United States Stem Cells Research Boundaries

By

Benoît Elichabe

SUBMITTED TO THE DEPARTMENT OF MIT SLOAN SCHOOL OF MANAGEMENT IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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AT THE
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Signature of the author: _____
MIT Sloan School of Management
May 11, 2007

Certified by: _____
Fiona Murray
Associate Professor
Management of Technology, Innovation and Entrepreneurship
MIT Sloan School of Management
May 11, 2007

Accepted by: _____
Debbie Berechman
Executive Director
MIT Sloan School of Management
May 11, 2007

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ABSTRACT

Recent empirical work has demonstrated the importance of a number of elements of scientific infrastructure that seem to be crucial particularly in fields such as molecular and cellular biology in which the materiality of research renders the process of replication and validation more complex. Scientific infrastructure has many interconnecting elements such as the ability to exchange material used in experiments, the ability to share ideas and information and the ability to share, exchange and promote the mobility of researchers.

We focus our investigation on stem cell research in the United States (US). Research in human developmental biology has led to the discovery of human stem cells. The science of stem cell therapies is about to enter a phase of research and development that could lead to unprecedented cures and palliative treatments. However, it is a highly regulated field of research and it raises an important amount of moral, religious and ethical concerns. We seek to examine the boundaries that have emerged in the US in this particular field and we try to understand their impact on the US market of fertilized eggs, embryos and human embryonic stem cells.

Thesis Supervisor: Fiona Murray
Title: Associate Professor
Management of Technology, Innovation and Entrepreneurship
MIT Sloan School of Management

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1. INTRODUCTION

Advances in biological sciences and the recent development of human embryonic stem cells (hESC) research are pushing the limit of science and expending the scope of medicine.

hESC are human cells that have the potential capability to differentiate into any human cells. This cell pluripotency is for the researchers a fantastic research tool to explore how early human cells become committed to the major lineages of the body, and how early cells differentiate to form a vast panel of the functional cells which ultimately aggregate into functional organs in the human being. The use of stem cells not only creates a new window on human developmental biology, but is also of great importance in medicine.

Indeed, several models of human diseases are still constrained by current animal models or by a lack of appropriate *in vitro* cell models. Because of their characteristics and potential, their scientific and medical potential is so huge these cells are therefore raising new expectations and bringing new hope for the development of innovative treatments for devastating diseases such as Parkinson, Alzheimer, cardiovascular diseases, cancers etc… even though such cellular treatments are far from being developed.

But in the meantime, since human embryonic stem cells are derived from the human embryo' cells, this research requires strong ethical considerations and raises religious and moral concerns.

One big concern lays on the history of stem cell research in the US, which is singular. One of the pioneers in this field of investigation was Professor Thomson, a developmental biologist at the University of Wisconsin.
Moreover, the fundamental nature of this research and the huge impact that the applications of stem cells can have in medicine put this field at risk for a potential anti-common effect. In addition, the breadth of the stem cells patents and the greediness of

their holder are a source of intense debate in the scientific community. As a consequence, the US government has set up strict regulations and restrictions around hESC research.

All these restrictions might have prevented stem cell lines material flows among scientists and between women or organization that wish to participate in providing the inputs into hESC research and scientists. In this work, we would like to highlight these boundaries that have emerged in the United States in the past decades.

The present work tries to give an overview of the current situation of stem cells in the US. We have found indeed that the literature on stem cells was fragmented and we have tried to assemble together one of the first synthetic documents on that field. Second, we have tried to understand which boundaries specifically emerged in stem cell research in the US and we tried to show their impact of stem cell researchers, both in the private and the public sector. Last, the present document mentions the premises of an on-going project that could lead to interesting discoveries. We have designed and started to selectively administrate a survey to stem cells researchers in order to understand the supply and the demand of the stem cell industry, and to evaluate the important of data withholding in stem cell research.

The document starts with a brief overview of the biology and the history of hESC. We try then to define the regulatory scope of that field of investigation as well as the intellectual property boundaries as their consequence. We review the process and the limit of the fertilized eggs donation, we brushes briefly the moral, ethical and religious questions that research on embryonic cells raise and we try to evaluate the impact of all these boundaries on the researchers and ultimately on the stem cell market. Last, we briefly mention our survey design and method and we conclude with some recommendations.

2. HUMAN EMBRYONIC STEM CELLS OVERVIEW

Definition

Human stem cells are specific cells present in almost all the organs of all human beings. We define and describe these cells by their functional attributes. As **Table 2.1** summarizes, stem cells are:

(a) Undifferentiated cells (lacking of tissue specific differentiation markers),

(b) Capable of proliferation,

(c) Capable of self-maintenance,

(d) Able to produce a large number of differentiated and functional progenies,

(e) Able to regenerate the tissue in which they are after an injury.

(f) Stem cells have flexibility in the use of all the options previously described.

Table 2.1. Stem cell criteria[1].

	Stem cells	Maturing cells
(a) Differentiation marker	No	Yes
(b) Capable of proliferation	Yes	No
(c) Capable of self-maintenance	Yes	No
(d) Capable of many progeny cells	Yes	No
(e) Capable of regenerating tissues after injury	Yes (long term)	No
(f) Flexibility in options	(b) – (e)	No

Ideally, a stem cell satisfies all these criteria but in practice researchers observe some experimental limitations such as the observation of quiescent stem cells that don't proliferate. However, three characteristics are widely identified by researchers as the strongest markers for identifying stem cells:

(1) Self-maintenance and the ability to vary self-maintenance,

(2) The ability to produce a large family of differentiated functional cells, and

(3) The ability to regenerate the tissue or elements of it.

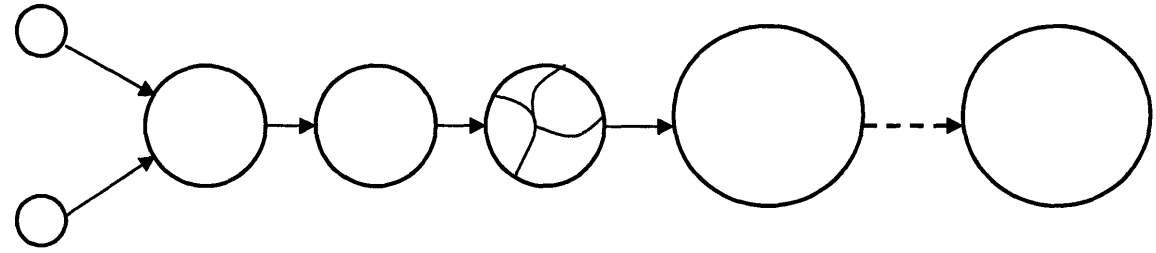
Therefore, when a cell has these three attributes, it is qualified as a stem cell. Based on this definition, the ultimate stem cell is therefore the fertilized egg. Formed from the

fusion of the female and male gametes, the fertilized egg is the single cell at the origin of an organism's life. It divides five to six times to give rise to cells lines that will in turn divide and form subsequently our various differentiated organs. At the beginning of this division process, each cell retains totipotency, that is, they all have the capability after several divisions and differentiation to form any cell line. Along this differentiation process, the cells lose their totipotency and are just left with multi- or pluripotency. The degree of plasticity that has a stem cell to form one or several cell lines is thus used to characterize the potency of stem cells. **Table 2.2** summarizes the common terminology of stem cells plasticity and **figure 2.1** shows the early development of the embryo from the fertilized egg.

Table 2.2. Stem cell plasticity[2].

Prefix	Plasticity	Cells example
Toti	All	Embryonic (early embryo)
Pluri	Several/Many	From blastocysts
Multi	Many/Much	From fetal tissue, blood cord and adult stem cells

Figure 2.1. Early development of the embryo[2]



Different stem cell types

Embryonic stem cells (ESCs)

ESCs come from a five- to six-day-old embryo, or blastocyst, and are pluripotent. Their first isolation was done by Cole and Edwards[3] in 1967 from pre-implantation blastocysts of rabbits. The first isolation of ESCs from the mouse was reported independently in 1981 by Evans and Kaufman[4] and Martin[5]. From there, it took almost 20 years for researchers to report the first isolation of pluripotent cells from human blastocysts: the breakthrough was done by James Thomson from the University of Wisconsin in 1998[6].

Germinal stem cells

Early in embryogenesis, a few cells are designated to become germinal cells; they migrate to the genital ridge (the primitive gonad) and are precursors of female or male gametes. These cells are totipotent but with little capacity of proliferation.

Somatic stem cells (or adult stem cells)

The cells of normal adult organs are continually being replaced by stem cells that live *in situ*, in the tissue they belong. These stem cells are spread out among the other differentiated cells in almost all our tissues or organs. They have little ability to produce different types of cells and little capacity of self-renewal[7]. Somatic or adult stem cells are known to be multipotent.

We will refer most of the time in our work to pluripotent Embryonic Stem Cells (ESCs).

3. A BRIEF HISTORY OF HUMAN EMBRYONIC STEM CELLS RESEARCH

The history of stem cell research includes work with both animal and human stem cells. At the beginning of the XXth century, the first stem cells were discovered when researchers found that some cells generated blood cells. Researchers then started to evaluate therapeutic application of these cells. One of them was bone marrow transplant from one human to another, since bone marrow contains a lot of adult stem cells. After several unsuccessful attempts, the reason of their failure was discovered in 1958 by Jean Dausset who identified the first human histocompatibility antigens. These proteins, on the surface of most cells, are called human leukocyte antigens, or HLA antigens, and are cell markers that give the immune system the ability to determine what belongs to the body. After this breakthrough, physicians succeeded in the 1960's to perform transplants between identical twins (with same HLA), then between non identical twins and in 1973 a team of physicians performed the first unrelated bone marrow transplant: stem cells entered then officially into medicine as a therapeutic tool.

Meanwhile, cellular research continued to progress and embryonic stem cells were isolated in 1967 from rabbit blastocysts and in 1981 from mouse blastocysts. At that time of the initial derivation of mouse ESCs, only few laboratories in the world had the expertise required to work with mouse embryos or simply with stem cells. But slightly later, in the 80's, the first knock-out mice from the homologous recombination of mouse ESCs was reported. The huge implications of this discovery opened ESCs interest to non-embryology specialists and drew very strong attention in mouse ESCs research among the scientific community.

Agencies started to fund ESC research and so did National Institutes of Health (NIH) in the US. Innovative projects spawned and developmental biology advanced quickly when in 1998 Professor James Thompson, from the University of Wisconsin and with federal funding, isolated primate stem cells from the inner cell mass of early embryos, and developed the first primate embryonic stem cell line. In the same year, John Gearhart from, the Johns Hopkins University, derived germ cells from cells in the fetal Gonadal tissue (primordial germ cells)[8].

Pluripotent stem cell "lines" were subsequently derived and developed from both sources. With them new hope emerged for the discovery of new types of treatment for various still unmet medical needs in diseases such as Parkinson, Diabetes, and Cancer, among others. Along with hope rose expectation not only from the scientific community but also from the population: stem cell research was to become a hot scientific and societal topic.

4. THE US hESC RESEARCH REGULATION

Introduction

hESC research requires by definition access to hESC lines. With the present technologies, the creation of a hESC line is derived from the blastocyst and requires therefore the destruction of a human embryo. But since the status of the human embryo is complex, hESC research raises controversial issues. Therefore, to circumvent any problems, most stem cell researchers use embryos that were created but not used in *in vitro* fertility (IVF) treatments to derive their stem cell lines.

As a consequence, the current infrastructure of the US stem cell research has its roots in the US IVF history and is regulated by the "human being protection" regulations.

This situation will remain true until a major technology breakthrough arises and permits the derivation of hESC without destroying the human embryo. For instance, researchers at Advanced Cell Technology (Worcester, MA) succeeded recently in obtaining a derivation of a hESC line using a process similar to preimplantation genetic diagnosis, in which a single blastomere is extracted from the blastocyst. Thus, since this technique does not interfere with the embryo's developmental potential, it would allow deriving hESC lines without killing human embryos[9], if its reliability were sufficient, which is not the case yet. One can hope that technological innovation will change the paradigm in stem cell research and will solve many of the issues surrounding this field.

Federal legislation of embryo research

De facto moratorium

Since the blastocysts used for human stem cell research typically come from IVF procedures, the hESC research regulation is closely linked to IVF regulation.

Due to the increasing number of IVF procedures in the 70's, the Department of Health and Human Services (DHHS) were at that time concerned by the moral implication and the safety of this new technique. It then created an Ethics Advisory Board (EAB) to evaluate the social, legal and ethical issues of human IVF and to review all applications for federal funding for research involving human IVF. On April 4, 1979, the EAB reported that such research was ethically acceptable but subject to several important requirements such as the informed consent of gametes donors. But as early as 1980, the EAB was disbanded before even having the time to give any approval for federal funding. Since EAB opinion was needed for federal funding, it created a *de facto moratorium* on federal funding for IVF research and other studies of early human embryos.

This situation pertained for more than a decade, until March 1993, when the Congress passed the National Institutes of Health Revitalization Act of 1993 that enacted in June 10 of the same year the authorization given by the 103rd Congress and the President Bill Clinton to support human embryo research. This law[10] ended the *de facto moratorium.*

An Advisory Board known as the Human Embryo Research Panel (HERP) was then created to establish which standards and requirements human embryo research projects should meet to trigger federal funding. The HERP identified several possible research areas among which was the derivation of stem cells from human embryos, as long as the embryos were donated with the full informed consent of the gametes donors. The field was then opened for federal funding, but in December 1994 President Clinton ordered to NIH to not allocate resources to "support the creation of human embryos for research purposes".

The "Dickey-Wicker Amendment"

Based on this statement, the NIH concluded that it could begin to fund hESC research on spare embryos coming from infertility treatment at IVF clinics without breaking President Clinton's rule. Project applications for federal funding then started to reach NIH but before it had time to release any funding decision, NIH was halted again, on January 26, 1996, with the enactment by the Congress of P.L. 104-99 that prohibited NIH from using funds during the financial year of 1996 for human embryo research. One can read[11]: "(a) None of the funds made available in this Act may be used for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term "*human embryo or embryos*" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells".

This ban, often referred as the "Dickey-Wicker Amendment" has been retained in each successive annual appropriation bill. As a consequence, because the derivation of stem cells from a blastocyst destroys the embryo, no public funding could be provided until further notice for human embryonic stem cell research in the United States.

Meanwhile, Professor Thomson published in Science[12] in November 1998 a major scientific discovery. After having derived *primate* stem cells with government funding that was allocated to his team starting 1995, he pursued research with private funds on *human* stem cells, which he was able to derive in 1998. Because of the great potential promised by this hESC derivation, NIH sought legal counsel from DHHS and in January 1999, DHHS concluded that scientists could use public funds for research on hESCs as long as the derivation of the cells was carried out with private funds. NIH thus began drafting guidelines governing funding for hESC studies, which it realized in December of

1999[13], allowing *de facto* federally funded research on hESCs derived in the private sector.

However, the guidelines allowed research on cells derived only from embryos leftover from fertility treatments and donated with the consent of the progenitors. In addition, if a fertility clinic were to profit from the sale of embryos used for stem cell derivation, research on those cells would not be allowed. After reviewing a lot of comments, NIH released its final guidelines[14] on August 25, 2000 and solicited applications for its first hESC research grants. The agency received several grant applications and established a committee to review the proposals.

The Bush Administration Policy

Researchers on stem cells could finally not benefit from this new regulation since just after his election, President George W. Bush finally explicitly stated on August 09, 2001 how the Federal Government would encourage stem cell research without inviting ethical abuses. "*First, we can encourage research on stem cells removed from sources other than embryos: adult cells, umbilical cords and human placentas. Many researchers see great potential in these cells -- and they have already been used to develop several new therapies. Second, we can encourage research on embryonic stem cell lines that already exist. These cells can reproduce themselves in the laboratory, perhaps indefinitely. Stem cell lines at the University of Wisconsin have been producing cells for over two years. More than 60 of these cell lines now exist around the world. According to the National Institutes of Health these lines are genetically diverse and sufficient in number for the research ahead*" [15].

