Stem Cells: Saving Lives or Crossing Lines

Supplemental Information

An Introduction to Stem Cells

By Kirstin Matthews, Ph.D.

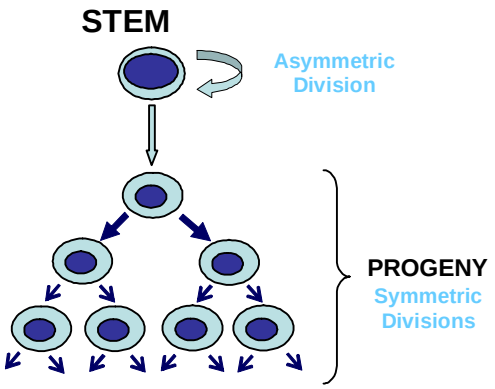
Overview

Stem cells are cells that have the potential to replicate themselves for indefinite periods and to divide, producing one of themselves and one cell of a different type (**differentiation**). In humans, stem cells have been located in: the early stages of development after fertilization (around 5-6 days); the umbilical cord and placenta; and in several adult organs.

Regardless of their source all stem cells have two general properties:

1) *Stem cells are capable of dividing and renewing themselves for long periods.* Unlike muscle cells, blood cells, or nerve cells – which do not replicate themselves – stem cells can divide continuously and keep their innate properties.

2) *Stem cells are undifferentiated and can give rise to multiple cell-types.* Stem cells do not have any tissue-specific structures that allow them to perform specialized functions. They cannot carry molecules of oxygen through the bloodstream like red blood cells or release signals to other cells, such as permitting the body to move or speak, as nerve cells do. Although stem cells do not have any tissue-specific structures, they can give rise to differentiated cells, including red blood cells and nerve cells.



Stem Cell Division. *The stem cell divides asymmetrically, generating one cell that repeats the feat indefinitely, and one cell that continues to divide symmetrically, dividing each time into two equal daughter cells. Reproduced with permission from the ISSCR.*

Stem cells have varying abilities to differentiate into different cell-types. One type of stem cell can give rise to any other cell-type of a given organism (for example, an embryonic stem cell). Other stem cells can only give rise to cells of a given tissue type (for example, bone marrow can produce blood stem cells) or only give rise to a few cell-types in a given tissue.

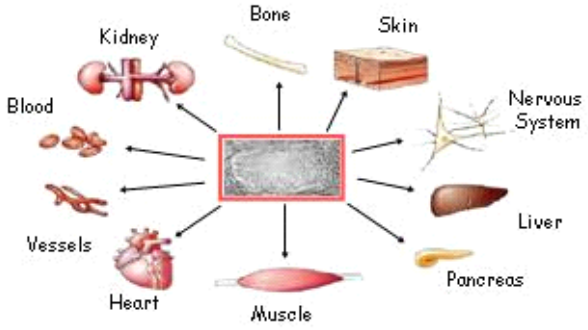
Scientists are just beginning to understand the **signals** in a body which can trigger cell differentiation. These signals can be created within a cell, triggered by a cell's genes, or by a neighboring cell that releases chemicals to promote differentiation in other cells. Determining what these signals are and what stem cells require to differentiate into different cell-types is an important research area necessary to utilize stem cells for therapies.

When cells differentiate, their abilities become more restricted. They often follow only a few prescribed pathways and can lose the capacity to replicate themselves. The ability of stem cells to replicate and remain unspecialized

until they are needed is an important area of research vital to understanding human development.

Stem cells offer a new look at old problems and diseases such as burns and diabetes. Although the field is relatively new, the impact of new discoveries could profoundly change medical research and therapy. Many of these new approaches involve the use of **somatic cell nuclear transfer** (sometimes known as **therapeutic cloning**) to produce recipient-specific tissue by creating embryonic stem cell lines.

This new area of research has great potential, but it is not without its controversies. Many ethical dilemmas are produced with the creation and destruction of human blastocysts as well as the potential to clone an entire human being (**reproductive cloning**). No matter where society designates the boundary to be for this research, or whether or not stem cells can live up to our high expectations, a great deal can be learned through careful and thoughtful studies.



Embryonic Stem Cells. *The potential of human embryonic stem cell colonies shown in the middle could potentially be grown in culture to the illustrated organs and more. Reproduced with permission from the ISSCR.*

Embryonic Stem Cells

Embryonic stem cells are derived exclusively from a fertilized egg that has been grown *in vitro* for 5 to 6 days to form a **blastocyst**. Within a blastocyst there is a small group of about 30 cells called the **inner cell mass**, which will give rise to the hundreds of highly specialized cells needed to make up an adult organism. Embryonic stem cells are obtained from this inner cell mass. For research purposes, embryonic stem cells are produced specifically from eggs that have been fertilized *in vitro*, or in a laboratory and not inside a woman's body, or ***in vivo***. Embryonic stem cells can come from a frozen fertilized egg or an egg which is fertilized *in vitro*.

Cell-Types Embryonic Stem Cells* Have Been Grown Into

Smooth Muscle
Heart Muscle
Nerves
Bone
Cartilage
Kidney
Red and White Blood Cells
Pancreas
Liver
Yolk Sac
Lymph Nodes
Endoderm

* Human

Embryonic stem cells can and do differentiate into all the specialized cells in the adult body. They could be induced to provide an unlimited source of specific and clinically important adult cells such as bone, muscle, liver or blood cells.

Adult Stem Cells

Adult stem cells are unspecialized or undifferentiated cells found among specialized cells in an adult tissue or organ. In some adult tissues, such as in bone marrow,

Cell-Types Adult Stem Cells* Have Been Grown Into

Red and White Blood Cells
Skin
Fat
Heart Muscle
Skeletal Muscle
Liver
Digestive Tract
Nerves
Cartilage
Pancreas
Cornea

* Human

muscle, or brain tissue, discrete populations of adult stem cells generate replacements for cells that are lost through disease, injury, or normal wear and tear. Adult stem cells are thought to reside in an area of each tissue where they may remain **quiescent,** or non-dividing, for many years until they are activated by disease or tissue injury. Where they are found, adult stem cells consist of a very small population of cells within each tissue.

Some adult stem cells retain the ability to form into specialized tissues other than the one from which they originated. For example, blood (**hematopoetic**) cells can differentiate into nerve, skeletal muscle, cardiac muscle, or liver cells. Brain stem cells can differentiate into blood or skeletal muscle cells. However, adult stem cells have a limited number of tissues they can differentiate into and do not have the same potential as embryonic stem cells to become any cell-type.

The environment that adult stem cells grow in has an important, but poorly understood, effect on their fate. The relationship between the adult stem cell environment and its ability to differentiate into other cell-types has also not been fully explained.

Distinctions between Embryonic and Adult Stem Cells

Most importantly, adult and embryonic stem cells differ in the type of differentiated cells they can become. While embryonic stem cells can be induced to differentiate into any cell-type, adult stem cells cannot. Most adult cells can only differentiate into the types of cells found in their environment or their particular tissue or organ from which they reside. Therefore in many vital organs, adults do not have the stem cells necessary to regenerate damaged areas; thus scar tissue will develop instead.

Another key difference between embryonic and adult stem cells is the volume of cells one can isolate and grow *in vitro*. Large numbers of embryonic stem cells can be grown *in vitro* from a single blastocyst. On the contrary, adult stem cells are rare and methods of growing them still need to be perfected. In addition, due to their limited numbers, it is difficult to isolate a group of adult stem cells in pure form, without having them contaminated with differentiated cells.

Potential Uses of Stem Cells

Stem Cells

While stem cell research is in its infancy and many of its proposed uses are hypothetical, the research has generated excitement among many scientists for its potential. One of the vital components of ongoing work is understanding the very nature of these cells; that is, to determine the conditions necessary to maintain undifferentiated stem cells as well as differentiating them along specific pathways. In order to truly determine whether or not these cells can be used therapeutically, investment must be made to understand the nature of the cells.

Although we are only beginning to discover what stem cells are capable of doing, scientist have proposed several potential uses.

1) *Abnormal Cell Division.* Many serious medical conditions, such as cancer and birth defects, are due to abnormal cell divisions or the inability of cells to turn themselves on and off properly. Having a better understanding of stems cells and their genetic and molecular controls would yield information about diseases and potential strategies for therapies.

