Order Code RL31015

Report for Congress

Stem Cell Research

Updated February 24, 2003

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Stem Cell Research

Summary

Embryonic stem cells have the ability to develop into virtually any cell in the body, and may have the potential to treat medical conditions such as diabetes and Parkinson's disease. The announcement by Clonaid of the birth of a cloned child has stirred debate over this type of research because cloned embryos are one possible source of embryonic stem cells. In August 2001 President Bush announced that for the first time federal funds will be used to support research on human embryonic stem cells, but funding will be limited to "existing stem cell lines." The National Institutes of Health (NIH) has established the Human Embryonic Stem Cell Registry which lists stem cell lines that are eligible for use in federally funded research and are ready to be shipped to scientists. Although at one time 78 cell lines were listed, only nine embryonic stem cell lines are currently listed in the NIH Registry. Scientists are concerned about the quality, longevity, availability and terms of use of the eligible stem cell lines. For a variety of reasons many believe research advancement will eventually require new embryonic stem cell lines and for certain applications stem cells derived from cloned embryos may offer the best hope for progress in understanding and treating disease.

In the past, President Bush stated he did not support federal funding of research on stem cells derived from either human embryos or fetal tissue obtained via abortion, but would support research using cells derived from fetal tissue obtained via miscarriages. However, many scientists contend that such tissue is for the most part unsuitable for research due to the condition of the tissue or the presence of genetic defects. Others point to the potential of adult stem cells obtained from tissues such as bone marrow. They argue that adult stem cells should be pursued instead of embryonic stem cells because they believe the derivation of stem cells from either embryos or aborted fetuses is ethically unacceptable. Other scientists believe adult stem cells should not be the sole target of research because of important scientific and technical limitations.

In the 108th Congress, H.R. 534 (Weldon), the Human Cloning Protection Act of 2003, was introduced on February 5, 2003. The House Judiciary Committee reported the bill on February 12, 2003. H.R. 534 is essentially identical to H.R. 2505 (Weldon) which passed the House in the 107th Congress. H.R. 534 would ban the process of human cloning when it is used for reproductive purposes as well as research and therapeutic uses which has implications for embryonic stem cell research. In addition, H.R. 534 would ban the importation of any product derived from an embryo created via cloning. In the 107th Congress, President Bush stated his support for the Weldon bill and the companion bill in the Senate, but 40 Nobel Laureates, who are in favor of nuclear transplantation technology for research and therapeutic purposes, announced their strong opposition to the legislation. S. 303 (Hatch), the Human Cloning Ban and Stem Cell Research Protection Act of 2003, was introduced on February 5, 2003. S. 303 would prohibit human reproductive cloning while allowing cloning for medical research purposes, including embryonic stem cell research. This report, which will be updated as needed, discusses the status of research and key issues associated with human embryonic stem cells.

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Background: Basic Research and Potential Applications

Basic Research. Although most cells within an animal or human being are committed to fulfilling a single function in an organ like the skin or heart, a unique and important set of cells exists that is not so specialized. These *stem cells* – cells that retain the ability to become many or all of the different cell types in the body – play a critical role in repairing organs and body tissues throughout life. Although the term "stem cells" refers to these repair cells within an adult organism, a more fundamental variety of stem cells is found in the early stage embryo. These embryonic stem cells may have a greater ability to become different types of body cells than adult stem cells.

The earliest embryonic stem cells are referred to as *totipotent,* indicating that they can develop into an entire organism because they can produce both the embryo and the tissues required to support it in the uterus. Later in development, embryonic stem cells lose the ability to form these supporting tissues, but are still able to develop into almost any cell type found in the body. These *pluripotent* embryonic stem cells are the current focus of intense research interest.

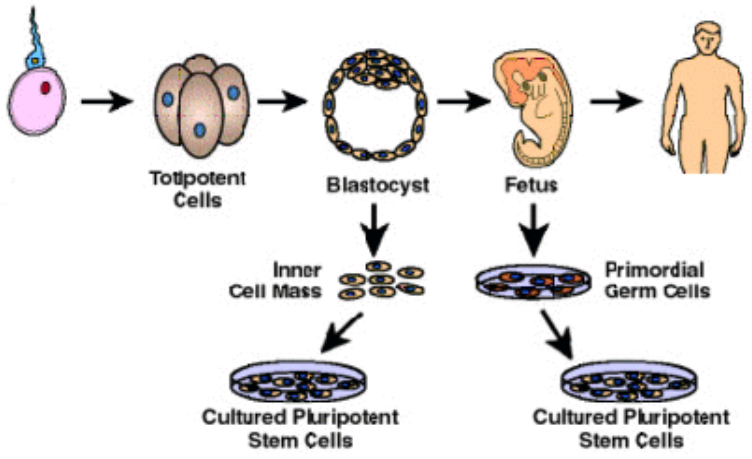
Possible Sources of Stem Cells
– 1-week-old embryos created via IVF for the treatment of infertility
– 5- to 9-week-old embryos or fetuses obtained through elective abortion
– embryos created via IVF for research purposes
– embryos created via SCNT (somatic cell nuclear transfer, or cloning)
– adult tissues (bone marrow, umbilical cord blood)

Embryonic stem cells were first isolated from mice in 1981, and until recently, scientists have used only animal embryonic stem cells in research. In November 1998, two groups published the results of their work on human stem cells from embryos or fetuses.[1] In both cases, the embryos and fetuses were donated for research purposes following a process of informed consent. University of Wisconsin researchers derived stem cells from 1-week-old embryos, also called blastocysts,

[1] For human development, the term embryo is used for the first 8 weeks after fertilization, and fetus for the 9th week through birth. In contrast, HHS regulations define fetus as "the product of conception from the time of implantation." (45 CFR 46.203)

produced via *in vitro* fertilization (IVF) for the treatment of infertility.[2] Because the stem cells are located within the embryo, the process of removing the cells destroys the embryo. Johns Hopkins University investigators derived cells with very similar properties from 5- to 9-week-old embryos or fetuses obtained through elective abortions.

