May 26, 2009

Via Electronic Submission

National Institutes of Health
ATT'N: NIH Stem Cell Guidelines
MSC 7997
9000 Rockville Pike
Washington, DC 20892-7997

Re: "National Institutes of Health Guidelines for Human Stem Cell Research" (Draft Guidelines)
74 Fed. Reg. 18,578 (April 23, 2009)

Dear Director, National Institutes of Health:

On behalf of the Family Research Council (FRC), this document responds to the above-captioned public notice in which the National Institutes of Health (NIH) has requested comment on draft guidelines titled "National Institutes of Health Guidelines for Human Stem Cell Research." The draft guidelines were written to implement President Barack Obama's Executive Order 13505, issued on March 9, 2009.

SUMMARY OF ISSUE

Human embryonic stem (ES) cell research is legal and unrestricted by federal law (though some states have restrictions), so researchers can create and kill as many embryos as they choose for any reason. Family Research Council (FRC) submits comment in response to guidance from the National Institutes of Health (NIH) on federal funding of human ES cell research.

The current debate concerns whether taxpayers should pay for research in which embryos are killed for their stem cells. This debate is not about "stem cell research". It is legal to perform research with stem cells that exist throughout various body organs, such as pancreas, liver, bone marrow, nose, and brain, and it is legal to do research on stem cells that are derived from human embryos. The only question is whether the federal government should fund human embryo research.

FRC objects to funding human ES cell research for several reasons.

First, such research requires the destruction of human embryonic life and is therefore unethical.

Second, FRC believes that such funding violates the legal prohibition on funding research in which embryos are created, harmed, or destroyed in research, a law known as the Dickey-Wicker provision (P.L. 110-161, the Consolidated Appropriations Act, 2009), which first became law in 1996.

Third, funding such research creates an incentive for researchers to create more human embryos for destruction, and the proposed NIH guidelines are guilty of creating this financial incentive even though they propose funding human ES cells from so-called "leftover" embryos.

Finally, funding such research diverts limited federal funds away from stem cell therapies that have shown and continue to show real therapeutic benefit for patients suffering from over 70 conditions. The preoccupation with human ES cells is unfortunate given inherent biological barriers to using these cells in patients, such as tumor formation, immune rejection, and chromosomal abnormalities, among others. While such research is currently legal, FRC believes that the American public would be better served by NIH focusing funding on stem cell research showing benefit to patients experiencing a host of diseases. This is not a debate over the legality of the issue, but what is and what should be funded by the federal government.

BRIEF HISTORY

In 1975, the federal government recognized that human embryos in the womb are to be protected as "human subjects" in federally funded research. It is important to note that in the current debate, human embryos that researchers want to destroy for their stem cells are at the same stage of development as those embryos in the womb that are protected by federal regulations.

Since 1996, the Dickey-Wicker appropriations rider has prevented federal funding for any research "in which" embryos are destroyed (P.L. 104-99). The law states that federal funds may not be used for "(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero" (in the womb). Since 1996, federal law has prohibited the use of federal funds to pay for research that would result in the killing of human embryos or placing them at risk, including research in which federal dollars do not pay for the direct destruction of the human embryo.

In 2000, the NIH guidelines approved by the Clinton administration allowed federal funding for research on stem cells derived from human embryos, so long as the specific act of destroying the embryos was not carried out with the use of federal funds. These new rules, promulgated by then-NIH Director Harold Varmus, were based on a 1999 HHS General Counsel memo written by Harriet S. Rabb ("Rabb Memo") expressing the opinion that the use of federal tax dollars for research using such stem cells would not violate the Dickey-Wicker ban as long as federal funds did not pay for the act of killing the embryo. Though these rules were issued in 2000, President Bush prevented them from being implemented.

On August 9, 2001, President Bush announced, in an address to the nation, his decision to begin federal funding of research on stem cell lines derived from human embryos who were killed prior to his announcement.

This was the first time the federal government funded human ES cell research. Some commentators strongly disapproved of this policy, whereas others thought the policy was ethically defensible and that it was a political compromise that prevented implementation of the Clinton-era NIH guidelines. Both the Bush and Clinton administrations seem to have adopted

the legal interpretation from the Rabb Memo that the Dickey-Wicker provision would not be violated so long as funds were not used on research that kills the human embryo, and since the ES cells are not human embryos, the ban accordingly did and does not apply. However, Bush's policy differed substantially from the Clinton rules in that, though the Clinton rules would have prevented using funds to directly destroy human embryos, they would have simultaneously created a continuing financial incentive to create and destroy embryos for research. In contrast, Bush's policy not only ensured that no federal funds would be used to directly destroy embryos, but it also restricted funds to stem cells that were derived from embryos in which the life-and-death decision had been previously made. Arguably, the Bush policy avoided generating any financial incentive to create more embryos for destructive research since no funds would be available for research on stem cells obtained from newly destroyed embryos after August 9, 2001.