2) *Drug Testing.* Stem cells could be used to test new drugs or medications by differentiating them to the particular cell-types that the drugs are targeting. This would offer a short-cut for scientists to sort out chemicals that can be used to treat diseases. By testing new drugs on stem cell lines, we could perform rapid screening of hundreds of thousands of chemicals that now are tested by more time-consuming processes. This could also potentially decrease the time that it takes to get a drug to market.

3) *Cell-Based Therapies.* Stem cells could be used for **cell-based therapies**. Stem cells could be directed to differentiate to a specific cell-type that then could be used as a renewable source of replacement cells and tissues. In order to be useful for cell-based therapies, stem cells must be made to:

   - *Differentiate into desired cell-types.* It is necessary for stem cell techniques to be improved until they can consistently and efficiently differentiate into a specific cell or type of cells without contamination by undifferentiated or improperly differentiated cells.

   - *Proliferate extensively and generate sufficient quantities of tissue.* The protocols for differentiating stem cells need to be refined so that large quantities of tissue can be produced in a relatively efficient manner.

   - *Survive in the recipient after the transplant.* Scientists must determine that the cells are healthy and viable after transplantation. They also should establish that the stem cells localized to the correct tissue in the recipient.

   - *Function appropriately for the duration of the recipient's life.* Not only do the cells need to be localized and survive, but they must also behave like the original cells. Currently, there are not enough data showing that stem cells are functional in their new environment when they are transplanted into organs. For cell-based therapies to be successful, the new cells need to function properly and interact properly with the original tissue.

Stem Cell Research Could Potentially Help:

Parkinson's
Alzheimers
Spinal cord injury
Stroke
Burns
Heart disease
Diabetes
Osteoarthritis
Rheumatoid arthritis
Birth Defects
Infertility
Pregnancy Loss
Leukemia
Brain Cancer
Muscular Dystrophy
Sickle Cell Anemia
Brain Trauma/Damage
Liver Disease
Metabolic Disorders
Deafness
Macular Degeneration
Retinitis Pigmentosa
Organ donation

- *Avoid harming the patient in any way.* One concern about using undifferentiated cells or stem cells is the risk of the stem cells having genetic abnormalities which could cause them to be cancerous or to be rejected due to tissue immune incompatibility. Adequate testing is necessary to make sure the cells used are healthy.

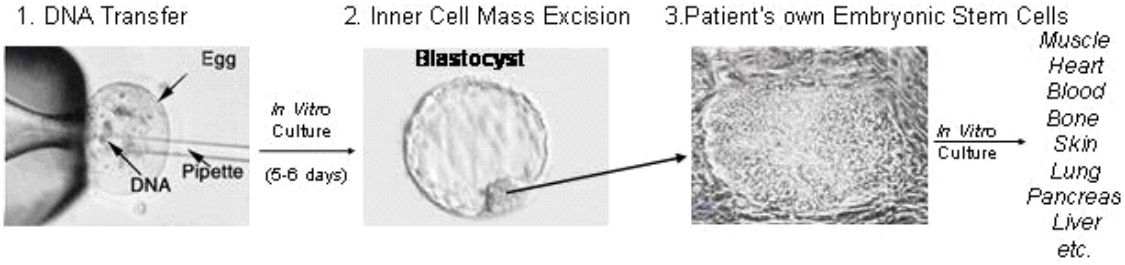
Embryonic Stem Cells

One of the most promising uses for embryonic stem cells is the study of the complex events that occur during human development. The earliest stages of human development have previously been difficult or impossible to study. By using embryonic stem cells, these studies can be performed with the goal of preventing or treating birth defects, infertility, and pregnancy loss.

The use of embryonic stem cells can also help scientists identify how undifferentiated cells become differentiated. Since these cells have the ability to become any type of cell in the adult body, they have a larger potential for medically viable tissues which can be derived and used in cell-based therapies.

Cloning

Somatic cell nuclear transfer is when the genetic material (**nucleus**) of an unfertilized egg is removed and replaced with the genetic material of a normal cell. The egg is then activated and allowed to grow. After it is allowed to grow into a blastocyst, embryonic stem cells are obtained from the inner cell mass. These embryonic stem cells can then be induced to become other differentiated cell-types.



Nuclear Transfer Procedure. *Image 1: DNA is being introduced into an egg; Image 2: After 5-6 days the egg has developed into a blastocyst; Image 3: Cultured embryonic stem cells, obtained from the inner cell mass. Reproduced with permission from the ISSCR.*

Much of the promise for embryonic stem cells lies in the potential of **deriving** or creating cell lines which are specific to a person. This technique can be used to create cell lines and study the development of different diseases (sometime call therapeutic cloning). For instance, by using a skin cell from a patient suffering with Parkinson's disease one could create a cell line that would show the researcher how the cell progressed from a normal to a diseased state. Not only could scientists study specific genetic diseases, but they could also create tissues that are compatible with the original donor.

Further, this technique can also be used to create tissues that are recipient-specific. In organ and tissue transplantation, a great concern is the rejection of transplanted tissue

by the recipients' immune system. If new cell lines were created to be identical to the recipient, this would no longer be a problem. Researchers from South Korea were the first to successfully clone human embryonic stem cell lines using somatic cell nuclear transfer. Their results were published in *Science* (Hwang et al, 2004).

Reproductive Cloning is when an egg undergoes somatic cell nuclear transfer and the resulting cell is allowed to grow to an infant that is an exact genetic copy of the somatic cell donor. Attempts at reproductive cloning have been error-prone and inefficient, resulting in the failure of most clones to develop. The most famous clone, Dolly (a sheep), was only created after multiple attempts and failures and then lived a shortened life (Wilmut et al, 1997).

Case Study: Juvenile Diabetes and Stem Cell Research

Juvenile diabetes, also known as type 1 diabetes, is essentially an **autoimmune** disease where one's own body starts attacking itself. In juvenile diabetes the body specifically destroys a pancreas cell, the **ß-cell**, which produces **insulin**. Insulin is an important hormone that balances blood sugar levels. Unregulated sugar levels in the blood can lead to severe problems such as kidney failure, blindness, stroke, and even death. Patients with juvenile diabetes are required to take multiple injections of insulin daily or have a continuous infusion of insulin through a pump just to survive. Also, they must constantly monitor their food intake and daily activities.

Scientists have been working for years to find a cure and are extremely optimistic about the potential use of stem cells to replace destroyed ß-cells. In a recently published study using mice, Harvard researchers determined that new ß-cells in the pancreas are formed through the replication of pre-existing ß-cells, rather than adult stem cells creating new ß-cells. These are the very cells being attacked and therefore their numbers are limited. This result means that in order to cure juvenile diabetes, scientists must rely on another source of ß-cells such as embryonic stem cells to generate new ß-cells.

American Stem Cell Research

Politics and Policies

By Kirstin Matthews, Ph.D.

Overview

In February of 1997, Dr. Ian Wilmut announced the creation of the first cloned mammal. The report, published in the science journal *Nature*, described a lamb, "Dolly," which was cloned using somatic cell nuclear transfer (SCNT). This landmark paper and the media attention it received created an immediate reaction from the public and politicians in Washington, D.C. who were concerned about the potential cloning of humans using this technique. Since Dolly's creation, congressional leaders have been trying to find a way to prevent human cloning and other allegedly unethical medical procedures while still allowing medical research to proceed unhindered.

In late 1998, the issue was further complicated by the announcement from researchers at the University of Wisconsin-Madison, led by Dr. James Thomson, who derived the first human embryonic stem cells from blastocysts. This marked the beginning of a new area of medical science, human embryonic stem cell research. With this new breakthrough, the issue of human cloning became considerably more complex, since SCNT was now linked to potential disease-curing research.

With each congressional session, a new crop of conflicting bills arises from both the House and Senate, and congressional hearings are called to bring witnesses in to validate either side, but no resolution appears to be in sight. Although many polls have shown that the vast majority of Americans disapprove of research which could produce a cloned human (83% in a 2002 poll by Research!America), there is still much public debate about the ethics of embryonic stem cell research. This debate resonates in the Congress and generates the current stalemate where lawmakers are unable to reach a consensus about medical research relating to embryonic stem cells.

