IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the matter of:

Reexamination Control. No. 95/000,154	Art Unit: 3991
U.S. Patent No. 7,029,913	Examiner: Gary L. Kunz
Issued: April 18, 2006	
Inventor: Thomson	
For: PRIMATE EMBRYONIC STEM CELLS	

DECLARATION OF DR. JEANNE F. LORING, PH.D.

SIR:

I, Jeanne F. Loring, do declare and state:

My Education and Experience Related to Human Embryonic Stem Cell Research

1. I received a B.S. in Molecular Biology in 1972 from the University of Washington and a Ph.D. in Developmental Neurobiology in 1979 from the University of Oregon.

2. I am currently a member of the faculty of the Burnham Institute for Medical Research, where I direct human embryonic stem (ES) cell research. I am Director of the Stem Cell Resource, NIH Human Embryonic Stem Cell Training Course, and Co-Director of the NIH Exploratory Center for Human Stem Cell Research. Prior to joining the faculty of the Burnham Institute in

January 2004, I held research and management positions at Hana Biologics, GenPharm International, Incyte Genomics, and Arcos BioScience. I have served as member and chair of an NIH clinical neurosciences study section and serve as an advisor for the Alzheimer's Association, the International Society for Stem Cell Research, the NIH, and the Bill and Melinda Gates Foundation and several stem cell and instrument companies.

3. I have extensive experience in ES cell derivation and culture, including deriving nine of the cell populations listed in 2001 on the NIH registry (CY12, CY30, CY40, CY51, CY81, CY82, CY91, CY92, CY10). I am a named inventor on several patents and patent applications in the fields of stem cell biology and transgenic technology, amongst others. I have authored more than fifty scientific papers, book chapters and essays, including a comprehensive laboratory manual on human stem cell technology ("Human Stem Cells: A Laboratory Manual"; Academic Press, 2007), and given numerous public presentations regarding topics within my field of scientific expertise, including predominantly ES cells. A copy of my curriculum vitae is attached hereto as Exhibit 1.

Reexamination of the '913 Patent

4. I am familiar with U.S. Patent No. 7,029,913 to Thomson titled, “Primate Embryonic Stem Cells” (“the '913 patent”). I have reviewed the '913 patent and the entire prosecution history that led to its issuance.

5. I am aware that the Foundation for Taxpayers and Consumer Rights, through its counsel the Public Patent Foundation, requested reexamination of the '913 patent, that the U.S. Patent and Trademark Office granted that request and issued an Office Action on March 30, 2007, and that the

owner of the '913 patent submitted a Response to the Office Action on May 30, 2007. I have reviewed the Office Action and the Response. I have also specifically reviewed the '913 patent's claims as amended by the Response.

6. I am aware that the initial application leading to the '913 patent was filed on January 20, 1995. At that time I was directing embryonic stem cell research at GenPharm International, a biotechnology company focused on using embryonic stem cells to generate medically useful cell lines and generically modified laboratory mouse models. My work focused on derivation of novel embryonic stem cell lines and methods for genetic manipulation of the cells. I was a recipient of NIH grants to fund development of methods for deriving embryonic stem cells from a variety of mammalian species, including the rat (NIH Grants #R43HD028869 and R44HD028869).

Williams

7. I am familiar with U.S. Patent No. 5,166,065 to Williams et al. titled, "In Vitro Propogation of Embryonic Stem Cells" ("Williams '065"). I have reviewed Williams '065 in its entirety.

8. Williams '065 teaches in great detail a method for isolating and culturing embryonic stem cells, including specifically human embryonic stem cells. Part of the method described by Williams '065 includes supporting the maintenance of pluripotential embryonic stem cells in vitro by using leukemia inhibitory factor ("LIF"). In fact, Williams '065 is primarily directed towards discussing the use of LIF for such purpose. However, Williams '065 does not state that the use of LIF is required in order to maintain embryonic stem cells, but rather that LIF can "substitute for"

feeder layers, which were already well known for their ability to do so. 1:58 – 62. Thus, Williams '065's discovery was merely that LIF could be used to maintain pluripotent embryonic stem cells when and if otherwise desirable, not that LIF was necessarily an improvement over feeder layers or that feeder layers should in all cases, or even generally, be eliminated.

9. In January 1995, Williams '065's disclosure was sufficient to enable one of ordinary skill in the art, with their general knowledge, common sense and creative ability, to derive and maintain human ES cells without using LIF and without undue experimentation. While one would have been inspired by Williams '065 to try culturing the cells with LIF alone, they would have also attempted to use LIF in combination with feeder cells and feeder cells without LIF. This is true not only because Williams '065 suggested it, but also because an ordinary artisan in the field at the time would have had advanced Ph.D. and/or M.D. degrees in biology and significant related research experience, and, thus, would have used Williams '065 as a guide to be followed loosely, while trying various alternatives, not as a recipe requiring strict adherence to its exact teachings.

Hogan

10. I am familiar with U.S. Patent No. 5,690,926 to Hogan titled "Pluripotential Embryonic Cells and Methods of Making Same" ("Hogan '926"). I have reviewed Hogan '926 in its entirety.

