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A Life Sciences Crucible

Stem Cell Research and Innovation Done Responsibly and Ethically

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Introduction and Summary

A Call to Innovation

It is time for the United States to stake its claim as the world leader in regenerative medicine, which promises to become a vital component of the cutting edge of life sciences research and innovation in the 21st century. To ensure research in this newly emerging field of life sciences is conducted responsibly and ethically, the federal government must reform its stem cell research policy in order to fund embryonic stem cell research that is robust and comprehensive as well as cautious and principled.

Regenerative medicine is a new therapeutic approach that works by cultivating a small sample of a patient's own cells, reprogramming them, and using them to heal the patient without the risk of rejection or severe side effects that usually result from introducing foreign therapeutic materials. The potential therapies range from transforming the pancreatic cells of diabetics so they can produce insulin to reconnecting the nerves in severed spinal cords. Indeed, there have already been some modest clinical applications where heart muscles and cartilage have been repaired with stem cells derived from bone marrow.

But that is just the tip of the iceberg. The greatest potential for regenerative medicine lies in scientists' ability to tap into the process of cell differentiation and development. This can only be achieved by tracing the development of human cells from the very beginning. To do so, scientists need to conduct research on embryonic stem cells so that they can discover how these all-purpose cells can change into any one of the more than 200 different cell types in the human body.

Moreover, by studying the development of embryonic stem cells scientists will be able to discover how the human genome goes about manifesting itself and creating unique individual persons. These efforts will provide us with unprecedented insights into human development, how it can go wrong, and how it can be fixed.

Opponents of embryonic stem cell research argue that there have been many scientific advances made using stem cells that do not come from embryos, such as bone marrow-derived stem cells, which are a type of adult stem cell. Opponents also point to so-called induced pluripotent stem cells, which are created when adult cells—say, skin cells—are reprogrammed to become all-purpose "pluripotent" cells. These arguments are valid, but

only up to a point. The reason: embryonic stem cells are both the original "master cells" capable of turning into any cell in the body as well as the "gold standard" against which all other stem cells must be compared

Scientists determine whether other types of stem cells hold the promise of delivering the kinds of regenerative medicine envisioned by life scientists by analyzing the surfaces of these alternative cells to see whether they have the same proteins and therefore the same capabilities as embryonic stem cells. Evidence suggests that these stem cell-specific proteins activate certain chemical pathways in the stem cells, which in turn allow them to maintain their pluripotency. Regardless of what type of stem cells prove to be the most useful, this process of embryonic stem cell comparison must be carried out for each therapeutic application, whether for Alzheimer's disease, Parkinson's disease, spinal cord injuries, or any of the other myriad conditions for which stem cell therapy might be possible.

Just as important: embryonic stem cells must be studied so that scientists can learn more about developmental biology. It is a longstanding research paradigm to study failures of development by determining when, where, and how genes malfunction. The ultimate goal is to develop a guidebook that will tell us exactly how each gene or combination of genes contributes to the development of a unique individual. This will greatly enhance our understanding of basic genetics and could allow scientists to develop drugs that can prevent the diseases from developing in the first place.

Additionally, embryonic stem cells can aid in the refinement of these new drugs since the cells can be differentiated into specific cell types upon which scientists can quickly test whether a drug has a desired effect. This will make the drug development process and then the clinical trial process much safer and more efficient.

The bottom line is that embryonic stem cell research is good science. It is necessary science, and it needs to be part of America's federally funded biomedical research enterprise if America is to retain its status as a global scientific leader. That's why embryonic stem cell research must be conducted responsibly and ethically, and why the incoming Obama administration must outline new federal research and funding oversight guidelines for embryonic stem cell research that are cautious and principled.

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A New Federal Embryonic Stem Cell Research Agenda

The first step toward renewing U.S. life sciences leadership must be taken by the executive branch. President Barack Obama has the option of either issuing an executive order or issuing a presidential memorandum to govern stem cell research. Either way, the primary objective of the executive document must be to lift the existing temporal restriction on the federal funding of embryonic stem cell research.

Developmental biologist James Thomson works at a microscope in his research lab at the University of Wisconsin-Madison.

Currently, federal funding is only available for research on the 21 lines of embryonic stem cells that were derived before August 9, 2001. Once this arbitrary limit is lifted, the National Institutes of Health will be able to issue grants to scientists who wish to research embryonic stem cells in accordance with guidelines for ethically derived cells, including:

- The stem cells must come from embryos that were originally created at *in vitro* fertilization clinics for the purpose of fertility treatment but are now stored at these IVF clinics because more were created than required to fulfill the patient's clinical need
- Proper written informed consent is obtained from the donors
- As part of the informed consent process, the embryo donors along with the physician determine that the embryos will never be implanted in a womb and would otherwise be destroyed
- There are no financial inducements and the donors understand the purpose of the research is not to eventually confer therapeutic benefits upon the donors

Embryonic stem cell research requirements along these lines should also be codified in legislation by the incoming 111th Congress and become law so that future presidents cannot obstruct this research.

In addition, it is current policy that no embryonic stem cells will be derived using federal funds. Federal funds will only pay for research on stem cells that have already been derived with private funds.

To enforce these ethical guidelines and to ensure that all stem cell research (embryonic or otherwise) is conducted cautiously and responsibly so as not to threaten the safety or autonomy of research subjects or the donors of research materials, the following administrative oversight requirements should be included either in the president's document or in legislation that should be passed in the first session of the 111th Congress:

- The National Institutes of Health should require that all research be conducted under the review of a stem cell research oversight committee that adheres to the standards put forth in the regulations issued by NIH and HHS as informed by the National Academies or the International Society for Stem Cell Research guidelines. Any embryonic stem cells that are not in compliance with these rules, or are derived from embryos that are not in compliance with these rules, will not be eligible for federal funding.

- The one caveat to this requirement is that the 21 cell lines that were approved by the Bush administration should be grandfathered into the new policy because federal funding has already been provided for research that is now well underway.

- The NIH or the Department of Health and Human Services should adopt these rules no more than 90 days after the executive order lifts the existing restriction.

Federal funds will only pay for research on stem cells that have already been derived with private funds.

If these requirements are articulated in a presidential document, then the 111th Congress should also codify them in legislation. The legislation should provide broad, principled ethical standards so that the science itself can evolve in the direction that experimentation and serendipity takes it—alongside easily adapted regulations governing the research based on the broad ethical standards approved by Congress. Specifically, the legislation should charge the Department of Health and Human Services with the duty to update at regular intervals its regulations for embryonic stem cell research in light of new science.

These policy guidelines will ensure that human embryonic stem cell research is carried out with the highest ethical standards. It will also ensure that U.S. public and private biomedical research laboratories live up to the highest scientific standards. In the pages that follow, we will examine in detail why these new guidelines are necessary and proper given the history of stem cell research during the Bush administration and the advances that have been made in the science since James Thomson of the University of Wisconsin at Madison first created this new life sciences arena 10 years ago. In short, this paper will demonstrate that our policy recommendations are based on good science and sound ethical principles.

Glossary of Scientific Terms in This Paper

Blastocyst. A hollow, microscopic ball of 50 cells to 250 cells (depending on the age and species). It is made up of a hollow outer layer called the trophoblast and contains the inner cell mass (also known as the embryoblast). Pluripotent stem cells are procured from the inner cell mass. The blastocyst arises in human development after the embryo, which starts as a single-cell zygote, has divided multiple times. After the blastocyst stage, the embryo implants in the uterus and begins the process of gastrulation.

Cell Line. A permanently established cell culture that will multiply and divide indefinitely if given the necessary resources

Chimera. An organism that contains two or more genetically distinct types of cells from two or more genetically distinct organisms, such as a mouse that has a liver made of human cells

Chromosome. A structure made of DNA and proteins, in a cell, that contains an organism's genes

Cloned Cell Line. A cell line derived from a single cell through cloning

Cloning. The creation of a genetically identical cell or group of cells

Differentiation. The increasing specialization of cells during development—a process that fits cells into a developmental path during the development of the embryo so that some stem cells differentiate into heart cells, some into kidney cells, and so on

Diploid. A cell or an organism containing two sets of chromosomes, usually one set from the mother and one set from the father (human cells have 46 chromosomes)

Embryo. A group of cells in the early states of development that is characterized by the formation of primitive organs, organ systems and fundamental tissues (in humans, the embryo lasts from implantation through about the end of the eighth week of development, after which time it becomes a fetus)

Gastrulation. A complex set of movements and cellular modifications that occur in early development after the diploid zygote (the product of the fusion of egg and sperm during fertilization) has undergone many divisions and has become a 50 cell to 250 cell blastocyst —a process that differs across species but usually results in the formation of three layers of cells, called the endoderm (interior gut lining), the mesoderm (muscle, bone, and blood), and the ectoderm (epidermal tissues and nervous system)

Gene. A segment of DNA located on a particular part of a chromosome that typically directs the formation of a specific enzyme or other protein

Haploid. A cell or organism containing one set of chromosomes (human sex cells—sperm and egg—each have 23 chromosomes)

Hybrid. An organism with a single set of cells resulting from the fusion of the egg and sperm from two genetically distinct organisms (a mule is a hybrid between a male donkey and female horse); in stem cell research, a hybrid is a zygote that is formed when the genome of one species is inserted into an empty ovum from another species

