

In The
**United States Court Of Appeals
For The Federal Circuit**

**CONSUMER WATCHDOG, (formerly known as
The Foundation for Taxpayer and Consumer Rights),**

Appellant,

v.

WISCONSIN ALUMNI RESEARCH FOUNDATION,

Appellee.

**Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board.**

OPENING BRIEF OF APPELLANT

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Dated: July 2, 2013

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CERTIFICATE OF INTEREST

Counsel for Appellant Consumer Watchdog certifies the following:

1. The full name of every party or amicus represented by me is:

Consumer Watchdog

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

NONE

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

NONE

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Daniel B. Ravicher, Sabrina Hassan, Public Patent Foundation

Dated: July 2, 2013

/s/ Daniel B. Ravicher
Daniel B. Ravicher

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Appellant Consumer Watchdog states as follows:

- (a) There have been no previous court appeals in this case.
- (b) We are aware of no other case that will be directly affected by the Court's decision in this case.

JURISDICTIONAL STATEMENT

This is an appeal from a Decision on Appeal of the Board of Patent Appeals and Interferences (now known as the Patent Trial Appeal Board) of the United States Patent and Trademark Office in *inter partes* reexamination No. 95/000,154 mailed January 22, 2013. A1. Consumer Watchdog timely filed a notice of appeal on March 21, 2013. A1831. This Court therefore has jurisdiction over this appeal under 35 U.S.C. § 141 and 28 U.S.C. § 1295(a)(4)(A) .

STATEMENT OF THE ISSUES

Whether an in vitro culture of human embryonic stem cells is patent eligible under 35 U.S.C. § 101.

Whether claims to an in vitro culture of human embryonic stem cells are anticipated or rendered obvious by prior art that discloses methods for deriving and maintaining mammalian embryonic stem cells that one of ordinary skill in the art would have expected would produce human embryonic stem cells if used with human embryos.

STATEMENT OF THE CASE

Appellant Consumer Watchdog (“CW”) is a not-for-profit public charity dedicated to providing a voice for taxpayers and consumers in special interest-dominated public discourse, government and politics. Appellee Wisconsin Alumni Research Foundation (“WARF”) is the assignee of U.S. Patent No. 7,029,913

issued April 18, 2006 (“the '913 patent”), entitled “Primate Embryonic Stem Cells.” The '913 patent's three claims cover in vitro cultures of human embryonic stem (“hES”) cells that are not markedly different from naturally occurring hES cells.

WARF's broad and aggressive assertion of the '913 patent has put a severe burden on taxpayer-funded research in the State of California where CW is located. Concerned that the '913 patent gives WARF the potential to completely preempt all uses of hES cells, including particularly for scientific and medical research, CW filed a request for *inter partes* reexamination of the '913 patent on July 17, 2006.

In its request, CW explained how prior art available at the time the '913 patent was filed provided step-by-step directions for the derivation and maintenance of mammalian embryonic stem cells. As such, the three claims of the '913 patent directed to hES cells were obvious in light of that prior art because one of ordinary skill in the art of ES cell derivation would expect that the same process for deriving other mammalian ES cells could also be used to derive hES cells. At minimum, it was obvious to try the known mammalian ES cell techniques with human embryos.

The PTO Board first agreed with CW that the claims were all invalid as anticipated by and obvious in light of the prior art. But it later flip-flopped and upheld the claims based, in part, on a biased and flawed declaration submitted by

an expert retained by WARF that was not questioned by the Board or CW and several errors regarding secondary considerations of obviousness. The Board never considered whether the claims to hES cells are patent eligible subject matter. CW now appeals to this Court to rule that each of the '913 patent's claims is invalid.

STATEMENT OF FACTS

Embryonic stem (“ES”) cells are cells from the cellular structure formed in the early gestation of vertebrates called a blastocyst. ES cells are “pluripotent” in that they retain the ability to differentiate into all of the various cell types that form a more mature (non-embryonic) organism. ES cells can be cultured and manipulated in vitro and then returned to the embryonic environment to contribute normally to the development of a mature organism. As such, ES cells have substantial potential for medical research and clinical purposes.

The '913 patent claims a replicating culture (i.e. cluster) of pluripotent hES cells and has an effective filing date of January 20, 1995. A164. At that time, much was already known about ES cells, as several publications had already taught how to create and maintain ES cells of various species.

For example, U.S. Patent No. 5,166,065, issued November 24, 1995 to Robert L. Williams et al. (“Williams”) taught methods for isolating and maintaining mammalian ES cells in vitro. A1847. Williams first taught specific methods for isolating ES cells from embryos of humans, mice, birds, sheep, pigs, cattle, goats and fish. A1853 (3:35-39). Williams specified that feeder cells may or may not be present in the culture medium in which isolation takes place. *Id.* (3:62-64). Second, Williams taught a process for maintaining the same animal ES cells in vitro while retaining their pluripotency, again in culture medium that may or may not contain feeder cells. *Id.* (4:12-23). Williams exemplified its methods with derivation of ES cells from murine (mouse) blastocysts using two different processes, one of which involved first letting the blastocyst attach to the culture dish and grow for a week and the other of which involved immunosurgery, or isolating the cells of the inner cell mass (ICM) of the embryo prior to culture. A1854-1855 (col. 6-8); A48. In both methods, the cells were then dissociated and cultured. A48-49.

Other researchers also contributed significantly to the body of stem cell knowledge before 1995. Examples include two publications authored by Robertson, one by Piedrahita, and a patent naming Hogan as the inventor. Elizabeth J. Robertson, Embryo-Derived Stem Cell Lines, in Teratocarcinoma Stem Cells (L.M. Silver et al., ed.), 10: 647-663 (1983), New York: Cold Spring

Harbor (hereinafter “Robertson '83”); Elizabeth J. Robertson, Embryo-Derived Stem Cell Lines, in *Teratocarcinomas in Embryonic Stem Cells: A Practical Approach*, Ch.4: 71-112 (1987), Oxford: IRL Press (hereinafter “Robertson '87”); Piedrahita et al., On The Isolation of Embryonic Stem Cells: Comparative Behavior of Murine, Porcine, and Ovine Embryos, 34 *Theriogenology* 879, 879-901 (1990) (hereinafter “Piedrahita”); and U.S. Patent No. 5,690,926 entitled “Pluripotential Embryonic Cells and Methods of Making Same,” issued November 25, 1997 with Brigid L. M. Hogan listed as the sole inventor (hereinafter “Hogan”).

