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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 2010-001854
Reexamination Control 95/000,154
Patent 7,029,913
Technology Center 3999

Decided: April 28, 2010

Before DONALD E. ADAMS, ROMULO H. DELMENDO, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal by the Third Party Requester from the Patent Examiner's confirmation of the patentability of claim 1-3 in an Inter Partes Reexamination of US Patent 7,029,913. The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b), 134, and 315. We reverse the Examiner.

STATEMENT OF THE CASE

The patent in dispute in this appeal is U.S. Patent No. 7,029,913 (issued Apr. 18, 2006) [hereinafter '913 patent], assigned to the Wisconsin Alumni Research Foundation [hereinafter WARF]. WARF is the patent owner and "Respondent" in this proceeding.

The named inventor of the '913 Patent is James A. Thomson. The '913 patent shares ancestry with two other related patents – U.S. Patent No. 5,843,780 (issued Dec. 1, 1998) and U.S. Patent No. 6,200,806 (issued Mar. 13, 2001) – both which were subject of separate reexamination proceedings, each culminating with the issuance of a Reexamination Certificate confirming the patentability of the claims.

The claims of the '913 patent are drawn to pluripotent human embryonic stem ("ES") cells. As explained in the patent:

> stem cells are undifferentiated cells which can give rise to a succession of mature functional cells. For example, a hematopoietic stem cell may give rise to any of the different types of terminally differentiated blood cells. Embryonic stem (ES) cells are derived from the embryo and are pluripotent, thus possessing the capability of developing into any organ or tissue type or, at least potentially, into a complete embryo.

('913 patent, col. 1, ll. 28-35.) Because of their ability to produce many different cell types, "[s]cientists already believe that human ES cell research will produce new ways of not just treating, but preventing, a wide range of

diseases, including AIDS, diabetes, Parkinson's, Alzheimer's and heart disease." Request for Inter Partes Reexamination 2 (filed July 17, 2006).

The Foundation for Taxpayer & Consumer Rights[1] [hereinafter Third Party Requester] filed a Request for Inter Partes Reexamination on July 17, 2006 under 35 U.S.C. §§ 311-318 and 37 C.F.R. § 1.913 of every claim of the '913 Patent as invalid under 35 U.S.C. § 103.

They asserted a substantial new question of patentability on the basis the following publications said not to be of record during prosecution of the '913 patent (Request for Inter Partes Reexamination at 3-4):

• 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), 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]; and

• 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].

[1] The Request stated that on "behalf of the Foundation for Taxpayer & Consumer Rights ('FTCR'), . . . the Public Patent Foundation ('PUBPAT') respectfully requests *inter parte* reexamination" (Request for Inter Partes Reexamination at 1).

The Request was granted (Order Granting Request for Inter Partes Reexamination (mailed Sept. 29, 2006)) and reexamination proceedings commenced. A set of anticipation and obviousness rejections under 35 U.S.C. § 102 and § 103, respectively, were instituted by the Examiner, but ultimately the Examiner withdrew all rejections and found claims 1-3 allowable (Action Closing Prosecution (mailed Feb. 25, 2008) [hereinafter ACP] & Right of Appeal Notice 80 (mailed Jun. 8, 2008) [hereinafter RAN]).

The Third Party Requester appeals from the Examiner's decision in finding all the claims allowable and contends that the rejections were improperly withdrawn. The Examiner's favorable patentability determinations with respect to the following withdrawn rejections are appealed:

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 (U.S. Patent No. 5,166,065 (issued Nov. 24, 1992) [hereinafter Williams]) (Ans. 6);

2. Claims 1-3 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious based on, Hogan (U.S. Patent No. 5,690,926 (issued Nov. 25, 1997) [hereinafter Hogan]) (Ans. 8);

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

4. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Piedrahita, 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).

The Third Party Requestor also appeals the Examiner's decision not to adopt the following rejection:

6. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, and Piedrahita (Request for Inter Partes Reexamination 11).

Claim 1 is the only independent claim on appeal. Claim 1 was amended several times during the reexamination proceeding. (Amendments dated May 30, 2007; Oct. 1, 2007; Oct. 2, 2007; & Oct. 4, 2007.) The amendments are indicated by underlining and brackets in claim 1, as reproduced below. The only other pending claims, claims 2 and 3, depend on claim 1; as they were not separately argued, claims 2 and 3 fall with claim 1. 37 C.F.R. § 41.31(c)(1)(vii).

Claims 1 reads as follows:

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

WILLIAMS – ANTICIPATION

The Third Party Requester appeals the Examiner's determination to withdraw the rejection of claims 1-3 under 35 U.S.C. § 102(b) as anticipated by Williams.

Statement of the Issues

There are two issues to be decided in this rejection:

1) Whether Williams described and enabled human embryonic stem cells derived from a pre-implantation embryo, the subject matter of claim 1?

2) Whether Williams' disclosure of human ES cells is negated by facts disclosed in the Cherny article?

Principles of Law

"[A] prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006).

> We think the Karrer patent, as a printed publication, describes to one skilled in this art not only the broad class but also this much more limited class within that broad class, and we think it is immaterial that Karrer did not expressly spell out the limited class as we have done here. It is our opinion that one skilled in this art would, on reading the Karrer patent, at once envisage *each member* of this limited class, even though this skilled person might not at once define in his mind the formal boundaries of the class as we have done here.
>
> A simple calculation will show that, excluding isomerism within certain of the R groups, the limited class we find in Karrer contains only 20 compounds. However, we wish to point out that it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved . . . it is of no moment that each compound is not specifically named or shown by structural formula in that publication.

In re Petering, 301 F.2d 676, 681-682 (CCPA 1962) (emphasis added).

> . . . although he did not actually premedicate the patients himself, anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art. *Donohue*, 766 F.2d at 533, 226 USPQ at 620 ("It is not,

> however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.").

Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001).

Findings of Fact ("FF")

The Williams patent

1. "Embryonic stem (ES) cells, the pluripotent outgrowths of blastocysts, can be cultured and manipulated in vitro and then returned to the embryonic environment to contribute normally to all tissues including the germline" (Williams, col. 1, ll. 9-13).

