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Expand and Regularize Federal Funding for Human Pluripotent Stem Cell Research*

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Human embryonic stem cell (hESC) research has sparked incredible scientific and public excitement as well as significant controversy. Because they are pluripotent, hESCs can in theory be differentiated into any type of cell found in the human body. Thus they evoke great enthusiasm about potential clinical applications. They are controversial because the method used to derive hESC lines destroys a 2-4 day old human embryo. Research and discoveries using human pluripotent stem cells are simultaneously cutting edge contributions to fundamental understanding and potentially invaluable sources of new treatments for some our most devastating diseases and injuries.

Stem cell science represents an important case of “use-inspired basic research,” a class of scientific work that Donald Stokes (1997) compellingly argued could be used to reframe the increasingly fragile “contract” between science and society (Guston & Kenniston 1994). In this case, however, federal funding restrictions, legal challenges, and public controversy imposed on the field's development. Thus, hESC research also offers a “laboratory” for examining the effects high level science policy decisions have on the trajectory of an emerging scientific field. Today, nearly fifteen years after the discoveries that made human pluripotent stem cell science feasible, continued federal funding for this research is highly uncertain. We believe that federal funding for human pluripotent stem cell science should be expanded and stabilized through legislation. Explaining why requires that we begin with a simplified, schematic history of the field.

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Background: Policy, Controversy, and Discovery

In 1998, two research teams led by James Thomson at the University of Wisconsin and John Gearhart at Johns Hopkins published articles reporting the successful derivation and culturing of human embryonic stem cell lines (Thomson et al. 1998; Shamblott et al. 1998). The discovery was heralded as *Science* magazine's 1999 breakthrough of the year, but scientists could not receive federal grants to support their research because a 1996 law, the Dickey-Wicker amendment, banned the use of federal tax dollars in research that creates, harms, or destroys human embryos. A legal opinion drawing a fundamental distinction between human embryos and stem cells derived from them served as the basis for successful efforts to develop policies to enable the NIH to fund hESC research under President Clinton. Grant review was halted soon after the inauguration of President George W. Bush. Prospects for federal funding of hESC research remained uncertain until August 9, 2001, when he issued an executive order allowing federal funding for research on a small number of cell lines created before that time. Federal money could not be used to derive new lines.

Science progressed despite these restrictions, but controversy continued as it became clear that the small number of viable and fundable cell lines were not appropriate for all scientific or therapeutic purposes (Rao & Auerbach 2006; Wang & Sun 2005; Martin et al. 2005) and were very genetically homogenous (Mosher et al 2010; Laurent et al. 2010). Congress passed bills expanding federal funding for hESC research in 2006 and again in 2007. President Bush vetoed both bills. At the end of 2007, new research reporting that hESC-like cultures —called human induced pluripotent stem cells (hiPSC)—could be made by reprogramming adult fibroblast cells obtained from skin biopsies (Takahashi et al 2007; Yu et al 2007) increased hopes for cures and for ending the political and ethical controversies surrounding hESCs. In 2008 *Science* announced hiPSC as the breakthrough of the year, and in 2009 Shinya Yamanaka, who is widely credited with the discovery of hiPSCs, received the prestigious Lasker Award for Basic Medical Research. Recently, though, the idea that hiPSCs are medical or eithcal panaceas has been subject to skepticism (Zhao et al 2011; Devolder 2010; Pera 2010; Lo et al. 2010; Kim et al 2010).

Stem cells occupied diametrically opposed positions in the presidential platforms of both the Democratic and Republican parties in 2008. Among President Barak Obama's campaign promises was a pledge to rescind the restrictions placed on hESC research under the Bush administration. In March 2009, President Obama issued an executive order doing just that. A month later, the NIH released draft guidelines for public comment. When the comment period closed in May they had received approximately 49,000 responses. Revised guidelines took effect in July 2009.[2] The impact of those new rules has been mixed. Several cell lines that had been eligible for funding were ruled ineligible under new ethical rules and many new cell lines were added to the registry. Newly eligible lines have yet to appear in significant numbers in research, which continues to rely disproportionately on a very small number of legacy cell lines (Scott et al. 2010).

[2] http://stemcells.nih.gov/policy/2009guidelines.htm accessed 06/09/2011.

