct interpretation of the facts.

One skilled in the art cannot consider Williams to teach an all-purpose recipe for isolating and culturing embryonic stem cells from all species so that a replicating in vitro cell culture of human ES cells is obtained. Instead, Williams’ contribution to the art is one discrete advancement to the then-current state of the art, namely that feeder layers, previously required in murine embryonic stem cell cultures, can be replaced by leukemia inhibitory factor (LIF) when isolating mouse ES cells. Even Williams’ speculation that his methods are applicable to non-murine species have proven untrue for primate/human ES cells because derivation and maintenance of primate/human ES cells is independent of LIF. (Stewart, ¶ 23).

Anticipation Requires Enablement

Williams does not enable a replicating in vitro cell culture of human ES cells that are capable of proliferation for over one year in the absence of exogenous LIF.

In a recent case, the Federal Circuit has reaffirmed that “to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art.” *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366, 1381 (Fed.Cir. 2006). The legal standard for an enabling anticipatory reference, requires that the prior art reference teach one of ordinary skill in the art to

make or carry out the claimed invention *without undue experimentation*. [Italics added.] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 (Fed.Cir. 2006); *Elan Pharmaceuticals, Inc. v. Mayo Foundation*, 346 F.3d 1051, 1053 (Fed.Cir. 2003). Enablement is a question of law based on underlying facts. *Minnesota Mining & Mfg. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed.Cir. 2002). Enablement is clearly a necessity for anticipation and Williams is not an enabling reference for human ES cells.

An anticipatory reference must place the public in possession of the invention. *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985). It is not enough for a reference to simply suggest that the disclosure contained therein can be used in a different way that is neither described nor enabled in the prior art reference, and be effective as an anticipatory reference for the unsupported suggestion.

The Examiner applies Williams as anticipating a replicating in vitro cell culture of human ES cells based only on the suggestion that the methods disclosed therein for murine cells would be applicable to human ES cells. It is not enough to simply note that Williams states that his method would “extend to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish...” (col. 3 lines 6-8), without more. Williams does not disclose any means for derivation of human or primate ES cells and if the skilled artisan followed Williams and applied the methods disclosed therein to human ES cell isolation, the artisan would fail (Stewart, ¶ 24). Even Williams himself could not extend his methods to the isolation of ES cells from other non-murine mammals (Cherny et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75: “[t]he murine model for totipotential stem cell isolation is yet to prove applicable to domestic animals”, page 574; and Stewart, ¶ 22). Here, if the Williams method was followed, according to Williams in Cherny/Williams (*Id*), ES cells would not be isolated from any non-murine species.

Some considerations that aid in determining the enabling character of a reference are: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented [in the reference], (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 838 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir. 1988).

Williams fails as an enabling anticipatory reference for the claimed invention under the *Wands* analysis for the following reasons: (1) the quantity of experimentation necessary was great as evidenced by how many others tried and failed to isolate human ES cells (Stewart, ¶¶ 22, 27, 28, 30, 31, 32); (2) there is simply no guidance for isolating human ES cells in the Williams reference (Stewart, ¶¶ 22-25); (3) there are no working examples of the isolation of human ES cells in the reference; (4) the nature of the invention by Dr. Thomson is the first isolation and culture of human ES cells, for which he is widely acclaimed (See Attachment A); (5) there were no examples of methods for isolating human ES cells in the art; in light of Williams' own subsequent statements, the skilled artisan would conclude that Williams' method cannot be used to isolate a human ES cell line, (6) even where the relative skill level of those skilled in the art is very high (Ph.D. level) (Stewart, ¶ 12); (7) in a very difficult and unpredictable art. Further (8), the claims specifically recite "a replicating in vitro cell culture of human embryonic stem cells," are not overly broad and do not read on mouse ES cells. A practitioner reading the cited references could not arrive at the presently claimed invention. Williams does not place the public in possession of the claimed invention.

Williams does not teach an all-purpose recipe for isolating and culturing embryonic stem cells from all species. Williams requires undue experimentation in order to practice the present invention and does not place the public in possession of the claimed invention as evidenced by Williams in Cherny/Williams, *Reprod. Fertil. Dev.* 6: 569-75 (1994).

Consistent with the state of the art and what Cherny and Williams published, even the Patent Office viewed the disclosure of Williams as not being enabled for anything more than murine ES cells and methods of isolating/culturing them. Throughout the file history of the Williams patent (and related patent applications), Williams was never able to overcome the Examiner's enablement rejection of claims encompassing non-murine ES cell culture. Since the application that matured into U.S. patent number 5,166,065 was filed in 1990, the consistent position of the U.S. Patent and Trademark Office and of the Examiners handling the Williams' patent applications over 17 years is that Williams *et al.* enabled only murine ES cell isolation and culture. The Patent Owner finds no basis in the Examiner's comments for a change in the Patent Office's position now and

respectfully maintains that Williams does not enable human embryonic stem cell isolation and, as such, cannot anticipate the present claims.

The failure by Williams eviscerates the “teaching” in his patent reference - and relied on by the Examiner - that his mouse ES cell method was equally applicable to a list of animals (cows, pigs, sheep, etc.) when, in fact, it was not. Its application to humans was never shown either. This failure further evidences the unpredictability of this art. (Stewart, ¶¶ 31, 32).

Failure of Others is Evidence of Non-Enablement

Besides Williams, many others failed to isolate ES cells from any non-murine species prior to Dr. Thomson’s invention. In fact, Dr. Stewart recites a long list of publications that disclose clear failure by others to isolate ES cell lines from non-murine species including rat, hamster, sheep, pig and even human (Stewart, ¶ 12-15).