Figure 1: Stem Cells via IVF Embryo or Fetal Tissue



Source: Figure 1 is based on a figure contained in a May 2000 report by the National Institutes of Health entitled *Stem Cells: A Primer*, which can be found at: [http://www.nih.gov/news/stemcell/primer.htm].

The Jones Institute for Reproductive Medicine, located in Norfolk, Virginia, announced in July 2001 that it had created human embryos via IVF for the purpose of deriving human embryonic stem cells.[3] A total of 162 oocytes (eggs) from 12 women were collected and fertilized with sperm donated by two men; 110 fertilized eggs developed, of which 40 developed to the blastocyst stage.[4] The inner cell masses were removed from the blastocysts resulting in three healthy embryonic stem cell lines. Each woman was paid from $1500 to $2000 for undergoing the egg donation procedure.

Although the Jones Institute work, which was begun in 1997, did not represent a research advance, according to experts in academia and industry, it is thought to be the first time in the United States that a human embryo had been created solely for the purpose of harvesting stem cells for research rather than for the treatment of infertile couples. A representative of the Jones Institute, Dr. William E. Gibbons, stated that several ethics panels approved the work, and contended that such "fresh"

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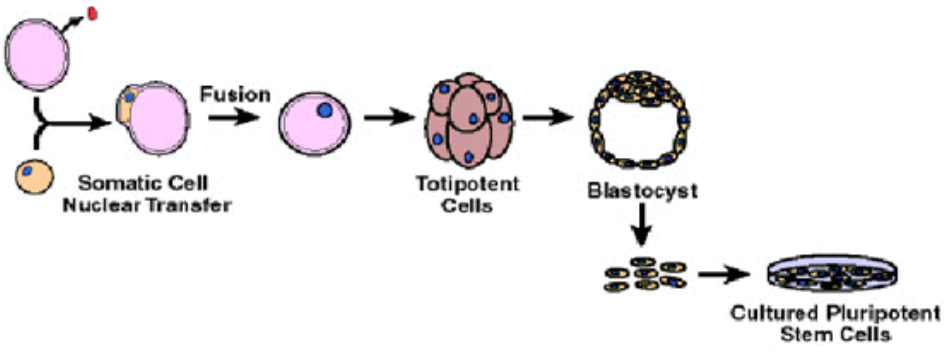
[2] IVF embryos that are produced in excess of need are usually frozen in liquid nitrogen for future use by the couple. If the couple decides that their family is complete, they may elect to discard the embryos, donate the embryos for research, or allow another couple to adopt the embryo.

[3] Stolberg, Sheryl Gay. Scientists Create Scores of Embryos to Harvest Cells. *The New York Times*, July 11, 2001, pp. A1, A15.

[4] Josefson, Deborah. Embryos created for stem cell research. *British Medical Journal*, v. 323, July 21, 2001, p. 127.

embryos may have advantages over the frozen embryos remaining after infertility treatment. Unlike couples utilizing fertility clinics, the egg donors were younger, "possibly yielding more robust embryos." The egg and sperm donors underwent psychological and medical evaluation and were informed of the research goals. In January 2002, Dr. Gibbons announced that although the Jones Institute intends to continue to study stem cells, because of political pressure it will no longer recruit human egg donors in order to produce stem cells.[5] Instead, the Jones Institute intends to focus on other methods to create cells for disease treatment.

Figure 2: Stem Cells via Somatic Cell Nuclear Transfer



Source: Figure 2 is from a May 2000 report by the National Institutes of Health entitled *Stem Cells: A Primer,* which can be found at: [http://www.nih.gov/news/stemcell/primer.htm].

Another potential source of embryonic stem cells is somatic[6] cell nuclear transfer (SCNT), also referred to as cloning. In February 1997 scientists in Scotland announced that they had used this procedure in 1996 to produce Dolly, the sheep. In SCNT, the nucleus of an egg is removed and replaced by the nucleus from a mature body cell, such as a skin cell. The cell created via SCNT would be allowed to reach the 1-week (blastocyst) stage and the stem cells would then be removed, as in the University of Wisconsin work. The December 27, 2002 announcement by Clonaid of the birth of a cloned child has contributed to the controversy over this type of research.[7]

On December 10, 2002, Stanford University announced plans to establish a privately funded institute that will use expertise in stem cell biology and cancer biology to develop novel treatments for cancer and other diseases.[8] An initial $12 million in funding from an anonymous donor will be used for the institute which will be headed by Dr. Irving Weissman, a Professor in Cancer Biology at Stanford.

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[5] Morello, Carol. Center shifts stem cell approach; Va Institute will stop creating human embryos for research. *The Washington Post*, Jan. 18, 2002, p. A14.

[6] A somatic cell is a body cell, as opposed to a germ cell, which is an egg or sperm cell.

[7] For further information, see CRS Report RL31358, *Human Cloning,* by Judith A. Johnson.

[8] For further information, see the Stanford University Medical Center website at: [http://mednews.stanford.edu/news_releases_html/2002/decreleases/stem-cell-QandA.html].

Scientists at the new Institute for Cancer/Stem Cell Biology and Medicine will develop a new series of stem cell lines, some through the process of SCNT, in order to study the disease process of a wide range of disorders including cancer, diabetes, cardiovascular disease, autoimmune disease, allergies, and neurological disorders such as Parkinson's and Lou Gehrig's disease. Initially the studies will be performed in mice; however, the work may be extended to human cells and eggs. The stem cell lines will allow investigators to better understand the biological and genetic basis of a disorder and thereby develop new treatments.

