Stem Cell Research: Federal Research Funding and Oversight

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Summary

Embryonic stem cells have the ability to develop into virtually any cell in the body, and may have the potential to treat injuries as well as illnesses, such as diabetes and Parkinson's disease. In January 2009, the Food and Drug Administration approved a request from Geron, a California biotechnology company, to begin a clinical trial involving safety tests of embryonic stem cells in patients with recent spinal cord injuries.

Currently, most human embryonic stem cell lines used in research are derived from embryos produced via in vitro fertilization (IVF). Because the process of removing these cells destroys the embryo, some individuals believe the derivation of stem cells from human embryos is ethically unacceptable. In November 2007, research groups in Japan and the United States announced the development of embryonic stem cell-like cells, called induced pluripotent stem (iPS) cells, via the introduction of four genes into human skin cells. Those concerned about the ethical implications of deriving stem cells from human embryos argue that researchers should use iPS cells or adult stem cells (from bone marrow or umbilical cord blood). However, many scientists believe research should focus on all types of stem cells.

In August 2001, President George W. Bush announced that for the first time, federal funds would be used to support research on human embryonic stem cells, but funding would be limited to "existing stem cell lines." NIH established a registry of 78 human embryonic stem cell lines that are eligible for use in federally funded research, but only 21 cell lines are currently available. Scientists are concerned about the quality and longevity of these 21 stem cell lines. Many scientists believe that research advancement requires access to new human embryonic stem cell lines. President Barack Obama has promised to lift the Bush restriction on stem cell research.

H.R. 873 (DeGette), the Stem Cell Research Enhancement Act of 2009, was introduced on February 4, 2009. The text of H.R. 873 is identical to legislation introduced in the 110th Congress, H.R. 3 (DeGette), and the 109th Congress, H.R. 810 (Castle). The bill would allow federal support of research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo, and thus if passed would negate the August 2001 Bush stem cell policy limitation. Stem cell lines must meet ethical guidelines established by the NIH, which would be issued within 60 days of enactment. H.R. 872 (DeGette), the Stem Cell Research Improvement Act of 2009, was also introduced on February 4, 2009. It is similar to H.R. 873 in that it adds the same Section 498D, "Human Embryonic Stem Cell Research," to the PHS Act, but it also adds another Section 498E, "Guidelines on Research Involving Human Stem Cells," which would require the Director of NIH to issue guidelines on research involving human embryonic stem cell within 90 days of enactment; updates of the guidelines would be required every three years. S. 487 (Harkin), introduced on February 26, 2009, is the same as H.R. 873, except it has an additional section supporting research on alternative human pluripotent stem cells. It is identical to a bill introduced in the 110th Congress, S. 5 (Reid).

During the 110th Congress, the Senate passed legislation (S. 5) in April 2007 that would have allowed federal support of research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo. The bill would have also provided support for research on alternatives, such as iPS cells. The House passed the bill in June 2007, and President Bush vetoed it on June 20, 2007. (The 109th Congress passed a similar bill, which also was vetoed by President Bush, the first veto of his presidency; an attempt to override the veto in the House failed.) On the related issue of human cloning, in June 2007 the House failed to pass a bill (H.R. 2560) that would have imposed penalties on anyone who cloned a human embryo and implanted it in a uterus.

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Introduction

On August 9, 2001, President George W. Bush announced that for the first time federal funds would be used to support research on human embryonic stem cells. However, funding would be limited to stem cell lines that had been created prior to the date of the policy announcement. President Barack Obama has promised to lift the Bush restriction on stem cell research and allow for the federal funding of research utilizing the hundreds of human embryonic stem cell lines created since the Bush 2001 policy. The change in stem cell policy is expected to occur either by executive order, by passing legislation that was twice vetoed by President Bush, or by both. However, even after the expected policy change, scientists will not be able to use federal funds for the derivation of new human embryonic stem cell lines or for research involving somatic cell nuclear transfer using human eggs unless Congress removes the existing Dickey Amendment from appropriations legislation.

Research involving human embryonic stem cells is of concern for some individuals because the stem cells are located inside the embryo, and the process of removing the cells destroys the embryo.[1] Many religious and socially conservative individuals believe the destruction of embryos for the purpose of harvesting embryonic stem cells is morally and ethically unacceptable. They argue that researchers should use other alternatives, such as iPS cells or adult stem cells (both discussed below), instead of embryonic stem cells.

Federal funding for the support human embryonic stem cell research has been limited because of the Bush 2001 policy. The National Institutes of Health (NIH) identified 78 human embryonic stem cell lines that would be eligible for use in federally funded research, but most were found to be either unavailable or unsuitable for research. Twenty-one cell lines are currently available under the Bush policy. Scientists are concerned about the quality and longevity of these 21 stem cell lines. Many believe research advancement requires the use of new human embryonic stem cell lines.

The former Director of NIH, Elias Zerhouni, stated in a hearing on March 19, 2007, before the Senate Labor, Health and Human Services (HHS), Education, and Related Agencies Appropriations Subcommittee that "It's not possible for me to see how we can continue the momentum of science and research with the stem cell lines we have at NIH that can be funded."[2] When asked if other avenues of research should be pursued instead, Dr. Zerhouni stated that "the presentations about adult stem cells holding as much or more potential than embryonic stem cells, in my view, do not hold scientific water. I think they are overstated."[3] He noted that competitors in Europe, China, and India are investing heavily in human embryonic stem cell research. "I think it is important for us not to fight with one hand tied behind our back here. I think it's time to move forward on this area. It's time for policy makers to find common ground, to make sure that NIH does not lose its historical leadership.... To sideline NIH on such an issue of importance in my view is shortsighted."[4] On May 8, 2008, Dr. Zerhouni made similar statements about the need

[1] For further information, see CRS Report RL33554, *Stem Cell Research: Ethical Issues*, by Erin D. Williams and Judith A. Johnson.

[2] Drew Armstrong, "NIH Chief's Opinion on Stem Cell Research Goes Afield of White House Policy," *CQ Today*, March 19, 2007.

[3] Ibid.

[4] John Reichard, "Zerhouni Makes Strong Case Against Bush Policy on Stem Cells, NIH Funding," *CQ Today*, March 19, 2005.

for additional embryonic stem cell lines and the value of pursuing all avenues of stem cells research at a hearing before the House Energy and Commerce Subcommittee on Health.[5]

Several states, such as California, Connecticut, Illinois, Maryland, and New Jersey, have responded by moving forward with their own initiatives to encourage or provide funding for stem cell research, and many others have considered similar action. Proponents of these state stem cell research initiatives want to remain competitive, as well as prevent the relocation of scientists and biotechnology firms to other states or overseas. However, without the central direction and coordinated research approach that the federal government can provide, many are concerned that the states' actions will result in duplication of research efforts among the states, a possible lack of oversight for ethical concerns, and ultimately a loss of U.S. preeminence in this important area of basic research.

The 110th Congress addressed the topic of stem cell research early in the first session. H.R. 3 (DeGette) was introduced on January 5, 2007, with 211 cosponsors, and passed the House on January 11, 2007.[6] The bill would have allowed federal support of research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo, and thus would have negated the August 2001 Bush stem cell policy limitation. The Senate passed S. 5 (Reid) on April 11, the House passed S. 5 on June 7, and President Bush vetoed the bill on June 20, 2007. S. 5 was the same as H.R. 3 except it has an additional section supporting research on alternative human pluripotent stem cells.[7]

Basic Research and Potential Applications

Most cells within an animal or human being are committed to fulfilling a single function within the body. In contrast, stem cells are a unique and important set of cells that are not specialized. Stem cells retain the ability to become some or all of the more than 200 different cell types in the body, and thereby play a critical role in repairing organs and body tissues throughout life. Although the term stem cells is often used in reference to these repair cells within an adult organism, a more fundamental variety of stem cells is found in the early-stage embryo. Embryonic stem cells may have a greater ability to become different types of body cells than adult stem cells.

