ONE



Information Booklet

The Science, Ethics and Regulation of Stem Cell Research

What is a stem cell and what are the different types of stem cells?

The body is made up of about 200 different kinds of specialized cells, including muscle cells, nerve cells, fat cells, skin cells. Each kind of cell has its own job and is essential for life.

A stem cell is a cell that has not yet specialized. All cells in the body are derived from stem cells. The process of cell specialization is called differentiation. Once the differentiation pathway of a stem cell has been decided, it can no longer become another type of cell.

Some stem cells have more developmental options than others. Totipotent cells have the ability to form an entire organism. Their potential is "total." A fertilized egg is totipotent, as are the very early cells resulting from the first four divisions of the fertilized egg, also called morula. See Figure 3.



Figure 1: A five-day old rabbit blastocyst. The arrow is pointing at the inner cell mass. The blastocysts are smaller than a grain of sand.



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Pluripotent stem cells have the ability to give rise to any type of cell, but not to an entire organism. This is because they lack the ability to contribute to cells of the placenta. Stem cells found in the early embryo, called embryonic

PLURIPOTENT describes the potential of a cell to form all cell types in an adult.

stem cells, are pluripotent and come from a tiny bag of 100 cells called the blastocyst. More specifically, the embryonic stem cells are obtained

from a blastocyst's inner cell mass (see Figure 2). The blastocyst is formed five days after fertilization and is a very early stage of the embryo, prior to implantation into the uterus. See Figure 3.

Embryonic germ cells are another example of a pluripotent stem cells. They are derived from cells in a fetus that eventually become the gametes (i.e., sperm or egg cells). See Figure 3.

Multipotent stem cells can become only one of a few cell types. Adult stem cells are multipotent and are found in virtually every organ in the body,

MULTIPOTENT describes the potential of a cell to form many, but not all, cells in an adult.

including the brain, skin and bone marrow. See Figure 3. However, they are rare and isolation is difficult. It appears that adult stem cells are

multipotent, but some may be pluripotent. For example, it has been suggested from experiments that cells from the bone marrow might give rise to cells in other parts of the body, including the liver and the brain. However, these results are still under investigation.

Under the right conditions, adult stem cells can divide for prolonged periods of time, producing a large number of undifferentiated stem cells, while embryonic stem cells can divide indefinitely in culture dishes. Because embryonic cells can be continuously grown and all are derived from the same blastocyst, they are often called embryonic stem cell lines. At this time, scientists are pursuing both adult and embryonic stem cell research, as both have advantages as well as technical challenges that need to be addressed.

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Figure 2: Picture of multipotent bone marrow stem cells, which are capable of turning into liver cells.

> Did you know? Embryonic germ cells can be harvested from aborted fetuses? Research on aborted fetal tissue is legal in Canada.







Medical potential of stem cells

Since stem cells can give rise to many different kinds of cells, they can be used to replace damaged cells in the body. To date, most research on the potential of stem cells, both adult and embryonic, to regenerate damaged tissue has been conducted on mice. While promising, research is still at a very early stage and more basic research is needed before stem cells can be used to treat human diseases. Here is a list of several human diseases that are, or may eventually be, treated with stem cells.

Non-Hodgkin's Lymphoma is a serious type of cancer that destroys infectionfighting white blood cells. Accounting for about 5% of all cancers, it develops in the lymphatic system — a crucial component of the body's immune system — and can spread to almost any part of the body. Already, doctors are using stem cells to treat this disease. See box.

Parkinson's Disease is a fatal disease caused by the breakdown of nerve cells in the part of the brain that produces the chemical signal dopamine. The loss of dopamine disrupts the brain's chemical balance and results in poor muscular co-ordination. Affecting about one in every 500 people, those with Parkinson's Disease eventually lose their ability to walk, talk, swallow and breathe. Stem cells may be able to replace damaged neural cells and restore proper brain chemical levels.

Type 1 Diabetes is a fatal disease that results from the destruction of pancreatic cells that produce insulin, a hormone needed to transport sugar from the blood to the cells. Type 2 diabetes occurs when the body cannot use insulin properly and its incidence is increasing rapidly due to sedentary lifestyles. Type 1 diabetes, which accounts for about five percent of all cases of diabetes, is controlled with daily insulin injections. Stem cells may one day offer a cure by providing replacement cells from the pancreas. Research is currently focused on converting adult and embryonic stem cells into appropriate cells of the pancreas for eventually treating Type 1 diabetes.