The effects expanded funding might have on research in this field were further obscured in August 2010 when a Washington, D.C. district judge, Royce Lamberth, issued a preliminary injunction to block implementation of the 2009 NIH guidelines and with them all federal funding for hESC research. The suit – brought against the NIH by a pair of adult stem cell researchers, the Christian Medical Association, and an embryo adoption agency – alleged that the NIH guidelines violated the Dickey-Wicker amendment. The ruling caused great consternation and uncertainty among stem cell scientists, stopped new funding for hESC research and raised the specter of a complete ban. A federal appeals court stayed the injunction pending consideration of the Obama administration's appeal. In April 2011 a three judge appeals panel reversed the district court's ruling in a 2-to-1 decision.

In July of this year, Lamberth granted summary judgment to the NIH, a finding that supports the Obama Administration's position that hESC funding can legally be expanded. Nevertheless, committed plaintiffs may appeal the case, which could lead to a legal battle that could progress to the Supreme Court.. As we enter the second half of 2011, despite an executive order to the contrary, pluripotent stem cell science faces the possibility of a more restrictive federal funding regime than held a decade ago under President Bush.

Arguments for expanded funding

We believe that federal funding for all human pluripotent stem cell research should be expanded.

There are now two methods that have been shown to successfully create pluripotent cells. Those lines can be made using donated frozen embryos scheduled to be discarded from IVF facilities or by the hiPSC method, which reprograms somatic cells using embryonic transcription factors. A third method of generating pluripotent cells, commonly called somatic cell nuclear transfer (SCNT), involves removing the nucleus from an egg cell and replacing it with a nucleus from a different cell in order to create an embryonic stem cell line genetically identical to the donor nucleus. SCNT has been successfully used to derive many mammalian pluripotent lines but has met limited success in primate cultures. As of this writing, only monkey lines have been established. The new NIH guidelines disallow lines made by SCNT from the U.S. registry, limiting funding for research pursuing this method to private and state sources.

Given this growing diversity of methods and sources, we invoke human *pluripotent* stem cell (hPSC) research rather than the more narrow and established case of human *embryonic* stem cell (hESC) research. We do so to suggest that funding decisions for the latter are, at least in the near term, inextricably intertwined with the prospects of new and exciting scientific discoveries in hiPSC research and possibly future sources of pluripotent cells such as SCNT (Scott et al. 2011).

When we contend that funding should be “expanded,” we mean three related things. First, the volume of funding for hPSC research should be increased. Second, the range of cell lines and methods of derivation eligible for funding should be encouraged to grow. Finally, federal funding for hPSC research should be regularized through unambiguous legislation

allowing researchers to plan and execute their often technically challenging, uncertain research programs on stable institutional ground.

Our position is based on three observations. First we note that both the clinical and the scientific potential of hPSC research are beginning to be realized. Expanded, regularized research support will accelerate those trends. Second, widely accepted ethical standards and effectively implemented institutional rules make the expansion of federal support for hPSC research unproblematic. Third, and finally, the uncertainty ongoing controversy, challenges, and rule revisions impose on stem cell scientists may be as damaging to the field as are restrictions.

Clinical, Scientific, and Institutional Development

Recent years have seen significant advances toward therapies as the Food and Drug Administration (FDA) has approved hESC-based clinical trials for patients whom spinal cord injuries have rendered paraplegic,[3] for Stargardt's Macular Dystrophy, a disease which causes progressive blindness in children, and for age related macular degeneration.[4] More progress is likely in the future as several new embryonic stem cell lines that carry markers for diseases such as hemophilia, Charcot-Marie-Tooth disease – a hereditary neurodegenerative disorder – Spinal Muscular Atrophy, and Duchene Muscular Dystrophy have been developed and approved for federal funding.

The process of creating “disease specific” stem cells from human embryos relies on preimplantation genetic diagnoses (PGD) and thus requires that scientists be able to identify and take advantage of opportunities presented by PGD that lead IVF clinics to forgo implanting an embryo with particular disease markers. Deriving disease specific iPS cell lines is much more easily done and such lines offer new opportunities to model diseases ranging from Parkinson's to Type 1 Diabetes and Down's Syndrome (Park et al. 2008; Zhu et al. 2011).

All five of the disease specific ES cell lines on the NIH registry and many of the disease specific iPS lines currently in use were developed by academic researchers. We believe that the development of these cell lines and their (possible) eligibility for federal funding represent an essential step toward the realization of some of the goals of regenerative and personalized medicine. We thus recommend both that more support be directed toward research using existing as well as new, genetically diverse, and potentially clinically useful lines. Moreover, the trend toward increasing numbers of available lines should be encouraged to continue.