Embryonic Stem Cells from IVF Embryos or Fetal Tissue

Embryonic stem cells were first isolated from mouse embryos in 1981 and from primate embryos in 1995. Animal embryos were the only source for research on embryonic stem cells until November 1998, when two groups of U.S. scientists announced the successful isolation of human embryonic stem cells. One group, at the University of Wisconsin, derived stem cells from five-

[5] An archived audio webcast of the May 8, 2008, hearing can be found at http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050808.StemCell.shtml.

[6] During the first session of the 109th Congress, the House passed identical legislation, H.R. 810 (Castle), in May 2005. In July 2006, the Senate passed H.R. 810 and President Bush immediately vetoed it, the first veto of his presidency. An attempt in the House to override the veto was unsuccessful.

[7] A pluripotent cell has the ability to differentiate into all of the various cell types that make up the body, but not the "extra-embryonic" tissues such as the components of the placenta.

day-old embryos produced via *in vitro* fertilization (IVF).[8] The work is controversial because the stem cells are located within the embryo and the process of removing them destroys the embryo. Many individuals who are opposed to abortion are also opposed to research involving embryos. The second group, at Johns Hopkins University, derived stem cells with very similar properties from five- to nine-week-old embryos or from fetuses obtained through elective abortion.[9] Both groups reported the human embryos or fetuses were donated for research following a process of informing one or more parents and obtaining their consent. The cells removed from embryos or fetuses were manipulated in the laboratory to create embryonic stem cell lines that may continue to divide for many months to years. The vast majority of research on human embryonic stem cells, both in the United States and overseas, utilizes cell lines derived via the University of Wisconsin method.

Induced Pluripotent Stem (iPS) Cells

In November 2007, two research groups, one at Kyoto University in Japan and the second at the University of Wisconsin, Madison, announced the development of embryonic stem cell-like cells, called induced pluripotent stem (iPS) cells, through the introduction of four genes into human skin cells.[10] Until this breakthrough, the characteristics displayed by the iPS cells were thought to occur only in cells found within the embryo. The research teams accomplished the reprogramming of the adult skin cells by using a retrovirus to transport the four genes into the skin cells. The teams each used a different set of four genes; the Kyoto group has subsequently achieved reprogramming using three genes.[11] The work on human iPS cells is based on earlier studies by the Kyoto group in mouse embryos that identified the genes active in early embryos and then used combinations of these genes to try and reprogram adult mouse cells. The successful mouse reprogramming study, using four mouse genes, was announced in June 2006. The analogous four human genes were used by the Kyoto group on the human skin cells.

Although development of iPS cells may one day lessen the need to study stem cells derived from the human embryo, scientists insist that work on human embryonic stem cells must continue for several reasons.[12] For example, it is unclear whether iPS cells share all the characteristics of embryonic stem cells, and therefore multiple comparisons between the two types of cells will be necessary. In addition, because scientists have used potentially cancer-causing retroviruses to

[8] The IVF embryos were originally created for the treatment of infertility. Excess embryos are often frozen for future use. A couple may elect to discard their excess embryos, donate the embryos for research, or allow another couple to adopt an embryo. The Society for Assisted Reproductive Technology and RAND conducted a survey of more than 430 infertility clinics to determine the number of frozen embryos in the United States; 340 clinics responded to the survey. Nearly 400,000 embryos have been frozen and stored since the late 1970s. The vast majority of embryos are being held to help couples have children at a later date. Patients have designated 2.8%, or about 11,000 embryos, for research. Scientists estimate these 11,000 could form up to 275 stem cell lines, perhaps much less http://www.rand.org/pubs/research_briefs/RB9038/index1.html.

[9] Scientists and physicians use the term "embryo" for the first eight weeks after fertilization, and "fetus" for the ninth week through birth. In contrast, the Department of Health and Human Services (HHS) regulations define "fetus" as "the product of conception from the time of implantation" (45 C.F.R. § 46.203).

[10] Gretchen Vogel and Constance Holden, "Field Leaps Forward with New Stem Cell Advances," *Science*, v. 318, November 23, 2007, pp. 1224-1225.

[11] Dennis Normile, "Shinya Yamanaka: Modest Researcher, Results to Brag About," *Science*, v. 319, February 1, 2008, p. 562.

[12] Constance Holden and Gretchen Vogel, "A Seismic Shift for Stem Cell Research," *Science*, v. 319, February 1, 2008, pp. 560-563.

transfer the reprogramming genes, these iPS cells would not desirable for therapeutic uses in patients. Therefore, alternative mechanisms to accomplish reprogramming would need to be developed. Scientists are in the process of investigating the use of other safer viruses to transfer the genes. Some groups are exploring chemical methods of achieving the same results by switching on genes in the adult cell rather than transferring in additional gene copies with a virus.

Embryonic Stem Cells Obtained via SCNT (Cloning)

Another potential source of embryonic stem cells is somatic cell nuclear transfer (SCNT), also referred to as cloning.[13] For certain applications, stem cells derived using SCNT may offer the best hope for understanding and treating disease. In SCNT the nucleus of an egg is removed and replaced by the nucleus from a mature body cell, such as a skin cell obtained from a patient. In 1996, scientists in Scotland used the SCNT procedure to produce Dolly the sheep, the first mammalian clone.[14] When SCNT is used to create another individual, such as Dolly, the process is called reproductive cloning. In contrast, scientists interested in using SCNT to create cloned stem cells would allow the cell created via SCNT to develop for a few days, and then the stem cells would be removed for research. Stem cells created via SCNT would be genetically identical to the patient, and thus would avoid any tissue rejection problems that could occur if the cells were transplanted into the patient. Creating stem cells using SCNT for research purposes is sometimes referred to as therapeutic cloning.

Although various scientific groups have reported success in using SCNT to create cloned embryos (which are then used to produce stem cell lines or live births) of a variety of different mammals (sheep, rabbits, cows), attempts at creating primate embryos via SCNT had been unsuccessful. However, in June 2007, researchers at the Oregon National Primate Research Center at Oregon Health and Science University announced the successful derivation of stem cells from a rhesus monkey embryo created via SCNT.[15] Results of the Oregon group were confirmed in November 2007.[16]

The unsubstantiated announcement by Clonaid in December 2002 of the birth of a cloned child have contributed to the controversy over research on human embryos.[17] More recently, charges of ethical and scientific misconduct have clouded the reputation of scientists involved in deriving stem cells from human embryos created via SCNT. In February 2004, scientists at the Seoul National University (SNU) in South Korea announced the first isolation of stem cells from a cloned human embryo and in May 2005 announced advances in the efficiency of creating cloned human embryos and in isolating human stem cells. Concerns about the SNU work arose in November 2005 when a U.S. co-author of the 2005 paper accused Hwang Woo Suk, the lead SNU researcher, of ethical misconduct.[18] In December 2005, a Korean co-author of the May 2005 paper stated that the research was fabricated and the paper should be retracted; Hwang agreed to

[13] A somatic cell is a body cell. In contrast, a germ cell is an egg or sperm cell.

[14] Dolly was euthanized in February 2003 after developing a lung infection. Some claim her death at six years was related to being a clone, but her ailment may also have occurred because she was raised indoors (for security reasons) rather than as a pastured sheep, which often live to 12 years of age. G. Kolata, "First Mammal Clone Dies," *New York Times*, February 15, 2003, p. A4.

[15] Elizabeth Finkel, "Researchers Derive Stem Cells From Monkeys," *ScienceNOW Daily News*, June 19, 2007.

