Exhibit 5
Part 45
To Third Declaration of
Joseph N. Hosteny

> Thomson and coworkers reported the derivation of ES cell lines from human blastocyst.
>
> Reubinoff '00 at 399.

Further, as Dr. Alan O. Trounson, one of the authors of Reubinoff '00, explains in his declaration (attached hereto in Appendix A), it was obvious at the time that, "had Bongso '94 simply not dispensed with the feeder layer in the passaging step, they would have successfully developed the claimed invention." Trounson Declaration at 6 - 7. Skilled practitioners reading Bongso et al. would have spotted - and some in fact did spot - this departure from the original methods for isolating mouse embryonic stem cells and would have repeated Bongso '94, but retained the use of the feeder layers. *Id.* A successful result of that modification was predictable to those of ordinary skill in the art at the time of Dr. Thomson's claimed invention. Thus, Bongso '94 actually supports the Examiner's rejection of the instant claims, and - in fact - could stand in combination with any one of the many references teaching methods for maintaining embryonic cells as separate grounds for rejection.

Examiner:

f. Bongso failed to isolate and maintain long term ES cell line without presence of LIF

The Examiner does not find the remarks of either the Patent Owner or the Third Party Requester to be persuasive with regard to the teachings of Bongso '94.

As the TPR indicates, Bongso '94 apparently succeeded in isolating human ES cells. These ES cells were isolated from pre-implantation embryos and exhibited the presence of alkaline phosphatase, stem cell-like morphology, and normal karyotype. However, as the Patent Owner points out, Bongso failed to go further and to maintain said ES cells in long term culture, presumbably because he failed to culture the human ES cells on embryonic fibroblast feeder layers without LIF. The human ES cells of Bongso continued in culture for only two cultures in the presence of human LIF before differentiating. Thus, Bongso fails to provide evidence that his embryonic stem cells are (1) capability of being maintained in an undifferentiated state for over one year when

cultured on fibroblast feeder layers without exogenous LIF; (2) have the potential to differentiate into the ectoderm, mesoderm, and endoderm; (3) are inhibited from differentiating when cultured on a fibroblast feeder layer.

Even though Bongso '94 may have actually isolated human ES cells using all of the knowledge in the prior art, he was unable to maintain these cells indefinitely in culture. Regardless of the explanation for this failure, Bongso did not achieve the critical element of the claimed invention--maintenance of human ES cells in the undifferentiated state in in vitro culture for a prolonged period without LIF.

Patent Owner: (Response, page 13, lines 5 - 14)

g. Summary of failure of others to isolate long term cultures of ES cells

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 non-enabling." *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.

Third Party: (Comments, page 16, line 8 to page 17, line 18)

g. None of the cited references teaches away from the invention

Lastly, on the issue of using feeder layers to maintain human embryonic stem cell cultures, it was well established that mouse embryonic stem (ES) cells and mouse embryonic carcinoma (EC) cells had extremely similar characteristics, such as by sharing the same unique combination of cell surface markers: the '913 patent concedes as much in its "Background of the Invention" section. '913 patent at 3:46 - 49 ("mouse

EC cells and mouse ES cells share the same unique combination of cell surface markers"). Likewise, it was expected that human ES cells would also be similar to human EC cells, which were known to be dependent on feeder cells for maintenance in culture. Pera et al., Isolation and Characterization of a Multipotent Clone of Human Embryonal Carcinoma Cells, 42 Differentiation 10 - 23, 10 and 15 (1989) ("Pera '89") (attached hereto in Appendix B). Pera '89 taught that although mouse-embryo-derived stem cells had a feeder cell requirement that could be replaced by LIF, human EC cells were dependent upon feeder cells for continuous growth in vitro. *Id.* at 10 and 21 ("a range of known growth factors and related substances [including LIF] failed to substitute for feeder layers in supporting the growth of [human EC] cells"). As such, it was entirely predictable that human ES cells would also be dependent upon feeder cells for maintenance.

Another critical flaw in the Patent Owner's purported evidence of the failure of others is that none of it expressly teaches away from the methods use. In *Dystar*, the Federal Circuit held that a reference should not be used as teaching away from a process unless it contains "specific language" expressly doing so. 464 F.3d at 1364 (*stating* "no specific language in these references teaches away from the invention," and "[w]e will not read into a reference a teaching away from a process where no such language exists." Here, not a single reference cited by the Patent Owner expressly states that the known methods for deriving and maintaining mammalian embryonic stem cells should not be pursued to also isolate and culture human (or primate) embryonic stem cells. Therefore, none of them can be considered a "teaching away" from the instant claims.

