IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination Control. No. 95/000,154		Art Unit:	3991
U.S. Patent No. 7,029,913		Examiner:	Gary L. Kunz
Issued:	April 18, 2006		
Inventor:	Thomson		
For:	PRIMATE EMBRYONIC STEM CELLS		

THIRD PARTY REQUESTER'S COMMENTS ON
***INTER PARTES* REEXAMINATION COMMUNICATIONS**

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 in the above entitled *Inter Partes* Reexamination, the Foundation for Taxpayer and Consumer Rights ("FTCR"), through its assigned counsel, the Public Patent Foundation ("PUBPAT"), respectfully submits these comments on the Office Action dated

March 30, 2007 ("Office Action"), and on the Patent Owner's Response to First Office Action dated May 30, 2007 ("Response").

SUMMARY

FTCR thanks the Examiner for issuing the Office Action and agrees with each of the five separate grounds given therein for rejection of all three claims of the '913 patent. In its Response, the Patent Owner amended the claims and made several arguments in an attempt to overcome the rejections. Upon review, even though the Patent Owner has narrowed the claims, none of the Patent Owner's arguments have sufficient merit to overcome the rejections. As such, the claims remain unpatentable.

INTRODUCTION

Before commenting on the specific grounds of rejection made by the Examiner, FTCR wishes to note that recent doctrinal developments in the law of obviousness support and strengthen the Examiner's rejections of the pending claims. Two months ago, 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." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) ("*KSR*") (*citing Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)). Secondary considerations, such as commercial success and the failure of others, the Court reminded, "*might* be utilized" to shed light on the inquiry, but, as the Court of Appeals Federal Circuit held just last

fall, "the presence of certain secondary considerations of nonobviousness [including commercial success and purported failures of others] are insufficient as a matter of law to overcome [a] conclusion that the evidence only supports a legal conclusion that [the claims] would have been obvious." Id. (emphasis added); *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F3d 1356, 1371 (2006) ("*Dystar*"). Thus, the Patent Owner's suggestion that secondary considerations are as important, if not more persuasive, than the three elements of the *Graham* test for obviousness is incorrect. Response at 14 (incorrectly saying "the Examiner *must* ... 4) evaluate evidence of secondary considerations" (emphasis added)).

The Patent Owner suggests in its Response that two factors, purported failures of others and public acclaim, rebut the Examiner's finding of obviousness. Response at 16. However, with respect to the Patent Owner's proffered evidence of failures of others, the truth is that not a single scientist in the field tried and failed to achieve what is covered by the pending claims, which is required in order for the evidence to be of any relevance to an obviousness analysis.[1] As such, the evidence of so-called "failures of others" is irrelevant to the issue of whether the pending claims were obvious.

Further, public acclaim is not a secondary consideration relevant to the obviousness inquiry unless it is bestowed by those of skill in the art.[2] None of the Patent Owner's evidence satisfies that condition, and thus none of it is relevant to whether the instant claims are obvious.

1 *See, e.g., Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006).

2 *See Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985) (dismissing a "praise for the claimed invention" argument); *Jenn-Air Corp. v. Modern Maid Co.*, 499 F.Supp. 320, 326-27 (D. Del. 1980) *aff'd*, 659 F.2d 1068 (3rd Cir. 1981) (discarding evidence of acclaim).

Regardless, simply because a scientific *accomplishment* was important does not necessarily mean that it was an *advance* worthy of patenting. Public acclaim can be the result of several factors, many of which are not the result of patentable invention.

Here, Dr. Thomson made his accomplishment because he had unique access to the physical and fiscal resources necessary to do so, not because he made a novel and non-obvious advance in the state of the art of human embryonic stem cells. Namely, while others in the art could not perform human embryonic stem cell research because of political and financial blockades placed in their way, Dr. Thomson benefited from special relationships that provided him with access to the embryos and funding necessary to do such research. It was those special relationships – not scientific inventiveness – that provided Dr. Thomson with an inside track to achieve his accomplishment. Had other embryologists been given access to the same resources Dr. Thomson had, they would have achieved – and in fact some did achieve – what he did. This is further justification for the Examiner's rejection of the instant claims in light of the Supreme Court's reassertion in *KSR* that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." 127 S.Ct. at 1746.

For these reasons, discussed more fully below with respect to each specific grounds of rejection made by the Examiner, FTCR believes that it is proper for the Examiner to maintain the rejections made in the Office Action against the pending claims.

In support of these Comments, FTCR submits the following Declarations under Rule 132 and in accordance with MPEP 2658-IV-G:

- Declaration of Dr. Douglas A. Melton, Ph.D. ("Melton Declaration");
- Declaration of Dr. Alan O. Trounson, Ph.D. ("Trounson Declaration");
- Declaration of Dr. Jeanne F. Loring, Ph.D. ("Loring Declaration"); and
- Declaration of Dr. Chad Cowan, Ph.D. ("Cowan Declaration").