Michael J. Fox Gives \$ to Research

Michael J. Fox is one of Canada's most wellknown celebrities. Two years ago he was forced to give up his TV series Spin City because of Parkinson's Disease. Eager to speed the development of a cure for this disease, he established a foundation that gives money to promising research projects. Of the \$17 million donated so far by the Michael J. Fox Foundation, more than \$4 million has gone to embryonic stem cell research.

Stem cells treat blood cancer

Scientists have discovered multipotent blood stem cells with the ability to become different kinds of blood cells. People with non-Hodgkin's lymphoma have cancerous white blood cells. White blood cells play a central role in the immune system. Today, this type of cancer can be treated with the patient's own blood stem cells. In this treatment, doctors first use low doses of chemotherapy to induce stem cells in the body to divide and make more cells. Following this procedure, the bone marrow is removed, and the patient is given full body radiation and more chemotherapy to kill his or her cancerous white blood cells. The patient's stem cells are separated from other cells in the bone marrow, including the cancer cells in culture dishes, and then reintroduced into the patient. Typically, the stem cells find their way to the bone marrow and differentiate into healthy white blood cells.





Rick Hansen was born on August 26, 1957, in Port Alberni, B.C. As an athletic teenager growing up in Williams Lake, B.C., he loved sports and fishing. In 1973, returning home from a fishing trip, the truck in which he was riding went out of control and crashed. He was paralyzed by the accident, and the doctors told the 15-year old boy that he could never walk again.

Rick Hansen persevered through rehabilitation and returned to high school to graduate. He learned wheelchair sports and was the first student with physical disability to graduate in Physical Education from the University of British Columbia. He became an elite wheelchair athlete, winning 19 international wheelchair marathons and three world championships as well as competing for Canada at the 1984 Olympics in Los Angeles.

Rick is the president and CEO of the Rick Hansen Man in Motion Foundation and the Rick Hansen Institute, organizations that to date have contributed more than \$137 million to the field of spinal cord injury research, awareness and rehabilitation.

Other diseases that may eventually be treated by stem cells:

- Muscular Dystrophy
- Alzheimer's Disease
- Amyotrophic Lateral Sclerosis
- Multiple Sclerosis
- Stroke



Spinal Cord Injuries

The spinal cord is a bundle of nerve cells that sends signals from the brain to the rest of the body. Injuries to the spinal cord can cause paraplegia. Stem cells may be able to replace these damaged nerve cells and so restore function in different parts of the patient's body.

Heart Disease

Every hour in Canada, five people die from heart disease, the leading killer of Canadians. During a heart attack, the arteries are blocked and blood supply to the heart is interrupted. As a result, heart muscle cells rapidly die. Other cells near the area of damage (known in medical terms as infarct) grow and expand to compensate for those dying muscle cells, but at other times the heart attack is so severe that the amount of heart muscle mass that is destroyed is immediately life threatening. Recent discoveries of stem cell-like cells in the heart have triggered intense interest. It maybe possible to grow "patches" of these cells to repair hearts damaged by disease or heart attacks. Research is currently ongoing to investigate the potential of these heart stem cells.

Blindness

There are different types of eye diseases that can lead to partial or total blindness. Retinitis Pigmentosa is caused by loss of photoreceptor cells in the retina. The photoreceptor cells are responsible for capturing and processing light. Macular Degeneration is caused when photoreceptor cells in another area of the retina called the macula die. The macula is responsible for fine visual detail. Canadian scientists at the University of Toronto have recently discovered that it may be possible to turn stem cells in the retina into photoreceptor cells to replace ones lost in diseases such as these. Research is currently ongoing to explore the potential of these retinal stem cells.

