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Brief in Support of Appeal

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Art Unit: 3991

Reexamination Control. No.: 95/000,154

Examiner: Gary L. Kunz

U.S. Patent No.: 7,029,913

Issued: April 18, 2006

Inventor: Thomson

For: PRIMATE EMBRYONIC STEM CELLS

THIRD PARTY REQUESTER'S APPEAL BRIEF

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

SIR:

The Third Party Requester, Consumer Watchdog, through its assigned counsel, the Public Patent Foundation at Benjamin N. Cardozo School of Law, respectfully submits this Appeal Brief in connection with the above-identified *inter partes* reexamination proceeding in support of its

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Daniel B. Ravicher, Esq., USPTO Reg. 47.015

appeal to the Board of Appeals and Interferences (the "Board") from a Right of Appeal Notice dated June 20, 2008 ("RAN"). Appellant commenced this Appeal by filing a Notice of Appeal on July 18, 2008, and hereby submits this Appeal Brief.

In accordance with 37 C.F.R. §41.20(b)(2), the fee for filing a brief in support of an Appeal is $510. Pursuant to 37 C.F.R. §1.27, Consumer Watchdog claims small entity status as a 501(c)(3) nonprofit organization. Thus, the fee for this Appeal Brief filed by Consumer Watchdog is reduced by half. The resulting fee of $255 is submitted herewith via credit card payment form PTO-2038.

Respectfully Submitted,

Date: September 18, 2008

_____

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I. REAL PARTY IN INTEREST

The real party in interest to the present reexamination proceeding is Consumer Watchdog, a 501(c)(3) not-for-profit charitable organization.

II. RELATED PROCEEDINGS

None.

III. STATUS OF THE CLAIMS

Claims 1-3 were confirmed by the Examiner in the ACP and RAN. Appellant appeals the confirmation of claims 1-3.

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to the ACP.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates generally to human embryonic stem cells. More precisely, the claims are directed to cell cultures of pluripotent human embryonic stem cells with the following properties: (i) they will proliferate in an in vitro culture for over one year in an undifferentiated state without the application of exogenous leukemia inhibitory factor; (ii) they maintain a karyotype in which the chromosomes are euploid through prolonged culture; (iii) they maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues

throughout the culture; and, (iv) they are inhibited from differentiation when cultures on a fibroblast feeder layer. Each of these characteristics are generally inherent to pluripotent human embryonic stem cells and, thus, the claims have a quite broad scope that encompasses virtually any culture of pluripotent human embryonic stem cells.

The sole independent claim, claim 1, reads as follows:

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

Claims 2 and 3 directly depend from claim 1. Claim 2 adds the limitation that "the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density." Claim 3 adds the limitation that "the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, and express alkaline phosphatase." These additional characteristics, like those contained in Claim 1, are nothing more than inherent characteristics of any pluripotent human embryonic stem cell culture.

VI. ISSUES TO BE REVIEWED ON APPEAL

Appellant appeals from the findings of patentability of claims 1-3 made by the Examiner in

the RAN. Specifically, Appellant contests the following rejections that were either (i) proposed by Appellant and not adopted by the Examiner or (ii) applied by the Examiner in the Non-Final Office Action dated March 30, 2007 ("NFOA"), but then withdrawn by the Examiner in the RAN:

1. Claims 1 – 3 are unpatentable under 35 U.S.C. §103(a) as being obvious over (i) 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 '83"), (ii) Robertson, Elizabeth J., "Embryo-Derived Stem Cell Lines," *Teratocarcinomas and Embryonic Stem Cells; A Practical Approach*, Oxford: 1RL Press, Ch. 4:71-112 (1987) ("Robertson '87") and (iii) 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. This rejection proposed by Appellant was not adopted by the Examiner.
2. Claims 1 – 3 are unpatentable under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Williams et al. (U.S. Patent No. 5,166,065) ("Williams"). This rejection was applied by the Examiner in the NFOA but then withdrawn in the RAN.

3. Claims 1 – 3 are unpatentable under 35 U.S.C. §102(e) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Hogan (U.S. Patent No. 5,690,926) ("Hogan"). This rejection was applied by the Examiner in the NFOA but then withdrawn in the RAN.

4. Claims 1 – 3 are unpatentable under 35 U.S.C. §103(a) as being obvious over Robertson '83 and Robertson '87 in view of Williams and Hogan. This rejection was applied by the Examiner in the NFOA but then withdrawn in the RAN.

5. Claims 1 – 3 are unpatentable under 35 U.S.C. §103(a) as being obvious over Piedrahita in view of Williams and Hogan. This rejection was applied by the Examiner in the NFOA but then withdrawn in the RAN.

6. Claims 1 – 3 are unpatentable under 35 U.S.C. §103(a) as being obvious over Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan. This rejection was applied by the Examiner in the NFOA but then withdrawn in the RAN.

VII. ARGUMENT

In the RAN, the Examiner made two mistakes of law which led the Examiner to make incorrect conclusions regarding the patentability of the instant claims. The first error of law made by the Examiner was that he applied too high of a standard for a reasonable expectation of success.

The second error of law made by the Examiner was that he applied too high of a standard for obviousness. These mistakes led the Examiner to incorrectly withdraw the rejections he had previously made in the NFOA that the instant claims were both anticipated by and obvious over the prior art of record. Those rejections were justified and, as such, should be reinstated.