FRC believes this legal interpretation is misguided in that Dickey-Wicker prevents any funding for research "in which" human embryos are created, harmed, or destroyed. Given the current science, human embryos are destroyed when the stem cells are obtained from them. Research on human ES cells is research tied to the destruction of the human embryos from whom they came.

After the August 9, 2001 Bush announcement, the NIH established a human ES cell registry that listed lines that were eligible to receive federal funding, and NIH is now funding infrastructure grants to make the ES cells available. NIH determined that there were 78 ES cell lines eligible for research funding in accordance with President Bush's policy. Since that time, NIH has worked to attract researchers to apply for grants to perform research on the eligible lines. Of the 78 eligible lines, 21 are currently receiving federal funds. The NIH reported as late as 2007 that over 3,000 additional shipments of human ES cells were available to researchers upon request. The NIH has stated that the approved ES cells reproduce indefinitely. The NIH has also stated they have been able to fulfill requests for basic research. Since President Bush's decision, federal funding has increased to over $90 million per year on human ES cells, totaling almost $480 million since 2002. Despite such funding levels, and in addition to over $1 billion in non-human ES cell research during the same period,[1] ES cells have yielded no treatments for any condition.

On the contrary, there continue to be breakthroughs with adult stem cell research for a variety of conditions. In fact, researchers have used non-ES cells to treat human patients for over 70 diseases[2] and shown novel ways of creating embryonic-like stem cells without harming or destroying human embryos. In addition to breakthroughs in early 2007 involving amniotic stem cells, Japanese and U.S. scientists in November 2007 published studies showing the capacity to reprogram normal human body cells into human embryonic-like stem cells that are identical in character to ES cells.[3] However, these pluripotent stem cells do not involve human embryos at all, nor do they involve the extraction and use of women's eggs or the controversial process of

[1] From NIH "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)", Table Updated January 15, 2009 accessed 25 May 2009 at http://report.nih.gov/rcdc/categories/PFSummaryTable.aspx
[2] See references at http://www.sciencemag.org/cgi/data/315/5810/328b/DC1/1 and http://stemcellresearch.org/facts/asc-refs.pdf
[3] Takahashi K *et al.*, Induction of pluripotent stem cells from adult **human** fibroblasts by defined factors, *Cell* 131, 861-872, 30 November 2007; published online 20 November 2007; Yu J *et al.*, Induced pluripotent stem cell lines derived from **human** somatic cells, *Science* 318, 1917-1920, 21 Decmber 2007, published online 20 November 2007

human cloning (somatic cell nuclear transfer). Researchers call these cells induced pluripotent stem cells, or iPS cells. They behave identically to human ES cells, can be created directly from patients for disease-specific cell lines, and potentially could genetically match the patients. Thus iPS cells could potentially bypass problems with immune rejection when using human ES cells in the clinical setting.

On March 9, 2009 President Barack Obama issued Executive Order 13505, which overturns President Bush's previous policy of funding human ES cells. The new executive order opens federal funding for newly created human ES cell lines utilizing newly created and destroyed human embryos so long as, per the Dickey-Wicker provision, the funds are not used directly to destroy the embryos. FRC objects to the executive order because it opens the floodgates for funding more ES cell research and generates an incentive for researchers to create and destroy more human embryos. Moreover, President Obama's executive order is vastly broader than even most proponents of such research claim is needed.

Specifically, President Obama's executive order does several things. First, it opens the door to funding research on stem cells taken from so-called "leftover" embryos created during the in vitro fertilization (IVF) process that were created initially for baby-making. Second, the executive order rescinded the statement of President Bush that allowed funding for research on human ES cells created prior to August 9, 2001.

Third, it revoked President Bush's Executive Order 13435 of June 20, 2007, which supplanted the August 9, 2001 statement. Executive Order 13435 expanded funding of research involving alternative methods of producing pluripotent stem cells, including the possible derivation of human ES cells without harming or destroying human embryos. Moreover, this executive order also placed priority on stem cell research with the greatest potential for near-term clinical benefit. By revoking President Bush's executive order, President Obama eliminates any such priority for NIH. Fourth, President Obama's executive order established a new policy for federal funding of stem cell research that involves cloned human embryos, human-animal hybrid embryos, and human parthenogenetic embryos.

President Obama designated NIH to draft guidelines for distributing funds for stem cell research. On April 23, NIH officially posted draft guidelines to regulate federal funding for human ES cell research. The proposed guidelines would fund research on human ES cells derived from human embryos created by the IVF process and that were created initially for the purpose of childbearing.