In conclusion, none of the Patent Owner's proffered evidence of the failure of others is relevant to the issue of whether the pending claims are obvious because none of it shows the failure of others to achieve the patented invention of *human* embryonic stem cells *cultured on fibroblast feeder layers* and *without the application of exogenous* LIF. Thus, this evidence does not rebut the Examiner's *prima facie* obviousness determination. Regardless, when viewed fairly and accurately, the evidence actually supports the Examiner rejection of the pending claims.

Examiner:

g. References establish difficulty and unpredictability in ES cell art

The Examiner does not find the comments of the Patent Owner or the Third Party Requester to be persuasive for the following reasons.

The Examiner agrees with the Third Party Requester that it is only in Bongso '94 that the scientist is actually attempting to isolate the claimed human ES cells. In each of

the other references, the researcher's goal is to isolate ES cells from a non-murine species. The Examiner also agrees with the Patent Owner that each of the cited references documents the failure of investigators to isolate ES cell from non-murine species and then to passage them on a long term basis (greater than one year) as a cell line and to establish all of the defining criteria for ES cells as set forth in the instant claims of Thomson '913. While several investigators have attempted to isolate ES-like cells, few (if any) researchers have established long term ES cell lines of non-murine species wherein all of the defining criteria for ES cells has been proven. For this reason the art of isolating and maintaining ES cell is deemed to be especially difficult and unpredictable. This unpredictability supports the conclusion that Williams '065 is not an enabling reference under 35 USC §102(b) even though it describes human ES cells prophetically as being isolatable using the same method that was used to isolated murine ES cells.

GROUNDS #4 (103(a)): Patent Owner's Response, Third Party Requester's Comments, and Examiner's Decision

Patent Owner: (Response, page 13, line 15 to page 16, line 27)

A. Williams '065 fails as a prima facie obviousness reference

The Examiner has rejected claims 1 - 3 under 35 U.S.C. 103(a) as being obvious over Williams alone, or as further evidence 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 Interference 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" characteristic 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 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 in 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 of 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/Williams et al., 1994 Reprod. Fertil. Dev. 6: 569 - 575), 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 this 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 pre-implanted 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 primate 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 invention, 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. (Steward 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; Steward 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.

Third Party: (Comments, page 17, lines 3 - 18)

A. Williams '065 supports a prima facie case of obviousness

Another critical flaw in the Patent Owner's purported evidence of the failure of others is that none of it expressly teaches away from the methods use. In *Dystar*, the Federal Circuit held that a reference should not be used as teaching away from a process unless it contains "specific language" expressly doing so. 464 F.3d at 1364 (*stating* "no specific language in these references teaches away from the invention," and "[w]e will not read into a reference a teaching away from a process where no such language exists." Here, not a single reference cited by the Patent Owner expressly states that the known methods for deriving and maintaining mammalian embryonic stem cells should not be pursued to also isolate and culture human (or primate) embryonic stem cells. Therefore, none of them can be considered a "teaching away" from the instant claims.

In conclusion, none of the Patent Owner's proffered evidence of the failure of others is relevant to the issue of whether the pending claims are obvious because none of it shows the failure of others to achieve the patented invention of *human* embryonic stem cells *cultured on fibroblast feeder layers* and *without the application of exogenous* LIF. Thus, this evidence does not rebut the Examiner's *prima facie* obviousness determination. Regardless, when viewed fairly and accurately, the evidence actually supports the Examiner rejection of the pending claims.

Examiner:

A. Williams '065 does not support a prima facie case of obviousness

The Examiner finds the comments of the Patent Owner to be persuasive with respect to the non-obviousness of the claimed invention over Williams '065. The 35 USC §103(a) rejection over Williams is withdrawn because the Examiner has failed to establish a *prima facie* case of obviousness since there was **no reasonable expectation of success** of isolating and maintaining primate/human ES cells and cell lines, especially in view of the failure of the prior art to isolate and maintain ES cell lines from bovine, ovine, and porcine (Piedrahita; Talbot '95), even though there existed a strong motivation to try to do so. Further evidence of unpredictability in the art of embryonic stem cell isolation and maintenance is the fact that the success of isolating ES cells in mice varied with the strain. Since there is no prima facie case of obvious-ness, there is no need to consider secondary considerations such as public acclaim.

