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

EXAMINER	
Padmashri Ponnaluri	
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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Daniel B. Ravicher, Esq.
PUBLIC PATENT FOUNDATION, INC.
1375 BROADWAY, SUITE 600
NEW YORK, NY 10018

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO 90/008102
PATENT NO. 5,843,780
ART UNI 3993

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 reply 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. 90/008,102	Patent Under Reexaminati n 5843780	
	Examiner Padmashri Ponnaluri	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 *17 July 2006* . b☐ This action is made FINAL.
c☒ A statement under 37 CFR 1.530 has not been received from the patent owner. (MAW)

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)

Re-Examination

Non-Final Detailed Action

This is a re-examination of US Patent 5,843,780, issued on December 01, 1998.

A request for reexamination of US Patent 5,843,780 is assigned the control number 90/008,102, which was filed by the Third Party Requestor on 7/17/06.

Reexamination was ordered for the 90/008,102 on 9/29/06.

No Patent Owner's statement was received in 90/008,102 proceedings.

Reexamination proceedings will be "***special***" throughout their pendency in the office.

Priority and Related Proceedings

US Patent No. 5,843,780 is issued from application 08/591,246, filed on January 18, 1996; which is a Continuation-in-part of 08/376,327, filed on January 20, 1995.

US Patent 6,200,806 B1 is a Divisional of 08/591,246 (issued as 5,843,780, the current patent), is currently undergoing ex parte reexamination as 90/008,139; and US Patent 7,029,913 from the same family of the current patent (the `780 patent), is currently undergoing inter parte reexamination as 95/000,154.

The 5,843,780 Patented Inventions

In the Thomson `780 patent 11 claims are present, of which claims 1, 3 and 9 are independent and claim 2 depends on claim 1; claims 4-8 depend on claim 3; and claims 10-11 depend on claim 9.

The representative claims are as following:

Claim 1. 'A purified preparation of primate embryonic stem cells which (i) is capable of proliferation in an in vitro culture for over one year, (ii) maintains a karyotype in which all the chromosomes characteristic of the primate species are present and not noticeably altered through prolonged culture, (iii) maintains the potential to differentiate into derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) will not differentiate when cultured on a fibroblast feeder layer.'

Claim 3. 'A purified preparation of primate embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-3 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have karyotypes which includes the presence of all of the chromosomes characteristic of the primate species and in which none of the chromosomes are noticeably altered.'

Claim 9. 'A method of isolating a primate embryonic stem cell line, comprising the steps of:

(a) isolating a primate blastocyst;

(b) isolating cells from the inner cell mass of the blastocyst of (a);

(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cells 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.'

Claim Interpretations and Relevant Case Law

The independent claim 1 recites 'a purified preparation of primate embryonic stem cells' which have inherent properties of true ES cells.

The present patent (the `780 patent) discloses that the 'pluripotent ES cells' (i) are capable of indefinite proliferation in vitro in an undifferentiated state; (ii) are capable of differentiation to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm) even after prolonged culture; and (iii) maintain a normal karyotype throughout prolonged culture' (see column 4, lines 5-12).Thus the above properties are considered as inherent properties of the pluripotent ES cells.

Further, the present claimed composition is considered as a composition in terms of function, property or characteristics.

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). See MPEP 2112.01.

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 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 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims

claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. See MPEP 2112.

The present claims 2 and 6 recite that 'the stem cells will spontaneously differentiate to trophoblast and produce chorianic gonadotropin when cultured to high density.'

The present patent (the `780 patent) specification discloses that the 'chorianic gonadotropin, expressed by trophoblast, is an essential molecule involved in maternal recognition of pregnancy in all primates, including humans' (see column 2, lines 34-36). Thus the primate or human ES cells inherently produce chorianic gonadotropin when differentiated to trophoblasts.

The present claims 3-4 recite the following inherent characteristics of the primate embryonic stem cells:

a) Negative for SSEA-1 marker;

b) Positive for alkaline phosphatase, SSEA-3-marker, SSEA-4-marker, TRA-1-60 marker and TRA-1-80 marker.

The present patent (the `780 patent) specification discloses that the morphology and cell surface markers of the primate ES cell line R278.5 are indistinguishable from human embryonic carcinoma (EC) cells, and differ significantly from mouse ES cells (see column 14, lines 23-25). The present patent further discloses that the primate ES and human EC cells express the combination of SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 markers and alkaline phosphatase (see column 14, lines 29-34). Thus, primate ES cells inherently have the presence of SSEA-3,

SSEA-4, TRA-1-60 and TRA-1-81 markers, and negative for SSEA-1-marker and express alkaline phosphatase activity.

