

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO.: 5,843,780  
ISSUED: December 1, 1998  
TO: Thomson  
FOR: PRIMATE EMBRYONIC STEM CELLS

ATTACHMENT TO FORM PTO-1465,  
REQUEST FOR *EX PARTE* REEXAMINATION

SIR:

On behalf of the Foundation for Taxpayer and Consumer Rights (“FTCR”), a nationally recognized not-for-profit organization that represents the interests of taxpayers and consumers, the Public Patent Foundation (“PUBPAT”) respectfully requests *ex parte* reexamination under 35 U.S.C. §§ 302 – 307 and 37 C.F.R. § 1.510 of every claim of United States Patent No. 5,843,780 (“the ‘780 patent”) issued December 1, 1998, to Thomson because they are all invalid under 35 U.S.C. §§ 102 and 103 and their existence is causing significant public harm.<sup>1</sup>

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<sup>1</sup> A copy of the ‘780 patent is attached hereto as Appendix A.

## **THE '780 PATENT IS CAUSING SIGNIFICANT PUBLIC HARM**

Human embryonic stem (“ES”) cell research possesses great promise to be the next frontier of medical advance. Scientists already believe that human ES cell research will produce new ways of not just treating, but preventing, a wide range of diseases, including AIDS, diabetes, Parkinson's, Alzheimer's and heart disease. Although the federal government has limited its funding of human ES cell research, many states, including most notably California which created a \$3 billion state taxpayer-funded institute for stem cell research in November 2004, have chosen to provide the support that is needed to foster such research here in America.

To achieve the promise of human ES research, however, scientists need to not only be funded, they also need to be free of unjustified restraints on their work. Unfortunately, human ES cell researchers are currently being restrained by the '780 patent and two other related patents, U.S. Patents Nos. 6,200,806 (“the '806 patent”) and 7,029,913 (“the '913 patent”). These three patents, which broadly claim any primate or human ES cell, are being widely and aggressively asserted by their owner against every human ES cell researcher in the United States. *Licensing Fees Slow Advance of Stem Cells*, Nature 435:272 (May 19, 2005).

By demanding significant financial consideration before allowing research to be performed, the owner of the '780, '806 and '913 patents is impeding, and in some cases literally stopping, domestic human ES cell research at its infancy. *Id.* This not only harms scientific advance here in the United States, it also has a harmful economic impact on Americans by diverting taxpayer dollars meant for research to pay for licensing fees. In the words of one

industry insider, this aggressive patent assertion is “stifling industrial research and investment.”

*Id.*

Although these scientific and economic concerns are admittedly not grounds to grant this request for reexamination, FTCCR respectfully requests that they be considered when determining whether questions regarding the validity of the '780 patent merit review by your office. As set forth more fully below, FTCCR believes that the '780 patent is invalid and, as such, should be eliminated as an impediment to American human ES cell research.

### **THE SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY**

The substantial new questions of patentability raised by this request are (1) whether all 11 claims of the '780 patent were anticipated by U.S. Patent No. 5,166,065 to Williams et al. (“Williams”) and (2) whether all 11 claims of the '780 patent were obvious in light of Robertson, et al., “Isolation, Properties and Karyotype Analysis of Pluripotential (EK) Cell Lines From Normal and Parthenogenetic Embryos,” *Teratocarcinoma Stem Cells*, Cold Spring Harbor Laboratory, Cold Spring Harbor, 10:647-663 (1983) (“Robertson 1983”), Robertson, Elizabeth J., “Embryo-Derived Stem Cell Lines,” *Teratocarcinomas and Embryonic Stem Cells; A Practical Approach*, Oxford: IRL Press, Ch. 4:71-112 (1987) (“Robertson 1987”) and Piedrahita, et al., “On The Isolation Embryonic Stem Cells: Comparative Behavior Of Murine, Porcine And Ovine Embryos,” *Theriogenology*, 34(5):879-901 (1990) (“Piedrahita”), either separately or when viewed together.<sup>2</sup>

These are substantial new questions of patentability because neither Williams,

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<sup>2</sup> Copies of Williams, Robertson 1983, Robertson 1987 and Piedrahita are attached hereto as Appendix B.