The President thus decided that for a cell line already in existence, research would be permitted because destruction of an embryo had already taken place, but he refused to allow publicly funded research on any cell lines created in the future thus preventing the federal government from acting in a way that would encourage the destruction of human embryos.

On August 27, 2001, NIH released a statement listing the ten entities that had already created stem cell lines eligible for federal funding. It announced as well plans to create the Human Embryonic Stem Cell Registry, which was launched on November 7, 2001 and which would contain more detailed information about the hESC lines eligible for federally funded research.[16]

Among approximately the 200 human embryonic stem cell lines currently available in the world (out of over 400 identified), only less than 80 meet the President's criteria and are produced and provided by the following entities:

Table 4.1. Human Embryonic Stem Cells that meet the eligibility criteria for federal funding[20].

Institutions	Derivations	Available lines
BresaGen, Inc., Athens, Georgia	4	3
Pochon CHA University, Seoul, Korea	2	0
Cellartis AB, Göteborg, Sweden	3	2
CyThera, Inc., San Diego, California	9	0
ES Cell International Pte Ld, Singapore	6	6
Geron Corporation, Menlo Park, California	7	0
Karolinska Institute, Stockholm, Sweden	6	0
Maria Biotech Co, Ltd, Seoul, Korea	3	0
MizMedi Hospital, Seoul Korea	1	0
National Center for Biological Sciences, Bangalore, India	3	0
Reliance Life Sciences, Mumbai, India	7	0
Technion-Israel Institute of Technology, Haifa, Israel	4	3
University of California, San Francisco, California	2	2
Göteborg University, Göteborg, Sweden	16	0
WARF, Madison, Wisconsin	5	5
Total	78	21

Note: Novocell has merged with CyThera and BresaGen in 2004.

In addition to announcing that federal funding would be available only for research on existing stem cell lines at the time of his speech, President Bush announced his opposition to funding research on stem cell lines derived from embryos that were deliberately and solely made for research purposes, whether by IVF or by somatic cell nuclear transfer (SCNT) despite strong disapproval from the scientific community; therefore, such research is legal in the US but ineligible for Government funding.

The Common Rule, March 19, 2002[21, 22]

The Common Rule describes when research activities involving hESCs, human embryonic germ cells derived from fetal tissue, or hESC- or germ cell-derived test articles are considered human subjects research and what regulatory controls apply to that research. These regulations are currently governing research on human beings in the US and have been accepted by most of the Federal Agencies (**see Appendix A**).

The Common Rule comprises notably subpart A of the DHHS regulations and requires the establishment of Institutional Review Boards (IRBs) to approve all federal funded human subject research involving the cells or test articles described above.
The rule defines especially the Human Subjects as a "living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." (45 CFR 46.102[f]).
Moreover, it defines "Research" as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR 46.102[d]).

The subpart B of the DHHS regulations contains more specific provisions application to federal grants and research that involve pregnant women, the fetus and human IVF. But the specific human blastocyst stage of the fetus development is not described. This unclear blastocyst status doesn't address the complex issues raised by hESC research making it controversial. For example, the case of a human blastocyst created in vitro and

used to derive hESCs, doesn't meet the administrative definition of the fetus which is defined as "*the product of conception from the time of implantation*".

This slack or flexibility in the federal policies governing embryonic stem cell research has an immediate regulatory impact at the State level: we observe indeed a strong inter-state variability.

The US inter-state variability in hESC research regulatory

Professor Spar, from Harvard Business School, observes that the US government has been reluctant to constrain high-growth, high-technology markets and industries[17]. This might be one of reasons that explain the lack of US national policy for hESC research. As a matter of fact, the interstate variability is huge. Table 4.2 segments the States into three categories according to their acceptance of hESC research (**see Appendix B** for specific details).

Table 4.2. Stem cell regulation in the US by State, as of January 2007[18, 19].

Encouraged (11)	No action taken (21)	Restricted (19)
CA, CO, CT, HI, IL, IN MA, MD, NJ, NY, VA.	AK, AL, DC, DE, FL, GA, ID, KS, KY, MO, MS, NC, NV, OR, SC, TX, VT, WA, WI, WV, WY.	AR, AZ, IA, LA, ME, MI, MN, MT, ND, NE, NH, NM, OH, OK, PA, RI, SD, TN, UT.

Following the Guidelines for hESC Research released in May 2005 by The Committee on Guidelines for Human Embryonic Stem Cell Research, institutions conducting hESC research were proposed to set up Embryonic Stem Cell Research Oversight (ESCRO) committees, in order to strengthen federal oversight on stem cell research.

As a result, the implementation of such guidelines by the Sates gave rise to local ESCROs in the States where stem cell research is allowed. ESCRO committees include representative of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hESC research. They are meant to provide an additional level of review and scrutiny and to help investigators in assessing which regulations might apply to proposed research activities, complementing IRBs activity.

5. THE INTELLECTUAL PROPERTY RIGHTS OF STEM CELLS

The path to HESC US Patents

As we have described above, hESC research derives from previous stem cell research done on primates and until 2001 it wasn't eligible for federal funding. However, NIH did granted funds for ESC research done on primate. As mentioned previously, one of the pioneers in that field is Professor James Thomson, from the University of Wisconsin. Professor Thomson reported in August 1995 the first isolation of embryonic stem cell lines obtained from the derivation of a cloned cell line from a rhesus monkey (Macaca mulatta) blastocyst that remained undifferentiated in continuous passage for over 1 year[23]. This work on non-human primate was subsequently further extended to the common marmoset (Callithrix jacchus) [24, 25], still with federal funding.

To apply his discovery to *human* embryonic stem cells, Professor Thomson had to look for private funding. He signed a sponsor agreement with Geron Corporation (Menlo Park, California) at the beginning of 1996[26] (**see Appendix I**) and he reported in his 1998 Science article published later that year the first successful isolation of hESC lines.

Even though prior to James Thomson, derivation of primate embryonic stem cells was described by Bongso et al.[27], their cells were not stable in long-term culture. Professor Thomson was in fact the first to describe successful primate stem cells derivation and *in vitro* primate stem cell culture that is *stable for longer than one year*.

He consequently filled two key patents (**see Appendix C**) in order to protect:

◊ His method of stem cells isolation,

◊ The definition of the characteristics of the primate ES cells (morphology, cell surface markers, development potential (pluripotency), karyotype, immortality, culture conditions, and differentiation to extra embryonic tissues).

His first patent was on *Primate* ESCs, the second on *Human* ESCs. He was also granted in April 2006 a third patent[43] on hESC that describes the preparation and the replication

of in vitro human embryonic stem cells culture, but it doesn't have the impact of these first two patens.

The Professor Thomson's Patents

354 US patents have "stem cells" in their title (including 74 that are specific to human), 817 patents contain "stem cells" in their abstract (from which 263 are specific to human) and 1,539 patents have an application on stem cells (including 697 on human). These several hundreds patents that regulate the US stem cell research cover a wide range of scope and content such as[28]:

(i) Isolated stem cells,

(ii) Methods of isolating stem cells,

(iii) Methods of cultivating stem cells,

(iv) Methods of differentiating stem cells,

(v) Therapeutic methods, and

(vi) Methods of administering stem cells.

But among all of them, the two first Thomson's patents are the most important patents because of their exceptional broad scope of coverage.

The US Patent number 5,843,780[29]

The first patent filled in January 18, 1996 and granted in December 1, 1998, claims on a purified preparation of primate ESCs and possesses already the broadest claim.

We can read: "We 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) (ii) maintains a karyotype in which all the chromosomes characteristic of the primate species are present and not noticeably altered through prolonged culture,

(iii) (iii) maintains the potential to differentiate into derivatives of endoderm, mesoderm and ectoderm tissues throughout the culture, and

(iv) (iv) will not differentiate when cultured on a fibroblast feeder layer."

The claim 9 can be read as follow: "9. A method of isolating a primate embryonic stem cell line, comprising the steps of..."

The choice of the word "primate" is clever and includes *de facto* the human beings.

The US Patent number 6,200,806[30]

The second patent was filled in June 26, 1998 and was granted in March 13, 2001. It claims an extension of the first patent on primate embryonic stem cells specifically to *human* embryonic stem cells.

We can read in claim 1 and 9 respectively: "1. A purified preparation of *pluripotent human* embryonic stem cells which

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

(ii) (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture,

(iii) (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and

(iv) (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer."

And the claim 9 can be read as follow: "9. A method of isolating a *pluripotent human* embryonic stem cell line, comprising the steps of..."

Thomson's primate ESC patents' coverage

Based on these patent claims, all hESCs that can live in culture for over one year, maintain the regular (euploid) number of chromosomes for the human species, and retain the pluripotent capacity to differentiate into any type of tissues are protected by IP laws. This is the case for potentially all the hESCs of significant research value. Therefore, the access to both the hESC lines and the method to prepare them is "locked" by Professor Thomson's patents.

6. THE ANTI-COMMONS POTENTIAL NATURE OF HESC RESEARCH

Dual knowledge and anticommons effect

hESCs provide a unique and important tool to study both the early human development and the mechanism of cell differentiation that leads to tissue formation. Besides their application in developmental biology, stem cells have the potential to be used in medicine to treat several unmet needs. As a consequence, the control of hESC by Professor Thomson has both a tremendous basic and applied value.

The distinction between upstream and downstream research application is a key concept in the patent field. Traditional patent law is predicated on a scheme in which innovators apply freely available upstream knowledge to develop patentable downstream technologies or products. Therefore, usually patent law denies patents on fundamental elements such as basic knowledge and creates exclusive property rights that encourage innovators to produce new technologies: it is the Common Law Prohibition Against Patenting Natural Laws, Natural Phenomena, and Abstracts Principles[33].

While one can argue that stem cells should have been protected by the Common Law since it is a fundamental basic knowledge that belongs to the Humanity, the patents granted to the Professor Thomson by the US PTO are still valid (even though currently challenged) and their scope is so broad that his holder can potentially exclude follow-on researchers from exploiting scientific discoveries on stem cells and stem cells-derived applications.

This phenomenon can result in an underuse of stem cells, which one can consider a public commons source of knowledge; this is known as the anticommons effect[57], which potentially can hinder the future knowledge production and cumulative innovation[58] in stem cells and all their related scientific applications and interactions. How Professor Thomson did to establish such an unprecedented control?

Professor Thomson, WARF and the negotiation with NIH

WARF and WiCell

Professor Thomson leveraged resources he had at his university. In fact, it is officially the Wisconsin Alumni Research Foundation (WARF) that owns the patents granted to Professor Thomson. WARF is a nonstock, nonprofit technology transfer office of the University of Wisconsin-Madison. It is a significant source of research support, independent of federal grants, that was founded in 1925 and has since supported scientific research at the University of Wisconsin-Madison by patenting the discoveries arising from the UW-Madison researchers, licensing the technologies to companies from commercialization and returning the licensing income to the UW-Madison to support future scientific endeavor. The proceeds are used to fund research, build facilities, purchase lands and equipment, and support faculties and graduate student fellowships each year, but WARF claims that it plays no role in determining how these dollars are distributed[31].

Professor Thomson assigned his stem cells patents to WARF and following the first one, the Foundation established in October 1999 the WiCell Research Institute, a UW Research Park-based non-profit subsidiary devoted to advance the science of stem cells. As one can read on WiCell website, *WiCell organization is focused on enhancing and expanding the study of human embryonic stem cells by generating fundamental knowledge, establishing research protocols, providing cell lines, research tools and training to scientists worldwide, and supporting efforts to unlock the therapeutic potential of this seminal scientific field*[32]. Professor Thomson was then appointed as WiCell's scientific director and pursued in parallel his research. Since October 2005, WiCell hosts the National Stem Cell Bank.

WARF and Geron Corporation (Menlo-Park, CA)

As we described above, Professor Thomson's research on human embryonic stem cells was privately funded by Geron Coporation in exchange of exclusive license rights of the patents' applications. A first agreement between WARF and Geron was done in 1995 on

the material described in the U.S. application Serial Number 08/376,327 filled January 20, 1995. This first patent application was later abandoned and used as a continuation-in-part for the patent applications numbers 08/591,246, 09/106,390 and 09/982,637 that led to the grant of the patents numbers 5,843,780, 6,200,806 and 7,029,913 we have described.

In this first agreement, number 95-0208, WARF granted to Geron a nonexclusive license, limited to the Licensed Field and the Licensed Territory, under the Licensed Patents to make, use and sell Therapeutic Products and Diagnostic Products collectively. The agreement gave Geron as well an option to expand the field of use to include these products for non-primate, including non-human[26].

Therefore, WARF granted in 1995 and 1996 to Geron the commercial exploitation of its coming primate stem cell patents. In exchange, Geron paid upfront fees, annual (and renewable) exclusivity fees, and committed itself to finance Professor Thomson's research for the next two years, until January 01, 1998.

Enters NIH in the negotiation

Since patent protection covers a period of 20 years, WARF has the legal right until 2015 to exclude everyone else in the US from making, using, selling, offering for sale, or importing a hESC covered by the claims without its permission[33].

In order to minimize a potential anticommons tragedy and to facilitate academic researchers an upstream access to stem cell research, the US Public Health Service negotiated with WARF a Memorandum of Agreement[34] (MOU) that was first signed in September 2001 (**see Appendixes D1 and D2**) and which sets up a zone of relatively free access to hESC lines for use in noncommercial reseach[35] and facilitate the dissemination of scientific materials among researchers by means of Material Transfer Agreements (MTA)[58]. To reach such agreement, the NIH leveraged the fact that it had previously sponsored research at Wisconsin on primate stem cell that led to the first patent granted in 1998 to WARF on primate embryonic stem cells. In fact, even though under the Bayh-

Dole Act of 1980 Wisconsin University owns the patents[36], the government retains certain rights, including a retained license to use the invention for government purposes[37] and "march-in rights" to oblige the granting of licenses to applicants on reasonable terms if necessary to achieve practical application of the inventions[33, 38]. Even though the NIH did not formally use these rights in its negotiation with WARF, the possibility that the federal agency could invoke these right has strengthened its bargaining position and in the end, this MOU gives researchers employed by the NIH, the Food and Drug Administration (FDA), and the Center for Disease Control and Prevention (CDCP) a license to use hESC lines for research at nearly marginal cost.

Development of MOUs

Other MOUs involving MTAs have been signed between the NIH and stem cell lines providers, under the respect of the patents owned by WARF. Generally speaking, the licensing agreements between WARF and researchers depend mostly on the type of research conducted and its application. For upstream and noncommercial research, MOUs apply, whereas for downstream research and development agreements, researchers need to sign a commercial licensing agreement with WARF. In that perspective, since WARF is a private and not for profit organization, it can offer its licensees confidentiality, which can be a competitive advantage when dealing with new product and process development issues[39].

7. EGGS' DONATION REGULATION AND ACCESS BOUNDARIES

SOURCES OF EMBRYOS USED FOR STEM CELL RESEARCH

The main sources of fertilized eggs used in stem cell research are the spare fertilized eggs from fertility clinics. Infertility is a very common condition among couples in a reproductive age, with a prevalence rate in the US of approximately 13-15%[44, 59].

The emergence of Assisted Reproductive Technology (ART) more than 20 years ago has enabled many couples to overcome fertility problems. ART refers not only to IVF but also to several variations of techniques tailored to patients' unique conditions such as the IntraCytoplasmic Sperm Injection (ICSI), the Gamete IntraFallopian Transfer (GIFT), the Zygote IntraFallopian Transfer (ZIFT), etc... In general, these procedures are associated with fertility treatment using drugs in order to increase success rates.

