TimeBase Pty Ltd. v. Thomson Corporation, The et al Doc. 41 Att. 50

Exhibit 5
Part 46
To Third Declaration of
Joseph N. Hosteny

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dissipates the *prima facie* holding and requires that 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 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, 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: 569-575). 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, line 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; 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. **Robertson '83 and '87 in view of Williams '065 and Hogan '92 creates a prima facie case of obviousness**
(page 28, line 14 to page 34, last line)

In the Office Action, the Examiner rejected all three claims as being obvious over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926. Office Action at 15. The Examiner found that, "[t]he difference between the combined teaching of Robertson '83 and Robertson '87 and claims 1 - 3 of the '913 patent is that the Robertson references disclose mouse embryonic stem cells while the '913 patent claims human embryonic stem cells," that "the Williams '065 patent does disclose human embryonic stem cells," and that "Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer." *Id* at 16 - 17. The Patent Owner made several arguments in its Response as to why the combined teaching of Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926 does not invalidate the pending claims, but those arguments are all without merit. Thus, the Examiner's rejection of the pending claims based on Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926 was and remains appropriate.

The Patent Owner first argues in the Response that one of skill in the art would not have applied Robertson's teachings relating to mouse embryonic stem cells to derive and maintain human embryonic stem cells. This is not scientifically defensible. First, as the Examiner recognized in the Office Action, a main reason scientists study mice is to learn things that can be applied to humans, Office Action at 17 ("goal of most of the animal studies is to ultimately prepare human ES cells that have numerous therapeutic possibilities"). To argue that what such scientists knew about the embryonic stem cells of other mammals was not relevant to human embryonic stem cells is simply ludicrous.

Further, although the Federal Circuit may have in the past implemented a rigid rule that a patent claim cannot be rendered obvious merely because it was "obvious to try," the Supreme Court in KSR expressly reversed that rule, saying:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." . . .When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictably solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under

§103.

127 S. Ct. at 1742. Here, even the Patent Owner admitted during prosecution of a parent application to the '913 patent that it was "obvious to try" applying methods known to work for the derivation and maintenance of embryonic stem cells in one species to derive and maintain embryonic stem cells for other animals. Amendment, July 17, 1986, U.S. Appl. No. 08/376,327, p. 6 (stating "[t]he methods from one class of animals might or might not be obvious to try in another animal." And "[t]his is a clear situation of 'obvious to try,' since one might be motivated from the cited reference to try this general approach") (attached hereto in Appendix C).

Drs. Melton, Trounson, Loring and Cowan also agree that it was obvious to try combining the prior art teachings relating to mammalian embryonic stem cell isolation and culture in order to derive and maintain human embryonic stem cells. Melton Declaration at 3; Trounson Declaration at 4; Loring Declaration at 6; Cowan Declaration at 3. This supports the Examiner's position that the result of that combination, which is claimed in the instant claims, was more likely the result of ordinary skill and common sense than patentable innovation.

Next, The Patent Owner argues that "[t]he central tenet of the Williams patent is the use of LIF to render independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells and explicitly in the present claims 1 -3." Response at 20. However, the Patent Owner reads Williams '065's disclosure too narrowly, limiting it to its preferred embodiment and not taking into account all of its teachings, suggestions and motivations as identified by the Examiner in the Office Action. While it may be true that Williams '065 was principally directed towards researching the ability to use LIF to maintain ES cells without feeder layers, its teachings did not exclude cultures maintained with only feeder cells in the absence of LIF. Loring Declaration at 3 - 4. Specifically, Williams '065 expressly states that LIF can "substitute" for feeder layers in supporting the maintenance of pluripotential ES cells. Williams '065 at 1:58 - 62, 3:62-64 ("LIF may be used to substitute for, or add to feeder cells"). Further, contrary to the Patent Owner's interpretation, a skilled artisan would not understand that Williams '065 is "directed to the *advantages* of LIF in isolating and maintaining ES cells." Response at 15 (emphasis added.) Rather, those of skill in the art understood Williams '065 to be directed to showing the *capability* of LIF to be used in isolating and maintaining ES cells. Loring Declaration at 3 - 4 ("Williams '065 discovery was merely that LIF could be used . . . , not that it was an improvement over feeder layers"). Thus, the Patent Owner's proposed interpretation of Williams '065 as requiring LIF should be rejected.