Robertson 1983, nor Robertson 1987 was of record during prosecution of the '780 patent and Piedrahita was not of record during prosecution of the instant application that led to the '780 patent. A detailed explanation of the pertinency and manner of applying Williams, Robertson 1983, Robertson 1987 and Piedrahita to every claim of the '780 patent is set forth below.

### **WILLIAMS ANTICIPATED THE CLAIMS OF THE '780 PATENT**

Williams issued on November 24, 1992. The earliest application to which the '780 patent claims priority was filed January 20, 1995, more than a year after Williams was issued. Therefore, Williams is prior art to the '780 patent under 35 U.S.C. § 102(b).

Williams taught a method for isolating ES cells of various animals, including specifically humans. Williams, 2:37-40 and 47-50, 4:18-19 and 6:51-66. Williams' method first isolated blastocysts and then isolated the inner cell mass (“ICM”), which was plated on embryonic fibroblasts. *Id.* at 5:19-34 and 6:51-66. From the ICM, Williams extracted ES cell colonies and cultured them on a media suitable to support their growth while maintaining their pluripotential nature. *Id.* at 3:54-55, 4:24-27, 5:19-34 and 6:51-66. Williams' ES cells “retain[ed] their pluripotential phenotype” and “the developmental potential to differentiate into all somatic and germ cell lineages.” *Id.* at 4:14 and 26-27.

As shown in Table 1 below, there is no difference between the primate ES cells disclosed by Williams and the ES cells claimed in the '780 patent, as Williams' primate ES cells contained, either expressly or inherently, all of the characteristics of the primate ES cells claimed in the '780 patent. There is also no difference between the method for isolation of primate ES

cells taught by Williams and the method claimed in the '780 patent.

<i>'780 Patent</i>	<i>Williams</i>
1. A purified preparation of primate embryonic stem cells which	Williams taught isolated ES cells of various animals, including primates and specifically humans. 2:37-40 and 47-50, 4:18-19 and 6:51-66.
(i) is capable of proliferation in an in vitro culture for over one year,	Williams' ES cells were maintained “for a time and under conditions sufficient for the derivation and / or maintenance of said ES cells.” 3:28-35. Williams' specifically maintained ES cells for “20 weeks” and there is no suggestion that they could not have been maintained for over one year. 4:10.
(ii) maintains a karyotype in which all the chromosomes characteristic of the primate species are present and not noticeably altered through prolonged culture,	Williams' ES cells “retained their stem cell phenotype.” 4:34-36 and 6:11-13.
(iii) maintains the potential to differentiate into derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and	Williams' ES cells “retain[ed] their pluripotential phenotype” and “the developmental potential to differentiate into all somatic and germ cell lineages.” 4:14 and 26-27.
(iv) will not differentiate when cultured on a fibroblast feeder layer.	Williams taught that “cell lines will [] retain the stem cell phenotype in vitro when cultured on a feeder layer of fibroblasts.” 1:43-48 and 3:28-35 and 54-64.
2. The preparation of claim 1 wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.	The '780 patent concedes that “Chorionic gonadotropin, expressed by the trophoblast, is ... in all primates, including humans.” '780 patent, 2:33-38. Therefore, it is inherent that Williams' primate ES cells met this limitation.
3. A purified preparation of primate embryonic stem cells wherein the cells are negative for the	The '780 patent concedes that “primate ES cell lines are negative for the SSEA-1 marker,

<i>'780 Patent</i>	<i>Williams</i>
SSEA-1 marker, positive for the SSEA-3 marker, positive for the SSEA-4 marker,	positive for the SSEA-3 marker, and positive for the SSEA-4 marker.” '780 patent, 4:13-15. Therefore, it is inherent that Williams' primate ES cells met these limitations.
express alkaline phosphatase activity,	The '780 patent concedes that “[a]lkaline phosphatase will also be present on all primate ES cells.” '780 patent, 10:51-52. Therefore, it is inherent that Williams' primate ES cells met this limitation.
are pluripotent,	Williams' ES cells “retain[ed] their pluripotential phenotype” and “the developmental potential to differentiate into all somatic and germ cell lineages.” 4:14 and 26-27.
and have karyotypes which includes the presence of all of the chromosomes characteristic of the primate species and in which none of the chromosomes are noticeably altered.	Williams' ES cells “retained their stem cell phenotype.” 4:34-36 and 6:11-13.
4. The preparation of claim 3 wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.	The '780 patent concedes that “a series of cell surface markers (alkaline phosphatase, SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81) ... are definitive markers for ... primate ES cells.” '780 patent, 17:32-36. Therefore, it is inherent that Williams' primate ES cells met these limitations.
5. The preparation of claim 3 wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.	Williams' ES cells were maintained “for a time and under conditions sufficient for the derivation and / or maintenance of said ES cells.” 3:28-35. Williams' specifically maintained ES cells for “20 weeks” and there is no suggestion that they could not have been maintained for at least one year. 4:10.
6. The preparation of claim 3 wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic	The '780 patent concedes that “Chorionic gonadotropin, expressed by the trophoblast, is ... in all primates, including humans.” '780