Patent Owner:

B. Public acclaim is evidence of non-obviousness
(Response, page 4, line 15 to page 6, line 6)

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 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 the 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 Heath and 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 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. 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 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 enables 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.

Third Party:

B. Public acclaim is not relevant to patentability
(Comments, page 17, last line to page 23, line 5)

In its Response, the Patent Owner cites a "level of acclaim" for Dr. Thomson that it argues is evidence of the validity of the pending claims. Response at 4 - 6 and Attachment A. However, evidence of public acclaim is irrelevant to the determination of a patent claim's validity, regardless of whether the basis for such acclaim is related to the particular patent claim or not. The only opinions that might be relevant are those of other scientists sufficiently skilled in the art, and even they are not always relevant. See *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985) (dismissing a "praise for the claimed invention" argument); *Jenn-Air Corp. v. Modern Maid Co.*, 499 F. Supp. 320, 326 - 327 (D. Del 1980), aff'd, 659 F.2d 1068 (3rd Cir. 1981) (discarding evidence of acclaim regarding Dr. Thomson's awards and recognition - none of which appears to have been bestowed on him by other human embryonic stem cell researchers -- is of no relevance to an analysis of the validity of the pending claims.

Even if one puts the applicability of the proffered evidence of "public acclaim" aside for a moment, FTCR does not dispute that Dr. Thomson made an important accomplishment in the science of human embryonic stem cells.[5] However, not all scientific accomplishments are necessarily deserving of patents. As Justice Kennedy stated for a unanimous Supreme Court just this Spring in KSR, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. at 1741. Here, Dr. Thomson's accomplishment was not a result of sufficient scientific ingenuity to be deserving of a patent, but rather was more attributable to his having special access to two limited resources that other embryonic stem cell researchers who were pursuing the same accomplishment at the same time did not have. Melton Declaration at 5 - 6; Loring Declaration at 10; Cowan Declaration at 5 - 6. Had others in the field been given the same access to those limited resources, they would have undoubtedly achieved -- and in fact some did achieve -- the same accomplishment as Dr. Thomson. Trounson Declaration at 6 - 7; Loring Declaration at 10; Reubinoff '00 at 399.

First, at the time of Dr. Thomson's accomplishment, in the mid to late 1990's, human embryos were not available to the vast majority of embryonic stem cell scientists. Melton Declaration at 6; Loring Declaration at 10; Cowan Declaration at 5 -

6.[6] This was because the issue of human embryos being used in scientific research, where they would necessarily be destroyed, was -- and still is -- highly politically controversial. In fact, many countries made such research entirely illegal.[7] Proof of the difficulty of obtaining human embryos in the face of such political hostility is the fact that Dr. Thomson himself had to rely on an Israeli colleague to personally carry human embryos into the United States from Israel for his use. As told by *Science* magazine:

> Thomson was working with Itskovitz-Eldor [of the Rambam Medical Center at the Technion in Haifa], who in 1997 had sent him more than a dozen frozen embryos donated by Israeli couples in IVF clinics. One of Itskovitz-Ildor's graduate students, Michal Amit, carried the frozen embryos to Thomson's lab and assisted in the project. Four of the five cell lines the team first described (*Science*, 6 November 1998, p. 1145) came from Israeli embryos.

In the Middle East, Pushing Back the Stem Cell Frontier, 295 Science 1818 (March 8, 2002) (attached hereto in Appendix C). The relationship with Dr. Itskovitz-Eldor gave Dr. Thomson unique access to human embryos that many other scientists did not have at the time.

