

Timeline

Note: Dates of particular significance for scientific advances are indicated in **bold**.

- 1958** Leroy Stevens, a scientist working at the Jackson Laboratory in Bar Harbor, Maine publishes his work on mouse teratocarcinomas and was the first person to identify the pluripotent tendencies of these cells. He characterized this strain of mice as strain 129.
- 1970** Stevens notes that the mouse primordial germ cells that gave rise to teratomas resemble cells of earlier embryos and upon transplantation into adult mice tissues are capable of differentiating into teratocarcinoma cells. He originally names these cells ES cells but because the cell differentiation path can also lead to cancerous cells the name EC cells has been given to this pluripotent precursor cell
- 1975** Beatrice Mintz and Karl Illmensee, from the Institute for Cancer Research in Philadelphia, demonstrate that ES cells can give rise to organisms, not just teratomas.
- 1981** Martin Evans at Cambridge University and Gail Martin at the University of California, San Francisco, successfully culture pluripotent mouse ES cells from inner cell masses of late blastocysts in medium conditioned by an established teratocarcinoma stem cell line.
- 1985-1992** Brigid Hogan, a professor of cell biology at the Vanderbilt University School of Medicine in Nashville, with Peter Donovan's group at the National Cancer Institute, determine specific factors in culture media (LIF) that induce ES cells to adopt differentiation fates.
- 1988** June 5. A California couple publicly announces that they plan to conceive a child to save the life of their 17-year old daughter who suffers from leukemia. Since this was before the time of pre-implantation genetic screening of embryos, the Ayala family recognized that they had a 1 in 4 chance of being a compatible donor. In 1990 the child, Marrisa-Eve was born and in 1991 a bone marrow transplant was conducted to save Anissa Ayala's life. In 1996 both sisters were healthy.
- 1990** [Britain Human Fertilisation and Embryology Act of 1990](#): Allows creation of embryos specifically for research but only to increase understanding of infertility and to improve techniques of *in vitro* fertilization. In 2001(see below), an amendment was passed that allows embryo research related to cell and tissue therapies including therapeutic cloning but the clones can not be made via somatic nuclear transfer.
- 1993** President Clinton, upon his election, lifts the twenty-year moratorium on fetal tissue **transplant** research by signing into law the **NIH Revitalization Act of 1993**. It was through this Act that *in vitro* fertilization(IVF) research was Congressionally sanctioned without prior approval of the Ethics Advisory Board. However, President Clinton immediately creates the **NIH Human Embryo Research Panel** to oversee the ethical dimensions of fetal and embryonic research. The newly appointed 19-member committee was comprised of physicians, scientists,

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- lawyers, and ethicists. Ten of the 19 members of this Panel received over \$21 million from the NIH between 1989 and 1999 to conduct embryonic research in non-human organisms.
- 1994 September. The NIH Human Embryo Research Panel advises that carefully designed studies on human embryos should be allowed and should receive government funding. In some cases, embryos could be created specifically for research purposes.
- 1994-2000 President Clinton through an executive directive, prohibits federal funding on research to support the creation of human embryos used exclusively for research purposes. Rather, federal funds can only be applied to research using human pluripotent stem cells derived from frozen embryos that were created for purposes of infertility treatment and were in excess of clinical need or from fetal tissue. In 1996, the executive order was enforced by Congress and they have passed a similar ban restricting NIH funding annually since that time. The ban defined "human embryo or embryos" to include any organism, not protected as a human subject under 45 C. F. R. 46 (Human Subject Protection regulations) that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg. The announcement came the same day the NIH Human Embryo Research Panel recommended that human embryos could be created for research purposes as long as no work was conducted on embryos beyond 14 days, prior to brain and nervous system development.) Late in 2000, President Clinton signs an executive order based on the NIH issues guidelines for federally funded embryonic stem cell research using cell lines derived from excess IVF embryos and developed by the private sector.
- 1996 Ian Wilmut of the Roslin Institute and his colleagues clone the first mammal using the somatic nuclear transfer technique. The lamb was cloned from a 6-year-old ewe, using tissue taken from the ewe's udder. Over 277 attempts were made, before success was reached. They named the sheep Dolly.
- 1997 October 3. An international team of scientists announce that they have cloned mice using a similar technique to the one that produced Dolly. The scientists used genetic material from the cumulus cells that surround the adult female ovary and transplanted this material into an emptied oocyte. Hence the first mouse clone was named Cumulina. The success rate was only 2 %, but Cumulina has now given rise to three generations of cloned mice using the same technique.
- 1998 November 6. Two research groups independently announce that they have derived stem cell lines from embryonic tissue. James Thomson's group at the Wisconsin Regional Primate Research Center used inner cell masses from *in vitro* fertilization clinic "leftovers" while John Gearhart's group at the Johns Hopkins University School of Medicine used primordial germ cells from aborted fetuses.**
- 1998 November 12. Jose Cibelli and Michael West of Advanced Cell Technology allow a *48 Hours* TV film crew to publicize their**