ETHICAL PROBLEMS WITH PROPOSED GUIDELINES

Proponents of federal funding of ES cell research argue that ES cells are the most promising to treat upwards of 100 million patients. Although they claim that it is unethical to create human embryos for the sole purpose of destructive research, they argue it is ethical to fund research on "leftover" human embryos that "would otherwise be discarded". They are referring here to embryos created by IVF but that have not yet been transferred to the womb for gestation to produce children.

Proponents have argued that we should fund research on these "excess" IVF embryos. In 2003, Rand published a report[4] showing over 400,000 frozen human embryos in storage in the United States. This report generated a renewed call for President Bush to expand his policy to incorporate these new embryos, especially since ES cell research proponents claim "they will be destroyed anyway."

However, the current estimated number of 400,000 "leftover" embryos will not satisfy the demands of research, especially if federal funds are promoting ES cell research and human embryo destruction. According to the Rand report, 88% of the 400,000 frozen embryos are destined for later transfer for gestation by the parents. The percent of embryos that are designated for research is 2.8%; that is, about 11,000 frozen embryos potentially available for ES cell research. Even if all of these embryos were made available for research, the best scientific estimate of the number of stem cell lines that would be derived from these embryos would be extremely limited. Rand estimated that at most, only 275 ES cell lines might result from existing available embryos. Dr. Raynard Kington, Acting Director of NIH, has publicly claimed that the draft guidelines could potentially fund research on a total of 700 human ES cell lines. However, it is unclear how Dr. Kington determined that figure. The NIH guidelines should also require the publication of information disclosing the location of the human embryos that were used to obtain the funded ES cell lines.

We reject as entirely utilitarian the argument that ES cell research is ethically legitimate given that embryos are supposedly going to be discarded and are of potential use in treating millions of patients. FRC believes that the destruction of innocent human life, including nascent human life, is unethical. FRC believes as a corollary that the federal government should not fund research that involves the destruction of human embryonic life. The NIH draft guidelines would ensure American taxpayers' complicity in what millions reasonably believe is the unethical destruction of human life.

While the debate over the utility of ES cell research continues as a scientific question, it clearly continues to be debated as an ethical and public policy matter. There is simply no clear consensus showing that the majority of Americans support *funding* for the use of any embryos in experiments.

Even the NIH guidelines acknowledge an implied concern about the moral status of the human embryo. This is evident in NIH's decision not to fund research on ES cells derived from human embryos specifically created for research, as well as ES cells from cloned embryos and parthenogenetic embryos. FRC believes that the NIH should not fund research that the agency itself acknowledges raises ethical concerns.

The Obama administration has stated that in its deliberative process it consulted with other bioethics and scientific bodies. It would be well to note that under the Clinton administration, the National Bioethics Advisory Committee (NBAC), which recommended funding of research that destroyed human embryos for stem cells, acknowledged that the government should only fund such research if no other alternatives were available. NBAC concluded:

[4] Hoffman DI *et al.*, Cryopreserved embryos in the United States and their availability for research, *Fertility and Sterility* 79, 1063-1069, 2003

"In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research… The claim that there are alternatives to using stem cells derived from embryos is not, at the present time, supported scientifically. We recognize, however, that this is a matter that must be revisited continually as science advances."[5]

Here the science can and should inform the discussion. Since 1999, advances using adult stem cells have shown positive benefit in patients for over 70 diseases and injuries. Moreover, alternative methods of obtaining "pluripotent" stem cells have been discovered. In short, the science has provided a way out of the ethical dilemma by offering "less morally problematic alternatives" that are already treating patients as well as providing ample stem cells for basic research, all without the need for human embryos. The NIH guidelines are in fact scientifically dated as well as morally problematic.

TECHNICAL PROBLEMS WITH PROPOSED GUIDELINES

The NIH draft guidelines also suffer from other, more specific problems. They state: "These draft Guidelines would allow funding for research using only those human ES cells that were derived from embryos created by IVF for reproductive purposes and were no longer needed for that purpose." Additionally, the NIH guidelines state that they will not fund (at present) research on human ES cells derived from embryos created by cloning, parthenogenesis or IVF embryos specifically created for research. Despite the draft guidelines' statement to that effect, NIH offers no legal basis for not funding such research given the fact that Executive Order 13505 clearly gives NIH the authority to fund such research. The draft guidelines contain no reporting requirements or benchmarks for determining at a later time whether they will proceed to fund such controversial research. The draft guidelines should contain rigorous criteria to be used to justify proceeding to fund any such research.

The guidelines offer several criteria for determining which ES cell lines are eligible for funding. First, the human embryos must have been created for reproductive purposes. Second, the human embryos must no longer be "needed" for reproductive purposes. Third, the human embryos must be donated for research purposes. Fourth, additional restrictions on the facilities are outlined. The proposed criteria contain large loopholes that would lead to the creation of additional embryos in order to destroy them for their stem cells.