Second, another effect of the political and legal hostility towards research using human embryos is that funding to support human embryonic stem cell research was extremely scarce, if not entirely unavailable, in the mid to late 1990's. In the United States, federal funding of such research, including that from the extremely important NIH, did not exist, and funding from private entities was at a very nascent stage. Melton Declaration at 5 - 6; Loring Declaration at 10; Cowan Declaration 5 - 6. The result was that only a very few lucky scientists were actually provided the money they needed to do work specifically on human embryonic stem cells. Dr. Thomson was one of the lucky ones capable of finding an oasis in the vast desert of human embryonic stem cell research funding. Specifically, Geron Corporation gave Dr. Thomson the money he needed to work on deriving and maintaining human embryonic stem cells.[8]

It was access to these extremely limited resources -- human embryos and funding to do research using human embryos -- that provided Dr. Thomson the ability to make his accomplishment relating to human embryonic stem cells. Melton Declaration at 5 - 6; Loring Declaration at 10; Cowan Declaration 5 - 6. Had other scientists in the field been given the same access to those limited resources, they, too, would have been able to make the same accomplishment Dr. Thomson did. *Id.* As Dr. Douglas A. Melton explains in his Declaration (attached hereto in Appendix A), this is because Dr. Thomson achieved his accomplishment by implementing an obvious method for deriving and maintain[ing] human embryonic stem cells. Melton Declaration at 5 - 6. In fact, a select group of other scientists who also had access to these limited resources were indeed successful at driving and maintaining human embryonic stem cells contemporaneously with Dr. Thomson. Trounson Declaration at 6 - 7; Reubinoff '00 at 399. As such, and returning to Justice Kennedy's cannon in KSR that "advances that

would occur in the ordinary course" should not be awarded patent protection, Dr. Thomson did not deserve to be awarded patents for his work. 127 S. Ct. 1741.

In closing on this issue, FTCR reiterates that it does not believe that Dr. Thomson was unworthy of the media attention and honors that he received as a result of his accomplishment. However, public acclaim of a scientific accomplishment does not mean that the accomplishment includes invention worthy of patent protection. In fact, many important technological accomplishments are the result of factors other than non-obvious scientific inquiry, such as access to limited resources, sufficient support to research and attempt the accomplishment, and a hospitable political climate. Similarly, as discussed above, it was those factors that enabled Dr. Thomson to achieve his human embryonic stem cell accomplishment, not patentable inventiveness. The fact that he received praise and recognition does not help to distinguish between what factors led to his accomplishment and, more specifically, does not mean that it was necessarily patent worthy. As such, the evidence proffered by the Patent Owner regarding public acclaim of Dr. Thomson's accomplishment is irrelevant to the determination of whether the pending claims were sufficiently inventive to be patentable. Thus, this evidence does not rebut the Examiner's *prima facie* obviousness determination either.

Examiner:

B(I). Public acclaim is a secondary consideration that must be evaluated

The Examiner does not find the remarks of the Patent Owner or the Third Party Requester to be persuasive. Evaluation of secondary considerations, such a public acclaim, in an obvious-ness rejection is not required when, as in this instance, the Examiner has failed to establish a *prima facie* case of obviousness. However, the Examiner elects to make the following remarks about the public acclaim issue.

When considering the issue of public acclaim, the Examiner must determine if the persons honoring the inventor are really those skilled in the art of the invention. However, the Patent Owner has not supplied sufficient information for the Examiner to determine if the persons who actually selected Dr. Thomson as an honoree were

his peers in the art of embryonic stem cell research. Of the nine instances of acclaim presented by the Patent Owner at pages 4 - 5, the one which is the most prestigious is the recognition of Dr. Thomson by the American Association for the Advancement of Science (AAAS) in an article in *Science* entitled, "Milestones of Science." AAAS is one of the most respected scientific organizations in the world. But even in this instance, the names and background of the people who made the actual selection of Dr. Thomson's work for this recognition are not provided. Therefore, even if the secondary consideration of public acclaim were required to overcome a prima facie case of obviousness, which it is not, there is insufficient evidence for the Examiner to make a proper determination. Finally, all that can be really said based upon the evidence of record, is that the public acclaim accorded Dr. Thomson for his isolation and maintenance of primate/human ES cells is consistent with a landmark or pioneering invention.

B(II). Declarants Avowal of Obviousness is Conclusionary and Based on Hindsight Analysis

Another argument repeatedly emphasized by the TPR and by the four declarants in Appendix A is that Dr.Thomson's invention of primate/human ES cells does not demonstrate real innovation but is merely a result of his having access to both funding and human embryos which most of his peers did not. These arguments have been fully considered but are not deemed persuasive.