***In Vitro* Fertilization.** An assisted reproductive technique in which fertilization occurs outside of the body in a petri dish, with some of the resulting embryos usually implanted into a female for development into a fetus

Induced Pluripotent Stem Cells. So called iPS cells are pluripotent stem cells derived from a non-pluripotent cell (such as an adult skin cell) by turning back its cellular clock through inducing the expression of certain traits

Multipotent Cell. Partially differentiated stem cells found in adult tissue capable of forming a limited number of cell types, such as hematopoietic cells—which can differentiate into red, white, or other forms of blood cells—or neural progenitor cells, which can become neurons or the gilal cells that insulate neurons

Neurulation. The stage in vertebrate development preceeding gastrulation that results in the formation of the neural tube, which eventually becomes the spinal cord

Nuclear Transfer. Replacing the nucleus in one cell with the nucleus from another cell

Pluripotent Cell. A cell type that has the ability to develop into three tissue types: the endoderm (interior gut lining), the mesoderm (muscle, bone, and blood), and the ectoderm (epidermal tissues and nervous system)

Primitive Streak. A band of cells that establishes the left-right orientation and head-tail ends of the embryo and which eventually develops into the spinal cord

Somatic cell. A cell that makes up the fully developed body of an organism. These are contrasted with germline cells, which are used for reproduction, and stem cells, which have yet to differentiate and form a fully developed organism

Somatic Cell Nuclear Transfer. SCNT is a specific form of nuclear transfer in which the source of the nucleus implanted is a somatic cell

Stem Cell. A cell that has the ability to divide indefinitely and give rise to specialized cells in culture or in an organism

Totipotent Cell. A cell that has the ability to develop into any cell type, including embryonic tissues

Undifferentiated. Cells that have not become specialized

Zygote. The diploid cell formed as a result of fertilization (in humans, this is formed by the fusion of an egg cell from a female and a sperm cell from a male)

New Science, New Promise; Old Policies, Old Debates

It's now clear that the Bush administration's policy preempted the participation of scientists, ethicists, patient advocates, investors and the general public in defining the ends and means of embryonic stem cell research.

Since James Thomson's 1998 discovery of how to derive human embryonic stem cells from human embryos,[1] there has been a vigorous debate about the ethical and policy implications of this promising new field of medical research. This debate has now gone on for a decade, and it is clear that the Bush administration's policy, which severely limited federal funding of human embryonic stem cell research, has hampered science to no good purpose. Although the Bush policy claims to balance science and ethics, in fact it has failed on both counts.

Bush administration officials wanted the policy to appear to be a reasonable compromise by allowing the NIH to approve as many cell lines as possible that were derived before the arbitrary date of August 9, 2001 (see the timeline on the right for a quick history of the research). The Bush administration originally claimed that there would be over 60 available lines. But after all of the lines were assessed for quality, it turned out that there were only 21 research-quality lines.

Now, after an investigation into the informed consent forms required from embryo donors, only 16 lines appear to meet both the appropriate qualitative and ethical standards. That investigation showed that five of the 21 human embryonic stem cell lines approved by the Bush administration for NIH research funding failed to meet even the most minimal requirement of informed consent by the donors.[2] Advocates for human embryonic stem cell research have long accused the Bush policy of invoking "ethics" simply out of political convenience. This incident certainly drives that point home.

Indeed, it's now clear that the Bush administration's policy preempted the participation of scientists, ethicists, patient advocates, investors and the general public in defining the ends and means of embryonic stem cell research and in evaluating the risks and benefits by placing unprecedented limits on a new field of science. The rigorous pursuit of scientific knowledge is the surest way to a greater understanding of disease and illness, new ways to heal the sick, and improvements in our quality of life, but all scientific research requires ongoing societal dialogue to ensure continuous ethical reflection based on a continuous stream of evidence and public testimony. The Bush administration's stem cell policies failed on both counts.

The scientific case for human embryonic stem cell research

Opponents of human embryonic stem cell research often champion human adult stem cells or umbilical cord blood stem cells as suitable alternatives.[3] They also consider the recent creation of so-called induced pluripotent stem cells, or iPS cells (see glossary on page 2 and the box on different types of stem cells on page 23 for more details), as a vindication of President Bush's restrictive embryonic stem cell research policy.[4] These iPS cells are created by using viruses that insert genes into human somatic (body) cells to make them pluripotent, or capable of becoming any one of the 200-plus different types of human cells. Refinements of this technology may someday eliminate the need for human eggs and/or embryos in research. Indeed, there have been recent findings that demonstrate the potential of iPS cells for curing disease.

Importantly, though, these medical breakthroughs will not come about without research on human embryonic stem cells, just as developments to date in iPS cell research would not have come about without research on human embryonic stem cells. Indeed, in July 2008 the New York State Stem Cell Foundation reported that its chief scientific officer, Kevin Eggan, produced adult stem cell lines from patients with Lou Gehrig's disease. Yet Eggan said he will still continue his work on human embryonic stem cell research and so-called Somatic Cell Nuclear Transfer (see glossary on page 2 for details into this line of stem cell research). "It's essential to note that we couldn't possibly be where we are now without first doing extensive work with human embryonic stem cells," he explained. "It will be essential to continue to do work with embryonic stem cells as they remain the stem cell gold standard."[5]

As Eggan observes, embryonic stem cells are the "gold standard." All cells brought forth as alternatives must be measured against them. Moreover, any alternative stem cells cannot just be generally similar to embryonic stem cells—they must be specifically similar for each therapy

A Brief History of Human Stem Cell Research

1974 National Research Act establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research within the Department of Health, Education, and Welfare to define policy for protection of human subjects during medical or scientific experiments.

1974 The 93rd Congress implements a ban on almost all federally funded fetal tissue research until the commission devises guidelines for it.

1975 Commission releases guidelines on federal funding of fetal and fetal tissue research. The guidelines establish an Ethics Advisory Board for fetal and fetal tissue research that originate from abortions.

1980 President Ronald Reagan decides not to renew the Ethics Advisory Board's charter. The EAB had recommended federally funded investigations into the safety of *in vitro* fertilizations using human embryos developed *in vitro* for no more than 14 days, but a de facto moratorium halts federal funding of human embryo research due to the EAB's disbanding.

1988 Human Fetal Tissue Transplantation Research Panel reopens the question and votes 18-3 to approve the federal funding of embryo research. Despite this level of support for the research, the Department of Health and Human Services accepts the testimony of three conservative dissenters who argue that embryo research would lead to an increase in abortions and in response extends the moratorium on this research.

1990 Congress attempts to override the moratorium through legislation but President George H.W. Bush vetoes the measure.

1993 HHS Secretary Donna Shalala lifts the moratorium on federal funding of human embryo research in accordance with President Bill Clinton's executive order.

1994 A National Institutes of Health human embryo research panel supports the research but thousands of letters urge President Clinton to reverse his earlier decision. He agrees. Federal funding of embryo research is stopped.

The Ethics of Procuring Human Embryonic Stem Cells

In 1998, the isolation of human embryonic stem cells from human embryos added a new dimension to the debate about the moral status of the embryo. Suddenly, Dr. James Thompson at the University of Wisconsin at Madison—the scientist who led the team to this pioneering discovery—presented his discipline as well as ethics and religious leaders with the need for moral guidelines that heretofore had been unnecessary.

Philosophical and religious views about the human embryo range from assigning it anything from full human moral status to no moral status. Philosophically, those who assign a human embryo no moral status, such as Princeton University professor Peter Singer, argue that it is not a person because it is not "capable of anticipating the future, of having wants and desires for the future," and is instead nothing more than a hollow ball of cells.[1] Proponents of this view suggest that research studies on embryos should follow the regulations for conducting research on any other group of cells.

In contrast, those who assign the embryo full human moral status affirm that all human abilities such as reason, emotion, and language are inherently rooted in the entity that comes into being upon fertilization. Consequently, they believe that embryos involved in research deserve human rights protections identical to those existing outside the womb. Among those who take this view are Robert George and Leon Kass, both members of the President's Council on Bioethics under President George W. Bush.[2, 3]

Religion informs some, but not all, views of the embryo. For example, the Catholic Church, along with many evangelical Protestant congregations, teaches that conception is the beginning of a unique human person's life and that persons at the embryonic stage of their lives should receive the same moral status as they would at any other stage of life. Other faiths—notably Islam, Judaism, and most mainline Protestant denominations such as Methodist, Episcopalian, and Presbyterian—believe that the embryo has some moral status but does not acquire full human moral status until various points after conception. For instance, according to Jewish law, full human status does not occur until birth, but fetuses are considered a potential human life and embryos up until 40 days after conception are of lesser value than the fetus.[4] Nevertheless, there are still many differences regarding the moral status of the embryo both within and among all of these faiths.

This plurality of philosophical and religious views has led to a general consensus in mainstream American bioethics that the human embryo has a special moral status, less than that of a born human person but greater than that of other collections of cells. Although this special moral status does not require that embryo research be prohibited, it does entitle the embryo to certain protections and requires the careful regulation of human embryonic stem cell research. This moral status establishes a special respect and consideration that all human embryos must be accorded in the process of considering whether and how research ought to proceed.

This consensus on research involving human embryos was arrived at by advisory bodies in the United States and Great Britain dating back nearly 30 years, allowing research on human embryos up until 14 days after fertilization. This "14-day rule" ensures that research on embryos ceases at the formation of the so-called primitive streak, a band of cells from which the embryo develops a nervous system. The emergence of the primitive streak marks the beginning of gastrulation, a period of development during which significant changes occur.