In November 2001, Advanced Cell Technology (ACT) of Massachusetts announced that it had created the world's first human embryos produced via cloning.[9] The stated goal of ACT's work is not to produce a cloned human baby (which requires implantation of the cloned embryo into a woman's uterus), but human embryonic stem cells. Other research groups have been successful in deriving stem cells from mice and cattle using SCNT. ACT used two techniques to produce human embryos — SCNT and a second process called parthenogenesis. ACT researchers obtained eggs from seven women, ages 24 to 32, who were paid $3000 to $5000.

In the SCNT approach, ACT scientists removed the nucleus from 19 eggs and replaced it with a nucleus from another adult cell. For 11 of the eggs, the nucleus came from a skin cell, for the remaining eight eggs, from cells which cling to the egg and are called cumulus cells. None of the eggs that received a skin cell nucleus divided; seven of the eggs with the cumulus cell nucleus began to divide. Two embryos divided into four cells each, and one embryo divided into six cells before division stopped. In parthenogenesis, an egg cell is treated with chemicals causing it to divide without being fertilized by a sperm. ACT exposed 22 human eggs to the chemicals. After 5 days, six eggs had matured into a larger mass of cells before division stopped. None of the embryos developed by ACT through either of the two techniques divided sufficiently to produce stem cells. A California biotechnology company, Geron Corporation, has also explored creating stem cells via SCNT.[10]

An alternate SCNT approach is the fusion of adult human cells with egg cells of other animals. In 1996, researchers at the University of Massachusetts fused a human cheek cell with a cow egg cell. The resulting hybrid cell had "embryo-like" characteristics and was generated for the purpose of making stem cells. This method was at one time being pursued by Advanced Cell Technology Co.[11]

Stem cells obtained from adult organisms are also the focus of research. There have been a number of recent publications on adult stem cells from a variety of different sources, such as bone marrow and the umbilical cord following birth. In addition, a number of private companies (such as ViaCell, MorphoGen, StemSource,

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[9] Cibelli, J.B., et al. Somatic Cell Nuclear Transfer in Humans: Pronuclear and Early Embryonic Development. *Journal of Regenerative Medicine*, v. 2, November 26, 2001. p. 25-31.

[10] Weiss, R. Embryo Work Raises Spector of Human Harvesting. *Washington Post*, June 14, 1999. p. A01.

[11] Hall, Stephen S. The Recycled Generation. *The New York Times Magazine*, January 30, 2000. p. 30-35, 46, 74, 78-79.

NeuralStem) are working on therapeutic uses of adult stem cells, and one company, Osiris Therapeutics, has four clinical trial programs underway.[12] Some advocate that adult stem cell research should be pursued instead of embryonic stem cells because they believe the derivation of stem cells from either IVF embryos or aborted fetuses is ethically unacceptable.

However, other scientists believe 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.

Potential Applications. Stem cell research was chosen by *Science* magazine in 1999 as its "breakthrough of the year." 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. Stem cells might be transplanted into the body to treat disease (diabetes, Parkinson's disease) or injury (e.g., spinal cord). The damaging side effects of medical treatments might be repaired with stem cell treatment. For example, cancer chemotherapy destroys immune cells in patients making it difficult to fight off a broad range of diseases; correcting this adverse effect would be a major advance.

Before stem cells can be applied to human medical problems, substantial advances in basic cell biology and clinical technique are required. In addition, the future regulatory decisions that will need to be made by a federal agency, such as the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), on individually created tissue-based therapies resulting from stem cell research promise to be extremely challenging. The potential benefits mentioned previously are 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 ensure that uncontrolled development, such as a cancerous tumor, does not occur. If stem cells are to be 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.

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[12] O'Keefe, B. New Research is an Easier Cell. *Fortune*, March 18, 2002. p. 38.

Other scientists point out, however, that if the SCNT technique (cloning) was employed using a cell nucleus from the patient, stem cells created via this method would be genetically identical to the patient, would presumably be recognized by the patient's immune system, and thus would avoid any tissue rejection problems that could occur in other stem cell therapeutic approaches. Because of this, many scientists believe that the SCNT technique may provide the best hope of eventually treating patients using stem cell for tissue transplantation. As mentioned in the previous section, ACT intends to derive stem cells from human embryos to develop new therapies for disease treatment.

Bush Administration Decision on Stem Cell Research

Stem Cell Speech. On August 9, 2001, President Bush announced that for the first time federal funds will be used to support research on human embryonic stem cells but funding will be limited to "existing stem cell lines where the life and death decision has already been made."[13] According to the speech, 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 in FY2001, the federal government would spend $250 million on research involving stem cells from other sources, such as umbilical cord blood, placenta, adult and animal tissues, "which do not involve the same moral dilemma."

A White House Fact Sheet provided further clarification of the President's remarks.[14] According to the fact sheet, federal funds will 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. NIH will examine the derivation of all existing stem cell lines and create a registry of those lines that satisfy these 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.

Reaction of Pro-Life Groups. Reaction to the Bush Administration decision on human embryonic stem cell research from religious groups and pro-life groups was mixed. Prior to August 9, 2001, President Bush had indicated that he did not support the federal funding of research on stem cells derived from either human embryos or fetal tissue obtained from abortions.[15, 16] Some groups, such as the U.S.

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[13] 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].

[14] The August 9, 2001, White House Fact Sheet on Embryonic Stem Cell Research can be found at: [http://www.whitehouse.gov/news/releases/2001/08/20010810.html].

[15] Kondracke, M. M. Bush wisely orders study of fetal, stem cell issues. *Roll Call*, February

(continued...)

Conference of Catholic Bishops denounced President Bush's decision as "morally unacceptable."[17] A spokesperson for the American Life League stated that President Bush "can no longer describe himself as pro-life."[18] Others took a more moderate stance. A spokesperson for the National Right to Life Committee stated that the NRLC commends "President Bush's decision to prevent the federal government from becoming involved in research and experimentation that would require the deliberate destruction of human embryos. In taking this position, the President has acted to save the lives that he could."[19] Other pro-life groups that have reacted positively to the President's decision include the Christian Legal Society, Focus on the Family, and the Christian Coalition.