Hogan described human, pluripotent ES cells derived from germ cells. A57-58. Piedrahita described protocols for isolating ES cells from murine, ovine (sheep) and porcine (pig) embryos. A64. Robertson '83 described isolation of pluripotent cells from blastocysts of mice. A63. Robertson '87 described the same two methods of producing ES cells described in Williams, one prescribing the transfer of intact blastocysts into culture for a limited period of continued growth and the other prescribing immunosurgery, both followed by dissociation and culture in conditioned medium. A74. Robertson '87 stressed that “feeder layers are absolutely essential for both the isolation of stem cell lines from embryos and for the routine maintenance of established cell lines.” A64.

It is undisputed that interest in hES cells was high at the time the '913 patent was filed. A77. However, much of the ES cell research prior to that time, including most of the examples above, attempted to advance hES cell research by using cells from other species. A340. The reason for using non-human cells was two-fold. First, the use of human embryos in research was, and continues to be, controversial. Many countries even made such research illegal. A309-310. Human embryos were therefore scarce and difficult to obtain for research. A342, A455-456. Second, funding to support hES cell research was also extremely scarce in the mid-to-late 1990s. A341-342, A455-456.

Dr. James A. Thomson at the University of Wisconsin was one of the lucky few stem cell researchers who managed to obtain both funding for hES cell research and human embryos with which to work. At a time when the federal government was not funding ES cell research, Geron Corporation funded Thomson's laboratory. A831. Thomson obtained human embryos through an Israeli colleague, Itskovitz-Eldor, who in 1997 sent Thomson frozen embryos donated from Israeli couples in IVF clinics. A830; A1859. Thomson's unique access to human embryos provided him the rare opportunity to succeed in isolating hES cells, and four of the five hES cell lines Thomson's team first described in 1998 came from the Israeli embryos. *Id.*

Thomson is listed as the sole inventor of the '913 patent, entitled "Primate Embryonic Stem Cells." Claim 1, the only independent claim, as amended reads:

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.

A101. Claims 2 and 3 are dependent on claim 1 and were not separately argued during the reexamination process, as they do not add limitations that affect the validity analysis.¹ See A45. As is evident from the claim language, the '913 patent claims a culture of hES cells itself, not a method of producing such hES cells. A55.

As noted above, Thomson was able to work with hES cells when most of his colleagues in the field could not. But when he filed the application in January 1995 that eventually resulted in the '913 patent, he had not yet received the human embryos from which he first isolated hES cell lines. Thus, the '913 specification,

¹ Although WARF amended claims 1-3 and added a fourth claim subsequent to reopening prosecution in 2010, the Board's latest decision dated January 22, 2013 stated that it was affirming the Examiner's decision in his July 30, 2009 Answer which confirmed the patentability of claims 1-3 as written at that time. A3.

which described Thomson's process for isolating and maintaining hES cells of the type claimed in the '913 patent, was written years before Dr. Thomson actually isolated hES cells. The cell lines described in the patent are exemplified by the isolation of ES cell lines from two non-human primate species, the marmoset and the rhesus monkey. A93 (6:11-15). Thus, Thomson claimed hES cells even though he had not yet made them. Instead, he had made ES cells of other mammals and used that as a basis to claim he could make hES cells.

Thomson described the method by which he obtained the monkey cell lines as follows:

The present invention is also a method of isolating a primate embryonic stem cell line. The method comprises the steps of isolating a primate blastocyst, isolating cells from the inner cellular mass (ICM) of the blastocyst, plating the ICM cells on a fibroblast layer (wherein ICM-derived cell masses are formed) removing an ICM-derived cell mass and dissociating the mass into dissociated cells, replating the dissociated cells on embryonic feeder cells and selecting colonies with compact morphology containing cells with a high nucleus/cytoplasm ratio, and prominent nucleoli. The cells of the selected colony are then cultured.

A92 (4:47-57).

In the '913 patent, Thomson acknowledged the body of ES cell knowledge that came before his research. For example, Thomson describes how the colony morphology of his monkey cell lines compares to that of mouse ES cells:

The colony morphology of primate embryonic stem cell lines is similar to, but distinct from, mouse embryonic stem cells. Both mouse and primate ES cells have the characteristic features of undifferentiated stem cells, with high nuclear/cytoplasmic ratios, prominent nucleoli, and compact colony formation. The colonies of primate ES cells are flatter than mouse ES cell colonies and individual primate ES cells can be easily distinguished.

A95 (9:57-66). Thomson also wrote about ES cells that had been isolated in other species:

Strong evidence of [the properties required of true ES cells] have been published only for rodents ES cells including mouse, hamster, and rat, and less conclusively for rabbit ES cells. However, only established ES cell lines from the rat and the mouse have been reported to participate in normal development in chimeras.

A92 (3:67-4:12) (internal citations omitted).

Multiple stem cell researchers succeeded in producing hES cells as claimed in the '913 patent following methods known in the art for mouse, rat, pig and sheep ES cells, such as methods taught in Robertson '83 and '87 and Piedrahita, before Thomson filed his patent. *See* A341, A454. They did not depend on Thomson's publications for their success. *Id.*

Believing that these facts rendered all three claims of the '913 patent invalid, CW requested *inter partes* reexamination of the '913 patent on July 17, 2006. After granting the request for reexamination, the Examiner found all of the pending claims allowable. A511. CW appealed to the Board of Patent Appeals and Interferences (now known as the Patent Trial Appeal Board). The Board reversed

the Examiner's decision on April 29, 2010 (“Reversal”) and designated new grounds of rejection, entitling WARF to reopen prosecution. The Board's rejections were as follows:

1. Claims 1-3 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious based on, Williams;
2. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, Williams, and Hogan;
3. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Piedrahita, Williams, and Hogan; and
4. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan.

WARF filed a Request to Reopen Prosecution along with an amendment and new evidence. A1713. In response, the Examiner determined that the claims were patentable over the rejections made by the Board. A17. On January 22, 2013, the Board affirmed the Examiner. (“Affirmance”). A3. CW now appeals.

SUMMARY OF ARGUMENT

As a threshold matter, the claims of the '913 patent are invalid under 35 U.S.C. § 101 for claiming subject matter that is not patent eligible. Specifically, the claimed hES cell culture falls within the “product of nature” exception to statutory subject matter. It is within the Court's discretion to address this issue despite the fact that the Board failed to address it below, and is especially appropriate in light of the recent Supreme Court ruling on Section 101 in *Ass'n. for Molecular Pathology v. Myriad Genetics, Inc.*, 2013 U.S. LEXIS 4540 (June 13, 2013).

The '913 patent's claims are also invalid because they were anticipated by Williams. The Board erred in finding that Williams did not teach the “cultured on a fibroblast feeder layer” claim limitation, as Williams expressly teaches using feeder cells during isolation. The Board's dependence on a biased and unchallenged declaration submitted by WARF late in these proceedings to interpret Williams in a manner inconsistent with its express teaching was legal error.