Before the formation of the primitive streak, the mass of cells called an embryo has no neurons and minimal organization, and is thus incapable of experiencing pain or suffering. Given this, the moral status of the embryo is considered to be much less than that of a fully developed human or even a fetus, which—according to the three-trimester structure of the Supreme Court's *Roe v. Wade* decision—acquires sufficient legal status upon viability to warrant a state's prohibition of abortion except when the life or health of the mother is at risk.

It is notable, however, that the debate about human embryonic stem cell research has not divided according to "pro-life" versus "pro-choice" lines. Many important public figures who are strongly opposed to abortion also advocate for human embryonic stem cell research. They recognize that virtually all philosophical and religious traditions emphasize that human suffering should be avoided or at least minimized, which is why they recognize the need for embryonic stem cell research to help find cures for degenerative diseases and other conditions.

For many religions, individuals are positively required to do what they can to improve a broken world. These powerful values predate collective human memory. They are part of our capacity to identify with the suffering of other human beings, even those who are strangers to us. These values motivate and justify medical research and medical care itself. The potential for human embryonic stem cell research to address sources of human misery that so far have resisted medical intervention is part of this ancient human project.

for which they may be used. Thus some adult stem cells or iPS cells may be useful because they are less likely to be rejected by patients' immune systems, but human embryonic stem cells may be useful because of their ability to differentiate into all 200 different types of human cells. Therefore, the various advantages of these various cells must all be studied so that they can be brought together to create the best therapies. No one kind of cell can do everything and that is why all avenues of stem cell research must be pursued.

It is still too early to tell what kind of stem cells will be most useful for therapeutic purposes. In fact, it is very likely that different kinds of cells will be used for different therapies using different strategies. Stem cell-based therapies may not take the form of actual human embryonic stem cell transplants, where healthy embryonic stem cells are differentiated into body cells used directly to repair the patient's diseased or damaged tissues—but it is clear that embryonic stem cells are needed as a research tool in order for some form of cell-reprogramming therapies to materialize. Australian embryologist and stem cell biologist Alan Trounson, for example, argues that the embryonic stem cells of patients with Alzheimer's, Parkinson's, muscular dystrophy, and cystic fibrosis all need to be studied so that we can find out how these diseases develop.[6]

The ultimate goal is to develop a guidebook that will tell us exactly how each gene or combination of genes contributes to the development of a unique individual. This will greatly enhance our understanding of basic genetics and possibly allow scientists to develop drugs that can prevent the diseases from developing in the first place. The hope is that human embryonic stem cells can be differentiated into specific cell types so that scientists can quickly measure whether a drug has a desired effect. This would make the drug development and clinical trial process much safer and more efficient. That's why it is vital that research is carried out using all types of stem cells, Scientists still are not certain which of these cells possess the right kinds of genetic, developmental, or molecular properties to be useful for the above purposes.[7]

Perhaps the most basic argument to be made in support of human embryonic stem cell research, however, is that all cells in the human body develop from the embryo. By studying embryonic stem cells, scientists may be able to gain basic knowledge about how to develop better cells to help the sick. Nevertheless, because iPS cells may turn out to have many of the same risks and benefits as embryonic stem cells, we intend all the recommendations in this paper to include research on iPS cells and all pluripotent cells regardless of their source.

1995 Congress bans the federal funding for research on embryos through the Dickey-Wicker Amendment, named after its sponsors Jay Dickey (R-AR) and Roger Wicker (R-MI). The amendment prohibits the use of federal funds for "the creation of a human embryo or embryos for research purposes; or 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))."[1]

1998 University of Wisconsin scientist James Thomson isolates human embryonic stem cells and shows their remarkable potential to rejuvenate and to specialize into tissues. This exciting discovery also initiates the ethical debate on human embryonic stem cell research because his team derives the stem cells through a process that destroys human embryos.

1999-2000 The NIH develops guidelines for funding human embryonic stem cell research, but presidential candidate George W. Bush declares his opposition to the research in a campaign speech so NIH remains cautious about entertaining funding proposals until after the presidential election.

August 2001 President Bush prohibits the federal funding of any research using stem cell lines derived after August 9, 2001, but his policy does not affect research in the private sector or research conducted with state funding.[2] The president claims that more than 60 stem cell lines are available for funding.

January 2004 The President's Council on Bioethics, chaired by Leon Kass, publishes "Monitoring Stem Cell Research,"[3] a report that contains "no proposed guidelines and regulations, nor indeed any specific recommendations for public policy." But according to Kass, the overarching goal of the report is "to convey the moral and social importance of the issue at hand and to demonstrate how people of different backgrounds, ethical beliefs, and policy preferences can reason together about it."[4]

April 26, 2005 The National Academies releases its "Guidelines for Human Embryonic Stem Cell Research."[5] In the news release, committee co-chair Richard O. Hynes explains, "A standard set of requirements for deriving, storing, distributing, and using embryonic stem cell lines—one to which the entire U.S. scientific community adheres—is the best way for this research to move forward."[6]

May 2005 The President's Council on Bioethics releases a white paper titled "Alternative Sources of Pluripotent Stem Cells."[7]

November 16, 2006 The President's Council on Bioethics, now chaired by Edmund Pellegrino, is updated on stem cell research and alternative sources of pluripotent stem cells by Hans Robert Schöler, Ph.D. director of the Cell and Developmental Biology Max Planck Institute for Molecular Biomedicine.[8,9]

December 21, 2006 The International Society for Stem Cell Research releases its "Guidelines for the Conduct of Human Embryonic Stem Cell Research."[10]

The inadequacy of the old policies

President Bush's policy permits federal funding of research only on human embryonic stem cell lines derived before August 9, 2001—a decision presented as an ethical compromise between a prohibition on all federal funding and permission to fund research on all embryonic stem cell lines. President Bush argued that the federal government and taxpayers would not be complicit in the destruction of embryos necessary to procure these stem cell lines because the pre-existing cell lines had not been derived specifically for federally funded research. The president also asserted that "more than 60 genetically diverse stem cell lines already exist."[8]

The Bush administration's eagerness to demonstrate that it was not inhibiting science led to its failure to ensure that the basic ethical standard of informed consent by embryo donors was respected.

In spite of the Bush administration's attempts to take the moral high ground, the August 9, 2001 deadline was not based on an ethical principle but rather was politically expedient and decidedly arbitrary. On its surface, the policy looked like an act of government restraint since the Bush administration simply limited federal funding for human embryonic stem cell research rather than universally banning it, allowing research on embryonic stem cell lines derived before the deadline. The theory underlying the decision was that scientists who derived cells not knowing whether they would be eligible for federal funding must not have derived the cells with federal funding as an incentive. Therefore the federal government and taxpayers would not be morally complicit in encouraging scientists to destroy embryos in order to derive stem cells from them.

Then researchers discovered that most of the alleged 60-plus lines eligible for federal funding either were not true embryonic stem cell lines or were not suitable for research for reasons such as poor quality and genetic diversity,[9] leaving only about 21 useful NIH-approved stem cell lines. Furthermore, recent news about the ethics of procuring the so-called BresaGen and Cellartis lines—five of the remaining 21 stem cell lines open to federal research—indicates that these stem cells were obtained without proper written consent. This means the number of ethically derived lines available is perhaps 16 or less.[10]

Ironically, then, the Bush administration's eagerness to demonstrate that it was not inhibiting science led to its failure to ensure that the basic ethical standard of informed consent by embryo donors was respected. Indeed, the Bush administration's rush to approve these lines is particularly perplexing considering that federal funding was not and cannot be used to destroy human embryos for any purpose, including deriving human embryonic stem cells from them. The so-called Dickey-Wicker amendment (see box on page 17 for a history of regulations and legislation governing stem cell research) to the HHS appropriations bill first passed in 1995 and renewed every year since prohibits the use of federal funds for "the creation of a human embryo or embryos for research purposes; or 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*."[11]

The upshot: no taxpayer money could ever have been used to destroy even leftover embryos for research. The Bush administration's apparent concern that federally spon-

sored human embryonic stem cell research would amount to committing taxpayers' money to embryo destruction was and is specious.

It is well past time for the NIH to be involved in funding and guiding human embryonic stem cell research as it is in medical science more generally. The current patchwork of state initiatives and regulations introduce wasteful legal and bureaucratic complexity into the overall enterprise of stem cell research. For instance, until November 2008, when voters amended the state constitution, it was illegal in Michigan to derive embryonic stem cells because the state constitution banned the destruction of embryos for research. As a result, researchers at Michigan's large and prestigious state universities had to import cells from out of state. Healthy stem cell research requires interstate collaboration among various institutions, including private industry and academia.