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- experiments in which somatic nuclear transfer using a human adult cell and a cow oocyte were fused to form a 16 cell chimeric blastocyst. The experiment received [wide press coverage](#). The experiment was originally conducted while Cibelli was working at the University of Massachusetts and the university received a patent in August of 1999 for the technology.
- 1999 April 12. Researchers at Osiris Therapeutics and the Johns Hopkins University School of Medicine coax human mesenchymal stem cells (hMSCs) from adults' bone marrow to develop into cartilage, fat and bone cells, *in vitro*. Cell differentiation was confirmed by biochemical assays and RT-PCR and researchers were successful in identifying the spatial organizations, mechanical forces, growth factors, hormones, and cytokines necessary for differentiation.
- 1999 The journal *Science* votes stem cell research its 1999 Breakthrough of the Year.
- 1998-2002 Dr. Michel Levesque, of Cedar's Sinai removes 10-15 neuronal stem cells (NSC) from the frontal lobe of a man suffering from Parkinson's. The cells were stimulated to grow using fibroblast growth factor and six million were made dopaminergic with various factors. In March 1999, a mix of NSCs and neurons was placed in the patient's left putamen and using the UPDRS (Unified Parkinson Disease Rating Scale) motor scale the patient improved 40-50 percent in certain tasks. More than two years after the experimental treatment, the man has no symptoms of the degenerative brain condition. A small clinical trial is underway.
- 2000 Martin Pera and colleagues derive human embryonic stem cells lines using human blastocysts. They also demonstrate that these ES cells are capable of differentiating into neuronal progenitor cells
- 2000 October 4. A Colorado couple creates a test-tube baby who was genetically screened and selected in the hope he could save the life of his 6-year-old sister, Molly Nash who suffers from the rare genetic disease, Fanconi anemia that prevents her body from making bone marrow. Baby Adam was born on August 29 and the transplant took place on September 26, umbilical cord blood cells from Adam were given to Molly at the University of Minnesota.
- 2000-2001 The 106th Congress proposes the creation of a **Human Pluripotent Stem Cell Review Group (HPSCRG)** to evaluate submitted research protocols for compliance with NIH ethical guidelines for ESC research established by the Clinton administration. The HPSCRG would also hold public meetings when a request proposed the use of a line of human pluripotent stem cells that has not been previously reviewed by the HPSCRG. The recommendations of HPSCRG members will then be reviewed by the Center for Scientific Review Advisory Committee (CSRAC), and if appropriate, approved in its public meetings. This committee was put into place in April 2001 and is chaired by Dr. James Kushner, a CSRAC member who is Chief of the Division of Hematology and Director of the

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General Clinical Research Center at the University Of Utah School Of Medicine. Under the Clinton administration HPSCRG was prepared to review proposals that involved the derivation of stem cells. Researchers would be eligible for federal funding only with prior HPSCRG approval of the protocol for such derivation. The Bush administration superceded this policy and subsequently eliminated the possibility of deriving new embryonic stem cell lines from embryos but the HPSCRG committee still oversees the derivation of stem cell lines from fetal tissue. (See **August 9, 2001**). The president also put into place a new ethics council, the Council on Bioethics headed up by Leon R. Kass, M.D. Chair. Addie Clark Harding Professor, College and the Committee on Social Thought at the University of Chicago.