2. "However, it is known that ES cells . . . will only retain the stem cell phenotype in vitro when cultured on a feeder layer of fibroblasts (such as murine STO cells . . .) or when cultured in medium conditioned by certain cells" (*id.* at col. 1, ll. 43-59).

3. "In work leading to the present invention, it has been found that LIF [leukaemia inhibitory factor] has the capacity to substitute for, or be added to, feeder layers (or conditioned medium) in supporting the maintenance of pluripotential ES cells in vitro." (*Id.* at col. 1, ll. 58-62.)

4. Williams described the "present invention" as "directed to a method for the isolation and maintenance of embryonic stem (ES) cells from animal embryos in vitro which method comprises deriving and/or maintaining said ES cells from said embryos in culture medium containing an effective amount of leukaemia inhibitory factor (LIF), for a time and under conditions sufficient for the derivation and/or maintenance of said ES cells." (*Id.* at col. 3, ll. 28-35.)

5. "The animal embryos may be isolated from a number of animal species such as humans, mice, birds (e.g. chickens), sheep, pigs, cattle, goats and fish." (*Id.* at col. 3, ll. 35-38.)

6. For supporting the growth of ES cells, the "culture medium may or may not contain feeder cells and LIF may be used to substitute for, or add to, said feeder cells." (*Id.* at col. 3, ll. 62-64.)

7. Williams described isolation of ES cells from murine blastocysts using two methods. (*Id.* at col. 6, l. 59 to col. 7, l. 4.)

8. The media contained LIF (*id.* at col. 6, l. 56).

9. "In the first method the blastocysts were allowed to attach to the culture dish and approximately 7 days later the outgrowing inner cell mass picked, trypsinised [sic] and transfered [sic] to another culture dish in the same culture media. ES cell colonies appeared 2-3 weeks later with between 5-7 individual colonies arising from each explanted inner cell mass." (*Id.* at col. 6, ll. 59-65.)

10. "The second method for isolation of ES cell lines used the immunosurgery technique (described in Martin, G. R. (1981) Proc. Natl. Acad. Sci. USA 78:7634-7638) where the trophectoderm cells are destroyed using anti-mouse antibodies prior to explanting the inner cell mass." (*Id.* at col. 6, l. 66 to col. 7, l. 3.)

11. "[B]lastocysts were treated by immunosurgery (as described in Martin, G. R. (1981) Proc. Natl. Acad. Sci. USA 78:7634-7638). The blastocysts were allowed to hatch from the zona pelucida, and then treated with anti-mouse antibodies and destroyed by the addition of complement. The exposed inner cell mass was then left to attach to a tissue culture dish and again treated with anti-mouse antibodies and complement. Within a few

days pluripotential stem cell colonies appeared and were dissociated and trypsinised [sic] as described above." (*Id.* at col. 8, ll. 22-31.)

Cherny

12. Cherny disclosed that "[i]nitial research into the isolation of domestic animal ES cells in our and other laboratories attempted to repeat the work carried out in mice by isolating cell lines directly from cultured preimplantation embryos." (Robert A. Cherny, *Strategies for the Isolation and Characterization of Bovine Embryonic Stem Cells*, 6 Reprod. Fertil. Dev. 569, 571 (1994) [hereinafter Cherny].)

13. "Published reports of such studies in pigs, cattle and sheep, together with our own research, indicated that cells which displayed some ES characteristics could be identified but the isolation of proven pluripotential ES cell lines remained elusive" (*id.*).

14. "The murine model for totipotential stem cell isolation is yet to prove applicable to domestic animals. However, criteria used in the identification of murine ES cells can serve as guidelines." (*Id.* at 574.)

Analysis

Claim 1 is drawn to a "replicating in vitro cell culture of pluripotent human embryonic stem cells derived from a pre-implantation embryo." The claim requires the stem cell culture to possess certain properties as recited in claim limitations (i) through (iv). The Third Party Requester contends that the Williams patent described human embryonic stem cells which would possess the claimed properties, anticipating the subject matter of claim 1.

Working examples

Respondent contends that "Williams is without any specific working example other than the mouse, and therefore could not establish a *prima facie* case of anticipation" of the claimed human embryonic stem cell culture (Res. App. Br.[2] 18).

Specific working examples are not necessary to establish anticipation. Anticipation has been found when the scope of embodiments described in a prior art publication were so limited in number that one of ordinary skill in the art could at once envisage the subject matter which is claimed. *In re Petering*, 301 F.2d at 681-82; *Bristol-Myers*, 246 F.3d at 1379.

In this case, human embryos are explicitly recited in a list of animal embryos that can be used as a source of embryonic stem cells (FF5). A species which is specifically disclosed in a prior art reference is anticipatory even though it appears "without special emphasis in a longer list." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005).

"[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Meyers*, 246 F.3d at 1379. For these reasons, we conclude that Williams described human embryonic stems, as claimed, despite its failure to disclose a working example in which human ES cells were actually made. There would have been reasonable basis to believe that such stem cells would possess properties (i) through (iv) recited in claim 1 because the Williams ES cells were derived from a pre-

[2] Second Amended Respondent's Brief (filed June 17, 2009) [hereinafter Res. App. Br.] (The response by WARF, the Respondent in this proceeding, to the Third Party Requestor's Appeal Brief).

implantation embryo, the same source of cells required by the claim. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977).

Respondent also argued that mouse ES cells have different cell markers than expressed in human ES cells and therefore can not anticipate the claimed human cells (Res. App. Br. 18). This argument is not persuasive. The rejection is based on Williams' disclosure of ES cells derived from human embryos (FF5), not Williams' description and exemplification of mouse cells.

Enablement

An anticipatory reference must be enabling. Respondent contends that Williams did not enable persons of ordinary skill in the art to make human embryo stem cells. As evidence of this, Respondent provided a declaration by Dr. Colin Stewart (Declaration of Dr. Colin Stewart (May 29, 2007) [hereinafter Stewart Dec.]) and the Cherny publication which listed the same Dr. Williams as a co-author who was an inventor of the Williams patent.

Dr. Stewart testified in his declaration that "Williams does not disclose a method for isolating primate/human ES cells" (Stewart Dec. ¶ 18). Dr. Stewart stated:

> When Dr. Thomson [the named inventor of the '913 patent] isolated his primate/human ES cells, he used a method that is not taught in Williams. Dr. Thomson isolated the inner cell mass (ICM) from the blastocyst by immunosurgery, a procedure that removes the trophoblast cells that enclose the ICM.

