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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,139	07/17/2006	6200806		4856

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EXAMINER	
Bennett Celsa	
ART UNIT	**PAPER NUMBER**
3991	IFW

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Please find below and/or attached an Office communication concerning this application or proceeding.

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO 90/008139
PATENT NO. 6,200,806
ART UNI 3991

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a replly has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,139	Patent Under Reexamination 6200806	
	Examiner Bennett Celsa	Art Unit 3991	

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

a☒ Responsive to the communication(s) filed on *29 September 2006*. b☐ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

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

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-11* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-11* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

DETAILED ACTION: *R examination: First Action on th M rits (FAOM)*

Procedural Posture:

The 3rd party Request (dated July 17, 2006) for *ex parte* reexamination of claims 1-11 of U.S. Patent No. 6,200,806 (Thomson) was ordered on September 29, 2006. No patent owner response has been received.

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 Pat. No.6,200,806 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.

The Claimed Invention

The instant claims are drawn to a purified preparation of pluripotent human embryonic stem cells (independent claims 1 and 3); a method of isolating a pluripotent human embryonic stem cell line (independent claims 9) and the resulting cell line (independent claim 11).

Priority of the Instantly Claimed Invention

U.S. Pat. No. 6,200,806 issued from 09/106,390 (filed 6/6/98) which is:
-a Div. of 08/591,246 (filed 1/18/96) (issued as U.S. Pat. No. 5,843,780); which is a
-a CIP of 08/376,327 (filed 1/20/95)(abandoned).

Cit d Docum nts

Newly Reference(s) cited by the 3rd party requester:
***1. Williams**, U.S. Pat. No. 5,166,065 (issued Nov. 24, 1992)*
***2.* Robertson (1983),** *Teratocarcinoma Stem Cells, (Cold Spring Harbor: 1983), Vol. 10 pages 647-663*
3. Robertson (1987), Teratrocarcinoma and Embryonic Stem Cells; A Practical Approach, (Oxford: 1RL Press: 1987) Vol. 4, pages 71-112;

Requester-provided Reference Previously Cited but not applied in 08/591,246 application:
***4. Piedrahita** et al.*, Theriogenology, Vol. 34(5) pages 879-901 (1990)

New Examiner-Cited References in this office action:
6.**Hogan,** U.S. Pat. No. 5,453,357 (issued September 26, 1995: filed October 8, 1992).
7.**Hogan**, U.S. Pat. No. 5,690,926 (issued November 25, 1997: filed March 25, 1994).
8. **Bongso** et al. Human Reproduction, Vol. 9, No. 11 (1994) pages 2110-2117.

1. Background of the Invention and Claim Terminology:

1. *"Stem Cells":* "in general, stem cells are undifferentiated cells which can give rise to a succession of mature functional cells." See instant '806 patent; col. 1, lines 20-23.

2. *"Embryonic Stem (ES) Cells"*: stem cells derived from the embryo that are pluripotent. See instant '806 patent at col. 1, lines 24-26.

3. *"Pluripotent"*: possessing the capability of developing into any organ or tissue type or, at least potentially, into a complete embryo. See instant '806 patent at col. 1, lines 26-28.

4. "*True ES Cells"* are "pluripotent" and :

(i) are 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).

See instant '806 patent col. 3, lines 52-59; patent col. 4, lines 8-17.

5. Strong evidence of the required properties of "true ES cells" have been published for rodent (mouse, hamster and rat) ES cells, less conclusively for rabbit. See instant '806 patent col. 3, line 59-top of col. 4 and citations therein.