Regarding the first criterion, NIH gives no explanation of how it will determine which embryos were created for which purpose or whether multiple purposes (reproduction and research) are permissible for funding. There is nothing in these guidelines to ensure a researcher cannot claim that human embryos were created as part of the IVF process to generate a child, when they were in fact created in excess to obtain more embryos for stem cell research. Moreover, there is nothing to prevent researchers from applying pressure on parents from the outset to ensure that additional embryos are created so the researcher can obtain "leftover" embryos for stem cell work.

[5] National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research*, Rockville, MD: September 1999, Volume I, at page 53.

Second, the NIH guidelines offer no criteria or explanations for determining whether the embryos in question are "no longer needed" for reproduction. That many parents decide later to have more children after storing their embryos for years is not considered here, in terms of any waiting period for the decision to give embryos to research. The guidelines also ignore the options parents have to give their embryos to other infertile couples wanting to adopt their embryos. Thus, the embryos are indeed still "needed" for reproduction. That the NIH guidelines would be silent on a matter that Congress has supported in the Embryo Adoption Information Campaign is very troubling.

Third, there is no requirement as to when the embryos are to be donated for research. There is no defined separation between the time a couple chooses to go through the IVF process for the purpose of reproduction and when they decide to donate their embryos for research. Parents making informed decisions about their choices should be given time to consider all the options. Unfortunately, the guidelines do not require any period of separation for such decisions to be made by the parents.

Fourth, the guidelines lack requirements for documentation of several additional factors pertinent to sound public policy. The guidelines should require documentation that all the options pertaining to the use of embryos "no longer needed" are explained to the parents. It is not evident who will be required to explain the various options to the parents, and this could even, under the proposed guidelines, include the ES cell researcher. Such a dual role creates a serious conflict of interest, thereby ensuring that the parents will receive biased information. Moreover, the guidelines fail to specify what, if any, options must be offered to the parents. Would parents be told in the documentation that hundreds of infertile couples have now pursued embryo adoption successfully to have children? Additionally, documentation is purportedly required to show that no financial inducements were offered for the donation of embryos to research. The guidelines fail to specify what, if any, compensation would be permissible. Nor do they limit the source of the compensation. The ambiguous requirement could be interpreted to mean that federal funding cannot be used as compensation to the parents, but private funding could.

Fifth, one of the most egregious loopholes in the guidelines is that they permit the stem cell researcher and the IVF doctor to be one and the same. These guidelines provide a financial incentive for IVF doctors to apply for federal funds for ES cell research. The guidelines say the IVF doctor and the ES cell researcher "should" be separate, but only when practicable, and do not in fact require any actual separation between the two. The guidelines allow the likely scenario where the IVF doctor creates more embryos than are needed for fertility purposes in order to generate more so-called "leftover" embryos for the doctor's own ES cell research using taxpayer funds.

Fundamentally, these guidelines create a conflict-of-interest for IVF doctors who are professionally obligated to be dedicated to the creation and preservation of healthy embryos for the purpose of baby-making for the parents. In allowing the IVF doctor to receive federal funds for human ES cell research, the guidelines encourage an attending physician to bring another set of goals into the doctor-patient relationship. Clearly, if the stem cell researcher is also the IVF parent's doctor, he or she would certainly have a financial incentive to create more embryos than

are needed for gestation so that he or she would have more "leftover" embryos for stem cell research using federal funds. The fact that the guidelines do not require separation between the IVF physician and the researcher deriving the ES cells from the embryos is a grave flaw.

Sixth, the guidelines do not prevent funding in which human ES cells are used to create human-animal hybrids or human-human chimeras. The guidelines only prohibit research in which human ES cells are "introduced into non-human primate blastocysts," but experiments in which human ES cells are placed into other animal embryos (*e.g.*, mouse, cow, sheep) are not prohibited. Likewise, there are no prohibitions on introduction of human ES cells into human embryos to form a human-human chimera, nor is there any prohibition on using human ES cells to form tetraploid embryos. This is grossly unethical.

Lastly, the guidelines do not require the donor(s) of human embryos to sign an informed consent agreement while generating embryos for reproductive purposes. They could be offered separate consent forms at the same time (thereby creating the scenario where the embryos are created for both reproduction and research, which would not qualify under the guidelines). Or different consent forms could be offered by the IVF doctor and the ES cell researcher in order to elicit donation.

DIVERTING FUNDS AWAY FROM REAL TREATMENTS

The NIH Guidelines will divert federal funding away from promising research treating people now with adult stem cells and will divert funds away from more promising sources of embryonic-like stem cells generated without the use of any human embryos.