(*Id.*)

Williams described two methods of isolating ES cells. The second method involved treating blastocysts "by immunosurgery" to destroy trophectoderm cells (FF10-11). Thus, the evidence supports the finding that Williams described immunosurgery in a method of isolating ES cells, the same technique Dr. Stewart testified was used by Dr. Thomson (Stewart Dec. ¶ 18).

Dr. Stewart also testified that Williams did not describe the "meticulous series of methods" utilized by Dr. Thomson (Stewart Dec. ¶ 18):

> He plated the isolated ICMs on mouse feeder layers and was very explicit in how the explanted ICMs were cultured, gently disassociated, replated on feeder layers to form colonies, and then expanded on feeder layers to maintain their stem cell characteristics to prevent their differentiation ('780 patent columns 7, 8 [sic] and 9).

(*Id.*)

This argument is not persuasive for several independent reasons. First, Dr. Stewart has not provided evidence that the Williams' method would not work when applied to human embryos. Even assuming differences between the method used by Williams to derive ES cells and Dr. Thomson's method for producing the claimed human ES cells, these differences do not alone establish that the Williams method would not succeed in isolating embryonic stem cells from human embryos. ES cells are claimed, not a method of making them. Consequently, differences in the isolation method do not alone distinguish the claimed cells from those produced using the Williams methods nor establish that the claimed subject matter was not enabled by the Williams patent.

Secondly, it appears that the method steps described by Dr. Stewart as unique to Dr. Thomson (Stewart Dec. ¶ 18) were broadly described in the Williams patent. Feeder cells were known in the art to have been utilized for deriving stems (FF2) and Williams says feeder cells can be used in its methods (FF6). Williams discloses dissociating cells within days after immunosurgery and after the inner cell mass had been left to attach to the culture plate (FF9-11).

With respect to the Cherny publication, the Respondent contends that the "Examiner correctly interpreted Cherny as demonstrating the failure or limited success of the Williams procedure for isolating mouse ES cells on ES cells of domestic animals." (Res. App. Br. 18). As evidence, Respondent cited Cherny's statement that the "murine model for totipotential stem cell isolation is yet to prove applicable to domestic animals." (FF14; Cherny at 574, col.1.) Respondent concluded that Williams' disclosure of human ES cells is therefore "negated by the Cherny article" (Res. App. Br. 19).

Cherny's statement about the inapplicability of the murine model to "domestic animals" does not "negate" the explicit disclosure in Williams of human ES cells. Respondent has not introduced evidence that Cherny's reference to a murine model was to the same murine model described in the Williams patent. For example, the inventors of the Williams patent are not the same as those listed as authors of the Cherny publication.[3] Therefore,

[3] The authors of the Cherny publication were Cherny, Stokes, Merei, Lom, Brandon, and Williams. The listed inventors of the Williams patent are Williams, Gough, and Hilton. The only common scientist to both is Dr. Williams.

there is insufficient evidence to conclude that Cherny's remarks about a murine stem cell model were a commentary on deficiencies in the Williams patent.

In addition to this, the Cherny publication involved domestic animal species, not humans or primates. Cherny stated that the "murine model" was "yet to prove applicable to domestic animals," not human pre-implantation embryos as claimed.

Finally, even if the Cherny statement was taken in a broader context to criticize the applicability of the murine model to other species, it does not "negate" the explicit disclosure of human embryonic stems in the Williams patent. "A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas Techs., Ltd.. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998); *see also Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1382 (Fed. Cir. 2006). Disparaging comments therefore do not necessarily negate an explicit enabling disclosure of a claimed invention.

LIF

Respondent contends that "Williams was principally directed towards researching the ability to use LIF to maintain murine ES cells without feeder layers" and that "[u]sing LIF in the absence of a feeder layer is contrary to" the claimed invention (Resp. App. Br. 18). Dr. Colin Stewart, a scientist having research experience with mouse embryonic stem cells, testified on behalf of Respondent that "while LIF has been established by Williams as a component of the feeder layer that enables long term undifferentiated culture

of mouse ES cells, LIF does not have the same effect on the long term undifferentiated culture of primate/human ES cells" (Stewart Dec. ¶ 23).

Claim 1 recites that the pluripotent human embryonic stem cells, derived from a pre-implantation embryo, "will proliferate in an in vitro culture for over one year in an undifferentiated state without the application of exogenous leukemia inhibitory factor." We interpret this limitation, as did the Examiner, as an "intended use" of the claimed cells. (Office Action in Inter Partes Reexamination at 5-6 (mailed Mar. 30, 2007).) That is, the claimed embryonic stem cells must be able to proliferate in an undifferentiated state without exogenous LIF. However, the claim does not exclude the ES cells from having been derived in the presence of LIF nor is the claim limited to particular method of ES cell production. Rather, the claim is a product claim, not a method of producing embryonic stem cells.

The PTO does not have the ability "to manufacture products or to obtain and compare prior art products." *In re Best*, 562 F.2d 1255. Thus, once "the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

In this case, Williams described human ES cells. Because the PTO has no way of proving that the cells would not possess the claimed LIF property, the burden properly shifted to the Respondent to prove otherwise. Dr. Stewart testified that LIF does not have the "same effect" on human ES cells as on mouse ES cells, but he did not establish that human ES cells derived from Williams methods would not have the claimed property of "proliferat[ing] in an in vitro culture for over one year in an undifferentiated

state without the application of exogenous leukemia inhibitory factor" or any of the other properties recited in the claim.

Summary

Williams described and enabled human embryonic stem cells derived from a pre-implantation embryo, anticipating the subject matter of claim 1. Claims 2 and 3 were not separately argued, and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

HOGAN – ANTICIPATION & OBVIOUSNESS

The Third Party Requester appeals the Examiner's determination to withdraw the rejection of 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 over, Hogan.

Statement of the Issue

The issue in this rejection is whether Hogan's description of ES cells derived from germ cells anticipated the claimed ES cells derived from a pre-implantation embryo?

Principles of Law

"It has long been the case that an old product is not patentable even if it is made by a new process. . . . However, a new product may be patented by reciting source or process limitations so long as the product is new and unobvious." *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1366 (Fed. Cir. 2009).