Third Party Requester's declarants are obviously accomplished scientists as documented by their curriculum vitae. However, their statements pertaining to the

obviousness of the isolation and maintenance of primate/human ES cells are flawed by hindsight reasoning. While there was undoubtedly compelling motivation to try to isolation and maintain primate/human ES cells using the techniques which worked with mouse ES cells, there was no **reasonable expectation of success when viewed at the time of the invention.** This lack of reasonable expectation of success flows from the difficult nature of the art and the failure of others skilled in the art to isolate and maintain ES cells from higher mammals including porcine, ovine, and bovine. At the time of the invention, established ES cells had only been isolated from mouse and hamster. Established rat ES cells lines were developed conclusively only after the time of the invention. Furthermore, even in the case of the mouse, the ability to isolate and maintain ES cells varied from strain to strain (Stewart declaration at ¶12).

Another factor to be considered in evaluating the Third Party declarations is whether or not the declarants are disinterested parties. Clearly, two of the four declarants appear to have a special interest in obviating the Thomson '913 patent. As the Patent Owner indicates in the Information Disclosure Statement filed July 24, 2007, Drs. Loring (09/199,703; 2002/0188963) and Trounson 09/436,164 and 2002/0160509) have previously filed patent applications which contained one or more claims that read on or encompass primate/human ES cells. Furthermore, Dr. Loring's claims expertise in the isolation and maintenance of human ES cells was underscored by the TPR in that she had "derived nine of the cell populations listed in 2001 on the NIH registry." However, the Patent Owner points out that this accomplishment of Dr. Loring's is called into question by the fact "that a printout of the NIH registry lists Loring's cells (CY12,

CY30, CY40, CY51, CY81, CY82, CY91, CY92, CY10) as failing to expand into undifferentiated cell cultures (see "CyThera, Inc." listing in Ref. A)."

Finally, the Examiner notes that the declarants' criticism of Dr. Thomson's having the advantage of access to requisite funding and human embryos is contradicted by the fact that the inventor isolated and maintained ES cells of non-human primates--not human ES cells as described in the specification of Thomson '913. While Thomson enabled the isolation and maintenance of human ES cells, he did not exemplify the human US cells in the '913 patent. This fact makes the access to human embryos further irrelevant to the patentability of the instant claims which are based upon the actual isolation of primate embryonic stem cells. Unlike human embryos, non-human primate embryos should have been widely available to other researchers.

GROUNDS #5: Claims 1 - 3 are rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Hogan (US 5,690,926). The complete explanation of this rejection at pages 12 - 14 of the Office action of 30 March 2007 is hereby incorporated by reference. The preponderance of the evidence of record supports the conclusion that the Hogan '926 patent is not an enabling reference under 35 USC §102(b) and also fails as a reference under 35 USC §103(a) because of the unpredictability in the art at the time of the invention, which leads to a lack of a reasonable expectation of success. Therefore, **this rejection has been withdrawn** for the following reasons.

GROUNDS #5 (102(b)/103(a)): Patent Owner's Response, Third Party Comments, and Examiner's Decision

Patent Owner:

A. Hogan '926 fails because it does not disclose each and every element (Response, page 16, line 28 to page 18, line 11)

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 the 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 applicant's 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 stem 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 is 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 (Steward, ¶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 inappliable 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.

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) above 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 SSES-1 positive and than 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; Steward 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.

Third Party:

A. **Hogan '926's EG cells are indistinguishable from the claimed invention** (Comments, page 23, line 7 to page 28, line 11)

In the Office Action, the Examiner rejected all three claims as being anticipated by or obvious over Hogan (U.S. Patent No. 5,690,926) ("Hogan '926"). Office Action at 12. The Examiner found that, "Hogan '926 discloses the identical human embryonic stem cells as claimed even though produced by [a] different process." *Id.* at 14. The Patent Owner made several arguments in its Response as to why Hogan '926's teaching of human embryonic stem cells does not invalidate the pending claims, but those arguments lack merit. Thus, the Examiner's rejection of the pending claims based on Hogan '926 was and remains appropriate.

The Instant Claims Are Not Patentably Distinguishable From Hogan '926

The Patent Owner first argues in the Response that Hogan '926's cells "are derived from primordial germ cells from post-implantation embryos," and cites what it characterizes as an admission by the Hogan '926 applicant to that fact. Response at 17 (*cited Amendment*, June 4, 1996, U.S. Appl. No. 08/217,921 (attached hereto in Appendix C)). However, that statement was made regarding what Hogan '926 wished to *claim*, not what Hogan '926 actually *taught*, which are undeniably two very different things. The Patent Owner's suggestion that Hogan '926's teaching is limited to what it claims should be rejected, as the method Hogan '926 taught could be applied to any embryo, pre- or post-implantation, despite the fact that its claims are limited to the latter.