Pre-"Dolly" Regulation

In the 1970s, rules were developed to govern the federal funding of research on human embryos for *in vitro* fertilization (IVF). The rules specified that all federally funded research on human embryos would need to be approved by a congressionally appointed ethics advisory board. Since no members for the board were ever appointed by Congress, this ethics advisory board never met and thus no embryo research was ever federally funded. In 1993, this rule was rescinded, but the Dickey Amendment, a **Department of Health and Human Services** (DHHS) 1996 appropriation rider, subsequently banned any federal funding of human embryo research and each year this amendment has been attached to the appropriation bill for the DHHS. Since that time, no federal funds have been allowed for embryo (and therefore embryonic stem cell) research, but private funding of research on embryos has been allowed and is completely unregulated.

Post-"Dolly" Debate

In February of 1997 after the public announcement about "Dolly", President Clinton charged the **National Bioethics Advisory Council** (NBAC) to study the issue of human cloning. In June of that year, NBAC released a report which determined that reproductive cloning was immoral and requested that a moratorium should be established until subsequent laws prohibiting it were passed (with a sunset period of 3-5 years). The members also suggested that the law be written so it would not interfere with biomedical research. Taking their suggestions, President Clinton offered a legislative proposal to bar anyone (either federally or privately funded) from attempting to clone a human through SCNT for 5 years. President Clinton's proposal was announced after several bills in the House and Senate had already been introduced (see Table 1). However, due to the fear that Congress was acting too quickly and might bar valid research, the majority needed to pass these bills was never attained and thus no legislation limiting such cloning was ever successfully passed into law.

In November of 1998, after Dr. Thomson announced the creation of the first human embryonic stem cell line, President Clinton asked NBAC to specifically address human embryonic stem cell research, which had not been discussed in 1997. In 1999, the

Table I - Bills Introduced in 1997-98 (105TH Congress)

Bill	Sponsor	Action
S. 368	Sen. Bond (R-MO)	The government would be permanently banned against using federal funds for cloning an individual.
H.R. 922	Rep. Ehlers (R-MI)	*Human Cloning Research Prohibition Act.* The government would be permanently banned against using federal funds for cloning an individual.
H.R. 923	Rep. Ehlers (R-MI)	*The Human Cloning Prohibition Act of 1997.* Cloning a human being through SCNT would be illegal and with a $5000 civil penalty for violations.
H.Doc. 105-97	Pres. Clinton	*The Cloning Prohibition Act of 1997.* It would bar everyone in the country, both private and publicly funded, from attempting to create a baby through SCNT. The ban would only last 3-5 years and proposed a $250,000 fine for anyone in violation.
S. 1574	Sen. Campbell (R-WY)	*Human Cloning Prohibition Act.* The bill would bar federal funding of research designed to clone a human or create a human embryo. It would also make it illegal and subject it to a $5000 fine.
S. 1601	Sen. Bond (R-MO)	*Human Cloning Prohibition Act.* The government would be permanently banned against using federal funds for cloning an individual. It would make the creation of a human embryo through SCNT a criminal act with a 10-year prison sentence. It would also prohibit the importation of human embryos which were created by SCNT. They would create a National Commission to Promote a National Dialogue on Bioethics.
S. 1602	Sen. Feinstein (D-CA) Sen. Kennedy (D-MA)	*Prohibition of Cloning Human Beings Act of 1998.* The bill would forbid creating a human by SCNT and bar federal funding for 10 years. It provided a $1 million fine for violations.

NBAC recommended that federal funding should be used to support both the research and creation of human embryonic stem cells. They also suggested amending the ban on embryo research (the Dickey Amendment) to allow the derivation and use of embryonic stem cells.

However, before the results of the NBAC deliberations were announced, the **National Institutes of Health** (NIH), specifically the legal council for the DHHS, determined that federal law (the Dickey Amendment) prohibited the use of federal funds to create human embryonic stem cell lines, but they did believe that it was legal to fund research on already existing lines. Private sources were never barred from deriving their own human embryonic stem cell lines and were actively pursuing this area of research. The NIH released guidelines for the federal funding of human embryonic stem cell research for public comment in 1999, followed by an updated version in 2000 in the *Federal Register*. Before NIH was able to grant money in response to research proposals, a new administration (President George W. Bush) took office and the previous rulings by the DHHS and NIH were set aside.

Meanwhile in the Senate, the Specter-Harkin bill (S.2015) was introduced as the *Stem Cell Research Act of 2000*. It called for the federal funding of the derivation and use of human embryonic stem cells from spare donated embryos (IVF), as long as the research did not lead to "reproductive cloning of a human being." This marked the first of many bi-partisan bills that Congress would see on this issue. The Specter-Harkin bill, like many future bills, was not passed into law.

When President Bush took office, one of his first actions was to temporarily stop all federal funding of human embryonic stem cell research (no grant had been given) while his administration considered their actions. On August 9, 2001, after several months of deliberation, President Bush announced that he would allow the federal funding of the research of human embryonic stem cells, but only those that had been derived before the date of the announcement could be used. Thus, no new embryonic stem cells could be created with federal funds, nor could federal funds be used to do research on new lines create after the August 9, 2001 deadline. NIH estimated at the time that there were as many as 60-75 cell lines available for research. However, since that time, NIH has revised its numbers downward. By the 2004 presidential campaign, NIH had only 22 lines available (see insert “Effect of President Bush’s Stem Cell Policy”).

Since the President’s August 9, 2001 decision, embryonic stem cell policy has remained unchanged. In November 2001, President Bush established the **President’s Council on Bioethics** (PCB), a group of experts (similar the NBAC), to address the issues of human cloning, embryonic stem cell research and other bioethical issues. In Congress, new bills were introduced in the 107th and 108th congress, and the Weldon-Stupak bill was passed in House in 2001 and 2003 to ban all forms of cloning and the use of SCNT, but neither passed in the Senate (see Table II and III). Almost every year we see each political side introduce their version of a law which would outlaw all human cloning or only reproductive cloning and either outlaw or permit the use of embryonic stem cells, but nothing has been signed into law.

Perhaps, the most interesting part of the congressional debate is the fact that views on the topic do not necessarily follow traditional party lines or a person's opinion on abortion or right to life. This new debate has produced the most unlikely bipartisan partnerships and has resulted in a deadlock in Congress, which has sharply constrained federally funded research on embryonic stem cells and human cloning. At the same time, the

Table II - Bills Introduced in 2001-2002 (107TH Congress)

Bill	Sponsor	Action
S. 704	Sen. Campbell (R-WY)	*Human Cloning Prohibition Act.* The bill would bar federal funding of research designed to clone a human or create a human embryo. It would also make it illegal and subject it to a $10 million fine, but to 10 years in prison and barred from federal funding for 15 years.
S. 723	Sen. Specter (R-PA) Sen. Harkin (D-IA)	*Stem Cell Research Act of 2001.* S.2015 reintroduced in April
S. 790	Sen. Brownback (R-KS) Sen. Bond (R-MO) Sen. Smith (R-NH)	*Human Cloning Prohibition Act of 2001.* This bill would prohibit all cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.
S. 1758	Sen. Feinstein (D-CA)	*Human Cloning Prohibition Act of 2001.* This bill would outlaw the cloning of a human being and give both a criminal and civil penalty for violations. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.
H.R. 1260	Rep. Kerns (R-IN)	*Ban on Human Cloning Act.* It bans SCNT for the intent of implanting the resulting product into a uterus. It sets forth a 5 year criminal penalty for violations.
H.R. 1608	Rep. Ehlers (R-MI)	*Human Cloning Prohibition Act of 2001.* This bill bans SCNT and violations can receive up to 2 years in prison.
H.R. 2059	Rep. McDermott (D-WA)	*Stem Cell Research Act of 2001.* This bill would amend the Public Health Service Act to allow the utilization and derivation of embryonic stem cell from embryos donated from *in vitro* fertilization clinics as long as the research does not result in reproductive cloning of a human.
H.R. 2505	Rep. Welton (R-FL) Rep. Stupak (D-MI)	*Human Cloning Prohibition Act of 2001.* This bill would prohibit all cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations. This was passed through the House in July 2001
H.R. 2608	Rep. Greenwood (R-PA) Rep. Deutsch (D-FL)	*Cloning Prohibition Act of 2003.* This bill will amend the FDA regulations to include the prohibition of reproductive cloning and require researchers to register in order to perform human SCNT. It applies civil and criminal penalties to anyone who violates the law.
S. 1893	Sen. Harkin (D-IA) Sen. Specter (R-PA)	*Human Cloning Ban and Stem Cell Research Protection Act of 2002.* Similar to S.1758.
S. 1899	Sen. Brownback (R-KS) Sen. Landrieu (D-LA)	*Human Cloning Prohibition Act of 2001.* Same as S. 790
S. 2076	Sen. Dorgan (D-ND) Sen. Johnson (D-SD)	*Human Cloning Prohibition Act.* This bill would prohibit reproductive cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.
S. 2439	Sen. Specter (R-PA) Sen. Feinstein (D-CA)	*Human Cloning Prohibition Act of 2002.* Based on the finding of the National Academies report and the National Bioethics Advisory Commission, this bill would outlaw the cloning of a human being and give both a criminal and civil penalty for violations. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.