Reaction of Scientific Community. Reaction to the Bush Administration decision from the scientific community was mixed as well. Many scientists were very concerned that federal funding for stem cell research could have been completely blocked, and therefore, they were relieved that the Bush decision allows some federal dollars to be used for the initial stages of basic research. However, there are some reservations about the future of research. Initially, much of the commentary from scientists focused on the number of stem cell lines available for federally funded research. While President Bush indicated in his speech that over 60 stem cell lines existed, a June 2001 NIH report on the status of stem cell research stated that about 30 cell lines had been derived from embryos or fetal tissue, another source of stem cells.[20] Scientists questioned the President's number because only a handful of embryonic stem cell lines had been described in scientific journals and meetings. They are also concerned about the quality, longevity, availability and terms of use of the stem cell lines.

On August 27, 2001, NIH released a statement identifying, at that time, the 10 universities and companies that had derived 64 embryonic stem cell lines eligible for use in federally funded research.[21] The NIH statement warned that in some cases, a

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[15] (...continued)
1, 2001; and, Kornblut, A. E. Bush says he opposes using fetal tissue from abortions. *The Boston Globe*, January 27, 2001.

[16] President Bush had indicated his support for stem cell research using cells derived from fetal tissue obtained from spontaneous abortions (miscarriages). However, scientists contend that such tissue is for the most part unsuitable for research due to the presence of genetic defects or other anomalies.

[17] United States Conference of Catholic Bishops, Office of Communications. Catholic Bishops Criticize Bush Policy on Embryo Research, August 10, 2001.

[18] The stem cell decision. *The San Francisco Chronicle*, Aug. 10, 2001, p. A3.

[19] Bush blocks stem cell funding that would destroy embryos. National Right to Life Committee News, August 9, 2001. [http://www.nrlc.org/news/2001/NRL08/bush.html]

[20] 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://www.nih.gov/news/stemcell/scireport.htm].

[21] The NIH statement can be found at: [http://www.nih.gov/news/stemcell/082701list.htm].

cell line may need to be expanded in size in order to be widely distributed and in other cases, a cell line will require further study before it will be made available.

The next day, two such companies (CyThera and Reliance Life Sciences) stated in media reports that they are only in the initial stages of characterizing their stem cell lines and would not be ready to provide cells to researchers for many months.[22] In Sweden, Goteburg University stated that of their 19 cell lines, only three are considered to be established.[23] The Karolinska Institute, also in Sweden, indicated that its embryonic stem cell lines "are not ready for research and must be scientifically validated."[24] On September 5, 2001, Secretary Tommy Thompson testified at a Senate hearing that only 24 of the 64 stem cell lines are fully characterized and ready to be sent out to scientists. Secretary Thompson stated that there are more than enough stem cell lines available for NIH funded basic research and seemed to suggest that the private sector would be able to fund research on disease treatments if additional human embryonic stem cell lines were required.

The Goteburg scientists plan to establish many more stem cell lines; they estimate that over 100 lines will be required for their own research needs. Scientists believe that more cell lines will be needed for a variety of reasons, such as if genetic problems are identified or mutations develop in the stem cell lines, to ensure adequate genetic diversity, and, in the future, to provide sterile lines for potential cell-based therapy. The human embryonic stem cell lines that have been isolated to date have all been grown on beds of mouse "feeder" cells.[25] The mouse cells secrete a substance that prevents the human embryonic stem cells from differentiating into more mature cell types (such as 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.

Xenotransplantation. 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)

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[22] Connolly, C. and R. Weiss. Stem cell colonies' viability unproven. *The Washington Post*, August 28, 2001, p. A1, A6.

[23] Ibid.; McNeil, D.G. Small lab in Sweden holds a huge trove of stem cells. *The New York Times*, Aug. 29, 2001, p. ; and, Reid, T.R. U.S. count of stem cell lines surprised Swedes, *The Washington Post*, Aug. 30, 2001, p. A20, A21.

[24] Lane, E. Differing tallies of stem cell lines. *Newsday*, Aug. 29, 2001, p. A22.

[25] However in February 2001, Geron Corporation researchers presented findings at a scientific meeting demonstrating that human embryonic stem cells can be maintained without mouse feeder cells. From NIH report *Stem cells: scientific progress and future research directions*, June 2001, p. 95-96.

human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs."[26] 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 in xenotransplantation.[27] During a Senate hearing on stem cell research held on September 5, 2001, Secretary Thompson stated that FDA is overseeing 17 INDs involving xenotransplantation in other areas of clinical research that involve patients. Therefore, 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 not unique to stem cell research nor insurmountable, many scientists believe it will be necessary to develop sterile cell lines before researchers can attempt to treat patients suffering from conditions such as diabetes or Parkinson's disease with stem cell transplantation. Some U.S. scientists have expressed the hope that eventually the President's Council on Bioethics (see the following section) will consider reasonable arguments that will allow new stem cell lines to be created. However, HHS Secretary Tommy Thompson has stated in the media that "neither unexpected scientific breakthroughs nor unanticipated research problems would cause Bush to reconsider the strict limits on stem cell funding he set" on August 9, 2001.[28] Secretary Thompson reiterated this position several times during a Senate hearing on stem cell research held on September 5, 2001. President Bush has stated that he would veto any legislation that alters the parameters outlined in his August 9, 2001 policy decision.[29]

President's Council on Bioethics. President Bush announced in his August 2001 speech the creation of a new bioethics council, consisting of leading scientists, doctors, ethicists, lawyers, theologians, and others. The function of the President's Council on Bioethics is to monitor stem cell research, recommend guidelines and regulations, and consider all of the medical and ethical ramifications of biomedical innovation. According to the White House, the council "will study such issues as embryo and stem cell research, assisted reproduction, cloning, genetic screening, gene therapy, euthanasia, psychoactive drugs, and brain implants."[30] The President's Council on Bioethics, was established for a period of up to 2 years by Executive Order 13237 on November 28, 2001. The council is chaired by Dr. Leon

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

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

[28] Brownstein, Ronald. Bush won't budge on stem cell position. *The Los Angeles Times*, August 13, 2001, p. A9.