Further, the Patent owner makes no argument that post-implantation embryos of Hogan '926 have any structural or functional difference from the pre-implantation embryos of the instant claims. In fact, there is no difference in the cells that are derived from either. Loring Declaration at 4 - 5. Lastly, even Dr. Thomson himself has recognized that human embryonic germ cells and human embryonic stem cells are very closely related and, thus, knowledge regarding one was expected to be insightful to the other. Zwaka, Thomas P., and Thomson, James A., *A Germ Cell Origin of Embryonic Stem Cells?*, 132 *Development* 227-233 (2005) (attached hereto in Appendix C). As such, this is not a patentable distinction between what Hogan '926 taught and the instant claims.

Second, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells are SSEA-1 positive. However, it was known that mouse embryonic stem (ES) cells and mouse embryonic carcinoma (EC) cells share the same unique combination of cell surface markers: the '913 patent concedes as much in its "Background of the Invention" section. '913 patent, 3: 46 - 49 ("mouse EC cells and mouse ES cells share the same unique combination of surface markers"). Also at the

time, it was expected that human ES cells would likewise express the same cell surface markers as human EC cells, which were known to be SSEA-1 negative, a fact admitted by the Patent Owner during prosecution of a parent application to the '913 patent. Andrew, *Human Teratocarcinomas*, 948 Biochim. Biophys. Acta 17 - 26, 26 (1988) ("Andrews '88") (attached hereto in Appendix B); Amendment, September 29, 1997, U.S. Appl. No. 08/591,246 (issued as U.S. Patent No. 5,843,780), p. 11 ("human cells in culture can be SSEA-1 negative . . . is admitted by the applicant") (attached hereto in Appendix C). As such, it was entirely predictable by those of skill in the art that human ES cells would also be SSES-1 negative.

The cells in Hogan '926 referred to by the Patent Owner were SSEA-1 positive because they were murine. Hogan '926 at 9:20 -10:45. It was well known that murine cells, be they EC or ES, are SSEA-1 positive. Loring Declaration at 5 (citing Solter, D., and Knowles, B.B., *Monoclonal antibody defining a stage-specific mouse embryonic antigen (SSEA-1)*, Proc. Natl. Acad. Sci. USA 75, 5565-5569 (1978) (attached hereto in Appendix B along with two other new references cited in the Loring Declaration but not expressly mentioned in these comments)). This fact doesn't distinguish Hogan '926 from the instant claims because one of ordinary skill in the art would have nonetheless expected human ES cell isolated according to Hogan '926's teaching to be SSEA-1 negative. *Id.*

Next, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells require exogenous LIF. However, Hogan '926 used LIF in its preferred embodiment because "[p]revious studies" showed LIF could promote survival of mouse primordial germ cells. 1:41-44. Specifically, Hogan '926 referred to Williams '065 for information about the use of LIF, which, as discussed above, taught that LIF was a "substitute" for feeder layers. 4:56-59. Furthermore, Hogan '926 expressly taught that, "the cells may be maintained on a feeder layer without the addition of growth factors." 6:39-40. And, the specification of Hogan '926's parent patent states, "FGF, LIF or SF may not be required for maintenance of ES cells." 1:4-5 (claiming priority as a continuation-in-part of U.S. Ser. No. 07/958,562, filed Oct. 8, 1992, now U.S. Pat. No. 5,453,357; U.S. Patent No. 5,454,357, 4:55-57 (emphasis added). Thus, Hogan '926 did not "require" LIF, as the Patent Owner claims.

Lastly, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926 cells cannot form trophoblast. Although it may be true that Hogan '926 germ cells do not form trophoblast, embryonic stem cells were known to be capable of doing so. Loring Declaration at 5. In humans, it was expected that although human embryonic germ (EG) cells may not form trophoblast, human embryonic stem cells would be able to do so, because there is a wide variety in the development potential of human ES and EG cells. *Id.* Further, some human EC lines, which were expected to predict human ES cell line behavior, had been shown to experience trophoblast-like differentiation. Andrews '88 at 29. Thus, one of ordinary skill in the art would have predicted that human pluripotent cells isolated according to Hogan '926's teaching could be able to form trophoblast. Loring Declaration 5 - 6. Therefore, this difference cited by the Patent Owner between the human embryonic stem cells of the instant claims on the one hand and the teaching of Hogan '926 on the other is

insufficient to justify departure from the general understanding and belief of the applicability of scientific knowledge between them.