I. The Examiner Made Two Fundamental Errors of Law

In this reexamination, the Examiner made two critical legal errors that led him to make incorrect conclusions regarding the patentability of the instant claims. First, the Examiner required the expectation of success to be an absolute certainty in order for it be considered "reasonable." This is too high a standard and conflicts with binding precedent. Second, the Examiner concluded that since human embryonic stem cell cultures as claimed had not existed before, they were not obvious. This effectively eviscerated the non-obviousness requirement by collapsing it into the Examiner's anticipation inquiry. This standard is too high and conflicts with binding precedent. Appellant respectfully submits that these errors of law made by the Examiner should be reversed on appeal.

1. The Examiner Applied an Erroneously High Standard for Reasonable Expectation of Success

The Federal Circuit has repeatedly found that the expectation of success provided by the prior art of record need not provide certainty or a guarantee in order for its disclosure to be

sufficient to invalidate a claim. *Pfizer v. Apotex*, 480 F. 3d 1348, 1364 (Fed. Cir. 2007). Rather, the expectation of success provided by the prior art to one of skill in the art need only need be "reasonable." Id. at 1364 ("a rule of law equating unpredictability to patentability ... cannot be the proper standard since the expectation of success need only be reasonable, not absolute.").

In this reexamination, the Examiner's findings of patentability rest heavily on his belief that the isolation and maintenance of human embryonic stem cells was not a certainty in light of the art of record. Without that certainty, the Examiner held that one of ordinary skill in the art could not have had a reasonable expectation of success in deriving and culturing human embryonic stem cells as claimed. This is too high of a standard, and violates the law. As a result, the conclusions reached by the Examiner that the claims were patentable because there was no reasonable expectation of success were incorrect.

A. Others did not fail to make the claimed invention

The linchpin of the Examiner's belief that the art was too unpredictable to lead to a reasonable expectation of success is purported evidence he claims showed the failure of others to isolate and maintain embryonic stem cells of various mammalian species. Upon inspection, however, it becomes readily apparent that none of the purported evidence of the failure of others cited by the Examiner to support his finding that there was no reasonable expectation of success

has sufficient nexus with the instant claims to be relevant. This nexus is required by Federal Circuit precedent in order for the purported failure of others to be relevant to the analysis of the reasonable expectation of success for the claims. To be sure, the Federal Circuit has repeatedly declared that, to be relevant, evidence of the "failure of others" must show that the others failed to "develop the claimed invention." *See*, *e.g.*, *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006). Without a direct relationship between the failed attempts and the claims themselves, the evidence is irrelevant to the inquiry of whether there was a reasonable expectation of success.

In the RAN, the Examiner cites the work of other embryonic stem cell scientists as "failures of others" to isolate mammalian embryonic stem cells. RAN at 22-37. However, the pending claims are to "*human* embryonic stem cells" that are "*cultured on fibroblast feeder layers*" and "*without the application of exogenous LIF*." A simple review of the cited references immediately recognizes that not a single piece of evidence cited by the Examiner on this point actually shows the failure of other stem cell scientists to develop "*human* embryonic stem cells" that are "*cultured on fibroblast feeder layers"* and "*without the application of exogenous LIF*," as all but one reference relates to species other than humans (or even primates) and the only piece of evidence related to humans did not attempt to culture its successfully isolated human embryonic stem cells

on fibroblast feeder layers. Therefore, since none of the evidence cited by the Examiner has sufficient nexus to the claims, it does not support the Examiner's finding that there was no reasonable expectation of success.

Even putting aside the issue of the applicability of the proffered evidence to the pending claims, a deeper review of that evidence shows that the Examiner's characterizations of that evidence are inaccurate. In fact, many of the references cited by the Examiner actually support the finding that there was sufficient predictability in the art to lead to a reasonable expectation of success in achieving the claimed invention. Specifically, of the 9 references cited by the Examiner as showing a failure of others to isolate and maintain mammalian embryonic stem cells, every single one of them actually successfully isolated mammalian embryonic stem cells. Several of the those references also expressly taught how to maintain the isolated embryonic stem cells in culture for an extended period of time.

i. Brook and Gardner; Brook et al.

First, the Examiner argues that Brook and Gardner, 94 Proc. Natl. Acad. Sci. 5709-5712 (1997) (“Brook '97”), and Brook et al., 52 Diabetes 205-208 (2003) (“Brook '03”), document the difficulty and unpredictability in applying the technique developed for isolating murine ES cells to all strains of mice and other mammals. RAN at 24. However, the Examiner concedes that,

"Neither Garnder & Brook nor Brook et al. demonstrates the failure of others in an attempt to isolate human ES cells on fibroblast feeder layers." Thus, there is no nexus between these references and the claims and, as such, they can not be used in determining whether there was a reasonable expectation of success.

Further on this point, Brook '03 was directed to the derivation of "highly germline-competent embryonic stem cells containing [nonobese diabetic]-derived genome," a much more specific type of embryonic stem cell than that currently claimed, which is more difficult to derive. Loring Declaration attached to Third Party Requester's Comments dated June 29, 2007, at 8 – 9 ("Loring Declaration"). Therefore, whether Brook '03 successfully accomplished that more difficult task is irrelevant to any analysis of whether the pending claims were obvious. As such, neither Brook '97 nor Brook '03 can be used to analyze whether there was a reasonable expectation of success.