What's more, the poisonous atmosphere at the federal level over the past eight years has bled over into shorted-sighted policies in several states. At least one prominent free-standing research institution, the Stowers Institute of Medical Research in Kansas City, Missouri, scrapped its plans for expansion due to the biennial threat of state initiatives attempting to reverse the narrowly passed 2006 amendment to the state constitution allowing human embryonic stem cell research.[12] Although the initiative did not make it on to the ballot this year, the Stowers Institute feels it might not be so lucky in the future.[13] Funding initiatives have also failed or been delayed in New Jersey and Florida.[14,15]

- **April 30, 2007** The National Academies releases the 2007 amendments for its guidelines.[11]
- **June 20, 2007** President Bush issues an executive order calling upon the HHS secretary to support and encourage research on alternative sources of pluripotent stem cells. He also requests that the Human Embryonic Stem Cell Registry be renamed the Human Pluripotent Stem Cell Registry.[12]
- **November 2007** Shinya Yamanaka of Kyoto University and James Thomson of the University of Wisconsin-Madison both publish papers on their separate discoveries of induced pluripotent stem cells. These pluripotent cells were created from skin cells that had four genes inserted into them with viruses. This procedure resulted in the skin cells acquiring properties similar to embryonic stem cells. Researchers were able to coax these so-called iPS cells into becoming beating heart cells and nerve cells.
- **May 2008** Robert Streiffer, a bioethicist at the University of Wisconsin-Madison, publishes a paper detailing his investigation into the consent forms for the federally approved human embryonic stem cell lines. Although 21 lines were viable at the time, he discovers that no more than 16 are both viable and ethically derived.
- **September 5, 2008** The National Academies releases the 2008 amendments for its guidelines.[13]
- **December 3, 2008** The International Society for Stem Cell Research releases its new "Guidelines for the Clinical Translation of Stem Cells."[14]
- **January 20, 2009** Barack Obama is sworn in as the 44th president of the United States, having promised to change the current restrictions on human embryonic stem cell research.

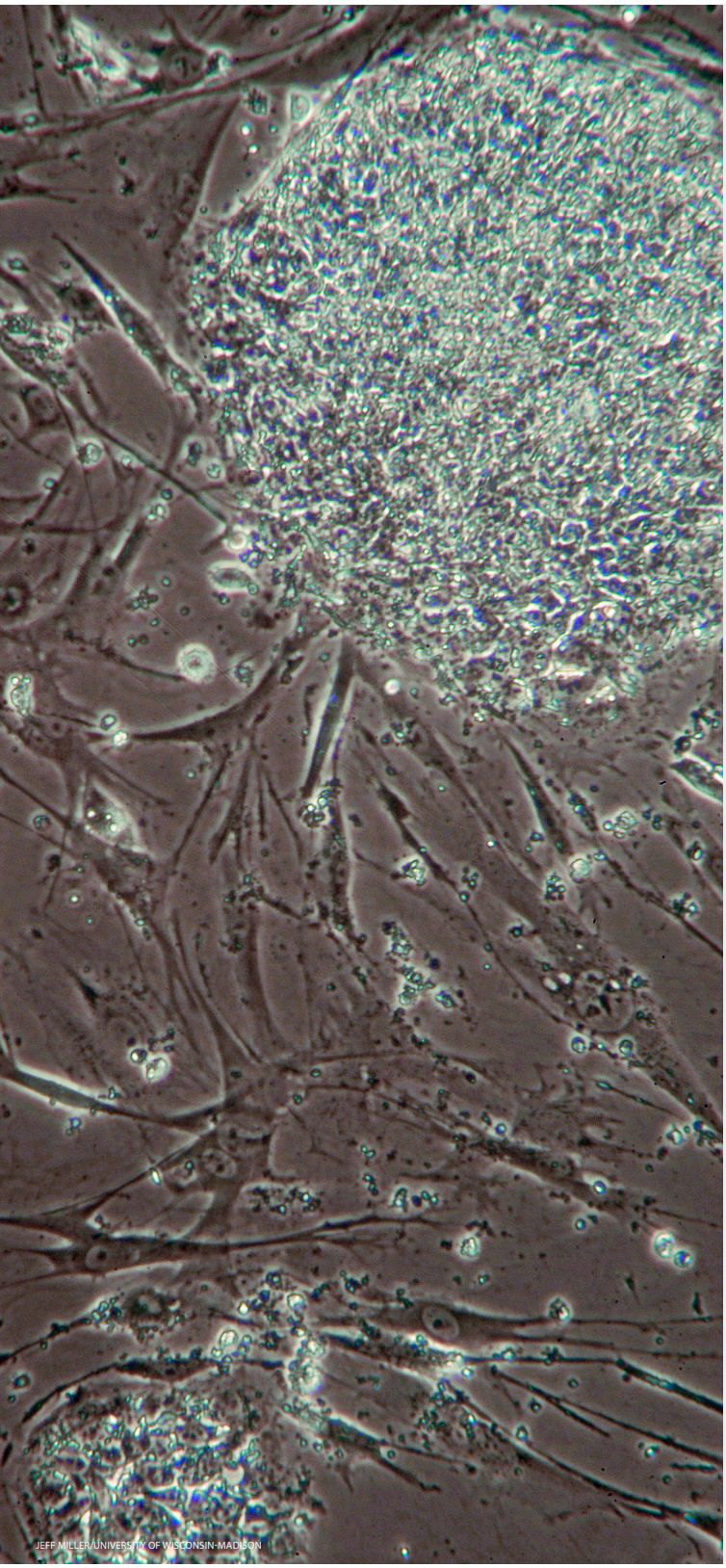
Current and Future Regulation of Human Embryonic Stem Cell Research

Research involving human embryonic stem cells must be appropriately regulated after the current federal policy is changed. In fact, it will have to be more heavily regulated than under the guidelines established by the Bush administration.

Case in point: the recent incident involving compromised consent forms that were used to procure human embryonic stem cell lines by the companies BresaGen and Cellartis—lines that the Bush administration declared to be ethically sound for scientific research—demonstrates how the small supply of highly-demanded federally funded lines led the National Institutes of Health to overlook the informed consent protocols.[1]

It is ironic that the Bush administration's ham-handed "ethics" of temporal restriction ended up overlooking a violation of the robust ethics of informed consent. That's why the incoming Obama administration and 111th Congress need to implement the policies we recommend in the main body of this paper so that the NIH does not find itself compromised or unable to carry out genuine ethical oversight.

Below, we detail the current regulatory environment that is in place at the NIH, other federal agencies, and other institutions. We also present the changes in policy for some of these agencies and institutions that we believe would result if the Obama administration adopted our policy proposals.



Microscopic view of a colony of original human embryonic stem cell lines from the James Thomson lab at the University of Wisconsin-Madison.

National Institutes of Health

The NIH regulates all NIH-funded research through the scientific and ethical review during its granting process. Clinical research that involves recombinant-DNA or gene-transfer research is further reviewed by the Recombinant DNA Advisory Committee, or RAC. If the research involves "protocols that raise novel or particularly important scientific, safety, or ethical considerations," then it will be discussed at one of the RAC's quarterly public meetings[2] Although only applicable to federally funded research, most institutions and peer-reviewed journals require compliance with the NIH guidelines and privately funded clinical researchers also solicit guidance from the RAC.

Unfortunately, the NIH's ethical review was compromised by the Bush administration, which did not want its purportedly brilliant compromise to come across as too stingy. The Bush policy put pressure on the NIH to approve the greatest possible number of "ethically derived" lines, resulting in the approval of lines that were not derived with proper informed consent but were still considered "ethical" because they were derived before August 9, 2001.

We recommend that the RAC undergo a slight expansion in order to oversee the translation of laboratory research into clinical research. We recommend the creation of a new Working Group for Pluripotent Stem Cell Clinical Research under the RAC. The primary mission of an expanded RAC would be to conduct prior review of pluripotent stem cell research that is about to go to the clinical stage.

Although the Food and Drug Administration alone will provide the ultimate oversight for such clinical trials, the expanded RAC will be important as stem cell research makes its first leap into the clinical realm. At this early stage, the FDA will be faced with a steep learning curve and will need to have its expertise supplemented by scientists, ethicists, patient advocates, representatives from private industry, and other concerned citizens. These parties can contribute to the formulation of general guidelines through the expanded RAC in order to aid the FDA and clinical researchers while the FDA becomes acclimated to this new field of clinical research. (See page 25 for further explanation and our recommendations on the RAC.)

National Academy of Sciences

The "Guidelines for Human Embryonic Stem Cell Research," released by the National Academies in 2005, are followed by most research institutions and codified by some states.[3] The NAS guidelines cover ethical procurement of gametes, derivation of cell lines, international collaboration, and a system of guidance at the local level through Embryonic Stem Cell Research Oversight committees.

ESCRO committees, composed of both scientists and members of the lay public, regulate the derivation of cell lines, conduct scientific reviews of research protocols, ensure compliance of all ongoing research projects with relevant regulations and guidelines, maintain registries of all human embryonic stem sell research conducted at institutions and all human embryonic stem cell lines derived or stored at institutions, and educate researchers involved in this research. An ESCRO committee may be part of a research institution, formed by a group of institutions, or a completely private body with which institutions contract.

Under our proposed policies, the Department of Health and Human Services, with the National Institutes of Health, will be required to issue regulations that require every institution receiving federal funding for human embryonic stem cell research to have the research approved and overseen by an ESCRO committee that adheres to the regulations formulated by NIH and HHS (as informed by the NAS or the International Society for Stem Cell Research).

The International Society for Stem Cell Research

The ISSCR is, according to its website, "an independent, non-profit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells, and to promote professional and public education in all areas of stem cell research and application." It is based in Deerfield, Illinois and its current president is Fiona M. Watt, DPhil from Cancer Research UK, Cambridge Research Institute. The ISSCR's president-elect is Irving L. Weissman of Stanford University.

The ISSCR released guidelines in December 2006 that are, for the most part, congruent with the NAS guidelines. In December 2008, the ISSCR released its suggested guidelines for the translation of human embryonic stem cell research into applied clinical therapies.