Evidence of failure by others is found in:

- Brook and Gardner, 1997, PNAS 94:5709-5712, Brook et al., 2003, Diabetes 52:205-208 – methods used to isolate mouse ES cells are not universally predictable across different strains of mice
- Brenin et al., 1997, Transplant Proc. 29:1761-1765 – rat ES cells were not isolated by Iannaccone et al., 1994, Dev. Biol. 163:288-292, rather Iannaccone’s cells were contaminating mouse ES cells; and Ouhibi et al., 1995, Mol. Reprod. & Dev. 40:311-324 – rat ES cells that can be passaged beyond passage four could not be isolated
- Doetschman et al., 1988, Dev. Biol. 127:224-227 – failure to isolate hamster ES cells capable of long term proliferation
- Piedrahita et al., 1990, Theriogenology 34:879-901 – failure to isolate ovine ES cells and doubtful isolation of porcine ES cells; and a later publication by Moore et al. (including Piedrahita), 1997, In Vitro Cell Dev Biol 33:62-71 showing porcine ES cells were not in fact isolated in the earlier publication
- Talbot et al., 1995, Mol. Reprod. & Dev. 42:35-52 – failure to isolate bovine ES cells

- Bongso, 1994, Human Reprod. 9:2110 – failure to isolate long term cultures of human ES cells; and Rubinoff et al. (including Bongso), 2000, Nature Biotech. 18:399-404 – acknowledgment of the earlier failure and Dr. Thomson’s success.

If others skilled in the art, having the requisite level of knowledge of the art, failed, in repeated attempts, to isolate non-murine ES cells, that failure is strong evidence that the cited references are *not* enabling for anticipation purposes. “Such failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.” *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir. 1985).

The overreaching statements by the Examiner that ES cell lines can be isolated from the embryos of other animals is not enabled, not even for Williams himself. Williams cannot anticipate and the rejection of claims 1-3 under 35 U.S.C. § 102(b) should be reconsidered and withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3 under 35 U.S.C. §103(a) as being obvious over Williams alone, or as further evidenced by the instant patent disclosure for demonstrating inherency, citing *Ex parte Novitski*, 26 USPQ 2d 1389 (Bd. App. & Inter. 1993). The Patent Owner respectfully traverses this rejection for the following reasons.

As a first matter, *Ex Parte Novitski* is inapplicable here. In that case, an obviousness rejection was upheld by the Board of Appeals and Interferences because the cited reference disclosed the claimed method. Here, Williams does not disclose the isolation of a replicating cell culture of human ES cells, and even Williams’ suggestion that his procedures for isolating mouse ES cells does not hold water, according to the Patent Office in the file history of Williams and related applications, and by Williams’ own admission in Cherny (*Id*). Moreover, the “inherent” characteristics of Dr. Thomson’s cells that the Examiner cites from Dr. Thomson’s disclosure, are Dr. Thomson’s actual discovery, his invention. How can a discovery itself render obvious that which was not known?

According to the Supreme Court ruling in *Graham v. John Deere*, 383 U.S. 1 (1960), in making a case for obviousness, the Examiner must 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. These principles have just been reconfirmed in *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350 (U.S. April 30, 2007).

In *KSR Int'l Co.*, the US Supreme Court restated the requirements for a finding of obviousness. Encouraging the application of common knowledge and common sense, the court took care to guard against hindsight bias and *ex post* reasoning and to distinguish the predictable from the unpredictable arts ("If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." Emphasis added.). The field of stem cell culture can only be viewed as a highly unpredictable art (in contrast to the throttle pedals of KSR). Because the skilled person in this art understands the significant unpredictability associated with primate/human ES cell isolation, the rejection of the claims under 35 U.S.C. §103(a) could only have been made with hindsight bias and *ex post* reasoning in the face of Dr. Thomson's success.

When applying 35 U.S.C. § 103, the following tenets of patent law must be followed: 1) the claimed invention must be considered as a whole; 2) the references must be considered as a whole; 3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and 4) reasonable expectation of success is the standard with which obviousness is determined (MPEP § 2141 II).

The deficiencies in Williams discussed elsewhere herein, although not repeated here, are equally applicable to the rejection of claims 1-3 under 35 U.S.C. §103(a) over Williams. Nowhere does Williams teach, enable or otherwise disclose an in vitro replicating cell culture of human ES cells as encompassed by the claims.

Furthermore, Williams does not disclose any cell that proliferates for over one year in an undifferentiated state that maintains a normal karyotype. Williams does not teach the skilled artisan even how to arrive at such a cell. Rather, Williams defines long term maintenance as being twenty two passages (approximately 100 cell generations or 10 weeks of culture). Williams suggests that the mouse ES cells can be maintained for

up to 20 weeks. Maintaining cells in culture for twenty weeks is not even close to the over one year time period achieved by Dr. Thomson's cells. Williams does not address karyotype or even chromosomal structure in his cells.

When viewed as a whole, a skilled artisan would understand that Williams is directed to the advantages of LIF in isolating and maintaining ES cells obtained from mice. In fact, the first line of the Williams specification states:

“This invention relates to the use of a previously discovered and characterized molecule, leukaemia inhibitory factor (LIF), in the isolation and propagation of embryonic stem cells in vitro.”

Williams then states in column 3, lines 6-16

“Thus, the invention extends to the generation and maintenance of ES cells from humans, mice, birds (e.g., chickens), sheep, pigs, cattle, goats and fish This invention also includes the use of LIF in culture media to modulate the survival and growth of human and other animal species”

But this is simply not true as Williams himself declares in Cherny (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75), along with others (Piedrahita et al., 1990, *Theriogenology* 34: 879-901, and Stewart, ¶¶ 22, 23, 30-32). Williams' own publication together with those of others recited herein evidence the enormous unpredictability in this art.