[16] Vogel and Holden, "Field Leaps Forward with New Stem Cell Advances," p. 1224.

[17] For further information, see CRS Report RL31358, *Human Cloning*, by Judith A. Johnson and Erin D. Williams.

[18] Gretchen Vogel, "Collaborators Split over Ethics Allegations" *Science*, November 18, 2005, p. 1100.

the retraction. On January 10, 2006, SNU stated that results of the 2004 paper were also a deliberate fabrication.[19] Despite these difficulties, scientists in a number of labs are continuing to work on deriving patient-matched stem cells from cloned human embryos.[20]

Stem Cells from Adult Tissue or Umbilical Cord Blood

Stem cells obtained from adult organisms are also the focus of research. In April 2007, researchers in Brazil published a preliminary report on attempts to treat 15 newly diagnosed type 1 diabetes patients with high-dose immunosuppressive chemotherapy followed by transplantation of the patient's own stem cells.[21] Although this experiment was first proposed by U.S. scientists, the risks associated with the procedure were judged to be to high (5% mortality) for a treatable disease that affects children.[22] Type 1 diabetes is thought to be an autoimmune disease in which the patient's immune system attacks the insulin-producing cells in the pancreas. Scientists are not certain about the exact mechanism of how the treatment works. One hypothesis is that the chemotherapy suppresses the patient's immune system and stops the destruction of the remaining insulin-producing cells in the patient's body, which is why early diagnosis is crucial in this approach. The patient's stem cells are then transfused back into the body, hopefully becoming part of an immune system that will not continue to attack the patient's insulin-producing cells.

A January 2007 report found that cells similar to embryonic stem cells can be found in amniotic fluid. However, the lead author of the report, as well as others in the field, caution that these cells are not a replacement for embryonic stem cells.[23] There have been a number of other publications on the abilities and characteristics of adult stem cells from a variety of different sources, such as bone marrow and the umbilical cord following birth. Bone marrow transplantation, a type of adult stem cell therapy, has been used for 50 years to treat patients for a variety of blood-related conditions.[24] Several private companies (such as MorphoGen, NeuralStem, Osiris Therapeutics, StemSource, ViaCell) are working on additional therapeutic uses of adult stem cells.

In 1999, David A. Prentice of the Family Research Council and other biomedical researchers founded Do No Harm: The Coalition of Americans for Research Ethics, a group that opposes stem cell research on the grounds that it is unethical because it destroys embryos and is unnecessary due to the success of adult stem cell therapy. Do No Harm has compiled a list of 73 diseases that it claims can be treated using adult stem cells.[25] In a July 2006 letter to *Science*,

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[19] Nicholas Wade and Choe Sang-Hun, "Researcher Faked Evidence of Human Cloning, Koreans Report," *The New York Times*, January 10, 2006, p. A1.

[20] Dennis Normile, Gretchen Vogel, and Constance Holden, "Cloning Researcher Says Work is Flawed but Claims Results Stand," *Science*, December 23, 2005, p. 1886-1887; Carl T. Hall, "UCSF Resumes Human Embryo Stem Cell Work," *The San Francisco Chronicle*, May 6, 2006, p. A.1.

[21] Julio C. Voltarelli, et al., "Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus," *Journal of the American Medical Association*, April 11, 2007, v. 297, p. 1568-1576.

[22] Comments made by NIH Director Elias Zerhouni during a May 8, 2008 hearing before the House Energy and Commerce Subcommittee on Health, audio webcast available at http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050808.StemCell.shtml.

[23] Rick Weiss, "Scientists See Potential in Amniotic Stem Cells; They Are Highly Versatile And Readily Available," *The Washington Post*, January 8, 2007, p. A1, A5.

[24] Frederick R. Appelbaum, "Hematopoietic-Cell Transplantation at 50," *The New England Journal of Medicine*, v. 357, October 11, 2007, pp. 1472-1475.

[25] http://www.stemcellresearch.org/facts/treatments.htm.

Smith et al. accuse Prentice of misleading the public and deceiving patients with the list because only nine of the adult stem cell treatments have been "fully tested in all required phases of clinical trials and approved by the U.S. Food and Drug Administration."[26] Prentice responded in a January 2007 letter that "Our list of [then] 72 applications, compiled from peer-reviewed articles, documents observable and measurable benefit to patients, a necessary step toward formal FDA approval and what is expected of new, cutting-edge medical applications."[27] Prentice also accused Smith et al. of "cruelly deceiving patients and the public" by promoting the "falsehood that embryonic stem cell cures are imminent." In a June 2007 exchange, Smith et al. continue to emphasize that the majority of treatments on the list haven't met FDA standards.[28] Prentice defended the list by pointing to tangible benefits to some patients.[29] Both sides again accused the other of misleading laypeople and deceiving patients.

Opponents of stem cell research advocate that adult instead of embryonic stem cell research should be pursued because they believe the derivation of stem cells from either IVF embryos or aborted fetuses is ethically unacceptable. Others believe that adult stem cells should not be the sole target of research because of important scientific and technical limitations. Adult stem cells may not be as long lived or capable of as many cell divisions as embryonic stem cells. Also, adult stem cells may not be as versatile in developing into various types of tissue as embryonic stem cells, and the location and rarity of the cells in the body might rule out safe and easy access. For these reasons, many scientists argue that both adult and embryonic stem cells should be the subject of research, allowing for a comparison of their various capabilities. Reports issued by the NIH and the Institute of Medicine (IoM) state that both embryonic and adult stem cell research should be pursued.[30]

In FY2004, the Consolidated Appropriations Act, 2004 (P.L. 108-199) provided $10 million to establish a National Cord Blood Stem Cell Bank within the Health Resources and Services Administration (HRSA). HRSA was directed to use $1 million to contract with the IoM to conduct a study that would recommend an optimal structure for the program. The study, *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*, was released in April 2005. The blood cell forming stem cells found in cord blood can be used as an alternative to bone marrow transplantation in the treatment of leukemia, lymphoma, certain types of anemia, and inherited disorders of immunity and metabolism. The IOM report provides the logistical process for establishing a national cord blood banking system, establishes uniform standards for cord blood collection and storage, and provides recommendations on ethical and legal issues associated with cord blood collection, storage and use.

On December 20, 2005, the President signed the Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129). The act provides for the collection and maintenance of human cord blood stem

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[26] Shane Smith, William Neaves and Steven Teitelbaum, "Adult Stem Cell Treatments for Diseases?"*Science*, v. 313, July 28, 2006, p. 439; as well as online in *Sciencexpress*, July 13, 2006, p. 1 http://www.sciencexpress.org.

[27] David A. Prentice and Gene Tarne, "Treating Diseases with Adult Stem Cells," *Science*, v. 315, January 19, 2007, p. 328.

[28] Shane Smith, William Neaves and Steven Teitelbaum, "Adult Versus Embryonic Stem Cells: Treatments," *Science*, v. 316, June 8, 2007, p. 1422.

[29] David A. Prentice and Gene Tarne, "Adult Versus Embryonic Stem Cells: Treatments—Response," *Science*, v. 316, June 8, 2007, p. 1422-1423.

[30] National Institutes of Health, Department of Health and Human Services, *Stem Cells: Scientific Progress and Future Research Directions*, June 2001, available at http://stemcells.nih.gov/info/scireport/. Institute of Medicine, *Stem Cells and the Future of Regenerative Medicine*, 2002, available at http://www.nas.edu.

cells for the treatment of patients and for research. It stipulates that amounts appropriated in FY2004 or FY2005 for this purpose shall remain available until the end of FY2007, and authorizes $60 million over FY2007-FY2010. The act also reauthorizes the national bone marrow registry with $186 million over FY2006-FY2010. In addition, it creates a database to enable health care workers to search for cord blood and bone marrow matches and links all these functions under a new name, the C.W. Bill Young Cell Transplantation program.