11. In the process of isolating and maintaining pluripotent embryonic cells, it is of no consequence whether the embryos used are pre- or post- implantation. The resulting pluripotent cells will be structurally and functionally similar. Thus, Hogan '926's teaching of the use of post-

implantation embryos does not in any way teach away from the isolation and maintenance of human ES cells derived from pre-implantation embryos.

12. The cell surface markers of human ES cells and mouse ES cells have been known to not be the same for some time. Solter, D., and Knowles, B.B., *Cell surface antigens of germ cells, embryos, and teratocarcinoma stem cells*, In: Principles and Management of Testicular Cancer (N. Javadpour, ed.), pp. 88-98, Thieme, Inc., New York (1986). It has also been known for some time that the markers that characterize mouse ES cells are identical to the markers that had previously been identified in mouse EC cells. Solter, D., and Knowles, B.B., *Monoclonal antibody defining a stage-specific mouse embryonic antigen (SSEA-1)*, Proc. Natl. Acad. Sci. USA 75, 5565-5569 (1978); Martin GR, Lock LF, *Pluripotent cell lines derived from mouse embryos cultured in medium conditioned by teratocarcinoma stem cells*, In Silver LM, Martin GR, Strickland S, eds. Teratocarcinoma Stem Cells. Cold Spring Harbor, NY:Cold Spring Harbor Press, 1983:635-646. Thus, it is not surprising that the markers claimed in the '913 patent for primate (human) ES cells are identical to markers previously identified in primate (human) embryonal carcinoma (EC) cells, also known as teratocarcinomas. Table 1 ("Human EC"). In fact, it was entirely predicable that human/primate ES cells would possess the same markers as human/primate EC cells.

13. There is a wide variety in the developmental potential of human ES and EG cells, which is perhaps dependent upon the precise time that the rapidly developing embryo is placed in culture. Therefore, generation of a particular cell type, such as cells bearing markers of trophoblast, may vary from cell line to cell line. Thus, there is no a priori reason to assume that

human pluripotent stem cells isolated according to Hogan's teaching would be incapable of differentiating into trophoblast, or into any other specific cell type.

Robertson '83 and Robertson '87

14. I am familiar with Robertson, et al., "Isolation, Properties, and Karyotype Analysis of Pluripotential (EK) Cell Lines From Normal and Parthenogenetic Embryos," *Teratocarcinoma Stem Cells*, Cold Spring Harbor Laboratory, Cold Spring Harbor, volume 10, pp. 647-663 (1983) ("Robertson 1983") and Robertson, Elizabeth J., "Embryo-Derived Stem Cell Lines," *Teratocarcinomas and Embryonic Stem Cells; A Practical Approach*, Oxford: 1RL Press, Ch. 4:71-112 (1987) ("Robertson 1987"). I have reviewed Robertson 1983 and Robertson 1987 and specifically their teachings regarding the isolation of mammalian ES cells. I am also generally aware of Dr. Robertson's work, as she was among the first to isolate ES cells and I followed the methods provided in Robertson 1987 when I derived my new ES cell lines.

15. Robertson 1983 and Robertson 1987 each taught, in precise detail, a step-by-step process for deriving pluripotential mouse ES cells. The process detailed in Robertson 1983 and Robertson 1987 and the claims of the '913 patent differ only in that Robertson 1983 and Robertson 1987 isolated mouse ES cells while the '913 patent claims human ES cells. At the time the first application leading to the '913 patent was filed, one of ordinary skill in the art of ES cell derivation would have predicted that the process taught by Robertson 1983 and Robertson 1987 for isolating mouse ES cells could be used to isolate ES cells of other mammals, including humans as claimed in the '913 patent, with a reasonable expectation of success.

Piedrahita

16. I am also familiar with Piedrahita, et al., "On The Isolation Embryonic Stem Cells: Comparative Behavior Of Murine, Porcine And Ovine Embryos," *Theriogenology*, 34(5):879-901 (1990) ("Piedrahita"). I have reviewed Piedrahita and specifically its teaching regarding the isolation of ES cells for several different mammalian species.

17. Piedrahita taught a method of isolating murine, porcine and ovine ES cells. The only difference between Piedrahita and the claims of the '913 patent is that Piedrahita isolated murine, porcine and ovine ES cells while the '913 patent claims human ES cells. However, at the time the first application leading to the '913 patent was filed, one of ordinary skill in the art of ES cell derivation would have predicted that the process taught by Piedrahita for isolating murine, porcine and ovine ES cells could be used to isolate ES cells of other mammals, including humans as claimed in the '913 patent, with a reasonable expectation of success.

18. In January 1995, Piedrahita's disclosure was sufficient to enable one of ordinary skill in the art, with their general knowledge, common sense and creative ability, to derive and maintain human ES cells for an extended period of time without using LIF and without undue experimentation. This is true not only because of what Piedrahita taught, but also because an ordinary artisan in the field at the time would have had advanced Ph.D. and/or M.D. degrees in biology and significant related research experience, and, thus, would have used Piedrahita as a guide to be followed loosely, while trying various alternatives, not as a recipe requiring strict adherence to its exact teachings.