The '913 patent's claims are also invalid because they were obvious in light of the numerous prior art teachings of ways to derive and maintain ES cells of several mammalian species. Each of the four reasons cited by the Board to support non-obviousness conflicts with the facts and law.

First, invention was not required for Thomson to derive and identify the colonies that contained primate ES cells, because the three characteristics Thomson taught as bases for selection of primate ES cells are the exact same three characteristics Thomson identified as common to mouse ES cells.

Second, the Board erred in finding that 2008 evidence that rat ES cells were not isolated until that year made it non-obvious to attempt to make primate ES cells in 1995 using the methods that succeeded for mouse and other mammalian ES cells. The '913 specification itself concedes that others had made rat ES cells, and information learned more than a decade later, in 2008, can not change what would have been obvious to one skilled in the art in 1995. Regardless of whether

Thomson thought rat cells had been isolated before 1995, the Board offers no reason one skilled in the art would not have applied the known successful methods of isolating other mammalian ES cells to primate and human embryos at that time.

Third, the Board erred in (i) finding that Dr. Melton's citation of Thomson's work with human ES cells in a scientific publication indicated that Melton somehow depended on Thomson's work and then (ii) using that finding as a reason to discount Melton's sworn statement that he had produced hES cells using the methods taught in the prior art without recourse to Thomson's publications. It is customary for scientists to credit those making certain accomplishments previously even if they did not follow the teachings and methods of those accomplishments.

Fourth, the Board erred in relying on industry acclaim for Thomson's successful isolation of hES cells in 1997-8 to support the validity of his 1995 patent application for primate ES cells. Acclaim is no more indicative of invention than it is of logistical achievement, especially in a climate where human embryos and funding for research thereon were scarce. Thus, the public acclaim received by Thomson is not a factor that should weigh in support of non-obviousness.

For these reasons, all three claims of the '913 patent are invalid under 35 U.S.C. §§ 101, 102, and 103.

ARGUMENT

I. Standard Of Review

This Court's standard of review of decisions of the Board is set forth in the Administrative Procedure Act. *Dickinson v. Zurko*, 527 U.S. 150, 152 (1999). This Court reviews the Board's legal conclusions without deference and reviews its findings of fact to determine if the factual findings are supported by substantial evidence. 5 U.S.C. § 706(2); *Hitzeman v. Rutter*, 243 F.3d 1345, 1353-54 (Fed. Cir. 2001). Patent eligibility under § 101 presents an issue of law that this Court reviews *de novo*. *Bancorp Servs., LLC v. Sun Life Assurance Co. of Can.*, 687 F.3d 1266, 1273 (Fed. Cir. 2012). Anticipation is a question of fact. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999). The Board's legal conclusions related to obviousness are reviewed *de novo*. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000).

II. The Court Should Rule The Claims Invalid Under Section 101

Section 101 of the Patent Act prescribes patent rights for “[whomever] invents or discovers any new and useful ... composition of matter, or any new and useful improvement thereof” 35 U.S.C. § 101. The Supreme Court has “long held that this provision contains an important implicit exception: Laws of nature, natural phenomena, and abstract ideas are not patentable.” *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). The § 101

patent-eligibility inquiry is a “threshold test.” *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). As such, whether claims are directed to statutory subject matter is a question to be addressed before subordinate questions such as those related to anticipation and obviousness. *See Alexsam, Inc. v. IDT Corp.*, 2013 U.S. App. LEXIS 10009, at 30 (Fed. Cir. May 20, 2013)(Mayer, J., dissenting); *Whitserve, LLC v. Computer Packages, Inc.*, 694 F.3d 10, 39 (Fed. Cir. 2012) (Mayer, J., dissenting).

A. The Claimed Cell Culture Is An Ineligible Product of Nature

The Supreme Court restated just last month that discovery and isolation of a product that occurs in nature does not render that product patent eligible under Section 101. *Ass'n. for Molecular Pathology v. Myriad Genetics, Inc.*, 2013 U.S. LEXIS 4540, at 25 (June 13, 2013) (“AMP”). The claims in *AMP* that the Supreme Court held were not eligible for patenting covered “isolated DNA.” *Id.* at 11.

The '913 patent claims a “replicating in vitro cell culture of pluripotent human embryonic stem cells derived from a pre-implantation embryo” in which the cells have certain enumerated characteristics exhibited by all ES cells. A101 (col. 21-22). As in *AMP*, the '913 patent's claims are drawn to neither a method of preparation nor a scientific application of the claimed composition. *AMP*, 2013 U.S. LEXIS 4540, at 31. They place no restriction on the conditions in which the ES cells should be grown or the methods of derivation and maintenance. The

enumerated factors in claim 1 merely identify properties that are inherent in all ES cells, including those that exist naturally. A92 (3:62-67). Indeed, if the claimed ES cells were not the same as natural ES cells, the claimed invention would offer very little benefit for medical research.

The '913 patent's requirement that the claimed culture of cells be in vitro is analogous to the claim limitation in *AMP* that the DNA be “isolated.” But here there is not even a chemical change between ES cells in an in vivo embryo and ES cells in an vitro culture as there is between human DNA in vivo and isolated DNA in vitro. *AMP*, 2013 U.S. LEXIS 4540, at 25 (“Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule.”).

The '913 patent does not in any way distinguish the claimed ES cells from those that exist in nature. Williams, the prior art patent, highlights the fact that the cells that scientists culture and those that exist in the natural embryo are intended to be identical: “Embryonic stem (ES) cells . . . can be cultured and manipulated in vitro and then returned to the embryonic environment to contribute normally to all tissues including the germline.” A1852 (1: 9-13).

WARF did not create or alter the properties inherent in stem cells any more than Myriad created or altered the genetic information encoded in the DNA it claimed. *AMP*, 2013 U.S. LEXIS 4540, at 22. Because the '913 claims merely

describe ES cells that are the same as ES cells inside a human embryo (*i.e.* they maintain the potential to differentiate, refrain from differentiation when cultured on a fibroblast feeder layer, etc.), the '913 patent gives WARF the right to preempt any and all making or using of any hES cells. Such broad claims to products of nature are not patent eligible under 101 and thus should be declared invalid. *Id.* at 21.

B. Addressing § 101 Is Proper Despite Not Being Raised Below

Section 101 was not addressed during the reexamination proceedings below, which occurred before the Supreme Court's recent decision in *AMP*. However, the Court may still consider whether the claims here are invalid under Section 101 because, “a court may consider an issue antecedent to ... and ultimately dispositive of the dispute before it, even an issue the parties fail to identify and brief.” *U.S. Nat'l Bank v. Indep. Ins. Agents*, 508 U.S. 439, 447 (1993) (citations and internal quotation marks omitted).