The Declarations are attached hereto in Appendix A. FTCR also submits new prior art in accordance with 37 CFR 1.948 and MPEP 2666.05-II, in that each new prior art reference is necessary to rebut a response of the Patent Owner. The new prior art is identified on the attached form PTO/SB/08b and copies are attached hereto in Appendix B. Lastly, copies of other documents cited herein are attached hereto in Appendix C for the convenience of the Examiner.

GROUNDS OF REJECTIONS 1 – 3 (PROPOSED BY THE THIRD PARTY REQUESTER)

The Examiner did not adopt the three grounds of rejection proposed by FTCR 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 ... .

Office Action at 7 – 8 (*citing* MPEP 2258E).[3] It appears as though the Examiner understood FTCR to have intended that the declaration by Dr. Loring be part of the proposed rejections. *Id.* at 6 – 8 (identifying the three grounds of rejection proposed by FTCR as being "in light of the declaration

3 FTCR wishes to politely point out that the section cited by the Examiner, MPEP 2258, is part of Chapter 2200, which relates to *Ex Parte* Reexaminations, not *Inter Partes* Reexaminations, such as the instant reexamination, which are dealt with in Chapter 2600. The relevant provision in that Chapter is 2658-IV-G, which states, "Affidavits under 37 CFR 1.131 and 1.132 may be utilized in a reexamination proceeding." The Declaration of Dr. Jeanne Loring was submitted along with the Request under Rule 132 and in accordance with MPEP 2658-IV-G.

by Dr. Jeanne F. Loring").

FTCR apologizes to the Examiner for any inconvenience, but did not submit the declaration with the intent that it be used for any improper purpose. Instead, FTCR submitted the declaration in order to explain the contents of the prior art submitted by FTCR 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.

Regardless, FTCR thanks the Examiner for formulating his own rejections of the claims based on the patent and printed publications submitted by FTCR in its request for reexamination. FTCR also thanks the Examiner for formulating rejections based on additional prior art not cited by FTCR in its request.

GROUNDS OF REJECTION 4: WILLIAMS '065

In the Office Action, the Examiner rejected all three claims as being anticipated by or obvious over Williams et al. (U.S. Patent No. 5,166,065) ("Williams '065"). Office Action at 9. The Examiner found that Williams '065 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 '065 and the ES cells instantly claimed." *Id.* at 11 – 12. The Patent Owner made several arguments in its Response as to why Williams '065's 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.

The Instant Claims Are Not Patentably Distinguishable From Williams '065

The Patent Owner first argues in the Response that Williams '065's cells require LIF. Response at 7. While it may be true that Williams '065 was principally directed towards researching the ability to use LIF to maintain ES cells without feeder layers, its teachings did not exclude cultures maintained with only feeder cells in the absence of LIF. Rather, Williams '065 expressly states that LIF can "substitute" for feeder layers in supporting the maintenance of pluripotential ES cells. Williams '065 at 1:58-62 and 3:62-64 ("LIF may be used to substitute for, or add to, feeder cells"). Contrary to the Patent Owner's interpretation, a skilled artisan would not understand that Williams '065 is "directed to the *advantages* of LIF in isolating and maintaining ES cells." Response at 15 (emphasis added). Rather, those of skill in the art understood Williams '065 to merely be directed to showing the *capability* of LIF to be used in isolating and maintaining ES cells. Loring Declaration at 3 – 4 ("Williams '065's discovery was merely that LIF could be used ..., not that it was an improvement over feeder layers"). Thus, the Patent Owner's proposed interpretation of Williams '065 as requiring LIF should be rejected.

Next, the Patent Owner argues that Williams '065 "merely suggested" that its method for deriving embryonic stem cells could be used to isolate ES cells of other species and that one of the inventors of Williams '065, Dr. Robert Lindsay Williams, "later retracted" that suggestion. Response at 7 (*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 '065 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 Patent Owner's characterization, Dr. Williams never "retracted" the teaching in Williams '065 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 Patent Owner next argues that Williams '065 is not applicable to the pending claims because it taught a different method than described in the pending patent's specification. Response at 8. However, the instant claims are directed to cell cultures, without any limitation as to what method is used to derive them. Response at 2. Therefore, whether a different method was used by Williams '065 is irrelevant to the validity of the pending claims.[4]

The Patent Owner next argues that Williams '065 does not invalidate the pending claims because it was not a sufficiently enabling disclosure. Response at 9 – 12. On this point, the Patent Owner 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

4 While it is irrelevant to the issue of the validity of the pending claims, as the Examiner stated in the Office Action, Williams '065 does in fact disclose virtually the same method as that described in the pending patent's specification. Office Action at 10 (*citing* Williams '065 at 6:50-66).

'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 '065 was an enabling disclosure.

Regardless, the Patent Owner reads Williams '065's disclosure too narrowly, limiting it to its preferred embodiment and not taking into account all of its teachings, suggestions and motivations as identified by the Examiner in the Office Action. Office Action at 12 ("Williams human ES cells will contain, either expressly or inherently, all of the characteristics of the human ES cells of the instant invention"). When read fully, Williams '065's 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. For example, although Williams '065 is primarily directed to the use of LIF to maintain ES cell cultures, one of ordinary skill in the art would have also attempted to use both LIF in combination with feeder cells and feeder cells without LIF, because they would have seen Williams '065 as a guide to be followed loosely, not as a recipe requiring strict adherence to its exact teachings. Loring Declaration at 4.