How can Williams be considered to render the present claims obvious when Williams himself admits that his technology would not suffice to isolate ES cells from other species? A major point of the Cherny/Williams reference is to provide a review of the ES cell field and how the successful methodology of isolating murine ES cells can be applied (or otherwise cannot be applied) to domestic animals. Cherny states

“initial research into the isolation of domestic animal ES cells in our and other laboratories attempted to repeat the work carried out in mice by isolating cell lines directly from cultured preimplanted embryos. Published reports of such studies in pigs, cattle and sheep, together with our own research, indicated that cells which display some ES cell characteristics could be identified but the isolation of proven, pluripotential ES cell lines remained elusive.”

Even Hogan (U.S. Patent No. 5,690,926; hereafter “Hogan”), also cited by the Examiner against the present claims, admits in the file history of her patent that the

generation of human ES cells from pre-implantation embryos was unpredictable (see reference to Hogan '926 below).

There can be no reasonable expectation of success here. It would have been unreasonable for a skilled artisan to apply the murine model disclosed in Williams or other references, to primates or humans in light of the many failures by others in doing so. (Stewart, ¶¶ 12, 22, 27, 28, 30, 32).

This rejection is the first of several based on § 103 in this Action. Even if the Examiner had successfully made a *prima facie* case for an obviousness rejection, that case would be rebutted by the objective indicia of nonobviousness that are recounted earlier in this Response and accumulated in Attachment A. The inventor, Dr. Thomson, has received – and continues to receive – wide acclaim for his invention - isolation and cultivation of human/primate ES cells. Were the invention obvious, others would not have repeatedly failed to accomplish it and such scientific and professional acclaim would not have been ascribed to its discoverer.

The subject art is complicated and unpredictable. (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-3 under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103 as being obvious over Hogan (U.S. Patent 5,690,926

Rejection under 35 U.S.C. §102(e)

Claims 1-3 were rejected under 35 U.S.C. §102(e) as being anticipated by Hogan. Specifically, the Examiner asserts that Hogan discloses non-mouse pluripotential stem

cells and therefore meets the limitations of claims 1-3. Hogan cannot anticipate the present invention because Hogan fails to disclose each and every element of the claims, either inherently or expressly. Hogan does not expressly or inherently disclose the present claims. Hogan does not show the identical invention in as complete detail as is contained in the present claims, rather Hogan shows culture of a different cell type obtained from a different starting source and having a different cell surface marker and therefore Hogan's cells are different cells having characteristics distinct from those claimed by Dr. Thomson.

Hogan's cells are derived from primordial germ cells from post-implantation embryos, and therefore, are not the present embryonic stem cells derived from pre-implantation embryos. Hogan admits as much in the file history of her patent where she states:

“At the time of the applicants invention it was known that other labs had tried very hard to isolate pluripotent embryonic stem cells from rat, pig and sheep without success. What seems to happen is that the inner cell mass cells differentiate very easily into endoderm and they fail to proliferate further as pluripotent embryonic stem cells. (In fact, there have been reports within the last year of success in obtaining cells from Rhesus monkey blastocysts and perhaps one recent success from rat blastocysts.) In view of the perceived problems isolating pluripotent stem cells from blastocysts and the differences between early embryos in divergent species, one skilled in the art would not expect that methods of obtaining stem cells from mice blastocysts would be directly applicable to other species.

Importantly, applicant's claimed invention does not use blastocysts to derive embryonic stem cells. Applicant uses a very different method to derive embryonic stem cells. As disclosed throughout the application and the murine and human primordial germ cell Examples, applicant's embryonic stems cells are derived from primordial germ cells dissected from post-implantation embryos.” (See Amendment dated June 4, 1996 responding to the December 4, 1995 Office Action in Application Serial No. 08/217,921, now U.S. Patent No. 5,690,926).

For this reason, Hogan's cells are also known in the art as embryonic germ (EG) cells (Stewart, ¶ 26).

At the bottom of page 13 of the Office Action, the Examiner notes that Hogan is silent on the key properties that actually distinguish Dr. Thomson's cells from Hogan's cells. The Examiner then states that “there are sufficient similarities” to satisfy the § 102 rejection. “Sufficient similarities” is not the test for an anticipation rejection. The

Examiner conveniently ignores the fact that Hogan's cells are SSEA-1 positive, whereas the presently claimed cells are SSEA-1 negative (Table 1, '780 patent; Stewart, ¶ 27), they require exogenous LIF for proliferation (Stewart, ¶ 27; and Hogan '926) and Hogan's cells cannot form trophoblast (Stewart, ¶ 27). Such picking and choosing cannot be used to support a rejection based on anticipation.

Hogan's cells are post-implantation embryo derived EG cells, not the ES cells of the present invention. EG and ES cells are not equivalents in how they are created, where they are derived from, and what they can differentiate into. Hogan is inapplicable and irrelevant as a reference.

Each and every element of the claims is not disclosed in Hogan and therefore the rejection of claims 1-3 under 35 U.S.C. § 102(e) over Hogan should be withdrawn.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3 under 35 U.S.C. §103(a) as being obvious over Hogan. The Examiner asserts that Hogan discloses ES cells and methods to isolate these cells, and therefore it would have been obvious to one of skill in the art to use the teachings of Hogan to arrive at the presently claimed invention. The Patent Owner respectfully traverses this rejection.

The deficiencies of Hogan discussed above are equally applicable to the instant rejection of claims 1-3 under 35 U.S.C. §103(a) over Hogan.

Hogan teaches EG cells derived from primordial germ cells obtained from post-implantation embryos. Hogan's methods for isolating her cells, and the characteristics of those isolated cells cannot render obvious a replicating in vitro cell culture of human ES cells obtained from pre-implantation embryos. There is nothing in Hogan that points the skilled artisan to the presently claimed human ES cells. Following Hogan and without the benefit of hindsight afforded by the present patent, the skilled artisan would expect to isolate EG cell lines that do not maintain karyotype when cultured in an undifferentiated state, that are SSEA-1 positive and that cannot form trophoblasts when induced to differentiate. Further, there is no expectation of success that a replicating in vitro cell culture of human ES cells would be obtained following the teaching of Hogan.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-3 under 35 U.S.C. § 103(a) over either Robertson '83 (Robertson I) and Robertson '87 (Robertson II) in view of Williams and Hogan

The Examiner rejected claims 1-3 as being obvious over Robertson I and Robertson II in view of Williams and Hogan. The Patent Owner respectfully traverses this rejection.

