UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

CONTROL NO.	FILING DATE	PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
95000154	07/17/2006	7029913	

DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA PA 19103-6996

EXAMINER
Gary L. Kunz

ART UNIT	PAPER
3991	

DATE MAILED:

03/30/2007

INTER PARTES REEXAMINATION COMMUNICATION

BELOW/ATTACHED YOU WILL FIND A COMMUNICATION FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE OFFICIAL(S) IN CHARGE OF THE PRESENT REEXAMINATION PROCEEDING.

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

DO NOT USE IN PALM PRINTER

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Daniel B. Ravicher
Public Patent Foundation
1375 Broadway, Suite 600
New York NY 10018

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination

REEXAMINATION CONTROL NUMBER *95/000,154*.

PATENT NUMBER *7,029,913*.

TECHNOLOGY CENTER *3999*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

Transmittal of Communication to Third Party Requester Inter Partes Reexamination	Control No.	Patent Under Reexamination	
	95/000,154	7029913	
	Examiner	Art Unit	
	Gary L. Kunz	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

OFFICE ACTION IN* INTER PARTES *REEXAMINATION	**Contr I No.** 95/000,154	**Patent Under Reexamination** 7029913	
	Examiner Gary L. Kunz	**Art Unit** 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on NONE
Third Party(ies) on 17 July 2006

RESPONSE TIMES ARE SET TO EXPIRE AS FOLLOWS:

For Patent Owner's Response:
2 MONTH(S) from the mailing date of this action. 37 CFR 1.945. EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956.
For Third Party Requester's Comments on the Patent Owner Response:
30 DAYS from the date of service of any patent owner's response. 37 CFR 1.947. NO EXTENSIONS OF TIME ARE PERMITTED. 35 U.S.C. 314(b)(2).

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

This action is not an Action Closing Prosecution under 37 CFR 1.949, nor is it a Right of Appeal Notice under 37 CFR 1.953.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims 1-3 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims 1-3 are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8. ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has: ☐ been received. ☐ not been received. ☐ been filed in Application/Control No 95000154.
10. ☐ Other _____

DETAILED ACTION

Inter Partes Reexamination: Non-Final Office Action

Decision Granting the Order

The Third Party Request (dated 17 July 2006) *for inter partes* reexamination of claims 1 - 3 of United Stated Patent Number 7,029,913 was granted on 29 September 2006.

Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,029,913 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282, and 2286.

Priority

U.S. Pat. No. 7,029,913 issued from application 09/982,637, filed 18 October 2001; which is continuation of application 09/761,289 filed on 16 January 2001, now abandoned; which is a continuation of application 09/106,390 filed 26 June 1998, now Pat. No. 6,200,806; which is a divisional of application 08/591,246, filed 18 January 1996, now Pat No. 5,843,780; which is a continuation-in-part of application no. 08/376,327, filed 20 January 1995, now abandoned.

Related Proceedings

A third party request for an ex parte reexamination for the related U.S. Patent No. 5,843,780 was filed 17 July 2006 and given control number 90/008,102. The request for ex parte reexamination was granted in the Order mailed 29 September 2006.

A third party request for an ex parte reexamination for the related U.S. Patent No. 6,200,806 was filed 17 July 2006 and given control number 90/008,139. The request for ex parte reexamination was granted in the Order mailed 29 September 2006.

Scope of Reexamination

The requester has raised the issue (see request pages 2 - 3) of significant public harm resulting from the instant patent.

Reexamination provides a complete reexamination of the patent claims on the basis of prior art patents and printed publications. 37 CFR §1.552; MPEP § 2258.

Thus, the third party requester's discussion of public harm is outside the scope of reexamination and has no bearing on this proceeding.

The Thomson '913 Patented Invention

The Thomson '913 invention is drawn to a composition comprising a replicating in vitro culture of human embryonic stem (ES) cells with a variety of functional and physical limitations.

Claim 1 requires that the human ES cells (a) are capable of proliferating in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor; (b) maintain a karyotype in which the chromosomes are euploid thoughout prolonged culture, (c) maintain the potential to differentiate to derivatives of endoderm,

mesoderm, and ectoderm tissues throughout the culture, and (d) are inhibited from differentiation when cultured on a fibroblast feeder layer.

Claim 2 depends from claim 1 and further requires that the human ES cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

Claim 3 depends from claim 1 and further requires that the human ES cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, and express alkaline phosphatase.