Others Did Not Fail To Make The Claimed Invention

In its Response, the Patent Owner cites the work of other embryonic stem cell scientists as "failures of others" to isolate mammalian embryonic stem cells. Response at 12. However, the pending claims are to *human* embryonic stem cells *cultured on fibroblast feeder*

layers and *without the application of exogenous LIF*. Response at 2. 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).

Upon inspection, it is immediately recognized that not a single piece of evidence provided by the Patent Owner on this point shows the failure of other stem cell scientists to develop *human* embryonic stem cells *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 proffered by the Patent Owner is relevant, it does not rebut the Examiner's *prima facie* obviousness determination.

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 Patent Owner's characterizations are inaccurate. In fact, many of the references cited be the Patent Owner actually support the Examiner's rejection of the pending claims as having indeed been obvious.

First, the Patent Owner 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"), show that "methods used to isolate mouse ES cells are not universally predictable across different strains of mice." Response at 12. However, Brook '97 actually 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").

Further, 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 at 8 – 9. Therefore, whether Brook '03 successfully accomplished that more difficult task is irrelevant to any analysis of whether the pending claims, or even broader claims to primate embryonic stem cells, were obvious. As such, neither Brook '97 nor Brook '03 provide any support for the Patent Owner's arguments regarding the validity of the pending claims. *Id.*

Second, the Patent Owner argues that Brenin et al., 29 Transplant Proc. 1761-1765 (1997) ("Brenin '97"), shows that "rat ES cells were not isolated by Iannaccone et al., 1994, Dev. Biol. 163:288-292 ('Iannaccone et al.'), rather Iannaccone's cells were contaminating mouse ES cells." Response at 12. However, Brenin '97 actually shows the opposite of what the Patent Owner claims, a successful derivation of rat ES cells:

> We have subcloned the original RESC-01 cell line and obtained from it rat ES cell subclones. The PCR of subclone 5 shows no evidence of mouse in cell culture preparations from this subclone. Karyotypes showed 100/100 metaphases to be rat. ... We have

> begun injecting cells from this subclone, and so far out of 18 viable offspring there are no chimeras.

1764. Further, Brenin '97 stated that out of ten mice and two rats injected with the rat embryonic stem cell subclones, there was only one isolated incident of a mouse developing a tumor later determined to be of mouse origin. *Id.* However, Brenin '97 believed that isolated incident was "spurious", or – at worst – implied that there was possibly a "stable low level" contamination resulting from contaminated cells being carried into the culture during the physical cloning. *Id.* Brenin '97 also said that, "[i]t is important to recognize that there are many possible explanations for this preliminary result." 1765. Thus, Brenin '97 did not – in fact – fail to derive mammalian embryonic stem cells as the Patent Owner claims. Loring Declaration at 9.

The Patent Owner attempts to support its position on this piece of evidence by claiming that Ouhibi et al., 40 Mol. Reprod. & Dev. 311-324 (1995) ("Ouhibi '95"), shows that "rat ES cells that can be passaged beyond passage four could not be isolated." Response at 12. However, as the Patent Owner's own expert, Dr. Colin Stewart, concedes in his declaration, "Ouhibi et al. ... succeeded in isolating rat cells from rat embryos." Declaration of Colin Stewart, D.Phil. ("Stewart Declaration") at 4. And while Ouhibi '95 may not have maintained those 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, not only did Ouhibi '95 actually succeed at deriving mammalian embryonic stem cells, it actually suggested not applying exogenous LIF, which the Patent Owner argues is an inventive aspect of the pending claims.

Third, the Patent Owner argues that Doetschman et al., 127 Dev. Biol. 224-27 (1988) ("Doetschman '88"), "fail[ed] to isolate hamster ES cells capable of long term proliferation." Response at 12. However, this is a mischaracterization of Doetschman '88, which actually succeeded at establishing "highly pluripotent" hamster ES cell lines and maintaining them "for over 3 months without loss of undifferentiated state." 224-26. As such, Doetschman '88 does not evidence a failure, as the Patent Owner suggests, but is instead further proof that the known methods for deriving mouse embryonic stem cells could be used to derive embryonic stem cells of other species. Loring Declaration at 9.

As its fourth offer of evidence of the failure of others to derive mammalian embryonic stem cells, the Patent Owner claims that Piedrahita et al., 34 Theriogenology 879-901 (1990) ("Piedrahita '90"), showed a "failure to isolate ovine ES cells and doubtful isolation of porcine ES cells," and that Moore et al., 33 In Vitro Cell. Dev. Biol. 62-71 (1997) ("Moore '97"), confirmed that failure. Response at 12. However, the Examiner was completely correct in the Office Action in finding that, "Piedrahita discloses murine, porcine and ovine ES cells." Office Action at 18. While Piedrahita '90 may not have actually isolated such ES cells, that does not make it evidence of a "failure," because its disclosure was sufficient to enable one of ordinary skill in the art to do so. Loring Declaration at 7.