This Court has previously held invalid under 101 claims that were on appeal from a Patent Office decision finding the claims invalid for obviousness and where the 101 issue was not raised or addressed during the Patent Office proceedings. *In re Comiskey*, 554 F.3d 967, 975 (Fed. Cir. 2007) (finding patent invalid on 101 grounds although rejection being appealed from PTO was based on obviousness); *see also Long Island Sav. Bank, FSB v. United States*, 503 F.3d 1234, 1244 (Fed. Cir. 2007).

Consideration of the 101 question is especially appropriate in light of the fact that the Supreme Court's recent *AMP* decision came after the Board's decision here. *Hormel v. Helvering*, 312 U.S. 552, 558-559 (1941) (noting that it is appropriate to hear legal theories not previously presented where “there have been judicial interpretations of existing law after decision below and pending appeal”); *Minton v. NASD*, 336 F.3d 1373, 1377 (Fed. Cir. 2003); *see also Highmark, Inc. v. Allcare Health Mgmt. Sys.*, 687 F.3d 1300, 1324 (Fed. Cir. 2012) (Mayer, J., dissenting) (“Had the trial court had the benefit of [the decisions in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010) and *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012)], it could have applied § 101 to invalidate Allcare's '105 patent at the summary judgment stage of the proceedings.”).

III. In Analyzing Anticipation, The Board Erred By Relying On A Biased And Unchallenged Declaration To Interpret A Prior Art Patent Contrary To The Plain Teaching Of Its Specification

In its decision, the Board concluded that:

[E]vidence support[ed] WARF's position that Williams does not describe using feeder cells to isolate embryonic stem cells. As argued by WARF, [*sic*] the instances in which feeder cells are utilized by Williams, the feeder cells were used to maintain ES cells, but not to derive them (Williams, col. 2, ll. 54-59; 2nd Stewart Decl. ¶ 11).

A7. The Board based its conclusion on a declaration by WARF's expert, Dr. Stewart, that mischaracterizes Williams. Specifically, Stewart incorrectly claims that the use of feeder cells was taught by Williams in conjunction with ES cell

maintenance, but not ES cell isolation. The reliance of the Board on the Stewart declaration rather than the language of the Williams specification itself was clear error because the portion of Williams that discussed isolation plainly included the use of feeder cells. Specifically, Williams taught:

a first aspect of the present invention relates to a method for the isolation of embryonic stem (ES) cells from animal embryos in vitro which method comprises deriving ES cells from said embryos in **culture medium**, said **culture medium** containing an effective amount of leukaemia inhibitory factor (LIF), for a time and under conditions sufficient for the development of said ES cells.

A1852 (2: 30-37) (emphasis added). Williams defined “culture medium” explicitly:

By ‘culture medium’ is meant a suitable medium capable of supporting growth of ES cells. Examples of suitable media useful in practicing the present invention are [specific examples given]. The **culture medium may or may not contain feeder cells and LIF may be used to substitute for, or add to, said feeder cells.**

A1853 (3: 54-64) (emphasis added).

It is evident from the above quotation that Williams defined culture medium for the isolation aspect of the invention rather than the maintenance aspect. The paragraph containing the quoted language immediately followed a paragraph that identified the species from which animal embryos can be isolated. A1853 (3:35-39). The paragraph containing the quoted language even concluded with a sentence teaching the effective derivation time. A1853 (4: 9-11). And, perhaps most tellingly, the paragraph containing the quoted language immediately preceded a paragraph that began, “Another aspect of the present invention contemplates a

process for maintaining animal ES cells in vitro” Thus, the quoted paragraph can not be said to be discussing ES cell maintenance, as the Board found, when Williams had not even yet begun to discuss maintenance when he taught feeder cells.

Stewart erroneously stated that Williams failed to teach the use of feeder cells during isolation by pointing to the lines above at 3:54-64 and concluding without explanation that they referred to ES cell growth rather than isolation. A1756. But despite the lack of support, the Board adopted Dr. Stewart’s reasoning and referenced an irrelevant line from Williams to corroborate his finding. A7 (citing lines from Williams that read, “In accordance with the present invention, it has been found that recombinant LIF and in particular recombinant human and murine LIF are effective substitutes for, or additives to, feeder layers or conditioned medium in maintaining ES cells in vitro.”).

The Board’s finding that Williams lacked enablement is especially contradicted by the fact that, in its analysis of anticipation by Williams in its original decision, the Board noted, “[f]eeder cells were known in the art to have been utilized for deriving stems ...” A53. The Board also noted as a finding of fact Robertson’s admonition that “feeder layers are absolutely essential for both the isolation of stem cell lines from embryos and for the routine maintenance of established cell lines.” A64.

In short, it was flawed logic for the Board to cite evidence that one step of Williams' process included feeder cells as proof that another step of the process did not. The fact that one step used feeder cells is not proof that another step did not. If anything, the use of feeder cells to maintain ES cells would make it more likely that feeder cells could, or indeed should, be used to derive those ES cells.

Stewart's misleading declaration and the Board's reference to irrelevant material prove nothing about whether or not Williams taught the use of feeder cells in ES cell isolation. A plain reading of Williams shows that it clearly taught the use of feeder cells during isolation. The Board's finding that Williams did not teach the use of feeder cells during isolation was not supported by substantial evidence and thus constitutes factual error. As this error (i.e. concluding that Williams did not teach using feeder cells to derive ES cells) was the Board's only reason for reversing its finding of anticipation (A5-7), the Board's initial rejection based on anticipation by Williams was correct, and the Court should reinstate that finding here.

IV. The Board Erred In Reversing Its Findings of Obviousness

In the Affirmance, the Board cited four reasons for its decision to flip-flop and find the '913 patent's claims non-obvious. Not only is each reason unsupported by the facts and law, even if one assumes they are supported by substantial evidence and a correct application of the law, they still do not contradict the Board's original determination that the claimed invention was invalid for being obvious to try. A74.

In short, the prior art teaching of methods for deriving mammalian ES cells would have, and indeed did, motivate one of ordinary skill in the art to attempt to derive hES cells in the same way. All one needed was access to human embryos, which is something Thomson eventually had when many others did not.

A. Isolation of Human Embryonic Stem Cells Did Not Require Innovation

The Board concluded that Thomson's identification of hES cells required innovation. A10. The Board's basis for this conclusion came from a declaration submitted by WARF's retained expert, Dr. Stewart, in which he said hES cell colonies are flatter and more compact than mouse ES cell colonies, that flat colonies of hES cells had not been described before Thomson's invention, and that there was a plethora of colonies to choose from. A1761; A9.