> A product-by-process claim is "one in which the product is defined at least in part in terms of the method or process by which it is made." . . . While the patent statute does not provide

> for product-by-process claims, the courts have long recognized the appropriateness of such claims. . . . The purpose of product-by-process claims is to allow inventors to claim "an otherwise patentable product that resists definition by other than the process by which it is made." . . . Thus, an inventor will not be foreclosed from the benefits of the patent system simply because a product is difficult to describe in words, or its structure is insufficiently understood.

SmithKline Beecham Corp. v. Apotex Corp, 439 F.3d 1312, 1315 (Fed. Cir. 2006) (citations omitted).

> Product-by-process claims, especially for those rare situations when products were difficult or impossible to describe, historically presented a concern that the Patent Office might deny *all* product protection to such claims. *See In re Butler*, 17 C.C.P.A. 810, 813 37 F.2d 623 (1930) ("Process claims are valuable, and appellant thinks he is entitled to them; but it is submitted that he should not be limited to control of the process when the article which that process produces is new and useful."). In the modern context, however, if an inventor invents a product whose structure is either not fully known or too complex to analyze (the subject of this case — a product defined by sophisticated PXRD technology — suggests that these concerns may no longer in reality exist), this court clarifies that the inventor is absolutely free to use process steps to define this product. The patent will issue subject to the ordinary requirements of patentability. The inventor will not be denied protection.

Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1294 (Fed. Cir. 2009).

Findings of Fact

15. Hogan described "human, pluripotential embryonic stem cell[s]." (Hogan, at col. 2, ll. 29.)

16. Hogan stated that the "invention further provides a method of making a pluripotential embryonic stem cell comprising culturing primordial germ

cells, embryonic ectoderm cells and/or germ cell progenitors . . . under cell growth conditions, thereby making a pluripotential embryonic stem cell." (*Id.* at col. 2, ll. 38-46.)

17. Hogan taught that "[p]rimordial germ cells (PGCs) in the mouse are thought to be derived from a small population of embryonic ectoderm (epiblast) cells set aside at the egg cylinder stage prior to gastrulation (Lawson and Pederson, 1992), or even earlier (Soriano and Jaenisch, 1986)." (*Id.* at col. 1, ll. 18-22.)

18. Dr. Stewart testified that Hogan "describes the isolation of embryonic germ (EG) cells from primordial germ cells obtained from post-implantation embryos." (Stewart Dec. 7: ¶ 26.)

19. Aflatoonian discloses that human embryonic germ cells (hEG) express SSEA-1 cell surface marker, but this marker is absent from undifferentiated human ES (hES) cells (Behrouz Aflatoonian & Harry Moore, *Human Primordial Germ Cells and Embryonic Germ Cells, And Their Use in Cell Therapy*, 16 Current Opinion in Biotechnology 530, 532 first column (2005) [hereinafter Aflatoonian]). "Notably, hEG cells express SSEA-1 cell-surface marker . . . This marker is absent from the inner cell mass of the human blastocyst . . . and absent from undifferentiated hES cells and only detected on cells following differentiation" (*id.*).

Analysis

Claim 1 is directed to pluripotent human embryonic stem cells "derived from a pre-implantation embryo." The phrase "derived from a pre-implantation embryo" is a product-by-process limitation. A product-by-process limitation defines a claimed product in terms of how it is made.

Product-by-process limitations are typically used to claim "a product whose structure is either not fully known or too complex to analyze." *Abbott Labs.*, 566 F.3d at 1294. When the way a product is made imparts some structural, chemical, or other characteristic on the product which distinguishes it from products made by other processes, the product-by-process limitation may serve as a basis for patentability. *Id.*; *see also Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993).

Hogan's cells were derived from germ cells; the claimed cells were derived from pre-implantation embryos. The sources of the stem cells are therefore different. The pivotal question in this rejection is whether derivation from a pre-implantation embryo confers some structural or other characteristic on the human stem cell that makes it different from the stem cells described in Hogan derived from germ cells.

Evidence was provided that human embryonic germ cells express SSEA-1 as a cell surface marker, but that human ES cells derived from human preimplantation embryos do not (FF19; Resp. App. Br. 18-19). The Examiner reasonably inferred from this teaching that Hogan's cells, produced from germ cells, or the epiblast cells from which the germ cells are derived (FF17), would express the SSEA-1 marker, but that human ES cells from pre-implantation embryos would not. The Requester did not establish error in the factual finding that SSEA-1 was differentially expressed in germ-derived versus pre-implantation-derived ES cells. Accordingly, we conclude that the product-by-process limitation that the human ES cells are "derived from a pre-implantation embryo" imparts a structural characteristic on the cells which distinguishes them from the cells described in Hogan.

The anticipation rejection of claims 1-3 by Hogan was therefore properly withdrawn by the Examiner.

Because there is no evidence that Hogan's embryonic stem cells could be converted into ES cells derived from a pre-implantation embryo, the alternative rejection of claims 1-3, as obvious in view of Hogan, was properly withdrawn, as well.

OBVIOUSNESS REJECTIONS 1, 3, 4, & 5

The Third Party Requestor appeals the Examiner's decision to withdraw the following rejections of claims 1-3 under 35 U.S.C. § 103(a) based on:

1. Williams;
3. Robertson '83, Robertson '87, Williams, and Hogan;
4. Piedrahita, Williams, and Hogan; and
5. Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan.

Statement of the Issues

The obviousness rejections (1, 3, 4, & 5) over the Williams, Robertson '83, Robertson '87, Hogan, and Piedrahita publications involve the same set of facts and issues. Consequently, the rejections have been addressed together.

The Third Party Requester contends that the Examiner erred by imposing an improperly high standard of obviousness when making the determination that claim 1 would not have been obvious to persons of ordinary skill in the art in view of the cited prior art. The issue to be decided in these rejections is therefore, what is the proper standard of obviousness to

be applied to the subject matter of claim 1, and whether claim 1, under the proper obviousness standard would have been obvious to persons of ordinary skill in the art. Claims 2 and 3 were not separately addressed by the Third Party Requester and therefore stand or fall with claim 1. 37 C.F.R § 41.37(c)(1)(vii).