At the conclusion of the Examiner's rationale for this and the remaining two rejections of the claims on the grounds of obviousness, he states on pages 17, 20 and 22 of the Office Action that the claims are obvious in the absence of clear and convincing evidence to the contrary. The Patent Owner disagrees. Clear and convincing evidence is not the legal standard for rebuttal of *prima facie* case for obviousness. Rather, "An applicant may rebut a *prima facie* case of obviousness by providing a 'showing of facts supporting the opposite conclusion.' Such a showing dissipates the *prima facie* holding and requires the examiner to 'consider all of the evidence anew'." *In re Kumar*, 413 F.3d 1361, 1368 (Fed. Cir. 2005) [emphasis in original]. Case law requires that the burden shifts to the applicant to rebut a *prima facie* obviousness determination by the PTO, but does not require a clear and convincing evidence standard. *In re Harris*, 409 F.3d 1339, 1343 (Fed.Cir. 2005).

The present claims are not obvious over the cited art. Robertson I and II each describe the initiation and culture of what would be considered by those in the field as mouse ES cells. Neither Robertson reference teaches or suggests that any of their methods or techniques are applicable to other any other species. Neither reference provides data or suggests that the techniques could be successfully applied to other species. The existence of mouse ES cells is acknowledged in the Background section in the present patent. Robertson I and II do no more than establish the state of the art at the time, that is, that mouse ES cells could be isolated.

Williams adds nothing to support the Examiner's case, particularly in light of his statements in Cherny/Williams (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75). Further, when taken as a whole, Williams is directed to the use of leukemia inhibitory factor (LIF) to aid in the creation and culture of embryonic stem cell lines in vitro. Williams teaches that the use of LIF substitutes for the use of feeder layers otherwise needed to maintain mouse embryonic stem cell lines in an undifferentiated state (see column 1 lines 51-62 and column 3 lines 62-65). The central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells (Stewart, ¶ 23), and explicitly contraindicated in the present claims 1-3.

With respect to Hogan, the Examiner contends that Hogan would motivate the maintenance of primate/human cells in vitro for a long period of time. This is incorrect. Hogan's cells are EG cells, not ES cells. The skilled artisan, upon reading Hogan, would not be motivated to follow Hogan to arrive at the presently claimed cells.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety. None of the cited references alone or together can support the obviousness rejection in the face of these facts.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art.

(Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-3 under 35 U.S.C. § 103(a) over Piedrahita in view of Williams and Hogan

The Examiner has rejected claims 1-3 as being obvious over Piedrahita in view of Williams and Hogan. The Examiner states that Piedrahita discloses murine, porcine, and ovine ES cells. However, Piedrahita fails to provide explicit motivation to isolate human ES cells according to the same procedure as used to isolate mouse, sheep and pig ES cells. The Examiner states that Williams discloses human ES cells alongside ES cells of many other animal species. Therefore, the Examiner asserts that Williams motivates the skilled artisan to combine the teachings of Piedrahita with Williams to isolate ES cells from humans. Further, the Examiner states that Hogan provides additional motivation for the isolation and maintenance of human ES cells in vitro for longer periods. The Patent Owner respectfully traverses this rejection.

The Examiner misreads Piedrahita. Piedrahita does not teach porcine (pig) or ovine (sheep) ES cells. In fact, this reference teaches that the methods used to create and culture mouse ES cells could not be made to work on porcine and ovine systems. While some cell cultures were initiated, ES cells as defined in the art were not in fact created from pig or sheep embryos as reported by Piedrahita. Piedrahita makes this clear in the Abstract section of the article. For example, Piedrahita states that

“While murine isolated ICM or intact embryos plated on STO or HEF feeders gave rise to cell lines with embryonic stem cell-like (ES-like) morphology, ovine embryos did not,” and “porcine ES-like cells did not undergo observable differentiation in vitro.” (See second sentence of the Abstract)

The main body of Piedrahita explains these conclusions in greater detail – see for example, page 894 of Piedrahita where it is stated that porcine ES-like cells did not differentiate when induced to do so. Further, in the discussion section of Piedrahita, it is noted that

“differences were observed in the type of colonies that could be isolated from each species.” (Page 896 of Piedrahita)

Only epithelial cells could be derived from ovine embryos and the porcine cell lines created by Piedrahita did not differentiate. In light of these data, Piedrahita writes

“One explanation is that the trigger for induction of differentiation varies with species.” (Page 896 of Piedrahita)

In fact, Piedrahita, in the last sentence of the article on page 897 offers that they do not know why the difficulties with the ovine and porcine systems arose, and do not know if the problems reside in the source materials, the age of the embryos, or the culture conditions.

What Piedrahita actually teaches is that the methodologies used to initiate ES cell cultures in the mouse did not work when applied to other systems and at least at the time of publication of Piedrahita, no methods were known to those skilled in the art for making ES cells in other species. The present patent addresses the difficulties posed by Piedrahita beginning at column 3 line 49.

Thus, citation of Piedrahita by the Examiner adds no new support for an obviousness rejection. When this reference is taken as a whole, Piedrahita teaches that when the methods used to create murine ES cells are applied to pig and sheep, ES cells as encompassed by the present claims, *are not made*. In other words, Piedrahita teaches away from applying the murine system to other species and therefore teaches away from the presently claimed invention.