[29] Bruni, Frank. Bush Says He Will Veto Any Bill Broadening His Stem Cell Policy. *The New York Times*, Aug. 14, 2001, p. A1.

[30] The August 9, 2001, White House Fact Sheet on Embryonic Stem Cell Research can be found at: [http://www.whitehouse.gov/news/releases/2001/08/20010810.html].

Kass, a biomedical ethicist on the faculty of the University of Chicago. On January 16, 2002, the White House announced the other 17 members of the council.

The first meeting of the President's Council on Bioethics was held on January 17-18, 2002, in Washington, D.C.[31] Dr. Kass announced that the first topic to be addressed by the Council would be human cloning. At the Council's second meeting on February 13-14, 2002, all Council members voted in opposition to reproductive cloning. However, they could not come to an agreement on articulating the precise nature of their objection, whether solely on safety grounds or which of the various moral objections were most important. On the issue of therapeutic cloning, what the Council prefers to call research cloning, the Council also could not come to agreement. Dr. Kass proposed that the Council's final report should reflect both the arguments supporting cloning for the purpose of medical treatment and those against. He asserted that the report should also provide the soundest arguments for each position and indicate how many Council members supported each viewpoint.

The third meeting of the Council was held on April 25 and 26, 2002. The Council heard presentations on the scientific and therapeutic promise of embryonic stem cells from John Gearhart of Johns Hopkins University and the potential of adult stem cells from Catherine Verfaillie of the University of Minnesota. In an informal vote, almost half of the 18 members of the Council voiced their support for the therapeutic use of human cloning. The May 2002 meeting was cancelled.

At the June 20, 2002, meeting, nine Council members voted to support cloning for medical research purposes, without a moratorium, provided a regulatory mechanism was established.[32] Because one member of the Council had not attended the meetings and was not voting, the vote seemed to be 9 to 8 in favor of research cloning. However, draft versions of the Council report sent to Council members on June 28, 2002, indicated that two of the group of nine members had changed their votes in favor of a moratorium. Both made it clear that they have no ethical problem with cloning for biomedical research, but felt that a moratorium would provide time for additional discussion.[33] The changed vote took many Council members by surprise, and some on the Council believe that the moratorium option, as opposed to a ban, was thrown in at the last minute and did not receive adequate discussion. In addition, some on the Council believe that the widely reported final vote of 10 to 7 in favor of a moratorium does not accurately reflect the fact "that the majority of the council has no problem with the ethics of biomedical cloning."[34] The final report, *Human Cloning and Human Dignity: An Ethical Inquiry*, was released at the July 11, 2002, meeting of the Council.

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[31] Transcripts of the Council meetings and papers developed by staff for discussion during Council meetings can be found at [http://www.bioethics.gov].

[32] Hall, S.S. President's Bioethics Council Delivers, *Science*, v. 297, July 19, 2002, p. 322-324.

[33] Ibid., p. 324.

[34] Ibid., p. 322.

Access to Stem Cell Lines. NIH is interested in obtaining access to all eligible stem cell lines for use in the NIH intramural research program as well as making the lines available to the wider research community. On September 5, 2001, Secretary Thompson announced at a Senate hearing that NIH had reached an agreement with the University of Wisconsin. A Memorandum of Understanding (MOU) was signed by NIH and the University on September 4, 2001.[35] According to an NIH news release, the MOU allows the University of Wisconsin stem cell lines to be used by "non-profit institutions that receive grants from the NIH under the same terms and conditions as those available to NIH scientists provided those institutions enter into a separate written agreement."[36] A number of other MOUs have been announced recently for research use of stem cell lines that meet the Bush Administration criteria: (1) April 5, 2002, ES Cell International Pte. Ltd., Melbourne, Australia; (2) April 24, 2002, BresaGen Inc, Athens, GA; (3) April 26, 2002, University of California, San Francisco.[37]

Many individuals have expressed concerns over the patents that have been filed or issued on stem cell lines because they fear a patent will limit access to a stem cell line or may make any access agreement difficult to negotiate. Because the Bush policy on federally funded embryonic stem cell research has limited research options to a discrete number of cell lines (arguably a monopoly of the laboratories or companies on the NIH Stem Cell Registry, see next section), Congress and other interested parties may pay close attention to how patents on exploitable stem cell inventions are used by the patent holders. Licensing policies and practices are likely to be closely watched.[38]

NIH Stem Cell Registry. The National Institutes of Health (NIH) has established the Human Embryonic Stem Cell Registry which lists stem cell lines that are eligible for use in federally funded research and currently available to be shipped to scientists.[39] As shown in **Table 1**, the NIH registry originally listed 14 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, eventually many of these stem cell lines were found to be either unavailable or unsuitable for research. As of February 24, 2003, the NIH registry listed a total of nine stem cell lines available from four sources: BresaGen, Inc. (one stem cell line); ES Cell International (five stem cell lines);

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[35] The Memorandum of Understanding is available on the NIH website at: [http://www.nih.gov/news/stemcell/WicellMOU.pdf].

[36] National Institutes of Health and WiCell Research Institute, Inc., sign stem cell research agreement. Sept. 5, 2001. Available at: [http://www.nih.gov/news/pr/sep2001/od-05.htm].

[37] The Memorandum of Understanding documents are available on the NIH website at: [http://www.nih.gov/news/stemcell/index.htm].

[38] For further information, see CRS Report RL31142, *Stem Cell Research and Patents: An Introduction to the Issues*, by Wendy H. Schacht and John R. Thomas.

[39] The registry is accessible to scientists and the general public via the NIH website; it contains basic scientific information about the cell lines as well as contact information. Information about the NIH Stem Cell Registry is available at: [http://escr.nih.gov/].