In 2004, 127,977 cycles were performed in the US in 411 fertility clinics. They resulted in 36,760 live births and 49,458 infants[45]. Such ART procedures can involve gametes from the couples themselves or from egg donors. In the US, around three quarters of ART procedures use fresh, fertilized embryos from the patients' own oocytes; around 14 percent used defrosted embryos from the patients' oocytes; around 8 percent used fresh, fertilized embryos from donor oocytes; and around 3 percent used defrosted embryos from donor oocytes.

Typically, protocols for stimulating the development of multiple ovarian follicles involve daily subcutaneous hormone injections over a period of 7 to 10 days[46]. Due to the ovarian hyperstimulation, various ART procedures result in the production of more embryos than are needed for fertilization. In IVF practices, transfer of more then three embryos per cycle increases risks for the mother and the offspring. As a result, "unneeded" embryos accumulate as far as the fertility treatment continues. In average, there is a "stock" accumulation of four frozen embryos per cycle and it was estimated in 2003 that more than 400,000 embryos were stored in the United. Even though the vast majority (88.2%) of these embryos are targeted for patient use[47, 48], once a couple decides to terminate the fertility treatment, for whatever reason, they have notably the option to donate the embryos for research purposes[48].

If a couple decides to do so, then there are several Federal requirements that rule the process in order to ensure that the couple is informed of the consequences of the donation, is doing it voluntarily and without inducements.

WHO CAN BECOME AN EGG DONOR?

Rules are States specific but some criteria are standard across the country, where egg donation is allowed. Not all women can donate eggs though. Commonly, egg donors must be of a certain age. The lower limit is usually set at 21 years old, to ensure that a woman can legally enter into a contract. Women cannot be no more than 35, this age reflecting the fact that older women respond less well to fertility drug treatments and that there is an increased risk for them to develop abnormal eggs, which would make pregnancy less likely or would eventually increase the risk of birth defect.

There is a selection process to donate an egg. An egg donor is required to undergo medical and psychological screenings. Before the screening, fertility clinic staffs should describe in depth the procedures and risks involved in the donation. After the screening, a written informed consent is required as we will see in the next section and potential donors usually have access to the results of their medical tests, whether or not they become a donor in the end.

First, egg donors undergo a general medical screening with a physical examination, including a blood check in order to measure the hormone levels, and an ultrasound exam of the uterus, ovaries and other pelvic organs. Then egg donors need to complete a detailed medical and psychological history about themselves and their close blood relatives. Some programs refuse at this stage smokers, people who drink alcohol or who are using both prescription and illegal drugs (some programs conduct unannounced drug tests during the screening and donation process). The next step is an infectious disease screening in order to minimize the risk that a donor egg could cause illness in the recipient. Are tested gonorrhea, Chlamydia, syphilis, hepatitis B and C, HTLV-1 and HIV. Last is a screening for inherited diseases where a check for donor's genetic disorder is conducted.

The last test is a psychological screening to make sure that egg donors will have no regrets or psychological problems, or find the procedures not traumatic.

The American Society for Reproductive Medicine suggests that a woman should not donate eggs if she:

- ✓ Has a serious psychological disorder,
- ✓ Abuses drugs or alcohol or has several relatives who do,
- ✓ Currently uses psychoactive medications,
- ✓ Has significant stress in her life,
- ✓ Is in an unstable marriage or relationship,
- ✓ Has been physically or sexually abused and not received professional treatment,
- ✓ Is not mentally capable of understanding or participating in the process.

Once potential egg donors have gone through the screening process and have fulfilled all the conditions, they can sign an informed consent if they want to donate their egg. It is widely accepted that, whenever possible, donors' decisions to dispose their blastocysts should be made *separately* from their decisions to donate them for research. Potential donors should be allowed to provide blastocysts for research only if they have decided to have those blastocysts discarded instead of donating them to another couple or storing them.

EGGS ACCESS FOR RESEARCH

Regulations

Ethical principles order that potential donors for hESCs research should make voluntary and informed choices about whether and how to donate their materials for research. Moreover, they should be proposed a clear option of "informed refusal", that is, the right to preclude any research use of embryos.

In order to assure that the procedure is done without possible coercion or exploitation of potential donors, an IRB review the consent process and ensure adherence to all Federal, State, local, and institutional regulations concerning the protection of human subjects in research. However, when hESCs research "*involves neither interactions nor interventions with living individuals or obtaining identifiable private information is not considered human subjects research [and therefore] IRB review is not required for such research*"[49].

Moreover, IRBs are permitted to waive the informed consent form if certain conditions of safety are met[50], for instance, when research is of minimal risk.

In addition to this Federal oversight, FDA regulations are considered as well when researchers aim at commercializing a product derived from the donated eggs. Under FDA regulations, there is a need to retain identifying information about the donors. If hESC lines obtained from donated materials are maintained for example with tracking codes, which might be a FDA requirement for clinical research, such research could then transforms donors into "research subjects" since study of the tissue could reveal information about them (unless the information is coded to be unidentifiable by the investigator).

The donor's voluntary and informed consent

Prospective donors should receive timely, relevant, and appropriate information to make informed and voluntary choices (**see Appendix E** for NIH informed consent guideline). As we have mentioned above, before considering the potential research use of the blastocysts, a prospective donor should have been presented with the option of storing the embryos, donating them to another woman or couple, donating them to research, or discarding them.

Some basic elements of information must be provided to prospective donors and be readily accessible during the informed consent process. Among these elements are:

- ✓ The risks involved, if any,
- ✓ All available options concerning the care and disposition of their embryos (including freezing for later use, donation to others for reproductive use, research use, or discard without research use),
- ✓ The variety of future research uses before giving consent to donate blastocysts for research.

Some infertility programs provide patients with multiple consent forms at the outset of treatment, forms that include options to donate to research, discard, or transfer any embryos that remain.

Terms of the eggs donation and donor's compensation

In the US, egg donors are legally compensated. Most fertility programs offer payment to egg donors for their time, effort and discomfort. Egg donors are required to sign one or more contracts with the fertility clinic they have chosen. These contracts bind legally the donors to their responsibilities and take place after the informed consent process. If the donation results in the birth of a baby, State legislations require the fertility clinic to keep certain information about the donor on file but as far as egg donation for hESC research is concerned, confidentially is kept.

After egg retrieval, donors receive the full, agreed upon amount no matter the number or quality of the eggs donated; women are routinely paid $4,000 and up to $12,400 per cycle[17, 46]. Once the eggs are retrieved, their donors have no more control over what happens to them and therefore they bear no responsibility and have no right in future commercial potential of derived product.

The US laws that rule the compensation for egg donation are vague and are a source of contentious issues. Indeed, the National Organ Transplant Act of 1984 prohibits the transfer "of any human organ for valuable consideration for use in a human transplantation if the transfer affects interstate commerce," but the Federal law neither bans nor directly regulates payments for gametes and embryos[46]. Moreover, the original NIH guidelines for hESC research developed in 2000[51] assert that "*to ensure that the donation of human embryos in excess of the clinical need is voluntary, no inducements, monetary or otherwise, should have been offered for the donation of human embryos for research purposes. Fertility clinics and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available*".

Thus, at the Federal level, monetary inducement is forbidden in order to avoid temptation for individuals to create extra embryos for research purposes, but monetary compensation is not forbidden as far as it doesn't create an incentive for the donation. Nonetheless, most assisted reproduction falls under State legislation rather than Federal law[52].

8. MORAL, ETHICAL AND RELIGIOUS BOUNDARIES

Moral considerations

The major objection by people to stem cell research is that it involves the destruction of an embryo or fetus. For the opponents, this constitutes the destruction of a potential human being and it is tight to the US debate about abortion. For the defenders of stem cell research the potential to provide potential treatments for unmet needs overrides this concern. Central to this debate is the definition of the beginning of life for a human being.

Opinions on this vary and some people consider that a fetus is a human being from the moment of its conception, others argue that it is not a human being until the embryo reaches 14 days and some people think that it is not before a baby is born that it is a human being. For the opponents, the most widely shared analysis of the moral status of the embryo focuses on the moment of the egg fertilization. They argue that because of its diploid structure and of its potential to represent a future unique individual, a fertilized egg is a full member of the humanity. Others even argue that it is at this moment that the "soul" enters the body.

Ethical considerations

Another major issue is associated with the fantastic potential of the cloning technology. It is potentially possible to create an embryo that is a genetic clone of the egg donor. Even though this might bring hope and treatment potential for the donor, opponents object that cloning technology creates a potential life for a specific purpose, which is not ethically correct, even if it is for a therapeutic goal.

Religious believes

Judaism, Islam, Buddhism, Hinduism, Taoism, and Christianity have all their own definition of the human being, the human embryo and stem cell research. We have listed in **Appendix F** a summary of definition criteria used by each of them.

International perspective

Even though these issues remain unsolved, the debate has evolved and has becoming clearer recently with the progress of science. In the US, The Prohibition of Human Cloning Act 2002 prohibits all types of human cloning by any method. The Research Involving Human Embryos Act 2002 allows for regulated use of an appropriate number of excess ART embryos in approved research programs. State and Territory governments are introducing supporting legislation to provide nationally consistent prohibition and regulation of use of excess ART embryos in research.

As demonstrated a recent study[63], the number of papers on ethical or legal aspects of hESC research was much bigger than the number of original publications describing experimental stem cell work. One way to step back from this hot debate might be to consider an international perspective. As observed Professor Murray, from MIT Sloan, and Professor Spar, from Harvard Business School, "*unlike their counterparts in North America and Europe, most Chinese researchers do not view the embryo as being imbued with an inherent moral value*"[60]. According to these authors, this "*distinctive attitude toward the embryo with its relatively lax regulatory system could help its researchers leap the translational gap between laboratory science and medical application*"[60].

9. IMPACT ON STEM CELL RESEARCHERS

When one takes into consideration all the boundaries described above, one realizes that the status of stem cell research in the US is singular. Thomson's patents have a huge regulatory impact on stem cell research and the legislation across states is not uniformed. We have tried in this thesis to critically analyze and assess the impact of all these boundaries on stem cell research. We have found that overall the impact of these boundaries on researchers' activities varies depending on many factors.

First, the source of funding a researcher get for a project on stem cell and the type of institution in which he will do his research limit the scope of his work. Second, the type of stem cells a researcher is using and the country where the researcher is currently

working have an economic impact since supply and demand in this industry is highly regulated by the stem cells intellectual property rights.

In the following section, we try to address these different possible scenarios. We start first by analysis the legislation regulating each case. Since the analysis involves many different interrelated layers and factors, we cannot transpose them in a simple matrix. Instead, we have split the analysis in three parts; whereas the researchers work for a private or academic institution, whereas they are using a new or an existing cell lines and whether they benefit a federal funding or not. Then we pursue a more details analysis where we try to concretely determine what is the boundaries'' impact in the researchers' day-to-day activity. In that section, we further dig our analysis into whether or not the stem cells are supplied by WARF itself or not. In the next chapter, we try to assess the impact of these boundaries on the US stem cells market.

Stem cell researchers regulatory environment

The regulatory environment governing stem cell research is complex. It is beyond the scope of this work to assess the legislations, their application and their implication is several countries, also we have restricted our analysis to the US country. We have found that the legislator segmented his approach in different layers that we have tried to summarize in **table 9.1** which lists what researchers on stem cells are allowed to do based on the legislation regulating each of the following case;

Table 9.1. Impact of stem cell research boundaries on researchers' work.

Source of funding restrictions	**Federal funding**	**Other funding**
Academia and private sector	❖ Need to use eligible human stem cell lines from NIH-approved cell lines providers. ❖ Can use or derive new animal embryonic stem cell lines. ❖ Can work on human embryonic germ cells obtained from aborted fetuses. ❖ Can carry out research projects using embryonic germ cell lines	❖ No restriction. ❖ Can even derive new lines of embryonic stem cells. ❖ A clear separation of the finds used to support this work from any other federally funded work of the laboratory is required though. ❖ All the above is subject to State law regulations.

	already derived. ❖ Can derive and study new embryonic germ cell lines. ❖ Can develop animal embryonic germ cell lines to assess the potential of these cells through animal models. ❖ Can work on human adult stem cells with no restriction other than those usual required to respect human subject protection and clinical research requirement. ❖ All the above is subject to State law regulations.	
Patent restrictions	**Academia**	**Private**
Federal funding	❖ MOU NIH-WARF and/or NIH/third parties ❖ Non-commercial agreement with WARF. ❖ Sign a MTA with WARF and/or third parties that provides them with existing human stem cell lines at marginal cost plus shipment cost. ❖ - Can derive new animal cell lines: if they use Prof. Thomson's technique to do so then fall under his patent restrictions.	❖ Commercial license agreement with upfront fees, royalties and options fees. ❖ Sign a MTA with WARF and/or third parties that provides them existing with human stem cell lines. ❖ Can derive new animal cell lines and if they use Prof. Thomson's technique for stem cell lines derivation then fall under his patent restrictions.
Other funding	❖ MOU NIH-WARF and/or NIH/third parties ❖ Non-commercial agreement with WARF. ❖ Sign a MTA with WARF and/or third parties that provides them with existing human stem cell lines at marginal cost plus shipment cost. ❖ Can derive new human cell lines: and if they use Prof. Thomson's technique to do so then fall under his patent restrictions.	❖ Commercial license agreement with upfront fees, royalties and options fees. ❖ Sign a MTA with WARF and/or third parties that provides them existing with human stem cell lines. ❖ Can derive new human cell lines: if they use Prof. Thomson's technique to do so then fall under his patent restrictions. ❖ Can use new methods to derive new cell lines.

Fed and States restrictions	**Upstream research**	**Downstream research**
Existing stem cell lines	❖ The Federal privacy rules might have been managed by the third party stem cell lines provider.	❖ If researchers seek to obtain FDA approval or new labelling of drugs, devices, or biologics used to human, then they are subject to regulation by FDA as well. ❖ If stem cell lines come from abroad, need FDA approval for importation.
New stem cell lines	❖ Need to comply with Federal patient privacy rule for donor.	❖ If researchers seek to obtain FDA approval or new labelling of drugs, devices, or biologics used to human, then they are subject to regulation by FDA as well.

Academic Researchers

Researchers using Stem Cells provided by WARF

Academic researchers willing to pursue noncommercial research using WiCell stem cells need to contact WARF to get approval for a non-commercial license agreement that falls under the MOU signed with NIH. The non-commercial agreement provides them with access to WiCell's stem cell lines for their research and allows them to freely publish their results.

The request should be made by the primary investigator. If eligible, then an annual Certification Statement confirming compliance with the restrictions on the use of Wisconsin Materials shall be supplied to WiCell by the recipient and the scientists receiving Wisconsin Materials under the terms of the "Simple Letter Agreement For The Transfer of Materials". The material will be distributed subsequently by WiCell.

Several restrictions apply to such non-commercial licensing.

1. The material must be used in compliance with any and all applicable governmental rules and regulations relating to the handling or use of stem cells.

2. Moreover, the researchers much warrant that they will not perform with the WiCell stem cells experiments that involve the following:
    i. Intermixing of Materials with an intact embryo, either human or nonhuman;
    ii. Implanting Materials or products of Materials in a uterus; and
    iii. Attempting to make whole embryos by any method.
3. Also, the WARF's stem cells are not to be used for diagnostic or therapeutic purposes and they may not be transferred by the Recipient to any third parties without the written consent of WiCell.