Finally, the Patent Owner argues that, "Hogan's cells are EG cells, not ES cells," and, "[t]he skilled artisan, upon reading Hogan, would not be motivated to follow Hogan to arrive at the presently claimed cells." Response at 30. However, as Dr. Thomson himself recognized, human embryonic germ cells and human embryonic stem cells are very closely related and, thus, knowledge regarding one is 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.

Even if one looks purely at Robertson '83 and Robertson '87 without Williams '065 or Hogan '926, the instant claims would still be obvious because one of ordinary skill in the art was motivated by both common knowledge and common sense to apply the results of mouse studies to human research, and specifically to use the methods taught by Robertson '83 and Robertson '97 for deriving mouse embryonic stem cells to derive human embryonic stem cells. Melton Declaration at 3: Trounson Declaration at 4; Loring Declaration at 6; Cowan Declaration at 3. To be sure, while there may have previously been some debate on the issue, the Federal Circuit expressly stated in *Dystar* that common knowledge and common sense are sufficient sources of motivation to combine references:

> In contrast to the characterization of some commentators, the suggestion test is not a rigid categorical rule. The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.
>
> . . .
>
> Contrary to some interpretations, we stated explicitly that evidence of a motivation to combine need not be found in the prior art references themselves, but rather may be found in "the knowledge of one of ordinary skill in the art, or, in some cases from the nature of the problem to be solved.
>
> . . .
> We noted that our predessor court held more that thirty years earlier that "common knowledge and common sense: were sufficient to establish a motivation to combine.
>
> . . .
> Our suggestion test is in actually quite flexible and not only permits, but requires, consideration of common knowledge and common sense.

464 F.3d at 1361 and 1366 - 67. Thus, Examiner's reliance on Williams '065 and Hogan '926 for providing the motivation to isolate and maintain animal ES cell (including human) in vitro for longer periods on a (fibroblast) feeder layer, while entirely correct and supported by the evidence, is not necessary to reject the pending claims as being obvious over Robertson '83 and Robertson '87. Office Action at 16 - 17.

As such, it was entirely appropriate and correct for the Examiner to reject the pending claims as being obvious over Robertson' 83 and Robertson '87 in view of Williams '065 and 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, this evidence does not rebut the Examiner's *prima facie* obviousness determination.

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 culturing human 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 '00 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 patent and, 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 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 Delaration 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 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 this accomplishment received praise and recognition does not help to distinguish between what factors let to the accomplishment and, more specifically, does not mean that the accomplishment was necessarily patent worthy.

Examiner:

A. **Robertson '83 and '87 in view of Williams '065 and Hogan '926 does not establish a *prima facie* case of obviousness.**

The Examiner finds the remarks of the Patent Owner persuasive with respect to the rejection of claims 1 - 3 as obvious over Robertson '83 and '87 in view of Williams '065 and Hogan '926.

The Examiner agrees with the Patent Owner that "clear and convincing evidence" is not the legal standard to rebut a *prima facie* case of obviousness. The Patent Owner only has to present evidence that supports the opposite conclusion. At that point the law requires the examiner to consider all of the evidence of record anew.

Both the Patent Owner and the Third Party Requester agree that each Robertson reference ('83 and '87) discloses a method for isolating and maintaining mouse ES cells in culture. Considering only the teachings of Robertson '83 or '87, the motivation to isolate primate/ human ES cells flows from common sense and from common knowledge in the art of embryonic stem cells concerning the desire to apply the results from mouse to primates/human tissue for the potential treatment of human diseases. As the Third Party Requester asserts, there is compelling motivation for the artisan to use the method of isolating and maintaining mouse ES cells as taught by the two Robertson references alone, even without Williams '065 and Hogan '926. The teachings of Williams '065 have been discussed previously at pages 7 - 48 of this Office action. The teachings of Hogan '926 have been discussed previously at pages 48 - 57 of this Office action.