Potential Applications of Stem Cell Research

Stem cells provide the opportunity to study the growth and differentiation of individual cells into tissues. Understanding these processes could provide insights into the causes of birth defects, genetic abnormalities, and other disease states. If normal development were better understood, it might be possible to prevent or correct some of these conditions. Stem cells could be used to produce large amounts of one cell type to test new drugs for effectiveness and chemicals for toxicity. The damaging side effects of medical treatments might be repaired with stem cell treatment. For example, cancer chemotherapy destroys immune cells in patients, decreasing their ability to fight off a broad range of diseases; correcting this adverse effect would be a major advance. Stem cells might be transplanted into the body to treat disease (e.g., diabetes, Parkinson's disease) or injury (e.g., spinal cord).

In January 2009, the Food and Drug Administration approved a request from Geron, a California biotechnology company, to begin a Phase I clinical trial involving safety tests of embryonic stem cells in 8 to 10 patients with recent spinal cord injuries.[31] In this first human subject trial using embryonic stem cells, the injected cells are intended to "help repair the insulation, known as myelin, around nerve cells, restoring the ability of some nerve cells to carry signals. There is also hope that growth factors produced by the injected cells will spur damaged nerve cells to regenerate."[32] Some scientists have expressed concern over the possibility that the transplanted cells may form a type of tumor called a teratoma, but extensive studies in rodents were performed to assure FDA that the stem cells did not causes tumors in animals.[33]

Before stem cells can be applied to human medical problems, substantial advances in basic cell biology and clinical technique are required. In addition, very challenging regulatory decisions will be required on any individually created tissue-based therapies resulting from stem cell research. Such decisions would likely be made by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). The potential benefits mentioned above would be likely only after many more years of research. Technical hurdles include developing the ability to control the differentiation of stem cells into a desired cell type (like a heart or nerve cell) and to ensure that uncontrolled development, such as cancer, does not occur. Some experiments may involve the creation of a chimera, an organism that contains two or more genetically distinct cell types, from the same species or different species.[34] If stem cells are to be

[31] Andrew Pollack, "FDA approves a stem cell trial," *New York Times*, January 23, 2009.

[32] Ibid.

[33] Jennifer Couzin, "Celebration and concern over U.S. trial of embryonic stem cells," *Science*, vol. 323 (January 30, 2009), p. 568.

[34] Chimeras have been created by scientists in a variety of different ways and have been the subject of research studies for many years. Human chimeras occur naturally when two eggs become fertilized and, instead of developing into twins, they fuse in the uterus creating a single embryo with two distinct sets of genes. For one example, see Constance Holden, "Chimera on a Bike?" *Science*, June 24, 2005, p. 1864.

used for transplantation, the problem of immune rejection must also be overcome. Some scientists think that the creation of many more embryonic stem cell lines will eventually account for all the various immunological types needed for use in tissue transplantation therapy. Others envision the eventual development of a "universal donor" type of stem cell tissue, analogous to a universal blood donor.

However, if the method used to create iPS cells or if the SCNT technique was employed (using a cell nucleus from the patient), the stem cells created via these methods would be genetically identical to the patient, would presumably be recognized by the patient's immune system, and thus might avoid any tissue rejection problems that could occur in other stem cell therapeutic approaches. Because of this, scientists believe that these techniques may provide the best hope of eventually treating patients using stem cells for tissue transplantation.

Current Regulatory Landscape

The Dickey Amendment

Prior to an August 2001 Bush Administration decision (see below), no federal funds had been used to support research on stem cells derived from either human embryos or fetal tissue.[35] The work at the University of Wisconsin and Johns Hopkins University was supported by private funding from the Geron Corporation. Private funding for experiments involving embryos was required because Congress attached a rider to legislation that affected FY1996 National Institutes of Health (NIH) funding. The rider, an amendment originally introduced by Representative Jay Dickey, prohibited HHS from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. The Dickey Amendment language has been added to each of the Labor, HHS, and Education appropriations acts for FY1997 through FY2008.[36] Through March 6, 2009, funding for FY2009 is provided in the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, P.L. 110-329, "under the authority and conditions" set by the Consolidated Appropriations Act, 2008, P.L. 110-161. The Dickey Amendment is found in Section 509 of Division G—Department of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2008, of P.L. 110-161. It states that:

> (a) None of the funds made available in this Act may be used for—
>
> (1) the creation of a human embryo or embryos for research purposes; or
>
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero

[35] However, federal funds have been provided for research on both human and animal adult stem cells and animal embryonic stem cells.

[36] The rider language has not changed significantly from year to year (however there was a technical correction in P.L. 109-149). The original rider can be found in Section 128 of P.L. 104-99; it affected NIH funding for FY1996 contained in P.L. 104-91. For subsequent fiscal years, the rider is found in Title V, General Provisions, of the Labor, HHS and Education appropriations acts in the following public laws: FY1997, P.L. 104-208; FY1998, P.L. 105-78; FY1999, P.L. 105-277; FY2000, P.L. 106-113; FY2001, P.L. 106-554; FY2002, P.L. 107-116; FY2003, P.L. 108-7; FY2004, P.L. 108-199; FY2005, P.L. 108-447; FY2006, P.L. 109-149; FY2007, P.L. 110-5; FY2008, P.L. 110-161.

> under 45 CFR 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
>
> (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 [the Human Subject Protection regulations] as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes [sperm or egg] or human diploid cells [cells that have two sets of chromosomes, such as somatic cells].

Clinton Administration Stem Cell Policy

Following the November 1998 announcement on the derivation of human embryonic stem cells, NIH requested a legal opinion from HHS on whether federal funds could be used to support research on human stem cells derived from embryos. The January 15, 1999, response from HHS General Counsel Harriet Rabb found that the Dickey Amendment would not apply to research using human stem cells "because such cells are not a human embryo within the statutory definition." The finding was based, in part, on the determination by HHS that the statutory ban on human embryo research defines an embryo as an *organism* that when implanted in the uterus is capable of becoming a human being. Human stem cells, HHS said, are not and cannot develop into an organism; they lack the capacity to become organisms even if they are transferred to a uterus. As a result, HHS maintained that NIH could support research that uses stem cells derived through private funds, but could not support research that itself, with federal funds, derives stem cells from embryos because of the federal ban in the Dickey Amendment.

Shortly after the opinion by the HHS General Counsel was released, NIH disclosed that the agency planned to fund research on stem cells derived from human embryos once appropriate guidelines were developed and an oversight committee established. NIH Director Harold Varmus appointed a working group that began drafting guidelines in April 1999. Draft guidelines were published in the *Federal Register* on December 2, 1999. About 50,000 comments were received during the public comment period, which ended February 22, 2000. On August 25, 2000, NIH published in the *Federal Register* final guidelines on the support of human embryonic stem cell research. The guidelines stated that studies utilizing "stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment." Under the guidelines, NIH would not fund research directly involving the derivation of human stem cells from embryos; this was prohibited by the Dickey Amendment.