Further, in actuality, Brook '97 repeatedly suggested applying its method for deriving mouse embryonic stem cells to other mammals. 94 Proc. Natl. Acad. Sci. at 5709 and 5712 ("[T]his approach to the derivation of germline-competent ES cell lines may not only prove generic for the mouse but also worth pursuing in other species of mammal", "Here we describe a simpler and more direct approach to the problem of devising a generic technique for deriving ES cell lines

in the mouse and hence, possibly, in other mammals" and "the present approach may be not only of general utility for the mouse but also applicable to other mammals"). Thus, it actually supports a finding that one of skill in the art would have had a reasonable expectation of success.

ii. Iannaccone et al, Brenin '97 and Ouhibi '95

Second, the Examiner cites Brenin et al., 29 Transplant Proc. 1761-1765 (1997) ("Brenin '97"), Iannaccone et al., 1994, Dev. Biol. 163:288-292 ('Iannaccone et al.'), and Ouhibi et al., 40 Mol. Reprod. & Dev. 311-324 (1995) ("Ouhibi '95") as references that he admits successfully isolated rate ES cells or rat ES-like cells. However, the Examiner claims that they do not establish that those cells meet all of the limitations of the claimed human ES cells. RAN at 27-29. Because of this, the Examiner holds that these references document a difficulty and unpredictability in isolating and maintaining ES cells in culture. However, as an initial matter, since these references do not relate to human embryonic stem cells, there is no nexus between them and the claims. As such, they can not be used in determining whether there was a reasonable expectation of success.

Regardless, the references actually support a finding of predictability and reasonable expectation of success. For example, while Ouhibi '95 may not have maintained its cell lines for an extended period of time, it suggested that such was the result of the culture conditions, not the method followed. 317. Further, Ouhibi '95 stated that it was well known that embryonic stem cell

work was being done on "other animal species, including sheep, hamster, pig, cow, mink and rabbit," and that, in fact, "various embryo-derived cell lines have been isolated." 311. Ouhibi '95 even discussed LIF and found that it did not need to be used in the process of deriving embryonic stem cells. Therefore, contrary to the Examiner's finding, Ouhibi '95 actually succeed at deriving mammalian embryonic stem cells.

iii. Doetshman

Third, the Examiner cites Doetschman et al., 127 Dev. Biol. 224-27 (1988) ("Doetschman '88"), which he concedes also succeeded in isolating mammalian embryonic stem cells (hamster). However, the Examiner found that Doetschman '88 failed to meet the long term proliferation limitation of the instant claims RAN at 29-31. As an initial matter, since this reference does not relate to human embryonic stem cells, there is no nexus between it and the claims. As such, it can not be used in determining whether there was a reasonable expectation of success.

Regardless, as the Examiner found, Doetschman '88 actually succeeded at establishing "highly pluripotent" hamster ES cell lines and maintaining them "for over 3 months without loss of undifferentiated state." RAN at 30 ("Doetschman '88 appears to have successfully isolated and maintained hamster ES cells in culture in the undifferentiated state for an extended period of time."). As such, Doetschman '88 does not evidence a failure, as the Examiner states, but is instead

actually proof of the opposite, that the known methods for deriving mouse embryonic stem cells could be used to derive embryonic stem cells of other mammalian species and that they could be maintained for a significant period of time.

iv. Piedrahita

As his fourth offer of evidence of the failure of others to derive mammalian embryonic stem cells, the Examiner claims that Piedrahita failed to isolate and maintain porcine and ovine embryonic stem cells with all of the limitations of the instant claims. RAN at 32-33. Again, as an initial matter, since this reference does not relate to human embryonic stem cells, there is no nexus between it and the claims. As such, it can not be used in determining whether there was a reasonable expectation of success.

Regardless, while Piedrahita may not have actually successfully maintained its isolated ES cells, that does not make it evidence of a "failure," because its disclosure was sufficient to enable one of ordinary skill in the art to do so. In addition, contrary to the Examiner's finding, Moore et al., 33 In Vitro Cell. Dev. Biol. 62-71 (1997) ("Moore '97"), actually confirmed the successful isolation of embryonic stem cell lines in various species, including rat, mink, rabbit, hamster, primates, sheep, cattle and swine. Moore '97 at 62 ("varying degrees of pluripotentiality have been demonstrated for each"). While it is true that Moore '97 stated that the inability to maintain

porcine ES cell lines was common, it did not attempt to isolate porcine ES cells itself, nor did it use feeder layers.

v. Talbot

Fifth, while finding that Talbot et al., 42 Mol. Reprod. & Dev. 35-52 (1995) ("Talbot '95") "achieved their goal of isolating bovine epiblasts with demonstrated pluripotency," the Examiner nonetheless held that Talbot '95 "emphasized" the technical difficulties and unpredictability in the art of ES cell isolation and maintenance for domestic animals. RAN at 34-35. However, Talbot is not directed to the isolation of embryonic stem cells. Further, Talbot '95 expressly "did not address the issue of the sustainable culture of undifferentiated bovine epiblast cells as ES cells," although it did expressly "demonstrate[] the pluripotency of bovine epiblasts in culture." Talbot '95 at 49. Thus, since Talbot '95 was not focused on isolating and maintaining embryonic stem cell cultures, it is disingenuous to claim that it "failed" to do so. As such, it has no nexus to the instant claims and, therefore, can not be used in determining whether there was a reasonable expectation of success.