The Patent Owner correctly emphasizes the unpredictable nature of the art of isolating and maintaining ES cells. (See the analysis of prior art references at pages 15 - 36). Mouse ES cells are the most intensively investigated embryonic stem cells, but

even with that experience, some strains of mice are fail to yield ES cells (Steward Declaration, ¶12). Furthermore, there was no conclusive evidence in the prior art that anyone had successfully isolated ES cells from domestic animals such as sheep, pig, and cattle using the same procedure as developed for the mouse. Therefore, for the artisan to jump directly from rodents to primates/human without first mastering the isolation and maintenance of higher mammals including sheep, pigs, and cattle underscores the lack of predictability in the art of isolating and maintaining ES cells at the time of Thomson's invention. It is this unpredictability that leads to the conclusion that there is no reasonable expectation of success. Without a reasonable expectation of success there can be no *prima facie* case of obviousness. Furthermore, without a *prima facie* case of obviousness, secondary considerations asserted by the Patent Owner such as public acclaim are unnecessary.

The TPR argues that ". . . although the Federal Circuit may have in the past implemented a rigid rule that a patent claim cannot be rendered obvious merely because it was "obvious to try," the Supreme Court in KSR expressly reversed that rule, saying:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." . . .When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictably solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

However, in the instant situation, it is the lack of expectation of success created by the unpredictability in the art which distinguishes this case from KRS. In KSR all of the combinable parts were mechanical parts for which there was no doubt how they would function when used together.

For the reasons presented above, the rejection of claims 1 - 3 under 35 USC §103(a) as obvious over Robertson '83 and '87 in view of Williams '065 and Hogan '926 has been withdrawn.

GROUNDS #7 (103(a)): Claims 1 - 3 are rejected under 35 U.S.C. §103(a) as being obvious over Piedrahita et al. (Theriogenology, 34(5): 879-901, 1990) in view of Williams '065 and Hogan '926. The complete explanation of this rejection at pages 18 - 20 of the Office action of March 30, 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 Piedrahita et al. in view of Williams '065 and Hogan '926 does not establish a prima facie case of obviousness because the unpredictability in the embryonic stem cell art creates a lack of a reasonable expectation of success. Therefore, **this rejection has been withdrawn.**

Patent Owner:

A. Piedrahita '90 in view of Williams '065 and Hogan '926 does not establish a *prima facie* case of obviousness

(Response, page 21, line 7 to page 23, line 21)

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 placed on STO or HEF feeders gave rise to cell line 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 the ovine embryos and 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 problem 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 mouse 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 et al., 1994, Reprod. Fertil. Dev. 6: 569-575). 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.

Third Party:

A. Piedrahita in view of Williams '065 and Hogan '926 supports obviousness

In the Office Action, the Examiner rejected all three claims as being obvious over Piedrahita '90 in view of Williams '065 and Hogan '926. Office Action at 18. The Examiner found that, "Piedrahita '90 discloses murine, porcine, and ovine ES cells," that "the Williams '065 patent does disclose human embryonic stem cells,' and that Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including

human) *in vitro* for longer periods on a (fibroblast) feeder layer." *Id.* at 18 - 19. The Patent Owner made several arguments in its Response as to why the teaching of Piedrahita '90 in view of Williams '065 and Hogan '926 does not invalidate the pending claims, but those arguments lack merit. Thus, the Examiner's rejection of the pending claims based on Piedrahita '90 in view of Williams '065 and Hogan '926 was and remains appropriate.

The Instant Claims Are Not Patentably Distinguishable From Piedrahita '90 In View of Williams '065 and Hogan '926

The Patent Owner first argues in the Response that one of skill in the art would not have applied Piedrahita '90's teachings relating to mouse, sheep, and pig embryonic stem cells in order to derive and maintain human embryonic stem cells. This is not scientifically defensible. First, as the Examiner recognized in the Office Action, a main reason scientists study mice, sheep and pigs is to learn things that can be applied to humans. Office Action at 19 ("goal of most studies of animal ES cells is to ultimately prepare human ES cells that have numerous therapeutic possibilities for treating human diseases.") To argue that what such scientists knew about the embryonic stem cells of other mammals was not relevant to human embryonic stem cells is simply ludicrous.