Under our recommendations, all federally-funded human embryonic stem cell research will follow regulations established by NIH and HHS, which are based upon the ISSCR and NAS guidelines. When crafting regulations, it will be up to the discretion of the HHS and the NIH to iron out the minor differences between these two sets of guidelines.

Local Oversight

Aside from local oversight through ESCRO committees, several additional layers of local oversight exist. These include:

- Institutional Review Boards, which operate within research institutions, regulate research involving human subjects or the procurement of human tissues by assessing the ethics of the research and requiring appropriate documentation of consent, remuneration, and application for participation

- Animal Care and Use Committees, which are defined as self-regulating entities that, under federal law, "must be established by institutions that use laboratory animals for research or instructional purposes to oversee and evaluate all aspects of the institution's animal care and use program."[4]

- Certain types of stem cell research that require the use of recombinant DNA technology require the approval of Institutional Biosafety Committees, or IBCs, which "were established under the NIH Guidelines for Research Involving Recombinant DNA Molecules to provide local review and oversight of nearly all forms of research utilizing recombinant DNA. Over time, many institutions have chosen to assign their IBCs the responsibility of reviewing a variety of experimentation that involves biological materials such as infectious agents, and other potentially hazardous agents such as carcinogens. This additional responsibility is assigned entirely at the discretion of the institution."[5] These committees are composed of at least five members, at least two of whom must be from outside the research institution.[6]

- Depending on the circumstances of a particular research project, other institutional committees, such as the radiation safety committee, conflict of interest committee, and the hospital clinical ethics committee might be involved. Each of these groups operate under various rules governing their composition, but are usually comprised of a combination of members from inside and outside the institution and almost always include members of the lay public in addition to scientists.

Nevertheless, some states have made serious and commendable efforts to step into the embryonic stem cell research breach. In 2004, California's voters approved Proposition 71, which authorized the unprecedented sum of $3 billion over 10 years for stem cell research, including embryonic stem cell research. The state government then established the California Institute for Regenerative Medicine in early 2005. To date, CIRM has awarded 229 grants totaling $614 million, including $72 million for human embryonic stem cell research.[16, 17]

New York also is well on its way to providing hundreds of million of dollars to research on stem cell medicine.[18] And Connecticut and Maryland have approved modest but significant sums ($100 million and $15 million, respectively) to advance the field.[19] But state initiatives cannot in and of themselves substitute for the ability of the NIH to organize complex science among many players. State-funded research could also lead to findings that will necessitate further research that the states may not be able to pursue without a rational federal funding policy.

Private funding also does not suffice as a substitute for federal funding of human embryonic stem cell research. Some opponents of federal funding feel that the inability to attract funding from venture capitalists indicates this research does not hold enough promise. Other opponents feel that there is enough private funding for human embryonic stem cell research and therefore federal funding is unnecessary. Both of these points are irrelevant. Venture capitalists never fund basic research. And even when private funding is available there is no reason the federal government should be removed from the business of funding basic scientific research.

In fact, the United States has long relied on a robust federal basic research agenda as a foundation for innovation. The purpose of agencies such as the NIH, the National Science Foundation, and the Department of Defense's Defense Advanced Research Projects Agency, or DARPA, is to fund basic scientific research. By definition, basic research may not have any direct application in the near future but will still contribute to a knowledge base from which the private sector can draw for applied research and innovation.

The products of basic research are often serendipitous and unforeseeable, but vital to our nation's economic growth and the enhancement of our quality of life. In its yearly R&D 100 awards, R&D Magazine has been giving an increasing proportion of its 100 yearly innovation awards to federally funded research. In a study of these awards, the Information Technology and Innovation Foundation demonstrates how the number of federally funded innovations among the top 100 over the past several decades rose from 41 in 1975 to 77 in 2006.[20] The incoming Obama administration and the 111th Congress must make sure that embryonic stem cell research is included in this mix of federally funded basic research.

Short-Term Policy Recommendations

The following recommendations are geared toward building a firm foundation for the ethically sound conduct of federally funded embryonic stem cell research. The president, Congress, HHS, and the NIH all have roles to play in instituting and maintaining this foundation, which includes the establishment of a stem cell bank and registry as a way of further galvanizing and streamlining national stem cell research.

Recommendations for the President

President Obama should lift the current limitations on human embryonic stem cell research by eliminating the restriction that currently allows federal funding only on lines derived before the arbitrary deadline of August 9, 2001. This policy should be replaced with an authorization of funding for research involving all ethically derived embryonic stem cell lines, which include strict informed-consent procedures and no financial inducements to donate eggs or embryos.

This new policy should be articulated in a presidential memorandum or, even better, an executive order so that the new president can make his intentions perfectly clear. Interestingly, the original policy put forth by President Bush in August 2001 was not created by executive order, but was simply a declaration of executive branch policy.[21] Bush's policy was expressed only in the text of his speech and a subsequent news release. Human embryonic stem cell research requires more direct and substantive federal oversight guidelines.

The president's declaration would not appropriate any new funds for embryonic stem cell research, as only Congress can appropriate funding. As the stem cell research system is normalized, however, NIH may recommend that more funds be made available for various forms of human stem cell research. Nevertheless, the order would make it possible for the NIH to go forward with providing grants for scientifically promising research without arbitrary restrictions. All other issues might best be sorted out by HHS and the NIH, as these two agencies develop long-term policy guidelines for this research. Alternatively, the president may want to include in his declaration specific ethical restrictions such as those already recommended by the NAS or the ISSCR.

Recommendations for HHS and NIH

During the presidential transition, the HHS transition team advising the president-elect should plan the ethical and procedural guidelines under which human embryonic stem cell research will operate. This will allow the NIH to ethically and responsibly proceed with expanded federal funding of this research within 90 days of the new presidential executive order.

The requirements drafted by the HHS transition team should include strong informed consent procedures and a prohibition on the federal funding of research involving cells derived from embryos that came from donors who were given financial inducements. They should also require that all research be conducted under the review of a stem cell research oversight committee that adheres to the standards put forth in regulations issued by NIH and HHS as informed by the National Academies or International Society for Stem Cell Research.

These recommendations will allow the NIH to ethically and responsibly proceed with expanded federal funding of this research within 90 days of the new presidential executive order.

Recommendations for Congress

The incoming 111th Congress should codify in law the NIH's responsibility to establish guidelines for embryonic stem cell research that are in line with those of either the NAS or the ISSCR. The state of California has already codified the NAS guidelines as law, and the recently introduced Stem Cell Research Enhancement Act of 2008, HR 7141, already includes requirements for the NIH director to establish guidelines with which all human embryonic stem cell research must comply. The bill also recommends that the NIH director consider guidelines from "nationally- and internationally-recognized scientific organizations." (See box on page 19 for more details on the legislation.)

In addition, the National Academies' Advisory Committee on Human Embryonic Stem Cell Research should continue to be a clearinghouse through which federal guidelines are refined and updated in light of emerging science. Most labs and research institutions already employ their own Stem Cell Research Oversight, or SCRO, committees to comply voluntarily with recommended oversight.

The new NIH regulatory arrangements should comply with relevant Congressional language, such as the Dickey-Wicker amendment, which prohibits the federal funding of research "in which human embryos are created, destroyed, discarded, or knowingly be subjected to risk of injury or death greater than allowed for research on fetuses *in utero*."[22] New legislation should also be kept as straightforward as possible so that any new stem cell technologies, techniques, or procedures that arise over the years—and they will arise quite rapidly—can be supported with federal funds without Congress having to explicitly authorize them through subsequent legislation. When the legislation is passed, the president should revise his executive order as needed to harmonize with the legislation.

Finally, since those suffering from disease are the most directly concerned with a reformed stem cell policy, it would also be prudent for the executive branch and Congress to engage patient advocacy groups in discussions of stem cell research priorities. This could be done through outreach efforts on the part of the NIH or HHS to seek their opinions and to include them in meetings of agency committees or advisory boards.

Recommendations for a Stem Cell Registry and Stem Cell Bank

In order to streamline research and improve research collaboration, the federal government should establish a national stem cell registry and possibly a national stem cell bank for all pluripotent stem cell lines, including both embryonic and iPS cell lines.

A stem cell registry is simply a database of all stem cell lines that are available to researchers through an organization such as the NIH. The registry contains all validated information about the cells, such as the date and place of their derivation, the informed consent protocols used to obtain the embryos or other cells from which the cell line originated, the biological and chemical makeup of the culture media used to nourish the cells, and the results of tests performed on the cells.

Current Stem Cell Legislation

Representatives Diana DeGette (D-CO) and Michael Castle (R-DE) recently introduced the Stem Cell Research Enhancement Act of 2008, H.R. 7141, which proposes to lift the current restriction on human embryonic stem cell research by authorizing the secretary of the Department of Health and Human Services to conduct and support such research regardless of the date upon which the stem cells were derived from embryos.

This legislation also establishes ethical requirements similar to those proposed in this report. Specifically, it requires that the cells be derived from excess embryos created by *in vitro* fertility clinics for fertility treatments that would otherwise be discarded. There must also be consultation with the donors, informed consent, and no financial inducements.

The bill also requires the director of the National Institutes of Health to issue guidelines 90 days after enactment and to update these guidelines no less frequently than every three years. It recommends that these guidelines take into account the guidelines already issued by national and international organizations (presumably, the National Academy of Sciences and the International Society for Stem Cell Research).