The present claim 5 recites that 'the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year', which is considered as an inherent property of the cell line after continuous culture.

The present claim 7 recites that 'the cells remain euploid for more than one year', which is considered as an inherent property of the cells.

The present claim 8 recites that 'the preparation of claim 3 wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into SCID mouse' is considered as an inherent property of the cells when injected into SCID mouse.

The present claim 9 recites method of isolating primate embryonic stem cell line.

The present claim 10 recites that the method of claim 9 further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

NOTE that the present claim 10 does not recite the period for maintenance of the isolated primate ES cells on a fibroblast feeder layer.

The present claim 11 is a product-by-process claim.

NOTE claim 11 recites 'a cell line developed by the method of step 9.'
In the claim 11, 'step 9' is considered as a typo, and the claim is considered as dependent on method of claim 9.

"[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).

"The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Document Cited by the Third Party Requester

1. US Patent 5,166,065, Williams et al (Williams) issued November 24, 1992.

2. Robertson et al. Teratocarcinoma Stem cells, 1983, 647-683, Cold Spring Harbor Laboratory, United States of America. (Robertson I).

3. Robertson et al. Teratocarcinomas and Embryonic Stem cells, A Practical Approach, 1987, Chapter 4:71-112, Oxford: IRL Press, England. (Robertson II).

4. Piedrahita et al, Theriogenology, November 1990, v 34, n 5: pages 879-901.

It is noted that Williams, Robertson I, Robertson II and Piedrahita were not cited in the application, which resulted into the current `780 patent.

Piedrahita reference alone was used in an obvious rejection (10/29/96) in the parent application 08/376,327. However, the application was subsequently abandoned (12/9/97).

Document Cited by the Examiner

1. US Patent 5,690,926 (Hogan), issued on November 25, 1997, and the effective filing date is March 25, 1994.

Hogan (the `926 patent) was not applied in a rejection to the present claims of the `780 patent.

2. Bongso et al (Human Reproduction. Vol. 9, No. 11, pages 2110-2117, 1984).

Bongso reference was applied in combination with other references in obviousness rejection to the present claims of the `780 patent. However, Bongso reference is now being presented and/or viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination.

Claim Rejections

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.

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. 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).

4. Claims 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,166,065 (Williams et al, issued on November 24, 1992).

Williams et al teach the method for the isolation of embryonic stem cells (ES) from human (primate) blastocyst (see column 2, lines 30-32; column 3, lines 6-7; column 3, lines 35-40; column 5, lines 25-26); plating the inner cell mass on embryonic fibroblast feeder layer (see column 5, lines 26-29, lines 52-55); selecting colonies with markers, which recognizes stem cell specific cell-surface antigens (see column 6, lines 2-5); culturing the cells for selected colonies (see column 6, lines 65-66). The currently claimed method of isolation of primate embryonic

stem cell line is same as the reference method. Thus Williams et al anticipate the present method claim 9.

Williams et al disclose that the use of leukemia inhibitory factor (LIF) to the fibroblast feeder layer in the maintenance of the ES cells in culture (see abstract) and the removal of LIF from the culture medium resulted in differentiation of ES cells (see column 6, lines 36-37). Thus, Williams et al anticipate the present claim 10.

5. 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 US Patent 5,166,065 (Williams et al, issued on November 24, 1992).

Williams et al teach method for isolation of embryonic stem (ES) cells from animal embryos (blastocyst), and maintenance of ES in vitro culture medium containing leukemia inhibitory factor (LIF) (see column 2, lines 30-35). Williams et al teach that the embryos used may be isolated from animals including humans (refers to the 'primate' of the present claims) (see column 2, lines 48-49). Williams et al teach generation, and maintenance of ES cells from humans (see column 3, lines 6-7). Williams et al further teach that the '*animal embryos*' include reference to '*animal blastocyst*' (see column 3, lines 38-39).

Williams et al teach that the ES cells are maintained in culture medium, containing effective amount of LIF for about 20 weeks (see column 4, lines 10). Thus the ES cells taught by the reference are **capable** of proliferation in vitro culture for over one year.

The ES cells taught by Williams et al maintain karyotype in which all chromosomes are characteristics of the primate species and not noticeably altered through culture.

Williams et al teach that the ES cells will retain the stem cell phenotype in vitro (see column 4, lines 34-36; column 6, lines 11-13). Williams et al teach ES cells retained the ability to differentiate by the formation of normal chimeras following reintroduction of the ES cells into preimplantation embryos (see column 5, lines 5-8; column 7, lines 10-40).