Further, although the Fed. Cir. may have in the past implemented a rigid rule that a patent claim cannot be rendered obvious merely because it was "obvious to try," the Supreme Court in KSR expressly reversed that rule, saying:

> The same constricted analysis led the Court of Appeals to conclude in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try" . . . When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

127 S. Ct. at 1742. Here, even the Patent Owner admitted during prosecution of a parent patent application to the '913 patent that it was "obvious to try" applying methods known to work for the derivation and maintenance of embryonic stem cells in one species to derive and maintain embryonic stem cells for other animals. Amendment, July 17, 1986, U.S. Appl. No. 08/376,327, p. 6 (stating "[t]he methods from one class of animal might or might not be obvious to try in another animal," and [t]this is a clear situation of 'obvious to try,' since one might be motivated from the cited reference to try this general approach.

Drs. Melton, Trounson, Loring, and Cowan also each agree that it was obvious to try combining the prior art relating to mammalian embryonic stem cell isolation and

culture in order to derive and maintain human embryonic stem cells. Melton Declaration at 4; Trounson Declaration at 5; Loring Declaration at 7; Cowan Declaration at 4. This supports the Examiner's position that the result of that combination, which is claimed in the instant claims, was more likely the result of ordinary skill and common sense than patentable innovation.

Second, the Patent Owner argues the "[Piedrahita] teaches that the methods used to create and culture ES cells could not be made to work on porcine and ovine systems." Response at 20. However, the Examiner was correct in the Office Action in finding that "Piedrahita discloses murine, porcine and ovine ES cells." Office Action at 18. While Piedrahita '90 may not have actually isolated such ES cells, that does not make it evidence of an impossibility of applying the methods for isolating and maintaining mouse ES cells to derive and culture porcine and ovine embryonic stem cells, because its disclosure was sufficient to enable one of ordinary skill in the art to do so. Loring Declaration at 7.

Next, the Patent Owner. argues that "[t]he 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 and explicitly contradicted in the present claims 1 - 3." Response at 20. However, the Patent Owner reads Williams '065's disclosure too narrowly, limiting it to its preferred embodiment and not taking into account all of its teachings, suggestions and motivations as identified by the Examiner in the Office Action. While it may be true that Williams '065 was principally directed towards researching the ability to use LIF to maintain ES cells without feeder layers, its teachings did not exclude cultures maintained with only feeder cells in the absence of LIF. Loring Declaration at 3 - 4. Specifically, Williams '065 expressly states that LIF can "substitute" for feeder layers in supporting the maintenance of pluripotential ES cells. Williams '065 at 1:58-62 and 3:62-64 ("LIF may be used to substitute for, or add to, feeder cell"). Further, contrary to the Patent Owner's interpretation, a skilled artisan would not understand that Williams '065 is "directed to the *advantages* of LIF in isolating and maintaining ES cells." Response at 15 (emphasis added.) Rather, those of skill in the art understood Williams '065 to merely be directed to showing the *capability* of LIF to be used in isolating and maintaining ES cells. Loring Declaration at 3 - 4 ("Williams '065's discovery was merely that LIF could be used . . ., not that it was an improvement over feeder layers"). Thus, the Patent Owner's proposed interpretation of Williams '065 as requiring LIF should be rejected.

Finally, the Patent Owner argues that, "Hogan specifically states that her post-implantation embryo derived cells are different from pre-implantation embryo derived cells," and that, "[t]he skilled artisan, upon reading Hogan would not be motivated to follow Hogan to arrive at the presently claimed cells." Response at 23. However, the Patent Owner makes no argument that post-implantation embryos of Hogan '926 have any structural 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. As such, this is not a patentable distinction between what Hogan '926 taught and the instant claims.

As such, it was entirely appropriate and correct for the Examiner to reject the pending claims as being obvious over Piedrahita '90 in view of Williams '065 and 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 '00 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 states 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 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 let to the accomplishment and, more specifically, does not mean that the accomplishment was necessarily patent worthy.