Both the volume and the visibility of more basic, published pluripotent stem cell research have increased dramatically in the last decade. The first full year in which any federal funding for hESC research was available was 2002 and the year after saw publication of 32 hESC papers worldwide. In 2010 we identified 574 hPSC publications, a rate of growth of

[3] http://www.geron.com/media/pressview.aspx?id=1235 accessed 06/22/2011.
[4] http://www.advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-clinical-trials-using-embryonic-stem-cells-to-tre/ accessed 06/22/2011.

well over an order of magnitude (Scott et al. 2011). The United States does the largest share of this research (~41% in 2008) (Loser et al. 2010). The discovery and very rapid development of hiPSC technology relied on scientific skills and protocols developed for hESC research. The impressive speed of development of this new technology may also have been driven by researchers' efforts to conduct hPSC research without restrictions (Scott & Pera 2008).

Among other important discoveries has been the derivation of functional cells from hESC lines similar to those found in the human heart (cardiomyocytes), liver (hepatocyte), and central nervous system (oligodendrocytes) (Zhang et al. 2009; Binah et al. 2007). These cells, like the pluripotent stem cells that spawned them, are important tools for use inspired basic research. The great therapeutic possibilities that come with being able to model diseases and test potential interventions *in vitro* are matched by the possibility of fundamental discoveries about human development.

In addition to notable scientific and therapeutic developments, the institutional infrastructure to support ethical, expanded funding in the United States has grown significantly in the last few years. The National Academy of Sciences' 2005 guidelines for hESC research have been widely adopted, revised to include other pluripotent cells, and become normative standards for the ethical use of human stem cells. The International Society of Stem Cell Research has promulgated guidelines that address the clinical use of stem cells and begin to establish rules for regulatory harmonization among countries conducting hPSC research. The establishment of local oversight mechanisms governed by stem cell research oversight (SCRO) committees brings local scientific, ethical, regulatory, and community expertise to bear on the deliberative process of approving stem cell research protocols.

The NIH stem cell registry process appears to be working effectively to insure that cell lines eligible for federal funding meet strict ethical guidelines. While we disagreed with the institute's initial decision to retroactively apply contemporary ethical standards to cell lines derived in accordance with policies in place at the time of their creation (Taylor 2009), the result of the NIH's uniform application of those new standards has been to develop a registry that we believe can be expanded. The creation of that infrastructure, however, has not been without cost. Prior inconsistencies in the NIH guidelines preempted lines made from earlier stages of the embryo. Requiring that foreign and domestic lines derived prior to July 7, 2009 must provide "protections at least equivalent" to the new rules means that some potentially useful lines are ineligible for federal funding.

In applying today's tighter ethical standards to established cell lines, the NIH was forced to make several very difficult, but we now believe correct decisions. In June of 2010, the NIH rejected 47 new embryonic stem cell lines submitted to the new federal registry by Reproductive Genetics Incorporated (RGI), a private fertility clinic specializing in pre-implantation genetic diagnosis. Forty two of the rejected lines carried mutations for specific diseases including hereditary breast cancer, cystic fibrosis, sickle cell anemia, and Huntington's disease. The committee advising the Director ruled that RGI's application " . . . did not meet the high ethical standards that are appropriate for federal funding of human embryonic stem cell research," a decision that several high profile stem cell scientists

characterized as a “missed opportunity” that is “detrimental to the research community” (Waldman, 2010).

The most widely used Bush era stem cell line, Wisconsin's H09, was almost rendered ineligible as well, sparking a scramble to locate, identify, and translate into English original consent documents signed more than a decade before at an Israeli fertility clinic.[5] Though the Obama guidelines removed several lines that were approved under Bush, the approach to these and other eligibility decisions has resulted in a situation where we believe there is general agreement about the ethical standards employed in the derivation of cell lines supportable with federal funds. The infrastructure that is now in place will support more effective and ethically defensible pursuit of expanded hESC research.

An earlier decision further illustrates the care with which the pedigree of newly approved cell lines is being scrutinized. In December 2009, the NIH limited the use of 27 cell lines derived by the Harvard Stem Cell Institute to research focused on type 1 diabetes in accordance with explicit language in the relevant informed consent documents. The HUES lines, as they are known, were among the first derived with private funds during the Bush years, and had been widely distributed. Several were becoming prominent in published literature and were expected to be approved for federal funding in the wake of Obama's executive order. Much research using these lines was outside the realm of type 1 diabetes.