- 2001 January 22. The British Parliament rules (212 to 92) that embryonic stem cell research can occur using government funding. Human embryos can be created for research purposes (therapeutic cloning) as long as no work is conducted on embryos beyond 14 days, prior to brain and nervous system development.
- 2001 January. The National Academy of Sciences released a report calling for a legal ban on human reproductive cloning as did the American Association for the Advancement of Science.
- 2001 May. In *Thomson v. Thompson 18*, actor Christopher Reeve and seven scientists file a federal lawsuit against the Bush administration for illegally withholding federal funding for stem cell research and halting the development of therapies that could, the plaintiffs argue, save lives.
- 2001 July 31. U.S. House of Representatives pass the Human Cloning Prohibition Act of 2001. The bill (H.R. 2505), approved by a 100 vote-margin (265 to 162) imposes a ban on the creation of cloned human embryos for any purpose, whether reproductive or therapeutic. If passed into law, both forms of cloning would be punishable by up to ten years in prison and a million-dollar fine. The House passed the measure over the objections of a long list of biomedical organizations, professional scientific societies, and patients' advocacy groups. The Senate has postponed (on several occasions) voting on any similar legislation until more information and time is given to the subject. Legislation proposed in the Senate is split and no decisions have been made) (please see January 2002) .
- 2001 July 11. Researchers at the Jones Institute for Reproductive Medicine in Norfolk, Virginia derive stem cell lines from human embryos created solely for the purpose of research. Embryos were created with the eggs of 12 women and sperm of two men- so no clones.**
- 2001 August 9. President Bush announces that federal funds would be available to support limited human embryonic stem cell research. The new policy provides that federal funds may be used for research on 64 existing stem cell lines (report) that have already been 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

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- donors. Pursuant to this new policy, no federal funds will 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) cloning of human embryos for any purposes. The policy also requires the creation of the [President's Council on Bioethics](#) to study stem cells and embryo research as well as other issues. In addition, during the fiscal year 2001 (FY2001), the government will spend \$250 million on research involving stem cells from other sources, *e. g.*, umbilical cord, placenta, adult and animal tissues.
- 2001 September. The National Institutes of Health (NIH) publishes a [report](#) which lists 14 universities and companies that have derived a total of 78 human embryonic stem cell lines which are eligible for use in federally funded research. However, perhaps only a third of the stem cell lines are fully characterized and ready to be used in research and a separate registry of cell lines that are available for shipping are listed at the [NIH Human Embryonic Stem Cell Registry](#). Scientists are concerned about the quality, longevity, availability and terms of use of the eligible stem cell lines. (http://www.usembassy.at/en/download/pdf/stem_cell.pdf)
- 2001 September. The National Institutes of Health signs an agreement making five human embryonic stem cell lines from the WiCell Research Institute of the University of Wisconsin available immediately to NIH researchers [Shadid, 2001 #61]. The new agreement allows the NIH to retain ownership rights to any discoveries made using these cells as the University of Wisconsin agreed to waive any reach-through rights for non-therapeutic purposes. However, because Geron Corporation funded a great deal of the research from the University of Wisconsin stem cell group, NIH researchers can not use these five stem cell lines for therapeutics or diagnostics and Geron will enforce licensing fees for any potential developments that could infringe on exclusive patents in this arena. Similar agreements were made for stem cell lines derived by ES Cell International, BresaGen Incorporated, and the University of California San Francisco in **April of 2002**.
- 2001 **November. Researchers at Advanced Cell Technology Institute announce in the online *Journal of Regenerative Medicine* that they have cloned human embryos using somatic nuclear transfer and parthenogenesis and hope to use these embryos to derive stem cell lines for therapeutic cloning purposes. The “human clones” did not survive past the 6 –cell stage .Many scientists claim that the research is preliminary and was not subjected to rigorous peer review and therefore does not provides a credible basis for the cloning of adult humans. The media hype behind this study is enormous**
- 2001 November. France and Germany push for an international ban on human cloning after hearing of Dr. Severino Antinori’s announced that he plans to produce a human clone by spring 2003. The U.N. forms the Ad Hoc Committee on an International Convention Against the Reproductive Cloning of Human Beings and meeting commence to draft a ban on