<i>'780 Patent</i>	<i>Williams</i>
gonadotropin.	patent, 2:33-38. Therefore, it is inherent that Williams' primate ES cells could differentiate to trophoblast and produce chorionic gonadotropin.
7. The preparation of claim 3 wherein the cells remain euploid for more than one year of continuous culture.	Williams' ES cells were maintained "for a time and under conditions sufficient for the derivation and / or maintenance of said ES cells." 3:28-35. Williams' specifically maintained ES cells, which inherently remained euploid, for "20 weeks" and there is no suggestion that they could not have been maintained for more than one year in the continuous culture. 4:10.
8. The preparation of claim 3 wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.	Williams' ES cells "retain[ed] their pluripotential phenotype" and "the developmental potential to differentiate into all somatic and germ cell lineages." 4:14 and 26-27. It is inherent that Williams' primate ES cells would maintain this capability if injected into a SCID mouse.
9. A method of isolating a primate embryonic stem cell line, comprising the steps of:	Williams taught a method for isolating ES cells of various animals, including specifically humans. 2:37-40 and 47-50, 4:18-19 and 6:51-66.
(a) isolating a primate blastocyst;	Williams' method first isolated blastocysts. 5:19-34 and 6:51-66.
(b) isolating cells from the inner cell mass of the blastocyst of (a);	Williams' method then isolated the inner cell mass ("ICM"). 5:19-34 and 6:51-66.
(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells masses are formed;	Williams' method then plated the ICM on embryonic fibroblasts. 5:19-34 and 6:51-66.
(d) dissociating the mass into dissociated cells;	From the ICM, Williams extracted ES cell colonies. 6:51-66.
(e) replating the dissociated cells on embryonic feeder cells;	Williams cultured the extracted ES cell colonies on a media suitable to support their growth while maintaining their pluripotential

<i>'780 Patent</i>	<i>Williams</i>
	nature. Williams' taught that this media "may ... contain feeder cells." 3:54-64 and 6:51-66.
(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and	Williams selected ES cell colonies that reached certain physical specifications. 6:63-65. It is inherent that the colonies selected by Williams could have compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli, as those would be colonies of special interest.
(g) culturing the cells of the selected colonies.	Williams' ES cells were then maintained for further analysis. 6:63-65.
10. A method as claimed in claim 9 further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.	Williams maintained ES cells on fibroblast feeder layers. 1:43-48 and 3:28-35 and 54-64.
11. A cell line developed by the method of step 9.	Williams taught using his method to develop cell lines. 6:65-66 ("the ES cell lines").

Table 1: Anticipation of the '780 Patent by Williams

Thus, Williams completely anticipated the '780 patent and, as such, renders each of its claims invalid.

**ROBERTSON 1983, ROBERTSON 1987 AND PEIDRHITA, EITHER SEPARATELY OR TOGETHER, RENDERED OBVIOUS THE CLAIMS OF THE '780 PATENT**

Robertson 1983 was published in 1983, Robertson 1987 was published in 1987 and Piedrahita was published in 1990. The earliest application to which the '780 patent claims priority was filed January 20, 1995, more than a year after Robertson 1983, Robertson 1987 and Piedrahita were each published. Therefore, Robertson 1983, Robertson 1987 and Piedrahita are each prior art to the '780 patent under 35 U.S.C. § 102(b).