Under such restrictions, researchers have access to the WiCell stem cell lines at what it is assumed to be marginal cost plus fees covering the shipment of the cells. This fee was until recently up to $5,000 per cell lines[34] and WARF lately reduced the price of cells to $500 and opened the possibility of rebates for academic investigators who had paid $5,000 before the contract went into effect[53, 54]. If the recipient is located in a foreign country, then an additional charge of up to $1,000 might be added due to higher shipment costs.

Once the order is placed and the payment is received, the stem cell lines are shipped to the recipient. Researchers have then possible access to a stem lines training, held by WiCell scientists, on how to properly execute hESC culture methods. They will subsequently use stem cells as per the legislations that apply in their respective countries.

Researchers using Stem Cells not provided by WARF

The MOU signed with the NIH plans such scenario. The WARF-NIH MOU mentions that "*Wisconsin patent rights may also be used in Public Health Service research programs involving materials other than Wisconsin materials that may be within the scope of an issued claim of Wisconsin patent rights (Third Party Material)*"[34].
Moreover it says that "*Suppliers of Third Party Materials are granted a limited, revocable, non-commercial, research license by WiCell under the Wisconsin Patent*

rights to provide such third party materials to Public Health Service research programs provided that such suppliers make such third party materials available on terms no more onerous than those contained in this agreement" [34].

Therefore, researchers who want to work with third party material need to sign first an agreement with WiCell before to enter into an agreement with the Third Party. Meanwhile, the Third Party needs to sign an agreement with WARF stipulating that they will provide stem cell lines at cost equivalent to that of WARF[35]. In the end then, researchers are not better or worse off, they are charged the same price but receive different stem cell lines. This is possible because the NIH signed other MOUs with other stem cell suppliers, as the one signed with BresaGen Inc. and effective April 24, 2002[55]. Overall, researchers need to sign two or three types of documents depending on where they are located.

American academic researchers (see **appendix G** for a list of US stem cell research institutes) sign first a MTA in a form approved by WiCell under the NIH MOU permitting the transfer of stem cell materials. Then they sign an Institutional Undertaking Regarding Applicable Law, which confirms that no applicable laws, regulations or contracts will be violated by the transfer or use of the stem cell lines by the recipient.

Academic researchers located in a foreign country might need to sign a third document which is a Statement that proves that no applicable foreign laws or regulations will be violated by the transfer or intended use of the stem cell lines.

These documents must usually be signed by an authorized person on behalf of the institution and by the principal investigator.

Therefore, academic researchers can do non-commercial research at their will, whatever the source of funding, as far as their activities satisfy the regulations sealed by the documents they have signed and they do not infringe the WARF's patents. Overall, WARF has signed over 200 US non-commercial license agreements with academic researchers[54].

Researchers working in private institutions

Researchers using Stem Cells provided by WARF

Then the MOU signed between WARF and NIH doesn't apply. Researchers need to enter with WiCell into an Industry Research License. The negotiation of the agreement terms is done between the researchers' entity and WARF on a case by case basis.

Under such agreements, researchers are allowed to pursue internal research, including the differentiation to any cell types as well as derivation of new lines, and they have access to human and non-human primate stem cell lines with the same legal restrictions than the academic researchers. Such agreement also defines the parameters for commercialization of products. In such perspective, then a separate Industry Commercial License Agreement must be negotiated before the product development or commercialization occurs.

Stem cell commercialization rights are defined by WARF by cell type and application. All fields are available for research therapy and diagnostic applications except research on heart, neural, and pancreatic cells for which WARF has granted the exclusive rights to Geron Corporation. Therefore, if a company or a private institution wants to develop therapies or diagnostics in these areas, it must beforehand negotiate with Geron Corporation for fees and royalties.

In all cases, an industry commercial license is subject to an initial upfront fee of $100,000[54] and up to $125,000[53, 56]. An annual maintenance fees to keep exclusivity can be negotiated, and has already been granted in the past for $25,000[54] and up to $40,000[53, 56], otherwise license are *de facto* non-exclusive. An option can be granted as well for $15,000 for an expansion of activity to non-primate animals. Royalties are usually negotiated on the base of a minimum royalty of $15,000 plus fixed earned royalties calculated at 4% of the selling price for therapeutic products and at 2% of the selling price for diagnostic products.

These terms vary and they are tailored to the size of the recipient company. WARF has for example accepted in the past payment both in cash and in stock. Generally speaking, licensees must provide to WARF with a broad development plan outlining its general

plan and timeline for developing product in the licensed field. It is such development plan that WARF challenged to Geron Corporation in 2001. WARF indeed sued Geron for breach in contract in August 2001 because it believed that Geron wan not providing development plan as per WARF expectation. Both companies finally entered in a third and final licensing agreement in January 2002.

Researchers using Stem Cells not provided by WARF

American researchers must still enter into an agreement with WARF to use the cells in commercial research under WARF's US patent rights. The same agreements as if they were using WiCell stem cells need to be signed and other license agreements need to be negotiated and signed with the Third Party that provides the stem cell lines. As for non-profit organizations, for profit institutions might be required to sign a Material Transfer Agreement in a form approved by WiCell, a document confirming that no applicable laws, regulations or contracts will be violated by the transfer or use of the stem cell lines and for researchers in a foreign country, a Statement that will prove that no applicable foreign laws or regulations will be violated by the transfer or intended use of the stem cell lines is needed.

Regarding the fees charged, only institutions that have MOUs with NIH have price regulations; other suppliers of hESC lines can charge as they wish for the cell lines[10].

10. CONSEQUENCES ON THE STEM CELL MARKET

The legislation and the boundaries affecting stem cell research have a certain impact on the dynamic of the stem cells market. We have tried to look at stem cell products as a new industry on its own, and not as part of the biotech industry. In order to perform our analysis we have looked first at how the stem cell business could be structured, then we have analysis the dynamic of this industry and we have ultimately plugged data found in the literature in order to better understand and illustrate at which stage the industry currently is .

The stem cells business

Upstream access

The MOUs signed between academic researchers and stem cell lines suppliers provide researchers with freedom to conduct non-commercial research, to publish and to file patents on any of their inventions using the WARF material and patent rights (both on primate and human ESCs).

In that business model, the material protected by rights can be used only for non-commercial research purposes under MOUs. MOUs also include MTAs that companies use when they send research materials to institutions. As such, companies implicated in MTAs are allowed to pursue research without obtaining commercial rights: as a result, they are not obliged to pay license fees. Moreover, the MOU signed by WARF with NIH provides implicit third-party rights to supply any of the federally approved stem cell lines, as long as the third party suppliers provide the material at a price not exceeding the one charged by WARF for their own derived stem cells. If a supplier wants to charge a price premium, then it needs to sign a commercial license with WARF in order to avoid contract infringement.

Under this academic licensing, academic researchers are therefore guaranteed to obtain hESC lines at nearly marginal cost, which is around $500 per line, as noted in the preceding section. A premium of $1,000 is charged for material sent oversees, covering thus transportation cost.

Even though, the price structure is identified for these products, it is not possible at this stage to evaluate precisely. **Figure 10.2** reports the aggregate sales data and forecast of all the products derived from stem cells, which takes into account stem cell lines sales but doesn't track them specifically.

Downstream access

The commercial research license requires that a company obtains a research license to conduct basic research using the primate ESC technology described by Professor Thomson and a commercial license in case the company wants to sell out therapeutic or diagnostic products that are derived from the patents claims.

As noted previously, a commercial license is subject to an initial upfront fee that could be over $100,000. Licenses are non-exclusive except if exclusivity is negotiated, and it is usually set as an annual maintenance fees of several thousands dollars. An option can be granted as well for a similar price, which allows for example an expansion of activity to non-primate, including non-human.

Royalties are usually on the base of a small flat fee charged for the licensed material and technique and the know-how provided to companies who receive the cells. On top of the flat base royalty fees, a fixed earned royalty fees calculated as a percentage of the selling price for therapeutic or diagnostic products is charged as well for the claims of the inventions of the licensed patents.

The market structure

The stem cell industry includes several diverse market participants ranging from stem cell banks and suppliers to preservation or processing companies and firms that develop therapeutics for various disorders. Even though there is no current consolidated data for this industry, we can evaluate the sales figures and forecast the sales potential of the stem cell therapy market. Participants in this market can be segmented into the following sub-categories, based on the source of stem cells:

- ✓ Adult stem cell companies,
- ✓ Embryonic stem cell companies,
- ✓ And umbilical cord blood derived stem cells.

The market drivers

Increase in R&D Funding

Despite the hectic US federal stem cells' regulatory environment encountered over the past decade, there has been an overall increase in stem cells R&D funding in the US. First, Venture capital firms have started to invest in stem cell research. This positive private trend is reported as well at the federal level, where NIH is continuously increasing his support to stem cell research, even though not to at a high growth rate (see **table 10.1**).

Table 10.1. NIH stem cell research annual funding in M$[40].

In million US$ - (Estimates)*	2003	2004	2005	2006	*2007**
Stem Cell Research - Human Embryonic	20	24	40	38	*39*
Stem Cell Research - Non-Human Embryonic	113	89	97	97	*96*
Stem Cell Research - Human Non-Embryonic	191	203	199	200	*200*
Stem Cell Research - Non-Human Non-Embryonic	192	236	273	274	*273*
Total Stem Cell Research	517	553	609	609	*608*

However, pharmaceuticals companies are still prudent and reluctant to invest and back-up research, mainly due to their bigger inertia in technologic adoption.

Reimbursement

Procuring reimbursement for stem cell-based products is expected to be a key driver for the success of the stem cell therapeutics business. Even though it is still too premature to depict a clear picture of what this key driver will be and how it will evolve in the coming years, one can say the level of R&D investment required and the high tech aspect of these potential new treatments might make their initial cost high. Moreover, private insurers might be concerned and prudent in the short run and might want to see positive therapeutic effects associated with cost savings before considering covering these new therapies. Therefore, in the short run, a lot of patient might not have access to these costly new treatments.

States Regulatory Developments

Although government changing regulations have been hectic in the United States over the past decade, in recent times there are indications that some States are taking interest in the application of stem cells for the welfare of the society. For example, the passage of the $3Bn Proposition 71 in California (the "California Stem Cell Research and Cures Initiative) is a major positive development in the area of stem cell research. There are no indications that in the future these regulations will be more restrictive and one might think that other States will follow California example.

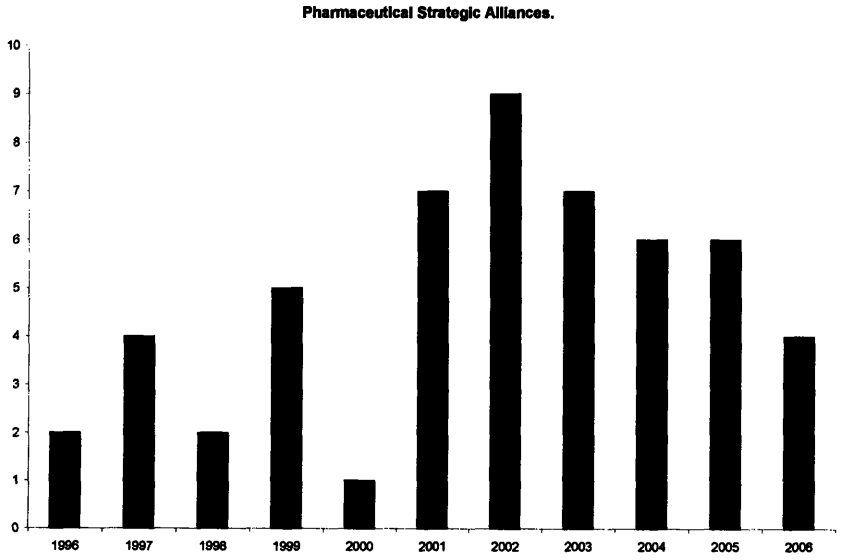
Aging Population

The aging population is a major factor driving the increasing need for developing new medical treatments that would treat patients faster and better, thus reducing the economic burden for the society. In addition, as noted, stem cells are potentially good treatment candidates for several unmet medical needs. They are likely to be used in incoming disruptive treatments for total knee implants, diabetes of children, joint disorders, bone marrow transplants for cancers, Parkinson disease etc...

Increase in Strategic Alliances

Several biotechnology companies are currently working in collaboration with academic and/or research institutions. As observes Professor Pisano[41], from Harvard Business School, the translational research efficiency is still to be improved in the biotechnology sector. Stem cell are in the best position to develop cell-based therapies but are technically at the front edge of science, thus requiring a close partnership between private companies and academic teams in order to merge downstream knowledge with science expertise, to understand and develop promising stem cell-based therapies. **Figure 10.1** reports the number of strategic alliance in the US involving stem cells materials. As a complement, **Appendix H** lists non-exhaustively the key alliances and licensing agreements that occurred since 1995 among firms in this industry.

Figure 10.1. Main 1995-2006* US stem cell strategic alliances[62].



* *Data collected until June 2006.*

It wasn't possible to explicitly obtain accurate data on strategic alliances involving biotech companies with academic institutions, but a search using Recap-Ip® software revealed that overall over 220 US contracts have been signed to date for the exchange of stem cells materials involving US companies.

Market Overview

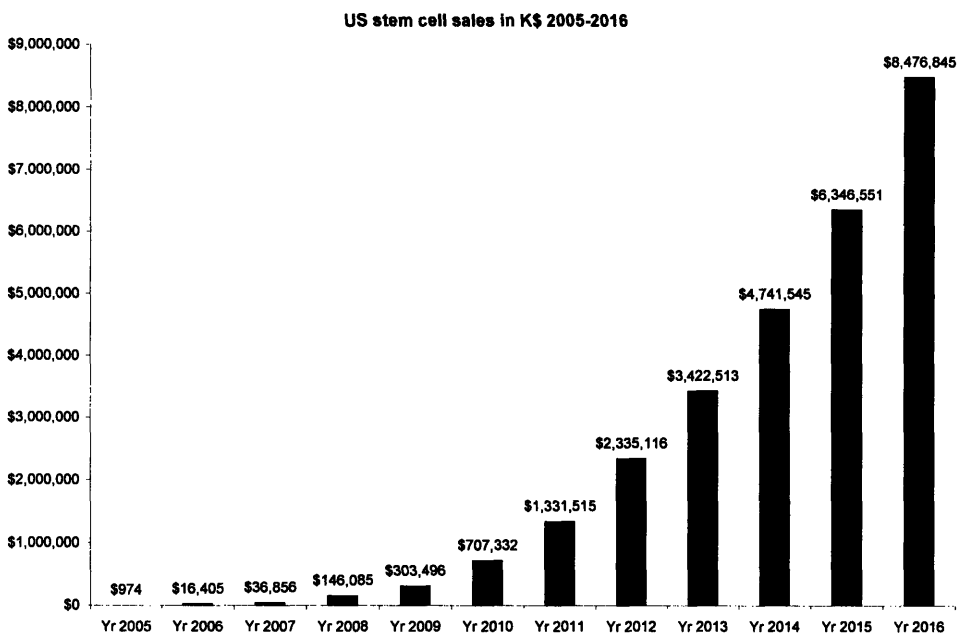
We have seen that bone marrow transplant was the first stem cell therapy attempts. Current stem cell therapeutic applications are for bone replacement, growth of fracture repair and concern a patient population of over 2.5 millions in the United States. Treatments for joints disorders and heart disease are to come in the coming years and stem cells are actively being investigated for a number of cancers such as metastatic breast cancer. **Table 10.2** summarizes stem cell current and potential coming treatments.

Table 10.2. Current and expected forthcoming stem cell treatment[42].