However, Stewart's bald biased claim that Thomson's colony selection required insight is inconsistent with and insufficient to overcome all of the other evidence regarding colony morphology, including evidence cited by the Board itself. First, even the Board acknowledged that language from the '913 patent conceded colony morphology of primate ES cells is "similar to" that of mouse ES cells and that both "have the characteristic features of undifferentiated stem cells, with high nuclear/cytoplasmic ratios, prominent nucleoli, and compact colony formation." A95 (9:57-62); A9. But these three similarities do not merely represent a partial overlap between hallmarks of mouse ES cells and hallmarks of hES cells.

Instead, these three characteristics common to mouse ES cells are the very same three characteristics that Thomson revealed in his “method of isolating a primate embryonic stem cell line” as the bases on which to choose colonies from those that form during the isolation process:

The method comprises ... replating the dissociated cells on embryonic feeder cells and selecting colonies with **compact morphology** containing cells with a **high nucleus/cytoplasm ratio**, and **prominent nucleoli**.

A92 (4: 48, 53-57) (emphasis added). If Thomson recognized flatness of cells was a key to their identification, Thomson failed to include such recognition in the instructions in the patent. Thus, the disclosure contained in the '913 patent itself does not support Stewart's (and thus the Board's) conclusion on that point.

Second, in its previous decision rejecting the '913 patent's claims, the Board rebutted WARF's argument regarding ordinary skilled scientists not knowing which colony to select by saying, “common sense would have directed her or him to pick different colony types to determine which possessed ES properties.” A75. The Board's second decision to the contrary assumes either that it would not have been sensible to test different colony types for ES properties (which, by Thomson's description, were visually obvious in any event) or that an ordinary skilled scientist would not have had common sense. The evidence citing a distinction between hES colonies and mouse ES colonies supports neither of those propositions.

In any case, the significance of the distinction between mouse ES cell colonies and hES cell colonies is vastly overstated. Thomson was not required to pick a hES colony out of a sea of mouse ES colonies. He instead had to select it from a culture of human cells. Like a mouse ES colony, the hES colony has the three “characteristic features” that distinguish it from surrounding non-ES cells. Thomson himself characterized the colony morphology of the mouse and primate as “similar” and pronounced identical hallmarks.

If the characteristic features of hES colonies didn’t immediately identify the colonies as such, common sense would have guided an ordinary skilled scientist to test different colony types for those features. It is thus not true that identifying the ES colonies in the human cell cultures required innovation or insight. The Board’s finding that such identification was an inventive act rather than an application of known technology is legally erroneous.

B. Obviousness Was Not Negated By Failure to Make Rat ES Cells

The Board relied on evidence that WARF cited in its Request to Reopen Prosecution to conclude that all attempts to make rat ES cells before 2008 had failed, and thus the path to isolating hES cells was not obvious in light of the prior art that taught how to isolate mouse ES cells. A10. The new evidence submitted by WARF late in the reexamination was a December 2008 publication by Buehr that found the process for reproducibly deriving ES cells from inbred mouse strains did

not yield ES cells when applied to the rat. *Id.*; A1790. In its earlier decision rejecting the '913 patent's claims, the Board had relied in part on the inventor's own statements in the '913 patent that rat ES cells had been isolated prior to 1995. A76. The earlier decision was the correct one.

There are several critical flaws in the Board's decision to rely on the Buehr publication instead of the '913 patent's own admissions about the prior art. First, the Board acknowledged in its earlier decision a difference of opinion within the field regarding the production of rat ES cells. A77. It pointed out that, regardless of whether WARF could resolve the question of the extent to which stem cells had been obtained from embryos of other species, case law supported finding that it was obvious to try when evidence cut both ways and there were "predictable options taught in the prior art for making ES cells." A77 (citing *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009)). Even if the Board found that WARF managed to resolve that question, nothing about the 2008 Buehr article changed the principle that options taught in the prior art were 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." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

Second and more importantly, regardless of whether Buehr conclusively established that all of the rat cells thought in 1995 to be ES cells were not ES cells, it does not change what a person skilled in the art thought in 1995. Section 103(a) forbids issuance of a patent when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a) (emphasis added); *see also KSR*, 550 U.S. at 406 . Thomson himself explicitly stated in the ‘913 patent specification that “[s]trong evidence of these [properties required of true ES cells] have been published only for rodents [*sic*] ES cells including ... rat,” and “established cell lines from the rat ... have been reported to participate in normal development in chimeras.” A92 (3:67- 4:12).

Thomson thus clearly believed in 1995 that rat ES cells had been produced. He at minimum did not question the assumption of ordinary skilled scientists that rat ES cells could be produced with the known and familiar techniques for deriving ES cells of other mammals. If after applying for and receiving the ‘913 patent Thomson came to believe that rat ES cells did not exist before 1995, that belief could not have changed his beliefs, or the beliefs of others, in 1995, which is the relevant time for an obviousness analysis. The Board's consideration of a publication from 2008 to determine what was obvious in 1995 was legal error.

C. The Evidence Does Not Support That Others Who Made Human Embryonic Stem Cells Depended On Thomson's Work

The Board held the '913 patent's claims non-obvious because, in part, it found that, “[t]hose (Melton) making human embryonic stem cells followed Thomson’s work.” A13. The Board made this finding despite the fact that it had originally stated as one basis for finding the claims obvious that both Drs. Melton and Cowan, scientists with expertise in cell culture who submitted declarations in the reexamination proceeding, stated that they had isolated hES cells by simply following methods taught for deriving mouse, rat, pig and sheep ES cells. A77. The Board’s flip-flop on this issue resulted from its decision to discount Dr. Melton’s sworn statement because he had cited Dr. Thomson’s work in his own published research on hES cells that appeared in the New England Journal of Medicine. A11. In short, the Board stated, “despite Dr. Melton’s statements to the contrary, in his own research in making human embryonic stem cells, Dr. Melton credited Dr. Thomson’ published work.” A12.

Dr. Melton’s sworn statement, however, was not “contrary” to his NEJM article. The fact that Dr. Melton did not depend on Thomson’s work to do his own was not a good reason to omit Thomson from the list of scientists Melton credited with earlier isolation of hES cells. The “published protocols” Melton referenced in his article noted Thomson’s work alongside the work of two other human ES cell researchers. A1774, 1776. This credit makes perfect sense given that the three cited

publications describing ES cells derived from human blastocysts preceded Dr. Melton's publication. For Dr. Melton to not credit other scientists with earlier publication of hES cell derivation, or for him to credit only scientists who published research describing ES cell derivation from other species, such as Robertson and Piedrahita, would amount to a false representation that Dr. Melton himself was the only scientist at the time to have derived hES cells. His citation to other scientists, including Dr. Thomson, was a respectable and conventional way to recognize the accomplishments of those who did related work before him, regardless of whether he used their work to perform his own research.