Other areas of research ineligible for NIH funding under the guidelines include (1) research in which human stem cells are utilized to create or contribute to a human embryo; (2) research in which human stem cells are combined with an animal embryo; (3) research in which human stem cells are used for reproductive cloning of a human; (4) research in which human stem cells are *derived* using somatic cell nuclear transfer (i.e., the transfer of a human somatic cell nucleus into a human or animal egg); (5) research *utilizing* human stem cells that were derived using somatic cell nuclear transfer; and (6) research utilizing stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

NIH began accepting grant applications for research projects utilizing human stem cells immediately following publication of the guidelines; the deadline for submitting a grant application was March 15, 2001. All such applications were to be reviewed by the NIH Human

Pluripotent Stem Cell Review Group (HPSCRG), which was established to ensure compliance with the guidelines. James Kushner, director of the University of Utah General Clinical Research Center, served briefly as chair of the HPSCRG. Applications would also have undergone the normal NIH peer-review process.[37] The first meeting of the HPSCRG was scheduled for April 25, 2001. The HPSCRG was to conduct an ethical review of human pluripotent stem cell lines to determine whether the research groups involved had followed the NIH guidelines in deriving the cell lines. However, in mid April 2001, HHS postponed the meeting until a review of the Clinton Administration's policy decisions on stem cell research was completed by the new administration following the election of George W. Bush.[38] According to media sources, the 12 HPSCRG members, whose names were not made public, represented a wide range of scientific, ethical and theological expertise and opinion, as well as at least one "mainstream Catholic."[39]

The Bush Administration conducted a legal review of the policy decisions made during the Clinton Administration regarding federal support of stem cell research, as well as a scientific review, prepared by NIH, of the status of the research and its applications. The scientific review was released on July 18, 2001, at a hearing on stem cell research held by the Senate Appropriations Subcommittee on Labor, Health and Human Services and Education.[40] The NIH report did not make any recommendations, but argued that both embryonic and adult stem cell research should be pursued.

Bush Administration Stem Cell Policy

On August 9, 2001, President George W. Bush announced that for the first time federal funds would be used to support research on human embryonic stem cells, but funding would be limited to "existing stem cell lines where the life and death decision has already been made."[41] President Bush stated that the decision "allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life." The President also stated that the federal government would continue to support research involving stem cells from other sources, such as umbilical cord blood, placentas, and adult and animal tissues, "which do not involve the same moral dilemma."

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[37] According to media sources, as of April 2001 only three grant applications had been submitted to NIH, and one was subsequently withdrawn. (*Washington FAX*, April 19, 2001.) Presumably, scientists were reluctant to invest the time and effort into preparing the necessary paperwork for the NIH grant application process when the prospects of receiving federal funding were uncertain under the new Bush Administration. (P. Recer, "Stem Cell Studies Said Hurt by Doubt," *AP Online*, May 2, 2001.) In a related development, one of the leading U.S. researchers on stem cells, Roger Pederson of the University of California, San Francisco, decided to move his laboratory to the United Kingdom for "the possibility of carrying out my research with human embryonic stem cells with public support." (Aaron Zitner, "Uncertainty Is Thwarting Stem Cell Researchers," *Los Angeles Times*, July 16, 2001, pp. A1, A8.) Human embryonic stem cell research was approved overwhelmingly by the House of Commons in December 2000 and the House of Lords in January 2001.

[38] Rick Weiss, "Bush Administration Order Halts Stem Cell Meeting; NIH Planned Session to Review Fund Requests," *Washington Post*, April 21, 2001, p. A2.

[39] Ibid.

[40] National Institutes of Health, Department of Health and Human Services. *Stem Cells: Scientific Progress and Future Research Directions*, June 2001. The NIH scientific report can be found at http://stemcells.nih.gov/info/scireport/.

[41] The August 9, 2001, *Remarks by the President on Stem Cell Research* can be found at http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html.

Under the Bush policy, federal funds may only be used for research on existing stem cell lines that were derived (1) with the informed consent of the donors, (2) from excess embryos created solely for reproductive purposes, and (3) without any financial inducements to the donors.[42] NIH was tasked with examining the derivation of all existing stem cell lines and creating a registry of those lines that satisfy the Bush Administration criteria. According to the White House, this will ensure that federal funds are used to support only stem cell research that is scientifically sound, legal, and ethical. Federal funds will not be used for (1) the derivation or use of stem cell lines derived from newly destroyed embryos, (2) the creation of any human embryos for research purposes, or (3) the cloning of human embryos for any purpose.

Regulation of Stem Cell Research

The Common Rule (45 CFR 46, Subpart A) is a set of regulations that govern most federally funded research conducted on human beings. Its three basic requirements are aimed at protecting research subjects: the informed consent of research subjects, a review of proposed research by an Institutional Review Board (IRB), and institutional assurances of compliance with the regulations. However, ex vivo embryos (those not in a uterus) are not considered "human subjects" for these purposes, but federally funded research on human embryos is regulated by the Dickey Amendment as described above. Stem cells and stem cell lines are also not considered "human subjects," nor are they governed by the Dickey Amendment.

Because of the lack of federal regulation of stem cell research, the National Academies developed voluntary guidelines for deriving, handling and using human embryonic stem cells.[43] Two HHS agencies, FDA and NIH, regulate some aspects of stem cell research, even if research on stem cell lines is not classified as "human subjects" research. FDA, the agency that ensures the safety and efficacy of food, drugs, medical devices and cosmetics, regulates stem cell research aimed at the development of any "product" subject to its approval. NIH, the medical and behavioral research agency within HHS, regulates stem cell research that it funds in compliance with President Bush's 2001 policy. NIH has created a Human Embryonic Stem Cell Registry that lists the human embryonic stem cell lines that meet the eligibility criteria as outlined in the Bush Administration stem cell policy.

National Academies Guidelines

In July 2004 the National Academies established the committee on Guidelines for Human Embryonic Stem Cell Research to develop voluntary guidelines for deriving, handling and using human embryonic stem cells due to the current lack of federal regulation of such research. The stated position of the National Academies is that there should be a global ban on human reproductive cloning and therefore the guidelines will focus only on therapeutic and research uses of human embryonic stem cells and somatic cell nuclear transfer.

[42] The White House, *Fact Sheet on Embryonic Stem Cell Research*, August 9, 2001, found at http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html.

[43] The National Academies bring together committees of experts in all areas of science and technology to address critical national issues and give advice on a pro bono basis to the federal government and the public. The National Academies is comprised of four organizations: the National Academy of Sciences (NAS), established by Abraham Lincoln in 1863; the National Academy of Engineering, established by NAS in 1964; the Institute of Medicine, established by NAS in 1970; and, the National Research Council, established in 1916 by NAS at the request of President Wilson.

The committee released its "Guidelines for Human Embryonic Stem Cell Research" on April 26, 2005. The document provides guidance on informed consent of donors and states that there should be no financial incentives in the solicitation or donation of embryos, sperm, eggs, or somatic cells for research purposes. The guidelines recommend that each institution conducting human embryonic stem cell research establish an oversight committee, including experts in the relevant areas of science, ethics, and law, as well as members of the public, to review all proposed experiments. The guidelines recommend that a national panel be established to oversee the issue in general on a continuing basis.

The Human Embryonic Stem Cell Research Advisory Committee met for the first time in July 2006 and held a number of meetings to gather information about the need to revise the guidelines. In February 2007, a revised version of the guidelines was published with minor changes affecting Sections 1 (Introduction) and Section 2 (Establishment of an Institutional Embryonic Stem Cell Research Oversight Committee).[44] The guidelines were updated again in September 2008 to reflect the advances with iPS cells by including a new section entirely devoted to this new area of research.[45]

International Society for Stem Cell Research Guidelines

In February 2007, the International Society for Stem Cell Research (ISSCR) released its "Guidelines for the Conduct of Human Embryonic Stem Cell Research."[46] The ISSCR guidelines were developed by a committee of scientists, ethicists, and legal experts from 14 countries in order to "facilitate international collaboration by encouraging investigators and institutions to adhere to a uniform set of practices."[47] In drafting the guidelines, the ISSCR committee used as a model the National Academies guidelines, the regulations of the California Institute for Regenerative Medicine, and "governmental regulations already in place in other countries, particularly that of the Human Fertilisation and Embryology Authority of the United Kingdom."[48]

In order to ensure the responsible development of safe and effective stem cell therapies for patients, the ISSCR released in December 2008 a second guidance document, "Guidelines for the Clinical Translation of Stem Cells." In addition, due to concerns over unproven stem cell therapies being marketed directly to patients, the ISSCR also developed a handbook to be used by patients and their doctors in evaluating a stem cell therapy.[49] In the press release for the guidelines they noted "[t]oo often rogue clinics around the world exploit patients' hopes by offering unproven stem cell therapies, typically for large sums of money and without credible scientific rationale, oversight or patient protections."[50] According to ISSCR, this concern was substantiated by a study conducted by the University of Alberta, Canada, which analyzed the claims of 19

[44] The 2007 Amendment to the 2005 Guidelines for Human Embryonic Stem Cell Research can be found at http://www.nap.edu/catalog/11278.html.