Cancer

Any of more than 100 diseases characterized by excessive, uncontrolled growth of abnormal cells, which invade and destroy other tissues, cancer can develop in almost any organ or tissue of the body (i.e., the lining of the stomach, blood, cells of the skin, etc.). Typically cells divide in a very regulated man-

ner. There is a control system that ensures that cells only divide when needed, so that they are not in excess and do not disrupt the normal balance of the body. Sometimes, this control system fails, in which case backup safety mechanisms take over. In order for a cell to become cancerous, both the control and the backup safety mechanisms must fail. There are different types of treatments for cancer (surgery, radiation therapy, chemotherapy), which typically rely on removing or killing off the cancerous cells. Often, the cancer recurs. There is now new evidence to show that stem cell-like cells within the tumor masses may be responsible for causing the uncontrolled growth.

Canadian Researchers at the University of Alberta developed The Edmonton Protocol, which established a set of procedures for transplanting islet cells (type of cells in pancreas), which can restore normal insulin production in people <u>with Type 1</u> diabetes.

Did you know?

This means that for cancer therapies to work, the treatments need defining. Currently research is focusing on identifying these stem cell-like cells in tumors.



Sources of embryonic stem cells

Embryonic stem cells are derived from the inner cell mass of blastocysts (a stage in the development of an embryo before it implants into the uterus). Embryonic stem cells may be derived from embryos created for reproductive purposes or for research purposes. In either case, the potential for the embryo to develop into a full organism is destroyed while deriving the embryonic stem cells. On the other hand, adult stem cells can be obtained from different tissues in the adult body, although this is often very difficult as there are very few adult stem cells in the adult. For example, blood stem cells can be obtained from the bone marrow, brain stem cells from the brain, retinal stem cells from the eye, muscle stem cells from muscle, etc. Obtaining adult stem cells generates less debate than obtaining embryonic stem cells, because it does not involve contentious issues linked to the debate about embryos.

So far, there are four different sources of embryonic stem cells:

1. Existing embryonic stem cell lines

An embryonic stem cell line is a culture of continually dividing embryonic stem cells, all of which are derived from one blastocyst. The cells retain their ability to become any type of cell. As of April 2003, there were approximately 11 existing embryonic stem cell lines approved by the National Institutes of Health (NIH) in the U.S. There are other embryonic stem cell lines in existence, which are not listed by the NIH. All these existing embryonic stem cell lines were derived from excess IVF embryos created for reproduction. This source of embryonic stem cells currently seems to be the least controversial, as the embryonic stem cells already exist and no further embryos need to be destroyed. However, it is not clear if these embryonic stem cell lines can be used in therapies to treat humans, as they have all been grown in culture in the presence of animal cells or animal products.

2. Excess in vitro fertilization embryos

In vitro fertilization (IVF) is a method of assisted reproduction used by those having difficulty conceiving a child. IVF is expensive, and the success rate for delivering a baby is only about 30%. In the laboratory, scientists fertilize an egg with a sperm and then implant the resulting embryo in a woman's uterus where it grows into a baby. Not all of the embryos created through IVF are used for implantation. These excess embryos are normally discarded or frozen for later use. Some of these excess embryos can be donated for research after informed consent and can be used to derive embryonic stem cells.

3. Embryos created by IVF for research

Scientists could create embryos through IVF for the specific purpose of deriving embryonic stem cells. Many who are in agreement with the derivation of embryonic stem cells from excess IVF embryos once intended for pregnancy do not support the creation of embryos solely for research. The current version of the Canadian legislation bans the creation of embryos by IVF treatments solely for research purposes. Immune response: a barrier to embryonic stem cell therapy

The human body possesses a powerful immune system that recognizes and attacks foreign invaders. Bacteria, viruses, even blood and organs from other humans don't stand a chance — the immune system kills and removes these foreign substances. Unfortunately, embryonic stem cells are no different. They too will be attacked by the immune system of the patient, unless the embryonic stem cells come from the patient's own body. But how is it possible to collect embryonic stem cells from a person who has already grown up? Normally these cells are harvested from an embryo. Therapeutic cloning offers one possible solution by creating embryonic cells that are genetically identical to the patient.





Figure 4: A scientist removes the the nucleus of an egg (little needle). The big needle (shown on the left) is used to hold the egg in place by suction.

Did you know?