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- cloning for reproductive purposes only. However, progress was stymied in September 2002, when negotiations were placed on hold due to opposition by the United States and the Vatican who prefer that the U.N. treaty ban all human cloning, including cloning for therapeutic purposes.
- 2002 **January 8. Ole Isacson's research group of Harvard Medical School in Boston announce untreated mouse ES cells can become dopamine-producing neurons in the brains of rats and reduce Parkinson-like symptoms in the animals by about 40%. However, 5 of the 25 rats died before behavioral testing could be done and were found to have teratoma-like tumors.**
- 2002 January to May. Between January and May of 2002, Senators Tom Harkin (D-IA) and Arlen Specter (R-PA) work on bills (S. 1893 and S. 2439) that proposed amendments to the Human Cloning Prohibition Act of 2001 (H. 2505). These amendments would allow scientists to use therapeutic-cloning techniques for medical research and this effort was duplicated in another bill (S. 1758) proposed by Senators Dianne Feinstein (D-CA) and Edward M. Kennedy. However, bill (S. 1899) authored by Senators Sam Brownback (R-KS) and Mary Landrieu (D-LA) mimics that of the House.
- 2002 **April. Ying et al. and Terada et al. publish papers demonstrating that adult stem cells display pluripotent properties due to cell fusion events with embryonic feeder cells. These feeder cells are used to provide the adult stem cells with a hospitable environment for growth and are known to be pluripotent. The work throws inherent adult stem cell plasticity into question.**
- 2002 June. **Research Involving Embryos and Prohibition of Human Cloning Bill 2002** is introduced into the Australian Federal Parliament June 27, 2002. This decision was disappointing to some parliament members who felt that recent work with adult stem cells negated the need for stem cell research involving embryonic sources [ABS, 2002 #74,]. This bill bans human reproductive cloning and other unacceptable practices and regulates research involving the use of excess assisted reproductive technology (ART) embryos that would otherwise be destroyed. The bill does not presently allow cloning for therapeutic purposes and rather places a 3-year ban on the process until legislation for this practice is in place. A moratorium rather than a ban was good news for Australian-based ES Cell International, who owns five of the nine embryonic stem cell lines listed in the U.S. stem cell registry.
- 2002 July 10. The new President's Council on Bioethics, chaired by Professor Leon Kass, presents its cloning report to the President. The Council held meetings from the start of the year and was unanimous in recommending a permanent ban on reproductive cloning. It was split, however, in its recommendations regarding therapeutic cloning. Ten members of the Council recommended a 4-year moratorium on therapeutic cloning, allowing time for further review and "democratic deliberation" of the issue. Seven members of the Council recommended in favor of therapeutic