Documents Cited by the Requester

Newly Cited Reference(s):

1. **Robertson et al.**, "Isolation, Properties and Karyotype Analysis of Pluripotential (EI) Cell Lines from Normal and Parthenogenetic Embryos," *Teratocarcinoma Stem Cells*, Cold Spring Harbor Laboratory, Cold Spring Harbor, 10:647 - 663 (1983).

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

Old Reference: Previously cited but not applied in 08/982,637 application:

3. **Piedrahita et al.**, "On the Isolation of Embryonic Stem Cells: Comparative Behavior of Murine, Porcine, and Ovine Embryos," *Theriogenology*, 34(5): 879-901 (1990).

Newly Cited Document:

4. **Declaration of Dr. Jeanne F. Loring**, Ph. D. (Appendix C of request)

Documents Cited by the Examiner

Old Reference: Previously cited in 09/106,390 but not cited or applied in 08/982,637:

5. **Williams et al.**, United States Patent Number 7,029,913, filed 31 May 1990, issued 24 November 1992.

Newly Cited Document

6. **Hogan, Brigid L. M.**, United State Patent Number 5,690,926, filed 25 March 1994, issued 25 November 1997,

Claim Interpretation

Claims 1 - 3 of the Thomson '913 patent are each directed to a replicating in vitro culture of human embryonic stem cells. Claims 2 and 3 depend directly from claim 1. The only differences among these claims are functional and physical limitations which are presented by the Thomson '913 patent to be inherent functions and physical markers of all human embryonic stem cells.

Claim 1 defines a culture of human embryonic stem cells according to the art accepted three criteria for identifying embryonic stem cells. First, embryonic stem cells are capable of proliferating (synonym of replicating) in vitro indefinitely (immortal) in an undifferentiated state. This replication in vitro requires a fibroblast feeder layer to provide the critical nutrients and growth factors to maintain the ES cells in the undifferentiated state. Second, ES cells maintain their euploid chromosome karyotype throughout prolonged culture. Third, ES cells are "pluripotent," meaning they possess the potential to differentiate into derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm). The Thomson '913 patent describes these inherent properties of embryonic stem cells at column 3, lines 60 to column 4, line 14 and column 4, lines 17 - 25.

In addition to the above fundamental inherent properties of ES cells in claim 1, claim 2 requires that ES cells "will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured in high density. The patent owner also teaches that primate embryonic stem cells inherently possess this ability to spontaneously differentiate into trophoblast in vitro and express chorionic gonadotropin

when cultured to a high density (column 12, lines 64 - column 13, line 4).

In addition to the above fundamental inherent properties of ES cells in claim 1, Claim 3 requires the human ES cells also be negative for SSEA-1 marker, positive for the SSEA-4 marker, and express alkaline phosphatase. The '913 patent owner also discloses that absence or presence of these markers in claim 3 are characteristic of primate ES cells (column 4, lines 60 - 63). In other words, true human ES cells defined by claim 1, will be negative for SSEA-1 marker, positive for the SSEA-4 marker, and will express alkaline phosphatase. Therefore, any primate ES cells which meet the requirements of claim 1, must also inherently meet the additional limitations in claims 2 and 3.

To the extent that the above claim 1 (i)-(iv) limitations are interpreted as "intended use" limitations, it is noted that "intended use" limitations used to define a composition must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

Accordingly, a reference teaching a "replicating in vitro culture of human embryonic stem cells," (however obtained) would anticipate claim 1 since the reference composition meets all of the structural requirements of the instantly claimed composition.

Grounds of Rejections: Proposed by the Third Party Requester

Ground #1: Robertson '83 and Robertson '87 renders claims 1 - 3 obvious in view of the declaration by Dr. Jeanne F. Loring.

Ground #2: Piedrahita renders claims 1 - 3 obvious in view of the declaration by Dr. Jeanne F. Loring.

Ground #3: The combined teachings of Robertson '83, Robertson '87, and Piedrahita renders claims 1 - 3 obvious in view of the declaration by Dr. Jeanne F. Loring.

Discussion of the Proposed Rejections

Ground #1: The Third Party asserts that Robertson '83 renders obvious claims 1 - 3 in view of the declaration by Dr. Jeanne F. Loring (request pages 4 - 7).