Regardless, to repeat the Examiner's own findings, "Talbot '95 achieved their goal of isolating bovine epiblasts with demonstrated pluripotency." RAN at 34. Thus, it seems entirely unjustifiable to characterize this reference as demonstrating a failure in the art.

vi. Bongso

Sixth, the Examiner found that Bongso et al., 9 Human Reprod. 2110-17 (1994) ("Bongso '94"), successfully isolated human ES cells, but "failed to go further and to maintain said ES cells in long term culture." RAN at 37. As an initial matter, Bongso '94 is unquestionable a proven success in the art of human embryonic stem cell derivation. To be absolutely clear, the human embryonic stem cells isolated and cultured by Bongso '94 are identical to those of the instant claims except that Bongso '94 cultured their cells using LIF and not feeder layers, while the instant claims use feeder layers and not LIF. Bongso '94 at 2110. On this point, Bongso '94 addressed the issue of feeder layer selection specifically:

> Since STO fibroblasts were not used in this study it is not possible to conclude whether or not they would be equally effective as a feeder layer. A feeder cell type similar to the species of the embryo may be more ideal than that of the heterologous species.

2116. Thus, Bongso '94 *expressly suggested* that *using a feeder cell* from a species similar to the embryo might be better. This would motivate those of ordinary skill in the art to modify the disclosed process by using feeder layers in order to achieve better cell proliferation.

In addition, Reubinoff et al., 18 Nature Biotech. 399-404 (2000) ("Reubinoff '00") shows that two of the authors of Bongso '94, Dr. Ariff Bongso and Chui-Yee Fong, along with other human embryonic stem cell researchers recognized – before Dr. Thomson publicized his

accomplishment – that using feeder layers instead of LIF would work better:

> Since [Bongso '94] did not use embryonic feeder cell support (required for proliferation of pluripotent human EC and nonhuman primate ES cells) but relied instead on LIF supplementation of the culture medium, these cells eventually underwent differentiation or death. Therefore, we subsequently employed a culture system incorporating embryonic fibroblast feeder cell layers to derive human ES cells from blastocysts. While this work was in progress, Thomson and coworkers reported the derivation of ES cell lines from the human blastocyst.

Reubinoff '00 at 399.

Further, as Dr. Alan O. Trounson, one of the authors of Reubinoff '00, explains in his Declaration (attached to the Third Party Requester's Comments dated June 29, 2007, in Appendix A) ("Trounson Declaration"), 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 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. *Id.* 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.

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. '917 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 to the Third Party Requester's Comments dated June 29, 2007, 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.

For these reasons, Bongso '94 is most properly viewed as a success in the art of human embryonic stem cell isolation and maintenance, not a failure as characterized by the Examiner.

B. Thomson achieved the claimed invention before others because he had special access to the resources necessary to do so, not because he did anything sufficiently inventive to merit a patent.

Appellant does not dispute that Dr. Thomson made an important accomplishment in the science of human embryonic stem cells. However, not all important scientific accomplishments are necessarily deserving of patents. As Justice Kennedy stated for a unanimous Supreme Court in *KSR International Co. v. Teleflex Inc.*, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. 1727, 1741 (2007) ("*KSR*"). 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 attached to the Third Party Requester's Comments dated June 29, 2007 ("Melton Declaration"), at 5 – 6; Loring Declaration at 10; Cowan Declaration attached to the Third Party Requester's Comments dated June 29, 2007 ("Cowan Declaration"), at 5 – 6. Had others in the field been given the same special 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 5 – 6.[1] 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.[2] 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-Eldor'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)

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1 For similar access to embryo issues, see Cherny '94 at 570 ("The limited availability of bovine embryos together with the low number of potentially chimaeric calves that can be produced for ES cell contribution analysis severely hinders ES cell research in cattle.")

2 For a list of the legal restrictions, in force during the mid-1990's, that inhibited human embryonic stem cell research, see the Third Party Requester's Comments dated June 29, 2007, at 19-20.

(attached to the Third Party Requestor's Comments dated June 29, 2007, 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 dessert 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.[3]

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

3 Vasilyuk, Z., Carpenter, M.L. and Haile, L.A., *The Case That Has Made IP For Stem Cells Significantly Clearer*, San Diego Daily Transcript (July 31, 2002) (available at http://www.sddt.com/reports/2002/07/intellectualproperty/tb.cfm, last visited June 28, 2007) ("the mid-1990s, when the federal government decided not to fund embryonic stem cell research[, ...] University of Wisconsin researcher Dr. James A. Thomson was in need of additional funds to continue his stem cell research studies that eventually resulted in the breakthrough in stem cell isolation. Geron stepped in to provide Thomson with funding for his laboratory").

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 explained, this is because Dr. Thomson achieved his accomplishment by implementing an obvious method for deriving and maintain 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 deriving 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. at 1741.

In closing on this issue, Appellant 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 ingenuity, such as access to limited resources, sufficient support to research and attempt the accomplishment, and a

hospitable political climate. Similarly, 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 Examiner correctly held in the RAN that 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. RAN at 47-48.