2. Claim Interpretation:

Reexamination Standard

Original patent claims will be examined only on the basis of prior art patents or printed publications applied under the appropriate parts of 35 U.S.C. 102 and 103. See MPEP § 2217. Thus an admission, *per se*, may not be the basis for establishing a substantial new question of patentability. However, an admission by the patent owner of record in the file or in a court record may be utilized in combination with a patent or printed publication. Admissions by the patent owner as to any matter affecting patentability may be utilized to determine the scope and content of the prior art in conjunction with patents and printed publications in a prior art rejection, whether such admissions result from patents or printed publications or from some other source. MPEP 2217. During reexamination, claims are given the broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims (*In re Yamamoto*, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984)). The statutory presumption of validity, 35 U.S.C. 282, has no application in reexamination (*In re Etter*, 756 F.2d 852, 225 USPQ 1 (Fed. Cir. 1985)). See MPEP 2258. "Reexamination will be conducted according to the procedures established for initial examination under the provisions of (35 U.S.C. 132 and 1331." 35 U.S.C. 305). Thus, reexamination is conducted afresh, without the burdens and presumptions that accompany litigation of an issued patent." *Laitram Corp. v. NEC Cow.*, 952 F.2d 1357, 1360 (Fed. Cir. 1991).

Instant Claim 1:

Claim 1 is a **composition claim** drawn to a purified preparation of pluripotent human embryonic stem cells which:

(i) will proliferate in an in vitro culture for over one year;
(ii) maintains karyotype in which the chromosomes are euploid and not altered through prolonged culture;
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture; and
(iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

As noted above, the instant patent describes "*True ES Cells*" as "pluripotent" which:

(i) are 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).

Any source of extrinsic or intrinsic evidence, including patentee's own application can be utilized to demonstrate "inherency". See *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat.App. & Inter. 1993) (use by BPAI of intrinsic patent application information to demonstrate inherency).

Accordingly, a reference teaching a "purified preparation of pluripotent human embryonic stem cells" (however obtained) are "True ES Cells" which, in accordance with patentee's definition **inherently**:

(i) will proliferate in an in vitro culture for over one year;
(ii) maintains karyotype in which the chromosomes are euploid and not altered through prolonged culture;
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture.

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 "purified preparation of pluripotent human embryonic stem cells" (however obtained) would anticipate claim 1 since the reference composition meets all the structural requirements of the instantly claimed composition.

Instant Claims 9-10

Claim 9 is drawn to a method of isolating a pluripotent human embryonic stem cell line comprising:

(a) isolating a human blastocyst;
(b) isolating cells from the inner cell mass of the blastocyte of (a);
(c) plating the inner cell mass cell on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed;
(d) dissociating the mass into dissociated cells;
(e) replating the dissociated cells or embryonic feeder cells;
(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli;
(g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line.

Claim 10 modified the method of claim 9 to further comprise "maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation". It is noted that claim 10 requires a maintaining step which is NOT limited timewise. The instant patent disclosure teaches that isolated pluripotential primate (human or non-human) cell lines are "capable of" remaining in an undifferentiated state if "maintained" on a fibroblast

feeder layer to prevent differentiation. See instant patent at col. 7, lines 35-42 and instant claim 10 *supra*.

Instant Claim 11

Claim 11 is a product by process claim reciting: A cell line developed by the method of claim 9 (for isolating a pluripotent human embryonic stem cell line). For purposes of patentability, a product-by-process claim is being interpreted by the USPTO as equivalent to a product claim.

35 U.S.C. 102/103: Product-by-Process Claims And Functional Limitations

i. Product-by-Process:

Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Once a product *appearing to be substantially identical* is found and a 35 U.S.C.102/103 rejection is made, the *burden shifts to the applicant* to show an unobvious difference. MPEP 2112.02

ii. Functional Limitations:

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function, property or characteristic is not explicitly disclosed by the reference, the

examiner may make a rejection under both 35 U.S.C.102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. See MPEP 2112. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a 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, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The PTO lacks facilities to compare prior art products to that claimed, therefore the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. See *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985); *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972); and MPEP 2112.01.

Multiple Reference 35 U.S.C. 102 Rejections

Although, normally, only one reference should be used in making a rejection under 35 U.S.C. 102 rejection, a 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure";

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent. MPEP 2131.01.