Table III - Bills Introduced in 2003-2004 (108TH Congress)

Bill	Sponsor	Action
S. 245	Sen. Brownback (R-KS) Sen. Landrieu (D-LA)	*Human Cloning Prohibition Act of 2003.* This bill would prohibit all cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.
S. 303	Sen. Hatch (R-UT) Sen. Feinstein (D-CA)	*Human Cloning Ban and Stem Cell Research Protection Act of 2003.* This bill would prohibit reproductive cloning while protecting therapeutic cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations.
H.R. 234	Rep. Welton (R-FL) Rep. Stupak (D-MI)	*Human Cloning Prohibition Act of 2003.* This bill would prohibit reproductive cloning while protecting therapeutic cloning. It sets forth penalties of 10 year imprisonment and $1 million fine for violations. This billed passed in the house alone.
H.R. 801	Rep. Greenwood (R-PA)	*Cloning Prohibition Act of 2003.* This bill will amend the FDA regulations to include the prohibition of reproductive cloning and require researchers to register in order to perform human SCNT. It applies civil and criminal penalties to anyone who violates the law.
H.R. 916	Rep. Stearn (R-FL)	*Human Cloning Research Prohibition Act.* The prohibition of using the use of federal funds to do SCNT to produce an oocyte.
H.R. 3960	Rep. Millender-McDonald (D-CA)	*Stem Cell Replenishment Act of 2004.* The authorization of federal funds for research on human embryonic stem cells regardless of the date they were derived.
H.R. 4531	Rep. Ackerman (D-NY)	*Ronald Reagan Memorial Stem Cell Research Act of 2004.* Authorizes the federal funding of embryonic stem cell research regardless of the date of derivation. $87 million will be appropriated for FY 2005.
H.R. 4682	Rep. Castle (R-DE)	*Stem Cell Research Enhancement Act of 2004.* The authorization of federal funds for research on human embryonic stem cells irregardless of the date they were derived. All embryos must be from donated excess from IVF clinics.
H.R. 4812	Rep. Deutsch (D-FL)	*Stem Cell Discovery Through Diversity Act.* Authorizes the federal funding of embryonic stem cell research regardless of the date of derivation. Funds may not be used to derive such cells from embryos. There will also be a new office known as the "Ronald Reagan Office of Human Stem Cell Research" at the NIH.

deadlock has virtually left the privately funded research involving embryonic stem cells and human cloning completely unregulated.

Momentum for expanding federal funding for embryonic stem cell research began to build again as the 2004 presidential campaigns kicked into gear. In April of 2004, 206 members of the House of Representatives (out of 435) signed a letter to President Bush urging him to expand the current federal policy on embryonic stem cell research to include new lines developed after August 9, 2001. Following the House's lead, the

Senators that advocated embryonic stem cell research also wrote a letter to President Bush with 58 signatures (out of 100). On May 10, 2004, former First Lady, Nancy Reagan publicly supported embryonic stem cell research at a fundraiser for juvenile diabetes. Although, privately she had supported the research with personal letters to congressmen, this was her first public statement on the topic. Nancy Reagan and the Reagan family are often thought of as icons for the Republican Party and conservative ideals. This public acceptance led the way for other Republicans to support the issues. One month later, President Reagan, a victim of Alzheimers, passed away. Stem cell research was immediately brought into the forefront as a campaign issue for the 2004 election. Senator Kerry supported the expansion of the research, while the President Bush explained his current policy and promised to maintain the status quo.

With the return of President Bush to office in 2005, the possibility for changing the current federal policy seems unlikely. However, with or without the expansion of federal funding, some states (such as California, Michigan, and Arkansas) are beginning to pick up the reigns by passing their own laws related to embryonic stem cell research (see page 15 "State Cloning Legislation"). In November 2004, Californians approved Proposition 71, or the *California Stem Cell Research and Cures Initiative*, which called for the creation of a "California Institute for Regenerative Medicine" and authorized $3 billion of state funds to support the effort over the next five years. The proposal also established the right to conduct embryonic stem cell research in California, but prohibits reproductive cloning. President Bush's policy only limits federal funding, but does not make the research itself illegal therefore the states are able to determine how they wish to regulate and fund research using state funds. California's new proposition allows the use of state funds to support embryonic stem cell research regardless of the date the cells were generated, to create new cell lines, and to use SCNT to create cell lines with specific genes. This new institute is expected to attract stem cell researchers and investors to California allowing it to corner the market on any promising findings.

Summary

The debates on stem cell research essentially started in 1997, after the first mammal, "Dolly," was cloned. Through the past 7 years, the United States government has not been able to agree on the best policy. The Bush Administration put into place a policy, which allows some research to proceed, but it failed to address the research that is taking place with private and other non-federal funds. The issue has also produced a stalemate in Congress on whether to allow the federal funding of embryonic stem cell research to be expanded. Whether we should fund embryonic stem cell research and therapeutic cloning and how to regulate the current research done with private funds are questions the next Congress and Bush Administration will need to address.

Effects of President Bush's Stem Cell Policy

In an effort to appease the advocates for embryonic stem cell research, but still stay true to his conservative base, President Bush allowed federal funding of research on human embryonic stem cells derived on or before August 9, 2001. At the time of the announcement, the NIH believed that there were 60-75 lines which met the qualification for federal funding. Since the announcement, scientists have found several problems with the cell lines which were approved:

1. Currently there are only 22 lines available for distribution by the NIH. Many of the other cell lines were either unavailable to researchers or had contamination problems, chromosomal abnormalities, or were unstable.

2. All the cells had been created using mouse cells; therefore, they cannot be used in humans for fear of spreading mouse viruses in humans. It also has been shown recently that all the lines tested contained mouse proteins on their surface which causes them to be rejected by the immune system in a human. This means the cells are unlikely to ever be used for medical purposes.

3. Older cell lines are more susceptible to chromosomal abnormalities than newer lines. So over time, the current stem cell lines will degrade and are not medically viable.

4. Several of the lines have been difficult to grow, giving them very limited uses.

5. Each approved cell line has the propensity to grow into only one specific cell-type. This decreases the breadth of research opportunities for scientists.

6. The cell lines lack genetic diversity necessary to create therapeutic treatment for a broad number of patients

7. There is an absence of disease-specific cell lines, thereby limiting stem cell research on genetic diseases.

Improvements in how scientists can grow the cells *in vitro* have made new cell lines created in other countries and from private funding (now numbering over 150 lines) more appealing than the lines approved for federal funding. This discourages scientists from using the cell lines, applying for the federal funds, or even entering the field. Most scientists, especially new faculty and graduate students, rely heavily on public funding during their careers.

This policy also limits the availability of subsequent discoveries to the general public. Since private firms will own any therapies derived from such research and may charge heavily to recoup their investments, they have no incentives to publicly release their data.

State Cloning Laws

By Kathryn Wheat and Kirstin Matthews, Ph.D.
The information in this section is provide to illustrate the diversity of approaches various states are taking with regard to regulation of human cloning and embryonic stem cell research. The brief summary is based on a review of relevant literature and websites and should be considered preliminary.