[45] The original 2005 Guidelines as well as the 2007 amended version and the 2008 amended version can be found at http://www.nap.edu/catalog.php?record_id=12553.

[46] The ISSCR Guidelines can be found at http://www.isscr.org/guidelines/index.htm.

[47] George Q. Daley, Lars Ahrlund-Richter, and Jonathan M. Auerbach, et al., "The ISSCR Guidelines for Human Embryonic Stem Cell Research," *Science*, vol. 315 (February 2, 2007), pp. 603-604.

[48] Ibid.

[49] The ISSCR Guidelines and the Patient Handbook are at http://www.isscr.org/clinical_trans/index.cfm.

[50] International Society for Stem Cell Research, "The ISSCR Releases New Guidelines to Shape Future of Stem Cell Therapy," press release, December 3, 2008, http://www.isscr.org/press_releases/clinicalguidelines.html.

internet sites offering "stem cell therapies," the vast majority of which "over promise results and gravely underestimate the potential risks of their offered treatments."[51]

FDA Regulation

All of the human embryonic stem cell lines listed on the NIH Human Embryonic Stem Cell Registry (see **Table 2**) have been grown on beds of mouse "feeder" cells. The mouse cells secrete a substance that prevents the human embryonic stem cells from differentiating into more mature cell types (nerve or muscle cells). Infectious agents, such as viruses, within the mouse feeder cells could transfer into the human cells. If the human cells were transplanted into a patient, these infected human cells may cause disease in the patient which could be transmitted to close contacts of the patient and eventually to the general population. Public health officials and regulatory agencies such as the FDA are specifically concerned about retroviruses, which may remain hidden in the DNA only to cause disease many years later, as well as any unrecognized agents which may be present in the mouse cells.

The FDA defines "xenotransplantation" as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs."[52] Under FDA guidelines, transplantation therapy involving Bush approved stem cell lines, which all have been exposed to mouse feeder cells, would constitute xenotransplantation. Xenotransplantation products are subject to regulation by the FDA under Section 351 of the Public Health Service Act (42 USC 262) and the Federal Food, Drug and Cosmetic Act (21 USC 321 et seq.). FDA has developed guidance documents and the U.S. Public Health Service has developed guidelines on infectious disease issues associated with xenotransplantation.[53]

During a Senate hearing on stem cell research held by the Health, Education, Labor and Pensions Committee on September 5, 2001, the HHS Secretary stated that the FDA was overseeing 17 investigational protocols involving xenotransplantation in other areas of clinical research that involve patients. Therefore, he said, the xenotransplantation-related public health concerns over the human embryonic stem cell lines may not necessarily preclude the development of treatments for patients. While the problems presented by xenotransplantation for clinical research are neither unique to stem cell research nor insurmountable, many scientists believe it will be preferable to use sterile cell lines when attempting to treat patients via stem cell transplantation, and scientists have been successful in developing human embryonic stem cells that can be maintained without the use of mouse feeder cells.[54]

[51] Ibid.

[52] Xenotransplantation Action Plan: FDA approach to the regulation of xenotransplantation. Available at http://www.fda.gov/cber/xap/xap.htm.

[53] These documents are available at http://www.fda.gov/cber/xap/xap.htm.

[54] National Institutes of Health, Department of Health and Human Services, *Stem Cells: Scientific Progress and Future Research Directions*, June 2001, pp. 95-96; Susanne Rust, "UW Grows Animal-Free Stem Cell Lines," *The Milwaukee Journal Sentinel*, January 2, 2006, p. A1.

NIH Research Funding and Stem Cell Registry

The August 9, 2001, Bush Administration policy statement on stem cell research and the NIH Stem Cell Registry effectively replaced the NIH stem cell guidelines that were developed under the Clinton Administration and never fully implemented. Grant proposals for embryonic stem cell research undergo only the normal peer-review process without the added review of the HPSCRG as had been specified under the Clinton NIH stem cell guidelines. In February 2002, NIH announced the approval of the first expenditures for research on human embryonic stem cells. Funding for stem cell research by NIH is shown in **Table 1**. The NIH website provides additional information about current stem cell activities and funding opportunities.[55]

The NIH Human Embryonic Stem Cell Registry lists stem cell lines that are eligible for use in federally funded research and currently available to be shipped to scientists.[56] As shown in **Table 2**, the NIH registry originally listed universities and companies that had derived a total of 78 human embryonic stem cell lines which were eligible for use in federally funded research under the August 2001 Bush Administration policy. However, many of these stem cell lines were found to be either unavailable or unsuitable for research. As of May 4, 2007, the NIH registry listed a total of 21 stem cell lines available from six sources.

Table 1. National Institutes of Health Funding

($ in millions)

Stem Cell Research	FY04	FY05	FY06	FY07	FY08
Human Embryonic	24	40	38	74	88
Non-Human Embryonic	89	97	110	120	150
Human Non-Embryonic	203	199	206	226	297
Non-Human Non-Embryonic	236	273	289	400	497
Human Cord Blood/Placenta	16	15	16	38	38
Non-Human Cord Blood/Placenta	3	3	4	9	9
Total, Stem Cell Research	**553**	**609**	**643**	**968**	**938**

Source: NIH website, January 15, 2009, http://report.nih.gov/rcdc/categories/PFSummaryTable.aspx.

[55] See http://stemcells.nih.gov/research/funding/.

[56] Information about the NIH Human Embryonic Stem Cell Registry is available at http://stemcells.nih.gov/research/registry/index.asp.

Table 2. NIH List of Human Embryonic Stem Cell Lines Eligible for Use in Federal Research

Name[0]	Number of stem cell lines	
	Eligible	Available
BresaGen, Inc., Athens, GA	4	3
Cell & Gene Therapy Institute (Pochon CHA University), Seoul, Korea	2	
Cellartis AB, Goteborg, Sweden	3	2
CyThera, Inc., San Diego, CA	9	0
ES Cell International, Melbourne, Australia	6	6
Geron Corporation, Menlo Park, CA	7	
Goteborg University, Goteborg, Sweden	16	
Karolinska Institute, Stockholm, Sweden	6	0
Maria Biotech Co. Ltd.—Maria Infertility Hospital Medical Institute, Seoul, Korea	3	
MizMedi Hospital—Seoul National University, Seoul, Korea	1	0
National Center for Biological Sciences/Tata Institute of Fundamental Research, Bangalore, India	3	
Reliance Life Sciences, Mumbai, India	7	
Technion University, Haifa, Israel	4	3
University of California, San Francisco, CA	2	2
Wisconsin Alumni Research Foundation, Madison, WI	5	5
Total	**78**	**21**

Source: NIH website, February 3, 2009, http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp.

a. Six table entries do not have stem cell lines available for shipment to U.S. researchers because of a variety of scientific, regulatory and legal reasons. The zeros entered in the "Available" column indicate that "the cells failed to expand into undifferentiated cell cultures."