Principles of Law

> In *KSR*, the Supreme Court stated that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct:
>
> 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. 550 U.S. at 421, 127 S. Ct. 1727. This approach is consistent with our methodology in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009); *In re Kubin*, 561 F.3d 1351, 1359, (Fed. Cir. 2009). *O'Farrell* observed that most inventions that are obvious were also obvious to try, but found two classes where that rule of thumb did not obtain.
>
> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified"

> solutions. 550 U.S. at 421, 127 S. Ct. 1727; *see also Procter & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the KSR requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S. Ct. 1727; *see also Procter & Gamble*, 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009).

> The district court acknowledged that the prior art suggested that there would be concern about the dissolution of a poorly water soluble acid-sensitive drug, but found that the prior art generally suggests that micronization could improve the dissolution of drospirenone. It concluded that a person having ordinary skill would have seen it as a viable option.
>
> . . . Bayer's own expert, Dr. James McGinity, testified that micronization is the first choice solution because it presents the best chance for success. So there remains adequate support for the conclusion that micronization was a viable option.

Bayer Schering, 575 F.3d at 1348.

Scope and content of the prior art

Robertson '83

20. Robertson '83 describes isolation of pluripotential cells from fertilized "delayed" blastocysts from female mice (Robertson '83, p. 649).

21. Robertson '83 describes an isolation procedure that involves: explanting blastocysts into tissue culture dishes, removing the inner cell mass (ICM) derived cell clumps after several days, disaggregating the ICM clumps using trypsin enzyme, transferring to tissue culture wells containing a layer of preformed inactivated fibroblast cells, and repeating disaggregation after a further 4 days (*id.*).

Robertson '87

22. Robertson '87 taught that "[t]wo methods were originally described to recover stem cells" (Robertson '87, p. 84).

23. "The technique given here is based on the first of these which was described initially by Evans and Kaufman (1). The overall strategy is to transfer intact blastocysts into culture and allow them to continue growth, for a limited period, until they achieve a stage which is equivalent to the early post-implantation embryo. The embryonic portion is then dissociated and culture of the cells is continued under conditions designed to be amenable to cell growth while encouraging stem cells to maintain the undifferentiated phenotype." (*Id.*)

24. The second "technique described by Martin (2) is slightly more complicated in two respects. Firstly the inner cell mass (ICM) of the embryo has to be selectively isolated by immunosurgical removal of the

trophectoderm cells prior to culture. Secondly, culture takes place in medium which has been conditioned by exposure to a culture of EC cells. However, if attempts are to be made using this technique it is relevant to note that a comparative study (16) has shown that conditioned medium has no significant effect on the overall efficiency of isolation of stem cells." (*Id.*)

25. "Of the two techniques the method of Evans and Kaufman (1) is the simpler and in the author's experience has been found reliably to give rise to stem cells at an acceptably high frequency (10-30% of embryos)." (*Id.*)

26. "The procedure for the derivation of stem cells from blastocysts is divided into two stages. During the first stage the embryos are transferred into tissue culture and left undisturbed to attach and grow. The second stage involves the mechanical disruption of the embryos and the culture of the embryo-derived cells." (*Id.*)

27. Robertson '87 provided an extensive description of protocols for blastocyst culture (*id.* at 85-86) and disaggregation of the inner cell mass (*id.* at 86-91; Ans. 10).

28. Robertson '87 taught that feeder cell layers "are absolutely essential for both the isolation of stem cell lines from embryos and for the routine maintenance of established cell lines" (Robertson, '87, at p. 75).

Piedrahita

29. Piedrahita described protocols for isolating ES cells from murine, ovine (sheep), and porcine embryos.

30. "While murine isolated ICM or intact embryos plated on STO or HEF feeders gave rise to cell lines with embryonic stem cell-like (ES-like) morphology, ovine embryos did not." (Piedrahita, at p. 879).

31. "The results of this study show that conditions which allow isolation of ES cells from murine embryos allow the isolation of porcine embryo-derived cell lines sharing some, but not all, the characteristics of murine ES cells." (*Id.*)

32. "Recently it has been shown that ES cells can be isolated from hamster embryos using feeders composed of murine primary embryonic fibroblasts (19)." (*Id.* at 880.)

33. "Evans et al. (20) have reported the isolation of porcine embryo-derived cell lines with ES-like morphology and a limited ability to differentiate in vitro." (*Id.*)

34. Piedrahita acknowledged that previous "[a]ttempts at isolating ovine ES cells by culturing embryos on ovine skin fibroblasts in the presence or absence of Buffalo rat liver (BRL) conditioned media have been unsuccessful (21)." (*Id.*)

35. Piedrahita's method involve isolating the ICM (e.g., using immunosurgery, mechanically, or with calcium ionophore), plating on feeder cells, dissociating with trypsin/EDTA, and transferring to fresh feeder cells (*id.* at 882; Ans. 12).

36. "The sequence of events leading to the production of embryo-derived colonies was found to be different for the three species examined." (Piedrahita, at p. 884.)

37. Table 1 shows that ES-like cells lines were obtained from murine and porcine embryos, but not ovine (*id.* at 886).

38. "Attempts to induce porcine embryo-derived cell lines with ES-like morphology to differentiate in vitro did not result in obvious morphological changes. It is not clear why differences are observed between porcine and murine ES-like cell lines in the extent of in vitro differentiation. One explanation is that the trigger for induction of differentiation varies with species. Evans et al. (20) reported induction of in vitro differentiation with porcine embryo-derived cells in media devoid of FBS and β_2-mercaptoethanol." (*Id.* at 896.)

39. "Whether the difficulties encountered in the isolation of ES cells from porcine and ovine embryos were due to inherent species differences, which make such isolation feasible, or whether the difficulties were due to inappropriate culture conditions or source of embryonic material (e.g. , embryos that were too young or too old) remains to be determined." (*Id.* at 897.)

Moore

40. The Moore publication was received by the journal on Oct. 9, 1995, accepted Jan. 8, 1996, and published in volume 33 of *In Vitro Cell. Dev. Biol.* having a date of 1997.