Examiner:

The Examiner finds the comments of the Patent Owner to be persuasive with respect to the rejection of claims 1 - 3 over Piedrahita '90 in view of Williams '065 and Hogan '926.

The Patent Owner argues that Piedrahita '90 only discusses ovine and porcine ES cells of but does not successfully isolate them using the procedure developed for murine ES cells. Neither the ovine nor porcine ES-like cells demonstrated that they were pluripotent. Only epithelial cells could be derived from the ovine embryos and the porcine cell lines created by Piedrahita could not even differentiate. Thus, the Patent Owner emphasizes that Piedrahita cannot be used in a prima facie case of obviousness because it actually teaches that murine isolation system is completely ineffective for isolating and maintaining ES cells from sheep and pig. The Examiner agrees with these remarks.

The Williams '065 patent was used by the Examiner to establish the motivation for applying the murine methodology for isolating and maintaining ES cells to human and other domestic animal embryos. However, the Patent Owner has pointed out that the teaching of Williams '065 is contradicted by his own words from the Cherny/Williams '94 paper:

> ES cell lines of proven totipotency have thus far been isolated only from the mouse. (second sentence of Abstract)
> Initial research into the isolation of domestic animal ES cell in our laboratories attempted to repeat the work carried out in mice by isolating cell lines directly from culture preimplantation embryos. Published reports of such studies in pigs, cattle, and sheep, together with our own research, indicated that cells which displayed some ES cell characteristics could be identified but

> the isolation of proven pluripotential ES cell lines remained elusive (Handyside et al. 1987; Piedrahita et al.; Notarianni et al .; Sims and First 1993).
>
> (Cherny/Williams '94 at page 571, left column, lines 3-13)

These remarks by Cherny/Williams about the work of Piedrahita, and their previous own work were made just about one year prior to Dr. Thomson's filing of his patent application. Such statements would strongly demotivate the artisan to try to isolate primate/human ES cells. Additionally, they underscore along with the other references already discussed in this action (see pages 16 - 36) that the art of ES cell isolation and maintenance was complexity and highly unpredictable at the time of the invention.

The Hogan '926 patent is consistent with this conclusion because the motivation of the inventor to isolate human pluripotent, ES-like cells from primordial germ cells was the failure of others to successfully use the mouse methodology with other types of animals to prepare ES cells. Writing after Piedrahita '90, Hogan observes.

> Since pluripotential embryonic stem cells (ES) can give rise to virtually mature cell type they are of great value for uses such as creating genetically manipulated animals. However, according to the published scientific literature, it has previously been possible only to obtain ES cells from mice. These murine ES cells were obtained from cultures of early blastocysts. Attempts at isolating ES cells from other animals apparently have failed. (column 1, lines 56 - 64)

Therefore, when taken as a whole, Piedrahita in view of Williams '065 and Hogan '065 cannot establish that the instant claims directed to proliferating in vitro cultures of primate/human ES cells without exogenous LIF are *prima facie* obvious. While the desire to obtain primate/human ES cells is compelling because of their enormous potential to grow into any cell type, the failure of others both demotivates other

scientists and underscores the complexity and unpredictability of the art of isolating and maintaining ES cells in culture.

Public acclaim is a secondary consideration of non-obviousness that must be fully considered. However, no secondary consideration is required when a case of prima facie obviousness has not been established. Furthermore, the weight given such public acclaim is a function of the knowledge, training, and experience of those honoring the invention and inventor. Apart from full knowledge of the background of the persons selecting the inventor for acclaim, the examiner has insufficient grounds for evaluating this evidence. The Third Party asserts that the issue of public acclaim raised by the Patent Owner is irrelevant to patentability. This is incorrect. Public acclaim one can conclude that public acclaim is consistent with a pioneering invention. But by itself, public acclaim carries little weight as evidence of non-obviousness.