Overview

While the United States has no laws on the books concerning human cloning, individual states have laws prohibiting one or all forms of cloning as well as restrictions on embryonic stem cell research. Arkansas, California, Iowa, Michigan, Rhode Island, North Dakota, Virginia, New Jersey, and South Dakota have laws that prohibit reproductive cloning. Arkansas, Iowa, Michigan, North Dakota, and South Dakota also prohibit therapeutic cloning (SCNT or non-reproductive medical application). Michigan also specifically prohibits the use of state funds for any human cloning, while Missouri prohibits state funding for reproductive cloning only. Virginia fails to define "human being," and so it is unclear if all human cloning is banned. California, New Jersey, and Rhode Island allow therapeutic cloning, and California and New Jersey have gone so far as to pass laws funding such research with state funds.

Some of the states that do not have specific laws on human cloning do place restrictions on embryonic research. Twenty states do not explicitly prohibit or allow embryonic research, but do address and prohibit certain means of obtaining a fetus/embryo for experimentation. Louisiana is the only state to prohibit experimentation on IVF embryos, and Illinois is the only state to prohibit experimentation on live embryos. These two states, as well as the other eighteen, do not specifically prohibit human cloning. Finally, twenty states neither address embryonic research nor human cloning and therefore have no policy or legislation on record.

States with Legislation Concerning Human Cloning

Arkansas (2003, 2004)

- Embryonic stem cell research is not specifically addressed.
- There is a ban on research on cloned embryos (therapeutic and reproductive cloning).
- Cloning is defined as asexual human reproduction, which is accomplished by introducing the genetic material from one or more human **somatic cells** into a fertilized or unfertilized **oocyte** whose nuclear material has been removed or inactivated so as to produce a living organism, at any stage of development, that is genetically virtually identical to an existing or previously existing human organism.

California (2004)

- The state specifically permits embryonic research and therapeutic cloning. However, reproductive cloning is banned.
- The law defines cloning as the nucleus transfer from a human cell from whatever source into a human or nonhuman egg cell from which the nucleus has been removed for the purpose of, or to implant with the resulting product to initiate a pregnancy that could result in the birth of a human being.
- **Funding:** Stem cell research is funded by the state. On November 2, 2004 the state passed a proposition (the *California Stem Cell Research and Cures Initiative*) which created the California Institute for Regenerative Medicine and authorized $3 billion dollars in state bonds to fund the research.

States with Cloning Legislation

	ESC*	Therapeutic
Arkansas	✓	
California	✓	✓
Iowa	✓	
Michigan	✓	
Missouri	✓	✓
New Jersey	✓	✓
North Dakota	✓	
Rhode Island	✓	
South Dakota	✓	
Virginia	✓	

*Some prohibit the derivation of embryonic stem cells, but don't specifically prohibit the research using existing lines.

Iowa (2004)

- Embryonic research is not addressed.
- There are bans on research on cloned embryos and research which destroys a human embryo.
- The state defines cloning as human asexual reproduction, accomplished by introducing the genetic material of a human somatic cell into a fertilized or unfertilized oocyte whose nucleus has been or will be removed or inactivated, to reproduce a living organism with a human or predominantly human genetic constitution.

Michigan (2004)

- Embryonic research is not specifically permitted and there is a ban on research on cloned embryos and live embryos.
- The state defines cloning as the use of human somatic cell nuclear transfer technology (transferring the nucleus of a human somatic cell into an egg from which the nucleus has been removed or rendered inert) to produce a human embryo.
- **Funding:** State funding banned for human cloning research.

Missouri (2004)

- Embryonic research is not specifically permitted. The state bans both reproductive and therapeutic cloning.
- The state defines cloning as the replication of a human person by taking a cell with genetic material and cultivating such a cell through the egg, embryo, fetal and newborn stages of development into a new human person.
- **Funding:** State funding banned for human reproductive cloning research.

New Jersey (2002-3, 2004)

- Embryonic research is not specifically permitted.

- They permit therapeutic cloning, but ban reproductive cloning.
- The state defines cloning as the replication of a human individual by cultivating a cell with genetic material through the egg, embryo, fetal and newborn stages into a new human individual.

North Dakota (2003, 2004)

- Embryonic research is not specifically addressed.
- The state bans both reproductive and therapeutic cloning.
- The state defines cloning as human asexual reproduction, which is accomplished by introducing the genetic material of a human somatic cell into a fertilized or unfertilized oocyte, the nucleus of which has been or will be removed or inactivated, to produce a living organism with a human or predominantly human genetic constitution.

Rhode Island (2004)

- Embryonic research is not specifically permitted.
- The state bans therapeutic cloning.
- Cell transfer and other cloning technologies are not included in the ban. Mitochondrial, cytoplasmic and gene therapy are not prohibited for research or animal creation.
- The state defines cloning as the use of somatic cell nuclear transfer for pregnancy prohibited (transferring the nucleus of a human somatic cell into an oocyte from which the nucleus has been removed.)
- The law will last until July 2010.

South Dakota

- Embryonic research is not specifically permitted.
- Therapeutic and reproductive cloning are banned.
- The state defines cloning as human asexual reproduction accomplished by introducing the nuclear material of a human somatic cell into a fertilized oocyte whose nucleus has been removed or inactivated to produce a living organism, at any stage of development, with a human genetic constitution.

Virginia

- Embryonic research is not specifically permitted.
- It is unclear if therapeutic cloning is permitted because the law failed to define a “human being”.
- Reproductive cloning is banned.
- The state defines cloning as the transferring the nucleus from a human cell from whatever source into an oocyte from which the nucleus has been removed or rendered inert in order to create a human being.

States with Restrictions on Embryonic Research, but no Legislation on Cloning*

Arizona, Florida, Indiana, Kentucky, Maine, Massachusetts, Minnesota, Montana, Nebraska, New Hampshire, New Mexico, Ohio, Oklahoma, Pennsylvania, Tennessee, Texas, Utah, Wyoming

Louisiana is the only state that bans research on IVF embryos, but this does not cover somatic cell nuclear transfer (SCNT); therefore you can still do reproductive or therapeutic cloning if you obtain a blastocyst from another source. Thus cloning is not explicitly restricted.

Illinois prohibits research on live embryos, but again, this does not completely restrict cloning.

**States do delineate what kind of embryonic research is prohibited, and this includes research on an aborted fetus/embryo, consent provisions, embryo or fetus resulting from sources other than abortion, and the sale of fetal/embryonic tissue.*

States with no Legislation on Either Cloning or Embryonic Research

Alabama, Alaska, Colorado, Connecticut, Delaware, Georgia, Hawaii, Idaho, Kansas, Maryland, Mississippi, Nevada, New York, North Carolina, Oregon, South Carolina, Vermont, Washington, West Virginia, Wisconsin

World Human Cloning Policies

By Kathryn Wheat and Kirstin Matthews, Ph.D.
The information in this section is provide to illustrate the diversity of approaches various different parts of the world are taking with regard to regulation of human cloning and embryonic stem cell research. The brief summary is based on a review of relevant literature and websites and should be considered preliminary.

Overview

World policies on human or reproductive cloning range from complete prohibition to no policies on record. Thirty-one countries, including France, Germany, and Russia, have banned human cloning altogether. Fifteen countries, such as Japan, the UK, and Israel, have banned human reproductive cloning, but permit therapeutic cloning. Some countries like Hungary and Poland do not explicitly prohibit embryonic stem cell research or therapeutic cloning, partially because their legislation was drafted before embryonic stem cells were first produced (1998). Many countries, similar to the United States, have yet to pass any official legislation concerning human cloning, thus allowing all types of stem cell and cloning research to occur.

World Cloning

	ESC*	Ther.		ESC	Ther.
United States	✓	✓	Latvia	✓	
Canada	✓	✓	The Netherlands	✓	
Mexico	✓	✓	Norway		
Costa Rica			Poland	✓	✓
Panama	✓		Portugal	✓	
Trinidad & Tobago			Russia	✓	
Argentina	✓		Slovakia	✓	
Brazil			Slovenia	✓	
Chile	✓		Spain	✓	✓
Columbia	✓	✓	Sweden	✓	
Ecuador			Switzerland		
Peru	✓		UK	✓	✓
Uruguay	✓		China	✓	✓
Austria			India	✓	
Belgium	✓	✓	Japan	✓	✓
Denmark	✓		Singapore	✓	✓
Finland	✓	✓	South Korea	✓	✓
France	✓		Thailand	✓	✓
Georgia	✓		Vietnam	✓	
Germany	✓		Australia	✓	
Greece	✓		New Zealand	✓	✓
Hungary	✓	✓	Israel	✓	✓
Iceland	✓		Turkey	✓	✓
Ireland			South Africa	✓	
Italy			Tunisia	✓	

*Some prohibit the derivation of embryonic stem cells, but do not specifically prohibit the research using existing lines.