State Laws that Restrict Stem Cell Research[57]

Many states restrict research on aborted fetuses or embryos, but research is often permitted with consent of the parent or parents. Almost half of the states also restrict the sale of fetuses or embryos. Louisiana is the only state that specifically prohibits research on in vitro fertilized (IVF) embryos. Illinois and Michigan also prohibit research on live embryos. Arkansas, Indiana, Michigan, North Dakota and South Dakota prohibit research on cloned embryos. Virginia may also ban research on cloned embryos, but the statute may leave room for interpretation because human being is not defined. (There may be disagreement about whether human being includes blastocysts, embryos or fetuses.) California, Connecticut, Illinois, Iowa, Massachusetts, New Jersey, New York, and Rhode Island have laws that prohibit cloning for the purpose of initiating a pregnancy, but allow cloning for research.

[57] The information in this section was obtained from "State Embryonic and Fetal Research Laws," updated January 2008 on the National Council of State Legislatures website, at http://www.ncsl.org/programs/health/genetics/embfet.htm, visited February 3, 2009.

Several states limit the use of state funds for cloning or stem cell research. Missouri forbids the use of state funds for reproductive cloning but not for cloning for the purpose of stem cell research, and Maryland's statutes prohibit state-funded stem cell researchers from engaging in reproductive cloning. Arizona law prohibits the use of public monies for reproductive or therapeutic cloning. Nebraska statutes limit the use of state funds for embryonic stem cell research. Restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars. State funding available under Illinois Executive Order 6 (2005) may not be used for reproductive cloning or for research on fetuses from induced abortions.

Despite restrictive federal and state policies, several states (California, Connecticut, Illinois, Indiana, Maryland, Massachusetts, New Jersey, New York, Ohio, Washington, Wisconsin, Virginia) are encouraging or providing funding for stem cell research (adult, embryonic, and in some cases SCNT as well), as they seek to remain competitive and prevent the relocation of scientists and biotechnology firms to other states or overseas.

Concerns Over Access to Stem Cell Lines

Many scientists, disease advocates and others remain concerned that federally supported research on human embryonic stem cells is limited to the number of cell lines that meet the criteria of the August 9, 2001 Bush policy. As stated above, currently 21 cell lines are available for research with federal dollars. Because the pre-August 9 cell lines were developed in the early days of human stem cell research using older 1990s techniques, the cell lines not only have the problems of xenotransplantion (described in the previous section on FDA regulation), but they are harder to work with, not well characterized, and genetically unstable compared to newer stem cell lines. In reaction to the limitations imposed by the Bush policy, several U.S. research groups have decided to develop additional human embryonic stem cell lines using private funding. Some research groups are using state funds as well. In order to perform this work, the research groups considered it necessary to build a new laboratory so that the group's federally funded research would be conducted separately from research on the new stem cell lines.

Worldwide Survey of Stem Cell Lines

A worldwide survey of laboratories conducted by the Boston Globe found that as of May 23, 2004, 128 human embryonic stem cell lines had been created since August 9, 2001; all would be ineligible for use in federally funded research under the Bush policy on stem cell research.[58]

A more recent survey of the number of human embryonic stem cell lines was released in June 2006.[59] The survey found that as of January 1, 2006, 414 human embryonic stem cell lines had been created in at least 20 countries. The authors of the survey state that "only limited data on characterization of these cell lines are publicly available. Currently it is not clear whether all lines are indeed pluripotent human embryonic stem cell lines." Database searches performed by the survey authors found that "derivation and at least partial characterization of only 43.2% of these cell lines have been published in peer-reviewed journals.... Publication in a peer-reviewed journal

[58] Gareth Cook, "94 New Cell Lines Created Abroad since Bush Decision," *Boston Globe*, May 23, 2004, p. A14.

[59] Anke Guhr, et al., "Current State of Human Embryonic Stem Cell Research: An Overview of Cell Lines and Their Use in Experimental Work," *Stem Cells 2006*, v. 24, p. 2187-2191, found at http://www.StemCells.com.

provides some information about the human embryonic stem cell-like characteristics, but it does not provide absolute certainty on their quality."

Congressional Letters on Bush Policy

In response to concerns over access to human embryonic stem cell lines, in April 2004, a group of over 200 Members of the House of Representatives sent a letter to President George W. Bush requesting that the Administration revise the current stem cell policy and utilize the embryos that are created in excess of need during the treatment of infertile couples.[60] The letter points out that an estimated 400,000 frozen IVF embryos[61] "will likely be destroyed if not donated, with informed consent of the couple, for research." According to the letter,

> scientists are reporting that it is increasingly difficult to attract new scientists to this area of research because of concerns that funding restrictions will keep this research from being successful. ... We have already seen researchers move to countries like the United Kingdom, which have more supportive policies. In addition, leadership in this area of research has shifted to the United Kingdom, which sees this scientific area as the cornerstone of its biotech industry.

Under the direction of the White House, then NIH Director Elias A. Zerhouni sent a letter in response to the House Members which restates the Bush Administration position against using federal funds for research involving the destruction of human embryos.[62] The letter from Dr. Zerhouni did contain the following sentence which some observers believed in 2004 indicated a potential future policy shift: "And although it is fair to say that from a purely scientific perspective more cell lines may well speed some areas of human embryonic stem cell research, the president's position is still predicated on his belief that taxpayer funds should not 'sanction or encourage further destruction of human embryos that have at least the potential for life."[63] At the time, White House spokesperson Claire Buchan stated that the sentence did not indicate the president's position had changed. Supporters of stem cell research point out that the letter concedes that science could benefit from additional stem cell lines and that the president's position now rests solely on ethical arguments.

A letter signed by 58 Senators urging President Bush to expand the current federal policy concerning embryonic stem cell research was sent on June 4, 2004.[64] The letter stated that "despite the fact that U.S. scientists were the first to derive human embryonic stem cells, leadership in this area of research is shifting to other countries such as the United Kingdom, Singapore, South Korea and Australia."[65]

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[60] See http://www.house.gov/degette/news/releases/040428.pdf.

[61] A survey conducted in 2002 and published in 2003 by the Society for Assisted Reproductive Technology and RAND determined that nearly 400,000 frozen embryos are stored in the United States, but most are currently targeted for patient use. See David I. Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research," *Fertility and Sterility*, vol. 79, May 2003, pp. 1063-1069.

[62] Rick Weiss, "Bush's Stem Cell Policy Reiterated, but Some See Shift," *The Washington Post*, May 16, 2004, p. A18.

[63] Letter from Elias A. Zerhouni, Director, National Institutes of Health, to The Honorable Diana DeGette and The Honorable Michael Castle, May 14, 2004.

[64] See http://feinstein.senate.gov/04Releases/r-stemcell-ltr.pdf.

[65] Ibid.

On July 14, 2004, former HHS Secretary Tommy Thompson announced in a letter to then Speaker of the House Dennis Hastert that NIH would establish Centers of Excellence in Translational Stem Cell Research.[66] The centers investigate how stem cells can be used to treat a variety of diseases. A National Embryonic Stem Cell Bank collects in one location many of the stem cell lines that are eligible for federal research funding. In the letter to Speaker Hastert, Secretary Thompson stated that "before anyone can successfully argue the stem cell policy should be broadened, we must first exhaust the potential of the stem cell lines made available with the policy."[67] In reaction to the announcement, the President of the Coalition for the Advancement of Medical Research stated that "creating a bank to house stem cell lines created before August 2001 does nothing to increase the wholly inadequate supply of stem cell lines for research."[68] On October 3, 2005, NIH announced that it had awarded $16.1 million over four years to the WiCell Research Institute in Wisconsin to fund the National Stem Cell Bank.[69] NIH also awarded $9.6 million over four years to fund two new Centers of Excellence in Translational Human Stem Cell Research, one at the University of California, Davis and the other at Northwestern University.