Further, contrary to the Patent Owner's assertion, 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.

Fifth, the Patent Owner claims that Talbot et al., 42 Mol. Reprod. & Dev. 35-52 (1995) ("Talbot '95"), showed a "failure to isolate bovine ES cells." Response at 12. 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. Loring Declaration at 9 – 10.

Sixth, the Patent Owner argues that Bongso et al., 9 Human Reprod. 2110-17 (1994) ("Bongso '94"), showed a "failure to isolate long term cultures of human embryonic stem cells," and that Reubinoff et al., 18 Nature Biotech. 399-404 (2000) ("Reubinoff '00"), showed "acknowledgment of the earlier failure and Dr. Thomson's success." Response at 13. It should first be noted that 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; Response at 2.

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 and motivated those of ordinary skill in the art to modify the disclosed process by using feeder layers in order to achieve better cell proliferation.

Also, Reubinoff '00 actually 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 hereto in Appendix A), it was obvious at the time that, "had Bongso '94 simply not dispensed with the feeder layer in the passaging step, they would have successfully developed the claimed invention." Trounson Declaration at 6 – 7. Skilled practitioners reading

Bongso et al, would have spotted – and some in fact did spot – this departure from the original methods for isolating mouse embryonic stem cells and would have repeated Bongso '94, but retained the use of 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 hereto in Appendix B). Pera '89 taught that although mouse-embryo-derived stem cells had a feeder cell requirement that could be replaced by LIF, human EC cells were dependent upon feeder cells for continuous growth in vitro. *Id*. at 10 and 21 ("a range of known growth factors and related substances [including LIF] failed to substitute for feeder layers in supporting the growth of

[human EC] cells"). As such, it was entirely predictable that human ES cells would also be dependent upon feeder cells for maintenance.

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

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

Public Acclaim Is Not Relevant to Patentability

In its Response, the Patent Owner cites a "level of acclaim" for Dr. Thomson that it

argues is evidence of the validity of the pending claims. Response at 4 – 6 and Attachment A. However, evidence of public acclaim is irrelevant to the determination of a patent claim's validity, regardless of whether the basis for such acclaim is related to the particular patent claim or not. The only opinions that might be relevant are those of other scientists sufficiently skilled in the art, and even they are not always relevant. *See Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985) (dismissing a "praise for the claimed invention" argument); *Jenn-Air Corp. v. Modern Maid Co.*, 499 F.Supp. 320, 326-27 (D. Del. 1980), aff'd, 659 F.2d 1068 (3rd Cir. 1981) (discarding evidence of acclaim except for one technical article). Therefore, the Patent Owner's submission of evidence regarding Dr. Thomson's awards and recognition – none of which appears to have been bestowed on him by other human embryonic stem cell researchers – is of no relevance to an analysis of the validity of the pending claims.

Even if one puts the applicability of the proffered evidence of "public acclaim" aside for a moment, FTCR does not dispute that Dr. Thomson made an important accomplishment in the science of human embryonic stem cells.[5] However, not all scientific accomplishments are necessarily deserving of patents. As Justice Kennedy stated for a unanimous Supreme Court just this Spring in *KSR*, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. at 1741. Here, Dr. Thomson's accomplishment was not a result of sufficient scientific ingenuity to be deserving of a patent, but

5 FTCR disagrees, however, with the Patent Owner's characterizations of Dr. Thomson's accomplishment. Specifically, FTCR does not agree with the Patent Owner's statements in the media and otherwise that Dr. Thomson was the first to actually derive human embryonic stem cells. Further, as is fully addressed in these Comments, Dr. Thomson's accomplishment was neither novel nor non-obvious.

rather was more attributable to his having special access to two limited resources that other embryonic stem cell researchers who were pursuing the same accomplishment at the same time did not have. Melton Declaration at 5 – 6; Loring Declaration at 10; Cowan Declaration at 5 – 6. Had others in the field been given the same special access to those limited resources, 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.[6] This was because the issue of human embryos being used in scientific research, where they would necessarily be destroyed, was – and still is – highly politically controversial. In fact, many countries made such research entirely illegal.[7] Proof of the difficulty of obtaining human embryos in the face of such political

6 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.")