Williams adds nothing to support the Examiner’s case, particularly in light of his statements in Cherny/Williams (Cherny/Williams et al., 1994, *Reprod. Fertil. Dev.* 6: 569-75). Further, when taken as a whole, Williams is directed to the use of leukemia inhibitory factor (LIF) to aid in the creation and culture of embryonic stem cell lines in vitro. Williams teaches that the use of LIF substitutes for the use of feeder layers otherwise needed to maintain mouse embryonic stem cell lines in an undifferentiated state (see column 1 lines 51-62 and column 3 lines 62-65). The central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells (Stewart, ¶ 23).

With respect to Hogan, the Examiner contends that Hogan would motivate the maintenance of human cells in vitro for a long period of time. Hogan specifically states that her post-implantation embryo derived cells are different from pre-implantation embryo derived cells. The artisan, upon reading Hogan would not be motivated to follow Hogan to arrive at the presently claimed cells.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety. None of the cited references alone or together can support the obviousness rejection in the face of these facts.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Rejection of claims 1-3 under 35 U.S.C. § 103(a) over either Robertson I, Robertson II, Piedrahita, separately or together in view of Williams and Hogan

The Examiner rejected claims 1-3 as being obvious Robertson I, Robertson II, and Piedrahita in view of Williams and Hogan. The Examiner contends that the claimed invention differs from Robertson I and II and Piedrahita by claiming human ES cells. The Examiner states that Williams discloses human ES cells along side with ES cells of other animal species. Therefore, the Examiner asserts that Williams motivates the skilled artisan to combine the teachings of Robertson I and II and Piedrahita with Williams to isolate ES cells from humans. Further, the Examiner states that Hogan provides additional motivation for the isolation and maintenance of human ES cells in vitro for longer periods. The Patent Owner respectfully traverses this rejection.

For the same reasons discussed above with respect to the rejection of claims 1-3 under 35 U.S.C. § 103(a) over either Robertson I and Robertson II in view of Williams and Hogan and the rejection of claims 1-3 under 35 U.S.C. § 103(a) over Piedrahita in view of Williams and Hogan, the Patent Owner submits that the deficiencies of the cited references discussed above, although not repeated here, are equally applicable to the present rejection.

The Office is directed once again to the objective indicia of nonobviousness provided herein as rebuttal to the § 103 rejections. That evidence is incorporated in this section of the Response in its entirety. None of the cited references alone or together can support the obviousness rejection in the face of these facts.

The subject art is complicated and unpredictable (Stewart Declaration; Cherny/Williams paper; Piedrahita reference). Even the persons responsible for the cited art were unsuccessful at deriving a method to isolate primate/human ES cells and characterizing them once discovered. (Williams, Hogan, Piedrahita; Stewart Declaration generally.) No single example of primate/human stem cell isolation is shown in the art. (Cited art; Stewart Declaration generally.) The inventor has been the subject of public and peer acclaim for his invention. In view of these facts, together with the differences between the art and the presently presented claims, it cannot be said that a *prima facie* case of obviousness remains.

Conclusion

For all the reasons stated above, the Patent Owner respectfully requests reconsideration and withdrawal of the rejections of the claims 1-3.

A copy of this response is being served on the Third Party Requester, per the Certificate of Service attached hereto.

WISCONSIN ALUMNI RESEARCH FOUNDATION



Date: May 30, 2007

By:

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ATTACHMENT A

ATTACHMENT B

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of this paper is being served on the Requester, The Foundation for Taxpayer and Consumer Rights, through its counsel:

Daniel B. Ravicher, Esq.
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
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via overnight delivery service on the date shown below.

May 30, 2007
Date

Joseph R. DelMaster, Jr.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination of U.S. 5,843,780

Art Unit: 3991

Inventor: Thomson, J.

Examiner: Padmashri Ponnaluri

Control No.: 90/008,102

DECLARATION OF COLIN STEWART, D.Phil.

I, Colin Stewart, hereby declare as follows:

1. I obtained my Doctorate in Philosophy (D.Phil.) degree in Mouse Embryology from the University of Oxford, UK, in 1980 and have been working as a research scientist in mouse embryology and mouse embryonic stem (ES) cells in various academic and commercial institutions from 1980 to the present. My research career has centered on the development and application of genetic manipulation techniques to studying embryogenesis, stem cells and disease formation in mammals using the mouse as a model organism. My Curriculum Vitae is attached to this Declaration.

2. While working on my D.Phil., I developed the technique of producing mouse chimeras by aggregating 8-cell stage embryos with EC cells. Subsequently, as a staff scientist at EMBL, I was the first to derive germline chimeras by aggregation of ES cells with 8-cell embryos, a technique that is now widely used in mouse genetics. I have also worked on the development of retroviral vectors as means to producing transgenic mice. I showed that embryonic carcinoma (EC) cells and early embryos have a powerful mechanism, associated with a de novo DNA methylation activity, that inactivates retroviral LTRs in embryonic stem cells.

3. I was a member of a group that discovered that the cytokine Leukemia Inhibitory Factor (LIF) was necessary to maintain mouse embryonic stem cells in culture. I and my coworkers subsequently showed that, paradoxically, LIF is primarily and transiently

expressed in the uterus. By creating one of the first knock-out lines in mice, we found that LIF is essential for embryo implantation.

4. We have been improving ES cell technology, particularly with regard to developing ES lines for gene manipulation studies in the C57BL6 strain of mice. We have gained extensive experience in working with this strain of ES cells and have supplied some 100 laboratories with our cell lines. C57BL6 ES cells have now been chosen to be the strain of choice in which all the genes in the mouse genome will be knocked-out.

5. In parallel with these studies, I pursued an interest in genomic imprinting with particular regard to the role of imprinting in mammalian development and disease. We were the first to show that embryonic germ (EG) cells could form germline chimeras. We were the first to derive ES cells from androgenetic and parthenogenetic embryos. These have been of significant use in understanding how genomic imprinting regulates embryonic growth and cell proliferation.