University of California at San Francisco (one stem cell line); and Wisconsin Alumni Research Foundation (two stem cell lines).

In February 2002, NIH announced the approval of the first expenditures for research on human embryonic stem cells.[40] The NIH website provides information on how scientists may apply to use existing funds or apply for administrative supplements to existing grants to conduct such research.[41] In April 2002, NIH announced the approval of four resource infrastructure enhancement awards for human embryonic stem cell research. The awards are expected to stimulate the use of such stem cells in basic research by providing funds for expansion, testing, quality assurance, and distribution of cell lines that meet the President's criteria for federal support of research on human embryonic stem cells.

Table 1. Original NIH List of Stem Cell Lines Eligible for Use in Federal Research[a]

Name	# of stem cell lines
BresaGen, Inc., Athens, GA	4
CyThera, Inc., San Diego, CA	9
ES Cell International, Melbourne, Australia	6
Geron Corporation, Menlo Park, California	7
Goteborg University, Goteborg,, Sweden	19
Karoliska Institute, Stockholm, Sweden	6
Maria Biotech Co. Ltd. – Maria Infertility Hospital Medical Institute, Seoul, Korea	3
MizMedi Hospital – Seoul National University, Seoul, Korea	1
National Center for Biological Sciences/Tata Institute of Fundamental Research, Bangalore, India	3
Pochon CHA University, Seoul, Korea	2
Reliance Life Sciences, Mumbai, India	7
Technion University, Haifa, Israel	4
University of California, San Francisco, CA	2
Wisconsin Alumni Research Foundation, Madison, WI	5

[a] Universities and companies in grey are no longer listed in the NIH Registry. Currently only nine stem cell lines are available from the four locations listed in white in the table.

[40] "NIH Strategies for Implementing Human Embryonic Stem Cell Research, February 28, 2002," available at: [http://www.nih.gov/news/stemcell/022802implement.htm].

[41] "Implementation Issues for Human Embryonic Stem Cell Research– Frequently Asked Questions," available at: [http://grants1.nih.gov/grants/stem_cells.htm].

Actions During the Clinton Administration

Dickey Amendment. Prior to the August 2001 Bush Administration decision, no federal funds had been used to support research on stem cells derived from either embryos or fetal tissue.[42] The work at the University of Wisconsin and Johns Hopkins University was supported by private funding from Geron Corporation. Private funding for experiments involving embryos was required because Congress attached a rider to legislation that affected FY1996 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. It has been added to the Labor, HHS and Education appropriations acts for FY1997 through FY2002.[43] For FY2003, the provision is found in Section 510 of Division G in H.J.Res. 2, which is the Labor, HHS and Education division of the Omnibus FY2003 appropriations bill. It prohibits HHS from using FY2003 appropriated funds for:

> (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(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] ... 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].

There is no similar federal prohibition on fetal tissue research; however, other restrictions do apply.

In January 1999 HHS determined that the ban on federal funding of human embryo research did not prohibit funding human embryonic stem cell research. NIH published guidelines for support of such research in August 2000. Some Members of Congress expressed strong disagreement with the HHS decision and stated that such research is banned by the Dickey amendment. NIH began accepting grant applications for research projects utilizing human stem cells immediately following publication of the guidelines. All applications were to be reviewed by the NIH Human Pluripotent Stem Cell Review Group (HPSCRG), which was established to

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[42] However, federal funds have been provided for research on adult stem cells. In FY2000, the total amount spent by NIH on stem cell research was $256 million. The total can be broken down as follows: human adult stem cell research, $147 million; animal adult stem cell research, $79 million; animal embryonic stem cell research, $30 million.

[43] The rider language has not changed significantly from year to year. 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; and, FY2002, P.L. 107-116.

ensure compliance with the guidelines. Applications would have also undergone the normal NIH peer-review process.

In mid-April 2001, the Bush Administration postponed the first meeting of the HPSCRG pending a review of Clinton Administration policy decisions on stem cell research.[44] According to media sources, only three grant applications were submitted to NIH, and one was subsequently withdrawn.[45] Presumably, scientists were reluctant to invest the time and effort into preparing an NIH grant application when the prospects of receiving federal funds were uncertain.

The Bush Administration's August 9, 2001, policy statement on stem cell research and the NIH Stem Cell Registry effectively replaces the NIH guidelines that were developed under the Clinton Administration. As a result, grant proposals for embryonic stem cell research will undergo only the normal peer-review process. There will not be a review by the Human Pluripotent Stem Cell Review Group as had been stipulated in the NIH Guidelines.

National Bioethics Advisory Committee Report. On November 14, 1998, following the announcement by the University of Wisconsin and Johns Hopkins University on the derivation of human embryonic stem cells, President Clinton asked National Bioethics Advisory Committee (NBAC) to conduct a review of the issues associated with stem cell research.[46] NBAC released its report entitled "Ethical Issues in Human Stem Cell Research" in January 2000.[47] In its report, NBAC recommended that federal funding support research to derive and use stem cells from fetal tissue as well as embryos remaining after infertility treatment. However, NBAC recommended that federal agencies should not support research involving the derivation or use of stem cells from embryos made for research purposes or from embryos made using SCNT.

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[44] Boahene, A. K. Stem cell research group cancels inaugural meeting pending HHS review of NIH research guidelines. *Washington FAX*, April 19, 2001.

[45] Recer, P. Stem Cell Studies said Hurt by Doubt. *AP Online*, May 2, 2001.

[46] NBAC was established by Executive Order 12975 on October 3, 1995; a September 16, 1999 executive order extended the NBAC charter until October 2001. NBAC made recommendations to the National Science and Technology Council on bioethical issues arising from research on human biology and behavior. NBAC also completed reports on human cloning, the use of human biological materials, and treating persons with mental disorders. NBAC has been replaced by the President's Council on Bioethics, which was described by the Bush Administration in its August 9, 2001, policy statement on human embryonic stem cell research. The President's remarks on embryonic stem cell research are available at: [http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html].