7 The following legal restrictions, in force during the mid-1990's, inhibited human embryonic stem cell research:

In the United States, the Dickey Amendment prevented the use of federal funds for stem cell research. 110 Stat 26, 34; 111 Stat. 3009, 3009-270 (covering fiscal year 1997); 111 Stat. 1467, 1516 (covering fiscal year 1998). Further, the research necessary to produce human embryonic stem cells as claimed in the '913 patent was prohibited in many states, including Arizona, Illinois, Louisiana, Maine, Massachusetts, Michigan, Minnesota, North Dakota, and Pennsylvania, that banned experiments using human embryos either completely or with only narrow exceptions inapplicable to the kind of research claimed in the '913 patent. Ariz. Rev. Stat. Ann. § 36-2302; 720 Ill. Comp. Stat. § 510/6-7; La. Rev. Stat. Ann. §§ 9:123, 9:129, 14:87.2; Me. Rev. Stat. Ann. tit. 22, § 1593; Mass. Gen. Laws ch. 112, § 12J(a); Mich. Comp. Laws §333.2685; Minn. Stat. §§ 145.421, 422; N.D. Cent. Code § 14-02.2-01; 18 Pa. Cons. Stat. §§3203, 3216. In addition, in Oklahoma, Pennsylvania, and Texas, it was illegal to buy or sell developmental human tissues. Okla. Stat. tit. 63, § 1-735; 18 Pa. Cons. Stat. § 3216(b)(3); Tex. Penal Code Ann. §48.02.

In Europe, Article 18.1 of the Council of Europe Convention on Human Rights and Biomedicine, April 4, 1997, requires "adequate protection of the embryo" where research is permitted, which would prohibit the destructive process required to harvest human embryonic stem cells. Further, the process of isolating and

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

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maintaining human embryonic stem cells as claimed in the instant claims was illegal in Austria, Denmark, France, Germany, Hungary, Iceland, Norway, Poland, Spain, part of Switzerland, and the United Kingdom. Fortpflanzungsmedizingesetz (Reproductive Medicine Law), § 9(1), *Bundesgestzblatt*, 4 June 1992, No. 105, p. 1299, 44 (2) Intl. Dig. Health Leg. 247 (1993); Law No. 503 of 24 June 1992 on the Scientific Ethics Committee System and the Examination of Biomedical Research Projects, §§ 14(1),(2), *Lovtidende*, 1992, Part A, 26 June 1992, No. 84, p. 2017, 43 (4) Intl. Dig. Health Leg. 758, 759 (1992); Law No. 94-654 of 29 July 1994, Journal Officiel de la Republique Francaise, 30 July 1994, p. 11060, 45(4) Intl. Dig. Health Leg. 498 (1994); Embryonenschutzgesetz (Embryo Protection Law), 13 December 1990, §§ 1.1(2), 2(1). Bundesgesetzblatt, Part I, 19 December 1990, p. 2746 (F.R.G.). 42(1) Intl. Dig. Health Leg. 60, 60-61 (1991); Law No. 79 of 17 December 1992 on the protection of the life of the fetus, *Magyar Kozlony*, 23 December 1992, No. 132, p. 4705, 44 (2) Intl. Dig. Health Leg. 249 (1993); Law No. 79 of 17 December 1992 on the protection of the life of the fetus, *Magyar Kozlony*, 23 December 1992, No. 132, p. 4705, 44 (2) Intl. Dig. Health Leg. 249 (1993); Regulation No. 568/1997 on Artificial Fertilization, 30 September 1997, Articles 22, 23; Law No. 56 of August 5, 1994 on the medical use of biotechnology, §3-1, *Norsk Lovtidend,* Part I, August 5, 1994, No. 16, pp. 1336, 46(1) Intl. Dig. Health Leg. 51 (1995); Law of 7 January 1993 on family planning, protection of human fetuses, and the conditions under which pregnancy termination is permissible, §§ 1-1, 7-23b(1), 44 (2) Intl. Dig. Health Leg. 253 (1993); Law No. 35/1988 of 22 November 1988, § 16(2), Boletin Oficial del Estado, 24 November 1988, No. 282, p 33373, 40(1) Intl. Dig. Health Leg. 81 (1989); Law of October 18, 1990 on reproductive medicine in humans, § 8, 44 (2) Intl. Dig. Health Leg. 256 (1993) (Switzerland: Basel-Stadt); Human Fertilisation and Embryology Act 1990 (c.37), § 3(1)(a) (available at http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm, last visited June 28, 2007). It was also arguably illegal and considered unethical in Ireland. Ir. Const., 1937, art. 40.3.3; Ireland Medical Council, *A Guide to Ethical Conduct and Behaviour*, § F.24.1, 5th Ed. (1998). It was also reported that research on embryos was prohibited by ethical committees in most European countries lacking legislation, including the Netherlands, Italy, and Eastern Europe. Schenker, J., "Assisted reproduction practice in Europe," 3(2) *Human Reproduction Update*, 173, 181 (1997).

In other parts of the world, Ecuador and Panama had laws that would have prevented stem cell research. Constitucion Politica de la Republica de Eduador de 1998, 5 June 1998, Art. 49; Codigo de la Familia, Law #3 of 17 May 1994, Art. 489 (Panama). In Canada, the legal status and eligibility of funding of embryonic research was in doubt, and in 1995 the government called for a voluntary moratorium on the buying and selling of embryos. Canadian Institutes of Health Research, "Human Stem Cell Research," p. 7-8 (available at http://www.cihr-irsc.gc.ca/e/pdf_14370.htm, last visited June 27, 2007). Research on embryos was also illegal except for narrow and inapplicable cases in Western Australia. Human Reproductive Technology Act 1991, §§ 6(1)(d), 14(1)(e)(iv), (2a), (available at http://www.austlii.edu.au/au/legis/wa/consol_act/hrta1991331/, last visited June 28, 2007). In Singapore, it was only legal to work on human embryos up to day 14 of embryonic growth. Bongso '94 at 2111.