GROUNDS #8 (103(a)): Patent Owner's Response, Third Party Requster's Comments, Examiner's Decision

Claims 1 - 3 are rejected under 35 U.S.C. §103(a) as being obvious over Robertson '83, Robertson '87, and Piedrahita '90 in view of Williams '065 and Hogan '926. The complete explanation of this rejection at pages 20 - 22 of the Office action of March 30, 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, Robertson '87, and Piedrahita '90 in view of Williams '065 and Hogan '926 does not establish a prima facie case of obviousness because the unpre-

dictability in the embryonic stem cell art created a lack of reasonable expectation of success at the time of the invention. Therefore, **this rejection has been withdrawn.**

Patent Owner:

A. Robertson '83 and '87 and Piedrahita in view of Williams '065 and Hogan '926 does not support prima facie obviousness
(Response, page 23, line 21 to page 24, line 19)

The Examiner rejected claims 1 - 3 as being obvious [over] Robertson I, Robertson II, and Piedrahita in view of William 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 rejection. 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 cell 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.

Third Party:

A. Robertson '83 and '87 and Piedrahita in view of Williams '065 and Hogan '926 does support the obviousness of the invention
(Comments, page 40, line 14 to page 41, line 9)

In the Office Action, the Examiner rejected all three claims as being obvious over Robertson '83, Robertson '87 and Piedrahita '90 in view of Williams '065 and Hogan '926. Office Action, 18. The Examiner found that, "[t]he difference between the combined teachings of Robertson '83, Robertson '87 and Piedrahita '90 and the instant claims 1 - 3 is that the Thomson '913 patent claims are directed to human ES cells while the combined teachings of Robertson '83, Robertson '87 and Piedrahita '90 are directed to ES cells of mice, sheep, and pigs," that "the Williams '065 patent does disclose human embryonic stem cells," and that "Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer." *Id.* at 18 - 19.

In the Response, the Patent Owner refers the Examiner to the arguments it made in response to the rejections based on Robertson '83, Robertson '87 in view of Williams '065 and Hogan '926 and on Piedrahita in view of Williams '065 and Hogan '926. Response at 23 -24. As such, FTCR similarly refers to its comments regarding those grounds of rejection for this grounds of rejection. In short, the Examiner's rejection of the pending claims based on Robertson '83, Robertson '87 and Piedrahita '90 in view of Williams '065 and Hogan '926 was and remains appropriate.

Examiner:

The Examiner finds the comments of the Patent Owner to be persuasivee with regard to the rejection of claims 1 - 3 as not being obvious over Robertson '83 and '87 and Piedrahita in view of Williams '065 and Hogan '926.

Each of the references in this rejection has already been thoroughly discussed in the earlier rejections. As explained repeatedly by the Patent Owner, each of the five references in this rejection teaches the failure of other scientists to isolate and maintain proven ES cells from animals other than rodents, many would even say mice alone. This repeated failure to transfer the success in mice to higher mammals such as

sheep, pigs, and cattle would undoubtedly demotivate the artisan to even attempt the most complex animals of all: primates and humans. Furthermore, the failure to establish ES cell lines of higher mammals documents the complexity and unpredictability of isolating and maintaining ES cells in culture.

Supplemental Amendment filed October 4, 2007

The Patent Owner filed the supplemental amendment in order to place the case in condition for allowance. Claim 1 was amended to recite "pluripotent" to make explicit an inherent characteristic of embryonic stem cells. There is support for this amendment at column 11, lines 25 - 28 of the '913 patent. Claim 1 was previously amendment at the time of the Patent Owner Response to specify that the human ES cells are "derived from a pre-implantation embryo." There is support for this amendment in the specification at least in column 8, lines 34 - 42 and column 9, lines 29 - 33. Finally, the Patent Owner clarifies meaning of the phrase "capable of proliferation in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor" in claim 1 by reciting "will proliferate in an in vitro culture for one year in an undifferentiated state without the application of exogenous leukemia inhibitory factor." There is support for this amendment at column 4, lines 19 - 25 of the specification.

None of these amendments to the claims is required to overcome the prior art rejections of the non-final action mailed March 30, 2007. However, these amendments do provide further clarity to the claims, and thus, places the case in condition for allowance.