6. I am currently a Principal Investigator at The Institute of Medical Biology, Biopolis, Singapore. I have held previous positions as a research scientist at the Roche Institute of Molecular Biology, the ABL Basic research program, the National Cancer Institute, and other research institutions.

7. I am a co-author, and in many cases, the senior author, of one hundred and forty four scientific articles reporting original research discoveries on mouse embryology and embryonic stem cells. Almost all of these articles have been published in peer-reviewed journals.

8. I have no financial interest in the outcome of the reexaminations of U.S. Patent Nos. 5,843,780; 6,200,806; or 7,029,913.

9. I have read the specification and claims of the above-referenced patents, as well as the Official Actions mailed March 30, 2007. I have further read the prior art references cited by the Examiners, and the materials that I cite to here, and have formed the opinions discussed below.

10. By way of background and general comments, I began working with mouse ES cells in the early 1980's. I met Dr. James Thomson while he was a postdoctoral fellow at the Wistar Institute in Philadelphia. During his tenure at the Wistar Institute in 1990, Dr.

Thomson visited my laboratory at the Roche Institute of Molecular Biology in order to learn how to isolate mouse ES cells using the methods that were published by Evans and Kaufman (1981, Nature 292:154) and Martin (1981, PNAS 78:7634). These methods have been reproducibly used by others, including myself, to isolate murine ES cells. However, at the time of Dr. Thomson's visit, no one knew what methods could be used to isolate ES cells from other species. In fact, Dr. Thomson and I discussed this very point during his visit and concluded that generation of primate or human ES cells could be very difficult.

11. When Dr. Thomson made his landmark invention of how to isolate primate/human ES cells and propagate them in an undifferentiated state for a duration of over one year, I, along with many others in the ES cell field, was surprised and pleased that he had managed to accomplish what others had for years tried and failed to do. Dr. Thomson's achievement of isolating primate/human embryonic stem cells and identifying their composition has been widely recognized by those with knowledge of the field as one of the major scientific breakthroughs in biology. Dr. Thomson's work was all the more remarkable because he achieved the seemingly impossible – he isolated primate/human ES cells that proliferated well past the stage where cells would normally either die or differentiate, and the cells maintained normal karyotype. In other words, Dr. Thomson's cells proliferated beyond a stage (known as the Hayflick limit) where cells would cease proliferating. This was a truly remarkable achievement.

12. Dr. Thomson's invention was all the more remarkable because the scientific literature was replete with examples of failures by others to isolate ES cells from any species except the mouse. Consistent with the scientific literature, those of us working in the field of embryonic stem cell research (almost all of us having multiple years of experience and advanced Ph.D. and/or M.D. degrees) recognized the difficulties in isolating ES cells from non-murine species. And, even within the murine species, it was recognized that the ability to reproducibly isolate ES cells varied among species, where the 129 strain reproducibly yielded ES cells whereas, for example, the CBA and FVB strains were difficult for the isolation of ES cells, and the ICR and NOD strains were either totally refractory or required the use of highly specialized techniques for their isolation (Brook and Gardner, 1997, Proc. Natl. Acad. Sci. USA 94:5709-5712; Brook et

al., 2003, *Diabetes*, 52:205-208). In other words, the methods used to isolate mouse ES cells initially discovered by Evans and Kaufman and Martin (cited above), are not universally applicable to the isolation of ES cells from embryos of species other than mice or even to the isolation of ES cells from different mouse strains. Moreover, even with the recognized success in isolating murine ES cells, there are several reports that describe the derivation of cell lines from mouse blastocysts in which the cells are not ES cells (Sherman, 1975, *Differentiation*, 11:51-67; Tanaka et al., 1998, *Science* 282:2072-2075; Kunath et al., 2005, *Development* 132:1649-1661).

13. In addition, while it was initially thought that rat ES cells could be isolated using the murine methods (Iannaccone et al., 1994, *Dev Biol.* 163: 288-292), it was later shown that the reported rat ES cells were contaminated with murine ES cells and that rat ES cells had not, in fact, been isolated (Brenin et al., 1997, *Transplant Proc.* 29:1761-1765). In another study on rat cells, Ouhibi et al. report that even though they succeeded in isolating rat cells from rat embryos, they could not culture these cells beyond four passages (Ouhibi et al., 1995, *Mol. Reprod. & Dev.* 40:311-324).

14. Further, the failure to isolate ES cells from explanted blastocysts from ovine embryos is reported in Piedrahita et al., 1990, *Theriogenology* 34:879-901 (Piedrahita). In this paper, mouse ES cells are established, but no ES cell lines could be derived from ovine embryos. While Piedrahita state that they isolated ES cells from porcine embryos, there were no data produced then, or since, to demonstrate that these cells were actually porcine ES cells or indeed that ES cells have been derived from any other ungulate or major domesticated species (Keefer et al. 2007, *Animal Reproduction Sci.* 98(1-2):147-168). In fact, in a paper co-authored by Piedrahita himself in 1997, they state that their porcine cells differentiated shortly after isolation (Moore and Piedrahita, 1997, *In Vitro Cell Dev. Biol. – Animal*, 33:62-71). And, in another article by Talbot et al., they state in the Abstract that “standard conditions for mouse ES cell culture did not maintain bovine epiblast cells in an undifferentiated state” (Talbot et al., 1995, *Mol. Reprod. & Dev.* 42:35-52).

15. Prior to Dr. Thomson’s invention, there were no publications of which I am aware that report successful isolation of ES cells from other species, using the murine ES cell isolation method, or in fact any other method. Although cells similar to murine ES

cells had been described as being isolated from hamster embryos, their capacity for long term proliferation and ability to form teratomas was not established (Doetschman et al., 1988, Dev. Biol. 127:224-227). Even Bongso failed to isolate human ES cells (see paragraphs 30 and 31 of this Declaration).