In 1997, scientists in Scotland created Dolly, the first animal cloned from a cell taken from an adult animal. Since then, several other animals have been cloned, including mice, pigs and a cat. Some of the clones have experienced medical problems. For instance, Dolly had developed a premature case of arthritis, and the cloned mice died young. Dolly was put down in February 2003 after developing a progressive lung disease. Most sheep live to be 11 or 12 years old. Dolly was only six years old when she died.



Somatic Cell Nuclear Transfer

1) Therapeutic Cloning

Scientists could harvest pluripotent embryonic stem cells from an adult using a process known as somatic cell nuclear transfer (see Figure 5). In somatic cell nuclear transfer, the nucleus of an adult's somatic (body) cell is fused with an egg that has had its own nucleus removed (see Figure 4). The egg then behaves like a reconstructed embryo. All the cells that arise from this embryo are genetically identical (i.e., a clone) to the original adult somatic cell. This is a very difficult procedure, and the chances of generating a reconstructed embryo are approximately 1in 100, in animal studies. Embryonic stem cells may be derived from the inner cell mass of these reconstructed embryos. The embryonic stem cells made by this therapeutic cloning procedure are genetically identical to the adult cell and can thus be used to treat that adult without generating an immune response (see box). Therapeutic cloning can also be used to generate embryonic stem cells from humans with specific diseases in order to study that disease. This is useful as existing embryonic stem cell lines made from discarded IVF embryos do not typically carry the genetic mutations that would be useful for studying various human diseases.

2) Reproductive Cloning

animals, this procedure also has a very low efficiency of

working successfully.

The purpose of reproductive cloning is to make new animals. This process has applications in farm animal reproduction, producing human proteins, creating animals, such as pigs, whose organs may be made more compatible with humans for transplanting into human patients, etc. Both therapeutic and reproductive cloning involve the creation of an embryo using somatic cell nuclear transfer. The embryo is genetically identical to the adult donor of the somatic cell. But thereafter, the processes diverge. The purpose of therapeutic cloning is to collect embryonic stem cells that can be used for medical treatment. Unlike reproductive cloning, the embryo is not implanted into a uterus and is used instead to derive embryonic stem cells.



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The Ethical Debate

Most of the controversy surrounding embryonic stem cells has to do with the moral status of the embryo. Does a human embryo have the same rights as a baby? Those who think that it does are generally opposed to embryonic stem cell research. They see the destruction of a human embryo as murder. Moreover, embryonic stem cell research may not be necessary. Adult stem cells, which can be harvested without destroying embryos, may hold as much medical promise as embryonic stem cells, although considerable research is required to determine the relative merits of embryonic stem vs. adult stem cells for different types of diseases.



"SHI'L FERNED TO THEM COLL REPLACE. RACK YOUR HAVOL."

However, the debate doesn't end there. People who

are willing to move ahead with embryonic stem cell research are still confronted with other issues. One of these is the commodification, or selling, of human embryos, eggs and sperm. Embryonic stem cell research creates a need for human cells, and one of the ways to fulfill this need is by offering people money for their cells. Many believe that this devalues human life by assigning it a price. Donor consent and the link between therapeutic and reproductive cloning are also concerns associated with embryonic stem cell research.

The cartoons on pages nine to 15 to illustrate these issues. Try to identify which opinion the artist is expressing. Is he or she opposed to all embryonic stem cell research? To some forms of embryonic stem cell research? Why?



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Embryonic stem cell legislation



The following table summarizes existing or proposed embryonic stem cell legislation or guidelines from a variety of countries as of July 2002. The countries are listed according to how permissive they are, with the most permissive country appearing first. Additional notes are provided at the end of the table.

Legislation in the United Kingdom is considered very permissive, as it was the first to allow for the creation of embryos solely for research. The embryos can be generated through therapeutic cloning or IVF. However, propos-

als for therapeutic cloning must be approved by the government's Human Fertilization and Embryology Authority.

Country	Therapeutic cloning	Embryos created for research	Excess embryos from IVF clinics	Existing ES cell lines
UK	1	1	1	1
Japan	1	1	1	1
Israel	1	✓	1	✓
Sweden	?	✓	1	✓
USA	?	1	\checkmark	✓
Canada	×	×	\checkmark	\checkmark
Australia	×	×	\checkmark	\checkmark
Germany	×	X	×	\checkmark
France	×	×	×	?