41. "Isolation of ES cell lines have been attempted in the rat (16), mink (34), rabbit (12), hamster (6, 25), primates (37), sheep (14, 24), cattle (9, 27, 28, 32), and swine (1, 9, 11, 21, 23, 24, 33, 35). Varying degrees of pluripotentiality have been demonstrated for each, yet only the mouse and rat have produced chimeric animals, with mouse ES cells being the only cells lines to date conferring germline transmission." (Karen Moore & Jorge A. Piedrahita, *The Effects of Human Leukemia Inhibitory Factor (HLIF) and*

Culture Medium on In Vitro Differentiation of Cultured Porcine Inner Cell Mass (PICM), 33 In Vitro Cellular Biology – Animal 62 (1997) [hereinafter Moore].)

42. As to porcine ES cells, Moore stated that "[p]luripotentiality varies, but inability to maintain cell lines for extended periods of time and lack of chimera production are common to all." (*Id.*)

Brook and Gardner

43. The Brook and Gardner publication was received by the journal for review on Feb. 21, 1997 and published in the May 1997 issue of the Proceedings of the National Academy of Science.

44. Brook and Gardner stated that "ES cell lines of proven ability to colonize the germ-line have been obtained at very low frequency in only a few mouse strains other than 129 [strain] and, as yet, no other species of mammal (1)." (F. A. Brook & R. L. Gardner, *The Origin and Efficient Derivation of Embryonic Stem Cells in the Mouse*, 94 Proceedings of the National Academy of Science – Developmental Biology 5709 (May 1997).)

Brook

45. The Brooks publication was published in the January 2003 issue of Diabetes.

46. Brooks taught that "derivation of embryonic stem (ES) cells from the NOD mouse has proved to be extremely difficult." (Frances A. Brook et al., *The Derivation of Highly Germline-Competent Embryonic Stem Cells Containing NOD-Derived Genome*, 52 Diabetes 205 (Jan. 2005).)

Iannaccone

47. Iannaccone described "the derivation of diploid rat embryonic stem cells" which "can differentiate extensively *in vivo*" and produced chimeras with rat blastocysts (Philip M. Iannaccone et al., *Pluripotent Embryonic Stem Cells from the Rat are Capable of Producing Chimeras*, 163 Developmental Biology 288 (1994) [hereinafter Iannaccone]).

48. Iannaccone taught that "[p]luripotent cells have been isolated from mink . . . , pig . . . , and hamster . . . but so far there are no published accounts of chimera formation with stem cells from species other than mouse." (*Id.* at 290.)

Ouhibi

49. Ouhibi described isolation of ES-like cells, RESC-01, from rat embryo (Nadia Ouhibi et. al., *Initial Culture Behaviour of Rat Blastocysts on Selected Feeder Cell Lines*, 40 Molecular Reproduction and Development 311 (1995)).

50. Ouhibi reported that they "have not been able to obtain cultures [of the RESC-01 cells] beyond passage 4" (*id.* at p. 317).

Brenin

51. Brenin was published in volume 29 of Transplantation Proceedings, dated 1997.

52. Brenin taught that while "ES cells from other species have been isolated . . . , the entire process, including the production of functional gametes from ES cells, has not been established in mammals other than the

mouse." (D. Brenin, *Rat Embryonic Stem Cells: A Progress Report*, 29 Transplantation Proceedings 1761 (1997).)

53. Brenin described "exhaustive application of standard mouse methodology" to produce rat ES cells (*id.* at 1762).

54. Brenin reported that the rat RESC-01 ES-like cell (of Iannaccone) "shows no evidence of mouse in cell culture preparations," but produced no chimeras when injected into hosts (*id.* at 1764).

55. However, Brenin reported that, when injected into nude mice, the DNA isolated from the one tumor that arose was of mouse origin, implying "a stable low level contamination with mouse ES cells persists in this population." (*Id.*)

56. Brenin concluded that the rat ES cells derive from rat blastocysts were possibly not pluripotent (*id.* at 1765).

57. However, Brenin stated that "populations with undifferentiated ES morphology and ES markers can be grown, for at least twelve passages from the rat" (*id.*), beyond the number originally described by Iannaccone.

Doetschman

58. Doetschman described "the establishment and maintenance of hamster ES cell lines and show[ed] they are highly pluripotent." (Thomas Doetschman, *Establishment of Hamster Blastocyst-Derived Embryonic Stem (ES) Cells*, 127 Developmental Biology 224 (1988).)

59. The hamster ES cells "appear to have a normal chromosome count" and "had been in culture for at least 25 passages" (*id.* at 227).

60. Doetschman stated they "are presently carrying out experiments to determine if the hamster ES cells can colonize the germ line when introduced back into hamster blastocysts." (*Id.*)

Talbot

61. Talbot taught isolation of pluripotent epiblasts from bovine blastocysts, but found that the "cells . . . all differentiated or senesced indicating that standard conditions for mouse embryonic stem cell culture do not maintain bovine epiblast cells in an undifferentiated state." (Neil C. Talbot, *In Vitro Pluripotency of Epiblasts Derived From Bovine Blastocysts*, 42 Molecular Reproduction and Development 35 (1995).)

The '913 patent

62. "Pluripotent cell lines have also been derived from preimplantation embryos of several domestic and laboratory animals species . . .." ('913 patent, col. 3, ll. 50-59).

63. "Whether or not these cells lines are true ES cells [sic] lines is a subject about which there may be some difference of opinion." (*Id.* at col. 3, ll. 60-62).

64. "True ES cells should: (i) be capable of indefinite proliferation in vitro in an undifferentiated state; (ii) maintain a normal karyotype through prolonged culture; and (iii) maintain the potential to differentiate to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm) even after prolonged culture." (*Id.* at col. 3, ll. 62-67).

65. "Strong evidence of these required properties have been published only for rodents [sic] ES cells including mouse . . . [,] hamster . .. , 1988), and rat

. . . , and less conclusively for rabbit ES cells . . . ." (*Id.* at col. 3, l. 67 to col. 4, l. 7; citations omitted.)

66. "However, only established ES cell lines from the rat . . . and the mouse . . . have been reported to participate in normal development in chimeras." (*Id.* at col. 4, ll. 8-12; citations omitted.)

Level of ordinary skill in the art

67. Persons of ordinary skill in the art, as evidenced by findings 1-66, were familiar with cell culture technology, mouse ES derivation, and able to apply mouse techniques to embryos from other species.