Anticipation: Enabling Suggestion

It is legally settled that anticipation does not require actual performance of a suggestion in a disclosure, but only requires that the suggestion be enabling to one of ordinary skill in the art. *Bristol-Meyers Squibb Co. v. Ben Venue Laboratories*, Inc. 246 F.3d 1368, 1379 (Fed. Cir. 2001); *In re Donohue*, 766 F.2d 531,533 (Fed. Cir. 1985). Accordingly, the threshold for enabling a reference for purposes of prior art under 35 USC 102 is much lower than the threshold for enablement under 35 USC 112, first paragraph required for a patented invention insofar that the prior art reference need not demonstrate utility. See e.g. in *Rasmusson v. Smithkline Beecham Corp.* 75 USPQ2d 1297 (Fed. Cir. 2005) (denial of 35 USC 120 priority to a parent application for claims directed to treating prostate cancer for lack of enablement did not preclude the use, as prior art, of a foreign filed published document related to the parent application against the same claimed invention). See also *Impax Labs., Inc. v. Aventis Pharmaceuticals, Inc.*, No. 05-1313 (Fed. Cir. Nov. 20, 2006) concurring with the *Rasmusson* holding.

NOTE: ALL OF THE REJECTIONS RECITED BELOW HEREIN INCORPORATE BY REFERENCE THE ABOVE-DISCUSSED:

1. ***Background of the Invention and Claim Terminology; and***
2. **Claim Interpretation**

in its entir ty.

Claim R j ctions - 35 USC § 102

1. 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 –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (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.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim Rejections - 35 USC § 103

2. 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.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-8 and 11 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hogan, U.S. Pat. No. 5,453,357 (issued September 26, 1995: filed October 8, 1992) alone, or as further evidenced by the instant patent disclosure for demonstrating inherency. See *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat.App. & Inter. 1993) (use by BPAI of intrinsic patent application information to demonstrate inherency).

The Instantly Claimed Invention

Claim 11 is a product by process claim reciting: A cell line developed by the method of claim 9 (for isolating a pluripotent human embryonic stem cell line[1]).

Claim 1 is a composition claim drawn to a purified preparation of pluripotent human embryonic stem cells which:

(i) will proliferate in an in vitro culture for over one year;

---

[1] comprising the steps of (a) isolating a human blastocyst; (b) isolating cells from the inner cell mass of the blastocyte of (a); (c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed; (d) dissociating the mass into dissociated cells; (e) replating the dissociated cells on embryonic feeder cells; (f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and (g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line.

(ii) maintains karyotype in which the chromosomes are euploid and not altered through prolonged culture;
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture; and
(iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

Claims 2-8 (dependent on claim 1) further define inherent properties of pluripotential human embryonic stem cells (See instant Thompson US 6,200,806 patent at col. 4):

a. cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density (instant claim 2);
b. cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have euploid karyotypes and in which none of the chromosomes are altered (instant claim 3);
c. cells are positive for the TRA-1-60, and TRA-1-81 markers (instant claim 4);
d. cells continue to proliferate in an undifferentiated state after continuous culture for at least one year (instant claim 5);
e. cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin (instant claim 6);
f. cells remain euploid for more than one year of continuous culture (instant claim 7); and
g. cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

Hogan '357 Patent teaching

The Hogan '357 patent reference discloses (e.g. see abstract; col. 1, lines 10-17; col. 2; lines 8-21; col. 3, lines 44-48) and claims (e.g. claims 1 and 8-13) obtaining purified mammalian (preferably human: e.g. see col. 4, lines 65- col. 5, line 30; col. 9, lines 6-16; and examples) pluripotent embryonic stem cells which can be maintained for at least 20 passages, but are capable of indefinite maintenance (see 'col. 4, lines 3-24). Accordingly, the patent reference's human pluripotent embryonic stem cells necessarily would proliferate in an *in vitro* culture for over one year as instantly claimed. Additionally, the reference mammalian (e.g. human) "pluripotential embryonic stem

cells" necessarily give rise to many differentiated cell types (i.e. ectoderm, mesoderm and endoderm) in the embryo or an adult. Further, the Hogan '357 human embryonic stem cells are pluripotent "True ES Cells" that:

(i) are capable of indefinite proliferation in vitro in an undifferentiated state;

(ii) maintain a normal karyotype through prolonged culture; and

(ii) maintain the potential to differentiate to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm).