EMBRYONIC STEM CELLS ARE UNSUITED FOR CLINICAL APPLICATIONS

The NIH Guidelines define human pluripotent stem cells as "human cells that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers." Proponents of federal funding for human ES cell research argue that because ES cells are pluripotent, they are the most promising to treat numerous diseases. Yet pluripotent stem cells, and particularly ES cells, are an unrealistic source for actual clinical therapies. The rapid growth of ES cells coupled with the lack of control over specific differentiation often leads to tumors in experimental animals. The bulk of the scientific evidence indicates that human ES cells are tumorigenic cells, unsuitable for the purposes outlined in the proposed guidelines, and therefore inappropriate for federal funding.

Animal studies highlight the danger of ES cells in transplants. Sensitive assays show that as few as two ES cells are enough to form a tumor.[6] The risk of tumor formation seen for ES cells is increased when using homologous hosts (*e.g.*, mouse ES cells into mice,[7] or potentially human ES cells into humans). Moreover, differentiation into specialized, non-growing cell types does not preclude tumor formation; ES cells appear to reverse specialization into a growing, tumor-

[6] Lawrenz B *et al.*, Highly sensitive biosafety model for stem-cell-derived grafts, *Cytotherapy* 6, 212-222, 2004
[7] Erdo F *et al.*, Host-dependent tumorigenesis of embryonic stem cell transplantation in experimental stroke, *J Cerebral Blood Flow Metab* 23, 780-785, 2003

forming state.[8] ES cells tend rapidly to accumulate mutations, increasing the chances of tumor formation.[9] A recent study notes that many IVF embryos, the targets of these guidelines, have chromosomal abnormalities,[10] increasing the likelihood that the result of implementing these guidelines will be even more abnormal ES cells. Indeed, studies note that ES cells have more in common with cancer cells than with normal cells.[11] A recent cautionary report showing tumor formation caused by fetal stem cells in a young boy[12] emphasizes the fact that young, pluripotent stem cells are clinically unsuitable.

ES cells also face significant hurdles related to transplant rejection. The cells actually seem to increase their immunogenicity upon differentiation, making them more susceptible to transplant rejection and inflammatory responses.[13]

INDUCED PLURIPOTENT STEM CELLS (iPS CELLS)

Induced pluripotent stem (iPS) cells provide a relatively easy method for creation of ES cells directly from virtually any tissue source or individual. These cells were first developed in 2006 in mice by the Japanese scientist Shinya Yamanaka.[14] In November 2007, Yamanaka's lab and the lab of Thomson in the U.S. showed that this same technique could work for human cells as well, easily producing human iPS cells directly from human tissue.[15] The straightforward technique involves "reprogramming" the genetic expression of a cell, altering the gene expression of a normal body cell by adding several master genes, and inducing the cell to behave as if it were an ES cell. The original Yamanaka reprogramming technique involved adding four genes directly to a human cell such as a skin fibroblast cell, with the genes added using a viral vector. The technique has advanced rapidly in less than three years, and reprogramming of iPS

---

[8] Roy NS *et al.*, Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes, *Nature Medicine* 12, 1259-1268, November 2006; Sipione S *et al.*, Insulin expressing cells from differentiated embryonic stem cells are not beta cells, *Diabetologia* 47, 499-508, 2004

[9] Maitra A *et al.*, Genomic alterations in cultured human embryonic stem cells, *Nature Genetics* ; 37, 1099-1103, October 2005; Draper JS *et al.*, "Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells", *Nature Biotechnology* 22, 53-54; January 2004; Humpherys D *et al.*; Epigenetic instability in ES cells and cloned mice; *Science* 293, 95-97; 6 July 2001

[10] Vanneste E *et al*., Chromosome instability is common in human cleavage-stage embryos, *Nature Medicine* 15, 577-583, May 2009

[11] Werbowetski-Ogilvie TE *et al*. Characterization of human embryonic stem cells with features of neoplastic progression, *Nature Biotechnology* 27, 91-97, January 2009; Somervaille TCP *et al*., Hierarchical maintenance of MLL myeloid leukemia stem cells employs a transcriptional program shared with embryonic rather than adult stem cells, *Cell Stem Cell* 4, 129-140, 6 Feb 2009

[12] Amariglio N *et al*., Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient, PLoS Med 6: e1000029. doi:10.1371/journal.pmed.1000029, 17 Feb 2009

[13] Swijnenburg R-J *et al.*, Embryonic stem cell immunogenicity increases upon differentiation after transplantation into ischemic myocardium, *Circulation* 112, I-166-I-172, 30 August 2005; Kofidis T *et al.*, They are not stealthy in the heart: embryonic stem cells trigger cell infiltration, humoral and T-lymphocyte-based host immune response, *European Journal of Cardio-thoracic Surgery* 28, 461–466, 2005

[14] Takahashi K and Yamanaka S, Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors, *Cell* 126, 663-676, 25 August 2006