> project. Four of the five cell lines the team first described (*Science*, 6 November 1998, p. 1145) came from Israeli embryos.

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

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

It was access to these extremely limited resources – human embryos and funding to do research using human embryos – that provided Dr. Thomson the ability to make his accomplishment relating to human embryonic stem cells. Melton Declaration at 5 – 6; Loring

8 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").

Declaration at 10; Cowan Declaration 5 – 6. Had other scientists in the field been given the same access to those limited resources, they, too, would have been able to make the same accomplishment Dr. Thomson did. *Id*. As Dr. Douglas A. Melton explains in his Declaration (attached hereto in Appendix A), this is because Dr. Thomson achieved his accomplishment by implementing an obvious method for deriving and maintain 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, FTCR reiterates that it does not believe that Dr. Thomson was unworthy of the media attention and honors that he received as a result of his accomplishment. However, public acclaim of a scientific accomplishment does not mean that the accomplishment includes invention worthy of patent protection. In fact, many important technological accomplishments are the result of factors other than non-obvious scientific ingenuity, such as access to limited resources, sufficient support to research and attempt the accomplishment, and a hospitable political climate. Similarly, as discussed above, it was those factors that enabled Dr. Thomson to achieve his human embryonic stem cell accomplishment, not patentable inventiveness. The fact that he received praise and recognition does not help to distinguish between what factors

led to his accomplishment and, more specifically, does not mean that it was necessarily patent worthy. As such, the evidence proffered by the Patent Owner regarding public acclaim of Dr. Thomson's accomplishment is irrelevant to the determination of whether the pending claims were sufficiently inventive to be patentable. Thus, this evidence does not rebut the Examiner's *prima facie* obviousness determination either.

GROUNDS OF REJECTION 5: HOGAN '926

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

The Instant Claims Are Not Patentably Distinguishable From Hogan '926

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

limited to what it claims should be rejected, as the method Hogan '926 taught could be applied to any embryo, pre- or post-implantation, despite the fact that its claims are limited to the latter.

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

Second, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells are SSEA-1 positive. However, it was known that mouse embryonic stem (ES) cells and mouse embryonic carcinoma (EC) cells share the same unique combination of cell surface markers; the '913 patent concedes as much in its "Background of the Invention" section. '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 hereto 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 Patent Owner were SSEA-1 positive because they were murine. Hogan '926 at 9:20 – 10:45. It was well known that murine cells, be they EC or ES, are SSEA-1 positive. Loring Declaration at 5 (*citing* Solter, D., and Knowles, B.B., *Monoclonal antibody defining a stage-specific mouse embryonic antigen (SSEA-1)*, Proc. Natl. Acad. Sci. USA 75, 5565-5569 (1978) (attached hereto in Appendix B along with two other new references cited in the Loring Declaration but not expressly mentioned in these comments)). This fact doesn't distinguish Hogan '926 from the instant claims because one of ordinary skill in the art would have nonetheless expected human ES cells isolated according to Hogan '926's teaching to be SSEA-1 negative. *Id.*

Next, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells require exogenous LIF. However, Hogan '926 used LIF in its preferred embodiment because "[p]revious studies" showed LIF could promote survival of mouse primordial germ cells. 1:41-44. Specifically, Hogan '926 referred to Williams '065 for information about the use of LIF, which, as discussed above, taught that LIF was a "substitute" for feeder layers. 4:56-59. Further, Hogan '926 expressly taught that, "the cells may be maintained on a feeder layer

without the addition of growth factors." 6:39-40. And, the specification of Hogan '926's parent patent states, "FGF, LIF or SF may *not* be required for maintenance of ES cells." 1:4-5 (claiming priority as a continuation-in-part of U.S. Ser. No. 07/958,562, filed Oct. 8, 1992, now U.S. Pat. No. 5,453,357); U.S. Patent No. 5,453,357, 4:55-57 (emphasis added). Thus, Hogan '926 did not "require" LIF, as the Patent Owner claims.

Lastly, the Patent Owner argues that Hogan '926 cannot invalidate the instant claims because Hogan '926's cells cannot form trophoblast. Although it may be true that Hogan '926'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 '926's teaching could be able to form trophoblast. Loring Declaration 5 – 6. Therefore, this difference cited by the Patent Owner between the human embryonic stem cells of the instant claims on the one hand and the teaching of Hogan '926 on the other is insufficient to justify departure from the general understanding and belief of the applicability of scientific knowledge between them.