Analysis

Prior to the filing date of this application, scientists had produced pluripotent embryonic stem cells from mice which proliferated in culture for long periods of time in the undifferentiated state and, under suitable conditions, were able to differentiate into any organ or tissue type ('913 patent, col. 1, ll. 28-35). The techniques for producing mouse ES cells had been applied, with varying success, to other mammals (FF30-34, 37-39, 41, 42, 44, 47-50, 52, 56-58, and 61-66). Based on the numerous disclosures of the application of embryonic stem technology in mice and other mammals, the Examiner, in a non-final Office Action, rejected the claims to human ES cells as obvious to persons of ordinary skill in the art under 35 U.S.C. § 103. (Non-Final Office Action (mailed Mar. 30, 2007).)

Although the Examiner initially determined the claims were obvious, the Examiner subsequently withdrew all the obviousness rejections in view of evidence that persuaded him that there would not have been a reasonable

expectation that the mouse techniques for producing stem cells would succeed in humans (*see* ACP & RAN).

The Third Party Requester in this proceeding contends that the Examiner erred in withdrawing the rejection by applying an improper standard of obviousness. The Requester contends that "the Examiner required the expectation of success to be an absolute certainty in order for it to be considered 'reasonable.'" (Second Amended Third Party Requester's Appeal Brief at 4 (filed May 21, 2009) [hereinafter Br.]). The Requester also contends that the Examiner "concluded that since human embryonic stem cell cultures as claimed had not existed before, they were not obvious. This effectively eviscerated the non-obviousness requirement by collapsing it into . . . [an] anticipation inquiry." (*Id.* at 5).

Under 35 U.S.C. § 103, "[a] patent may not be obtained . . . if 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." This determination is made, inter alia, after determining the scope and content of the prior art and the level of ordinary skill in the art to which the invention pertains. In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), the Supreme Court warned against confining the obviousness analysis to a "formalistic" approach, but rather encouraged the analysis to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Thus, while the requirement that there be a "reasonable expectation of success" (*Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009)) may be one useful standard in assessing the obviousness of an

invention, it is not the only standard to be applied when making a patentability determination under Section 103.

The Supreme Court has held that an invention may be proved obvious by showing that a combination of elements was "obvious to try." Where "there are a finite number of identified, predictable solutions" within the "technical grasp" of the ordinary skilled artisan, the invention "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421. A solution is not "predictable" when "the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Bayer Schering*, 575 F.3d. at 1347 (quoting from *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). The "obvious to try" standard focuses on the predictability of a solution as a "viable option" to solve a problem. *Bayer Schering*, 575 F.3d at 1348. A solution which had been known to work when applied to one system might, in some circumstances, be obvious to try in another. If the solution succeeded, the invention likely would have been obvious to persons of ordinary skill in the art.

In this case, the prior art explicitly taught two principal ways to produce embryonic stem cells. In one technique, blastocyst "were allowed to attach to the culture dish and approximately 7 days later the outgrowing inner cell mass picked, trypsinised [sic] and transfered [sic] to another culture dish in the same culture media" (FF9). The second method involved treating the blastocyst with antibodies to destroy trophectoderm – called "immunosurgery" – and then performing dissociation and trypsinizing steps (FF10-11). Both Williams (FF9-11) and Robertson '87 (FF23-24) described

the same basic techniques. Piedrahita also appeared to apply a similar strategy, involving immunosurgery and trypsin dissociation (FF35).

Based on these familiar techniques, the path to deriving human ES cells had a definite starting point with explicit landmarks along the way. A person of ordinary skill in the art, highly skilled in cell culture technology (FF67), was not required to design new protocols or explore new approaches, but rather would follow a path already taken in the mouse. In sum, there were a "finite number of identified" and "predictable" solutions which would have been readily applied by one of ordinary in the art to produce human embryonic stem cells. *KSR*, 550 U.S. at 421.

An invention is not obvious to try when an inventor would have had to attempt all the possibilities in a field, vary all parameters, and try numerous possible choices "'where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful . . . .'" *Bayer Schering*, 575 F.3d at 1347. Respondent argued that the claimed invention was not "obvious to try" because of the complexity of the prior art and the lack of predictability (Resp. App. Br. 13 & 15-16). Respondent provided some evidence to support this position, which we review in more detail below.

Testimony in the form of a written declaration was provided by Dr. Colin Stewart, a scientist with expertise in embryonic stem cells. Dr. Stewart, testified about Dr. Thomson's claimed invention involving primate/human ES cells (Stewart Dec. ¶ 11). Dr. Stewart stated:

> Dr. Thomson isolated the inner cell mass (ICM) from the blastocyst by immunosurgery, a procedure that removes the trophoblast cells that enclose the ICM. He plated the isolated ICMs on mouse feeder layers and was very explicit in how the

> explanted ICMs were cultured, gently disassociated, replated on feeder layers to form colonies, and then expanded on feeder layers to maintain their stem cell characteristics to prevent their differentiation ('780 patent columns 7, 8 and 9). This meticulous series of methods is not described in Williams.

(*Id.* at ¶ 18.)

Dr. Stewart's testimony does not convince us that it would not have been obvious to apply mouse techniques to human embryos. Immuno-surgery had been described as part of isolation protocols described in Williams, Robertson '87, and Piedrahita (FF10, FF11, FF24, & FF35). Feeder cells were also recognized as part of standard protocols (FF2, FF6, FF21, FF28, & FF32); and cells were dissociated in the prior art protocols to produce ES cells (FF11, FF21, FF23, FF27, & FF35). Respondent has not established that the protocol followed by Dr. Thomson necessitated him to "try all possibilities in a field unreduced by direction," but rather the evidence of record points to significant guideposts that would have led the skilled worker in the right direction to successful isolation of human ES cells.

Dr. Stewart also testified in his declaration that the human embryonic stem cell colonies observed in human cell cultures were "distinctly different" than mouse ES colonies and "it would not be immediately apparent what cells/colonies to choose for further study without the insight exhibited by Dr. Thomson." (Stewart Dec. ¶ 19). A person of ordinary skill in the art, having followed the protocols described by Williams and Robertson '87, would have recognized that differences between species had been observed during ES cell production (FF36) and common sense would have directed her or him to pick different colony types to determine which possessed ES properties.