As such, it was entirely appropriate and correct for the Examiner to reject the pending claims as being anticipated by or obvious over Hogan '926.

Others Did Not Fail To Make The Claimed Invention

As discussed above, none of the Patent Owner's proffered evidence of the failure of others is relevant to the issue of whether the pending claims are obvious because none of it shows a failure to achieve the patented invention. Thus, the evidence does not rebut the Examiner's *prima facie* obviousness rejection.

Even if one assumes *arguendo* that such evidence is relevant, when viewed correctly, it actually supports the Examiner's rejection of the pending claims. And, contrary to the Patent Owner's arguments, the science of isolating and maintaining embryonic stem cells was predictable, as shown by the fact that other scientists were successful at deriving and maintaining human embryonic stem cells contemporaneously with Dr. Thomson. Trounson Declaration at 6 - 7; Reubinoff '99 at 399.

Public Acclaim Is Not Relevant to Patentability

Also as discussed above, the evidence proffered by the Patent Owner regarding public acclaim of Dr. Thomson's accomplishment is irrelevant to the determination of whether the pending claims were sufficiently inventive to be patentable. Thus, this evidence does not rebut the Examiner's *prima facie* obviousness determination either.

Even if one assumes arguendo that such evidence is relevant, not all scientific accomplishments are necessarily deserving of patents and, as Justice Kennedy stated for a unanimous Supreme Court just this Spring in KSR, "[g]ranting patent protection for advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. 1741. Here, Dr. Thomson's accomplishment was not a result of sufficient scientific ingenuity to be deserving of a patent, but rather was more attributable to his having special access to two limited resources that other embryonic stem cell researchers who were pursuing the same accomplishment at the same time did not have. Melton Declaration at 5 - 6; Loring Declaration at 10; Cowan Declaration at 5 - 6. Had others in the field been given the same special access to those limited resources, namely human embryos and funding to do research using human embryos, they would have achieved -- and in fact some did achieve -- the same accomplishment as Dr. Thomson. Trounson Declaration at 6 - 7; Loring Declaration at 10; Reubinoff '00 at 399.

Relatedly, the fact that his accomplishment received praise and recognition does not help to distinguish between what factors led to the accomplishment and, more specifically, does not mean that the accomplishment was necessarily patent worthy.

Examiner:

A. Hogan fails as a reference under both 35 USC §102(b) and §103(a)

The Examiner finds the comments of the Patent Owner to be persusaisve with regard to the teachings of Hogan '926. Hogan '926 neither anticipates nor renders obvious the instantly claimed primate/human ES cells of Thomson '913.

At page 17, lines 9 - 32, the Patent Owner argues that the ES (EG) cells derived by Hogan '926 differ from the primate/human ES cells claimed by Thomson '913 because Hogan's cell are derived from primordial germ cells in post-implantation embryos instead of from pre-implantation embryos. While both the starting materials and the isolation procedures employed by Hogan '926 versus Thomson '913 are clearly different, these differences do not permit one to automatically conclude that the ES or EG cells isolated therefrom and thereby, respectively, must necessarily be different. These differences in source materials and processes for isolation only increase the likelihood that the isolated cells are different, but are not positive evidence of final cell differences.

At page 17, last four lines to page 18, line 11, The Patent Owner argues next that the primate/human ES cells of Thomson '913 are clearly different from the EG/ES cells disclosed by Hogan '926 because primate/human ES cells are marker SSEA-1 negative while Hogan's ES/EC cells are SSEA-1 positive. This is a false comparison, i.e., not a comparison of "apples to apples", because Thomson's ES cells are derived from primates/humans versus the exemplified ES/EG cells of Hogan '926 to which the Stewart Declaration (¶26) refers are mouse EG cells not human EG cells. Hogan '926

further emphasizes that the fact that the mouse EG cells are SSEA-1 positive is consistent with mouse primordial germ cells, mouse undifferentiated embryonal carcinoma (EC) and mouse ES cells all possessing the same shared SSEA-1 positive marker (Hogan, column 10, lines 1 - 4). A valid comparison would be a side-by-side comparison of Thomson's primate ES cells and the exemplified and claimed human ES/EG cells of Hogan '926 (see column 12, lines 15 - 62 and claims 6 - 7). Consistent with the mouse data, since human embryonal carcinoma (EC) cells are SSEA-1 negative, the artisan would also have expected human ES and EG cells also to be SSEA-1 negative. However, Hogan '926 is silent about the presence or absence of this cell surface marker in the isolated human EG cells. Therefore, the only way to unequivocally resolve this issue and that is to turn to subsequent scientific publications.