**Robertson 1983 and Robertson 1987 Rendered the '780 Patent Obvious**



More than a decade before the initial application leading to the '780 patent was filed, Robertson 1983 taught a step-by-step process for isolating pluripotential mammalian ES cells. Robertson 1983's process included the steps of: (i) isolating a blastocyst, (ii) removing the ICM from the blastocyst, (iii) placing the ICM on fibroblast cells, (iv) isolating stem cells once they became apparent, and (v) maintaining the isolated ES cells on feeder layers. Robertson 1983 at 649. Robertson 1983's ES cells were pluripotential, were maintained over a significant time period and retained a normal euploid karyotype. *Id.* at 647, 654 and 660 (“the B2B2 line has now been shown to retain normal XY karyotype after more than 45 passage generations”).

A few years later, Robertson 1987 again taught the step-by-step process for isolating pluripotential mammalian ES cells, this time giving even further detail regarding each specific step. For example, Robertson 1987 gives highly technical instruction on preparing feeder layers, collecting blastocyst stage embryos, transferring the embryos into culture, culturing the blastocysts, disaggregating the ICM, identifying ICM-derived colonies, expanding ES cells and culturing ES cells. Robertson 1987 at 76-94. Since Robertson 1983 and Robertson 1987 were penned by the same person and since Robertson 1987 expressly cites Robertson 1983, one of ordinary skill in the art would have been motivated to combine their teachings. Robertson 1987 at 112 (*citing* Robertson 1983).

The only difference between Robertson 1983 and Robertson 1987 and the claims of the '780 patent is that Robertson 1983 and Robertson 1987 isolate mouse ES cells while the '780 patent claims primate ES cells. However, Dr. Jeanne F. Loring, a leading research

embryologist at the Burnham Institute in La Jolla, California, who was directing ES cell research and specifically focusing on derivation of novel ES cell lines at the time the earliest priority application for the '780 patent was filed, states in the attached declaration that,

[A]t the time the first application leading to the '780 patent was filed, it was obvious to one of ordinary skill in the art of ES cell derivation that the process taught by Robertson 1983 and Robertson 1987 for isolating mouse ES cells could be used to isolate ES cells of other mammals, including primates as claimed in the '780 patent, with a reasonable expectation of success.

Declaration of Dr. Jeanne F. Loring, p. 3.<sup>3</sup> In support of her opinion, Dr. Loring cites several conversations she had with other stem cell scientists prior to January 20, 1995, regarding how Robertson's method for deriving mouse ES cells could also be used to isolate human ES cells. *Id.* at 5-7. As such, Robertson 1983 and Robertson 1987 rendered each of the claims of the '780 patent invalid because they were no more than obvious implementations of Robertson's method.

With respect to those elements of the '780 patent's claims not found expressly in Robertson 1983 and Robertson 1987 – such as producing chorionic gonadotropin when cultured to high density, being negative for the SSEA-1 marker, positive for the SSEA-3 marker and positive for the SSEA-4 marker, expressing alkaline phosphatase and being positive for the TRA-1-60 and TRA-1-81 markers – they are all attributes that the '780 patent concedes are inherent to primate ES cells. '780 patent, 2:33-38 (“[c]horionic gonadotropin, expressed by the trophoblast, is ... in all primates, including humans”), 4:13-15 (“primate ES cell lines are negative for the SSEA-1 marker, positive for the SSEA-3 marker, and positive for the SSEA-4 marker”), 10:51-52 (“[a]lkaline phosphatase will also be present on all primate ES cells”), and 17:32-36 (“a series of

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3 The Declaration of Dr. Jeanne F. Loring, Ph.D. is attached hereto as Appendix C.

cell surface markers (alkaline phosphatase, SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81) ... are definitive markers for ... primate ES cells”). Therefore, those claim limitations provide no unobvious difference over Robertson 1983 and Robertson 1987.

Although the '780 patent goes to great lengths to explain why human ES cells are more important and more beneficial for scientific research than mouse ES cells, it does not sufficiently address why a well known method for isolating mouse ES cells would not also work to isolate primate ES cells. In fact, the method of isolating ES cells described and claimed in the '780 patent (claims 9 and 10) is the exact same process taught by Robertson 1983 and Robertson 1987 more than a decade earlier. '780 patent, 4:34-44. Thus, any argument that the process taught by Robertson 1983 and Robertson 1987 would not have been expected to work for primates is belied by the fact that the '780 patent – in fact – concedes that it did.