C. There is no express teaching away from the claimed invention

Another critical flaw in the Examiner's cited evidence of the failure of others is that none of it expressly teaches away from the methods used. The Federal Circuit has held that a reference should not be read as teaching away from a process unless it contains "specific language" expressly doing so. *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F3d 1356, 1364 (2006) ("*Dystar"*) *(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 Examiner expressly states that the known methods for deriving and maintaining mammalian embryonic stem cells should not be pursued to also isolate and culture human embryonic stem cells. Therefore, none of them can be

considered a "teaching away" from the instant claims.

2. The Examiner Applied an Erroneously Too High Standard For Obviousness

In *KSR*, the Supreme Court reaffirmed its holding in *Graham v. John Deere* that obviousness is principally a three-prong analysis whereby "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." 127 S. Ct. at 1734 (*citing Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)). Since the *KSR* decision, the Federal Circuit has restated that the obviousness inquiry also requires a showing that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention and that the skilled artisan would have had a reasonable expectation of success in doing so. *Pfizer v. Apotex*, 480 F. 3d 1348, 1361 (Fed. Cir. 2007) ("*Pfizer v. Apotex*").

A. The Examiner correctly found there was sufficient motivation.

The examiner correctly held there was significant motivation at the time for scientists to use the then-known methods for isolating and maintaining mouse embryonic stem cells in order to isolate and maintain embryonic stem cells of other mammals, including humans. For example, the Examiner found "there was undoubtedly compelling motivation to try to isolation and maintain primate/human ES cells using the techniques which worked with mouse ES cells" [sic] and "there

is compelling motivation for the artisan to use the method of isolating and maintaining mouse ES." RAN at 49 and 66. And neither the Patentee nor the Examiner has argued that an ordinary artisan in the field of embryonic stem cell isolation and maintenance would not have been both aware of and motivated to combine the teachings of the prior art of record. As a result, the only issue that the Examiner cites as not supporting a confirmation of the claims is that he believes there was unpredictability in the art which led to a lack of a reasonable expectation of success. RAN at 49.

B. It was obvious to try to isolate and maintain human embryonic stem cells using the known methods for deriving and culturing mouse embryonic stem cells.

In addition to holding that there was motivation to apply the known techniques for deriving embryonic stem cells to isolate human embryonic stem cells, the Examiner also found that the claimed invention was obvious-to-try. RAN at 22 ("the artisan at the time of the invention may well have been motivated to try to isolate primate/human ES cells using the known technique for isolating murine ES cells"). 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, predictable 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 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 animal 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").

Further still, four renowned stem cell scientists, Drs. Melton, Trounson, Loring and Cowan also each 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 4; Trounson Declaration at 5; Loring Declaration at 7; Cowan Declaration at 4.

C. When there is sufficient motivation, a claimed invention that was obvious-to-try is obvious if there are a limited number of parameters to try.

As discussed above, the Examiner's standard for a reasonable expectation of success was too high. As the Federal Circuit recently held, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer v. Apotex*, 480 F. 3d at 1364. In that case, the Federal Circuit continued to say that "a rule of law equating unpredictability to patentability ... cannot be the proper standard since the expectation of success need only be reasonable, not absolute." The Federal Circuit also stated that if (i) there is sufficient motivation to try a claimed invention and (ii) there are a limited number of parameters to try, then the claimed invention is obvious. 480 F.3d at 1366.

In this case, all parties agree there is sufficient motivation and that it would have been obvious to try to isolate and maintain human embryonic stem cells as claimed by using the well known methods for deriving and culturing stem cells of other mammals. The only remaining issue, then, is whether the number of parameters to try was large or small. If the number of parameters to try is small, then binding Federal Circuit precedent dictates that the resulting claimed invention was a predictable result and, thus, obvious. This standard is applied in discussing each of the separate issues appealed by Appellant below.

II. The Claims Are Unpatentable Over the Art of Record

When scrutinized with correct legal standards, the instant claims are not patentable over the prior art of record. Specifically, as discussed more fully below, the claims were anticipated by both Williams and Hogan and obvious over Robertson '83, Robertson '87 and Pidrahita, either separately or when viewed together, in view of Williams and Hogan.

1. Issue 1: The Claims Were Obvious Over Robertson '83, Robertson '87 And Piedrahita, Either Separately Or When Viewed Together

In the RAN, the Examiner did not adopt three grounds of rejection proposed by the Appellant. Those three grounds were: (i) the claims were obvious over Robertson '83; (ii) the claims were obvious over Piedrahita; and, (iii) the claims were obvious over Robertson '83, Robertson '87 and Piedrahita. In support of those proposed grounds of rejection, the Appellant submitted a Declaration under Rule 1.132. The Examiner rejected these three grounds of rejection proposed by Appellant because he held:

> It is improper to use the declaration by Dr. Jeanne F. Loring instead of a patent or printed publication to provide the motivation for preparing human embryonic stem cells ... .

NFOA at 7 – 8. It appears as though the Examiner understood Appellant to have intended that the declaration by Dr. Loring be part of the proposed rejections. RAN at 7 – 10 (identifying the three grounds of rejection proposed by Appellant as being "in view of the declaration by Dr. Jeanne F.