Robertson '83, Robertson '87 and Piedrahita

19. At the time the first application leading to the '913 patent was filed, one of ordinary skill in the art would have combined the teachings of Robertson 1983, Robertson 1987 and Piedrahita, as they each relate to the derivation of mammalian ES cells. Further, Robertson 1987 was written by the same author as Robertson 1983 and both Robertson 1987 and Piedrahita expressly cite Robertson 1983.

20. Robertson 1983, Robertson 1987 and Piedrahita combined teach virtually the same method for isolating ES cells of various mammalian species, including mouse, rodent, pig and sheep. The only difference between their combined teaching and the claims of the '913 patent is that they isolated mouse, murine, porcine and ovine ES cells while the '913 patent claims human ES cells. However, at the time the first application leading to the '913 patent was filed, one of ordinary skill in the art of ES cell derivation would have predicted that the process taught by Robertson 1983, Robertson 1987 and Piedrahita for isolating mouse, murine, porcine and ovine ES cells could be used to isolate ES cells of other mammals, including humans as claimed in the '913 patent, with a reasonable expectation of success.

The Work of Others

21. I am familiar with Brook and Gardner, 94 Proc. Natl. Acad. Sci. 5709-5712 (1997) ("Brook and Gardner"), and Brook et al., 52 Diabetes 205-208 (2003) ("Brook et al."). I have reviewed both Brook and Gardner and Brook et al. and their teachings regarding the isolation of mammalian ES cells. Brook and Gardner was successful at isolating mammalian ES cells and even

suggested that their approach could work for other mammals. Brook et al. admirably attempted to isolate highly germline competent ES cells carrying the NOD mutations, which is a more difficult task to perform than isolating wild type ES cells. Thus, neither Brook and Garner nor Brook et al. manifest a failure to isolate mammalian ES cells.

22. I am also familiar with Brenin et al., 29 Transplant Proc. 1761-1765 (1997) ("Brenin et al.") and Ouhibi et al., 40 Mol. Reprod. & Dev. 311-324 (1995) ("Ouhibi et al."). I have reviewed both Brenin et al. and Ouhibi et al. and their teachings regarding the isolation of mammalian ES cells. Both Ouhibi et al. and Brenin et al. showed success at deriving pluripotent cells from rat embryos. Neither Brenin et al. nor Ouhibi et al. manifest a failure to isolate mammalian ES cells. It should be noted that germ line transmission, a common test of pluripotence in mouse ES cell lines, cannot be used to test pluripotence in human ES cells. Thus, germ line transmission cannot be a requisite for defining cells from any species as pluripotent or as ES cells.

23. I am also familiar with Doetschman et al., 127 Dev. Biol. 224-27 (1988) ("Doetschman et al."). I have reviewed Doetschman et al. and its teaching regarding the isolation of mammalian ES cells. Doetschman et al. was successful at isolating hamster ES cell lines and maintaining them for a significant period of time. Thus, Doetschman et al. does not manifest a failure to isolate mammalian ES cells.

24. I am also familiar with Talbot et al., 42 Mol. Reprod. & Dev. 35-52 (1995) ("Talbot et al."). I have reviewed Talbot et al. and it is not directed to the isolation and maintenance of mammalian ES cells. Thus, Talbot et al. cannot be said to manifest a failure to isolate and maintain

mammalian ES cells, when it didn't attempt to do so.

25. Although I had the scientific capability to isolate and culture human ES cells well before January 1995, I personally was unable to do so until 1998 because I did not have access to human embryos or the funding needed to pursue such work. I believe that many fellow scientists also had the scientific knowhow at that time, but similarly were prevented from doing so because of the difficulty with obtaining those necessary resources.

In Closing

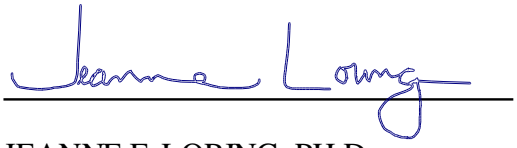
26. Dr. Thomson deserved the recognition he received for his work relating to human embryonic stem cells because he was able to get the human embryos and financial support needed for such work. He did not, however, make a scientific advance that was surprising to those of us with skill in the art. It was his ability to secure those extremely limited resources that provided him the ability to achieve his accomplishment. Had I or any other stem cell scientist been given human embryos and sufficient funding, we could have made the same accomplishment, because the science required to isolate and maintain human embryonic stem cells was obvious at the time.

27. I have not been compensated by either the Foundation for Taxpayer and Consumer Rights, the Public Patent Foundation or any other party in exchange for this declaration, nor do I have any financial interest in the outcome of the reexamination of U.S. Patent No. 7,029,913.

28. I declare that all statements made herein of my own knowledge are true and that all statements made herein on information are believed to be true. I further declare that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment or both under Section 1001, Title 18 of the United States Code.

June 28, 2007

Date



JEANNE F. LORING, PH.D.

EXHIBIT 1

CURRICULUM VITAE