The ES cells disclosed by Williams et al do not differentiate when cultured on a fibroblast feeder layer.

Williams et al teach that Eagles medium on a feeder layer of primary embryonic fibroblasts is used to maintain (in undifferentiated state) the ES cells (ES Cell line D3) (see column 5, lines 26-29). Thus the ES cells taught by Williams et al do not differentiate when cultured on fibroblast feeder layer.

The ES cells taught by Williams et al maintain potential to differentiate into derivatives of endoderm, mesoderm and ectoderm.

Williams discloses that the ES differentiate into all somatic and germ cell lineage when reintroduced into blastocyst (see column 4, lines 45-53). Williams et al disclose that the ES cells (D3) maintained the ability to differentiate (see lines bridging column 5 and 6). Further the reference discloses that the ES cells retained the ability differentiate into multiple cell types following the removal of LIF indicating that these cells have retained pluripotential phenotype (see column 7, lines 6-44).

Williams et al teach that the ES cells used in developing chimeric animals (see column 7, lines 6-44). Williams teaches that the ES cells maintained in LIF contributed to the development of all somatic tissue (see column 7, lines 39-44). Thus, it is inherent that the ES cells taught by

the reference differentiate into cells derived from mesoderm, ectoderm, and endoderm germ layers when the cells are injected into a SCID mouse.

As discussed in claim interpretation *supra,* the primate or human ES cells inherently produce chorianic gonadotropin when differentiated to trophoblasts. Further, as discussed in claim interpretation *supra*, the presence of the cell surface markers (SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 markers) is inherent characteristics of the primate (human) embryonic stem cells. Thus, ES cells disclosed by Williams et al contain, either expressly or inherently all of the characteristics of the primate ES cells as claimed.

Williams et al disclose several ES cell lines.

As discussed in the claim interpretation supra, the present claims 1-8 are considered as a composition in terms of function, property or characteristics.

Where the claimed product and the prior art product are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require Patentee to prove that the prior art products do not necessarily possess the characteristics of the claimed product. See *In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971).* The claimed ES cell composition appears to be the same or obvious variations of the reference teachings, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific ES cell composition of the instant versus the reference composition. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed ES cell composition is different from the one taught by prior art and to establish the patentable differences. See in re

Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

6. Claims 1-8 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 US Patent 5,690,926 (Hogan).

Hogan discloses non-mouse, including human (primate), pluripotential stem cell which can: a) be maintained on feeder layer for at least 20 passages: and b) give raise to embryoid bodies and multiple differentiated cell phenotypes in monolayer culture (see column 2, lines 29-34; column 5, lines 1-4). Hogan discloses isolated human (primate) pluripotential ES cells (see reference claims 6-7).

Hogan discloses that ES cells are maintained (in undifferentiated state) on feeder layer for at least 20 passages, **however the ES cells can be capable of indefinite maintenance** (see column 5, lines 14-16). Thus the ES cells taught by the reference are **capable** of proliferation (in an undifferentiated state) in vitro culture for over one year.

The ES cells disclosed by Hogan maintain the karyotype.

Hogan discloses that the pluripotential ES cells can populate the germ cell line and give rise to a plurality of terminally differentiated cells, which comprise the adult specialized organs, but also regenerate themselves (see column 4, lines 24-30). Hogan discloses that the ES cells had a normal karyotype (see column 10, lines 27-29).

Hogan discloses that the pluripotential ES cells can continue to be maintained (in an undifferentiated state) in the composition comprising FGF, LIF and membrane associated Steel Factor (SF), and soluble SF in an amount to enhance the growth and continue proliferation of the

ES cells (see column 5, lines 30-32). Hogan further teaches that typically the composition of the invention includes a feeder layer, and the feeder layers can be either be cells or cell lines cultured for the purpose of culturing pluripotential ES cells (see column 5, lines 58-60). Hogan discloses that alternatively, the ES cells may be maintained on a feeder layer without the addition of growth factors, and optionally LIF can be added to enhance maintenance (in an undifferentiated state) (see column 6, lines 39-41). Hogan discloses the use of mouse or human embryo fibroblast feeder cells (see column 8, lines 20).

Hogan discloses screening for alkaline phosphatase positive ES cells (see column 8, lines 61-64).

Hogan discloses that the ES cells were injected into nude mice to produce chimera (refers to the present claim 8)(see column 7, lines 25-37; column 9, lines 8-19).