Loring").

However, Appellant did not submit the declaration with the intent that it be used for any improper purpose. Instead, Appellant submitted the declaration in order to explain the contents of the prior art submitted by Appellant as part of its request for reexamination. In particular, the declaration was intended to explain the understanding of what the prior art disclosed to, and what motivations or suggestions *it* provided to those of ordinary skill in the art. Thus, the Examiner's failure to adopt the Appellants proposed rejections was error.

However, Appellant notes that the Examiner formulated his own rejections of the claims based on the printed publications submitted by Appellant in its request for reexamination. Thus, the substantive issued raised by those references are discussed below.

2. Issue 2: The Claims Were Anticipated By Or, In The Alternative, Obvious Over Williams

In the NFOA, the Examiner rejected all three claims as being anticipated by or obvious over Williams. NFOA at 9. The Examiner found that Williams disclosed human embryonic stem cells and a method for preparing such embryonic stem cells that was "essentially the same procedure" as described in the pending patent's specification. *Id.* at 10. Further, the Examiner concluded that, "there is no structural difference between the pluripotential human ES cells disclosed by Williams and the ES cells instantly claimed." *Id.* at 11 – 12. The Patent Owner made several arguments in

its response to the NFOA as to why Williams' teaching of human embryonic stem cells does not invalidate the pending claims, but each of the Patent Owner's arguments are without merit. Thus, the Examiner's rejection of the pending claims based on Williams '065 was and remains appropriate.

In the RAN, the Examiner withdrew its rejection despite maintaining its finding that Williams indeed suggested that its method for deriving embryonic stem cells could be used to isolate ES cells of other species. This is because the Examiner believed that one of the inventors of Williams, Dr. Robert Lindsay Williams, "later contradicted" that suggestion. RAN at 16 (*citing* Cherny et al., 6 Reprod. Fertil. Dev. 569-75 (1994) ("Cherny '94")). In Cherny '94, however, Dr. Williams did not retract the teaching in Williams that methods for isolating ES cells in one species could be used for other species. In fact, Cherny '94 reiterated this understanding by saying, "the ability to culture murine ES cells to produce unlimited numbers of cells while still retaining their developmental potential provides a strong incentive for the isolation of domestic animal ES cells." Cherny '94 at 569. Further, Cherny '94 also said that although the murine model for stem cell isolation has "yet" to prove applicable to domestic animals, "criteria used in the identification of murine ES cells can serve as guidelines." *Id*. at 574. Thus, contrary to the Examiner's characterization, Dr. Williams never "retracted" the teaching in Williams that methods of deriving

and maintaining mouse ES cells could be used to isolate and culture human embryonic stem cells. Instead, he actually reiterated it.

The Examiner next argues that Williams does not invalidate the pending claims because it was not a sufficiently enabling disclosure. RAN at 19-39. On this point, the Examiner again refers to Cherny '94 and claims that it shows Dr. Williams could not extend his method to the isolation of ES cells from other non-murine mammals. *Id.* However, Cherny '94 was expressly directed towards "[t]he isolation, culture and preliminary characterization of bovine primordial germ cell-derived (PGCd) cells," not the derivation of human embryonic stem cells that are the subject of the instant claims. Cherny '94 at 569 (Abstract). Thus, Cherny '94 is not relevant to the issue of whether Williams was an enabling disclosure.

Regardless, the Examiner reads Williams' disclosure too narrowly, limiting it to its preferred embodiment and not taking into account all of its teachings, suggestions and motivations. When read fully, Williams disclosure was indeed sufficient to enable one of ordinary skill in that art to isolate and maintain human embryonic stem cells, especially when one considers the high level of skill of an ordinary artisan in this field and the general knowledge, common sense and creative ability that they would posses. Further, as discussed above, the Examiner's standard for showing a reasonable expectation of success was too high. Although success may not have been a certainty,

one of ordinary skill in the art still had a reasonable expectation of success in deriving and culturing human embryonic stem cells as claimed from the teachings of Williams alone.

Further still, even if Williams did not anticipate the claims, it nonetheless rendered them obvious because, as discussed above, (i) one of ordinary still in the art would have been motivated to try Williams' method to isolate and maintain human ES cells, (ii) it was in fact obvious-to-try to do that, and (iii) there was only a limited number of parameters that one of ordinary skill in the art would have to try in order to successfully achieve the claimed invention (such as with LIF or without LIF, and with feeder layers or without feeder layers). Thus, one of ordinary skill in the art would have had a reasonable expectation of success in deriving human ES cells by using Williams' teaching.

Supporting these conclusions is the fact that, as discussed above, others did not fail to achieve the claimed invention as believed by the Examiner. Of the 9 references cited by the Examiner as showing a failure of others to isolate and maintain mammalian embryonic stem cells, every single one of them actually successfully isolated mammalian embryonic stem cells. Several of the those references also expressly taught how to maintain the isolated embryonic stem cells in culture for an extended period of time. As such, those references are not a proper basis for the Examiner's finding of unpredictability leading to a lack of a reasonable expectation of success.

Thus, the rejection made by the Examiner in the NFOA was correct and should be reinstated.