Finally, the bill stipulates that all research conducted or supported by the NIH comply with these guidelines. The NIH director is also given discretion with regard to the retroactivity of the guidelines and whether they should apply to other human stem cells, such as umbilical cord stem cells or those derived from bone marrow.

This piece of legislation would be highly effective in getting federally funded human embryonic stem cell research off the ground, especially if President Barack Obama does not move swiftly with an executive order or presidential memorandum. Of course this House legislation will need a Senate companion piece so that both can be passed and presented to the president for signing. Although a Senate version of the 2008 bill has not yet been introduced, it should not be a difficult undertaking since both houses of Congress passed both the Stem Cell Research Enhancement Acts of 2005 and 2007 before President George W. Bush vetoed the measures.

In contrast, a stem cell bank is a centralized location where the cells are physically stored so that a research organization can distribute them to approved researchers who request them. Banks and registries are useful because they help to coordinate research and facilitate research collaboration. Without banks or registries, the distribution and shipment of stem cell lines is left up to the lab that derived them. This is a costly and time-consuming process that can require the hiring of dedicated technicians to create subcultures of their more popular stem cell lines, do the legal paperwork, and ship the lines. It would be much easier if the lab could just make a one-time shipment to a bank, which would then take care of everything else.

A stem cell registry and bank would greatly enhance research collaboration, which has historically been one of the major drivers of innovation in the United States.

A stem cell registry and bank would greatly enhance research collaboration, which has historically been one of the major drivers of innovation in the United States. A recent study by the Information Technology and Innovation Foundation urged that the federal government improve federal funding of research collaboration.[23]

Currently, the NIH maintains a registry of only those 21 approved stem cell lines approved for research by the Bush administration. The NIH also contracts out the maintenance of the National Stem Cell Research Bank to the WiCell Research Institute at the University of Wisconsin-Madison, which was established through a $16 million, four-year contract in 2005.[24] The WiCell bank contains 18 of the 21 lines; another line is held by the University of California-San Francisco and two others by Cellartis AB, a private Swedish/British company.[25] The National Stem Cell Bank contract expires in September 2009 and needs to be reconsidered, modified, extended, or terminated depending on the utility and desirability of continuing the bank.

Ultimately, it remains the responsibility of the new Congress and President Obama to determine whether to continue or expand the national stem cell bank. But further difficulties may very well arise if federal funding of embryonic stem cell research suddenly opens up and unleashes a deluge of new cell lines for banking. Since under the current business model WiCell has been unable to bank stem cells at economies of scale—at WiCell it will cost $16 million to hold 18 lines for four years—the NIH and WiCell may not be in the best position to get up to speed on cell banking in a cost-effective manner.

We recommend that the NIH explore multiple options and encourage competition among the many institutions across the country that store biological materials, including WiCell. The NIH can then arrange a new contract with the institution or combination of institutions that can maintain the most cost-effective bank.

If private companies become involved in stem cell banking, however, the NIH must be diligent in ensuring that the company acts simply as a holding service and does not take legal possession of the cell lines. The lab that derived the stem cells should retain legal possession, and the cell lines should retain only the stipulations and restrictions put on them by the deriving lab and its institutions and funders.

Given the difficulty of getting a large and cost-effective stem cell bank up and running, the NIH should focus its initial efforts on expanding its existing stem cell registry and making sure that it is comprehensive. The NIH's existing pluripotent stem cell registry sets a precedent for a national stem cell registry, but it is woefully incomprehensive.

This registry must be expanded to contain all cell lines for which federal funding is approved, and should also go beyond compiling the usual and rather basic information that it has maintained thus far. This expanded stem cell registry should be more sophisticated and offer information about the origin, history, and quality of the lines, as well as whether the lines are compatible with the laws governing embryo and egg procurement in various states, locales, or institutions. This registry would strongly encourage voluntary registration and thus facilitate collaboration among research groups.

In June 2007, President Bush attempted to expand the NIH's stem cell registry by changing the name from the Human Embryonic Stem Cell Registry to the Human Pluripotent Stem Cell Registry.[26] Nearly a year has passed and the NIH still has not settled on a definition of "pluripotent" that would set criteria for whether a given stem cell line would be allowed in the registry.[27] Due to the failure of national-scale efforts such as these, we recommend funding for projects intended to stimulate competition among private contractors in order to create a model for a sophisticated national stem cell registry that would then be developed specifically for the NIH.

The benefits of a stem cell registry are overwhelming, and even private entities that may be reluctant to bank their cells will still have clear incentives to register them. For example, listing stem cell lines on a registry makes more researchers (and hence potential customers) aware that the lines exist. When it comes to stem cell banks, however, many for-profit companies may perceive challenges and be more resistant to banking their cells. Some for-profit owners of stem cell lines might not want to share their lines with every research group for reasons such as quality control, the amount of time it takes to deposit cells into a bank, and the expectation of a certain payment.

Still, stem cell banking reduces costs for companies by providing federally funded stem cell vetting comparisons of lines from multiple institutions. Banking also improves efficiency for researchers by providing a centralized source of research-quality stem cells and improving research collaboration. Ultimately, despite the initial difficulties the NIH and other institutions might have in developing a cost-effective business model for stem cell banking, there will nevertheless be long-term payoffs. Therefore, the stem cell bank should be supported by academic research institutions and for-profit companies alike. If carried out in a smart, efficient, and innovative manner, banks and registries will achieve the goal of streamlining research and fostering collaboration by providing researchers with a uniform display of all available cell lines.

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Long-Term Policy Issues

These recommendations address the long-term challenges that will have to be overcome in order to ensure that stem cell research leads to medical innovations in a safe, speedy, and cost-efficient manner. First of all, the allowance of federal funding for human embryonic stem cell research should not discourage states from continuing their own human embryonic stem cell research funding efforts. The intellectual property environment will also need to be structured so that it is efficient and incentivizes innovation without imposing excessive financial burdens on those who want to build upon other scientists' innovations. Most importantly, HHS should charge its Recombinant DNA Advisory Committee with addressing the ethical and safety issues of testing stem cell-based therapies on human subjects.

State Issues

Despite the federal-level focus of our policy suggestions, some state-specific issues still need to be considered in light of the threats they pose to an expansion of federally funded human embryonic stem cell research. The current patchwork of state policies that cover this research presents problems for researchers hoping for interstate collaboration. Although it is perfectly within states' rights to determine their own research policies, they should still make interstate collaboration a goal. Aside from this basic concern, there is also the possibility that other state-level problems could arise from expanded federal funding of embryonic stem cell research.

Given the current state of the U.S. economy, some states that currently support this research might see the opportunity to receive federal funding as a green light to slash their own funding efforts. But if President Obama implements the policies we are recommending, then federal funding will merely be authorized, not appropriated, for research. It will still be up to the NIH to decide how to distribute its funds, which in turn will depend on how much funding Congress decides to appropriate to the NIH.

It would be tragic if the allowance of federal funding for all ethically derived human embryonic stem cell lines resulted in less state funding and a subsequent slowdown of research progress. We urge states to avoid reducing their present funding allocations for this research given the potential to drive this research with combined state and federal funding on many cell lines. We are optimistic that many of the leading states for stem cell research will see federal funding as a supplement to—not a replacement for—their own

funding, which has already started the ball rolling on many additional human embryonic stem cell lines above and beyond the current federally-approved 21 lines.

Apart from funding issues, some states have adopted laws that either explicitly or implicitly ban or inhibit human embryonic stem cell research. Hopefully, with a robust and comprehensive federal policy, states will be encouraged to repeal or revise these laws in order to take full advantage of federal research dollars. Thus, the states would allow talented research scientists in academia and industry throughout the nation to maximize their efforts.