The proposed 103(a) rejection of claim 1 - 3 as obvious over Robertson '83 and Robertson '87 in view of the declaration by Dr. Jeanne F. Loring **is not adopted** as proposed in the request. It is improper to use the declaration by Dr. Jeanne F. Loring instead of a patent or printed publication to provide the motivation for preparing human embryonic stem cells when the prior art printed publications disclose murine embryonic stem cells.

> Affidavits or declarations which explain the contents or pertinent dates of prior art patents or printed publications in more detail may be considered in reexamination, but any rejection must be based upon the prior art patents or printed publications as explained by the affidavits or declarations. The rejection in such circumstances **cannot** be based on the affidavits or declarations as such, but must be based on the prior art patents or printed publications. MPEP 2258E (emphasis added)

Ground #2: The Third Party asserts that Piedrahita renders obvious claims 1 - 3 in view of the declaration by Dr. Jeanne F Loring (request pages 7 - 11).

The proposed 103(a) rejection of claims 1 - 3 as obvious over Piedrahita in view of the declaration by Dr. Jeanne F. Loring **is not adopted** as proposed in the request. It is improper to use the declaration by Dr. Jeanne F. Loring instead of a patent or printed publication to provide the motivation for preparing human embryonic stem cells when the prior art printed publications only disclose mammalian (murine, ovine, porcine) embryonic stem cells. See MPEP 2258E as cited above.

Ground #3: The Third Party asserts that the combined teachings of Robertson '83, Robertson '87 and Piedrahita renders obvious claims 1 - 3 in view of the declaration by Dr. Jeanne F. Loring (request pages 11 - 12).

The proposed 103(a) rejection of claims 1-3 as obvious over the combined teachings of Robertson '83, Robertson '87 and Piedrahita in view of the declaration by Dr. Jeanne F. Loring **is not adopted** as proposed in the request. It is improper to use the declaration by Dr. Jeanne F. Loring instead of a patent or printed publication to provide the motivation for preparing human embryonic stem cells when the prior art printed publications disclose mammalian (murine, ovine, porcine) embryonic stem cells. See MPEP 2258E as cited above.

Claim Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Grounds #4: Claim Rejection -- 35 USC 102(b) (formulated by examiner)

Claims 1 - 3 are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as obvious over Williams et al. (5,166,065) alone, or as further evidenced by the instant patent disclosure for demonstrating inherency See E*x parte Novitski, 26 USPTq 2d 1389 (Bd. Pat. App. & Inter. 1993)*

Williams '065 issued on November 24, 1992. The earliest application possible effective filing date for Thomson '913 is January 20, 1995, the filing date for application no. 08/376,327. Therefore, Williams '065 is prior art to Thomson '913 under 35 USC 102(b).

The three claims of the Thomson '913 patent are directed to human embryonic stem cells in in vitro cell cultures defined by a combination of functional and physical characteristics. See "The Thomson '913 Patented Invention" and "Claim Interpretation" above for a more detailed explanation of the claimed invention.

At col. 8, lines 4 - col. 9, line 6, Thomson '913 discloses a method for isolating human ES cells comprising:

(1) isolating an animal blastocyst (col. 8, lines 38- 44);

(2) isolating cells from the inner cell mass of the blastocyte of (1) (col. 8, line 45 - 53);

(3) plating the inner cell mass on embryonic fibroblasts, wherein the inner cell mass-derived cell masses are formed (col. 8, lines 53 - 56);

(4) dissociating the mass into individual cells (col. 8, lines 58 - 62);

(5) replating the dissociated cells on embryonic feeder cells (col. 8, lines 63 -

64);

(6) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli (col. 8, lines 65 - col. 9, line 1); and

(7) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent embryonic stem cell line (col. 9, lines 1 - 5).

Williams '065 discloses human embryonic stem cells at col. 2, lines 30 - 40; col. 3, lines 35 - 47; and col. 4, lines 18 - 19. Williams '065 also discloses a method for preparing such embryonic stem cells at column 6, lines 50 - 66 which is essentially the same procedure as disclosed by Thomson '913 above comprising:

(1) isolating blastocysts (col. 6, line 52 - 58);

(2) isolating cells from the inner cell mass of the blastocyte of (1) (col. 6, lines 66 - col. 7, line 4);

(3) plating the inner cell mass on embryonic fibroblasts (or just LIF), wherein the inner cell mass-derived cell masses are formed (col. 7, line 1 - 3);

(4) dissociating the mass into dissociated cells (col. 8, lines 29 - 31);

(5) replating the dissociated cells on embryonic feeder cells (or LIF alone) (col. 8, lines 29 - 31);

(6) selecting ES cell colonies arising from explanted inner cell mass (col. 6, lines 63 - 66); and

(7) culturing ES cell colonies on embryonic feeder layers or with LIF alone(col. 6, lines 65 - 66).