[15] Takahashi K *et al.*, Induction of pluripotent stem cells from adult **human** fibroblasts by defined factors, *Cell* 131, 861-872, 30 November 2007; published online 20 November 2007; Yu J *et al.*, Induced pluripotent stem cell lines derived from **human** somatic cells, *Science* 318, 1917-1920, 21 Decmber 2007, published online 20 November 2007

cells has now been accomplished completely without the use of added DNA sequences, by using added protein reprogramming factors.[16]

The behavior of iPS cells appears virtually indistinguishable from ES cells. Thomson's group in their seminal paper producing human iPS cells noted:

> "The human iPS cells described here meet the defining criteria we originally proposed for human ES cells, with the significant exception that the iPS cells are not derived from embryos."[17]

Thomson has also pointed out the ethical advantage of iPS cells:

> "These cells possess the therapeutically desired characteristics of ES cells, namely indefinite self-renewal and pluripotency, without the requirement of human embryo destruction."[18]

Prof. Ian Wilmut, cloner of Dolly the sheep, has noted that "the technique of cloning is no longer applicable," "The de-differentiation of somatic cells didn't require the use of human embryos as, technically speaking, it wasn't necessary. The first iPS cells were produced and identified through studies on mouse embryos," and "The iPS technique to obtain stem cells is now the most efficient technique for researchers, in particular for research on inherited diseases," and "iPS cells are more useful than embryonic cells."[19]

Thus, iPS cells fulfill the desire to create ES cells, with the added advantage of easy and cheap creation directly from a patient, and the potential for transplant match, but do all of this without the use of embryos, eggs, or cloning. Within one year after announcement of the first human iPS cells, at least 315 human iPS cell lines had been generated, and over 500 total human iPS cell lines have been reported. In addition, iPS cell lines from patients suffering from various diseases have been created, covering 13 different diseases.[20]

In summary, iPS cells provide all of the desired characteristics of pluripotent ES cells, and also distinct advantages in terms of their ethical creation as well as ease and cost of creation, and production directly from patients.

---

[16] Zhou H *et al.*, Generation of Induced Pluripotent Stem Cells **Using Recombinant Proteins**, *Cell Stem Cell* 4, 381-384, 8 May 2009, published online 23 April 2009

[17] Yu J *et al.*, Induced pluripotent stem cell lines derived **from human somatic cells**, *Science* 318, 1917-1920, 21 December 2007, published online 20 November 2007

[18] Swaney DL *et al.*, Human embryonic stem cell phosphoproteome revealed by electron transfer dissociation tandem mass spectrometry, *Proc. Natl. Acad. Sci. USA* 106, 995-1000, 27 January 2009

[19] "Interview du professeur Ian Wilmut par Gènéthique", accessed at: http://www.genethique.org/tribunes_mensuelles/mai_2009.asp ; for English translation, see: http://ethicalstemcellresearch.blogspot.com/2009/05/read-this-wilmut-king-of-cloning-says.html

[20] For a list of iPS cell publications and current human iPS cell lines, please see the links at: http://www.frcblog.com/2009/05/update-on-ips-cells/

ADULT STEM CELLS

Adult stem cells provide a readily available and flexible source of stem cells for the treatment of disease. Only adult stem cells have shown any real successes in therapeutic applications. A wealth of published scientific papers document that adult stem cells are a much more promising source of stem cells for regenerative medicine. Some adult stem cells actually do show pluripotent flexibility in generation of tissues, meaning that they can generate most or all of the different tissues of the body; such sources include bone marrow,[21] peripheral blood,[22] umbilical cord blood,[23] nasal mucosa,[24] amniotic fluid,[25] and testicular tissue.[26]

The real success for adult stem cells, however, is their ability to repair and replace damaged tissue, *i.e.*, actually accomplish regenerative medicine. Pre-clinical results provide voluminous evidence that adult stem cells are effective in treating animal models of disease. More importantly, adult stem cells are already being used clinically to treat dozens of diseases in human patients, relieving suffering and saving lives. Early successes and many of the continuing results use adult stem cells, most often from bone marrow or umbilical cord blood, in conjunction with chemotherapy or radiation, in treatments for various cancers, including ovarian cancer, retinoblastoma, brain tumors, testicular cancer,[27] various lymphomas including Hodgkin's lymphoma[28] and Non-Hodgkin's lymphoma,[29] chronic[30] and acute[31] leukemias, breast cancer,[32] renal cell carcinoma,[33] and numerous other cancers. Similar methodology has

---

[21] D'Ippolito G *et al.*, Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential, *J. Cell Science* 117, 2971-2981, 15 July 2004

[22] Zhao Y *et al.*; A human peripheral blood monocyte-derived subset acts as pluripotent stem cells; *Proceedings of the National Academy of Sciences USA* 100, 2426-2431; 4 March 2003

[23] McGuckin CP *et al.*, Production of stem cells with embryonic characteristics from human umbilical cord blood, *Cell Proliferation* 38, 245-255, August 2005