[47] The NBAC report is available at: [http://bioethics.georgetown.edu/nbac/].

National Academies Reports on Stem Cells and Human Cloning

On September 11, 2001, the National Academies released a report entitled *Stem Cells and the Future of Regenerative Medicine*.[48] The report recommends that research on both adult and human embryonic stem be pursued. Due to concerns over changing genetic and biological properties of existing stem cell lines, the report indicates that in the future the development of new stem cell lines will be necessary. The report recommends continued federal funding for both adult and human embryonic stem cell research. The report argues that because publicly funded research would be conducted with peer review, open scientific exchange and public oversight, the promise of stem cell research in developing medical therapies is more likely to be fulfilled in an efficient and responsible manner. Lastly, the report recommends that research on approaches that prevent immune rejection of stem cells and stem cell-derived tissues, including SCNT, be actively pursued.

On January 18, 2002, the National Academies released its report entitled *Scientific and Medical Aspects of Human Reproductive Cloning*.[49] The panel recommends that the U.S. ban human reproductive cloning that is aimed at creating a child. Based on the results of animal cloning experiments, the panel is concerned for the safety of both the woman and the fetus and judged the procedure to be too dangerous for use in humans at the present time. It recommends that the ban should be legally enforceable and carry substantial penalties rather than be based on voluntary actions. It should be reconsidered within 5 years, but only if compelling new data on safety and efficacy are presented and a national dialogue on the social and ethical issues suggests that a review is warranted. However, the panel concluded that research using SCNT to produce stem cells should be permitted because of the considerable potential for developing new therapies and advancing biomedical knowledge. This position is in agreement with the previous National Academies report on stem cells.

State Legislation on Embryonic Stem Cell Research

On September 22, 2002, California Governor Gray Davis signed a bill that allows research using embryonic stem cells from any source, including SCNT. The new law requires that people receiving infertility treatments be provided information about donation of embryos for research; the sale of embryos is prohibited. The state plans to provide funds to support the research.[50]

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[48] The National Academies are the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council. The National Academies' report on stem cell research is available at: [http://www.nap.edu/catalog/10195.html?onpi_topnews_091101].

[49] The National Academies' report on human cloning is available at: [http://www.nap.edu/catalog/10285.html?onpi_topnews_011802].

[50] Connolly, Ceci. Calif. To Enact Bill Promoting Stem Cell Research. *The Washington Post*, September 22, 2002, p. A12.

On December 5, 2002, a bill was introduced in the Massachusetts Senate that would allow state funds to be used for embryonic stem cell research[51]. Similar legislation has been introduced in New Jersey and Pennsylvania. In contrast, Iowa, Michigan and Virginia have "banned cloning for research or reproduction."[52] Louisiana and Rhode Island have banned cloning for reproductive purposes but not for use in stem cell research.

Congressional Actions

Stem Cell Research. Due to the problems of quality, longevity, and availability of the existing embryonic stem cell lines that are eligible for federal research funding under the Bush August 2001 decision, the 108th Congress is likely to see legislation introduced that is similar to proposals considered in the 107th Congress to allow stem cell research. Those opposed to embryonic stem cell research may try to impede access to human embryos, impose limitations on private funding, or place a moratorium on human embryo research.

Cloning Research. The announcement on December 27, 2002, by Clonaid of the birth of a cloned child has stirred debate over stem cell research because cloned embryos are one possible source of embryonic stem cells.

In the 108th Congress, H.R. 534 (Weldon) the Human Cloning Protection Act of 2003, was introduced on February 5, 2003. On February 12, 2003, the House Judiciary Committee reported the bill by a vote of 19-12. H.R. 534 would ban the process of human cloning as well as the importation of any product derived from an embryo created via cloning. Under this measure, cloning could not be used for reproductive purposes or for research on therapeutic purposes, which would have implications for embryonic stem cell research. H.R. 534 is essentially identical to the measure which passed the House in the 107th Congress.[53] The only difference is that H.R. 534 does not require the General Accounting Office (GAO) to conduct a study on the impact of the cloning on medical technology. H.R. 534 includes a criminal penalty of imprisonment of not more than 10 years and a civil penalty of not less than $1 million. During the February 12, 2003, mark-up session four amendments were defeated by 12-19 or by voice vote. The amendments attempted to either limit the ban to 3 years, exempt the importation of medical treatments from the ban, exempt the use of cloning in research, or in the creation of additional stem cell lines. A fifth amendment that would add the GAO study was withdrawn when Chairman Sensenbrenner assured his support if it was added to the bill during floor debate.

H.R. 234 (Weldon), the Human Cloning Prohibition Act of 2003, was introduced on January 8, 2003. H.R. 234 is similar to the measure which passed the House in the 107th Congress (H.R. 2505), but it does not contain the ban on

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[51] Softcheck, John T. Massachusetts Measure Would Permit Use of State Funds for Stem Cell Research. *The Washington Fax,* December 11, 2002.

[52] Ibid.

[53] In the 107th Congress, H.R. 2505 (Weldon) passed the House by a vote of 265-162 on July 31, 2001.

importation of products derived from therapeutic cloning. The bill includes a criminal penalty of imprisonment of not more than 10 years and a civil penalty of not less than $1 million. It also requires the General Accounting Office to conduct a study to assess the need (if any) for any changes of the prohibition on cloning in light of new developments in medical technology, the need for SCNT to produce medical advances, current public attitudes and prevailing ethical views on the use of SCNT and potential legal implications of research in SCNT. The study is to be completed within 4 years of enactment of H.R. 234. A companion bill, S. 245 (Brownback), was introduced on January 29, 2003. It is identical to H.R. 234, except that it amends the Public Health Service Act (42 U.S.C. 289 et seq.) instead of Title 18 of the United States Code. S. 245 has been referred to the Senate Health, Education, Labor, and Pensions Committee.