Additionally, Williams '065 established that the embryonic stem cells which he isolated from mice using the above isolation procedure possessed the critical defining characteristics of all ES cells: (1) immortality--capable of proliferating in in vitro culture for over one year without the application of exogenous leukemia inhibitory factor (col. 4, line 65 to col. 5, line 5) and (2) pluripotency--maintain the potential to differentiate to

derivatives of endoderm, mesoderm, and ectoderm tissue throughout the culture (col. 5, lines 5 - 8), and (3) inhibition from differentiating in the presence of a fibroblast feeder layer (col. 3, lines 62 - 64). Immortality, pluripotency, and inhibition of differentiation by fibroblast feeder layer, and maintenance of euploid karyotype throughout culture are limitations of the human ES cells in each of claims 1 - 3 in Thomson '913. All embryonic stem cells prepared according to the method of Williams '065 will possess the standard defining characteristics of all embryonic stem cells--immortality, pluri-potency, differentiation inhibited by a fibroblast feeder layer, and maintenance of the euploid karyotypes. Human embryonic stem cells will also possess the four additional inherent functions and markers as disclosed by Thomson '913 below:

(1) differentiate spontaneously to trophoblast and produce chorionic gonadotropin when cultured in high density (claim 2 of Thomson '913) (col. 3, lines 8 - 14);

(2) are negative for the SSEA-1 marker (claim 3 of Thomson '913) (col. 4, lines 26 - 31);

(3) are positive for SSEA-4 marker (claim 3 of Thomson '913) (col. 4, lines 26 - 31); and

(4) express alkaline phosphatase (col. 4, lines 26 - 31).

These functional and physical characteristics of human embryonic stem cells described in claims 1 - 3 of Thomson '913 are presented as properties of human ES cells at column 4, lines 17 - 67 of Thomson '913.

Based upon the evidence of reocrd, there is no structural difference between the pluripotential human ES cells disclosed by Williams '065 and the ES cells instantly

claimed, as Williams human ES cells will contain, either expressly or inherently, all of the characteristics of the human ES cells of the instant invention. Further, there is no difference between the method for isolation of ES cells taught by Williams '065 and the instant claimed method in Thomson '913.

Where the instantly claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, the PTO can require the instant patentee to prove that the prior art products do not inherently possess the characteristics of his claimed product. See *In re Ludtke* 441, F. 2d 660,169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, joint or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best*, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F. 2d 531, 173 USPQ 685 (1972)

Here the prior art of Williams '065 discloses the identical human embryonic stem cells as claimed by Thomson '913 produced by an identical process. Therefore, the human ES cells taught by Williams '065 anticipate and/or render obvious the human ES cells claimed by Thomson '913.

Grounds #5: Claim Rejection -- 35 USC 102(b) (formulated by examiner)

Claims 1 - 3 are rejected under 35 USC 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as obvious over Hogan (US 5,690,926).

Claims 1 - 3 are described above under the heading "The Thomson '913 Patented Invention" and "Claim Interpretation" above.

Hogan '926 discloses a composition of human embryonic stem cells at column 12, lines 14 - column 13, line 13. These human embryonic stem cells were isolated from either testes from a 10.5 week human embryo (column 12, lines 19 - 22) or from postnatal mammalian testis (column 12, line 61 - column 13, line13). In both cases, the cells were plated on feeder cell layers (column 12, line 27 - 29; column 13, lines 10 - 13). These human embryonic stem cells were maintained for at least 20 passages and gave rise to differentiated cells of multiple phenotypes in monolayer culture (claim 7, parts (1) and (2). The human embryonic stem cells were grown over a feeder cell layer in order to maintain the undifferentiated state (column 12, lines 27 - 31 and column 13, lines 10 - 13). Additionally, these human embryonic stem cells expressed alkaline phosphatase activity (column 13, lines 52 - 56). Most of the isolated embryonic stem cells had a normal karyotype (column 10, lines 27 - 30).

Hogan '926 is silent with regard to their human embryonic stem cells (human pluripotential cells) possessing the following functional or physical characteristics recited by the '913 patent owner:

(a) ES cells will spontaneously differentiate to trophoblast and produce gonadotropin when cultured to high density.