Melton did, as the Board found, "follow" Thomson's work—but he did so only in a chronological sense. A13. The fact that Melton did his work "according to published protocols [that he modified]" does not mean he relied on the publications he cited. It means that if a scientist reading the Melton research wanted to repeat his experiments, (s)he could follow the steps in the cited publications to achieve the same results.² Alternatively, and importantly, (s)he could follow the steps taught in Williams since, as established above, Williams teaches the same steps.

² Analogously, a person might write about deducing the length of a hypotenuse of a right triangle "according to the Pythagorean theorem stated in Math Text X." But citation to Math Text X merely gives the reader a resource to imitate the calculation; it does not indicate that the author of Math Text X deserves credit for Pythagorus' discovery.

Melton's sworn statement that he derived hES cells "without recourse to Dr. Thomson's publications or patents" (A341) is consistent with the acknowledgments he made in his NEJM article: he did his hES cell research without depending on other hES cell research, and yet he credited other hES researchers for their earlier work with human embryos. His sworn statement should not have been discounted by the Board.

D. Acclaim By the Scientific Community Does Not In Itself Support a Finding of Non-Obviousness

The fourth basis for the Board's non-obviousness finding was noted acclaim in *Harvard Magazine* and other examples of recognition of Thomson by scientists. A11. Such acclaim does not support a finding of non-obviousness in this case because it did not result from Thomson's patent. Instead Thomson received acclaim for work with the human embryos that he managed to obtain years after he filed for the '913 patent.

Given the advanced state of the art and the scarcity of human embryos and funding to support hES cell research in 1995, the "breakthrough" needed for the isolation and maintenance of hES cells was of the logistical, not innovative, type. Thomson's manufacture of hES cells was acclaimed because hES cells are useful and their production had not been reported before, but that does not mean his feat required invention. Acclaim is warranted for many things other than inventiveness, and in this case it was warranted by Dr. Thomson's ability to procure human

embryos to which he could apply the known techniques for deriving mammalian ES cells as taught by, e.g., Williams. Thomson was the first to derive hES cells not because he invented something new or non-obvious, but instead because he had special access to the necessary human embryos and funding.

The Examiner involved in the appeal proceeding below considered and erroneously rejected the argument that access to human embryos was relevant to the validity of the invention. A1649. His mistake resulted from his quotation of the language from 35 U.S.C. 103(a) which states that “patentability shall not be negated by the manner in which the invention is made.” A1653. But the Examiner misunderstood the argument, as Appellant does not argue that Thomson’s receipt of embryos and funding “negative” his invention. Rather, it is the prior art that renders Thomson's work anticipated and obvious that “negatives” Thomson's claims. The fact that obtaining embryos and funding was difficult merely negates secondary considerations of non-obviousness. Any argument about other scientists’ “failure” to produce hES cells or long-felt unmet need or critical acclaim does not indicate that the way to derive hES cells was not obvious. Instead, it evidences merely other scientists' lack of resources.

Indeed, neither the Board, nor the Examiner, nor WARF has cited any evidence of a scientist who had access to human embryos who failed to derive hES cells. Nor is there any reference in the record that would have taught ordinary

skilled scientists to not use feeder cells to derive hES cells as claimed in the '913 patent. All the Board cites, and all WARF can cite, is the fact that others did not actually derive hES cells. But they fail to recognize that was due to a lack of access to human embryos and financial resources, not a lack of knowledge of how to do so.

CONCLUSION

Claims 1-3 of the '913 patent are each invalid because they cover ineligible subject matter and were anticipated and obvious. The Court should rule each claim of the '913 patent invalid.

Dated: July 2, 2013

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

THE FOUNDATION FOR TAXPAYER & CONSUMER RIGHTS
Requester and Appellant

v.

Patent of WISCONSIN ALUMNI RESEARCH FOUNDATION
Patent Owner and Respondent

Appeal 2012-011693
Reexamination Control 95/000,154
Patent 7,029,913
Technology Center 3999

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and
JEFFREY B. ROBERTSON,¹ *Administrative Patent Judges.*

LEBOVITZ, *Administrative Patent Judge.*

¹ Jeffrey B. Robertson has replaced Romulo H. Delmendo who participated in the original Board decision.

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DECISION ON APPEAL

This is new decision under 37 C.F.R. § 41.77(f) in response to 1) the Patent Owner's Request to Reopen Prosecution after a decision by the Board which instituted new grounds of rejection; and 2) the Examiner's subsequent determination under 37 C.F.R. § 41.77(d) that the new rejections have been overcome.

The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b), 134, and 315. We withdraw the rejections set forth in the Board Decision dated January 29, 2010 and affirm the Examiner decision in the Answer dated July 30, 2009 confirming the patentability of claims 1-3 of US Patent 7,029,913.

STATEMENT OF THE CASE

The patent in dispute in this appeal is U.S. Patent No. 7,029,913 (issued Apr. 18, 2006) ("the '913 patent"), assigned to the Wisconsin Alumni Research Foundation ("WARF"). Dr. James Thomson is listed as the sole inventor. The claims are drawn to human embryonic stem (hES) cells.

The '913 patent is the subject of an inter partes reexamination. After reexamination before the Examiner, the Examiner found all the pending claims allowable. (Action Closing Prosecution (mailed Feb. 25, 2008) & Right of Appeal Notice 80 (mailed Jun. 8, 2008)). The Third Party Requester appealed that determination to the Board.

In the Board decision on the appeal dated April 29, 2010 ("Decision"), we reversed the Examiner's determination not to adopt certain rejections of claims 1-3 of the '913 Patent and designated the new rejections

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as new grounds of rejection, entitling Patent Owner to re-open prosecution.

The new rejections are as follows:

1. Claims 1-3 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious based on, Williams² (Examiner's Answer ("Ans") 6);

3. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83,³ Robertson '87,⁴ Williams, and Hogan⁵ (Ans. 9);

4. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Piedrahita,⁶ Williams, and Hogan (Ans. 12); and

5. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan (Ans. 13).

In response to the new grounds of rejection, WARF filed a Request to Reopen Prosecution ("Req. Reopen") accompanied by an amendment and new evidence. The amendment amended Claims 1-3 and added claim 4. The Third Party Requester did not file comments subsequent to the Board decision or subsequent to WARF's Request.

² Robert L. Williams et al., U.S. Patent No. 5,166,065 (issued Nov. 24, 1992).

³ Elizabeth J. Robertson et al., Isolation, Properties, and Karyotype Analysis of Pluripotentiality (EK) Cell Lines from Normal and Parthenogenetic Embryos, in *Teratocarcinoma Stem Cells* (L.M. Silver et al., ed.), 10: 647-663 (1983).