Hogan discloses method for isolation of pluripotential stem cells from human (primate) primordial germ cells and human embryonic gonads (see column 12). Hogan discloses that the ES cells from human embryos can be produced using methods described for murine (see column 12, lines 17-19). Hogan discloses the use of mixture of human or mouse embryo fibroblast feeder cells in the method for isolation and maintenance of human ES cells (see column 12, lines 27-34, lines 45-46). The feeder cells used to maintain the ES cells in the Hogan reference is exact same as the embryonic feeder cells used in the present claimed method.

As discussed in the claim interpretation *supra,* the primate or human ES cells inherently produce chorianic gonadotropin when differentiated to trophoblasts, and the presence of the cell surface markers SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 markers is inherent.

Hogan does not explicitly teach that the ES cells proliferate in vitro culture for over one year. However, Hogan discloses that the ES cells can be maintained indefinitely in an undifferentiated state, which is considered as ES cells maintained at least one year (see column 5, lines 14-16).

The presently claimed purified preparation of embryonic stem cells is claimed in terms of functional properties, i.e., maintains the potential to differentiate into derivatives of ectoderm, mesoderm and endoderm tissues. Hogan specifically does not teach that the ES cells maintain the potential to differentiate into derivatives of ectoderm, mesoderm and endoderm tissues. Hogan discloses that the pluripotential ES cells can populate the germ cell line and give rise to a plurality of terminally differentiated cells, which comprise the adult specialized organs. However, where the claimed product and the prior art product are identical or substantially identical, the PTO can require Patentee to prove that the prior art products do not necessarily possess the characteristics of the claimed product. See *In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971).*

The claimed ES cell composition appears to be the same or obvious variations of the reference teachings, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific ES cell composition of the instant versus the reference composition. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed ES cell composition is different from the one taught by prior art and to establish the patentable differences. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

7. 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 (Human Reproduction, vol. 9, No. 11, pp 2110-2117, 1994).

The present claim 11 recites 'a cell line developed by the method of step 9.'

As discussed in the claim interpretation supra, the claim is considered as product-by-process claim, in which patentability of a product does not depend on its method of production. Thus claim 11 broadly encompassed any cell line. Bongso discloses ES cell line from human (primate) blastocyst. Bongso ES cells are derived from substantially identical method as the current claim 9. However, where the claimed product and the prior art product are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require Patentee to prove that the prior art products do not necessarily possess the characteristics of the claimed product. See *In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971).* The claimed product appears to be the same or obvious variations of the reference teachings, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific method of producing the product (cell line) of the instant versus the reference method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is different from the one taught by prior art and to establish the patentable differences. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

8. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Robertson I, Robertson II, Piedrahita, taken separately or together in view of Williams et al (US Patent 5,166,065) and Hogan (US Patent 5,690,926).

Robertson I taught a step-by-step process for isolating pluripotential mammalian ES cells. Robertson I method included the steps of: (i) isolating a blastocyst, (ii) removing the ICM from the blastocyst, (iii) placing the ICM on fibroblast cells, (iv) isolating stem cells once they became apparent, and (v) maintaining the isolated ES cells on feeder layers. The ES cells disclosed by Robertson I were pluripotential, were maintained over a significant time period and retained a normal euploid karyotype (see page 647, 654 and 660) and inhibited from differentiation when cultured on fibroblast feeder layer.

Robertson II teaches step-by-step process for isolating pluripotential mammalian ES cells. Robertson II teaches highly technical instruction on preparing feeder layers (see page 76-78), collecting blastocyst stage embryos (see pages 78-80), transferring the embryos into culture (see page 80), culturing the blastocysts (see page 81), disaggregating the ICM (see pages 86-91), identifying ICM-derived colonies, expanding ES cells (see pages 92-95) and culturing ES cells (see page 102-103).

The method of isolating ES cells in the present claimed method is the exact same method taught by Robertson references (Robertson I and Robertson II).

Piedrahita teaches a method of isolating murine (rodent), porcine (pig) and ovine (sheep) ES cells (see pages 882-883). Piedrahita discloses a method for preparing said ES cells comprising:(1) isolating an animal blastocyst (see pages 881-882); (2) isolating inner cell mass from blastocyst; (3) plating the inner cell mass on embryonic fibroblast feeder layers; (4)

dissociating new inner cell masses into individual cells (see page 882); (5) replating the dissociated cells onto embryonic feeder cells (see page 882); (6) selecting ES cell colonies arising from explanted inner cell mass based on morphology (see page 882); and (7) culturing ES cell colonies on embryonic feeder layers (see pages 882 -883). The method of isolating ES cells in the present claimed method is the exact same process taught by Piedrahita.