Current Applications	Expected to be Approved by the FDA in the coming 36 months
❖ Replacement for bone harvesting in spine fusion surgery ❖ Bone growth and void fill in fresh fractures ❖ Bone growth and void fill in non-union fractures	❖ Prochymal (treatment for graft vs. host disease) ❖ Two (possibly three) treatments for damaged heart muscle due to heart disease ❖ Chondrogen (repair of knee cartilage)

Based on the current stem cell therapeutic and diagnostic products sold on the market and the promising treatments that are expected to come on the market, the market for stem cell products is expect to overshoot the one billion annual bar in 2011 (**see figure 10.2**).

Figure 10.2. US annual stem cell sales in K$[42].



Companies

(ranked in order of revenues generated from the sale of stem cell therapies or related products)

Blackstone Medical

Osiris Therapeutics

NuTech Medical

ViaCell

Aastrom Biosciences

Cytori

Geron

Stem Cell Inc.

BioE

Even though, 10 years projection is likely to be inaccurate for such a young industry, if we take into account the latest published forecasts, stem cell therapies and related products are expected generate revenues of almost $8.5 billions in 2016. According to the actual commercial licensing agreements, and assuming that the legal environment will remain unchanged despite the strong current challenges that Professor Thomson' patents are undergoing, with royalties fees charged to companies at a rate of around 5% of annual sales of the commercial therapeutic or diagnostic products, one can estimate that the annual WARF royalty revenues will be almost $254M in 2015, last year of its IP protection, without taking into account the other income generated by the licenses (commercial or not).

11. CONCLUSION AND DISCUSSION

Stem cells are a fantastic research tools for pushing the limit of development biology science. Moreover, they have the potential for new treatments of still unmet medical needs that are growing along with the aging of the population. Despite all these positive

aspects that bring new hope in human medicine, stem cell research is a singular field of researcher, mostly in the US.

Indeed, the intellectual property rights of stem cells are under an unusual tight control. The USPTO has in fact granted two broad patents in 1999 and in 2001 to Professor Thomson (who transmitted them to WARF) that have sealed the field in the US. Many researchers complain for many years that the Thomson's patents have restricted their access to something that should belong to common knowledge. They argue that this special situation in the US has hinder research (fundamental or applied) and development of stem cell products as compared to other countries or to the US had the patents were not granted, or at least in not such a broad way.

Other authors have argued that this is not necessarily true. They have analyzed the impact in publication stem cell research coming from American researchers and found that even though the volume of production might have been lower that one could have expected, the quality of the publication remains very high, thus suggesting that high quality research can still be done despite the control by WARF.

We have tried in this thesis to critically assess what is the day-to-day constraint that stem cells researchers face at work. We have considered the problem under many angles and we found that upstream access for researchers appears to not have been hindered by the current legislation. The boundary that has a higher impact on upstream research, though we have not quantified it, seems to be the moral and ethical status of the embryo, for which regulation is very strict.

On the downstream side, WARF did use and is still using its power and charges expensive fees for the commercial use of the material covered by its patents. Even though WARF claims that they charge fees according to the size of the company they have an agreement with, this fees might be perceived as a barrier to entry for a lot of potential new entrants since on top of it, huge investment are still to be made to overcome the difficulties inherent to the strong technicity of the stem cell materials.

We have tried via this thesis to give a thorough and as much exhaustive possible overview of the boundaries that have emerged in stem cell research in the US. Even though such comprehensive document was not seen before in the literature, we believe that additional work interesting would complement greatly this thesis. First, a research project that could study more in depth stem cell products' supply and demand and more precisely the dynamic of data withholding in this research field could be a very good topic to explore and could be compared with the work done by Campbell et al on genetics[64]. Second, a more thorough understanding of the dynamic of the supply.

We have design a questionnaire for such purpose that we plan to administrate ultimately electronically (**see Appendix I**) to stem cell researchers in the US and abroad. We believe that this thesis will serve as a base and will be a very good complement for the analysis of the data collected by this survey.

Appendix A. The Common Rule[21].

Office for Human Research Protections
Department of Health and Human Services
Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles

Date: March 19, 2002

Scope: This document describes when research activities involving human embryonic stem cells (hESCs), human embryonic germ cells derived from fetal tissue, or hESCor germ cell-derived test articles are considered human subjects research and what regulatory controls apply to that research.

Target Audience: Investigators who conduct research with these cells and test articles, sponsors of such research, institutions where the research is conducted, and Institutional Review Boards (IRBs) that review human subject research involving these cells or test articles.

APPLICABLE REGULATIONS AND LAWS

• Research involving these cells or test articles that is conducted or supported by the Department of Health and Human Services (HHS) or performed at an institution that has agreed under an OHRP (Office for Human Research Protections)-approved assurance to apply HHS regulations to all of its human subjects research may be subject to HHS human subjects protection regulations (Title 45 CFR Part 46, including Subpart B, 45 CFR 46.206), as described below.

• All clinical research involving drugs, devices, and biological products regulated by FDA, including cells or test articles regulated as drugs, devices, and biological products, is also subject to FDA regulations governing investigational new drugs (INDs) or devices (IDEs) (Title 21 CFR Parts 312 or 812), regardless of the source of support. This clinical

research is also subject to FDA's IRB and informed consent regulations (Title 21 CFR Parts 50 and 56).

• In addition, clinical research involving the transplantation of cells or test articles derived from human fetal tissue into human recipients is subject to Public Law 103-43, "Research on Transplantation of Fetal Tissue" (42 U.S.C. § 289g–2(a)).

• Other Federal, State or local laws may also apply to transplantation or other research involving these cells or test articles.

CONDITIONS REGARDING FEDERAL FUNDING OF RESEARCH ON HUMAN EMBRYONIC STEM CELLS

• Research involving the derivation and use of human embryonic germ cells from fetal tissue may be conducted with Federal support.

• Research on existing human embryonic stem cell lines may be conducted with Federal support if the cell lines meet the U.S. President's criteria which he announced on August 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html).

• Research involving the derivation of new stem cells from human embryos or the use of human embryonic stem cells that are not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with Federal support.

GUIDANCE

Under HHS regulations at 45 CFR Part 46, human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

HHS-conducted or supported research that involves neither interactions nor interventions with living individuals or obtaining identifiable private information is not considered human subjects research. Accordingly, *in vitro* research and research in animals using already derived and established human cell lines, from which the identity of the donor(s) cannot readily be ascertained by the investigator, are not considered human subject research and are not governed by the HHS or FDA human subject protection regulations

appearing at 45 CFR Part 46 and 21 CFR Parts 50 and 56. IRB review is not required for such research.

Use of Identifiable Private Information

HHS-conducted or supported research that uses human cell lines where the donor(s) may be identified, including cells that retain links (such as a code) to identifying information is generally considered human subject research that is governed by 45 CFR Part 46 because the donors are human subjects. IRB review and approval is required for such research.

Appendix B. Stem cell legislation in the US by States[18, 19].

State/Jurisdiction Statute Section	Specifically permits research on fetus/embryo	Restricts research on aborted fetus/ embryo	Consent provisions to conduct research on fetus/embryo	Restricts research on fetus or embryo resulting from sources other than abortion	Restrictions of purchase/sale human tissue for research
Arizona §§36-2302, 2303	No	Yes, prohibits research on aborted living/non-living embryo or fetus	No	Yes, prohibits the use of public monies for cloning for research	No
Arkansas §§20-17-802, 20-16-1001 to 1004	No	Yes, prohibits research on aborted live fetus	Yes, consent to conduct research on aborted fetus born dead	Yes, prohibits research on cloned embryos	Yes, prohibits sale of fetus/fetal tissue
California Health & Safety §§ 123440, 24185, 12115-7, 125300-320, 2006 SB 1260	Yes	Yes, prohibits research on aborted live fetus	Yes, consent to donate IVF embryo to research	Prohibits sale of embryos and oocytes. Prohibits payment in excess of the amount of reimbursement of expenses to be made to any research subject to encourage her to produce human oocytes for the purposes of medical research.	Yes, prohibits sale for the purpose of reproductive cloning or for stem cell research
Connecticut 2005 SB 934	Yes, on embryos before gastrulation (a process during embryonic development)	No	Yes, consent to donate IVF embryo to research	No	Yes, prohibits payment for embryos, embryonic stem cells unfertilized eggs or sperm donated following IVF treatment
Florida §390.0111	No	Yes, prohibits on aborted live fetus	No	No	No
Illinois 720 ILCS 510/6, 510/12.1 Executive Order 6 (2005)	Yes, under E.O. 6 (2005) permits funding of research that involves adult stem cells, cord blood stem cells, pluripotent stem cells, totipotent stem cells, progenitor cells, the product of somatic cell nuclear transfer or any combination of those cells	Yes, prohibits on aborted living/nonliving fetus	Yes, written consent to perform research on cells or tissues from a dead fetus other than from an abortion	Yes, prohibits research on fetus/fertilized embryo; prohibits funding under E.O. 6 (2005) of research on fetuses from induced abortions and the creation of embryos through the combination of gametes solely for the purpose of research	Yes, prohibits sale of fetus/fetal tissue; also prohibits award of funds for stem cell research under E.O. 6 (2005) to a person who purchases or sells embryonic or fetal cadaveric tissue for research
Indiana §35-46-5-1, 2005 Senate Enrolled Act No. 268	Yes, permits fetal stem cell research on placenta, cord blood, amniotic fluid or fetal tissue	Yes, prohibits research on aborted living/non-living embryo or fetus	Yes, consent required for fetal stem cell research	Yes, prohibits research on cloned embryos	Yes, prohibits sale of human ovum, zygote, embryo or fetus
Iowa §§707B.1-4	No	No	No	Yes, prohibits research on cloned embryos	Yes, prohibits transfer or receipt of oocyte, embryo or fetus for somatic cell nuclear transfer
Kentucky §436.026	No	No	No	No	Yes, prohibits sale of fetus/fetal tissue

Louisiana §14: 87.2	No	No	No	Yes, prohibits research on fetus/embryo in utero, in vitro fertilized embryo	No
Maine 22§1593	No	No	No	Yes, prohibits research on fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation	Yes, prohibits sale of fetus/fetal tissue
Maryland SB 144	Yes	No	Yes, written consent to donate unused IVF material to research	Yes, prohibits donation of unused oocytes for state funded stem cell research.	Yes, prohibits valuable consideration for the donation or production of IVF material
Massachusetts 112§12J, 2005 SB 2039	Yes, on embryos that have not experienced more than 14 days of development (not including days frozen)	Yes, prohibits research on embryo/live fetus	Yes, written consent to perform research on a dead fetus and informed consent to donate egg, sperm, or unused preimplantation embryos created for IVF	Yes, prohibits research on live embryo or fetus; also prohibits creation on fertilized embryo solely for research	Yes, prohibits sale of neonate, embryo or fetus for illegal purposes; prohibits sale of embryos, gametes or cadaveric tissue for research
Michigan §§333.2687-2688, §§333.16274-16275, 333.20197, 333.26401-26403, 750.430a	No	Yes, live embryo/ fetus	Yes, written consent of mother to donate dead embryo, fetus or neonate to research	Yes, prohibits research on a live embryo or fetus, cloned embryo	No
Minnesota §§145.421, 422	No	No	No	Yes, prohibits research on a live embryo or fetus up to 265 post fertilization	Yes, permits the sale/purchase of cell culture lines from nonliving human conceptus
Missouri §§188.036, 037	No	Yes, prohibits research on a fetus alive pre-abortion	No	No	Yes, prohibits receipt of valuable consideration for aborted fetal organs or tissue
Montana §50-20-108(3)	No	Yes, prohibits research on a live fetus	No	No	No
Nebraska §§28-342, 346, 71-7606	No	Prohibits research on aborted live fetus or the use of state funds for research on fetal tissue obtained from an abortion	No	Yes, limits the use of state funds for embryonic stem cell research; restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars	Yes, prohibits sale, distribution or donation of viable aborted child
New Hampshire §§168-B-1, 15	No	No	No	Yes, prohibits the maintenance of a unfrozen fertilized pre-embryo past 14 days	Yes
New Jersey 2002-2003 SB1909/AB2840	Yes	No	Yes	No	No
New Mexico §24-9A-1, 3, 5	No	No	No	Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation	Yes, prohibits abortion for the purpose of selling the fetus to researchers

North Dakota §14-02.2-01, 2; HB 1424	No	Yes, prohibits research on a living/non-living embryo or fetus	Yes, requires consent to conduct research on a nonliving fetus or embryo other than from an abortion	Yes, prohibits research on a fetus born or extracted alive; cloned embryos	Yes, prohibits the sale of a fetus to be used for illegal purposes
Ohio §2919.14	No	Yes, prohibits research on a living/non-living embryo or fetus	No	No	Yes, prohibits sale of fetus or fetal remains from an abortion
Oklahoma 63 §1-735	No	Yes, prohibits research on a fetus/embryo	No	No	Yes, prohibits sale of fetus or fetal remains
Pennsylvania 18 §§3203, 3216	No	Yes, prohibits research on a live embryo or fetus	Consideration may not be given to mothers consenting to research; in cases involving abortion, consent must be provided after decision to abort	No	Yes, consideration may not be given to mothers consenting to research or other transferring tissue except for expenses involved in actual retrieval, storage, etc.
Rhode Island §11-54-1	No	No	Yes	Yes, prohibits research on a fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation	Yes, prohibits sale of neonate, embryo or fetus for illegal purposes
South Dakota §§34-14-16, 17, 20; 34-23A-17	No	Yes, prohibits research on a living/non-living embryo or fetus	No	Yes, prohibits research on embryo outside of a woman's body; research on cells or tissues derived from an embryo outside a woman's body	Yes, prohibits sale of embryo
Tennessee §39-15-208	No	No	Yes, consent required to conduct research on aborted fetus	No	Yes, prohibits sale of aborted fetus
Texas Penal Code §48.02	No	No	No	No	Prohibits sale of fetus/fetal tissue
Utah §§76-7-301, 310	No	No	No	Yes, prohibits research on a live fetus, fertilized embryo post-implantation	Yes, prohibits sale of fetus/fetal tissue; also prohibits sale of live unborn children, which is not defined, but are referred to in abortion statute
Virginia §32.1-162.32-2	No	No	No	May prohibit research on a cloned embryo or fetus	Yes, prohibits shipping or receiving of the product of human cloning for commerce
Wyoming §35-6-115	No	No	No	No	Yes, prohibits sale, distribution or donation of live or viable aborted child, defined to include embryos, for experimentation

Appendix C. The two key Thomson' patents.

United States Patent **5,843,780**[29]

Thomson **December 1, 1998**

Primate embryonic stem cells

Abstract

A purified preparation of primate embryonic stem cells is disclosed. This preparation is characterized by the following cell surface markers: SSEA-1 (-); SSEA-3 (+); SSEA-4 (+); TRA-1-60 (+); TRA-1-81 (+); and alkaline phosphatase (+). In a particularly advantageous embodiment, the cells of the preparation have normal karyotypes and continue to proliferate in an undifferentiated state after continuous culture for eleven months. The embryonic stem cell lines also retain the ability, throughout the culture, to form trophoblast and to differentiate into all tissues derived from all three embryonic germ layers (endoderm, mesoderm and ectoderm). A method for isolating a primate embryonic stem cell line is also disclosed.

Inventors: **Thomson; James A.** (Madison, WI)

Assignee: **Wisconsin Alumni Research Foundation** (Madison, WI)

Appl. No.: **08/591,246**

Filed: **January 18, 1996**

Current U.S. Class: **435/363** ; 435/366; 435/373

Current International Class: C12N 5/06 (20060101); C12N 005/06 ()

Field of Search: 435/363,366,373

Primary Examiner: Woodward; Michael P.

Assistant Examiner: Brumback; Brenda G.

Attorney, Agent or Firm: Quarles & Brady

Government Interests

This invention was made with United States government support awarded by NIH NCRR Grant No. RR00167. The United States government has certain rights in this invention.