[24] Murrell W *et al.*, Multipotent stem cells from adult olfactory mucosa, *Developmental Dynamics* published online 21 March 2005

[25] De Coppi *et al.*, Isolation of amniotic stem cell lines with potential for therapy, *Nature Biotechnology* published online 7 January 2007; doi:10.1038/nbt1274

[26] Conrad S *et al.*, Generation of pluripotent stem cells from adult human testis, *Nature* 344-349, 20 November 2008

[27] Bhatia S *et al.*; High-dose chemotherapy as initial salvage chemotherapy in patients with relapsed testicular cancer; *J. Clin. Oncol.* 18, 3346-3351; Oct. 19, 2000

[28] Peggs KS *et al.*, Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantion, *Lancet* 365, 1934-1941, 4 June 2005; Tabata M *et al.*; Peripheral blood stem cell transplantation in patients over 65 years old with malignant lymphoma--possibility of early completion of chemotherapy and improvement of performance status; *Intern Med* 40, 471-474; June 2001

[29] Buadi FK et al., Autologous hematopoietic stem cell transplantation for older patients with relapsed non-Hodgkin's lymphoma, *Bone Marrow Transplant* 37, 1017-1022, June 2006

[30] Elliott MA *et al.*, Allogeneic stem cell transplantation and donor lymphocyte infusions for chronic myelomonocytic leukemia, *Bone Marrow Transplantation* 37, 1003-1008, 2006

[31] Eapen M *et al.*, Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study, *Lancet* 369, 1947-1954, 2007

[32] Damon LE *et al.*; High-dose chemotherapy and hematopoietic stem cell rescue for breast cancer: experience in California; *Biol. Blood Marrow Transplant* 6, 496-505; 2000

[33] Barkholt L *et al.*, Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe, *Annals of Oncology* published online 28 April 2006

utilized adult stem cells in treatments for various anemias, including sickle cell anemia[34] and Fanconi's anemia[35]. This technique has also been used successfully to treat patients with various autoimmune diseases, including multiple sclerosis,[36] systemic lupus,[37] Crohn's disease,[38] and juvenile (Type I) diabetes.[39] Various immunodeficiencies including SCID have been treated successfully as well.[40] Adult stem cells have also shown success in ameliorating the effects of various genetic metabolic disorders such as Hurler's syndrome,[41] Krabbe's leukodystrophy,[42] and others. These life-saving treatments continue to improve and to increase, but need increased support with further federally funded clinical trials.

Published patient results have also shown the usefulness of adult stem cells for repair of acute and chronic cardiac damage,[43] growing new corneas to restore sight to blind patients,[44] treatment of limb ischemia and wounds,[45] successful amelioration of the effects of stroke,[46] and treating

---

[34] Krishnamurti L *et al.*, Stable long-term donor engraftment following reduced-intesity hematopoietic cell transplantation for sickle cell disease, *Biol. Blood Marrow Transplant* 14, 1270-1278, 2008; Bernaudin F *et al.*, Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease, *Blood* 110, 2749-2756, 2007

[35] Bitan M *et al.*, Fludarabine-based reduced intensity conditioning for stem cell transplantation of fanconi anemia patients from fully matched related and unrelated donors, *Biol Blood Marrow Transplant.* 12, 712-718, July 2006

[36] Burt RK *et al.*, Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study, *The Lancet Neurology* 8, 244-253, March 2009

[37] Burt RK *et al.*, Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus, *Journal of the American Medical Association* 295, 527-535, February 1, 2006

[38] Kreisel W *et al.*, Complete remission of Crohn's disease after high-dose cyclophosphamide and autologous stem cell transplantation, *Bone Marrow Transplantation* 32, 337-340, 2003

[39] Couri CEB *et al.*, C-peptide levels and isulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus, *Journal of the American Medical Association* 301, 1573-1579, 2009; Voltarelli JC *et al.*, Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus, *Journal of the American Medical Association* 297, 1568-1576, 11 April 2007

[40] Grunebaum E *et al.*, Bone marrow transplantation for severe combined immune deficiency, *Journal of the American Medical Association* 295, 508-518, 1 February 2006

[41] Cox-Brinkman J *et al.*, Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome, *Bone Marrow Transplantation* 38, 17-21, 2006

[42] Escolar ML *et al.*, Transplantation of umbilical cord-blood in babies with infantile Krabbe's disease, *New England Journal of Medicine* 352, 2069-2081, 19 May 2005