The story of one Harvard line in particular, HUES9, is emblematic of the challenges shifting rules, and uncertain legal and administrative standards impose on hPSC research. Immediately following the Obama executive order, HUES9 was the most commonly used non-federally approved cell line (Scott et al 2010). For reasons no one entirely understands, different cell lines sometimes manifest distinct characteristics in culture. HUES9 is well known among scientists for its ability to easily differentiate into central nervous system (CNS) cells, a property that prompted scientists working on neuronal cells with non-federal research support, from, for instance, the California Institute for Regenerative Medicine (CIRM), to begin projects using HUES9 for CNS research.

We have been interviewing both established and junior stem cell scientists for a year as part of an ongoing project studying the effects policy changes have on scientific decision-making. One junior researcher working with HUES9 described her reaction to the Obama executive order and subsequent NIH decision about “her” cell line in a fashion that encapsulates many of the challenges we associate with the uncertainty caused by fluid and sometimes inconsistent application of policy. While the senior investigators we have interviewed are often quite forthright in their evaluations of recent and past policy decisions, younger investigators tend to couch their reactions in terms very specific to their own ongoing projects. In this case, the ways in which policy implementation can impact entire lines of research and nascent careers are on clear display.

> The day the Obama Executive Order came out, it was huge excitement. . . In my lab we have a lot of federal money and I thought ‘Finally! I can use this money,” because the things that we do are very expensive. Then the whole NIH review came

[5] http://www.wicell.org/index.php?option=com_content&task=view&id=385&Itemid=170 Accessed 06/22/2011.

> around and [HUES9] got taken back off the list. For my purposes it got taken back of the list. This was a horrible time for me because I invested so much. I told my boss 'I'm not going to do that again with another line.'[6]

Several features stand out in this account. A new line of research was begun during the Bush years using CIRM funding. After months of work with HUES9, the research began to pay off with a set of high profile papers. Just as this student was poised to graduate, the Obama policy offered hope that she could expand this promising research using federal funds at the next stage of her career. Her hopes were dashed when the NIH review panel limited funding for this particular cell line to diabetes research. She is now considering leaving the field entirely. Here we have graphic evidence of the impacts not of restrictive policies but of difficult to predict efforts to expand research support (Levine 2011).

In sum, we take the last several years of hPSC research to be a story of scientific success despite challenges, of growing clinical impact, and of important institutional developments that provide the basis for expanded funding while emphasizing the need for stable, unambiguous policies for a field that remains under legal threat. The question remains where hPSC science and therapies would be if researchers and institutions had the benefit of a decade of federal funding and consistent regulatory policy. Invoking Stokes (1997) once again, stem cell researchers overwhelmingly select their questions and methods based on the potential relevance to real world problems. Though curiosity-driven research has long been a feature of early human development and cell biology, use-inspired basic research finds a high degree of affinity with applied approaches, a union that is important to the common good.

We believe that now is the right time to expand federal funding for hPSC research in hopes of accelerating scientific discoveries that may more quickly move toward the clinic. Accomplishing those goals requires that we think of expansion in several related ways. First, more funding for researchers in the US will speed rates of discovery and may incentivize talented young scientists to continue working in this field. Second, a wider range of eligible hPSC lines and particularly of disease specific ES cell lines will increase the likelihood that fundamental discoveries can move quickly to the bedside. Steps must be taken to allow support for approaches to develop disease specific cell lines

Third, both the level and the character of support for hPSC research should be made as stable as possible. While we believe various stakeholders have set the institutional groundwork necessary to support a broader range of better funded hPSC research, scientists' reactions to some of the more difficult decisions that were taken in the course of implementing the Obama administration policy suggest the challenges that uncertain, changeable federal funding create. A legal decision that curtailed or banned federal support for hPSC will have direct negative consequences in that it would undermine (at least in the U.S.) much of the progress we describe above.

The specter of legal and policy risks above and beyond the usual run of scientific and professional uncertainties is also having telling indirect consequences. Worries about the

[6]Interview conducted June, 2010 by Jason Owen-Smith.

stability and availability of funding lead investigators to be conservative in their choice of cell lines. They thus underutilize newly approved materials, rendering past institutional victories less effective (Scott et al. 2009; 2010). As our brief discussion of HUES9 suggests, uncertainty brought on by political and legal forces beyond the control of researchers at the bench make this field and particularly work with newer, untried materials more challenging for young investigators who may choose other areas of study. In short, expanding funding for now via administrative fiat is not enough. Legislation that replaces the Dickey-Wicker amendment with a law that clearly and unequivocally assures more stable federal support for hPSC research is necessary. Such legislative steps will allow American hPSC scientists the freedom of motion and access to resources essential to accelerating both basic and translational discovery using all manner of technically feasible, ethically supportable methods to develop human pluripotent stem cell lines.

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