3. Issue 3: The Claims Were Anticipated By Or, In The Alternative, Obvious Over Hogan

In the NFOA, the Examiner rejected all three claims as being anticipated by or obvious over Hogan. NFOA at 12. The Examiner found that, "Hogan '926 discloses the identical human embryonic stem cells as claimed [] even though produced by different processes." *Id.* at 14. The Patent Owner made several arguments in its response to the NFOA as to why Hogan'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 was and remains appropriate.

In the RAN, the Examiner withdrew this rejection because he believed there were six issues that distinguished Hogan from the claims. First, the Examiner held that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells were 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. '917 patent, 3:46-49 ("mouse EC cells and mouse ES cells share the same unique combination of cell 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. Andrews, *Human Teratocarcinomas*, 948 Biochim. Biophys. Acta 17-36, 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 to the Third Party Requestor's Comments dated June 29, 2007, in Appendix C). As such, it was entirely predictable by those of skill in the art that human ES cells would also be SSEA-1 negative.

The cells in Hogan '926 referred to by the Examiner were SSEA-1 positive because they were murine. Hogan 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 to the Third Party Requestor's Comments dated June 29, 2007, in Appendix B). This fact doesn't distinguish Hogan from the instant claims because one of ordinary skill in the art would have nonetheless expected human ES cells isolated according to Hogan's teaching to be SSEA-1 negative. *Id*.

Second, the Examiner found that Hogan cannot invalidate the instant claims because Hogan's cells were only maintained for at least 20 passages, which is less than that of the instant

claims, which are limited to maintaining human embryonic stem cells in culture in an undifferentiated state for at least one year. However, Hogan did not teach that such was not capable and it was within the knowledge of one of skill in the art to use feeder layers to do so. As just one example, Bongso '94 expressly suggested using feeder layers to maintain a culture of embryonic stem cells for an extended period of time. Bongso '94 at 2116.

Next, the Examiner found that Hogan cannot invalidate the instant claims because Hogan's cells require exogenous LIF. However, Hogan 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 referred to Williams for information about the use of LIF, which, as discussed above, taught that LIF was a "substitute" for feeder layers. 4:56-59. Further, Hogan 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'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. 5,453,357, 4:55-57 (emphasis added). Thus, Hogan did not "require" LIF, as the Examiner found.

Fourth, the Examiner held that Hogan did not anticipate the claims because Hogan "failed to establish that human EG cells maintain normal karyotype through prolonged culture. However,

nothing in Hogan says that its EG cells do not maintain normal karyotype through prolonged culture and there is no reason to think such would be the case. Thus, absent any proof to the contrary, it is inherent in Hogan that its EG cells would maintain normal karyotype through prolonged culture.

The Examiner then held that Hogan cannot invalidate the instant claims because Hogan's cells cannot form trophoblast. Although it may be true that Hogan's 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 developmental potential of human ES and EG cells. *Id*. Further, some human EC cell 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's teaching could be able to form trophoblast. Loring Declaration 5 – 6. Therefore, this difference cited by the Examiner between the human embryonic stem cells of the instant claims on the one hand and the teaching of Hogan on the other are insufficient to justify departure from the general understanding and belief of the applicability of scientific knowledge between them.

Lastly, the Examiner held that Hogan could not anticipate the claims because Hogan "failed to establish that human EG cells are positive for SSEA-4 cell surface marker. However, nothing in Hogan says that its EG cells are not positive for SSEA-4 cell surface marker and there is no reason to think such would be the case. Thus, absent any proof to the contrary, it is inherent in Hogan that its EG cells are positive for SSEA-4 cell surface marker.

Even if Hogan did not anticipate the claims, it nonetheless rendered them obvious because, as discussed above, (i) one of ordinary still in the art would have been motivated to try Hogan's method to isolate and maintain human ES cells, (ii) it was in fact obvious-to-try to do that, and (iii) there was only a limited number of parameters that one of ordinary skill in the art would have to try in order to successfully achieve the claimed invention (such as with LIF or without LIF, and with feeder layers or without feeder layers). Thus, one of ordinary skill in the art would have had a reasonable expectation of success in deriving human ES cells by using Hogan's teaching.

Supporting these conclusions is the fact that, as discussed above, others did not fail to achieve the claimed invention as believed by the Examiner. Of the 9 references cited by the Examiner as showing a failure of others to isolate and maintain mammalian embryonic stem cells, every single one of them actually successfully isolated mammalian embryonic stem cells. Several of the those references also expressly taught how to maintain the isolated embryonic stem cells in

culture for an extended period of time. As such, those references are not a proper basis for the Examiner's finding of unpredictability leading to a lack of a reasonable expectation of success. Thus, the rejection made by the Examiner in the NFOA was correct and should be reinstated.

4. Issue 4: The Claims Were Obvious Over Robertson '83 And Robertson '87 In View Of Williams and Hogan

In the NFOA, the Examiner rejected all three claims as being obvious over Robertson '83 and Robertson '87 in view of Williams and Hogan. NFOA at 15. The Examiner found that, "[t]he difference between the combined teachings 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 to the NFOA 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.

In the RAN, the Examiner withdrew his rejection because he found that there was a lack of

expectation of success created by unpredictability in the art. However, as discussed above, under binding recent Federal Circuit case law, there is a reasonable expectation of success and the claims are thus obvious if, (i) one of ordinary still in the art would have been motivated to combine the teachings in the prior art, (ii) it was in fact obvious-to-try to do that, and (iii) there was only a limited number of parameters that one of ordinary skill in the art would have to try in order to successfully achieve the claimed invention. *Pfizer v. Apotex*, 480 F. 3d at 1366.