Innovation and Intellectual Property Issues

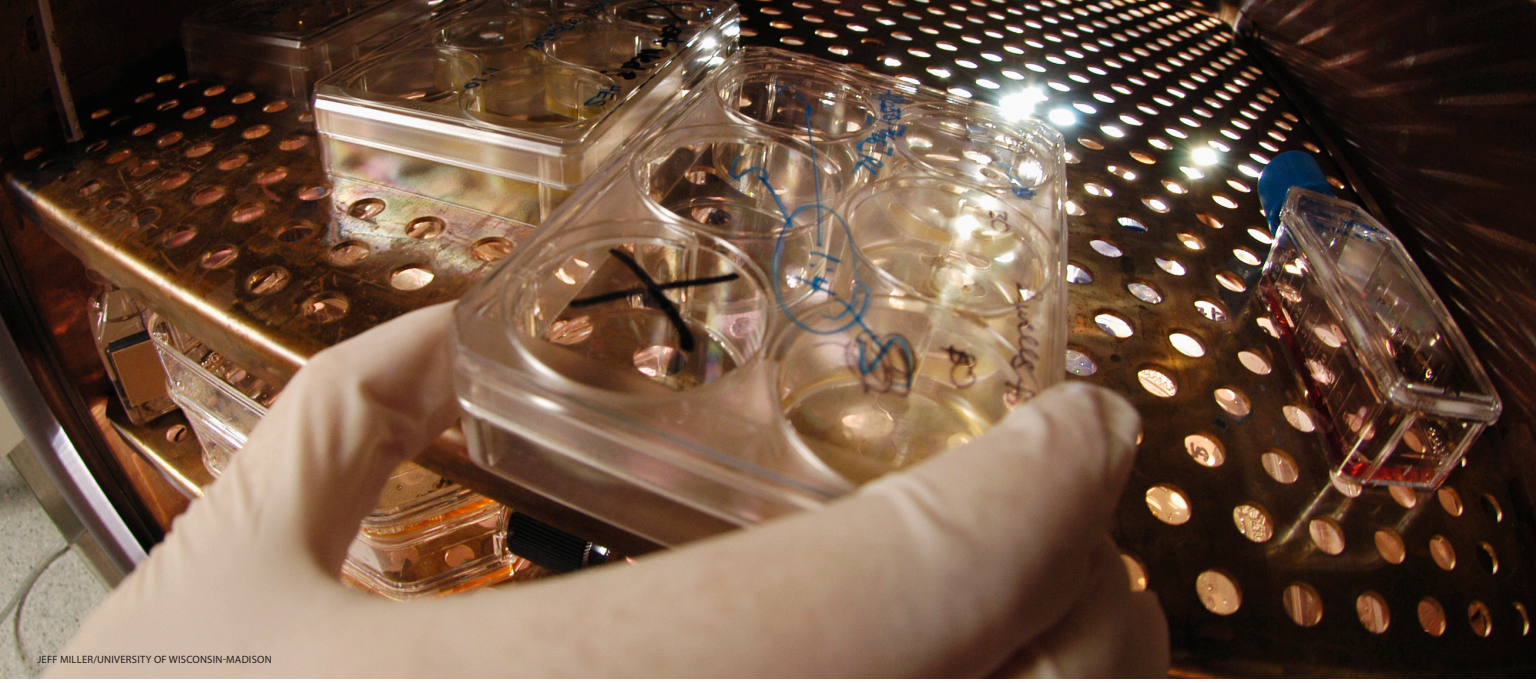
Although basic scientific research on embryonic stem cells is important in its own right, nothing is more valuable than the lives that will be saved and improved with the therapies and cures that may arise from it. In order to develop, produce, and distribute these possible cures, however, the federal government, state governments, universities, and private industry all need to work together to get stem cells from bench to bedside in an efficient, equitable, and safe manner.

Although basic scientific research on embryonic stem cells is important in its own right, nothing is more valuable than the lives that will be saved and improved with the therapies and cures that may arise from it.

One of the mechanisms that allows research to be translated into cures while also strengthening regional economies is licensing partnerships between research institutions and local corporations. These arrangements are made possible by the so-called Bayh-Dole Act, which allows universities to patent the results of federally funded research and then license to corporations the right to develop products from those results. The federal funding of stem cell research will generate many of these patents.

Currently, companies in private industry have to pay a licensing fee to the Wisconsin Alumni Research Foundation, or WARF, which holds the patents on the human embryonic stem cell derivation process that James Thomson of the University of Wisconsin-Madison developed as well as the cells obtained by that process. Once a company begins selling a technology based on this patent, it then has to pay royalties to WARF.

Some consumer rights organizations have argued that these patents are too broad and that the licensing fees paid by federally funded scientists were a waste of taxpayer-generated research dollars. These organizations called for a reexamination of the patents, and in March 2007 the United States Patent and Trademark Office issued a preliminary rejection of the patents on the grounds that the patent holder's findings were obvious based on earlier patents on the derivation of mouse stem cells. However, the rejections were reversed in February and March 2008 after further review that determined it was unreasonable to predict that the same methods used on mouse cells could be used to derive human embryonic stem cells. As of now, there is still some anticipation that new legal questions will arise over whose claim to the iPS cell creation process (see box on page 23 for an explanation and history of iPS developments) will take priority.[28]



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Although its original patents may seem restrictive at first, WARF has made the cells and methodologies available to academic researchers without licensing fees. According to the WARF website:

> Academic scientists using these cell lines and methodologies face no restrictions on patenting or publishing their own novel work. Currently, two vials containing approximately 6 million stem cells that are capable of establishing multiple new colonies are priced for academic researchers at $500.[29]

The cell lines are maintained and shipped by the National Stem Cell Bank at WiCell, which is an affiliate of WARF. The revenues from any materials, technologies, or methodologies that WARF licenses to companies are all used to fund further research at the University of Wisconsin-Madison.

The patenting of various techniques and cells would allow for more competition and give many companies the opportunity to compete and generate profits by developing therapies. Indeed, it generally takes a decade or more and millions of dollars to take medical discoveries to the market, and companies need to be sure that their investments are protected with patents. That is why it is important that research institutions also develop relationships with industries that could take the findings into the clinical stage.

Consumer rights groups correctly contend that patents can increase the cost of basic research to taxpayers, foundations, and institutions. But the WARF arrangement strikes a good balance between spurring academic research and protecting private-sector investments. Other universities and research institutions should adopt similar arrangements so that they can facilitate further academic research while also rewarding their own researchers and corporate licensees for making discoveries that lead to clinical applications.

Expanded Recombinant DNA Advisory Committee

Considering the extraordinary interest and controversy in this field, it is especially important to ensure accountability to both the wider biomedical research community and the general public when stem cells enter into clinical trials. The stem cell research community, regulators, and patients face a learning curve for weighing the risks and benefits of the clinical applications of these products. An unanticipated adverse event could have major ramifications for the stem cell research community as a whole.

At least in the early years of clinical trials there will be precious little stem-cell expertise in the federal regulatory system. Therefore, it is imperative that the small community of the most knowledgeable human embryonic stem cell researchers be utilized to advise on the safety and scientific validity of potential therapeutic trials. And the general public should have an opportunity to engage with the research, bioethics, business, and patient advocacy communities by observing and commenting on these issues.

The goal should be for all of these parties to lend their input on the possible risks and benefits of clinical trials involving pluripotent stem cells so that researchers and regulators follow ethical, safety, and scientific guidelines in this new field of clinical research. To facilitate this process, we recommend the expansion of the Recombinant DNA Advisory Committee, which the NIH formed in 1974. The RAC, under its current mandate, reviews "human gene transfer trials conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research." If the trials involve "protocols that raise novel or particularly important scientific, safety, or ethical considerations," then the RAC will discuss the research at one of its quarterly public meetings.[30]

In addition to assessing therapies that utilize recombinant DNA, the RAC should specifically also assess clinical protocols that utilize pluripotent stem cells or their partially differentiated progeny. It is important that all forms of pluripotent stem cells, regardless of their source, fall under the ambit of the expanded RAC, since each form has particular risks and ethical concerns associated with it. For instance, therapies involving both human embryonic stem cells and iPS cells will involve ethical considerations about cell donation, donor compensation, and informed consent. They will also both involve scientific and safety considerations surrounding the genes, proteins, and vectors used for reprogramming the cells as well as the so-called feeder cells and growth mediums that the stem cells were placed on while they were cultivated in Petri dishes.

This policy would not require a radical restructuring of the existing RAC, as it is already made up of multiple working groups. Indeed, some pluripotent stem cell therapies will no doubt incorporate recombinant DNA. Rather, we recommend that a new Working Group for Pluripotent Stem Cell Clinical Research be established. The standing members of the RAC would contribute members to the new working group while also bringing in outside members to contribute their views on and knowledge of pluripotent stem cell research.

Although the U.S. Food and Drug Administration alone will provide the ultimate oversight for such clinical trials, the expanded RAC will be important as pluripotent stem cell research makes its first leap into the clinical realm. At this early stage in the game, the FDA will be faced with a steep learning curve and will need to have its expertise supplemented by scientists, ethicists, patient advocates, representatives from private industry, and other concerned citizens.

The FDA will be faced with a steep learning curve and will need to have its expertise supplemented by scientists, ethicists, patient advocates, representatives from private industry, and other concerned citizens.

These parties can contribute to the formulation of general guidelines through the expanded RAC in order to aid the FDA and clinical researchers while the FDA becomes acclimated to this new field of clinical research. The supplemental expertise and input provided by this expanded RAC will also help the FDA develop formal protocols that it can employ over the long term for pluripotent stem cell research. Nor do we anticipate this being a "one-size-fits-all" type of review process, since the RAC has different levels of review for different therapies. This will help the entire stem cell research infrastructure incorporate public input and earn public confidence as the research transitions into the medical arena.

Indeed, one of the original intentions behind the RAC's formation was to allay the public's fears of recombinant DNA technology by letting the public in on the discussion. It was not long before the public's anxieties that recombinant DNA research would lead to the creation of biological monstrosities subsided. Nowadays, members of the public rarely attend the RAC's open meetings, but the RAC still provides the research community with the ability to assess where specific lines of recombinant DNA research are headed and what safety precautions should be taken.

Finally, we wish to emphasize that this expanded RAC should be as minimally burdensome as possible. It will not be charged with enforcing, sanctioning, authorizing, or approving any form of research or research protocol. It would act as a service to the FDA, the stem cell research community, and the general public by bringing all stakeholders to the table to discuss the science and ethics of this new kind of clinical research in a public forum.

The RAC maintains a balance between accountability and confidentiality because it is governed by the Federal Advisory Committee Act, which allows the committee to be open to the public while also maintaining confidential business information.[31] This policy has provided private entities with the confidence to put their clinical trials through this committee's review process even though the only clinical trials that are required to go through it are those that are federally funded. Industry understands the benefit of getting on the same page with the NIH and other members of the research community in a public forum without having to reveal proprietary information.