[43] Herbots L *et al.*, Improved regional function after autologous bone marrow-derived stem cell transfer in patients with acute myocardial infarction: a randomized, double-blind strain rate imaging study, *Eur. Heart Journal* 30, 662-670, 2009; Burt RK *et al.*, Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases, *Journal of the American Medical Association* 299, 925-936, Feb 2008; Joseph J *et al.*, Safety and effectiveness of granulocyte-colony stimulating factor in mobilizing stem cells and improving cytokine profile in advanced chronic heart failure, *American Journal of Cardiology* 97, 681-684, 1 March 2006; Strauer BE *et al.*, Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease, *Journal of the American College of Cardiology* 46, 1651-1658, 1 November 2005

[44] Inatomi T *et al.*, Midterm results on ocular surface reconstruction using cultivated autologous oral mucosal epithelial transplantation, *American Journal of Ophthalmology* 141, 267-275, February 2006

[45] Tateishi-Yuyama E et al.; Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial; Lancet 360, 427-435; 10 August 2002; Badiavas EV and Falanga V, Treatment of chronic wounds with bone marrow-derived cells, *Archives of Dermatology* 139, 510-516, 2003

[46] Shyu W-C *et al.*, Granulocyte colony-stimulating factor for acute ischemic stroke: a randomized controlled trial, *Canadian Medical Association Journal* 174, 927-933, 28 March 2006

liver disease.[47] An early clinical trial has shown effectiveness of the patient's own adult stem cells at treating Parkinson's disease,[48] and several reports now document clinical improvement using adult stem cells for treatment of spinal cord injury.[49] Adult stem cells have also already shown their utility in tissue-engineering applications to treat patients, including growth of functional bladders[50] and a published case of a new windpipe.[51]

Adult stem cells have distinct advantages over other stem cell types. In most cases the patient's own stem cells can be used for the treatment, circumventing problems of immune rejection. Adult stem cells do not have the problem of tumor formation that is associated with embryonic stem cells. Adult stem cells also show a homing ability to damaged tissue, allowing development of minimally invasive administration techniques.

The citations given above for adult stem cells are only a sampling (for a representative list of references, please see: http://www.sciencemag.org/cgi/data/315/5810/328b/DC1/1 and http://stemcellresearch.org/facts/asc-refs.pdf). Adult stem cells already show the ability to deliver therapeutic benefit to patients, and resources should be devoted to improving current adult stem cell therapies and developing the full promise of these useful cells.

CONCLUSION

1. ES cell research is legal and unrestricted. However, just as U.S. taxpayers should not have to pay for abortions, they should not have to pay for destructive research on embryos.
2. Furthermore, ES cell research should not be funded when there are ethical alternatives such as adult stem cells and iPS cells. In 1999, even President Clinton's National Bioethics Advisory Commission (NBAC) acknowledged broad agreement in our society that early human embryos "deserve respect as a form of human life" (NBAC, Ethical Issues in Human Stem Cell Research, 1999, p. ii). The Commission actually concluded that research requiring the destruction of these human lives should be seen as a last resort, saying: "In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research." (Id., p. 53). The Commission recommended funding ES cell research because it thought at that time that no alternatives existed; but it said this factual judgment "must be revisited continually as science advances."

---

[47] Terai S *et al.*, Improved liver function in liver cirrhosis patients after autologous bone marrow cell fusion therapy, *Stem Cells* 24, 2292-2298, Oct 2006

[48] Levesque MF *et al.*, Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: five-year post-operative outcome, *The Open Stem Cell Journal* 1, 20-29, 2009

[49] Geffner LF *et al.*, Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: Comprehensive case studies, *Cell Transplantation* 17, 1277-1293, 2008; Mackay-Sim A *et al.*, Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial, *Brain* 131, 2376 - 2386, September 2008; Lima C *et al.*, Olfactory mucosa autografts in human spinal cord injury: A pilot clinical study, *Journal of Spinal Cord Medicine* 29, 191-203, June 2006

[50] Atala A *et al.*, Tissue-engineered autologous bladders for patients needing cytoplasty, *The Lancet* 367, 1241-1246, 15 April 2006

[51] Macchiarini P *et al.*, Clinical transplantation of a tissue-engineered airway, *The Lancet* doi: 10.1016/S0140-6736(08)61598-6, published online 19 November 2008

3. There now exist several alternatives to ES cells. The iPS cell reprogramming technique produces cells that are indistinguishable from ES cells without the use of embryos, eggs, or cloning, and with the advantage that this technique is easier and cheaper and produces cells directly from a patient.
4. The successes of adult stem cells in improving health and saving lives are now well documented. Studies over the past decade show that adult stem cells can effectively and ethically deliver therapeutic benefit to patients. If the federal government considers the patients first, stem cell research funding would be directed primarily to adult stem cells.

Thank you for your consideration of these comments.

Respectfully submitted on behalf of the Family Research Council,

David A. Prentice, Ph.D.
Senior Fellow for Life Sciences
Family Research Council
801 G St, NW
Washington, DC 20001
Voice: 202-393-2100
Fax: 202-393-2134
dap@frc.org
www.frc.org