See instant '806 patent col. 3, lines 52-59; patent col. 4, lines 8-17.

Although produced differently, the Hogan '357 reference teaching of isolating a purified preparation of pluripotent human embryonic cell line anticipates the instant claim11 pluripotent human embryonic cell line produced by the instant claim 9 method.

Additionally, the Hogan '357 reference teaching of isolating a purified preparation of pluripotent human embryonic cell line (within the scope of instant claim 1 which is not limited by method of production) necessarily possesses all the inherent features of human pluripotential embryonic stem cells of the instant claims and thus anticipates instant claims 1-8.

Accordingly, since the instantly claimed and prior art products are identical or substantially identical, (or are produced by identical or substantially identical processes), the PTO can require the patentee to prove that the prior art products do not necessarily or 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, jointly

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).

5. Claims 1-8 and 11 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hogan, U.S. Pat. No. 5,690,926 (issued November 25, 1997: filed March 25, 1994) alone, or as further evidenced by the instant patent disclosure for demonstrating inherency.

The Instantly Claimed Invention

Claim 11 is a product by process claim reciting: A cell line developed by the method of claim 9 (for isolating a pluripotent human embryonic stem cell line).

Claim 1 is a composition claim drawn to a purified preparation of pluripotent human embryonic stem cells which:

(i) will proliferate in an in vitro culture for over one year;
(ii) maintains karyotype in which the chromosomes are euploid and not altered through prolonged culture;
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture; and
(iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

Claims 2-8 (dependent on claim 1) further define inherent properties of pluripotential human embryonic stem cells. (See instant Thompson US 6,200,806 patent at col. 4).

Hogan '926 Patent teaching

The Hogan '926 patent reference discloses (e.g. see abstract; col. 1, lines 10-18; col. 2; lines 28-36; col. 4, lines 18-30;) and claims (e.g. claims 1 -7) obtaining purified

mammalian (preferably human: e.g. see col. 5; col. 7, lines 10-20; col. 12; and examples) pluripotent embryonic stem cells which can be maintained for at least 20 passages, but are capable of indefinite maintenance. Accordingly, the patent reference's human pluripotent embryonic stem cells necessarily would proliferate in an *in vitro* culture for over one year as instantly claimed. Additionally, the reference mammalian (e.g. human) "pluripotential embryonic stem cells" necessarily give rise to many differenetiated cell types (i.e. ectoderm, mesoderm and endoderm) in the embryo or an adult. Additionally, the Hogan '926 human embryonic stem cells are pluripotent "True ES Cells" that:

(i) are capable of indefinite proliferation in vitro in an undifferentiated state;

(ii) maintain a normal karyotype through prolonged culture; and

(ii) maintain the potential to differentiate to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm).

See instant '806 patent col. 3, lines 52-59; patent col. 4, lines 8-17.

Although produced differently, the Hogan '926 reference teaching of isolating a purified preparation of pluripotent human embryonic cell line anticipates the instant claim11 pluripotent human embryonic cell line produced by the instant claim 9 method.

Additionally, the Hogan '926 reference teaching of isolating a purified preparation of pluripotent human embryonic cell line (within the scope of instant claim 1 which is not limited by method of production) necessarily possesses all the inherent features of human pluripotential embryonic stem cells of the instant claims and thus anticipates instant claims 1-8.

Accordingly, since the instantly claimed and prior art products are identical or substantially identical, (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 necessarily or 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, jointly 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).