⁴ Elizabeth J. Robertson, Embryo-Derived Stem Cell Lines, in *Teratocarcinomas in Embryonic Stem Cells: A Practical Approach*, Ch. 4: 71-112 (1987), Oxford: IRL Press.

⁵ Brigid L. M. Hogan, U.S. Patent No. 5,690,926 (issued Nov. 25, 1997)

⁶ Piedrahita et al., *On The Isolation of Embryonic Stem Cells: Comparative Behavior of Murine, Porcine, and Ovine Embryos*, 34 *Theriogenology* 879, 879-901 (1990).

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The Examiner reviewed all evidence of record anew and determined that claims 1-3 and new claim 4 are patentable over the cited prior art of record as set forth in Rejections 1 and 3-5 (Examiner's Determination under 37 CFR ¶ 41.77(d), p. 17).

We agree with the Examiner's determination.

1. ANTICIPATION BY WILLIAMS

Initially, we reversed the Examiner's determination that Williams did not anticipate the claims to human embryonic stem cells. First, we found that Williams disclosed human embryos in a list of animal embryos that could be used as a source of embryonic stem cells (FF5) (Decision 10). Second, we determined that Williams was enabling to make human embryo stem cells (Decision 11-14). WARF had argued that Williams was not enabling, but we found that WARF did not provide persuasive evidence that the Williams' method would not work when applied to human embryos (*id.* at 12).

To address the new grounds of rejection, WARF provided a second declaration by Colin Stewart, D. Phil. (Second Stewart Declaration (2nd Stewart Decl.), filed June 29, 2010). Dr. Stewart states in his declaration that he obtained a doctorate in Mouse Embryology and that his "research career has centered on the development and application of genetic manipulation techniques to studying embryogenesis, stem cells and disease formation in mammals using the mouse as a model organism." (2nd Stewart Decl. ¶ 1.) Dr. Stewart is therefore qualified as an expert in the subject matter of this appeal.

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Dr. Stewart testified in his written declaration that the Williams patent is not enabled to produce human embryonic stem cells. Dr. Stewart stated that Williams' method of isolating stem cells without feeder cells did not work when applied to human embryo cells (2nd Stewart Decl. ¶¶7-11). Dr. Stewart testified:

8. Williams discloses two methods for isolating murine embryonic stem (ES) cells from a blastocyst. The first requires the direct plating of a murine blastocyst onto a plastic tissue culture dish in the presence of the cytokine (growth factor) LIF. The second involves performing immunosurgery on a murine blastocyst and then subsequently plating the resulting inner cell mass (ICM) on a plastic tissue culture dish in the presence of LIF. While these methods are suitable for murine ES cells, the do not work when applied to human blastocysts or human ICMs.

10. The reason that neither Williams method will work to isolate hES [human embryonic stem] cells is that hES cells can only be isolated by plating a human post-immunosurgery ICM on a feeder layer of cells. The addition of LIF to the culture will have no effect on helping to isolate hES cells.

As evidence of this, Dr. Stewart cited the Bongso publication, published after the filing date of the '913 patent:

13. My position is supported by the report of Bongso who followed the Williams ICM [inner cell mass from human blastocysts] method and plated human post-immunosurgery derived ICM onto a tissue culture dish that contained LIF, but the dish did not contain a feeder layer of cells. Bongso noted that this method failed to isolate a replicating in vitro cell culture of pluripotent hES cells. This failure was reported by Bongso et al. in 1994 (Human Reproduction 9: 2110-2117; "Bongso"). This supports my position that hES cells can only be isolated by plating a post-immunosurgery derived ICM on a feeder layer of cells.

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WARF's evidence is persuasive (Req. Reopen 7-10).

First, the evidence supports WARF's position that Williams does not describe using feeder cells to isolate embryonic stem cells. As argued by WARF, the instances in which feeder cells are utilized by Williams, the feeder cells were used to maintain ES cells, but not to derive them (Williams, col. 2, ll. 54-59; 2nd Stewart Decl. ¶ 11).

In addition, we agree with WARF that Bongso reported negative results without feeder cells. Bongso wrote:

Our preliminary studies prior to this report demonstrated clearly that, in the absence of an initial feeder layer and subsequent HLIF, the ICM cells were difficult to sustain or always differentiated into fibroblast-like cells.

Bongso, pp. 2115-2116.

As WARF has provided persuasive evidence that Williams did not enable one of ordinary skill in the art, at the time the invention was made, to make human embryonic stem cells as claimed, we withdraw the anticipation rejection of claims 1-3 over the Williams patent.

2. OBVIOUSNESS REJECTIONS

In the Decision, we reversed the Examiner's determination that claims 1-3 were not obvious under 35 U.S.C. § 103(a) over 1) Williams; 2) Robertson '83, Robertson '87, Williams and Hogan; 3) Piedrahita, Williams and Hogan; 4) Robertson '83, Robertson '87, Piedrahita, Williams and Hogan. In reaching this conclusion, we grouped all the rejections together, since they involved the same set of facts and issues (Decision 20). After considering all the evidence of record, we stated that "it would have been *obvious to have tried* the known mouse protocols on human embryos, and

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because such protocols would have resulted in human stem cells, we conclude that the claimed human embryonic stems would have been obvious to persons of ordinary skill in the art” (Decision 38 (emphasis added)).

The so-called “obvious to try” standard is applicable when there is a finite number of identified, predictable solutions” available to one of ordinary skill in the art that would have routinely led to the claimed invention.

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.

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Whether an invention is “obvious to try” is just another factor to be considered in making an obviousness determination. As made clear by the Supreme Court, and subsequently by the Federal Circuit, there is no one test or single standard for determining obviousness. Rather, all the evidence of record must be considered:

This court cannot, in the face of *KSR*, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art.

In re Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

While we acknowledged in the original Decision that there was uncertainty as to whether the prior art stem cell technology would work in

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human embryos, we found this outweighed by the strong reason to make human embryonic stem cells (“obvious to try”) and the prior art technology to do so (Decision 36). However, WARF has now cited evidence that identifying human embryonic stem cells was not routine because human stem cells do not have the same morphology as mouse embryonic stem cells and thus it would not have been known which cells to select during the stem cell derivation process.

Dr. Stewart testified that Dr. Thomson “succeeded in part” in isolating hES cells “because he was the first to identify the particular morphology of primate ES cells” (2nd Stewart Decl. 34).