Third Party Requester's Response to Amendment filed October 4, 2007

The Third Party Requester (TPR) argues at length that none of the specific amendments to the claims defines the claims of the '913 patent over the prior art. The examiner agrees with the position that none of the amendments proposed by the Patent Owner, in and of themselves, overcomes the prior art of record. This is because the amendments only further clarify and define the invention. Even without the supplemental amendment filed October 4, 2007, the claims are free of the prior art. The reasons for the withdrawal of all rejections of records have been explained repeatedly throughout this Office action and are, once again, reiterated under "Summary of Reasons for Patentability" supra.

Conclusion

Each of the five rejections of claims 1 - 3 of the Thomson '913 patent presented in the previous non-final Office action has been withdrawn. Claims 1 - 3 are allowable.

Summary of Reasons for Patentability

The prior art of record fails to disclose a replicating in vitro cell culture of human embryonic stem cells derived from a pre-implantation embryo which (1) will proliferate in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor; (2) will maintain a karyotype in which chromosomes are euploid through prolonged culture; (3) will maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture; (4) are inhibited from differentiation when cultured on a fibroblast feeder layer; (5) will spontaneously

differentiate to trophoblast and produce chorionic gonadotropin when culture to high density; (6) are negative for the SSEA-1 marker; (7) are positive for the SSES-4 marker; and (8) express alkaline phosphatase. Furthermore, the preponderance of the evidence of record is quite clear that the instantly claimed replicating in vitro culture of human embryonic stem cells are not obvious because of the highly complex and unpredictable nature of the art of isolating and maintaining embryonic stem cells leading to a lack of a reasonable expectation of success. Without a reasonable expectation of success, there can be no prima facie case of obviousness.

Action Closing Prosecution

This is an ACTION CLOSING PROSECUTION (ACP); see MPEP § 2671.02.

(1) Pursuant to 37 CFR 1.951(a), the patent owner may once file written comments limited to the issues raised in the reexamination proceeding and/or present a proposed amendment to the claims which amendment will be subject to the criteria of 37 CFR 1.116 as to whether it shall be entered and considered. Such comments and/or proposed amendments must be filed within a time period of 30 days or one month (whichever is longer) from the mailing date of this action. Where the patent owner files such comments and/or a proposed amendment, the third party requester may once file comments under 37 CFR 1.951(b) responding to the patent owner's submission within 30 days from the date of service of the patent owner's submission on the third party requester.

(2) If the patent owner does not timely file comments and/or a proposed amendment pursuant to 37 CFR 1.951(a), then the third party requester is precluded from filing comments under 37 CFR 1.951(b).

(3) Appeal **cannot** be taken from this action, since it is not a final Office action.

Extensions of Time

Extensions of time under 37 CFR §1.136(a) will not be permitted in these proceedings because of the provisions of 37 CFR §1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 USC §314 requires that

inter partes reexamination proceedings "will be concluded with special dispatch" (37 CFR §1.937. Extensions of time in *inter partes* reexamination proceedings are provided for in 37 CFR §1.956.

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings have been merged) in the reexamination proceedings in the manner provided in 37 CFR §1.903. See 37 CFR §1.530(f).

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

> *Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination*, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.
This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is

strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished applications my be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions about access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this Ex parte Reexamination proceeding should be directed to:

By Mail to:

Attn: Mail Stop "Inter Partes Reexam"
Central Reexamination Unit
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to:

(571) 273-9900
Central Reexamination Unit

By hand to:

Customer Service Window
Randolph Building
401 Dulany Street
Alexandria VA 22314

Conferee:

DEBORAH D. JONES
CRU SPE-AU 3991

Gary L. Kunz
Primary Examiner
Art Unit 3991

Conferee:

BENNETT M. CELSA
CRU EXAMINER - AU 3991
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, VA 22313-1450
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DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA PA 19103-6996

EXAMINER	
Gary L. Kunz	
ART UNIT	**PAPER**
3991	

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03/30/2007

INTER PARTES REEXAMINATION COMMUNICATION

BELOW/ATTACHED YOU WILL FIND A COMMUNICATION FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE OFFICIAL(S) IN CHARGE OF THE PRESENT REEXAMINATION PROCEEDING.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this communication.