6. Claims 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams U.S. Pat. No. 5,166,065 (issued Nov. 24, 1992).

The Instantly Claimed Invention

Instant claim 9 is drawn to:

A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of:

(a) isolating a human blastocyst;
(b) isolating cells from the inner cell mass of the blastocyte of (a);
(c) plating the inner cell mass cell on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed;
(d) dissociating the mass into dissociated cells;
(e) replating the dissociated cells or embryonic feeder cells;
(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli;
(g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line.

Claim 10 (dependent on claim 9) further requires maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation. (See instant Thompson US 6,200,806 patent at col. 4)

Williams '065 patent teaching

Williams teaches a method for isolating ES cells of various animals, including specifically humans (see Williams, column 2, lines 37-40 and 47-50; column 4, lines 18-19; and column 6, lines 51-66). The Williams' method first isolated blastocysts (Williams col. 6, lines 52-58) and then isolated the inner cell mass ("ICM") (Williams col. 6, lines 66-col. 7, line 4), which was plated on embryonic fibroblasts (see Williams at column 5, lines 19-34; column 6, lines 51-66; and col. 7, lines 1-3). From the ICM, Williams extracted dissociated ES cell colonies (Williams at col. 8, lines 29-31), replated the dissociated cells on embryonic feeder cells (Williams col. 8, lines 29-31) and selected ES cell colonies arising from the explanted ICM (Williams col. 6, lines 63-66) which were placed on a media suitable to support their growth while maintaining their pluripotential nature (Williams at column 3, lines 54-55; column 4, lines 24-27; column 5, lines 19-34; and column 6, lines 51-66). Williams' ES cells "retain[ed] their pluripotential phenotype" and "the developmental potential to differentiate into all somatic and germ cell lineages" (see Williams at column 4,lines 14 and 26-27), thus anticipating method claim 9. Williams further teaches the use of a fibroblast feeder layer to prevent differentiation and thus retain stem cell phenotype (Williams at col. 1, lines 42-45), thus anticipating instant claim 10. In this respect it is noted that LIF (leukemia inhibitory

factor) may supplement or substitute for the fibroblast feeder layer (Williams at col. 51-62).

7. Claims 1-8 and 11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Williams, U.S. Pat. No. 5,166,065 (issued Nov. 24, 1992) alone, or as further evidenced by the instant patent disclosure for demonstrating inherency.

The Instantly Claimed Invention

Claim 11 is a product by process claim reciting: A cell line developed by the method of claim 9 (for isolating a pluripotent human embryonic stem cell line).

Claim 1 is a composition claim drawn to a purified preparation of pluripotent human embryonic stem cells which:

(i) will proliferate in an in vitro culture for over one year;
(ii) maintains karyotype in which the chromosomes are euploid and not altered through prolonged culture;
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture; and
(iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

Claims 2-8 (dependent on claim 1) further define inherent properties of pluripotential human embryonic stem cells.

Williams '065 patent teaching

As described *supra,* the William patent anticipates the instant claim 9-10 method of isolating a pluripotent human embryonic stem cell line.

In this regard, Williams teaches a method for isolating ES cells of various animals, including specifically humans (see Williams, column 2, lines 37-40 and 47-50; column 4, lines 18-19; and column 6, lines 51-66). The Williams' method first isolated blastocysts (Williams col. 6, lines 52-58) and then isolated the inner cell mass ("ICM") (Williams col. 6, lines 66-col. 7, line 4), which was plated on embryonic fibroblasts (see Williams at column 5, lines 19-34; column 6, lines 51-66; and col. 7, lines 1-3). From the ICM, Williams extracted dissociated ES cell colonies (Williams at col. 8, lines 29-31), replated the dissociated cells on embryonic feeder cells (Williams col. 8, lines 29-31) and selected ES cell colonies arising from the explanted ICM (Williams col. 6, lines 63-66) were placed on a media suitable to support their growth while maintaining their pluripotential nature (Williams at column 3, lines 54-55; column 4, lines 24-27; column 5, lines 19-34; and column 6, lines 51-66). Williams' ES cells "retain[ed] their pluripotential phenotype" and "the developmental potential to differentiate into all somatic and germ cell lineages" (see Williams at column 4,lines 14 and 26-27) thus anticipating claim 9. Williams further teaches the use of a fibroblast feeder layer to prevent differentiation and thus retain stem cell phenotype (Williams at col. 1, lines 42-45: as in instant claim 10).