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

Others Did Not Fail To Make The Claimed Invention

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

Even if one assumes *arguendo* that such evidence is relevant, when viewed correctly, it actually supports the Examiner's rejection of the pending claims. And, contrary to the Patent Owner's arguments, the science of isolating and culturing human embryonic stem cells was predictable, as shown by the fact that other scientists were successful at deriving and maintaining human embryonic stem cells contemporaneously with Dr. Thomson. Trounson Declaration at 6 – 7; Reubinoff '00 at 399.

Public Acclaim Is Not Relevant to Patentability

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

Even if one assumes *arguendo* that such evidence is relevant, not all scientific accomplishments are necessarily deserving of patents and, as Justice Kennedy stated for a unanimous Supreme Court just this Spring in *KSR*, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. at 1741.

Here, Dr. Thomson's accomplishment was not a result of sufficient scientific ingenuity to be deserving of a patent, but rather was more attributable to his having special access to two limited resources that other embryonic stem cell researchers who were pursuing the same accomplishment at the same time did not have. Melton Declaration at 5 – 6; Loring Declaration at 10; Cowan Declaration at 5 – 6. Had others in the field been given the same special access to those limited resources, namely human embryos and funding to do research using human embryos, they would have achieved – and in fact some did achieve – the same accomplishment as Dr. Thomson. Trounson Declaration at 6 – 7; Loring Declaration at 10; Reubinoff '00 at 399.

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

GROUNDS OF REJECTION 6: ROBERTSON '83 AND ROBERTSON '87 IN VIEW OF WILLIAMS '065 AND HOGAN '926

In the Office Action, the Examiner rejected all three claims as being obvious over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926. Office Action at 15. The Examiner found that, "[t]he difference between the combined 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 as to why the combined teaching of Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926 does not invalidate the pending claims, but those arguments are all without merit. Thus, the Examiner's rejection of the pending claims based on Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926 was and remains appropriate.

The Instant Claims Are Not Patentably Distinguishable From Robertson '83 And Robertson '87 In View Of Williams '065 And Hogan '926

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

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

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." ... When there is a design need or market pressure to solve a problem and there are a finite number of identified, 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") (attached hereto in Appendix C).

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 3; Trounson Declaration at 4; Loring Declaration at 6; Cowan Declaration at 3. This supports the Examiner's position that the result of that combination, which is claimed in the instant claims, was more likely the result of ordinary skill and common sense than patentable innovation.

Next, the Patent Owner argues that "[t]he central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells and explicitly contradicted in the present claims 1 – 3." Response at 20. However, the Patent Owner reads Williams '065's disclosure too

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

Finally, the Patent Owner argues that, "Hogan's cells are EG cells, not ES cells," and, "[t]he skilled artisan, upon reading Hogan, would not be motivated to follow Hogan to arrive at the presently claimed cells." Response at 20. However, as Dr. Thomson himself recognized, human embryonic germ cells and human embryonic stem cells are very closely related and, thus, knowledge regarding one is expected to be insightful to the other. Zwaka, Thomas P., and Thomson, James A., *A Germ Cell Origin of Embryonic Stem Cells?*, 132 Development 227-233

(2005) (attached hereto in Appendix C). As such, this is not a patentable distinction between what Hogan '926 taught and the instant claims.

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

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

common sense.

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

As such, it was entirely appropriate and correct for the Examiner to reject the pending claims as being obvious over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926.

Others Did Not Fail To Make The Claimed Invention

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

Even if one assumes *arguendo* that such evidence is relevant, when viewed correctly, it actually supports the Examiner's rejection of the pending claims. And, contrary to the Patent Owner's arguments, the science of isolating and culturing human embryonic stem cells was predictable, as shown by the fact that other scientists were successful at deriving and maintaining human embryonic stem cells contemporaneously with Dr. Thomson. Trounson Declaration at 6 – 7; Reubinoff '00 at 399.

Public Acclaim Is Not Relevant to Patentability

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

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

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

GROUNDS OF REJECTION 7: PIEDRAHTA '90 IN VIEW OF WILLIAMS '065 AND HOGAN '926

In the Office Action, the Examiner rejected all three claims as being obvious over Piedrahita '90 in view of Williams '065 and Hogan '926. Office Action at 18. The Examiner found that, "Piedrahita '90 discloses murine, porcine, and ovine ES cells," that "the Williams '065 patent does disclose human embryonic stem cells," and that "Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer." *Id*. at 18-19. The Patent Owner made several arguments in its Response as to why the teaching of Piedrahita '90 in view of Williams '065 and Hogan '926 does not invalidate the pending claims, but those arguments lack merit. Thus, the Examiner's rejection of the pending claims based on Piedrahita '90 in view of Williams '065 and Hogan '926 was and remains appropriate.

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

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

embryonic stem cells of other mammals was not relevant to human embryonic stem cells is simply ludicrous.

Further, although the 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").

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. This supports the Examiner's position that the result of that combination, which is claimed in the instant claims, was more likely the result of ordinary skill and common sense than patentable innovation.