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- cloning, as long as standards are developed for the regulation of such research.
- 2002 July. The Singapore government will allow the cloning of human embryos for certain research projects giving the island state some of the world's most liberal guidelines for stem cell research. This is good news for ES Cell International, an Australian biotech firm that conducts its research in Singapore.
- 2002 **December 11. Stanford University announces that it will derive a new series of embryonic stem cell lines using somatic nuclear transfer technology. This method of derivation is prohibited under federal funding, but Stanford is investing \$12 million dollars from an anonymous donor in its new Institute for Cancer/Stem Cell Biology and Medicine being headed up by Irving Weissman.**
- 2003 January. Dr. Brigitte Boisselier: scientific director of Clonaid, "The First Human Cloning Company" announces that two human clones have been born. The company and efforts are supported by the Raelian Movement cult, who believes that human life is the result of extraterrestrial genetic experiments. Parents of the supposed "clones" refuse to have the children undergo DNA testing for verification of such a claim and the press believes that the entire announcement might be a hoax to drum up media attention.
- 2003 January 28. President Bush declares that all human cloning should be banned during his State of the Union Address
- 2003 February. U.S. House of Representatives passes the Human Cloning Prohibition Act (H.R.534) 241:145, which bans both reproductive and therapeutic cloning with severe fines and criminal charges
- 2003 October. California passes state law to develop a registry for stem cell lines developed from human embryos secured through IVF clinics.
- 2004 January. New Jersey passes state law that allows researchers to use private funding to conduct stem cell research.
- 2004 **February. South Korean researchers, Woo Suk Hwang and Moon, publish that they are the first to clone a human embryo using SCNT from a female cumulus cell and have it reach the 100-150 cell stage. Viable clones were only obtained when the donor and recipient was the same person. Cells from the ESC line was propagate for one year and were shown to develop into cartilage, bone, and muscle when implanted in a SCID mouse.**
- 2004 March. The President's Council on Bioethics publishes a report that recommends a ban on reproductive cloning but supports stem cell research on embryos 14 days and younger.
- 2004 August 11. The UK issues the first license to develop cloned human blastocysts via SCNT to a research team in Newcastle University.
- 2004 November 2. California passes legislation to support the development of new stem cell lines despite President Bush's decision to restrict federal funding to those lines created before August 9, 2001. Proposition 71 provides \$3B in state bonds over the next ten years for stem cell research

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- which will be overseen by a 29-member Independent Citizen's Oversight Committee headed up by Dr. Philip Pizzi, Dean of Stanford University. Other states begin to develop legislation as well.
- 2005 February. South Korean team headed up by Hwang and Moon establishes eleven patient-specific embryonic stem cell lines using somatic nuclear transfer cloning technology. The patients ranged in age including one young boy. The paper is accompanied by a review of the human subjects research protocols involved in stem cell technologies.**
- 2005 April. The U.S. Stem Cell Research Council, an advisory group for the President, proposed national ethical guidelines for human embryonic stem cell research and recommended research institutions establish oversight committees to enforce them.
- 2005 June. Alison Murdoch and Miodrag Stojkovic of the UK succeed in the production of human blastocysts via cloning. The researchers used embryonic stem cells as nuclear donors and inserted these nuclei into enucleated oocytes.**
- 2005 October. Gerry Schatten, the American collaborator on the Hwang 2005 paper severs ties with the South Korean team and asks for the retraction of the paper due to unethical conduct.
- 2005 October. Two research teams publish reports online that attempt to address the loss of life issue associated with the derivation of ESCs. Lanza's group establishes ESC lines from one cell of an 8-cell mouse blastomere, which maintain the embryo's viability in the womb, while Jaenisch's team used altered nuclear transfer in mice to create mutant embryos incapable of uterine implantation.**
- 2006 January. Stojkovic severs ties with Murdoch on grounds of unscientific and unethical protocol. He claims that she made announcements of preliminary work before peer review, and that she did not credit the researchers involved. Stojkovic goes on to head the Prince Felipe Research Center in Spain.**
- 2006 January. Hwang is investigated and it is determined that the work on the 2004 and 2005 human cloning papers was fraudulent and that unethical protocols were used in oocyte donation.**
- 2006 February. Gerry Schatten, the American collaborator on the Hwang 2005 paper is investigated and found to have been negligent in reviewing the data and behaved in an unethical manner with respect to financial compensation and credit for work.**
- Future Stem cell therapies or stem cell research bans??**