Accordingly, the William's patent teaches pluripotent human embryonic stem cells that are"True ES Cells" and:

(i) are capable of indefinite proliferation in vitro in an undifferentiated state;

(ii) maintain a normal karyotype through prolonged culture; and

(ii) maintain the potential to differentiate to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm).

See instant '806 patent col. 3, lines 52-59; patent col. 4, lines 8-17.

Based on the evidence of record, there is no structural difference between the pluripotential human ES cells disclosed by Williams 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 and the instant claimed method.

Accordingly, since the instantly claimed and prior art products are identical, or substantially identical, and 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, jointly 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).

8. Claim 11 is rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bongso et al. Human Reproduction, Vol. 9, No. 11 (1994) pages 2110-2117.

The Instantly Claimed Invention

Claim 11 is a product by process claim reciting: A cell line developed by the method of claim 9 (for isolating a pluripotent human embryonic stem cell line). For purposes of patentability, a product-by-process claim is being interpreted by the USPTO as a product claim.

Bongso et al. article teaching

Bongso et al. teach the isolation from human embryos of human cell lines having stem cell-like morphology (e.g. are alkaline phosphase positive and maintain pluripotentiality for two passages). See Abstract; page 2114, column 2.

Based on the evidence of record, there is no difference between the pluripotential human ES cell lines disclosed by Bongso et al. and the ES cell line(s) within the scope of instant claim 11. Although the instantly claimed human stem cells are produced differently, there is no evidence of record that the method steps, as recited in claim 9, would result in human stem cells distinguishable from those produced by the Bonso et al. reference.

Accordingly, since the instantly claimed and prior art products are identical, or substantially identical, the PTO can require the instant patentee to prove that the prior art product is distinguishable from the instantly claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). For the PTO is unable 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).

9. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over ***Robertson (1983)***, Teratocarcinoma Stem Cells, (Cold Spring Harbor: 1983), Vol. 10 pages 647-663; ***Robertson (1987)***, Teratrocarcinoma and Embryonic Stem Cells; A Practical Approach, *(Oxford: 1RL Press: 1987) Vol. 4, pages 71-112;* ***Piedrahita*** *et al.*, Theriogenology, Vol. 34(5) pages 879-901 (1990), taken separately or together in view of **Williams,** U.S. Pat. No. 5,166,065 (issued Nov. 24, 1992) and **Hogan**, U.S. Pat. No. 5,690,926 taken separately or in combination.

Robertson '83 teaches a step-by-step process for isolating pluripotential mammalian embryonic stem (ES) cells (see page 649, first two paragraphs) comprising:

(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. See *Robertson (1983)* at pages 647, 649, 654 and 660.

The ES cells described by Robertson '83 were (a) pluripotent; maintaining their 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.

Four years later, the Robertson '87 reference described in greater detail the process for isolating pluripotent mammalian ES cells. Robertson '87 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).

Piedrahita discloses murine (mouse), porcine (pig), and ovine (sheep) pluripotenial ES cells (Abstract, first three paragraphs on page 880) and their preparation 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).

Accordingly, the Robertson '83, Robertson'87 and Piedrahita ES cells meet all of the standard criteria for pluripotential embryonic stem cells.

The co-authored Robertson '83 and '87 (the '87 article cites Robertson '83) articles, as well as the Piedrahita article, all teach *mammalian* pluripotential embryonic stem cells (all 3 teach mice, with pig and sheep further taught by Piedrahita) as well as teaching identical procedures for their isolation from blastocysts.