Here, the only difference between the claims and the combined teachings of Robertson '83 and Robertson '87 in view of Williams and Hogan is that the claims are directed to human embryonic stem cells while the prior art is direct to other mammalian species. However, as discussed above, the Examiner correctly found that there was motivation to use the prior art methods to isolate and maintain human embryonic stem cells and that it was obvious to try to do that. Since this would involve only changing one parameter (the species), one of ordinary skill in the art would have had a reasonable expectation of success in deriving human ES cells by combining the teachings of Robertson '83 and Robertson '87 in view of Williams and Hogan. Thus, the rejection made by the Examiner in the NFOA was correct and should be reinstated.

5. Issue 5: The Claims Were Obvious Over Piedrahita In View Of Williams and Hogan

In the NFOA, the Examiner rejected all three claims as being obvious over Piedrahita in

view of Williams and Hogan. NFOA 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 to the NFOA as to why the teaching of Piedrahita 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 in view of Williams '065 and Hogan '926 was and remains appropriate.

In the RAN, the Examiner withdrew his rejection because he found that there was a lack of expectation of success created by unpredictability in the art. However, as discussed above, under binding recent Federal Circuit case law, there is a reasonable expectation of success and the claims are thus obvious if, (i) one of ordinary still in the art would have been motivated to combine the teachings in the prior art, (ii) it was in fact obvious-to-try to do that, and (iii) there was only a limited number of parameters that one of ordinary skill in the art would have to try in order to successfully achieve the claimed invention. *Pfizer v. Apotex*, 480 F. 3d at 1366.

Here, the only difference between the claims and the teaching of Piedrahita in view of Williams and Hogan is that the claims are directed to human embryonic stem cells while the prior

art is direct to other mammalian species. However, as discussed above, the Examiner correctly found that there was motivation to use the prior art method to isolate and maintain human embryonic stem cells and that it was obvious to try to do that. Since this would involve only changing one parameter (the species), one of ordinary skill in the art would have had a reasonable expectation of success in deriving human ES cells by following the teaching of Piedrahita in view of Williams and Hogan. Thus, the rejection made by the Examiner in the NFOA was correct and should be reinstated.

6. Issue 6: The Claims Were Obvious Over Robertson '83, Robertson '87 And Piedrahita In View Of Williams and Hogan

In the NFOA, the Examiner rejected all three claims as being obvious over Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan. NFOA at 18. The Examiner found that, "[t]he difference between the combined teachings of Robertson '83, Robertson '87 and Piedrahita and 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 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. The Patent Owner made several arguments in its response to the NFOA as to why the combined

teachings of Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan does not invalidate the pending claims, but those arguments lack merit. Thus, the Examiner's rejection of the pending claims based on the combined teachings of Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan was and remains appropriate.

In the RAN, the Examiner withdrew his rejection because he found that there was a lack of expectation of success created by unpredictability in the art. However, as discussed above, under binding recent Federal Circuit case law, there is a reasonable expectation of success and the claims are thus obvious if, (i) one of ordinary still in the art would have been motivated to combine the teachings in the prior art, (ii) it was in fact obvious-to-try to do that, and (iii) there was only a limited number of parameters that one of ordinary skill in the art would have to try in order to successfully achieve the claimed invention. *Pfizer v. Apotex*, 480 F. 3d at 1366.

Here, the only difference between the claims and the combined teachings of Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan is that the claims are directed to human embryonic stem cells while the prior art is direct to other mammalian species. However, as discussed above, the Examiner correctly found that there was motivation to use the prior art method to isolate and maintain human embryonic stem cells and that it was obvious to try to do that. Since this would involve only changing one parameter (the species), one of ordinary skill in

the art would have had a reasonable expectation of success in deriving human ES cells by following the combined teachings of Robertson '83, Robertson '87 and Piedrahita in view of Williams and Hogan. Thus, the rejection made by the Examiner in the NFOA was correct and should be reinstated.

[continued on next page]

III. CONCLUSION

For these reasons, Appellant respectfully submits that the Examiner made two critical mistakes of law that led him to incorrectly withdraw the rejections he had previously made in the NFOA that the instant claims were both anticipated by and obvious over the prior art of record. Those rejections were sound and should be reinstated. As such, Appellant respectfully requests that the Board reverse the Examiner's confirmation of claims 1-3 and reject those claims in their entirety.

Respectfully Submitted,

Date: September 18, 2008

_____

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VIII. CLAIMS APPENDIX

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

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

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

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.

XI. CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. §1.943(c)

Pursuant to 37 C.F.R. §1.943(c), the undersigned certifies that this Third Party Requester's Appeal Brief contains 10,992 words and is therefore in compliance with the limitations set forth therein.

Date: September 18, 2008

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CERTIFICATE OF SERVICE

The undersigned certifies that a true and correct copy of the attached THIRD PARTY REQUESTER'S APPEAL BRIEF in its entirety, including all accompanying documents, is being deposited with the U.S. Postal Service as Express Mail on the date of the signature below in an envelope addressed to:

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