(b) ES cells are negative for the SSEA-1 marker.

(c) ES cells are positive for the SSEA-4 marker.

Even though the Hogan '926 patent is silent with regard to the above markers, there are sufficient similarities of the human embryonic stem cells claimed by Thomson '913 to those human embryonic stem cells disclosed by Hogan '926 (see above summary) that the examiner has established a *prima facie* case of anticipation. The fact that the methods of preparing said human embryonic stem cells are different is irrelevant when the products produced by those different methods are the same.

Where the instantly claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, the PTO can require the instant patentee to prove that the prior art products do not inherently possess the characteristics of his claimed product. See *In re Ludtke* 441, F. 2d 660,169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, joint or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best*, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F. 2d 531, 173 USPQ 685 (1972)

Here the prior art of Hogan '926 discloses the identical human embryonic stem cells as claimed by Thomson '913 even though produced by different processes. Therefore, the human ES cells taught by Hogan '926 anticipate the human ES cells claimed by Thomson '913.

Grounds #6: Claim Rejection -- 35 USC 103(a) (formulated by xaminer)

Claims 1 - 3 of are rejected under 35 USC 103(a) as being obvious over Robertson '83 and Robertson '87 in view of Williams '065 and Hogan '926.

Claims 1 - 3 are described above under the heading "The Thomson '913 Patented Invention and "Claim Interpretation" above.

Robertson '83, filed more than a decade before the earliest effective filing date of the '913 patent, teaches a step-by-step process for isolating pluripotential mammalian embryonic stem (ES) cells at page 649, first two paragraphs. The process taught by Robertson '83 for the isolation of EM cells comprises the steps of (1) isolating a blastocyst, (2) removing the inner cell mass (ICM) from the blastocyst, (3) plating the ICS on a fibroblast feeder layer, (4) isolating stem cells once they become apparent, and (5) maintaining the isolated ES cells on feeder layers. The ES cells described by Robertson '83 were (a) pluripotent, meaning that they maintain the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout culture (page 647, lines 14 - 15; page. 652, "In Vivo Differentiation"), (b) capable of proliferating in in vitro culture for over one year without the application of leukemia inhibitory factor (45 passage generations; third paragraph, page 654), (c) retained a normal euploid karyotype throughout prolonged culture (pages 654, third paragraph; page 660, second full paragraph), and (d) are inhibited from differentiation when cultured on fibroblast feeder layer. The means that the ES cells of Robertson '83 meet all of the standard criteria for embryonic stem cells.

Four years later, the same Robertson '97 reference described in greater detail the process for isolating pluripotent mammalian ES cells. Robertson '97 provided an extensive description of the preparation of **(1)** the feeder layer (page 76, "2.4.1 Preparation of feeder layers from STO cells" to page 78, line 7), **(2)** the collection of the blastocyst stage embryo (page 78, "Collection of Embryos" to page 80, line 11), **(3)** the transfer the embryos into culture (page 80, "3.2.2. Transferring embryos into culture" through page 81; page 85.- 86), **(4)** disaggregating the ICM (page 86, "4.3 Disaggregation of the inner cell mass" through page 91), **(5)** identifying ICM-derived colonies (page 92, first two paragraphs), **(6)** identifying and expanding ES cells (page 92, third paragraph to page 95, end of fourth paragraph), and **(7)** culturing the ES cells (page 102, first full paragraph through page 103, line 8). The motivation to combine the teachings of Robertson '83 with Robertson '87 comes from the fact that (a) both references describe mouse embryonic stem cells and procedures for preparing said mouse ES cells and each of these references was authored by the same person (Robertson) and (b) the Robertson '87 reference cites Robertson '83.

The difference between the combined teachings of Robertson '83 and Robertson '87 and claims 1 - 3 of the '913 patent is that the Robertson references disclose mouse embryonic stem cells while the '913 patent claims human embryonic stem cells.

However, the Williams '065 patent does disclose human embryonic stem cells along with the embryonic stem cells of other animal species--birds, chickens, mice, sheep, pigs, cattle, goats, and fish (col. 2, lines 30 - 40 and lines 47 - 50; col. 3, lines 42 - 48; and col. 4, lines 17 - 21). This disclosure of human ES cells alongside ES cells

of many other animal species make it clear that goal of most of the animal studies is to ultimately prepare human ES cells that have numerous therapeutic possibilities.

Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer. In this regard, Hogan discloses non-mouse (including human; see Hogan patent claims, particularly claims 7 - 8) pluripotential stem cells which can: (a) be maintained on feeder layers for at least 20 passages or indefinitely (col. 5, lines 14 -1 6); and (b) which give rise to embryoid bodies and multiple differentiated phenotypes in monolayer culture (see Hogan at col. 2, lines 29 - 40; col. 5, lines 1 - 4).

Therefore, the claimed human embryonic stem cells would have been obvious to the person of ordinary skill in the art at the time of the invention wanting to extend the isolation of embryonic stem cells from one species of mammals (mice) to another species of mammals (humans) by using the procedure taught by the combined disclosures of Robertson '83 and Robertson '87. Williams '065 and Hogan '926 (either along or together) provide the motivation for isolating human embryonic stems cells instead of mouse embryonic stem cells which is the implicit therapeutic possibilities of using said human pluripotent ES cells to generate specific differentiated human tissue as a replacement for diseased cells or organs. Consequently, the claimed human embryonic stem cells are *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

The four additional functional and physical limitations (other than pluripotential,

immortality with exogenous LIF, euploidy indefinitely during passaging, and maintaining undifferentiated state in vitro when grown on a fibroblast feeder layer) not expressly found in Robertson '83) are all attributes which the '913 patent concedes are inherent to human ES cells. These inherent attributes of human ES cells disclosed by the '913 patent are: **(1)** production of chorionic gonadotropin when human ES cells are cultured to high density ('913; col. 4, lines 39 - 41); **(2)** testing negative for the SSEA-1 marker ('913; col. 4, lines 26 - 29); **(3)** testing positive for the SSEA-4 marker (col. 4, lines 26 - 29); **(4)** expressing alkaline phosphatase ('913, col. 4, lines 29 - 31).

Grounds #7: Claim Rejection - 35 USC 103(a) (formulated by examiner)

Claim 1 - 3 are rejected under 35 USC 103(a) as being obvious over Piedrahita et al. (Theriogenology, 34(5): 879-901, 1990) in view of Williams '065 and Hogan '926.

Claims 1 - 3 are described above under the heading "The Thomson '913 Patented Invention" and "Claim Interpretation" above.

Piedrahita '90 discloses murine, porine, and ovine ES cells (Abstract, first three paragraphs on page 880).

Piedrahita '90 also discloses a method for preparing said ES cells comprising: (1) isolating an animal blastocyst (pages 881, last paragraph through first three paragraphs on page 882); (2) isolating inner cell mass from blastocyst (Ibid) (3) plating the inner cell mass on embryonic fibroblast feeder layers. (4) dissociating new inner cell masses into individual cells (page 882, last paragraph), (5) replating the dissociated cells onto embryonic feeder cells (page 882, last paragraph), (6) selecting ES cell colonies arising from explanted inner cell mass based on morphology (page

882, last paragraph), and (7) culturing ES cell colonies on embryonic feeder layers page 882 , last paragraph through page 883 first paragraph).

Piedrahita '90 fails to provide explicit motivation to isolation human ES cells according to the same procedure as used to isolate mouse, sheep and pig ES cells.

However, the Williams '065 patent does disclose human embryonic stem cells along with the embryonic stem cells of other animal species--birds, chickens, mice, sheep, pigs, cattle, goats, and fish (col. 2, lines 30 - 40 and lines 47 - 50; col. 3, lines 42 - 48; and col. 4, lines 17 - 21). This disclose of human ES cells alongside ES cells of many other animal species makes it clear that goal of most of studies of animal ES cells is to ultimately prepare human ES cells that have numerous therapeutic possibilities for treating human diseases.

Additionally, Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer. In this regard, Hogan discloses non-mouse (including human; see Hogan patent claims, particularly claims 7 - 8) pluripotential stem cells which can: (a) be maintained on feeder layers for at least 20 passages or indefinitely (col. 5, lines 14 -1 6); and (b) which give rise to embryoid bodies and multiple differentiated phenotypes in monolayer culture (see Hogan at col. 2, lines 29 - 40; col. 5, lines 1 - 4).