Further, there is no evidence of any (i) teaching away from using Robertson 1983's and Robertson 1987's method to isolate primate ES cells or (ii) failure of others to isolate primate ES cells using Robertson 1983's and Robertson 1987's method. To the contrary, other persons with ordinary skill in the art recognized that “[t]he development of mouse ES cells in 1981 provided the paradigm, and, much of the technology, for the development of human ES cells.” U.S. Patent No. 6,875,607, 1:26-29. Thus, all of these secondary considerations further support the conclusion that the '780 patent was obvious in light of Robertson 1983 and Robertson 1987.

*Piedrahita Alone Rendered the '780 Patent Obvious*

Piedrahita taught a method of isolating murine (rodent), porcine (pig) and ovine (sheep) ES cells. Piedrahita at 882-883. The blastocysts were isolated and then the cells from

the ICM were isolated. The ICM was then placed on an embryonic fibroblast feeder layer (Piedrahita taught the use of both STO and HEF feeder layers). After plating, the growing ICM was dissociated and replated onto fresh feeder layer. ES cells were then selected based on a large nucleus and prominent nucleoli. These selected cells were then cultured on fresh feeder layer in order to prevent differentiation. Piedrahita's ES cells were pluripotential, were maintained over a significant time period and retained a normal euploid karyotype. *Id.* at 883-884 and 888 (“maintained for 42 passages with no sign of decreased growth rate or obvious morphological changes”).

The only difference between Piedrahita and the claims of the '780 patent is that Piedrahita isolated murine, porcine and ovine ES cells while the '780 patent claims primate ES cells. However, Dr. Loring states in the attached declaration that,

[A]t the time the first application leading to the '780 patent was filed, it was obvious to one of ordinary skill in the art of ES cell derivation that the process taught by Piedrahita for isolating murine, porcine and ovine ES cells could be used to isolate ES cells of other mammals, including primates as claimed in the '780 patent, with a reasonable expectation of success.

Declaration of Dr. Jeanne F. Loring, p. 4. As such, Piedrahita rendered each of the claims of the '780 patent invalid because they were no more than obvious implementations of Piedrahita's method.

With respect to those elements of the '780 patent's claims not found expressly in Piedrahita – such as producing chronic gonadotropin when cultured to high density, being negative for the SSEA-1 marker, positive for the SSEA-3 marker and positive for the SSEA-4

marker, expressing alkaline phosphate and being positive for the TRA-1-60 and TRA-1-81 markers – they are all attributes that the '780 patent concedes are inherent to primate ES cells. '780 patent, 2:33-38 (“[c]horionic gonadotropin, expressed by the trophoblast, is ... in all primates, including humans”), 4:13-15 (“primate ES cell lines are negative for the SSEA-1 marker, positive for the SSEA-3 marker, and positive for the SSEA-4 marker”), 10:51-52 (“[a]lkaline phosphatase will also be present on all primate ES cells”), and 17:32-36 (“a series of cell surface markers (alkaline phosphatase, SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81) ... are definitive markers for ... primate ES cells”). Therefore, those claim limitations provide no unobvious difference over Piedrahita.

Although the '780 patent concedes that, “[p]luripotent cell lines have also been derived from preimplantation embryos of several domestic and laboratory animals species,” it argues that “[w]hether or not these cell lines are true ES cells lines is a subject about which there may be some difference of opinion” and that “[s]trong evidence of these required properties have been published only for rodents ES cells.” 3:39-58. However, the '780 patent fails to mention the “strong evidence” of Piedrahita that leaves no “difference of opinion” regarding its teaching of pluripotent ES cells of mammals other than rodents.

In fact, the method of isolating ES cells described and claimed in the '780 patent (claims 9 and 10) is the exact same process taught by Piedrahita several years earlier. '780 patent, 4:34-44. Thus, any argument that the process taught by Piedrahita would not have been expected to work for primates is belied by the fact that the '780 patent – in fact – concedes that it did.

Further, there is no evidence of any (i) teaching away from using Piedrahita's method to isolate primate ES cells or (ii) failure of others to isolate primate ES cells using Piedrahita's method. Thus, these secondary considerations further support the conclusion that the '780 patent was obvious in light of Piedrahita.