The teaching of the Robertson '83, Robertson '87 and Piedrahita articles, taken separately, or in combination, nevertheless *differ* from the instantly claimed invention in failing to isolate *human* pluripotential embryonic stem cells from blastocysts.

However, the Williams '065 patent reference discloses human pluripotential embryonic stem cells along with 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) and a method to isolate these pluripotential embryonic stem cells from blastocysts. This Williams '065 disclosure of human ES cells alongside ES cells of many other animal species illustrates the goal of most animal studies which is the ultimate preparation of human ES cells having numerous therapeutic possibilities. In this regard, Williams teaches a method for isolating ES cells of various animals, including *specifically humans* (see Williams, column 2, lines 37-40 and 47-50; column 4, lines 18-19; and column 6, lines 51-66). The

Williams' method first isolated blastocysts (Williams col. 6, lines 52-58) and then isolated the inner cell mass ("ICM") (Williams col. 6, lines 66-col. 7, line 4), which was plated on embryonic fibroblasts (see Williams at column 5, lines 19-34; column 6, lines 51-66; and col. 7, lines 1-3). From the ICM, Williams extracted dissociated ES cell colonies (Williams at col. 8, lines 29-31), replated the dissociated cells on embryonic feeder cells (Williams col. 8, lines 29-31) and selected ES cell colonies arising from the explanted ICM (Williams col. 6, lines 63-66) which were then placed on a media suitable to supporting growth while maintaining their pluripotential nature (Williams at column 3, lines 54-55; column 4, lines 24-27; column 5, lines 19-34; and column 6, lines 51-66). Williams' ES cells "retain[ed] their pluripotential phenotype" and "the developmental potential to differentiate into all somatic and germ cell lineages" (see Williams at column 4,lines 14 and 26-27). Williams further teaches the use of a fibroblast feeder layer to prevent differentiation and thus retain stem cell phenotype (Williams at col. 1, lines 42-45).

The Williams method of obtaining animal, including human, pluripotential stem cells corresponds to the techniques employed by the Robertson '83, Robertson '87 and Piedrahita references as well as the instantly claimed method.

As discussed above, the Williams '065 patent, taken alone, provides the motivation for isolating human embryonic stems cells, instead of mouse (and pig or sheep) embryonic stem cells, for ultimate therapeutic use, such as the use of differentiated human ES cells to generate human tissue for replacement therapy.

Further, Hogan 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: e.g. see Hogan patent claims, particularly claims 6-7) pluripotential stem cells which can: a) be maintained on feeder layers for at least 20 passages *or indefinitely* (col. 5, lines 14-16); and b) which give rise to embryoid bodies and multiple differentiated cell phenotypes in monolayer culture (see Hogan at col. 2, lines 29-40; col. 5, lines 1-4).

The level of ordinary skill in the art is high (phD and/or MD level).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to extend the blastocyst method of isolating embryonic stem cells from one (or more) mammallian species (mice and/or pigs and/or sheep) to another (humans) by using the blastocyst procedure taught by the Robertson '83, Robertson '87, Piedrahita and/or Williams '065 patent references to obtain human pluripotential embryonic stem cells, which may be maintained (indefinitely if desired e.g. for greater than 1 year) with a reasonable expectation of success.

Thus, the instant method of making human pluripotential embryonic stems is *prima facie obvious*, as is the resulting human pluripotent embryonic stem cells that necessarily possess the instantly claimed intrinsic properties (e.g.euploidy, production of chorionic gonadotropin; negative for the SSEA-1 marker; positive for the SSEA-4 marker; and expressing alkaline phosphatase) inherent to human embryonic stem cells. See instant Thompson US 6,200,806 patent at col. 4.

Conclusion

Claims 1 -11 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136 (a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR 1.555(a)). Extensions of time in ex parte reexamination proceedings are provided for in 37 CFR 1.550(c).

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).

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on M-F from 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached at 571-272-1535.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

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