16. I am very familiar with the role of leukemia inhibitory factor (LIF) in the maintenance of embryonic stem cells in culture and I am a coauthor of a paper published in Nature (Williams et al., 1988, Nature, 336:684-687; Ref. 22 on my CV) with Dr. Robert L. Williams where we reported that LIF maintains the developmental potential of embryonic stem cells. This paper forms the basis of the Williams patent (Williams; U.S. Patent No. 5,166,065) cited by the Examiner in the Office Actions in the Thomson patents at issue here.

Williams, U.S. Patent No. 5,166,065 (Williams)

17. I have reviewed Williams. This patent describes a method for establishing and maintaining mouse ES cells in an undifferentiated state where the mouse fibroblast feeder layer was replaced by LIF. As stated in the opening sentence of the patent, the invention relates to the use of a previously discovered and characterized molecule, LIF, in the isolation and propagation of ES cells in vitro. This patent seems to represent an improvement over the previously published methods for maintaining mouse ES cells in culture.

18. Williams does not disclose a method for isolating primate/human ES cells, and is deficient in this regard in several ways. When Dr. Thomson isolated his primate/human ES cells, he used a method that is not taught in Williams. Dr. Thomson isolated the inner cell mass (ICM) from the blastocyst by immunosurgery, a procedure that removes the trophoblast cells that enclose the ICM. He plated the isolated ICMs on mouse feeder layers and was very explicit in how the explanted ICMs were cultured, gently disassociated, replated on feeder layers to form colonies, and then expanded on feeder layers to maintain their stem cell characteristics to prevent their differentiation ('780 patent columns 7, 8 and 9). This meticulous series of methods is not described in Williams.

19. Moreover, the primate ES cell colonies that Dr. Thomson selected for further study were compact and flatter than mouse ES cell colonies. If left alone they tend to

differentiate at the center of the colony. Mouse ES cell colonies are distinctly different in that they are compact, often tear-drop shaped mounds. If left alone they will tend to differentiate at the periphery. Flat, compact colonies were not known to exist before Dr. Thomson's invention. It should be remembered that at this stage in the process, the culture dish contains a heterogeneous mixture of cells and debris and it would not be immediately apparent what cells/colonies to choose for further study without the insight exhibited by Dr. Thomson. Only after Dr. Thomson's invention would I be able to distinguish primate/human ES cell colonies from mouse ES cell colonies if they were presented to me as a mixture of colonies on a culture dish.

20. Furthermore, the mouse ES cells isolated by Williams differ in other aspects from the primate/human ES cells isolated by Dr. Thomson. For example, Table 1 in column 11 of the '780 patent establishes that the cell surface marker expression of mouse ES cells differs from that of primate/human ES cells in no less than five (5) different markers. Thus, if one were to use the cell surface marker expression disclosed by Williams to select an ES cell, one would not isolate a primate/human ES cell. Further, mouse ES cells do not spontaneously differentiate into trophoblast in culture, let alone differentiate into trophoblast that produces chorionic gonadotropin.

21. I have been conducting basic research in stem cells and embryology for thirty (30) years. I understand that an embryo from any species contains a multitude of different cells at all stages of differentiation at any given point in time. When Dr. Thomson isolated his primate/human ES cells, he managed to accomplish what others had tried and failed to do for so long. He isolated cells and propagated them in culture, from an embryonic stage where the cells themselves may not even exist in the same natural state in vivo. Even if they do exist, they may do so only transiently (before they move on to the next stage in their development), so that one could not possibly say what properties these cells would have until they are isolated and tested.

22. There is nothing in Williams that tells the reader how to isolate primate/human ES cells. Williams suggests that his technique is applicable to derivation of ES cells from other species. However, even Williams himself admits that this was not the case when he later applied his methods to other domestic animals (Cherny et al., 1994, *Reprod. Fertil. Dev.* 6:569-575).

23. In any event, if the whole point of Williams was to improve establishment of ES cells by eliminating the feeder layer, it is true, even today, that Williams' methods are not applicable to the derivation and maintenance of primate/human ES cells. Murine ES cells, unlike all primate/human cells, are dependent on an exogenous source of LIF to retain their stem cell properties. Mouse ES cells cannot even be grown on mouse feeder layers that do not produce LIF (Stewart et al., 1992, Nature 359:76-79). However, while LIF has been established by Williams as a component of the feeder layer that enables long term undifferentiated culture of mouse ES cells, LIF does not have the same effect on the long term undifferentiated culture of primate/human ES cells (Thomson et al., 1998, Science 282:1145-1147; Amit et al., 2000, Dev. Biol. 227:271-278).

24. Williams was presumably issued his patent because his methods were considered to be an improvement of prior art mouse ES cell isolation and, had his findings not been such an improvement, no patent would have issued. However, in my opinion, Williams provides nothing of value to a scientist attempting to isolate primate/human ES cells because his methods did not work then, and do not work now, to isolate primate/human ES cells.

25. Williams never isolated a primate/human ES cell and Dr. Thomson's invention was the first isolation of these cells. In fact, in 1988, when our Nature paper was published and the Williams patent application was filed, (Williams et al., 1988, Nature, 336:684-687; Ref. 22 on my CV), I did not know how to successfully isolate primate/human ES cells. This remained true both before and following Dr. Thomson's visit to my laboratory in 1990.

Hogan, U.S. Patent No. 5,690,926 (Hogan '926)

26. I have reviewed Hogan '926. Hogan '926 describes the isolation of embryonic germ (EG) cells from primordial germ cells obtained from post-implantation embryos. Dr. Thomson's cells are derived from pre-implantation embryos. For this reason, although Hogan's cells are referred to in the Hogan '926 patent as ES cells, they are more commonly known in the art as embryonic germ (EG) cells.