It should be noted that during prosecution of the '780 patent's parent application, U.S. Patent Application No. 08/376,327 (“the '327 application”), the Examiner applied Piedrahita in rejecting the then pending claims. *Office Action*, January 17, 1996, p. 5. In making the rejection, the Examiner stated,

The only apparent difference between the method of Piedrahata [sic] et al. and that of the instant claims is that the claims isolate primate ES cells whereas Piedrahata [sic] et al. isolates murine, porcine and ovine ES cells. However, one of ordinary skill in the art would have a reasonable expectation of success in isolating primate ES using the same method taught by Piedrahata [sic] et al for isolating murine, porcine or ovine ES cells.

*Id.* at 6.<sup>4</sup>

The applicant responded to the Piedrahita rejection by arguing that “persons of high skill in the art still do not believe that they can predict whether methods worked out in one species will or will not work in another distantly-related species” and that “work from mice or sheep does not provide sufficient guidance, in this art, to demonstrate a reasonable expectation of success in primates.” *Amendment*, July 23, 1996, pp. 6-7.<sup>5</sup> However, those conclusory arguments were completely unsupported with any evidence and correctly found unpersuasive by the Examiner, who responded to the applicant's arguments by making the Piedrahita rejection final

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4 A copy of the January 17, 1996, *Office Action* is attached hereto as Appendix D.

5 A copy of the July 23, 1996, *Amendment* is attached hereto as Appendix E.

and stating that,

... the method of Piedrahata [sic] is identical to the claimed process with the exception of the source of the cells. The reference has applied the method to murine, porcine and ovine animals, three diverse categories of mammals and therefore the method could be applied to other mammals such as primates with a reasonable expectation of success.

*Office Action*, October 28, 1996, p. 4.<sup>6</sup>

In the face of the final rejection, the applicant abandoned the '327 application and shifted prosecution to a continuation-in-part application, U.S. Patent Application No. 08/591,246 (“the '246 application”). The '246 application, the instant application that issued as the '780 patent, was reviewed by completely different examiners and at no time during its prosecution was the Piedrahita reference either cited or made of record by the applicant, despite the fact that the applicant obviously knew of its existence and that the Examiner of the parent application found it to be highly material. Thus, the rejection made in the '327 application based on Piedrahita was never overcome by the applicant.

*Robertson 1983, Robertson 1987 and Piedrahita Together Rendered the '780 Patent Obvious*

The combined teachings of Robertson 1983, Robertson 1987 and Piedrahita further render the '780 patent obvious because they use virtually the same process to isolate ES cells of several different mammalian species. Dr. Loring states in the attached declaration that,

[A]t the time the first application leading to the '780 patent was filed, it was obvious to one of ordinary skill in the art of ES cell derivation that the process taught by Robertson 1983, Robertson 1987 and Piedrahita for isolating mouse, murine, porcine and ovine ES cells could be used to isolate ES cells of other mammals, including primates as claimed in the '780 patent, with a reasonable

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<sup>6</sup> A copy of the October 28, 1996, *Office Action* is attached hereto as Appendix F.

expectation of success.

Declaration of Dr. Jeanne F. Loring, p. 5. Thus, since the same process was known, at the time the earliest claimed priority application for the '780 patent was filed, to work to isolate various types of mammalian ES cells, one of ordinary skill in the art would have expected the process to work for primate ES cells as well because primates are yet another type of mammal and are no more different from mice, rats, pigs, and sheep than they are each from each other.

One of ordinary skill in the art would have been motivated to combine the teachings of Robertson 1983, Robertson 1987 and Piedrahita because they are directed to exactly the same field of scientific endeavor, namely the isolation of mammalian ES cells. In addition, Robertson 1987 was written by the same author as Robertson 1983 and Robertson 1987 and Piedrahita both expressly cited Robertson 1983, thus incorporating it by reference. Robertson 1987 at 112 (*citing* Robertson 1983); Piedrahita at 900 (*citing* Robertson 1983). As such, when viewed together, Robertson 1983, Robertson 1987 and Piedrahita render each of the claims of the '780 patent invalid because it would have been obvious that the method described in those references for isolating ES cells of several different mammalian species could be expected to work to isolate primate ES cells as well.

[continued on next page]



## CONCLUSION

For the reasons set forth above, each of the claims of the '780 patent are invalid for being anticipated by Williams and for being obvious in light of Robertson 1983, Robertson 1987 and Piedrahita. As such, PUBPAT, on behalf of FTCR, respectfully requests that they be reexamined *ex parte* and ultimately canceled.

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Date

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