Parent Case Text

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. application Ser. No. 08/376,327 filed Jan. 20, 1995.

Claims

We 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.

2. The preparation of claim 1 wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

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.

4. The preparation of claim 3 wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. The preparation of claim 3 wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. The preparation of claim 3 wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. The preparation of claim 3 wherein the cells remain euploid for more than one year of continuous culture.

8. 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 a SCID mouse.

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.
10. A method as claimed in claim 9 further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.
11. A cell line developed by the method of step 9.

United States Patent **6,200,806**[30]

Thomson **March 13, 2001**

Primate embryonic stem cells

Abstract

A purified preparation of primate embryonic stem cells is disclosed. This preparation is characterized by the following cell surface markers: SSEA-1 (-); SSEA-4 (+); TRA-1-60 (+); TRA-1-81 (+); and alkaline phosphatase (+). In a particularly advantageous embodiment, the cells of the preparation are human embryonic stem cells, have normal karyotypes, and continue to proliferate in an undifferentiated state after continuous culture for eleven months. The embryonic stem cell lines also retain the ability, throughout the culture, to form trophoblast and to differentiate into all tissues derived from all three embryonic germ layers (endoderm, mesoderm and ectoderm). A method for isolating a primate embryonic stem cell line is also disclosed.

Inventors: **Thomson; James A.** (Madison, WI)

Assignee: **Wisconsin Alumni Research Foundation** (Madison, WI)

Appl. No.: **09/106,390**

Filed: **June 26, 1998**

Primary Examiner: Clark; Deborah J. R. *Attorney, Agent or Firm:* Quarles & Brady LLP

Parent Case Text

CROSS REFERENCES TO RELATED APPLICATIONS

This application is a divisional of U.S. Ser. No. 08/591,246 which was filed on Jan. 18, 1996, issued as U.S. Pat. No. 5,843,780, Dec. 1, 1998 and is a continuation-in-part of U.S. Ser. No. 08/376,327 which was filed on Jan. 20, 1995, abandoned.

Claims

I claim:

1. A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an in vitro culture for over one year, (ii) maintains a 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.

2. The preparation of claim 1, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. A purified preparation of pluripotent human embryonic stem cells wherein the 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.

4. The preparation of claim 3, wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. The preparation of claim 3, wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. The preparation of claim 3, wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. The preparation of claim 3, wherein the cells remain euploid for more than one year of continuous culture.

8. 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 a SCID mouse.

9. 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 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.

10. A method as claimed in claim 9, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. A cell line developed by the method of claim 9.

Appendix D1. The WARF-NIH MOU[34].

Memorandum of Understanding
between
WiCell Research Institute, Inc.
and
Public Health Service
U.S. Department of Health and Human Services

This Memorandum Of Understanding (hereinafter "Agreement"), effective September 5, 2001, by and between the Public Health Service of the U.S. Department of Health and Human Services as represented by the Office of Technology Transfer, having an address at National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852 ("PHS") and the WiCell Research Institute, Inc., a Wisconsin nonprofit corporation having an address at 614 Walnut Street, Madison, Wisconsin 53705 ("WiCell"). PHS and WiCell are referred to herein as the "Parties".

WHEREAS certain technologies and materials concerning primate embryonic stem cells and their cultivation claimed in U.S. Patent 5,843,780, U.S. Patent 6,200,806, U.S. Patent Application 09/522,030 and corresponding U.S. or foreign patent rights and any patents granted on any divisional and continuation applications of any type but only to the extent it claims an invention claimed in a patent application listed herein ("Wisconsin Patent Rights") have usefulness in basic research conducted or funded by PHS as well as potential utility for commercial applications; and

WHEREAS specific human embryonic stem cell line materials, their unmodified and undifferentiated progeny or derivatives ("Wisconsin Materials") have been derived consistent with the Presidential Statement of August 9, 2001 from the research efforts of James A. Thomson of the University of Wisconsin -Madison working alone or with other investigators; and

WHEREAS PHS has a basic mission on behalf of the U.S. Government for the conduct and support of health research performed at its own facilities or through funding agreements to other institutions ("Recipient Institutions"); and

WHEREAS PHS funded primate research studies at the University of Wisconsin – Madison that led to certain discoveries claimed in Wisconsin Patent Rights and therefore the Government has certain use and other rights to the intellectual property comprising the Wisconsin Patent Rights granted by law and regulation; and

WHEREAS Wisconsin Materials were made using solely private funds and are the proprietary, tangible property of WiCell and, as such, their ownership is not subject to the rights and obligations granted the Government in the Wisconsin Patent Rights; and

WHEREAS the Wisconsin Alumni Research Foundation of the University of Wisconsin – Madison ("WARF") and WiCell have a mission to serve the public good and desire to serve the public interest by making the Wisconsin Materials and the Wisconsin Patent Rights widely available to PHS and other academic researchers; and
WHEREAS WiCell represents that it has received a license, with the right to grant sublicenses, to Wisconsin Patent Rights from WARF and that WiCell also owns or otherwise has the right to distribute Wisconsin Materials to third parties; and

WHEREAS WiCell desires to exercise Wisconsin Patent Rights and distribute Wisconsin Materials without placing undue restrictions or burdens upon health research conducted or funded by PHS;

NOW, THEREFORE, the Parties hereby agree to the following terms and conditions regarding use of Wisconsin Materials or Wisconsin Patent Rights for research conducted either by PHS or on behalf of PHS by its contractors:

(1) The Parties agree that Wisconsin Patent Rights are to be made available without cost for use in the PHS biomedical research program subject to the following conditions:

(a) Wisconsin Patent Rights may be used in research programs involving Wisconsin Materials only in programs in compliance with all applicable statutes, regulations and guidelines for research of this type. Specifically, PHS agrees that its research programs will exclude: (i) the mixing of Wisconsin Materials with an intact embryo, either human or non-human; (ii) implanting Wisconsin Materials or products of Materials in a uterus; and (iii) attempting to make whole embryos with Wisconsin Materials by any method. An annual Certification Statement confirming compliance with the restrictions on the use of Wisconsin Materials shall be supplied to WiCell by PHS and the scientists receiving Wisconsin Materials under the terms of the "Simple Letter Agreement For The Transfer of Materials." PHS agrees that Wisconsin Materials are to be returned to WiCell or destroyed upon a material breach of the terms of the Simple Letter Agreement for the Transfer of Materials Agreement by PHS.

(b) Wisconsin Patent Rights may also be used in PHS research programs involving materials other than Wisconsin Materials that may be within the scope of an issued claim of Wisconsin Patent Rights ("Third Party Materials"). This research may be conducted only in PHS research programs using Third Party Materials that are derived consistent with the Presidential Statement of August 9, 2001 and in compliance with all applicable statues, regulations and guidelines.

(c) Suppliers of Third Party Materials are granted a limited, revocable, non-commercial, research license by WiCell under the Wisconsin Patent Rights to provide such Third Party Materials to PHS research programs provided that such Suppliers make such Third Party Materials available on terms no more onerous than those contained in this Agreement. Specifically, but without limitation, Suppliers of Third Party Materials shall not be permitted to directly or indirectly receive rights (either actual or contingent) for themselves or others under

agreements or arrangements governing the supply or use of Third Party Materials. The use of Wisconsin Patent Rights in PHS research programs utilizing Third Party Materials shall be for teaching or non-commercial research purposes only. As used herein, non-commercial research purposes specifically excludes sponsored research wherein the sponsor receives a right whether actual or contingent to the results of the sponsored research, other than a grant for non-commercial research purposes to the sponsor. The Wisconsin Patent Rights may not be used with Third Party Materials for commercial purposes or the direct benefit of research sponsor, except as such research sponsor is permitted to use Wisconsin Patent Rights under a separate written agreement with WiCell or WARF. Specifically, Third Party Materials shall not be used in a PHS research program where rights (either actual or contingent) have already been granted to a research sponsor who does not have a separate written agreement with WiCell permitting commercial use of Wisconsin Patent Rights.

(d) The Parties recognize that Wisconsin Patent Rights may be used in PHS research to make patentable discoveries ("PHS Patent Rights"), which themselves may eventually be the basis of commercial products that benefit public health. Any grant of Wisconsin Patent Rights that may be needed by a third party for commercialization of PHS Patent Rights shall be done by a separate written agreement with WiCell permitting such use of Wisconsin Patent Rights under terms not less favorable than other similar commercial licenses to the extent such rights are available.

(2) The Parties agree that Wisconsin Materials are to be made available by WiCell for use in PHS biomedical research programs, either by PHS or on behalf of PHS by its contractors. For purposes of transferring Wisconsin Materials to PHS or PHS contractors, WiCell agrees to utilize the Simple Letter Agreement For The Transfer of Materials including the following conditions:

(a) Wisconsin Materials are the property of WiCell and are being made available to investigators in the PHS research community as a service by WiCell. Ownership of Wisconsin Materials shall remain with WiCell.

(b) Wisconsin Materials are not to be used for diagnostic or therapeutic purposes.

(c) Wisconsin Materials may only be used in compliance withall applicable statutes, regulations and guidelines relating to their handling or use. Specifically, PHS agrees that its research program will exclude: (i) the mixing of Wisconsin Materials with an intact embryo, either human or non-human; (ii) implanting Wisconsin Materials or products of Materials in a uterus; and (iii) attempting to make whole embryos with Wisconsin Materials by any method. An annual Certification Statement confirming compliance with the restrictions on the use of Wisconsin Materials shall be supplied to WiCell by PHS and the scientists receiving Wisconsin Materials under the terms of the Simple Letter Agreement For The Transfer of Materials. PHS agrees that Wisconsin Materials are to be

returned to WiCell or destroyed upon a material breach of the terms of the Simple Letter Agreement for the Transfer of Materials by PHS.

(d) The use of Wisconsin Materials shall be for teaching or non-commercial research purposes only. As used herein, non-commercial research purposes specifically excludes sponsored research wherein the sponsor receives a right whether actual or contingent to the results of the sponsored research, other than a grant for noncommercial research purposes to the sponsor. The Wisconsin Materials may not be used for commercial purposes or the direct benefit of research sponsor, except as such research sponsor is permitted to use Wisconsin Materials under a separate written agreement with WiCell or WARF. Specifically, Wisconsin Materials shall not be used in a PHS research program where rights (either actual or contingent) have already been granted to a research sponsor who does not have a separate written agreement with WiCell permitting such commercial use of Wisconsin Materials.

(e) Wisconsin Materials may not be transferred by PHS or its contractors to third parties without the written consent of WiCell.

(f) PHS agrees to acknowledge the source of Wisconsin Materials in any publications or other disclosures reporting their use.

(g) In order to facilitate potential novel collaborative research interactions between PHS and WiCell that may utilize Wisconsin Materials, PHS agrees to identify the titles of its planned research in its individual requests for samples of Wisconsin Materials. This information is to be provided to facilitate new interdisciplinary collaborations among individual scientists at PHS and WiCell, but not to obligate either Party to a specific program of research utilizing Wisconsin Materials.

(h) The Parties recognize that Wisconsin Materials may be used in the PHS research program to make discoveries of different materials ("PHS Materials") which themselves may eventually be the basis of commercial products that benefit public health. Any grant of rights to Wisconsin Materials or Wisconsin Patent Rights that may be needed by a third party for commercialization of PHS Materials shall be done by a separate written agreement with WiCell permitting such use of Wisconsin Materials or Wisconsin Patent Rights under terms not less favorable than other similar commercial licenses to the extent such rights are available.

(i) Any Wisconsin Materials delivered pursuant to this Agreement are understood to be experimental in nature and may have hazardous properties. WiCell makes no representations and extends no warranties of any kind, either expressed or implied. There are no express or implied warranties of merchantability for fitness for a particular purpose, or that the use of the Wisconsin Materials will not infringe any patent, copyright, trademark or other proprietary rights. Unless

prohibited by law, PHS assumes all liability for claims for damages which may arise from the use, storage, handling or disposal of Wisconsin Materials except that, to the extent permitted by law, WiCell shall be liable to PHS when the damage is caused by the gross negligence or willful misconduct of WiCell.

(j) A transmittal fee may be requested by WiCell to cover its preparation and distribution costs for samples of Wisconsin Materials requested by PHS. Such fees will be the responsibility of the requesting PHS laboratory and are not expected to exceed Five Thousand Dollars ($5,000) or as specified in the appropriate schedule of a U.S. Government procurement accompanying the PHS Simple Letter Agreement for the Transfer of Materials.

(3) Upon WiCell's written request, PHS agrees to provide without cost reasonable quantities of any PHS Materials that it makes in the course of its research program to WiCell for research purposes only after PHS has publicly disclosed or reasonably characterized such PHS Materials. For PHS Patent Rights, PHS also agrees to continue its current policy of retaining the right to grant research licenses to either non-profit or for-profit institutions.

(4) WiCell agrees that it shall make Wisconsin Patent Rights and Wisconsin Materials available for use by non-profit Recipient Institutions under separate written agreements in accordance with the terms and conditions outlined above. WiCell agrees that any non-profit Recipient Institutions currently licensed under the Wisconsin Patent Rights or Wisconsin Materials may amend its license, in a separate written agreement, in accordance with the terms and conditions outlined above.

(5) Notwithstanding any terms of this Agreement, nothing herein shall be construed to diminish or supersede any rights or authorities available to PHS as a U.S. government agency. The provisions of this Agreement and the obligations hereunder with respect to the Wisconsin Patent Rights shall be in effect only during the term of the Wisconsin Patent Rights. However, the provisions of this Agreement and the obligations hereunder with respect to the Wisconsin Materials shall continue as long as Wisconsin Materials, their derivatives or progeny continue to be used by PHS or its Contractors.

(6) Nothing contained herein shall be considered to be the grant of a commercial license or right under the Wisconsin Patent Rights or to Wisconsin Materials. Furthermore, nothing contained herein shall be construed to be a waiver of WiCell's patent rights under the Wisconsin Patent Rights or WiCell's property rights in Wisconsin Materials.

IN WITNESS WHEREOF, the Parties agree to the foregoing and have caused this Agreement to be executed by their duly authorized representatives.

WiCell Research Institute	**Public Health Service**
By:	By:
Name:	Name:
Title:	Title:

Appendix D2. The WARF-NIH MOU[34]

Sample Simple Letter Agreement for the Transfer of Materials to PHS Scientists and PHS Contractors

In response to RECIPIENT's request for MATERIAL (____ sample of Human Embryonic Stem Cells, WiCell Ref: _____, and its unmodified and undifferentiated progeny or derivatives) for a research program entitled _____ WiCell Research Foundation, Inc. ("PROVIDER") asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

1. The above MATERIAL is the property of the PROVIDER and is made available as a service to the research community. Ownership of the MATERIAL shall remain with PROVIDER and transfer of the MATERIAL to the RECIPIENT shall not affect PROVIDER's ownership of the MATERIAL.

2. This MATERIAL is not to be used for diagnostic or therapeutic purposes.

3. The MATERIAL will be used for teaching or non-commercial research purposes. As used herein, non-commercial research purposes specifically excludes sponsored research wherein the sponsor receives a right whether actual or contingent to the results of the sponsored research. The MATERIAL may not be used for commercial purposes or the direct benefit of research sponsor, except as such research sponsor is permitted to use MATERIAL under a separate written agreement with PROVIDER. Specifically, MATERIAL shall not be used in a research program where rights (either actual or contingent) have already been granted to a research sponsor who does not have a separate written agreement with PROVIDER permitting such use of MATERIAL.

4. The MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agree to make the MATERIAL available, under a separate Simple Letter Agreement to other scientists for teaching or non-commercial research purposes only.