Respondent has devoted considerable resources to the argument that there was "a high degree of unpredictability" in the mammalian stem cell field (Resp. App. Br. 4). Respondent contends that this unpredictability translated into a lack of reasonable expectation of success that "puts this invention on the patentable side of any obvious-to-try-analysis under *KSR*." (*Id.* at 13). Respondent asserts there "was no evidence to predict how different cells would respond to different variations in culturing methods, or predict what characteristics the cells would display in culture." (*Id.*)

We have considered the evidence provided by Respondent, including numerous pre- and post-filing publications. There is no doubt from the evidence that the techniques for producing embryonic stem cells from mouse embryos had varying success in other species.

Despite the shortcomings described for ES cells derived from certain mammalian species, isolation of pluripotent stem cells had been reported in rat and hamster (FF41, FF42, FF50, & FF56-59). Consistently, the inventor, Dr. Thomson, explicitly acknowledged in the '913 patent that there was strong published evidence that ES cells had been produced from rat and hamster cells (FF65). Therefore, even were there uncertainty as to whether the mouse ES techniques would achieve success when applied to a particular mammalian species or strain, this would not have changed the determination that it would have been obvious to have tried these techniques on human embryos. As in *Bayer Schering*, there were a small number of known options to make embryonic stem cells. These options were known to work, albeit not in every species in which they had been tried, and therefore remained "viable" and "obvious to try" techniques to derive human embryonic stem cells.

Dr. Thomson recognized there had been various published attempts described in the scientific literature at making ES cell lines from domestic and laboratory animal species, but there was "some difference of opinion" as to whether they were true "ES cells" (FF63 & 64). These differences in opinion have played out in this proceeding. The parties dispute the extent to which ES cells had been obtained from porcine, ovine, bovine, and rat embryos (e.g., as described in FF12-14, FF29-42, & FF47-61). However, when Dr. Thomson, himself – an expert in embryonic stem cell technology – could not resolve this question, the Board is in no position to determine an answer. Nonetheless, the fact that certain evidence "cut both ways," as it does here, did not preclude the court in *Bayer Schering*, 575 F.3d at 1350, from determining that the claimed invention would have been "obvious to try" in view of the predictable options explicitly taught in the prior art for making ES cells.

The facts support Dr. Thomson's statement that stem cells had been obtained in hamsters and rat. Stem cell technology therefore worked in at least some species in which it had been applied. Cherny, despite limited success in domestic animals, was not dissuaded that the mouse stem cell protocols would be useful to follow in other species. Cherny explicitly concluded that "criteria used in the identification of murine cells can serve as guidelines." (FF14).

It is undisputed that interest in producing human embryonic stem cells was high. According to testimony by Drs. Melton and Cowan, both scientists with expertise in cell culture, human ES cells were successfully isolated "by simply following those methods taught for deriving mouse, rat, pig and sheep ES cells." (Declaration of Dr. Douglas A. Melton at ¶ 13

(June 29, 24007); *see also* Declaration of Dr. Chad Cowan at ¶ 14 (June 29, 2007)). Because it would have been obvious to have tried the known mouse protocols on human embryos, and 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.

The Examiner improperly withdrew the rejections of claim 1 as obvious in view of Williams; Robertson '83, Robertson '87, Williams, and Hogan; Piedrahita, Williams, and Hogan; and Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan.

OBVIOUSNESS REJECTION 6

The Third Party Requestor appeals the Examiner's determination to not to adopt its proposed rejection of claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, and Piedrahita.

The Examiner stated that the rejection would not be adopted because the Requester had improperly relied upon a declaration by Dr. Jeanne F. Loring as providing motivation. Communication to Third Party Requester 7, dated Mar. 30, 2007.

We agree that the Examiner's decision not to adopt the rejection was correct, but for a different reason. The prior art cited in this rejection is redundant to the art in rejections 1-5, but rejection 6 did not rely on Williams as did rejections 1-5. Williams taught human embryonic stem cells and provided additional evidence of the techniques utilized to isolate stem cells. Accordingly, the scope and content of the cited prior art is not as complete as it was for rejections 1, 3, 4, & 5.

SUMMARY

The Examiner's decision to withdraw the following rejections of claims 1-3 under 35 U.S.C. § 103(a) is reversed:

1. Williams;

3. Robertson '83, Robertson '87, Williams, and Hogan;

4. Piedrahita, Williams, and Hogan; and

5. Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan.

The Examiner's decision not to adopt the proposed rejection of claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, and Piedrahita is affirmed.

NEW GROUNDS OF REJECTION

37 C.F.R. § 41.77(a) states that "[t]he reversal of the examiner's determination not to make a rejection proposed by the third party requester constitutes a decision adverse to the patentability of the claims which are subject to that proposed rejection which will be set forth in the decision of the Board of Patent Appeals and Interferences as a new ground of rejection . . . ." Accordingly, for the reasons given above, we enter the following new grounds of rejection of claims 1-3 under 35 U.S.C. § 103(a) based on:

1. Williams;

3. Robertson '83, Robertson '87, Williams, and Hogan;

4. Piedrahita, Williams, and Hogan; and

5. Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan.

37 C.F.R. § 41.77(b) states:

> (b) Should the Board reverse the examiner's determination not to make a rejection proposed by a requester, the Board shall set forth in the opinion in support of its decision a new ground of rejection; or should the Board have knowledge of any grounds not raised in the appeal for rejecting any pending claim, it may include in its opinion a statement to that effect with its reasons for so holding, which statement shall constitute a new ground of rejection of the claim. Any decision which includes a new ground of rejection pursuant to this paragraph shall not be considered final for judicial review. When the Board makes a new ground of rejection, the owner, within one month from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal proceeding as to the rejected claim:
>
> (1) *Reopen prosecution.* The owner may file a response requesting reopening of prosecution before the examiner. Such a response must be either an amendment of the claims so rejected or new evidence relating to the claims so rejected, or both.
>
> (2) *Request rehearing*. The owner may request that the proceeding be reheard under § 41.79 by the Board upon the same record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Requests for extensions of time in this *inter partes* reexamination proceeding are governed by 37 C.F.R. § 1.956. *See* 37 C.F.R. § 41.79.

REVERSED; 37 C.F.R. § 41.77(b)

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