United Nations

The United Nations (UN) is currently considering two different draft resolutions regulating human cloning - one from Costa Rica and one from Belgium. The Costa Rican draft calls for an international convention to prohibit both therapeutic and reproductive cloning, while the Belgian draft calls to ban reproductive cloning only and permits the decision on therapeutic cloning to be up to each country. All countries agree on a ban of reproductive cloning, but some countries prefer the Costa Rican draft because they believe that therapeutic cloning disrespects human dignity and has potential for abuse. Advocates for the Belgian proposal believe that therapeutic cloning findings should be shared internationally so each country can make their own decision. On October 22, 2004, the UN postponed a decision on the resolutions for one year leaving the issue unresolved. (This was the second such postponement.)

North America

United States

- Officially, embryonic stem cell research, therapeutic cloning and reproductive cloning are legal as there is currently no federal regulation or policies overseeing it.
- Reproductive and therapeutic cloning are specifically not federally funded. However, research on human embryonic stem cells is federally funded if these cell lines were created before August 9, 2001. Private industry research is not affected by these policies and is allowed to proceed with the creation of new stem cell lines.
- Some individual states have made their own laws against reproductive and/or therapeutic cloning. (See page 15 “State Cloning Legislation”).

Canada

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- Researchers can use an embryo from IVF if it is no longer needed for reproductive purposes and consent is given by the donor. Creating a human clone is restricted to improving or providing instruction in assisted reproduction procedures.
- In 2003, the Canadian House of Commons passed a bill allowing the Assisted Human Reproductive Agency the ability to grant permission for embryonic stem cell research and therapeutic cloning.

Mexico

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned (the laws were just amended in 2004).

Costa Rica

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- Any manipulation of an embryo's genetic code is prohibited, as well as any experimentation on the embryo (two laws as of 1995 and 1998).

Panama

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning and the funding of such activities are as of 2004.

Trinidad and Tobago

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- The law states that the manipulation of **ovum**, **zygotes**, and/or embryos for the purpose of producing one that is genetically equivalent to a living or deceased human being, embryo, zygote, or fetus -- or implantation of this -- is prohibited. The ovum may not be retrieved to be fertilized, to mature outside of the human body, or to be implanted (as of 1999).

South America

Argentina

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- The law specifically states that experiments concerning cloning of human cells in order to generate human beings are prohibited.

Brazil

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- The current policy prohibits the genetic manipulation of the germline (or a gene which can be passed to ones offspring) and intervention of the human genetic material *in vivo.*
- As of 1995, the Brazilian Biosafety Technical Commission of the Ministry of Science and Technology concluded that this law inherently bans human cloning. The law is currently under review.

Chile

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning and the funding of such activities are as of 1993. This law is currently under review
- The law states that the cloning of human beings and interventions which results in the creation of a human being genetically identical to another is prohibited.

Columbia

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- The criminal code (2000) prohibits fertilization of a human ovum with intent other than procreation and prohibits genetic manipulation for the purpose of reproductive cloning. The code does allow the fertilization of human **ova** for research and diagnostic purposes, if they is a therapeutic goal.

Ecuador

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- Research on human embryos (and therefore cloning) is prohibited as of June 1998.

Peru

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are banned.
- Fertilization of a human ovum with intent other than procreation is prohibited, as well as human cloning (General Health Law, 1997).

Uruguay

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are as of 2003.

- The law states that human cloning is prohibited, as is manipulating human cells or genetic materials by cloning in order to create an identical human being, pre-embryo (blastocyst), or embryo.

Europe

Austria

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- Reproductive medicine is acceptable only within stable heterosexual relationships for the purpose of reproduction. Embryos can be used only for implantation in the woman who has donated the **oocytes**, and for no other purposes. Donation of embryos or **gametes** is prohibited (Federal Law of 1992 Regulating Medically Assisted Procreation).

Belgium

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned as of May 2003.

Denmark

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning and the funding of such activities are as of 2003.
- The law states that research on human reproductive cloning and somatic cell nuclear transfer is forbidden, thereby prohibiting therapeutic cloning.

Finland

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- Research done for the purposes of curing or preventing serious hereditary disease is allowed, but reproductive cloning is prohibited (Medical Research Act of 1999).

France

- Embryonic stem cell research is allowed, but therapeutic and reproductive cloning are banned.
- Research on human embryonic stem cells is now allowed until embryos are 6-8 days old. However, there is no government funding for such research. Embryos cannot be created specifically for research -- scientists must use existing embryos from IVF. Embryonic stem cell lines are typically imported from abroad.
- A new agency for biomedicine is to be created in Jan 2005, which will regulate embryonic stem cell research.

Georgia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are.
- Human cloning through the use of genetic engineering is prohibited (1997 Law on Health Care).

Germany

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- It is Illegal to create any new stem cell lines after December 2001.
- In a recent report, the National Ethics Council said that cloning for research purposes should not be allowed.

Greece

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- The law states that reproductive cloning is prohibited, as well as the creation of human embryos solely for research purposes (as of 2003).

Hungary

- Embryonic stem cell research and therapeutic cloning are not specifically prohibited, but reproductive cloning is.
- The national law (1997) does not explicitly address or prohibit embryonic stem cell research or therapeutic cloning.

Iceland

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are (Act on Artificial Fertilisation, 1996).

Ireland

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- Human cloning is prohibited because the "right to life of an unborn child is equal to that of the mother" as stated in the Constitution of Ireland.

Italy

- Embryonic stem cell research as well as therapeutic and reproductive cloning is banned.
- The law prohibits embryo manipulation, germline modification and human cloning for reproductive or therapeutic research purposes (Assisted Medical Procreation Law, 2004).

Latvia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning and the funding of such activities are, as of the 2002 Law on Sexual and Reproductive Health.
- Human cloning and the use of medical techniques to create a human being genetically identical to another, alive or dead, is prohibited.

The Netherlands

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- Human reproductive cloning is prohibited, and research on embryos is strictly regulated (The Embryos Act, 2002).

Norway

- Embryonic stem cell research, as well as therapeutic and reproductive cloning is banned.
- Research on embryos and the use of techniques aimed at the production of genetically identical individuals is prohibited (The Medical Use of Biotechnology, 1995).

Poland

- Human reproductive cloning prohibited, but therapeutic cloning and embryonic stem cell research is not explicitly prohibited (as of 1993).
  This bill is currently under review.

Portugal

- Embryonic stem cell research is permitted, but reproductive cloning is banned and therapeutic cloning is implicitly prohibited.
- The law states that the cloning of human beings is prohibited (National Council of Ethics for the Life Sciences, 1997).

Russia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are.
- For a five-year period starting in 2002, human cloning is prohibited, as well as the import and export of human cloned embryos (Law on Temporary Prohibition of Human Reproductive Cloning, 2002).

Slovakia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are.
- No human beings may be created with identical genes; therefore, cloning is prohibited (as of 1994 and 2003).

Slovenia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are.
- Human cloning for reproductive and therapeutic purposes is prohibited by the Law on Medically Assisted Reproduction (2000) and the Penal Code (2002).

Spain

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- Any therapeutic intervention, investigation, or research activity in pre-embryos *in vitro,* pre-embryos, or embryos and fetuses *in utero* will be authorized only if it does not alter the genetic makeup of the embryo, and as long as it is not aimed at one particular individual or race-selection. Research on *in vitro* embryos is allowed with parental consent, after the embryos have been frozen for five years or more.
- The law was passed in 1998 and amended in 2003 and 2004.

Sweden

- Embryonic stem cell research is permitted, but therapeutic and reproductive cloning are banned.
- These issues are covered in the *in vitro* Fertilization Law of 1988 and 1991 Law (Act Concerning Measure for the Purposes of Research or Treatment in Connection with Fertilized Human Oocytes, 1993).

Switzerland

- Embryonic stem cell research as well as therapeutic and reproductive cloning is currently banned.
- The law is currently being reviewed and an election is scheduled for November 28, 2004 to permit therapeutic cloning.
- Any form of cloning and any intervention involving the genetic heritage of human gametes and embryos is prohibited. Only the number of human oocytes that are to be implanted in medically assisted procreation methods may be developed to the embryo stage outside the body of a woman (Federal Order of December 1998).