Japan is quite lenient as well. Legislation was created by a subcommittee of the Japanese government. Rather than being authorized by one regulatory body, stem cell and embryo research proposals must be approved by an expert panel consisting of government members and researchers.



In Israel, guidelines allowing embryo creation (through therapeutic cloning and IVF) have been approved by a national bioethics committee. Although these regulations are not criminally enforceable, it is expected that institutions seeking federal funding will follow them.

Sweden is the country with the greatest number of existing stem cell lines eligible for American federal funding. Opposition to stem cell research has been much quieter in Sweden than North America. Large Swedish companies are investing in this new field of biotechnology. On the issue of therapeutic cloning, the Swedish Research Council disapproves, but says it could be "ethically defensible."

In the United States, federal funds for embryonic stem cell research are only available for stem cell lines created before August 9, 2001. These stem cell lines must have been derived from excess IVF embryos. Nonetheless, regulation is far less restrictive in the private sector — there are no regulations! A law to ban all forms of cloning is currently being debated.

Canada has voluntary guidelines established by the Canadian Institutes of Health Research (CIHR). These guidelines apply to all federally funded research. National legislation, which is very similar to the guidelines but would apply to all research, is in the works and is explored later in the module.

Similar to Canada, Australia's guidelines are on their way to becoming

law. Licensed research on discarded IVF embryos is allowed, and in 2001, a parliamentary committee sought a three-year moratorium on therapeutic cloning.

Germany has one of Europe's most restrictive embryonic stem cell research policies. In January 2002, the German parliament took a major step in deciding to allow the strictly licensed import of stem cell lines into the country. The imported stem cells must have been created prior to 2002.

France's regulations are similarly prohibitive. Embryonic stem cell research is currently banned. The Assembly of the French parliament has been considering research on existing stem cell lines.







USEFUL Science WEB SITES

www.stemcellnetwork.ca

The best and most comprehensive Web site on stem cell science, news, events, policy and research in Canada. Frequently Asked Questions for students on science of stem cells.

http://www.stemcells.ca

A very good Canadian site on the ethics, science and regulation of stem cell research, including links to some other very good sites and articles.

http://www.nap.edu/books/0309076307/html/

An excellent and accessible review of the field has been produced by the U.S. National Academy of Sciences, entitled Stem Cells and the Future of Regenerative Medicine.

http://www.nih.gov/news/stemcell/primer.htm

National Institutes of Health (US) Stem Cell Primer. Similar to the Student Resource Booklet for this teaching resource.

http://www.nih.gov/news/stemcell/index.htm

National Institutes of Health (US) Stem Cell Information.

http://www.nih.gov/news/stemcell/scireport.htm

Stem Cells: Scientific Progress and Future Research Directions contains extensive information into the science of stem cells.

In the news

www.stemcellnetwork.ca

The best and most comprehensive website on stem cell science, news, events, policy and research in Canada.

http://www.stemcellnetwork.ca/main.en.asp

News about stem cells, plus information about stem cell science and Canadian legislation.

http://www.stemcellresearch.org/news.htm

Site containing links to all recent articles (from July 1999 to as recent as the previous day)

http://www.stemcellresearchnews.com/

Stem Cell Research News. Site of newslinks.

http://www.newscientist.com/hottopics/cloning/

Recent news on stem cell research, cloning. Site of newslinks.



Legislation

www.stemgen.org

Comprehensive database on the legal, social and ethical aspects of stem cell research. Frequently Asked Questions for students on ethics and policy related to stem cells.

www.stemcellnetwork.ca

The best and most comprehensive website on stem cell science, news, events, policy and research in Canada.

http://www.hc-

sc.gc.ca/english/protection/reproduction/ Link to read Bill C-13.

http://www.hc-sc.gc.ca/english/media/releases/2002/2002_34bk7.htm Health Canada: The International Scene.

http://www.hhmi.org/bulletin/mar2002/stemcells/global.html

Howard Hughes Medical Institute: Are Stem Cells the Answer? A Global Struggle to Deal with Human Embryonic Stem Cells. A country-by-country approach to the debate.

http://www.parl.gc.ca/

Access Canada's draft legislation about stem cells by typing "stem cells" in the search engine.