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

Next, the Patent Owner argues that "[t]he central tenet of the Williams patent is the use of LIF to render embryonic mouse stem cells independent of feeder cells, a teaching which is demonstrably wrong for human embryonic stem cells and explicitly contradicted in the present claims 1 – 3." Response at 20. However, the Patent Owner reads Williams '065's disclosure too narrowly, limiting it to its preferred embodiment and not taking into account all of its teachings, suggestions and motivations as identified by the Examiner in the Office Action. While it may be true that Williams '065 was principally directed towards researching the ability to use LIF to maintain ES cells without feeder layers, its teachings did not exclude cultures maintained with only

feeder cells in the absence of LIF. Loring Declaration at 3 – 4. Specifically, Williams '065 expressly states that LIF can "substitute" for feeder layers in supporting the maintenance of pluripotential ES cells. Williams '065 at 1:58-62 and 3:62-64 ("LIF may be used to substitute for, or add to, feeder cells"). Further, contrary to the Patent Owner's interpretation, a skilled artisan would not understand that Williams '065 is "directed to the *advantages* of LIF in isolating and maintaining ES cells." Response at 15 (emphasis added). Rather, those of skill in the art understood Williams '065 to merely be directed to showing the *capability* of LIF to be used in isolating and maintaining ES cells. Loring Declaration at 3 – 4 ("Williams '065's discovery was merely that LIF could be used ..., not that it was an improvement over feeder layers"). Thus, the Patent Owner's proposed interpretation of Williams '065 as requiring LIF should be rejected.

Finally, the Patent Owner argues that, "Hogan specifically states that her post-implantation embryo derived cells are different from pre-implantation embryo derived cells," and that, "[t]he skilled artisan, upon reading Hogan would not be motivated to follow Hogan to arrive at the presently claimed cells." Response at 23. However, the Patent Owner makes no argument that post-implantation embryos of Hogan '926 have any structural difference from the pre-implantation embryos of the instant claims. In fact, there is no difference in the cells that are derived from either. Loring Declaration at 4 – 5. As such, this is not a patentable distinction between what Hogan '926 taught and the instant claims.

As such, it was entirely appropriate and correct for the Examiner to reject the pending claims as being obvious over Piedrahita '90 in view of Williams '065 and Hogan '926.

Others Did Not Fail To Make The Claimed Invention

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

Even if one assumes *arguendo* that such evidence is relevant, when viewed correctly, it actually supports the Examiner's rejection of the pending claims. And, contrary to the Patent Owner's arguments, the science of isolating and culturing human embryonic stem cells was predictable, as shown by the fact that other scientists were successful at deriving and maintaining human embryonic stem cells contemporaneously with Dr. Thomson. Trounson Declaration at 6 – 7; Reubinoff '00 at 399.

Public Acclaim Is Not Relevant to Patentability

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

Even if one assumes *arguendo* that such evidence is relevant, not all scientific accomplishments are necessarily deserving of patents and, as Justice Kennedy stated for a unanimous Supreme Court just this Spring in *KSR*, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 127 S. Ct. at 1741.

Here, Dr. Thomson's accomplishment was not a result of sufficient scientific ingenuity to be deserving of a patent, but rather was more attributable to his having special access to two limited resources that other embryonic stem cell researchers who were pursuing the same accomplishment at the same time did not have. Melton Declaration at 5 – 6; Loring Declaration at 10; Cowan Declaration at 5 – 6. Had others in the field been given the same special access to those limited resources, namely human embryos and funding to do research using human embryos, they would have achieved – and in fact some did achieve – the same accomplishment as Dr. Thomson. Trounson Declaration at 6 – 7; Loring Declaration at 10; Reubinoff '00 at 399.

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

GROUNDS OF REJECTION 8: ROBERTSON '83, ROBERTSON '87 AND PIEDRAHTA IN VIEW OF WILLIAMS '065 AND HOGAN '926

In the Office Action, the Examiner rejected all three claims as being obvious over Robertson '83, Robertson '87 and Piedrahita '90 in view of Williams '065 and Hogan '926. Office Action, 18. The Examiner found that, "[t]he difference between the combined teachings of Robertson '83, Robertson '87 and Piedrahita '90 and instant claims 1 – 3 is that the Thomson '913 patent claims are directed to human ES cells while the combined teachings of Robertson '83, Robertson '87 and Piedrahita '90 are directed to ES cells of mice, sheep, and pigs," that "the Williams '065 patent does disclose human embryonic stem cells," and that "Hogan '926 provides

additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer." *Id*. at 18-19.

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

CONCLUSION

In light of the foregoing, FTCR respectfully submits that the rejections of claims 1 – 3 are proper and should be maintained.

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Date

/s/ Daniel B. Ravicher

Daniel B. Ravicher, Esq.
U.S.P.T.O. Reg. No. 47,015
PUBLIC PATENT FOUNDATION, INC.
1375 Broadway, Suite 600
New York, NY 10018
Tel: (212) 545-5337
Fax: (212) 591-6038
www.pubpat.org

Attorneys for the Foundation for Taxpayer and Consumer Rights