Piedrahita teaches the isolated ES cells differentiated in *in vitro* and *in vivo* (see pages 883-884, 889), the ES cells are pluripotential, maintained (in an undifferentiated state) over a significant time period and retained a normal euploid karyotype (see pages 883-884 and 888).

As discussed in the claim interpretation *supra,* the primate or human ES cells inherently produce chorianic gonadotropin when differentiated to trophoblasts, and the presence of the cell surface markers SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 markers is inherent.

The claimed invention differs from the Robertson references (Robertson I and Robertson II) and Piedrahita reference by claiming primate ES cells.

Robertson references (Robertson I and Robertson II) teach murine ES cells and methods for isolation of the ES cells; Piedrahita teaches method of isolating murine (rodent), porcine (pig) and ovine (sheep) ES cells.

The method of isolating ES cells in the present claimed method is the exact same process taught by Robertson references and Piedrahita reference. Robertson references and Piedrahita reference teach isolating the ICM from the blastocyst. Neither Robertson references nor the Piedrahita reference teach the method for isolating ES cells from primate blastocyst and maintenance of the isolated primate ES cells in vitro for longer periods.

However, Williams et al teach method for isolation of embryonic stem (ES) cells from animal embryos, and maintenance of ES in vitro culture medium containing leukemia inhibitory factor (LIF) (see column 2, lines 30-35). Williams et al teach that the embryos used may be isolated from animals including humans (primate), mice, birds (chickens), sheep, pigs, cattle, goats and fish (see column 2, lines 48-49). Williams et al teach maintenance of ES cells in vitro while retaining their pluripotential phenotype (see column 3, lines 6-7). Thus, Williams et al provides motivation for isolation of human (primate) ES cells and maintenance of derived ES cells *in vitro*.

The method of isolating human ES cells in the Williams reference is the exact same method taught by Robertson references and Piedrahita reference, except the source of the ES cells. Williams et al teach generation and maintenance of ES cells from humans (primate), pigs, sheep, cattle, goat and fish. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Robertson references, Piedrahita reference with the teachings of Williams et al such that pluripotential ES cells from humans (primate) are isolated.

Further, Hogan provides additional motivation to the method of isolation and maintenance of the human (primate) ES cells in vitro for longer periods. Hogan discloses non-mouse, including human (primate), pluripotential stem cell, which can: a) be maintained on feeder layer for at least 20 passages: and b) give raise to embryoid bodies and multiple differentiated cell phenotypes in monolayer culture (see column 2, lines 29-34; column 5, lines 1-4). Hogan discloses the isolated human (primate) pluripotential ES (see reference claims 6-7).

Hogan discloses that ES cells are maintained on feeder layer for at least 20 passages, however the ES cells can be capable of indefinite maintenance (in an undifferentiated state) (see column 5, lines 14-16). Hogan discloses the use of mixture of human or mouse embryo fibroblast feeder cells in the method for isolation and maintenance of human ES cells. The feeder cells used to maintain the ES cells in the Hogan reference is exact same as the embryonic feeder cells used in the present claimed method.

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use embryonic fibroblast feeder cells to maintain the primate (human) ES cells in an undifferentiated state for prolonged or indefinite periods, and the primate (human) ES cells cultured in the mouse or human embryonic fibroblast feeder layer inherently maintain in an undifferentiated state.

Accordingly, it would have been obvious to one skilled in the art at the time the invention was filed to the method of isolating ES cells from primates, and maintaining the isolated ES cells on feeder cells for periods longer than one year. A person skilled in the art would have been motivated to isolate primate (human) ES cells, and maintained in un differentiated state for prolonged periods, since the ES cells are pluripotential and can be used in gene therapy.

Conclusion

Claims 1-11 are rejected.

A shortened statutory period for reply to this action is set to expire **TWO MONTHS** from the mailing date of this action. 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

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).

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by a 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 are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248. See 37 CFR 1.550 (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). In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, will be governed by the

requirements of 37 CFR 1.116, after final rejection and 37 CFR 41.33 after appeal, which will be strictly enforced.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

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 to

By Mail to:

Attn: Mail Stop "Ex Parte Reexam"
Central Reexamination Unit
Commissioner for 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

Padmashri Ponnaluri
Primary Examiner
Unit 3991
05 January 2007

Conferee:

DEBORAH D. JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT

Conferee:

BENNETT M. CELSA
CRU EXAMINER - AU 3991