27. Hogan's cells differ from Dr. Thomson's cells in several other ways as well. Hogan's cells are SSEA-1 positive (Hogan '926 at column 10, lines 1-2), whereas Dr. Thomson's cells are SSEA-1 negative (Table 1, column 11, '780 patent). Hogan's cells

simply cannot form trophoblast, whereas Dr. Thomson's do. Hogan's cells require different growth factors and culture conditions for their establishment and are dependent on LIF for their maintenance for long term culture. According to Hogan in her own publication (Labosky et al., 1994, Development 120:3197-3204), Hogan's cells exhibit different developmental characteristics in that they can frequently give rise to chimeras that develop abnormally. Hogan states that this is due to altered expression of imprinted genes in the germ cells from which they are derived (Labosky et al., 1994, Development at pages 3201-3204).

28. Hogan's cells are simply not the same as Dr. Thomson's cells. Hogan '926 does not even teach how to isolate Dr. Thomson's primate/human ES cell. If the techniques disclosed in Hogan were followed, one would not isolate Dr. Thomson's ES cells.

29. The Examiner's discussion of Hogan '926 also states that the unique properties of Dr. Thomson's cells are inherent to the cell once isolated. I must disagree. Dr. Thomson's primate/human ES cells were never known prior to his invention. Any property that he ascribes to his cells continues to define and refine the novelty of the cells and further distinguishes his cells from prior art cells disclosed in Hogan or Williams.

Bongso et al., 1994, Human Reproduction 9: 2110 (Bongso)

30. I have reviewed the Bongso article that the Examiner employs against the Thomson patents. The Examiner asserts that Bongso either teaches or makes obvious Dr. Thomson's primate/human ES cells. In my opinion, Bongso does neither. One of the very important aspects of Dr. Thomson's invention was the fact that he not only succeeded in isolating primate/human ES cells, he also managed to isolate cells that could be maintained for over one year in culture. Bongso is another example of the failure of others prior to Dr. Thomson's work. Bongso's cells, isolated from ICM tissue, died after only two passages. In fact, in a later publication by Bongso, he acknowledges that his failure was due to his attempt to derive the ES cells using medium supplemented with LIF alone and no feeder layer. In this paper, Bongso states that Dr. Thomson was the first to isolate primate/human ES cell lines (Rubinoff et al., 2000, Nature Biotech. 18:399-404). Bongso cannot by definition have isolated human ES cells when Bongso himself admits otherwise.

31. At the time of the publication of Bongso in 1994, and the filing of Dr. Thomson's first patent application in 1995, there was an enormous level of unpredictability in the field regarding how to isolate anything other than mouse ES cells. As discussed elsewhere in this Declaration, Bongso was only one of many who tried and failed to isolate ES cells from a variety of species. No one knew which available methods, if any, to use to isolate primate/human ES cells and therefore no one knew what would work to isolate these cells. Bongso did nothing to reduce the level of unpredictability because Bongso, by his own admission, also failed to isolate the cells.

Piedrahita et al., 1990, Theriogenology 34:879-901 (Piedrahita)

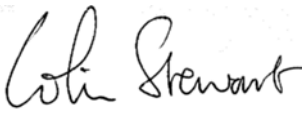
32. I have reviewed the Piedrahita et al. publication. Contrary to the Examiner's contention that this paper supports the notion that Dr. Thomson's invention was obvious, the paper further supports my statements that the art was highly unpredictable at the time. Piedrahita et al. inform that the methods used to isolate mouse ES cells were not portable and could not be used to isolate ES cells from other species. Piedrahita et al. state that it was not possible to isolate ovine ES cells. Further, although Piedrahita et al. claim they have isolated porcine ES cells, no tests were performed to confirm this claim.

Robertson papers

33. I have also reviewed the two Robertson papers cited by the Examiner as rendering Dr. Thomson's invention obvious. In my opinion, neither of these papers provides any information that would lead one to conclude that the murine ES cell isolation methods were in any way applicable to the isolation of primate/human ES cells.

I declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made under penalty of perjury with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5/29/2007

By 

Colin Stewart, D.Phil.

CURRICULUM VITAE

Name: Colin Stewart, D.Phil.
Place of Birth: Newcastle-Upon-Tyne, England
Citizenship: UK

Education:

1972-1975 B.Sc. (Honors), Zoology, University of Bristol, UK
1975-1976 M.Sc. Immunology, University of Birmingham, UK
1976-1980 D.Phil. Mouse Embryology, University of Oxford UK

Chronology of Employment:

1981-1983 Postdoctoral Fellow, Heinrich-Pette-Institut, Hamburg, Germany
1984-1988 Staff Scientist, Cell Differentiation Program, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
1988-1992 Assistant Member, Roche Institute of Molecular Biology, Nutley, NJ
1992-1995 Associate Member, Roche Institute of Molecular Biology, Nutley, NJ
1996-1999 Director, Cancer and Developmental Biology Laboratory, ABL-Basic Research Program, NCI-FCRDC, Frederick, MD
1999-2007 Laboratory Chief, Cancer and Developmental Biology Laboratory/CCR/NCI, National Cancer Institute at Frederick, Frederick, MD.
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Societies:

1988-Present American Association for the Advancement of Science
1994-1996 Fellow of the New York Academy of Sciences
1990-Present Society for the Study of Reproduction

Professional Activities:

1987 Visiting Professor at the University of Louvain-la-Neuve, Belgium; lecture course entitled "The Genetic and Experimental Analysis of Mammalian Development"

1992 Chairman and Co-organizer of NIEHS Workshop on Genomic Imprinting

1993-1995 Adjunct Professor at Columbia University

1993-1996 Member of National Science Foundation Panel on Developmental Mechanisms

1994-1995 Member of Frederick Cancer Research and Development Center Scientific Advisory Committee to the National Cancer Institute

1995 Member of NICHD Population Research Committee

2001–2004 Instructor Cold Spring Harbor Laboratory Mouse Embryology Course

2004 Proposer and Co-organizer Novartis Foundation Symposium 264 – Nuclear Organization in Development and Disease.

2004- Member of Faculty of 1000 (Cell Biology)

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