Congressional Actions

111th Congress—Stem Cell Research

H.R. 873 (DeGette), the Stem Cell Research Enhancement Act of 2009, was introduced on February 4, 2009. The text of H.R. 873 is identical to legislation introduced in the 110th Congress, H.R. 3 (DeGette), and the 109th Congress, H.R. 810 (Castle). The bill would allow federal support for research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo, and thus if passed would negate the August 2001 Bush stem cell policy limitation. It would amend the Public Health Service (PHS) Act by adding a new Section 498D, "Human Embryonic Stem Cell Research." The new section would direct the Secretary of HHS to conduct and support research that utilizes human embryonic stem cells regardless of the date on which the stem cells were derived from a human embryo. Stem cell lines must meet ethical guidelines established by the NIH. In order to be eligible for federal research, stem cell lines must have be derived from embryos that were originally created for fertility treatment purposes and were in excess of clinical need. In addition, only embryos that the individuals seeking fertility treatments had determined would not be implanted in a woman, and would be discarded, would be eligible for stem cell derivation. Written consent would be required for embryo donation. The Secretary, in consultation with the Director of NIH, would promulgate guidelines 60 days after enactment. No federal funds would be used to conduct research on unapproved stem cell lines. The Secretary would annually report to Congress about stem cell research.

[66] Andrew J. Hawkins, "NIH Stem Cell Bank, Centers of Excellence Will Fast-Track Translational Research, Says Thompson," *Washington FAX*, July 15, 2004.

[67] Ibid.

[68] Ibid.

[69] NIH Press Office, "NIH Awards a National Stem Cell Bank and New Centers of Excellence in Translational Human Stem Cell Research," October 3, 2005, http://www.nih.gov/news/pr/oct2005/od-03.htm. The website for WiCell and the National Stem Cell Bank can be found at http://www.wicell.org/.

H.R. 872 (DeGette), the Stem Cell Research Improvement Act of 2009, was also introduced on February 4, 2009. It is similar to H.R. 873 in that it adds the same Section 498D, "Human Embryonic Stem Cell Research," to the PHS Act, but it also adds another Section 498E, "Guidelines on Research Involving Human Stem Cells," which would require the Director of NIH to issue guidelines on research involving human embryonic stem cell within 90 days of enactment; updates of the guidelines would be required every three years.

S. 487 (Harkin), the Stem Cell Research Enhancement Act of 2009, was introduced on February 26, 2009. S. 487 is the same as H.R. 873, except it has an additional section supporting research on alternative human pluripotent stem cells.[70] This section would amend the Public Health Service Act by adding a new Section 498E, "Alternative Human Pluripotent Stem Cell Research." The new section would require the Secretary of HHS to develop techniques for the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of a developing body, and may result in improved understanding of treatments for diseases, but that are not derived from a human embryo. The Secretary, after consulting with the Director of NIH, would be required to (1) provide guidance concerning the next steps for additional research, (2) prioritize research that holds the greatest potential for near-term clinical benefit, and (3) take into account techniques outlined by the President's Council on Bioethics and any other appropriate techniques and research. The Secretary would be required to prepare and submit to the appropriate committees of Congress an annual report describing the activities and research conducted. S. 487 would authorize such sums as may be necessary for FY2010 through FY2012. The bill is identical to a bill in the 110th Congress, S. 5 (Reid), which passed the Senate and House and was vetoed by President Bush in June 2007.

110th Congress—Stem Cell Research

Members of the 110th Congress indicated weeks prior to the start of the Congress that they would address the topic of stem cell research early in the first session. This prediction was fulfilled; stem cell research was one of the topics addressed in the first 100 hours of the 110th Congress. This section briefly describes legislation that received floor action during the 110th Congress.

H.R. 3 (DeGette), the Stem Cell Research Enhancement Act of 2007, was introduced on January 5, 2007, with 211 cosponsors, and passed the House by a vote of 253 to 174 on January 11, 2007.[71] The Senate passed a companion bill, S. 5 (Reid), on April 11 by a vote of 63 to 34. The House passed S. 5 on June 7 by a vote of 247 to 176. President Bush vetoed the bill on June 20, 2007, and signed an executive order directing the Secretary of HHS to "conduct and support research on the isolation, derivation, production and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body any may result in improved understanding of or treatments for diseases and other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus."[72] S. 5 was the same as H.R. 3, except it had an additional section supporting research on alternative human pluripotent stem cells.

[70] A pluripotent cell has the ability to differentiate into all of the various cell types that make up the body, but not the "extra-embryonic" tissues such as the components of the placenta.

[71] During the first session of the 109th Congress, the House passed identical legislation, H.R. 810 (Castle), in May 2005. In July 2006, the Senate passed H.R. 810 and President Bush immediately vetoed it, the first veto of his presidency. An attempt in the House to override the veto was unsuccessful.

[72] The White House, Office of the Press Secretary, "Executive Order: Expanding Approved Stem Cell Lines in (continued...)

One other bill received floor action during the 110th Congress. S. 30 (Coleman), the Hope Offered through Principled and Ethical Stem Cell Research Act, or HOPE Act, was passed by the Senate on April 11, 2007, by a vote of 70 to 28. Parts of S. 30 are similar to S. 5. S. 30 would have amended the Public Health Service Act by adding a new Section 498D, "Human Pluripotent Stem Cell Research." The bill would have required the Secretary of HHS to develop techniques for the isolation, derivation, production, or testing of stem cells that have the flexibility of embryonic stem cells and that may result in improved understanding of treatments for diseases and other adverse health conditions. Such work would not involve the creation of a human embryo for research purposes or the destruction or discarding of, or risk of injury to, a human embryo other than those that are naturally dead. Naturally dead was defined as having naturally and irreversibly lost the capacity for integrated cellular division, growth, and differentiation characteristic of an organism, even if some cells of the former organism may be alive in a disorganized state. The bill also required the Secretary to provide guidance concerning the next steps required for research and to prioritize research that holds the greatest potential for near-term clinical benefit. In the case of stem cells from a naturally dead embryo, certain assurances would be required from the researchers. An annual report describing the activities and research conducted would have been required for preparation by the Secretary and submitted to the appropriate committees of Congress. Lastly, the bill would have directed the Secretary to contract with the Institute of Medicine (IOM) to conduct a study to recommend an optimal structure for an amniotic and placental stem cell bank program. The IOM was to have completed the study and submit a report to HHS and Congress no later than 180 days after enactment.

110th Congress—Cloning

On June 6, 2007, the House failed to pass H.R. 2560 (DeGette), the Human Cloning Prohibition Act of 2007, by a vote of 204 to 213. The bill would have amended the Food, Drug and Cosmetic Act by adding a prohibition on human reproductive cloning. It defined human cloning as the implantation of the product of human SCNT technology into a uterus or the functional equivalent of a uterus. The bill would have set a criminal penalty of not more than 10 years in prison and a civil penalty of the greater of $10 million or two times "any gross pecuniary gain derived from such violation."

In contrast, cloning legislation that did not receive floor action would have banned not only reproductive applications of human cloning, but also research on therapeutic uses, which has implications for stem cell research (H.R. 2564 and S. 1036). Advocates of the dual legislative ban say that allowing any form of human cloning research to proceed raises serious ethical issues, and would inevitably lead to the birth of a baby who is a human clone. Critics argue such a ban would have curtailed medical research and prevented Americans from receiving life-saving treatments created overseas.

(...continued)

Ethically Responsible Ways," June 20, 2007, found at [http://www.whitehouse.gov/news/releases/2007/06/print/20070620-6.html].

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