S. 303 (Hatch), the Human Cloning Ban and Stem Cell Research Protection Act of 2003, was introduced on February 5, 2003. The bill would ban human reproductive cloning but allow cloning for medical research purposes, including stem cell research. S. 303 would make reproductive cloning a crime punishable with a 10-year prison sentence and a $1 million fine. S. 303 has been referred to the Senate Judiciary Committee.

During floor debate in the 107th Congress, supporters of a ban on human cloning (such as that contained in H.R. 534 introduced in the 108th Congress) argued that a partial ban on human cloning (such as that contained in S. 303 introduced in the 108th Congress) would be impossible to enforce. Critics of the ban on human cloning argued that SCNT creates a "clump of cells" rather than an embryo, and that the measure would curtail medical research and prevent Americans from receiving life-saving treatments created overseas.

President Bush stated his support for a prohibition on all forms of human cloning and endorsed the cloning ban legislation introduced in the 107th Congress. However, 40 Nobel Laureates, who are in favor of nuclear transplantation technology (SCNT) for research and therapeutic purposes, announced their strong opposition to the legislation.[54] The statement asserted that the legislation "would impede progress against some of the most debilitating diseases known to man." Former President Gerald Ford stated his strong opposition to the legislation in a April 25, 2002, letter to President Bush.[55] In the letter, Ford indicated that during his administration, the controversy over recombinant DNA research was "successfully addressed with 'careful thought' and the implementation of safety regulations."[56] Former President Ford expressed his "full support for therapeutic cloning, arguing a prohibition of this technology 'would adversely impact scientific research and should not become

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[54] The American Society for Cell Biology statement by the 40 Nobel Laureates is available at: [http://www.ascb.org/publicpolicy/Nobelletter.html].

[55] Hafner, L. Revised Feinstein/Kennedy Cloning Bill Has Criminal and Civil Penalties, Requires Research Review. *Washington Fax*, May 2, 2002.

[56] Ibid.

law.'"[57] Former First Lady Nancy Reagan has indicated she also is opposed to legislation that would limit embryonic stem cell research and its promise in aiding patients afflicted with serious diseases which have no treatment, such as Alzheimer's disease. In 1994, it was disclosed that former President Ronald Reagan was suffering from the effects of Alzheimer's disease. In a recent letter to Senator Orrin Hatch, Mrs. Reagan states her support for stem cell research and S. 303 which will allow the use of therapeutic cloning.[58]

The U.S. Supreme Court has recognized in past cases certain personal rights as being fundamental and protected from government interference.[59] Some legal scholars believe a ban on human cloning may be struck down by the Supreme Court because it would infringe upon the right to make reproductive decisions which is "protected under the constitutional right to privacy and the constitutional right to liberty."[60] Other scholars do not believe that noncoital, asexual reproduction, such as cloning, would be considered a fundamental right by the Supreme Court. A ban on human cloning research may raise other constitutional issues: scientists' right to personal liberty and free speech. In the opinion of some legal scholars, any government limits on the use of cloning in scientific inquiry or human reproduction would have to be "narrowly tailored to further a compelling state interest."[61] However, no case involving these issues is scheduled to come before the Supreme Court this term.

Ethical Issues

The central controversy surrounding human stem cell research is the source of the cells. The debate primarily arises from differences in deeply held religious and philosophic views. For most who believe that the embryo is a human being from the moment of fertilization, the derivation of stem cells from either very early or pre-implantation embryos created by IVF or from the tissues of aborted fetuses is ethically unacceptable. From this viewpoint, even though the Bush Administration August 9 policy decision on stem cell research does not support activities which *directly* destroy embryos, support of research on components of the embryo is deeply disturbing.

Supporters of this view argue that the possible benefits of stem cell research cannot and should not justify the actions necessary to obtain the cells. Opponents of stem cell research propose that research on *adult* stem cells, which they claim could provide similar therapeutic benefits without the need for embryonic or fetal cells, be

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[57] Ibid.

[58] Complete text of the Reagan letter can be found at: [www.senate.gov/~hatch/].

[59] For further discussion of these issues and their relationship to human cloning, see CRS Report RL31422, *Substantive Due Process and a Right to Clone*, by Jon O. Shimabukuro.

[60] Andrews, L. B. Is There a Right to Clone? Constitutional Challenges to Bans on Human Cloning. *Harvard Journal of Law and Technology*, summer 1998. p. 643-680.

[61] Ibid., p. 667.

supported instead. Not all scientists agree, however, that adult stem cells hold as much potential as embryonic stem cells.

Those who support embryonic stem cell research believe that pre-implantation embryos do not have the same moral and legal status as persons. They acknowledge that embryos are genetically human, but hold that they do not have the same moral relevance because they lack specific capacities, including consciousness, reasoning and sentience.[62] The NBAC received testimony from witnesses of many religious traditions that were open to the use of early embryos (remaining from infertility treatments) for stem cell research as well as many who were opposed. "Jewish and Islamic ethicists supported stem cell research while Protestant and Catholics were mixed. ... [W]hile the early human embryo is worthy of respect, it ought not to be given personal moral status until there has been sufficient development of the embryo."[63]

Supporters argue that the potential human health and scientific benefits the research holds should be an ethical argument for its support. Patient groups have also asserted that, because of the potential of human stem cells for the treatment of disease, it is immoral to discourage such research because it could save many lives. In addition, supporters believe that the oversight which would come with federal grant support would result in better and more ethically controlled research in the field than if funding was from private sources alone. Supporters also argue that the efforts of both federally supported and privately supported researchers are necessary to keep the United States at the forefront of what they believe is a very important, cutting edge area of science.

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[62] Presentation by Steinbock, B., Department of Philosophy, SUNY, Albany, New York. NIH Human Embryo Research Panel Meeting. February 3, 1994.

[63] Wildes, Kevin W. The Stem Cell Report. *America*, October 16, 1999. p. 12-14.