35. As noted in my previous Declaration dated May 29, 2007 at paragraph 19, the primate ES cell colonies that Dr. Thomson selected for further study were compact and flatter than mouse ES cell colonies. Mouse ES cell colonies are distinctly different in that they are compact, often tear-drop shaped mounds. Flat, compact colonies of hES cells had not been described at any time before Dr. Thomson's invention. It should be remembered that at this stage in the process, the culture dish contains a heterogeneous mixture of cells and debris, a plethora of colonies, and it would not have been apparent what cells/colonies to choose for further study without the insight exhibited by Dr. Thomson.

Dr. Stewart's testimony is consistent with the disclosure in the '913 Patent. The '913 Patent described the isolation of primate ES cells:

The colony morphology of primate embryonic stem cell lines is similar to, but distinct from, mouse embryonic stem cells. Both mouse and primate ES cells have the characteristic features of undifferentiated stem cells, with high nuclear/cytoplasmic ratios, prominent nucleoli, and compact colony formation. The colonies of primate ES cells are flatter than mouse ES cell colonies and individual primate ES cells can be easily distinguished.

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'913 Patent, col. 9, ll. 57-64. Thus, a preponderance of the evidence supports WARF's argument that Dr. Thomson, in deriving embryonic stem cells from human embryos, did more than just follow the path that had already been taken in the mouse (Decision 34). Rather, the invention took innovation by Dr. Thomson.

As discussed above, whether an invention is obvious because it is "obvious to try," must be weighed against other evidence of nonobviousness in the record. In this case, WARF provided new rebuttal evidence of repeated failures to make rat embryonic stem cells using the available stem cell technology. The Buehr⁷ publication was cited by WARF as

. . . conclusive evidence that the path was not so definite [for isolating human embryonic stem cells], the landmarks not so explicit, and the solutions not so predictable. Buehr discloses, for the first time, in 2008, twenty-seven years after the first isolation of murine ES cells, the isolation of rat ES cells. All of the attempts to make rat ES cells that occurred before Buehr failed.

Req. Reopen 20. The failure, until 2008, to make rat stem cells using the available stem cell technology is another factor which militates against a finding of obviousness.

Consistently, in a post-filing date publication on stem cell science that appeared in the *Harvard Magazine*, July-August 106(6):36-45, 37 (2004), it was stated:

Nevertheless, harvesting and maintaining a line of stem cells from any animal is "not routine at all," explains Andrew McMahon, professor of molecular and cellular biology. No one has been able to derive stem cells from rats, for example, even

⁷ Buehr et al., "Capture of Authentic Embryonic Stem Cells from Rat Blastocysts," *Cell*, 135: 1287-1298, 2008.

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though mice and rats are closely related. So it was an astounding breakthrough when, in 1998, University of Wisconsin researcher James Thomson successfully established and sustained several human stem-cell lines in culture.

Dr. Thomson's isolation of hES was characterized as a "breakthrough" in the *Harvard Magazine* article. To further support this statement, WARF cited numerous examples of recognition and accolades by the lay and scientific community of Dr. Thomson's work with human embryonic stem cells (Req. Reopen 28-29). Thus, the invention of human embryonic stem cells by Dr. Thomson was highly praised by scientists.

In the original Decision, we had recognized the shortcomings in the prior art for making stem cells of certain animal species, including rat, but we had found this offset by the evidence of record, including a declaration by Dr. Douglas Melton that that human ES cells were successfully isolated "by simply following those methods taught for deriving mouse, rat, pig and sheep ES cells" (Decision 37).

WARF provided new evidence in the Request to Reopen Prosecution that Dr. Melton's declaration should be given less weight. We agree. WARF noted that Dr. Melton had said in his declaration that "we have successfully isolated human ES cells in our lab by simply following these methods taught for deriving mouse, rat, pig and sheep ES cells. We did so without recourse to Dr. Thomson's publications or patents" (Melton Decl. 13). However, WARF provided Dr. Melton's own scientific publication in *The New England Journal of Medicine* in which he described the isolation of hES cell lines (Cowan et al. 2004, *New Eng. J. Med.* 350 (13) 1353-1356; Req. Reopen 25). WARF states:

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In that paper, Dr. Melton refers to Dr. Thomson's seminal paper in *Science* in 1998 . . . as guiding the isolation of their (Cowan and Melton's) hES cells. For example, . . . the authors state that "97 inner cell masses were isolated, and 17 individual human embryonic stem-cell lines . . . were derived according to published protocols that we modified in terms of medium composition, enzymatic disassociation, and procedures for freezing and thawing . . .," citing to Thomson et al. *supra*.

Even more probative is the fact that in this very same publication, Dr. Melton nowhere credits Robertson '83 or Robertson '87, or Piedrahita, references that according to Dr. Melton in his Declaration submitted in the present proceedings, informed him as to how to isolate his hES cells "without recourse to Dr. Thomson's publications or patents." Declaration of Melton, paragraph 13.

Req. Reopen 26.

Thus, despite Dr. Melton's statements to the contrary, in his own research in making human embryonic stem cells, Dr. Melton credited Dr. Thomas's published work.

In sum, while there was a strong reason to have made human embryonic stem cells, the closest prior art cited in this proceeding – the Williams patent – did not make them or enable making them because it did not describe utilizing feeder cells to derive them or describe which cells in the derivation culture were the human embryonic stem cells.

There was reason to try other available prior art methods for making human embryonic stem cells. However, strong evidence of non-obviousness outweighs the countervailing evidence of obviousness. This nonobviousness evidence includes:

- The isolation of human embryonic stem cells required innovation;

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- The failure to make stem cells from closely related species, particularly rat;
- Those (Melton) making human embryonic stem cells followed Thomson's work; and
- Acclaim by both the lay and scientific community.

CONCLUSION

Upon reconsideration of the new evidence provided by WARF, the rejections set forth in the Board Decision dated January 29, 2010 are withdrawn and we affirm the Examiner decision in the Answer dated July 30, 2009 confirming the patentability of claims 1-3 of US Patent 7,029,913.

AFFIRMED

ack

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CERTIFICATE OF FILING AND SERVICE

I hereby certify that, on this the 2nd day of July, 2013, I electronically filed the foregoing with the Clerk of Court using the CM/ECF System, which will send notice of such filing to the following registered users:

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I further certify that, upon acceptance and request from the Court, the required paper copies of the foregoing will be deposited with United Parcel Service for delivery to the Clerk, UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT, 717 Madison Place, N.W., Washington, D.C. 20439.

The necessary filing and service were performed in accordance with the instructions given to me by counsel in this case.

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CERTIFICATE OF COMPLIANCE
With Type-Volume Limitation, Typeface Requirements,
And Type Style Requirements

1. This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because:

this brief contains 7,201 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because:

this brief has been prepared in a proportionally spaced typeface using OpenOffice 3 in 14 Times New Roman.

July 2, 2013

/s/ Daniel B. Ravicher

Daniel B. Ravicher