5. The RECIPIENT agrees to acknowledge the source of the MATERIAL in any publications reporting use of it.

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

Unless prohibited by law, RECIPIENT assumes all liability for claims for damages which may arise from the use, storage, handling or disposal of MATERIAL except that, to the extent permitted by law, PROVIDER shall be liable to the RECIPIENT when the damage is caused by the gross negligence or willful misconduct of the PROVIDER.

7. The RECIPIENT agrees to use the MATERIAL only in compliance with all applicable statutes, regulations and guidelines relating to their handling, use or disposal. Specifically, RECIPIENT agrees that its research program will exclude: (i) the mixing of MATERIAL with an intact embryo, either human or non-human; (ii) implanting MATERIAL or products of MATERIAL in a uterus; and (iii) attempting to make whole embryos with MATERIAL by any method. RECIPIENT shall supply an Annual Certification Statement confirming compliance with the restrictions on the use of MATERIAL supplied by PROVIDER. RECIPIENT agrees that MATERIAL is to be returned to PROVIDER or destroyed upon a material breach of the terms of this Agreement by RECIPIENT.

8. The MATERIAL is provided with a transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. The amount of the fee for this transfer of MATERIAL will be indicated here: _____

The PROVIDER, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER will then send the MATERIAL.

PROVIDER INFORMATION and AUTHORIZED SIGNATURE

Provider Scientist: _____
Provider Organization: _____
Address: _____
Name of Authorized Official: _____
Title of Authorized Official: _____
Signature of Authorized Official: _____
Date: _____

RECIPIENT INFORMATION and AUTHORIZED SIGNATURE
Recipient Scientist: _____
Recipient Organization: _____
Address: _____
Name of Authorized Official: _____
Title of Authorized Official: _____
Signature of Authorized Official: _____
Date: _____

ANNUAL CERTIFICATION

Annual Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

Recipient Scientist: _____
Date: _____
Recipient Scientist: _____
Date: _____
Recipient Scientist: _____
Date: _____

Appendix E. Guidelines for Research Using Human Pluripotent Stem Cells That Is Eligible for NIH Funding

A. Utilization of Human Pluripotent Stem Cells Derived From Human Embryos

1. Submission to NIH

Intramural or extramural investigators who are intending to use existing funds, are requesting an administrative supplement, or are applying for new NIH funding for research using human pluripotent stem cells derived from human embryos must submit to NIH the following:

a. An assurance signed by the responsible institutional official that the pluripotent stem cells were derived from human embryos in accordance with the conditions set forth in section II.A.2 of these Guidelines and that the institution will maintain documentation in support of the assurance;

b. A sample informed consent document (with patient identifier information removed) and a description of the informed consent process that meet the criteria for informed consent set forth in section II.A.2.e of these Guidelines;

c. An abstract of the scientific protocol used to derive human pluripotent stem cells from an embryo;

d. Documentation of Institutional Review Board (IRB) approval of the derivation protocol;

e. An assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells;

f. The title of the research proposal or specific subproject that proposes the use of human pluripotent stem cells;

g. An assurance that the proposed research using human pluripotent stem cells is not a class of research that is ineligible for NIH funding as set forth in section III of these Guidelines; and

h. The Principal Investigator's written consent to the disclosure of all material submitted under Paragraph A.1 of this section, as necessary to carry out the public review and other oversight procedures set forth in section IV of these Guidelines.

2. Conditions for the Utilization of Human Pluripotent Stem Cells

Derived From Human Embryos

Studies utilizing pluripotent stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without Federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment.

a. To ensure that the donation of human embryos in excess of the clinical need is voluntary, no inducements, monetary or otherwise, should have been offered for the donation of human embryos for research purposes. Fertility clinics and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available.

b. There should have been a clear separation between the decision to create embryos for fertility treatment and the decision to donate human embryos in excess of clinical need for research purposes to derive pluripotent stem cells. Decisions related to the creation of embryos for fertility treatment should have been made free from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To this end, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person.

c. To ensure that human embryos donated for research were in excess of the clinical need of the individuals seeking fertility treatment and to allow potential donors time between the creation of the embryos for fertility treatment and the decision to donate for research purposes, only frozen human embryos should have been used to derive human pluripotent stem cells. In addition, individuals undergoing fertility treatment should have been approached about consent for donation of human embryos to derive pluripotent stem cells only at the time of deciding the disposition of embryos in excess of the clinical need.

d. Donation of human embryos should have been made without any restriction or direction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

e. Informed Consent

Informed consent should have been obtained from individuals who have sought fertility treatment and who elect to donate human embryos in excess of clinical need for human pluripotent stem cell research purposes. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether or not to donate their embryos for research purposes.

Informed consent should have included:

(i) A statement that the embryos will be used to derive human pluripotent stem cells for research that may include human transplantation research;

(ii) A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the embryo;

(iii) A statement as to whether or not information that could identify the donors of the embryos, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of human pluripotent stem cells;

(iv) A statement that derived cells and/or cell lines may be kept for many years;

(v) Disclosure of the possibility that the results of research on the human pluripotent stem cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development;

(vi) A statement that the research is not intended to provide direct medical benefit to the donor; and

(vii) A statement that embryos donated will not be transferred to a woman's uterus and will not survive the human pluripotent stem cell derivation process.

f. Derivation protocols should have been approved by an IRB established in accord with 45 CFR 46.107 and 46.108 or FDA regulations at 21 CFR 56.107 and 56.108.

Appendix F. HESC Research: An intercultural perspective[61].

There are six positions that various religious traditions have adopted regarding the research on HESC.

1. No human embryo research is permitted and no explicit permission is given to perform research on existing HESC.
2. Research is permitted only on remaining embryos no longer needed for reproduction.
3. Research is permitted only on remaining embryos no longer needed for reproduction.
4. Research is permitted both on remaining embryos (option 3) and on embryos created specifically for research purposes through IVF.
5. Research is permitted both on remaining embryos (option 3) and on embryos created specifically for research purposes through somatic cell nuclear transfer into human eggs or zygotes.
6. Research is permitted both on remaining embryos (option 3) and on embryos created specifically for research purposes through the transfer of human somatic cell nuclei into nonhuman animal eggs.

Religious beliefs:

a. Judaism: Option 3 is allowed and options 4 and 5 are not explicitly discussed at the moral level
b. Islam: Option 3 is compatible with Islam and it is not clear for option 4 and 5.
c. Buddhism: Buddhist ethic is most compatible with option 1 and Buddhist tradition in principle could accept option 3 and perhaps option 5.
d. Hinduism: Option 3 seems allowed.
e. Taoism: advocate Option 1.
f. Christianity:
    - Roman Catholicism: option 1 but Prof. Farley accepts option 3 and seems to accept option 5.
    - Eastern Orthodoxy: Option 1 but Father Demopulos declarations approximate option 2.
    - Protestant traditions: depending on the groups it can be option 1 o option 3 with conditions.

Appendix G. US stem cell research institutes.

Black Family Stem Cell Institute, Mount Sinai School of Medicine
http://www.mssm.edu/

California Institute for Regenerative Medicine (CIRM)
www.cirm.ca.gov/

Harvard Stem Cell Institute, Harvard University
http://www.hsci.harvard.edu

Laboratories of the Society for Developmental Biology, Purdue University
http://www.purdue.edu/

Pittsburgh Development Center of Magee-Women's Research Institute
www.mwri.magee.edu/

Sloan-Kettering Institute
http://www.mskcc.org/mskcc/html/44.cfm

Stanford University School of Medicine/Institute for Cancer/Stem Cell Biology and Medicine
http://med.stanford.edu/

Stem Cell Institute of New Jersey
http://www2.umdnj.edu/scinjweb/

University of California, San Francisco
http://www.ucsf.edu

University of Minnesota Stem Cell Institute
http://www.stemcell.umn.edu/

University of Minnesota Stem Cell Institute
http://www.stemcell.umn.edu/

University of Wisconsin Stem Cell Institute
http://www.wisc.edu.libproxy.mit.edu/

Appendix H. Chronology of main strategic alliances.

95/96	Geron Collaboration in HSC with UC San Francisco.
95/96	Geron in-licensed rhesus monkey SC technology from WARF.
Sep. 96	Biotransplant - exclusive worldwide rights to use Activated Cell Therapy's bone marrow stem cell isolation device.
Oct. 96	ImClone Systems - exclusively licensed worldwide rights to stem cell, gene therapy and related application of the delta-like protein and gene from the NIH.
Jun. 96	Osiris Therapeutics dealed with Novartis for the development of 3 mesenchymal stem cell (MSC) gene therapy for osteoporosis, OA, cage repair. DV= 63, EQ=10, PC=8%, cv=125
Sep. 97	Geron licensed patent filins related to the identification and uses of human primordial SC from John Hopkins U.
Mar. 98	Osiris Therapeutics pay 1M research funding to University of Genoa for exclusive WWD right to mesenchymal stem cells and related stroma cell technology.
Sep. 98	Osiris Therapeutics use Tissue Matrix Delivery System from Collagenesis for use in the delivery of MSCs.
Mar. 99	Aastrom Biosciences collaborated with Duke U. to further develop Aastrom Replicell, automated system designed to produce clinical quantities of cells, including SC.
Jul. 99	Aastrom Biosciences negotiated one-year licensed exclusive rights with Gambro (Norway) to sell Aastrom Replicell in Europe. In exchange of royalties.
Jul. 99	Aastrom Biosciences negotiated three-year licensed exclusive rights with Micromin AG (Swiss) to sell Aastrom Replicell in Europe. In exchange of royalties on sales.
Aug. 99	BioWhittaker to manufacture and market Osiris stem cell products in exchange of 5MM upfront equity investment of 770K shares at 6.%$ each and royalties on sales.
99	Geron renegotiated with WARF.
Jun. 00	Geron collaborated with Celera Genomics to determine functions of genes in HESC.
Jan. 01	Cerus Corp signed a partnership with Kirin Brewery's pharmaceutical unit to develop stem cell transplant products for cancer application using Cerus's Helinx technology.
Feb. 01	CryoCell entered a research collaboration with University of South Florida for treatment of neurodegenerative diseases using umbilical cord blood stem cells.
Mar. 01	Raven Biotechnologies agreed with ImmunoGen to identify protein targets and antibodies to develop ovarian cancer therapies using Raven's technologies.
Jun. 01	ES Cell International signed a partnership with Quark Biotech to research the causes of HESC differentiation and renewal.
Jun. 01	Aastrom Biosciences signed a partnership with Neoprobe Corp. to use Aastrom Replicell technology to develop an immune system cancer therapy.
Nov. 01	Psychiatric genomics licensed worldwide rights to use ReNeuron neural HSC in the discovery of mental disorder therapies.
Nov. 01	Paradigm Genetics will use its MetaVantage platform to determine biochemical profiles of adult SC provided by StemCo Biomedical.
Jan. 02	Geron signed a new agreement with WARF.
Apr. 02	Chromos Molecular and MorphoGen perform stem cell research.
Jun. 02	Stem Cell Inc. obtained license rights to certain human neural SC from BioWhittaker

	for use in research and educational program.
Jun. 02	Centocor signed a collaborative research agreement with Neuronyx to use Neuronyx's stem cells, derived from bone marrow, as cardiovascular drugs.
Sep. 02	WiCell will use Ariad's technology to control the function of its own line of HESC. In exchange Ariad receives the option to license technology and patents from WiCell to use in future dvpt and commercialization of any discoveries that result from the collaboration.
Sep. 02	ReNeuron licenses stem cell patents from Amrad.
Nov. 02	PharmaStem licenses stem cell IP of umbilical cord blood storage and placenta bllob preservation to stem cell banking company Anthrogenesis
Dec. 02	Athersys gets exclusive rights from Un Minnesota to an adult stem cell technology.
Dec. 02	Curis licenses stem cell IP to ES Cell to develop new treatments for diabetes.
Jan. 03	ES Cell international gets development and marketing rights to Stanford's technology.
Feb. 03	Stembanc licenses PharmaStem Therapeutics' patents relating to cryopreservation, reanimation and therapeutic use of SC from umbilical cord and placenta blood.
Mar. 03	Osiris agreed with Boston Scientifics to develop a gene therapy based on Osiris MSC
Apr. 03	VistaGen and Sanwa Kagaku will partner in creating discovery tools using VistaGen's stem-cell technologies.
Aug. 03	JCR Pharmaceuticals gets rights to Osiris stem cell technology.
Sep. 03	StemCyte licenses PharmaStem's cord blood preservation IP.
Dec. 03	Multicell gets rights to Rhode Island Hospital's stem cells.
Dec. 03	Amgen and ViaCell collaborate in stem cell therapies.
Feb. 04	Securacell Inc. licensed rights from PharmaStem Therapeutics' patent portfolio covering the collection, the storage and the preservation of fetal and neonatal SC.
Apr. 04	California Cryobank licenses PharmaStem's patents.
Jun. 04	Erion and Stemline collaborate on stem cell for cancer.
Jul. 04	ES Cell gets rights to use the NSCC's stem cells.
Sep. 04	ViaCell licenses Tyho Galileo Research Laboratory patent focusing on the field of oocyte and embryo cryopreservation technologies.
Nov. 04	Geron grants Revivicor rights to NT technology.
Mar. 05	Genzyme and ViaCell enter diabetes deal to find a way of transplanting pancreatic stem cells.
Apr. 05	Icoria and Vesta therapeutics sign liver stem cell agreement.
Jul. 05	ReNeuron and StemCells in cross-licensing deal.
Aug. 05	ViaCell gets stem cell growth factor technology for John Hopkins University.
Nov. 05	Cytoris and Olympus form a JV for stem cell therapy discovery.
Nov. 05	Stem Cell Sciences and University of Nice pursue stem cell research applied to Duchenne Muscular Dystrophy.
Mar. 06	Geron licenses Univeristy of Oxford stem cell patents.
May. 06	Athersys and Angiotech will jointly develop stem cell therapeutics for CV diseases.
Jun. 06	J&J signs deal with ViaCell for cardio stem cell therapeutics.
Jun. 06	Cellartis and Invitrogen agreed to jointly develop HESC lines.

Appendix I. Survey to stem cell researchers*.

** Survey designed with the input of Wesley Cohen from Duke University.*

In this first section, we would like to better understand your research

1. Which one of the following best describes the primary goal of your current research activity?

- Exploration of a new window on human developmental biology ☐
- Transplantation ☐
- Tissue engineering ☐
- Gene therapy ☐
- New model of human disease(s) ☐
- Other (please specify) _____

2. If your research is on a new model(s) of human disease(s), could you please specify the clinical application?

- Type 1 diabetes in children ☐
- Primary Immunodeficiency Diseases ☐
- Diseases of Bone and Cartilage ☐
- Cancer ☐
- Other (please specify) _____

3. When do you foresee any clinical application of your work, if any?

- By 2010 ☐
- By 2015 ☐
- After 2015 ☐
- Not applicable, my research is fundamental ☐

4. Which type(s) of stem cells do you use in your research?

- Adult ☐
- Embryonic ☐
- Germ ☐

5. To which animal model do you apply your research?

- Human ☐
- Mice ☐
- Other (please specify) _____

The following items ask about your research input

6. In the last 3 years, did you request research input from academic or industry scientists outside your own organization?

- Yes ☐
- No (please skip to Q28) ☐

7. In total, during the last 3 years, how many requests did you make, and how many were not fulfilled? Please answer for requests to both academic and industry scientists.

Requests to:	**Academic scientists**	**Industry scientists**
a. Total number of requests made	_____#	_____#
b. Number not fulfilled	_____#	_____#

8. For each of the following types of research inputs, were all of your requests fulfilled, were some fulfilled, or were none fulfilled? Please answer for requests to both academic and industry scientists. If you did not make requests for that research input, please enter NA.