In order to distinguish Thomson's primate/human ES cells from Hogan's human EG cells, there needs to be only a clear difference in a single cell surface marker.

1. Similarities between primate/human ES cells and human EG cells

(1) Both are pluripotent, meaning they can differentiate into ectoderm, mesoderm, and endoderm (Hogan, claims 6 and 7).

(2) Both can be maintained in the undifferentiated state in culture in the presence of feeder cell layers (Hogan, claims 6 and 7).

(3) Both are positive for alkaline phosphatase (Hogan, column 12, lines 52 - 56).

2. Thomson '913 Criteria Undetermined in Hogan '926

(a) Can human EG cells be maintained in culture in the undifferentiated state without exogenous leukemia inhibitory factor (LIF)?

(b) Can human EG cells be maintained in culture in the undifferentiated state for at least one year?

(c) Can human EG cells maintain normal karotype throughout prolonged culture?

(d) Can human EG cells spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density?

(5) Are human EG cells positive for SSEA-4 cell surface marker?

3. Documented Difference between primate/human ES cells and human EG cells

Human ES cells are SSEA-1 negative while human EG cells are SSEA-1 positive. See page 532, left column, lines 13 - 23 in Aflatoonian et al., "Human primordial germ cells and embryonic germ cells, and their use in cell therapy," *Current Opinion in Biotechnology* 2005, 16: 530-535.

4. Hogan '926 does not anticipate Thomson's ES cells

The pluipotent human EG cells isolated by Hogan '926 cannot anticipate nor render obvious the primate/human pluripotent ES cells claimed by Thomson '913 because:

(a) Thomson's ES cells were negative for the SSEA-1 cell surface marker while EG cells are positive for this same marker.

(b) Thomson's ES cells were maintained in culture in an undifferentiated state for at least one year. Hogan claims human EG cells that have been maintained for at least 20 passages.

(c) Hogan '926 fails to establish that her human EG cells can be cultured without exogenous LIF in the undifferentiated state for at least one year.

(d) Hogan '926 failed to establish that human EG cells maintain normal karotype through prolonged culture.

(e) Hogan '926 failed to establish that human EG cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

(f) Hogan '926 failed to establish that human EG cells are positive for SSEA-4 cell surface marker.

Further evidence of record of the difference between Thomson's primate/human ES cells and the human EG cells of Hogan '926 is provided by Dr. Loring declaration where she implicitly acknowledges the lack of identity betweens the ES cells of Thomson '013 and those of Hogan '926 in her use of the word "similar" to describe the relationship between these to types of pluripotent but different cells: "The resulting pluropotent cells will be structurally and functionally similar." (page 4, paragraph 11).

Therefore, Hogan '926 does not teach all of the elements of claims 1 - 3 of Thomson '913 as required for a *prima facie* case of anticipation. Furthermore, Hogan '926 cannot be used to establish a *prima facie* case of obviousness either since there is

no teaching in Hogan '926 or in the prior art explaining how the artisan could transform the human EG cells of Hogan '926 into the primate/human ES cells of Thomson '913.

GROUND #6: Claims 1 - 3 are rejected under 35 U.S.C. §103(a) as being obvious over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926. The complete explanation of this rejection at pages 15 - 18 of the Office action of 30 March 2007 is hereby incorporated by reference into this Office action. The preponderance of the evidence of record supports the conclusion that the rejection of claims 1 - 3 over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926 does not establish a *prima facie* case of obviousness because the unpredictability in the art creates a lack of a reasonable expectation of success. Therefore, **this rejection has been withdrawn.**

GROUNDS #6 (103(a)): Patent Owner's Response, Third Party Requester's Comments, Examiner's Decision

Patent Owner:

A. Robertson '83 and '87 in view of Williams '065 and Hogan '926 does not create case of prima case of obviousness
(Response, page 19, line 15 to page 21, line 7)

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 a *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