GLOSSARY

ADULT STEM CELL

An undifferentiated cell found in tissues of the adult body. Adult stem cells can make copies of themselves or specialize.

AMYOTROPHIC LATERAL SCLEROSIS

(also known as Lou Gehrig's Disease) A rapidly progressive fatal disease involving the degeneration of nerve cells and muscle paralysis. Stem cell research may provide new treatments for this and other diseases.

ALZHEIMER'S DISEASE

A degenerative brain disease, which begins with memory loss and progressing to dementia. Stem cell research may provide new treatments for this and other diseases.

BLASTOCYST

A hollow sphere made up of an outer layer of cells and the inner cell mass, a cluster of embryonic stem cells. A blastocyst exists five days after fertilization before implantation. In humans it is the size of a sand grain and is made up of roughly 100 cells.

CELL LINE

A group of cells that come from a common ancestor cell and that can be grown and maintained in culture indefinitely.

CLONING

The process of creating a cell that is genetically identical to another cell through somatic cell nuclear transfer. There are two types of cloning: therapeutic cloning and reproductive cloning (see definitions that follow).

DIABETES

A disease that occurs when the body does not properly produce or use insulin, a hormone that converts food to energy. Diabetes is classified as either Type 1 or the more common Type 2. Researchers are hopeful that stem cells may be able to treat Type 1 Diabetes.

DIFFERENTIATION

The process by which stem cells specialize into a certain type of cell.

NUCLEUS

The programming center of a cell that contains all the genetic information.

EMBRYO

A very early stage in development.

EMBRYONIC GERM CELLS

Pluripotent cells found in the cells of a fetus that eventually become the gametes (egg or sperm).

EMBRYONIC STEM CELLS

Cells taken from a blastocyst's inner cell mass which have the ability to specialize or differentiate into virtually any of the body's tissues.

FETUS

A developing organism from the end of the embryonic stage to birth.

GAMETES

Cells involved in reproduction. The male gamete is called a sperm and the female gamete is called an ovum (egg).

IMMUNE RESPONSE

A bodily response to foreign "invaders" that involves the formation of antibodies and other factors to protect the body.

INNER CELL MASS

A cluster of embryonic stem cells in a blastocyst.

IN VITRO FERTILIZATION (IVF)

The fertilization of an egg by a sperm outside of a woman's body. In vitro is Latin for in glass.

MULTIPOTENT

Having the ability to give rise to a limited number of different cell types.

NON-HODGKIN'S LYMPHOMA

A cancer of the lymphatic system that is sometimes treated with adult stem cells.

NUCLEUS

The part of a cell that contains the genetic material (DNA).

PARKINSON'S DISEASE

A progressive disease of the nervous system characterized by muscle tremors and weakness. Researchers hope to use stem cells to find a cure or treatment for this debilitating disease.

PLASTICITY

The degree to which stem cells can differentiate into different cell types.

PLURIPOTENT

Having the capability of forming all types of cells in the body, but not tissues like the placenta needed to support a fetus. Pluripotent stem cells can therefore not give rise to an entire fetus.

REPRODUCTIVE CLONING

The transformation of a somatic cell into an embryo by somatic cell nuclear transfer. The embryo is then transplanted into a woman's uterus where it develops into an infant.

SOMATIC CELL

A cell that is neither an egg nor a sperm

SOMATIC CELL NUCLEAR TRANSFER

The process by which a somatic cell is transformed into an embryo. Somatic cell nuclear transfer involves fusing a somatic cell with an unfertilized egg that has had its nucleus removed.





STEM CELL

A cell that has the potential to give rise to specialized cells, and that has the ability to divide and make copies of itself.

THERAPEUTIC CLONING

The process by which an adult cell nucleus is fused with an ennucleated egg to form a reconstructed embryo. The reconstructed embryo is used as a source of embryonic stem cells.

TOTIPOTENT

Having the ability to give rise to an entire ortganism.

TUMOUR

A mass of tissue with no physiological function. Tumours can be benign (non-cancerous) or malignant (cancerous).

Zygote

A fertilized egg created by the union of sperm and egg.