Recent Scientific Discoveries in Stem Cell and Regenerative Medical Research

The various types of stem cell and regenerative medical research together constitute a complex enterprise. Below are brief descriptions of the major research efforts, along with a list of some recent findings and publications in each field. All of these research techniques have shown promise in recent years and all should be part of America's stem cell research enterprise alongside human embryonic stem cell research.

***In Vivo* Reprogramming**

This is a technique in which genes are introduced into cells that are still in the body. These new genes change the identity of the cells so that they can serve a different function. This less invasive form of regenerative medicine therapy might prove to be more effective than transplantation of stem cells.

Doug Melton and his team at Harvard University in 2008 identified a specific combination of three gene transcription factors (Ngn3, Pdx1, and Mafa) that reprograms non-insulin-producing exocrine pancreatic cells in adult mice into cells that closely resemble insulin-producing β-cells. The three factors were transferred into the exocrine cells of diabetic mice by an adenovirus, which is a different kind of virus than the retroviruses used to make so-called induced pluripotent cells (see below for description) and does not permanently integrate the new—and possibly cancer-causing—genes into the cells.

The newly formed β-cells were able to improve glucose levels, increase glucose tolerance, and increase insulin levels. This proved that the identity and functions of cells could be changed while they are still in the body without the use of human embryonic stem cells. Melton, however, says "embryonic stem cells offer a unique window in human disease and remain a key to the long-term progress of regenerative medicine."[1]

Indeed, without research on the embryonic pancreas, Melton's team would not have been able to identify the proper transcription factors for reprogramming.[2]

Umbilical Cord Blood Stem Cells

When a newborn's umbilical cord is clamped, the leftover blood from the umbilical cord can be stored so that adult multipotent stem cells (see below for description) can be extracted from it. Physicians have widely utilized these cells in therapies for patients with various forms of anemia and blood cancers. Scientists initially thought these stem cells could only differentiate into blood cells, but more recent research in mice has shown that they can also turn into brain cells. This finding suggests that umbilical cord blood stem cells are more multipotent than other adult stem cells but not pluripotent like embryonic stem cells.

Umbilical cord blood stem cells may have multiple uses. Parents could store a child's umbilical cord blood for the child's own private use, though this may not be a good therapeutic strategy because the cells might carry the same disease-causing genes. Perhaps the best way to utilize umbilical cord blood cells is to store them in a large and genetically diverse public cord blood bank. This would increase the probability that a patient will find stem cells from a donor that are a sufficiently close genetic match and therefore carry minimal risk of rejection.

In 2004, the federal government set aside funds for the Department of Health and Human Services to facilitate the development of a central system for cord blood banking. In 2005, President George W. Bush signed the Stem Cell Therapeutic and Research Act, which supports the building of a bank of cells from 150,000 ethnically diverse donors.[3] Recent research developments include:

- Francesco Frassoni and his team at the University of Genoa transfused umbilical cord blood cells into patients undergoing chemotherapy in a Phase I clinical trial. Preliminary results suggest that the transfused cells helped the patients recover from the treatments.[4]

- Shigetaka Asano's team at the University of Tokyo discovered that umbilical cord blood transplants from unrelated donors have the same effects as bone marrow transplants from related donors.[5]

- David H. McKenna and his team at the University of Minnesota Medical Center found a way to differentiate umbilical cord blood stem cells into functioning lung cells.[6]

- Walter C. Low's team at the University of Minnesota was able to reverse the effects of a stroke through an umbilical cord blood stem cell transplant in rats.[7]

Induced Pluripotent Stem Cells

Induced pluripotent stem cells are created when a body cell from a fully developed person, known as a somatic cell, is turned into a pluripotent stem cell, which can then turn into any other body cell. Two labs achieved this for the first time with human cells in 2007 by using viruses to insert four new genes into the genomes of skin cells.[8, 9] Both labs were able to determine that the iPS cells were pluripotent by finding the same biochemical markers of pluripotency that are present in human embryonic stem cells.

If it could be made safe and routine, this process could bypass the need to derive pluripotent cells from human embryos. Scientists have also shown how these cells can be coaxed into becoming nerve cells and heart muscle cells. Recent research developments include:

- George Q. Daley and his team at Harvard developed disease-specific stem cell lines for 20 diseases using iPS cells.[10]

- Rudolf Jaenisch and his team at the Whitehead Institute in Cambridge, Massachusetts developed pluripotent stem cells without the carcinogenic c-Myc gene. The team instead used a naturally occurring signaling molecule called Wnt3a, which is known to speed up the conversion of adult cells to pluripotent stem cells.[11]

- Kevin Eggan and his joint team at Harvard and Columbia developed human motor neurons from the skin cells of patients with Lou Gehrig's Disease.[12]

- Shinya Yamanaka and his team at Kyoto University developed iPS cells from the liver cells and intestinal lining of mice and found that the retroviruses used to generate iPS cells do not have to insert the genes into specific sites in the DNA. This suggests that it is possible to insert the genes into places that do not lead to tumor growth.[13]

- W. Robb MacLellan and his team at the University of California-Los Angeles developed cardiac cells using reprogrammed mouse skin cells.[14]

- Konrad Hochedlinger and his team from Harvard induced pluripotency in mouse fibroblasts and liver cells using adenoviruses—a type of virus that does not permanently integrate new DNA into the host cell's genome—to carry genetic factors into the cells without integrating the factors into the cell's DNA. This process was highly inefficient, as only about 0.0001 percent to 0.001 percent of the cells became pluripotent.[15]

- Linzhao Cheng's team at Johns Hopkins University noted that it would not have been able to improve the efficiency and pace of generating human iPS cells from adult tissue without the previous research it had done on maintaining pluripotency in human embryonic stem cells.[16, 17, 18]

Adult Multipotent Stem Cells

Adult stem cells can turn into multiple types of body cells but only a fraction of the 200-plus body cells that pluripotent stem cells can turn into. Adult multipotent stem cells can be procured from bone marrow, body fat, and other sources. Scientists have begun to demonstrate how they may be useful for vascular or muscle therapies. Recent research developments include:

- Froilan Granero-Molto from Anna Spagnoli's team at the University of North Carolina's School of Medicine reported at the June 26, 2008 meeting of the Endocrine Society that their research group found that adult stem cells aid in the healing of bone fractures in mice.[19]

- Louis Ignarro and his team at the University of California at Los Angeles School of Medicine reported that they were able to convert human fat stem cells into smooth muscle cells.[20]

Embryonic Stem Cells

Embryonic stem cells are the "gold standard" of all stem cells. They can turn into all of the 200-plus kinds of cells in the body and are invaluable in investigating the usefulness of the other stem cells. Embryonic stem cell research is equally important in developing a developmental biology guidebook that will tell researchers exactly how each gene or combination of genes contributes to the development of a unique individual. This will greatly enhance understanding of basic genetics and may eventually allow scientists to develop drugs that can prevent some diseases from developing in the first place. Recent research developments include:

- Barbara Panning and her team at the University of California at San Francisco identified seven protein subunits that control the fate of embryonic stem cells.[22]

- Eric S. Lander and his team at Harvard and MIT discovered how the DNA sequence of human embryonic stem cells determines the initial progression of cell differentiation and that a complex nucleus-based mechanism might be the key to maintaining pluripotency.[23]

- Ali Brivanlou and a team from Rockefeller University in New York, along with scientists from France and Greece, found that human and mouse embryonic stem cells are able to maintain their pluripotency throughout multiple cell divisions by way of a chemical pathway known as Wnt. This chemical pathway is activated by a protein known as BIO which can be administered to the cells in order to prevent them from differentiating.[24]

- Emmanuel Baetge and his team at CyThera Inc. in San Diego differentiated embryonic stem cell lines into endoderm tissue, which is a precursor to the tissue that makes up various internal organs like the pancreas.[25]

- Austin Smith at the University of Edinburgh found that a specific inhibitory factor (leukemia inhibitory factor) drives self-renewal of mouse embryonic stem cells.[26]

- Xianmin Zeng along with scientists from Novocell Inc., the Buck Institute for Age Research, and Invitrogen Corp. identified more than 600 proteins found in undifferentiated human embryonic stem cells.[27]

- Christine Mummery's multi-institutional team from the Netherlands conducted a meta-analysis comparison of published data sets that was able to distinguish 32 intracellular proteins and 16 plasma membrane proteins that are present in multiple human embryonic stem cell lines but not in differentiated cells, and were therefore likely to include proteins important for the maintenance of pluripotency in these cells.[28]

As these findings demonstrate, regenerative medical therapeutic potential lies in each of these approaches, but none of these approaches can do it alone. Rudolf Jaenisch, for example, would not have been able to devise his method for creating less carcinogenic iPS cells if Ali Brivanlou's team had not first discovered that human embryonic stem cell renewal is governed by the chemical pathway known as Wnt. This example reinforces the point that human embryonic stem cells are the "gold standard" of pluripotent cells and that research in this arena is needed in order for research with cells from alternative sources to be clinically applicable.

On a larger scale, the studies by Xianmin Zeng's and Christine Mummery's teams demonstrate the sheer multitude of protein factors in human embryonic stem cells that contribute to full-blown pluripotency. Most of these protein factors, along with genetic factors, need to be compared in non-embryonic stem cells to see if they are adequate. That's why human embryonic stem cells remain the gold standard for every single therapy that is developed from alternative-source stem cells.

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