	Request to academic scientists fulfilled				**Request to industry scientists fulfilled**			
Type of research input	**All**	**Some**	**None**	**NA**	**All**	**Some**	**None**	**NA**
Stem cell line(s)	☐	☐	☐	☐	☐	☐	☐	☐
SC line analysis tool kit(s)	☐	☐	☐	☐	☐	☐	☐	☐
Fertilized human eggs	☐	☐	☐	☐	☐	☐	☐	☐
Technical support & training	☐	☐	☐	☐	☐	☐	☐	☐
Feeder layer &support cells	☐	☐	☐	☐	☐	☐	☐	☐
Culture media and sera	☐	☐	☐	☐	☐	☐	☐	☐
Selected reagents for cell characterization	☐	☐	☐	☐	☐	☐	☐	☐
Unpublished information or findings	☐	☐	☐	☐	☐	☐	☐	☐
Other (please specify) _____	☐	☐	☐	☐	☐	☐	☐	☐

If all your requests were fulfilled, please skip to Q10.

9. As a result of failure(s) to receive a requested research input, how often have each of the following occurred?

Request to:	**Academic scientists**					**Industry scientists**				
Number of times unfulfilled request resulted in...	**0**	**1-2**	**3-5**	**6-10**	**>10**	**0**	**1-2**	**3-5**	**6-10**	**>10**
• Delayed completion of the experimental by more than one month	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Having to change research approaches	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Abandoning a promising line of research	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
• Having to develop the research input in my own lab	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

10. How important were each of the following in preventing you from producing the research input yourself, instead of requesting it from another investigator? Please answer on the following scale from 1 to 5.

	Not important at all 1	2	3	4	Very Important 5
• The time or cost required to produce the research input	☐	☐	☐	☐	☐
• My lab does not have the capabilities to produce the research input	☐	☐	☐	☐	☐
• Patent(s) prevented duplicating the research input	☐	☐	☐	☐	☐

11. Was the request directed to an academic or an industry scientist?

Academic ☐
Industry ☐

12. Was the request research input patented?

Yes ☐
No ☐
Don't know ☐

13. As a condition to fulfilling the request, did the sender ask you to sign a licensing agreement, Material Transfer Agreement (MTA) and/or a Memorandum of Understanding (MOU)?

Yes (MTA) ☐
Yes (MOU) = ☐
Yes (license) ☐
No (skip to Q21) ☐

14. If the sender asked you to sign a license, which type of license was it?

Commercial license agreement ☐
Non-commercial license agreement ☐

15. Was there any clause of exclusivity in the license agreement?

Yes ☐
No ☐

16. Was there any negotiation regarding the terms of the agreement?

Yes ☐
No (skip to Q21) ☐

17. Was your organization's technology transfer office or patent counsel involved in the negotiations?

Yes ☐
No ☐

18. How long did the negotiations last?

Less than 1 week ☐
1 week to less than 1 month ☐

1 month to less than 6 months ☐
6 months or more ☐

19. During the negotiation, was there any period during which the research had to stop while waiting for the conclusion of the negotiations?

Yes ☐
No (skip to Q21) ☐

20. How long was the project stopped waiting for the outcome of the negotiations?

Less than 1 week ☐
1 week to less than 1 month ☐
1 month to less than 6 months ☐
6 months or more ☐

21. If the requests involved stem cell lines and fertilized eggs, can you please specify what the projected payment per cell line and/or per fertilized egg was/were even if there were no agreement or it was not concluded?

Stem cell line _____ $
Fertilized egg _____ $

22. To which provider(s) do you buy your stem cell line(s)?

CyThera Inc - San Diego ☐
BresaGen Inc - Athens GA ☐
Geron Corp - Menlo Park ☐
University Of California SF ☐
WiCell - Wisconsin ☐
National Center for Biological Sciences, Bangalore - India ☐
Reliance Life Sciences, Mumbai - India ☐
Technion-Israel Institute of Technology, Haifa - Israel ☐
Pochon CHA University, Seoul - Korea ☐
Maria Biotech Co, Ltd, Seoul - Korea ☐
MizMedi Hospital, Seoul - Korea ☐
ES Cell International Pte Ld - Singapore ☐
Cellartis AB, Göteborg - Sweden ☐
Göteborg University, Göteborg - Sweden ☐
Karolinska Institute, Stockholm - Sweden ☐
Other (please specify) _____ ☐
I use our own derived cell line(s) ☐

23. Do you think that these stem cell lines are of equal quality?

Yes ☐
No ☐

24. How important are the following criteria in your choice of stem cell line(s) as a research tool?

	Not important at all				Very Important
	1	2	3	4	5
Quick availability	☐	☐	☐	☐	☐
Inexpensive	☐	☐	☐	☐	☐
Federally approved (for US researchers)	☐	☐	☐	☐	☐
Easy to replicate	☐	☐	☐	☐	☐
Stable in long-term culture	☐	☐	☐	☐	☐
Prior good experience with the line(s)	☐	☐	☐	☐	☐
Other (please specify) _____	☐	☐	☐	☐	☐

25. If you use US federally approved stem cell lines in your research, how well in your opinion these lines fit to your research need?

Not well at all				Very well
1	2	3	4	5
☐	☐	☐	☐	☐

26. Which stem cell line do you use as a principal research tool? _____

27. In your opinion, is there a need for an international stem cell line standard?

Yes ☐
No ☐

Requests made by others for research inputs

28. In the last 3 years, have you received after-publication requests for research inputs from academic or industry scientists?

Yes ☐
No (skip to Q34) ☐

29. In total, in the last X years, how many requests did you receive, and how many did you not fulfill? Please answer for requests from both academic and industry scientists.

Requests from:	Academic scientists	Industry scientists
Total requests received	_____#	_____#
Number not fulfilled	_____#	_____#

30. In the last 3 years, have you ever denied a request from academic or industry scientists for research inputs?

Yes ☐
No (skip to Q34) ☐

31. When you denied a request, what type of research input was involved?

Stem cell line(s) ☐
Stem cell line analysis tool kit(s) ☐
Fertilized human eggs ☐

Technical support and training ☐
Feeder layer and support cells ☐
Culture media and sera ☐
Selected reagents for cell characterization ☐
Unpublished information or findings ☐
Other (please specify) _____ ☐

32. Was this request from an academic or an industry scientist?

Academic ☐
Industry ☐

33. How important were each of the following reasons for not fulfilling the request? Please answer on a scale from 1 to 5, where 1 is not at all important, and 5 is very important.

	Not important at all				**Very Important**
	1	**2**	**3**	**4**	**5**
• My need to protect my research group's ability to publish	☐	☐	☐	☐	☐
• My need to protect the commercial value of the results	☐	☐	☐	☐	☐
• My need to honor the requirements of a research sponsor	☐	☐	☐	☐	☐
• Having had my own requests for inputs denied	☐	☐	☐	☐	☐
The cost or effort required to produce the research input	☐	☐	☐	☐	☐
• Concern that sharing the research input might make me liable for patent infringement	☐	☐	☐	☐	☐
• The person making the request would not accept my terms for the material transfer or license	☐	☐	☐	☐	☐
• Sending the research input would violate the terms of other agreements (e.g. MTA, license)	☐	☐	☐	☐	☐

The following items ask how you choose our research projects

34. Please think about your most recently initiated major project. By "major," we mean the project on which you spent the bulk of your time. When choosing that research project, how important were each of the following considerations? Please answer on a scale from 1 to 5, where 1 is not at all important and 5 is very important. Please answer NA if the criterion is not applicable.

	Not important at all					**Very Important**
	1	**2**	**3**	**4**	**5**	**NA**
• Access to sufficient funding	☐	☐	☐	☐	☐	☐
• The commercial potential of possible inventions	☐	☐	☐	☐	☐	☐

• The health benefit for society of the projected result	☐	☐	☐	☐	☐	☐
• The potential increase in personal income from commercializing an application of my research.	☐	☐	☐	☐	☐	☐
• How interesting the project appears to be	☐	☐	☐	☐	☐	☐
• The patentability of the projected research results	☐	☐	☐	☐	☐	☐
• The research area is unencumbered by patents on research inputs	☐	☐	☐	☐	☐	☐
• The likely effects on my chance for promotion or a new job	☐	☐	☐	☐	☐	☐
• The scientific importance of the research	☐	☐	☐	☐	☐	☐
• The feasibility of the proposed research project	☐	☐	☐	☐	☐	☐
• The likelihood of starting a new firm based on the research	☐	☐	☐	☐	☐	☐
• Whether *Human Embryonic* stem cells are involved	☐	☐	☐	☐	☐	☐
• The type of funding involved (NIH/VC/Non-Profit etc…)	☐	☐	☐	☐	☐	☐
• The clinical alignment of the project with my expertise	☐	☐	☐	☐	☐	☐
• The moral considerations surrounding the source of the cells	☐	☐	☐	☐	☐	☐
• The religious considerations	☐	☐	☐	☐	☐	☐

35. Please think about the most recent case where you seriously considered initiating a major research project and decided not to pursue it at that time. How important were each of the following in dissuading you from pursuing that project? Please answer on a scale from 1 to 5, where 1 is not at all important and 5 is very important. IF YOU HAVE NEVER DECIDED AGAINST PURSUING A MAJOR RESEARCH PROJECT AFTER SERIOUS CONSIDERATION, PLEASE SKIP TO Q37. Please answer NA if the criterion is not applicable.

	Not important at all					**Very Important**
	1	**2**	**3**	**4**	**5**	**NA**
• I was unable to get sufficient funding	☐	☐	☐	☐	☐	☐
•The commercial potential of possible inventions was not good	☐	☐	☐	☐	☐	☐
• The health benefits for society of the projected results were not significant	☐	☐	☐	☐	☐	☐
• There was little potential for increased personal income from commercializing an invention.	☐	☐	☐	☐	☐	☐
• The project was not very interesting	☐	☐	☐	☐	☐	☐

• The projected research results would not be patentable	☐	☐	☐	☐	☐	☐
• There were too many patents covering needed research inputs.	☐	☐	☐	☐	☐	☐
• The terms demanded for access to needed research inputs were unreasonable	☐	☐	☐	☐	☐	☐
• The research was unlikely to improve my chance for promotion or a new job	☐	☐	☐	☐	☐	☐
• The research was not scientifically important	☐	☐	☐	☐	☐	☐
• The project did not appear feasible	☐	☐	☐	☐	☐	☐
• Too many competing groups were pursuing similar projects	☐	☐	☐	☐	☐	☐
• The research was not likely to provide the basis for starting a new firm	☐	☐	☐	☐	☐	☐
• I was too busy with other projects	☐	☐	☐	☐	☐	☐
• The project did not involve hESC	☐	☐	☐	☐	☐	☐
• The clinical non-alignment of the project with my expertise	☐	☐	☐	☐	☐	☐
• The type of funding was not compatible with the activity of my organization and/or with my personal motivation	☐	☐	☐	☐	☐	☐
• Moral considerations surrounding the source of stem cells	☐	☐	☐	☐	☐	☐
• Religious considerations	☐	☐	☐	☐	☐	☐

36. Which type(s) of funding did you receive from the project(s) you chose to pursue?

NIH grants	☐
State funding	☐
Venture capital	☐
Philanthropic venture	☐
Not-for-profit organization	☐
Industry Company	☐
Wealthy individual	☐
Other (please specify) _____	☐

37. Can you please specify whether the research purpose of the funding you received was for fundamental or clinical research applications?

	Fundamental Research	Clinical research
NIH grants	☐	☐
State funding	☐	☐
Venture capital	☐	☐
Philanthropic venture	☐	☐
Not-for-profit organization	☐	☐
Industry Company	☐	☐

Wealthy individual		☐	☐
Other (please specify)	_____	☐	☐

38. Can you please specify the *annual* amount of money the following investors eventually invested in your projects? Please enter "0" if no money was received.

Venture capital	_____$
Philanthropic venture	_____$
Not-for-profit organization	_____$
Wealthy individual	_____$

39. Can you please evaluation approximately what percentage of your research is financed *this year* by the following items? Can you please evaluate what was this percentage *5 years ago*?

	This year	5 years ago
Venture capital	_____%	_____%
Philanthropic venture	_____%	_____%
Not-for-profit organization	_____%	_____%
Wealthy individual	_____%	_____%

Patenting, Licensing and Regulatory.

40. In the last 3 years, have you conducted research that required information or knowledge that was covered by someone else's patent? Please exclude cases where you were covered by a license that predated this research.

Yes	☐
No (skip to Q46)	☐
Don't know (skip to Q46)	☐

41. In the last 3 years, how many such cases have there been?

1–2	☐
3–5	☐
6–10	☐
More than 10	☐

42. Was the patent owner from academia or industry?

Academia	☐
Industry	☐

43. Were you able to quickly (within one month) receive permission to use the patented research input?

Yes (skip to Q45)	☐
No	☐

44. Did any of the following occur due to the delay or inability to receive permission?

Delayed completion of the experiment by more than one month ☐ Yes ☐ No

Having to change research approaches to complete the study	☐ Yes	☐ No
Abandoning a promising line of research.	☐ Yes	☐ No

45. For this permission (which may have come in the form of a license), what was the projected payment for the first year of use? Please include the requested payment amount even if the agreement was not concluded.

Zero	☐
$1 to less than $100	☐
$100 to less than $500	☐
$500 to less than $1,000	☐
$1,000 to less than $10,000	☐
$10,000 to less than $100,000	☐
$100,000 or more	☐

46. Do you regularly check on patents on tangible or knowledge inputs into your research?

Yes	☐
No	☐

47. Do you think that the US stem cell patents have an impact on your research on stem cells?

Yes	☐
No (skip to Q50)	☐
I don't work in the US (skip to Q50)	☐

48. How important is the impact of the US stem cell intellectual property rights on the following items? Please answer on a scale from 1 to 5, where 1 is not at all important, and 5 is very important.

	Not important at all				**Very Important**
	1	**2**	**3**	**4**	**5**
It has hinder my research activity	☐	☐	☐	☐	☐
It has prevented me from publishing articles	☐	☐	☐	☐	☐
It has discouraged me to pursue interesting projects	☐	☐	☐	☐	☐
It has more impact on upstream research	☐	☐	☐	☐	☐
It has more impact on downstream research	☐	☐	☐	☐	☐
It has reduced the level of communication among researchers	☐	☐	☐	☐	☐
It has affected the overall US progress of science in this field	☐	☐	☐	☐	☐

49. How do you find the stem cell regulations in your State?

Clear	Yes	☐	No	☐
Easy to understand	Yes	☐	No	☐
Restrictive	Yes	☐	No	☐

Progressive Yes ☐ No ☐

50. Have you applied or do you have already a patent in this field?

Yes ☐
No ☐

51. In your opinion, what is the most favorable State in the US to pursue stem cell research? _____

52. Can you please explain briefly why? _____

53. In your opinion, what is the most favorable country in the world to pursue stem cell research? _____

54. Can you please explain briefly why? _____

Please tell us about yourself

a. What is your gender?

Female ☐
Male ☐

b. What is(are) your highest degree(s)?

BA ☐
BSc ☐
MA ☐
MD ☐
MSc ☐
PharmD ☐
PhD ☐
Other_____ ☐

c. Where have you obtained your highest degree(s)?

Africa ☐
Asia ☐
Australia ☐
Canada ☐
Europe ☐
Latin America ☐
US ☐

d. Are you a US citizen or US permanent resident?

Yes ☐
No ☐

e. How many years of research experience do you have in stem cells?

0-3	☐
4–5	☐
6–10	☐
More than 10	☐

f. Which of the following best describes your current primary institutional affiliation?

University (excluding university hospital)	☐
Hospital (including university hospital)	☐
Government or nonprofit research institute	☐
Large firm (500+ employees)	☐
Small or medium-sized firm (including startup firms)	☐

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