United Kingdom

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- Therapeutic cloning is regulated by Human Fertilization and Embryology Authority (HFEA) in order to understand the development of embryos and to develop treatments for serious disease.
- HFEA gave the first license to Newcastle Centre for Life (Aug 2004), where therapeutic cloning will be used.

Asia

China

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- "Guidelines for Research on Human Embryonic Stem Cells" released in 2004 by China's Ministry of Science and Technology, and Ministry of Health.

India

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- There are specific principles for human genetics research, while all research on cloning is prohibited.
- The Indian Council of Medical Research released the Consultative Document on Ethical Guidelines for Biomedical Research on Human Subjects (2000), which cover the guidelines.

Japan

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- Production of cloned human embryos will be limited to basic research or regenerative medicine only (Bioethics Committee of the Council for Science and Technology Policy).

Singapore

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- The law allows the harvesting of stem cells from cloned human embryos, but it prohibits cloned embryos from developing more than two weeks.

South Korea

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- The government approved research on somatic cell nuclear transfer based on guidelines of National Ethics Committees.
- As of January 2004, reproductive cloning is banned.

Thailand

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- The law is stated in "Regulations on Human Cloning, 2002", by the Medical Council of Thailand, and in "Stem Cell Guidelines" by BIOTEC and National Health Foundation.

Vietnam

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are.
- Human cloning and surrogacy banned as of May 2003.

Oceania

Australia

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- The law specifically states that one cannot intentionally create a human embryo clone; you may only harvest and do medical research with human embryos from donors (Prohibition of Cloning Act, 2002).

New Zealand

- Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.
- In 2004, the Human Assisted Reproductive Technology Bill was amended to ban reproductive cloning and genetically engineered babies.

Middle East

Israel

- Embryonic stem cell research and therapeutic cloning is permitted, but reproductive cloning is banned.
- Human reproductive cloning and germline genetic engineering is prohibited.
- The law was amended on March 2004 - Prohibition of Genetic Interventions (Human Cloning and Genetic Manipulations of Reproductive Cells).

Turkey

- Embryonic stem cell research is not specifically prohibited.
- Therapeutic cloning is allowed, but reproductive cloning is not (as of 1996).

Africa

South Africa

- Embryonic stem cell research is permitted, but all forms of cloning (reproductive and therapeutic) are banned.
- The law specifically states that the cloning of human cells is prohibited, and genetic manipulation of gametes or zygotes outside of the body is also prohibited (as of 1983).

Tunisia

- Embryonic stem cell research is not specifically prohibited, but therapeutic and reproductive cloning are as of 1997.
- The law states that any technology of related to human cloning is banned.

Case Study: The United Kingdom

Regulation of Stem Cell Research

Based on materials from the Department of Health, the Wellcome Trust, the MRC, and the UK Stem Cell Bank

Overview

The UK Government is supportive of research into all types of stem cells from adults to fetuses, cord blood to embryos subject to carefully prescribed guidelines. Research using surplus human embryos from IVF and embryos created for research, by fertilization, or somatic cell nuclear replacement (cloning) is permitted in the United Kingdom under license from The Human Fertilisation and Embryology Authority (HFEA). As a condition of the license, cell lines established by the research must not be transferred to third parties and must be deposited in the UK Stem Cell Bank. This bank was established in May 2004 and is overseen by an independent committee chaired by Lord Naren Patel. Most funding of UK stem cell research comes from the research councils, notably the Medical Research Council (MRC). Finally, a Local or Multi-centre Research Ethics Committee must also approve any embryonic stem cell research project in the UK.

Human Fertilisation Embryology Authority

The HFEA is a statutory body created in 1991 by the Human Fertilisation and Embryology Act to license and monitor research and fertility clinics in the UK. The HFEA was created in response to public concern about the potential risks of infertility treatments and embryo research. The mission of the HFEA is to address the issues of *in vitro* fertilization (IVF), donor insemination, and more recently embryonic stem cell research. The agency also regulates the storage of eggs, sperm, and embryos, reviews all new developments in treatments and research, and advises ministers. HFEA is actively involved in the public debate on the ethics of IVF and embryo research

In addition, HFEA monitors clinics that do research on or conduct IVF, donor insemination treatments, or human embryo research. The HFEA Code of Practice provides clinics with detailed guidelines. Clinics may be inspected at any time to ensure that they maintain the highest medical and professional standards. The activities of HFEA were designed to safeguard the interests of patients, children, the general public, doctors, service providers, the scientific community, and also future generations.

The purposes for which embryos can be used in research are listed in Schedule 2 of the Human Fertilisation and Embryology Act 1990 and in the Human Fertilisation and Embryology (Research Purposes) Regulations 2001. These purposes are:

- Promoting advances in the treatment of infertility.
- Increasing knowledge about the causes of congenital disease.
- Increasing knowledge about the causes of miscarriages.
- Developing more effective techniques of contraception.
- Developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

- Increasing knowledge about the development of embryos.
- Increasing knowledge of serious disease.
- Enabling any such knowledge to be applied in the development of treatments for serious disease.

The HFEA has 18 members including its current chair Ms. Suzi Leather. All members are appointed by the UK Health Minister under rigorous standards laid down for public bodies in the UK. The members determine HFEA policies, review treatments, and research license applications. Under the Human Fertilisation and Embryology Act, more than half of the members must come from disciplines other than medicine and human embryo research. The HFEA reports to the Secretary of State, and publishes its report annually.

The HFEA is the official organization which grants licenses allowing researchers to create human embryonic stem cells through somatic cell nuclear transfer. In August of 2004, the HFEA granted its first license (valid for one year) to Newcastle Centre for Life and Dr. Alison Murdoch. Stem cells created under this license will be used for research purposes only. Research must be completed before the embryo is 14 days old. Research using human/animal chimeras is currently not permitted. Each proposal to the HFEA is fully peer reviewed.

Medical Research Council

The UK MRC is an independent, national organization established in 1913 and funded by the public. The MRC promotes research in all areas of medical and related science with the aim of improving human health and quality of life (similar to the NIH in the United States, yet not part of the government). The MRC reports to the Office of Science and Technology, which is part of the Department of Trade and Industry. The MRC governing body is a council of 15 members, which meets six times a year. The council is responsible for overseeing the MRC policy, research direction, management oversight, and other related issues.

The mission of the MRC is to encourage and support high-quality research with the aim of improving human health, producing skilled researchers, advancing and disseminating knowledge and technology; and promoting dialogue with the public about medical research. The MRC works though its council, scientific boards, and committees to determine which research to support. Since the MRC is not a government department, it is independent in determining how to spend money allocated. Although it is an independent organization, it works closely with the government health departments, other research councils, industry leaders, and others to identify and respond to current and future health needs. The council also advises the government on matters relating to biomedical research and health-related questions.

The MRC budget is around $800 million (£430 million). Spending is split between grants to universities and the National Health Service (NHS), and funding MRC research centers. The MRC has over 50 research centers, employing over 3000. One of these centers is the UK Stem Cell Bank.

UK Stem Cell Bank

Sponsored by the MRC and the Biotechnology and Biological Sciences Research Council (BBSRC), the UK Stem Cell Bank provides an independent and competent

facility to produce, test, and release existing stem cell lines and new stem cell lines derived from adult, fetal and embryonic human tissues. Part of their mission requires **characterizing** stem cell lines for use in the UK and abroad. The bank presents information to the public on the cell lines and the technology used in their preparation and characterization. They will also be responsible for maintaining stem cell lines that are prepared under Good Manufacturing Practice (GMP) conditions. Under UK law, only materials derived under GMP can be used as therapeutics in humans. The UK Stem Cell Bank is managed by a steering committee chaired by Lord Naren Patel.

Materials were prepared by Kirstin Matthews, Ph.D.

Glossary

adult stem cell - An unspecialized or undifferentiated cell found among specialized cells in a tissue or organ, which can renew itself and differentiate into a specialized cell.
autoimmune disease – A disease where ones own body starts attacking itself and destroying ones own cells.
ß-cell – A cell in the pancreas which is responsible for the production and regulation of insulin.
blastocyst – A preimplanted embryo of 30-150 cells that is 5-6 days-old.
cell-based therapies –Treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or depleted adult cell populations or tissues.
characterizing stem cells – Determining how a cell grows, where the cell came from, how it was derived, and if there are any chromosomal abnormalities.
cloning – In biology, it is the act of producing an exact copy of a sequence of DNA, cell, tissue, or organism.
Department of Human and Health Services (DHHS) - The United States government's principal agency for protecting the health of all Americans. It provides essential human services, especially for those who are least able to help themselves.
deriving – The creation of a cell line from one original cell or set of cells.
differentiation – The process of unspecialized cells transforming into specialized cells.
embryo – In humans, the developing organism from the time of fertilization until the end of the eight week, when it become known as a fetus.
embryonic stem cell - An unspecialized or undifferentiated cell found in the inner cell mass of a blastocyst, which can renew itself and differentiate into a specialized cell.
fetus – A developing human from the eighth week after fertilization to birth.
gamete – a mature sexual reproductive cell (sperm or egg) having a single set of unpaired chromosomes.
hematopoetic stem cell – An adult stem cell from which all white and red blood cells evolve.
Human Fertilisation and Embryology Authority (HFEA) – The governmental authority in the United Kingdom that regulates in vitro fertilization and embryo research.
inner cell mass – A small group of about 30 cells in a blastocyst which will gives rise to the hundreds of highly specialized cells needed to make up an adult organism; embryonic stem cells are derived from this group.
insulin – A hormone in the body that balances blood sugar levels.
in vitro – From the Latin for “in glass”; in a laboratory dish, test tube, or artificial environment.
***in vitro* fertilization (IVF)** – An assisted reproduction technique in which fertilization is accomplished outside the body.
in vivo – In the living subject; the natural environment.
juvenile diabetes – Also known as type 1 diabetes, it is an autoimmune disease where the ß-cells in the pancreas are destroy and therefore the individual loses some or all of their ability to regulate and produce insulin. Left untreated it can have severe side effects such as kidney failure, blindness, stroke and even death.
Medical Research Council (MRC) - The national organization in the United Kingdom that promotes research in all areas of medical and related science.
National Bioethics Advisory Council (NBAC) - A committee of experts during the Clinton administration that was formed in 1995 to provide advice and make recommendation to appropriate government entities related to bioethical issues. Their charter expired in October 2001.

National Institutes of Health (NIH) – An agency of the Department of Human and Health Serves, its mission is the pursuit of knowledge about nature and behavior of living systems. It provides leadership and direction to programs designed to improve the health by conducting and supporting research: in the causes, diagnosis, prevention, and cure of human diseases; in the processes of human growth and development; in the biological effects of environmental contaminants; in the understanding of mental, addictive and physical disorders; in directing programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

nucleus – A structure within a living cell that contains the cell's DNA and controls it metabolism, growth, and reproduction.

oocytes – A female cell that develops into an ovum (egg) after meiosis; an egg before maturation.

ovum (plural is ova) – The female reproductive cell or egg.

pluripotent –The ability of a single cell to develop into many different cell types of the body.

President's Council on Bioethics (PCB) - A committee of experts during the Bush administration that was formed in 2001 (after the NBAC was disbanded) to provide the President with advice on bioethical issues that may emerge as a result of biomedical science and technology.

proliferation – Expansion of a population of cells by the continuous division of single cells into two identical cells.

quiescent – A cell that does not divide or replicate.

reproductive cloning - When an egg undergoes somatic cell nuclear transfer and the resulting cell is allowed to grow to an infant that is an exact copy of the donor.

signals – Internal and external factors that control the changes in cell structure and function.

somatic cell –Any cell of a plant or animal other than the germ (sperm or egg) or germ precursor cell.

somatic cell nuclear transfer - When the genetic material (nucleus) of an egg is removed and replaced with the genetic material of a normal cell.

stem cell - An unspecialized cell that can replicate itself for indefinite periods through cell division and under certain conditions become a specialized cell.

therapeutic cloning - When embryonic stem cells created by somatic cell nuclear transfer are studied *in vitro* and used for cell-based therapies, but never are implanted in a female or grown past 14 days.

undifferentiated cell – A primitive cell that does not have any tissue-specific structures that allows it to perform specialized functions. Not having changed to become a specialized cell.

zygote – The cell (and the organism that develops from the cell) resulting from the union of an ovum and spermatozoon (also referred to as a fertilized ovum).

Further Suggested Readings

Introduction to Stem Cells

(1) International Society for Stem Cell Research: www.isscr.org
(2) NIH, Stem Cell Basics: http://stemcells.nih.gov/info/basics/
(3) National Research Council and Institute of Medicine. (2002) Stem Cells and the Future of Regenerative Medicine. Washington D.C.: National Academy Press
(4) Embryonic Stem Cell Research at the University of Wisconsin-Madison: http://www.news.wisc.edu/packages/stemcells/facts.html#1
(5) National Parkinson Foundation: http://www.parkinson.org/site/apps/s/content.asp?c=9dJFJLPwB&b=108269&ct=153765
(6) Juvenile Diabetes Research Foundation: www.jdrf.org
(7) Hwang, W.S., et. al. (2004) Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst. Science 303:1669-74.
(8) Wilmut, I., et. al. (1997) Viable Offspring Derived from Fetal and Adult Mammalian Cells. Nature 385:810-13.

American Politics and Policies

(1) Thomas, Legislative Information on the Internet: http://thomas.loc.gov
(2) American Association for the Advancement of Science. (2003) Regulating Human Cloning. Washington D.C.: AAAS.
    a. http://www.aaas.org/spp/cstc/briefs/cloning/index.shtml
(3) Proposition 71 – Official Title and Summary by the Attorney General: http://www.ss.ca.gov/elections/bp_nov04/prop_71_entire.pdf
(4) Research!America: www.researchamerica.org
(5) Bonnicksen, A.L. (2002) Crafting a Cloning Policy, From Dolly to Stem Cells. Washington D.C.: Georgetown University Press.
(6) Thomson, J.A. et. al. (1998) Embryonic Stem Cell Lines Derived from Human Blastocysts. Science 282:1145-7.
(7) Wilmut, I., et. al. (1997) Viable Offspring Derived from Fetal and Adult Mammalian Cells. Nature 385:810-13.

State Legislation

(1) The Institute of Biotechnology & the Human Future: http://www.thehumanfuture.com/topics/humancloning/clon_policy.htm
(2) National Conference of State Legislatures: http://www.ncsl.org/programs/health/genetics/rt-shcl.htm and http://www.ncsl.org/programs/health/genetics/embfet.htm
(3) President's Council on Bioethics. (2004), *Monitoring Stem Cell Research*: http://www.bioethics.gov/reports/stemcell/index.html

World Human Cloning Policies

(1) The Database of Global Policies on Human Cloning and Germ-line Engineering: http://www.glphr.org/genetic/genetic.htm
(2) The Institute on Biotechnology and the Human Future: http://www.thehumanfuture.com/topics/humancloning/clon_policy.htm
(3) Stem Cells: http://robby.nstemp.com/photo6.html
(4) Global Lawyers and Physician for Human Rights
(5) North America: http://www.glphr.org/genetic/n_america.htm

(6) Asia: http://www.glphr.org/genetic/asia2.htm
(7) Europe: http://www.glphr.org/genetic/europe.htm
(8) New Zealand: http://www.glphr.org/genetic/oceania.htm
(9) Foreign Press Center (Japan): http://www.fpcj.jp/e/shiryo/jb/0427.html
(10) International Society for Stem Cell Research: http://www.isscr.org/scientists/legislative.htm
(11) World Health Net: http://www.worldhealth.net/p/416,1565.html
(12) Wellcome Library Bioethics Web: http://bioethicsweb.ac.uk/browse/mesh/C0027978L0027978.html

UK Stem Cell Policy

(1) The Department of Health http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/StemCell/fs/en
(2) The Wellcome Trust: http://www.wellcome.ac.uk/en/genome/geneticsandsociety/hg15b001.html
(3) HFEA: http://www.hfea.uk.gov
(4) MRC: http://www.mrc.ac.uk
(5) UK Stem Cell Bank: http://www.nibsc.ac.uk/divisions/cbi/stemcell.html

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