Therefore, the claimed human embryonic stem cells would have been obvious to the person of ordinary skill in the art at the time of the invention wanting to extend the isolation of embryonic stem cells from several species of mammals (mice, sheep, and) to another species of mammals (humans) by using the procedure taught by the

disclosure of Piedrahita '90. Williams '065 and Hogan '926, alone or together, provide the motivation for isolating human embryonic stems cells instead of mouse, sheep, or pig embryonic stem cells, which is the implicit therapeutic possibilities of using said human pluripotent ES cells to generate specific differentiated human tissue as a replacement for diseased cells or organs. Consequently, the claimed human embryonic stem cells are *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

Grounds #8: Claims Rejection - 35 USC 103(a) (formulated by examiner)

Claims 1 - 3 are rejected under 35 USC 103(a) as being obvious over Robertson '83, Robertson '87, and Piedrahita '90 in view of Williams '065 and Hogan '926.

Claims 1 - 3 are described above under the heading "The Thomson '913 Patented Invention: on pages 3 - 4.

The teachings of Robertson '83 and 'Robertson '87 are set forth above at pages 11 - 13. The teachings of Piedrahita '90 are set forth above at pages 14 - 15.

The difference between the combined teachings of Robertson '83, Robertson '87, and Piedrahita '90 and instant claims 1 - 3 is that the Thomson '913 patent claims are directed to human ES cells while the combined teachings of Robertson '83, Robertson '87, and Piedrahita '90 are directed to ES cells of mice, sheep, and pigs.

However, the Williams '065 patent does disclose human embryonic stem cells along with the embryonic stem cells of other animal species--birds, chickens, mice,

sheep, pigs, cattle, goats, and fish (col. 2, lines 30 - 40 and lines 47 - 50; col. 3, lines 42 - 48; and col. 4, lines 17 - 21). This disclose of human ES cells alongside ES cells of many other animal species makes it clear that goal of most of studies of animal ES cells is to ultimately prepare human ES cells that have great therapeutic possibilities for treating human diseases.

Additionally, Hogan '926 provides additional motivation to isolate and maintain animal ES cells (including human) *in vitro* for longer periods on a (fibroblast) feeder layer. In this regard, Hogan discloses non-mouse (including human; see Hogan patent claims, particularly claims 7 - 8) pluripotential stem cells which can: (a) be maintained on feeder layers for at least 20 passages or indefinitely (col. 5, lines 14 -1 6); and (b) which give rise to embryoid bodies and multiple differentiated phenotypes in monolayer culture (see Hogan at col. 2, lines 29 - 40; col. 5, lines 1 - 4).

Therefore, the claimed human embryonic stem cells would have been obvious to the person of ordinary skill in the art at the time of the invention wanting to extend the isolation of embryonic stem cells from several species of mammals (mice, sheep, and) (as taught by the combined disclose of Robertson '83, Robertson '87,and Piedrahita '90) to another species of mammals (humans) by using the procedure taught by the disclosure of these three prior art references. Williams '065 and Hogan '926, alone or together, provide the motivation for isolating human embryonic stems cells instead of mouse, sheep, or pig embryonic stem cells, which is the implicit therapeutic possibilities of using said human pluripotent ES cells to generate specific differentiated human tissue as a replacement for diseased cells or organs. Consequently, the claimed

human embryonic stem cells are *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

Conclusion

Claims 1 - 3 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in *inter partes* reexamination proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to the patent owner in a reexamination proceeding. Additionally, 35 USC 314(c) requires that *inter partes* reexamination proceedings "will be concluded with special dispatch" (37 CFR 1.937). Patent owner extensions of time in *inter partes* reexamination proceedings are provided for in 37 CFR 1.956. Extensions of time are not available for third party requester comments, because a comment period of 30 days from service of patent owner's response is by statute. 35 USC 314(b)(3).

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings have been merged) in the reexamination proceedings in the manner provided in 37 CFR 1.248. See 37 CFR 1.530(f).

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be

formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Further Correspondence

All correspondence relating to this *inter partes* Reexamination proceeding should be directed to:

By Mail to:

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

By FAX to:

(571) 273-9900
Central Reexamination Unit

Hand-Deliver any communications to:

Customer Service Window
Attn: Central Reexamination Unit
Randolph Building, Lobby Level
401 Dulany Street
Alexandria VA 22314

Any inquiry concerning this communication or earlier communications from the examiner, or as to the status of this proceeding, should be directed to the Central Reexamination Unit at telephone number (571) 272-775.

Conferee:

BENNETT M. CELSA
CRU EXAMINER - AU 3991

Gary L. Kunz
Primary Examiner
Art Unit 3991

Conferee:

DEBORAH D. JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT