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CRC

Proposal 2008-02
Human Embryonic Stem Cell Research

October 2008

Report 353

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CITIZENS RESEARCH COUNCIL OF MICHIGAN

PROPOSAL 2008-02
HUMAN EMBRYONIC STEM CELL RESEARCH

OCTOBER 2008

REPORT 353

CITIZENS RESEARCH COUNCIL OF MICHIGAN

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CONTENTS

I. Stem Cell Research in Michigan 1
A. Michigan Law 1
B. Federal Policy 1
C. Proposal 2008-02: Human Embryonic Stem Cell Research 1

II. Regenerative Medicine 3
A. Stem Cell Basics 3
B. Why Embryonic Stem Cell Research? 8

III. Other States' Policies on Embryonic Stem Cell Research 11
A. States Funding Human Embryonic Stem Cell Research 11

IV. Issues Raised by Human Embryonic Stem Cell Research 13
A. Bioethics 13
B. Life Sciences Business Sector 14
C. Embryonic Stem Cells Are Not Currently Used in Therapies 15

V. Michigan Impact 16

FIGURES

1. Stem Cell Research Timeline 5
2. Human Blastocyst 6
3. Comparison of Different Kinds of Stem Cells 8
4. State Laws on Human Embryonic Stem Cell Research 11

Proposal 2008-02: Human Embryonic Stem Cell Research

On November 4, 2008, Michigan electors will vote on a citizen initiated proposal to amend the State Constitution to allow for research on human embryos and the creation of new embryonic stem cell lines in the State of Michigan.

Stem Cell Research in Michigan

This analysis includes a glossary of scientific terms on page 4 to help readers better understand **stem cell** research. Terms that are included in the glossary are highlighted in **bold** throughout the paper.

Michigan Law

The State of Michigan currently has some of the most restrictive laws in the nation respecting human **embryonic stem cell** research. It is illegal for researchers to conduct non-therapeutic research that jeopardizes the life or health of a human **embryo**, **fetus**, or neonate. Non-therapeutic research is defined as scientific research that is not designed to improve the health of the research subject.[1] This definition encompasses research on embryos to derive human **embryonic stem cell lines**. Michigan law also prohibits the **cloning** of a human embryo for both reproductive and research purposes.[2] Violating Michigan law prohibiting research on a human embryo is a felony with punishment of up to five years in prison.[3] Violating Michigan's law against human cloning is also a felony punishable by up to 10 years in prison and a $10 million fine.[4]

Michigan law effectively prohibits researchers from creating new human embryonic stem cell lines in the state, but it does not keep scientists from conducting research using embryonic stem cell lines created outside of the state. Michigan researchers may also study **adult stem cells** because that work does not involve the destruction of human embryos.

Federal Policy

Research on human embryos and embryonic stem cells is not restricted by federal law; however President Bush's policy restricts federal funding to research on human embryonic stem cell lines created prior to August 9, 2001 (the date that President Bush announced this policy).[5] This funding policy was viewed by the administration as a compromise because it provided funding for research on embryonic stem cell lines already in existence while limiting future research on human embryos and the creation of new embryonic stem cell lines. Additionally, federally funded stem cell research must be conducted on stem cell lines derived from embryos that were created for reproductive purposes but no longer needed and donated with the informed consent of the donors without any financial inducements. Embryonic stem cell research conducted with federal funding is regulated by the National Institutes of Health (NIH), which is the federal government's leading biomedical research facility.

Federal regulations do not restrict embryonic stem cell research using state or private funds. While this may not seem to place very stringent limits on embryonic stem cell research, federal funding is very important to scientific research and provides support for many researchers. According to the Life Sciences Institute at the University of Michigan, federally funded research is preferable in many instances because it ensures that the research and results adhere to the highest ethical standards because they are subject to federal oversight, rules, and regulations.[6]

Proposal 2008-02: Human Embryonic Stem Cell Research

If passed, this proposal would amend the Michigan Constitution to allow for research on human embryos in Michigan. This research would allow for new embryonic stem cell lines to be created in the state. Research on human embryos in Michigan would be subject to federal regulations and restricted to embryos that were created for the purpose of fertility treatment, but are scheduled to be discarded because they were either 1) left over after fertility treatment and no longer needed by the donor or 2) unsuitable for implantation into a woman's uterus. Embryos could be donated only with the informed, written consent of the donor(s). The following stipulations would apply to human embryonic stem cell research:

Proposed Constitutional Amendment

If Proposal 2008-02 passes, the following language will be inserted into the Michigan Constitution as Article I, Section 27:

1) Nothing in this section shall alter Michigan's current prohibition on human cloning.

2) To ensure that Michigan citizens have access to stem cell therapies and cures, and to ensure that physicians and researchers can conduct the most promising forms of medical research in this state, and that all such research is conducted safely and ethically, any research permitted under federal law on human embryos may be conducted in Michigan, subject to the requirements of federal law and only the following additional limitations and requirements:

    a. No stem cells may be taken from a human embryo more than fourteen days after cell division begins; provided, however, that time during which an embryo is frozen does not count against this fourteen day limit.

    b. The human embryos were created for the purpose of fertility treatment and, with voluntary and informed consent, documented in writing, the person seeking fertility treatment chose to donate the embryos for research; and

        i. the embryos were in excess of the clinical need of the person seeking the fertility treatment and would otherwise be discarded unless they are used for research; or

        ii. the embryos were not suitable for implantation and would otherwise be discarded unless they are used for research.

    c. No person may, for valuable consideration, purchase or sell human embryos for stem cell research or stem cell therapies and cures.

    d. All stem cell research and all stem cell therapies and cures must be conducted and provided in accordance with state and local laws of general applicability, including but not limited to laws concerning scientific and medical practices and patient safety and privacy, to the extent that any such laws do not:

        i. prevent, restrict, obstruct, or discourage any stem cell research or stem cell therapies and cures that are permitted by the provisions of this section; or

        ii. create disincentives for any person to engage in or otherwise associate with such research or therapies or cures.

3) Any provision of this section held unconstitutional shall be severable from the remaining portions of this section.

1) No cells would be taken from an embryo more than 14 days old (this time limit is suspended while embryos are frozen). Most embryonic stem cells are derived from three- to five-day-old **blastocysts**.

2) It would be against the law to purchase or sell human embryos for stem cell research purposes.

3) All research would be required to be conducted in accordance with applicable state and local laws provided that these laws do not prevent, discourage, or create disincentives for permissible stem cell research. This section prevents the State or local governments from creating laws to restrict embryonic stem cell research beyond the restrictions listed in the proposed constitutional amendment and detailed here. This provides unique constitutional protection to stem cell research. It is unclear how far-reaching this section would be: "discourage" is a subjective term and laws to regulate the research may be construed as discouraging it. How broadly this section of the proposal would be interpreted would depend on the courts.

If passed, research on human embryos mainly would be regulated by the federal government. This would not make Michigan unusual; many states leave it to the federal government to regulate the research. Current federal regulations are limited to funding, but the policy could change with the next president.

The proposal would not change Michigan's current ban on the cloning of human embryos. Michigan's ban prohibits cloning embryos for reproductive purposes, which involves implanting a cloned embryo into a woman's uterus, as well as for therapeutic or research purposes. The proposed language in section 27(1) states that "nothing…shall alter Michigan's current prohibition on human cloning." This language does nothing to strengthen Michigan's law against human cloning because it does not put the actual ban into the Michigan Constitution. However, it also does not weaken or change Michigan's current law prohibiting human cloning and does not condition the nature of future legislation.

Regenerative Medicine

Regenerative medicine[7] is a scientific and medical discipline that is focused on utilizing the body's own regenerative capabilities to repair or replace diseased or defective tissues and organs in the human body and to find new therapies for diseases and conditions that currently have limited or no treatment options (e.g., Parkinson's disease and paralysis). The goal of regenerative medicine is to restore function to damaged cells, tissues, and organs through a better understanding of:

1) Stem cells and their ability to develop into specialized cells and tissues.

2) Tissue engineering and scientists' ability to construct tissues, and potentially organs, on matrices made of biological materials in order to test therapies for safety and effectiveness before testing them in animals and humans.

3) The ability of organs and tissues to repair themselves.

Stem Cell Basics

The human body consists of over 200 different types of cells and all of these cells originate from stem cells found in the early embryo. While nearly all of the cells in the human body contain the complete set of genes necessary to build and maintain a human being, as an embryo develops and its cells specialize, they turn off genes that they no longer need. Stem cells have three general properties:

1) They are capable of long-term self-renewal. A starting population of embryonic stem cells that proliferates for many months in a laboratory can yield millions of cells through cell division. This makes stem cells unique because most other cells, such as specialized muscle or blood cells, have little or no capacity to replicate themselves.

2) They are unspecialized cells meaning that they do not have tissue-specific structures that allow them to perform specific functions. An example of a specialized cell is a red blood cell, which works

Stem Cell Research: A Constitutional Issue?

Proposal 2008-02 would amend the Michigan Constitution to allow for research on human embryos and to lessen the restrictions on human embryonic stem cell research. There is no compelling argument that this is fundamentally a constitutional issue. Michigan's current ban on research that destroys a human embryo is statutory, not constitutional. Of nine states that have laws permitting the research, only two (California and Missouri) have a constitutional provision allowing for embryonic stem cell research; the remaining seven states have statutory provisions.

An argument for a constitutional amendment, rather than a statutory initiative, is to prevent the legislature from thwarting the will of the people by repealing or amending the proposal after passage. However, a statutory initiative in Michigan is not subject to a gubernatorial veto and requires the approval of three-fourths of both houses of the legislature to be amended or repealed.

Glossary of Scientific Terms[1]

Adult Stem Cell: An undifferentiated cell found in a differentiated tissue that can renew itself and differentiate (with certain limitations) to give rise to all the specialized cell types of the tissue from which it originated.

Blastocyst: A pre-implantation embryo of about 150 cells produced by cell division following fertilization. The blastocyst is a sphere made up of an outer layer of cells (the trophoblast), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

Cell Culture: Growth of cells *in vitro* in an artificial medium for experimental research.

Clone: Generate identical copies of a molecule, cell or organism. There are many types of cloning, including therapeutic and reproductive cloning. Therapeutic cloning involves combining a patient's somatic cell nucleus and an enucleated egg to harvest embryonic stem cells from the cloned embryo. Reproductive cloning refers to the production of an animal by nuclear transfer.

Differentiation: The process whereby an undifferentiated embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell.

Embryo: In humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it is called a fetus.

Embryonic Stem Cell: Pluripotent (undifferentiated) cells derived from a 5-day-old pre-implantation embryo that have the potential to become all cells in the body.

Embryonic Stem Cell Lines: Embryonic stem cells that have been cultured under *in vitro* conditions to allow proliferation without differentiation for months to years.

Fetus: A developing human from approximately eight weeks after conception until the time of its birth.

Gene: A functional unit of heredity that is a segment of DNA found on chromosomes in the nucleus of a cell. Genes direct the formation of an enzyme or other protein.

Hematopoietic Stem Cell: A stem cell that gives rise to all red and white blood cells and platelets.

***In Vitro* Fertilization:** A technique that unites the egg and sperm in a laboratory, instead of inside the female body.

Induced Pluripotent Stem Cell: Adult cells reprogrammed to an embryonic stem cell–like state by being forced to express gene products important for maintaining the pluripotency of embryonic stem cells.

Microenvironment: The molecules and compounds, such as nutrients and growth factors in the fluid surrounding a cell in an organism or in the laboratory, which play an important role in determining the characteristics of the cell.

Morula: A pre-implantation embryo of about 16 to 30 cells produced by cell division following fertilization. The developmental stage prior to the blastocyst.[2]

Multipotent: Ability of a single stem cell to develop into more than one cell type of the body.

Plasticity: The ability of one cell type to form other cell types.

Pluripotent: Ability of a single stem cell to give rise to all of the various cell types that make up the body.

Regenerative Medicine: A treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues.

Somatic Cell: Any body cell other than gametes (egg or sperm).

Stem Cell: Cells with the ability to self-renew and give rise to specialized cells.

Teratoma: A multi-layered benign tumor.

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[1] In *Stem Cell Information* (World Wide Website). Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2008 (cited 20.Aug.08). Available at stemcells.nih.gov/info/glossary.

[2] The National Academies. *Understanding Stem Cells: An Overview of the Science and Issues from the National Academies*. Available at dels.nas.edu/dels/rpt_briefs/Understanding_Stem_Cells.pdf (cited 15.Sep.08).

with other red blood cells to carry molecules of oxygen through the blood stream.

3) They can be induced to become cells with special functions, such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas, through a process called **differentiation**.

It is believed that stem cells may be the basis for treating many diseases and conditions in the future, but scientists do not yet completely understand their function and essential properties. Current stem cell research is aimed at understanding the factors in living organisms that normally regulate cell proliferation and self-renewal; determining how stem cells remain unspecialized for many years; and identifying the signals, from both inside and outside of cells, that cause stem cells to become specialized cells. Internal signals are controlled by a cell's **genes**. External signals include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in a cell's **microenvironment**.

Figure 1
Stem Cell Research Timeline

1956:	First successful bone marrow transplant between a related donor and recipient
1973:	First successful bone marrow transplant between an unrelated donor and recipient
1981:	Embryonic stem cells isolated from mouse blastocysts
1988:	Blood stem cells from adult mice are purified and characterized
1992:	Stem cells are identified in the adult human brain
1998:	Researchers at the University of Wisconsin-Madison isolate the first human embryonic stem cells in a laboratory
2002:	Pancreatic cells derived from mouse embryonic stem cells cure diabetes in mice
2004:	The type of nerve cell lost in Parkinson's disease is produced from human embryonic stem cells
2005:	Human embryonic stem cells shown to differentiate into active functioning nerve cells when placed in mouse brains*
2006:	Embryonic stem cells first grown without animal products in the culture*
	Researchers in Japan (Kyoto University) and the U.S. (Massachusetts Institute of Technology, Harvard University, and the University of California) modify mouse skin cells so that they behave like embryonic stem cells (creating mouse iPS cells)*
2007:	Researchers at Kyoto University, the University of Wisconsin, and the Massachusetts Institute of Technology modify human skin cells so that they behave like embryonic stem cells (creating human iPS cells)*
2008:	Scientists at Harvard reprogram adult cells' function in mice*

*Results of these experiments must be consistently replicated by other researchers before they become generally accepted by the scientific community.

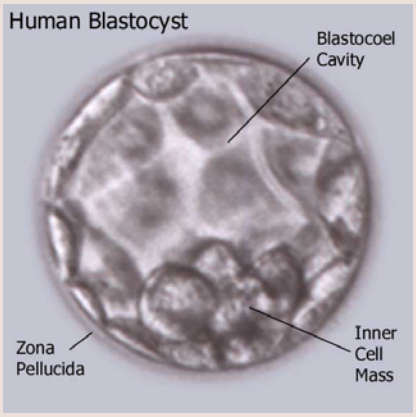
Sources: Timeline for Bone Marrow Transplants. In *Biotechnology Learning Hub* (World Wide Website), 2007 (cited 25.Sep.08). Available at www.biotechlearn.org.nz/themes/biotech_therapies/timeline_for_bone_marrow_transplants; The National Academies, *Understanding Stem Cells: An Overview of the Science and Issues From the National Academies*, Pp. 16-17; Siegel, Bernard (Genetics Policy Institute). "The Rise of the Pro-Cures Movement," *Burrill Stem Cell Report*, October 2007, Pp. 24-30; Stein, Rob. "Scientists Reprogram Adult Cells' Function." *Washingtonpost.com*, 28.Aug.08.

Because it is impossible to know where the next medical breakthrough will come from, research is currently being conducted on embryonic and adult stem cells. The National Academies[8] issued ethical guidelines for stem cell research and the advisory committee[9] notes that research on all stem cell types will likely prove useful for regenerative medicine. The guidelines offer a common set of ethical standards in an area that is without national standards due to the lack of comprehensive federal funding and federal oversight of stem cell research. The guidelines regulate the donation and use of embryos in research (e.g., donors should not be paid for eggs or embryos) and prohibit reproductive cloning, among other things.[10] These guidelines, while adopted by many researchers voluntarily, are not legally binding. However, many institutions conducting this research require researchers to follow these or similar guidelines issued by the National Institutes of Health and the U.S. Department of Health and Human Services.

Embryonic Stem Cells. Embryonic stem cells are derived from a blastocyst, which is a three- to five-day-old pre-implantation human embryo (see **Figure 2**). The term embryo can be used to refer to all stages of development from fertilization to when the embryo becomes a fetus. Blastocyst refers to a more precise phase of development. It is a hollow, microscopic ball of cells that is smaller than the period at the end of this sentence, but it contains all the material necessary to develop into a complete human being if implanted into a uterus. Human embryonic stem cells are isolated by transferring the inner cell mass, a group of approximately 30 cells in the blastocyst, into a plastic laboratory culture dish with a nutrient-rich liquid and allowing the cells to proliferate over the course of several months. At the end of six months, the original 30 cells of the inner cell mass may yield millions of embryonic stem cells.

Embryonic stem cells are **pluripotent**, which means that they are capable of generating all cells in the human body under the right conditions (they cannot, however, make a new embryo or fetus because they lack the ability to make extra-embryonic tissues, such as the placenta). This makes embryonic stem cells more flexible than adult stem cells, which are partially specialized. They are also easier to collect and maintain than adult stem cells. As long as embryonic stem cells are grown in culture under the right conditions, they remain unspecialized; however, if they are allowed to clump together, they begin to differentiate into specialized cells spontaneously. Scientists are working to better understand stem cell differentiation because they need to be able to control differentiation before stem cells would be useful in therapies. Undifferentiated stem cells could not be used directly for therapies because they can cause a type of benign tumor called a **teratoma** if transplanted into a patient; once cells differentiate and become specialized, they do not form tumors.

Figure 2
Human Blastocyst



Source: Molecular Biology Photo Gallery. In *Molecular Station* (World Wide Website), 2007 (cited 23.Sep.08). Available at www.molecularstation.com/molecular-biology-images/504-cell-biology-pictures/28-human-blastocyst.html.

Scientists continue to work with existing embryonic stem cell lines, but also create new stem cell lines due to the challenges associated with maintaining cell lines over time, which include the fact that they can accumulate harmful genetic mutations. Embryonic stem cells are derived from human embryos that were fertilized *in vitro* and then donated for research with the informed consent of the donors. These embryos were not created for research purposes, but are the "left over" embryos of patients using ***in vitro* fertilization** (IVF) to conceive. IVF involves a surgical procedure to retrieve a woman's eggs after she has undergone an

intense regimen of fertility drugs to induce her ovaries to produce multiple mature eggs. Doctors typically fertilize all the donated eggs in order to maximize the chance of producing viable embryos to be implanted in the womb. In normal development, a blastocyst would implant in a woman's uterus and would develop into a mature organism with its outer cells forming the placenta and the cells of the inner cell mass becoming the more specialized cell types of the body. Since not all fertilized eggs are implanted, there is a large excess of embryos stored in freezers in IVF clinics around the country. With the informed consent of the donors, these embryos can be used to derive embryonic stem cell lines. Embryonic stem cells can only be derived from pre-implantation embryos, prior to the specialization of their cells and the formation of organs.

Adult Stem Cells. Adult stem cells (sometimes referred to as somatic stem cells) are undifferentiated cells that are found among differentiated cells in a tissue or organ. They include cells derived at all stages of human development from fetal development to adulthood. Even though adult stem cells are undifferentiated, they are more specialized than embryonic stem cells and they have generally turned off the genes required to make cells from tissue types other than their tissue of origin. This makes them **multipotent**, meaning that adult stem cells can renew themselves and differentiate to yield the major specialized cell types of the tissue or organ that they reside in. While they can renew themselves, they have a more limited capacity for replication than embryonic stem cells. Their primary role in a living organism is to maintain and repair the tissue in which they are found. They are believed to reside in a specific area of each tissue where they divide infrequently until they are activated by disease or injury. They may contain more DNA abnormalities than embryonic stem cells, which can be caused by sunlight, toxins, and errors in making more DNA copies during the course of a lifetime.

Adult stem cells are difficult to identify because their origin is unknown; they are inconspicuous in size, shape, and function; and each tissue contains only a very small number of stem cells. However, scientists have recently found adult stem cells in many more tissues than they once thought possible, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, and liver. Scientists believe that there may be many more types of adult stem cells that have yet to be found and isolated.

Research on adult stem cells began in the 1950s when scientists discovered stem cells in bone marrow. Scientists have been using **hematopoietic (blood) stem cells** for decades to treat patients with diseases such as leukemia, sickle cell anemia, bone marrow damage, some metabolic disorders, and immunodeficiencies. Hematopoietic stem cells can differentiate to become any blood cell type and further research is needed to determine if they can produce other cell types as well. Doctors have also been using skin stem cells to treat victims of severe burns with skin transplants. Scientists can now grow sheets of skin by culturing the stem cells from small pieces of healthy skin. Research continues on ways to identify new adult stem cells, grow adult stem cells in **cell culture**, maintain adult stem cells in the laboratory, and manipulate adult stem cells to generate specific cell types so that they can be used to treat injury or disease.

Induced Pluripotent Stem (iPS) Cells. Scientists have recently engineered human adult cells to become pluripotent creating **iPS cells**. Scientists use a virus to reprogram adult cells so that they can once again turn on genes that they have previously turned off allowing for more versatility like embryonic stem cells. This research is fairly new (see **Figure 1**) and while iPS cells are similar to, they are not the same as embryonic stem cells. If scientists can identify and control the mechanisms that underlie iPS cell **plasticity**, then iPS cells may one day allow scientists to create patient- and disease-specific cell lines and become the basis of therapies for many serious diseases. However, since the cells are created using a virus, which predisposes them to cancer, they are currently unsuitable for use in humans.

Figure 3
Comparison of Different Kinds of Stem Cells

	Advantages	Disadvantages
Embryonic Stem Cells	• Pluripotent: can produce all cell types • Good supply: large source of excess from IVF clinics • Relatively easy to collect, purify and maintain in the laboratory • Long-term self-renewal: can be induced to replicate themselves • Can be used to study early human cell development	• Limited number of cell lines available for federally funded research • Undifferentiated stem cells could not be used directly for transplants because they can cause tumors in humans • May cause problems of immune rejection if transplanted into patients • Ethical issues surround destruction of human blastocysts
Adult Stem Cells	• Have been used successfully to treat some patients (e.g., bone marrow transplants) • Stem cells genetically matched to patient • No ethical issues associated with using them	• Multipotent: can only produce a limited number of cell types • Not found in all tissues of the human body • Difficult to identify, isolate and grow in the laboratory
iPS Cells	• Pluripotent: can produce all cell types • Allows for creation of cell lines genetically customized to the patient (in theory) • Fewer ethical issues associated with using them • Fairly easy to create – does not require materials (i.e., human eggs or embryos) that are difficult to obtain	• Research is in the early stages – scientists may be years away from making iPS cells as versatile as embryonic stem cells • Created using a virus, which disposes them to cancer and makes them currently unsuitable for use in humans

Sources: The National Academies, *Understanding Stem Cells: An Overview of the Science from the National Academies*; National Institutes of Health, *Stem Cell Basics*; University of Michigan, Stem Cell Research and Life Sciences Institute, Center for Stem Cell Biology.

Why Embryonic Stem Cell Research?

Many scientists believe that human embryonic stem cells have the potential to benefit medicine in many ways, including helping scientists understand the complex events that occur during early human development, testing and screening new medications, and providing therapies for previously incurable diseases. However, the advancement of stem cell research is not without obstacles, including technical, financial, legal, and ethical hurdles.

Potential Benefits. Studying embryonic stem cells may give scientists a better understanding of early human cell development and the role that genes play in that development. This is an area of research where adult stem cells cannot replace the potential of embryonic

stem cells. Studying early cell development may help scientists understand how genetic mutations affect normal cell development; how infectious agents invade and attack human cells; how genetic and environmental factors are involved in the development of birth defects, cancer, and other diseases; and what happens to cells during normal aging. A better understanding of these processes may suggest new strategies for therapy.

Stem cells may be useful in testing new medications much in the same way that cancer cell lines are currently used to screen potential anti-tumor drugs. Stem cells may provide a valuable source of human cells for drug testing without risking the health of animal or human test subjects. Further research may allow scientists to produce cell lines with certain genetic qualities in order to test potential treatments. Stem cells could also help scientists to identify and understand the effects of toxic substances found in drugs, food, and the environment. Embryonic stem cells are viewed as important to testing medications and toxins because they are easier to grow and maintain in the laboratory than adult stem cells. If realized, this potential benefit would likely make drug discovery more efficient and cost effective.

Embryonic and adult stem cells have potential for use in cell-based therapies. Embryonic stem cells are believed to have greater potential because of their pluripotency. However, as discussed above, scientists are discovering ways to increase the plasticity of adult cells. Stem cells that can be controlled and differentiated into specific cell types offer the possibility of a renewable source of replacement cells and tissues to treat diseases and injuries, including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, arthritis, muscular dystrophies, and liver diseases. For example, in patients with Type I Diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's immune system. Stem cell research raises the possibility that scientists may be able to direct the differentiation of stem cells in cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics. This process of cell transplantation would be similar to organ transplantation.

Hurdles to Research. Embryonic stem cell research faces many *technical* hurdles, including the fact that scientists do not yet understand stem cells or their processes well enough to reliably manipulate and control them. Before the advancements discussed above can be realized, scientists need to be able to control stem cell proliferation and differentiation and ensure that stem cell transplants will survive and function in a patient. Embryonic stem cells create potential problems of immune rejection that might possibly be addressed with the use of adult stem cells or with therapeutic cloning. While promising, human embryonic stem cell research has been conducted for only the past 10 years. It may be many more years before the research yields any kind of therapy, and many years after that before the therapy is proved safe and effective in patients.

Financial hurdles to human embryonic stem cell research include the limitation of federal funding to stem cell lines created prior to August 2001. Federal funds drive much medical research and are behind many scientific advances. The human embryonic stem cell lines approved for federal funding are limited in number (only 21 stem cell lines available as of March 2007) and none model human disease. They are also all contaminated with animal tissue because scientists have only recently discovered how to grow stem cells in cell culture without animal tissue. Federal policy requires researchers to ensure that no federal funds are used indirectly to support laboratories conducting research on human embryonic stem cell lines created after August 2001. This creates cumbersome tracking and reporting requirements for researchers. *Legal* issues surrounding embryonic stem cell research include intellectual property concerns and proper enforcement of diverse state and federal laws.

Ethical issues abound when analyzing human embryonic stem cell research and they are discussed in more detail further in the analysis. They revolve around the question of when life begins and the potential that embryos have to develop into a human being if implanted into a woman's uterus. Embryonic stem cell research results in the destruction of the embryo and its potential for life.

Alternatives to Human Embryonic Stem Cell Research

Induced Pluripotent Stem (iPS) Cells. As discussed above, iPS cells present the possibility that scientists will be able to induce adult cells to behave like embryonic stem cells. However, this research is in a very early stage and has yet to be proved effective. Scientists may be many years away from making an adult cell as versatile as an embryonic stem cell, if it is even possible.

Reprogrammed Adult Cells. In August 2008, scientists at the Harvard Stem Cell Institute announced that they have reprogrammed adult cells' function in mice by turning one type of fully formed adult cell into another.[1] The creation of reprogrammed adult cells is unique from the creation of iPS cells, which involves turning adult cells into embryonic-like stem cells and then inducing them to differentiate into a desired cell type. Reprogramming adult cells skips the step of turning adult cells into embryonic-like stem cells and involves reprogramming adult cells directly into another cell type. The current process for creating reprogrammed adult cells uses viruses and would pose health risks in human subjects. Scientists are looking for chemicals that might effectively and safely replace the viruses. This research is in a early stage and probably a long way from being used in humans.

Morula Cells. The **morula** is the developmental stage prior to the blastocyst. It is a solid ball of approximately 16 to 30 cells and early research indicates that it may be able to sustain the loss of a few cells without developmental damage, allowing the remaining cells to continue to develop into a human being. Researchers have shown that isolated cells from a mouse morula can produce embryonic stem cells while the remaining morula cells continue to develop into a healthy mouse. This research is also in an early phase and has not yet been successful in a human morula. Cell extraction from the morula is currently being used in some IVF clinics to screen for genetic disorders. Ethical issues arising from this process involve the possibility of harm to the morula and the fact that the long-term effects of removing cells from a morula are not yet known.

Umbilical Cord Blood Cells. Stem cells found in umbilical cord blood hold much promise for treating diseases that are currently treated with hematopoietic stem cells because they are more accessible than stem cells in bone marrow and their extraction poses no risk to the mother or infant because they are removed after birth when the umbilical cord is no longer needed and would be disposed of anyway (blood stem cells can also be found in placentas). Cord blood banking is an option for parents in two ways: 1) they can pay to store their infant's cord blood in a private bank so that the stem cells are available only to them in the unlikely and unfortunate event that their child or other family members need them in the future or 2) some hospitals now offer the opportunity to donate their child's cord blood to a public bank where it would be available for anyone needing blood stem cell therapies.

Umbilical cord blood is currently used to treat patients who have undergone chemotherapy to destroy their bone marrow due to cancer or other blood-related disorders. While these stem cells are an important area of study and treatment, they are a type of adult stem cell because they are more specialized than embryonic stem cells. They have the ability to generate all types of blood and immune system cells, but there is no evidence that they could be used to treat diseases that do not involve the blood or immune system.

Amniotic Fluid Stem Cells. Researchers have just begun to examine the potential of amniotic fluid stem cells, which can be cultivated without any harm to the mother or fetus. Early study indicates that amniotic fluid stem cells may have many of the same traits as embryonic stem cells, but scientists working with them have emphasized that they are not a replacement for embryonic stem cells.[2]

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[1] Harvard Stem Cell Institute researchers turn one form of adult mouse cell directly into another. In *Harvard Stem Cell Institute Spotlight* (World Wide Website). Harvard Stem Cell Institute, 27.Aug.08 (cited 4.Sep.08). Available at www.hsci.harvard.edu/spotlight/2952.

[2] Weiss, Rick. "Scientists See Potential in Amniotic Fluid Cells." *Washington Post*, 8.Jan.07.

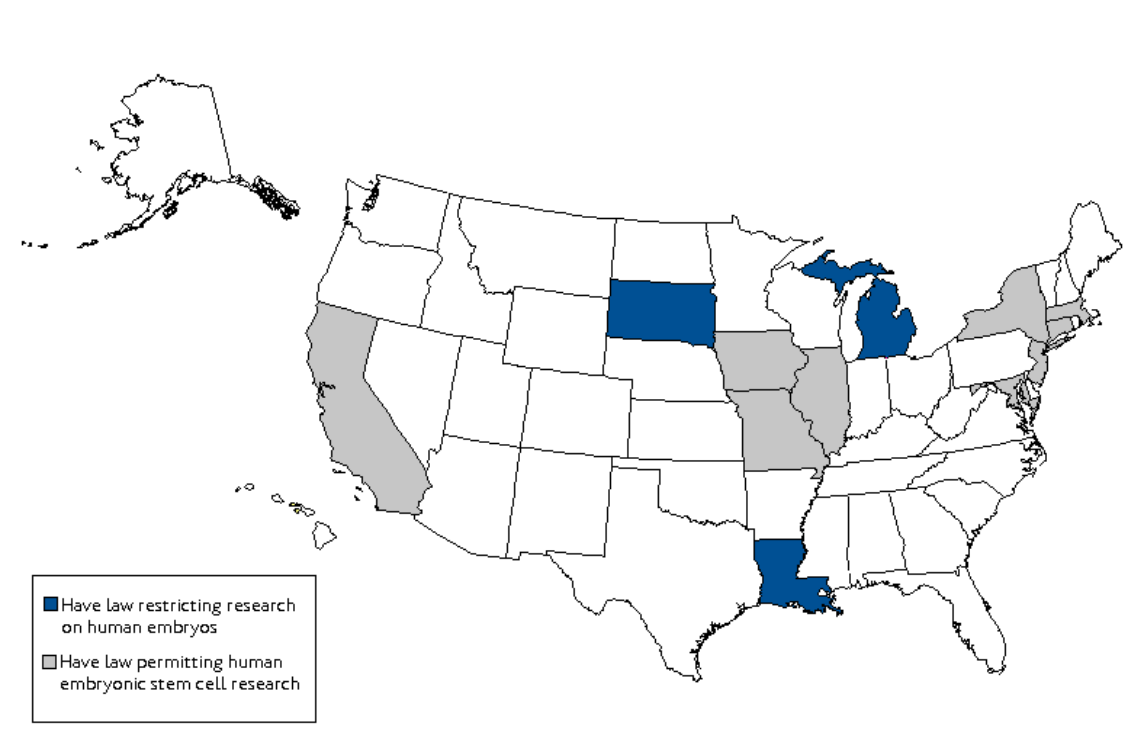
Other States' Policies on Embryonic Stem Cell Research

Since the federal government's policy does not ban research on human embryos, it leaves the door open for states to take action on the research. As **Figure 4** shows, three states have laws on the books banning research on human embryos. Some other states have laws restricting public funding of research or banning cloning for research purposes. Nine states have passed legislation specifically permitting embryonic stem cell research, which often includes ethical guidelines for the research (e.g., consent requirements). Embryonic stem cell research is permitted in all states that have not taken legislative action to ban it, even if they do not have a law on the books specifically permitting it, because the research is permitted under federal law. Federal restrictions are limited to funding, which means that states have to specifically ban the research to make it against the law.

States Funding Human Embryonic Stem Cell Research

Eight states[11] have gone further than simply permitting embryonic stem cell research and have provided state funds for the research to help counteract federal restrictions on the funding of embryonic stem cell research. Voters in California approved the largest stem cell research public funding program when they passed Proposition 71 in 2004, which created the California Institute of Regenerative Medicine (CIRM) and

Figure 4
State Laws on Human Embryonic Stem Cell Research



Source: State Embryonic and Fetal Research Laws. In *Stem Cell Research* (World Wide Website). National Conference of State Legislatures, January 2008 (cited 5.Aug.08). Available at www.ncsl.org/programs/health/genetics/embfet.htm; and Vestal, Christine. "Embryonic Stem Cell Research Divides States." *Stateline.org*, 21.Jun.07 (cited 2.Sep.08). Available at www.stateline.org/live/printable/story?contentId=218416.

authorized the issuance of $3 billion in general obligation bonds over the subsequent 10 years for stem cell research. Some states, including Ohio, Indiana and Virginia, have provided state funding for adult stem cell research, but not for embryonic stem cell research.

Stem Cell Research in Wisconsin. Elements of both the public and private sector in Wisconsin are attempting to brand the state as a leader in stem cell research. Stem cells were first isolated in the laboratory at the University of Wisconsin-Madison and the patents that govern embryonic stem cell technology are held by the Wisconsin Alumni Research Foundation. WiCell Research Institute is affiliated with the University of Wisconsin-Madison and maintains the National Stem Cell Bank distributing stem cell lines to researchers worldwide.

While Governor Doyle has been unable to convince the Wisconsin Legislature to appropriate funds for stem cell research, he has been a vocal supporter of increased federal funding and has created a $750 million investment fund, which includes both public and private money, to build the Wisconsin Institutes for Discovery where embryonic stem cell research will be conducted.[12] Furthermore, an informal confederation of Wisconsin businesses and groups have come together to form the group Wisconsin Edge, which advocates for the therapeutic and economic benefits of stem cell research to Wisconsin. A key point that the group communicates to Wisconsin residents and businesses is that investment in stem cell research is a form of economic development and can lead to new companies locating in Wisconsin and bringing jobs and dollars to the state.

2006 Ballot Proposal in Missouri

Constitutional Amendment 2 passed in Missouri in 2006 by a margin of 51 to 49 percent. It amended the State Constitution to permit human embryonic stem cell research. It also put a ban against human cloning in the Constitution. However, it specifically defined cloning to include reproductive cloning, but not therapeutic cloning.

Supporters of embryonic stem cell research put the measure on the ballot to protect the research against the Missouri Legislature's attempts to ban it. It was hoped that passage would make Missouri a new center for embryonic stem cell research, however, that has not happened as supporters of the research have run into both political and financial roadblocks. For example, some lawmakers continue to introduce bills to bar some types of research and to block funding for embryonic stem cell research.[1]

The debate over embryonic stem cell research and therapeutic cloning rages on in Missouri. Opponents of the research attempted, but failed, to get a proposal on the ballot this year that would have banned somatic cell nuclear transfer (i.e. therapeutic cloning).[2] And a pro-life group has set the stage for a funding battle this year by attempting to block $21 million in public funds from going to the Life Sciences Research Board for embryonic stem cell research.[3]

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[1] Davey, Monica. "Stem Cell Amendment Changes Little in Missouri." *The New York Times*, 10.Aug.07.

[2] Stafford, Margaret. "Missouri Appeals Court Looks at Stem Cell Ballot." *Columbia Missourian*, 26.Mar.08.

[3] Ertelt, Steven. "Missouri Legal Battle Against Embryonic Stem Cell Research Funding in October." *LifeNews.com*, 12.Aug.08 (cited 12.Sept.08). Available at www.lifenews.com/printpage.php.

Issues Raised by Human Embryonic Stem Cell Research

Bioethics

Bioethics is defined as "a field of study concerned with the ethics and philosophical implications of certain biological and medical procedures, technologies, and treatments…"[13] Human embryonic stem cell research raises ethical concerns that are studied and debated along with its medical potential.

The ethical issue underlying most of the problems people have with stem cell research is the question of when life begins. Opponents of embryonic stem cell research argue that life begins at the moment of conception or fertilization, making research on "living" embryos unethical. If this premise is accepted, it has implications beyond embryonic stem cell research to abortion, fertility treatments, and even some forms of contraception. Proponents of stem cell research counter that embryonic stem cells are derived from pre-implantation embryos that consist of approximately 150 undifferentiated cells with no heart, nervous system, limbs, or specialized human tissues of any kind. They would argue that the "pro-life" position is to fund and support research that has the potential to help scientists understand the cause of many diseases and provide therapies for those suffering from disease and injury.

Even some who are not necessarily ethically opposed to human embryonic stem cell research may have ethical concerns around the research because it can be viewed as putting society on a "slippery slope." The concern is that if research on human embryos is allowed today, then what will be allowed tomorrow? The creation of embryos specifically for research? Payment for human embryos? The fear is that techniques to conduct embryonic stem cell research may be misapplied and lead to unforeseen consequences, such as a market for human embryos or further questionable research. It must be noted though that the current proposal would simply allow for research on human embryos left over after fertility treatment and put Michigan in line with most other states. It would not allow for the creation of embryos specifically for research purposes and it would explicitly prohibit payment for human embryos for stem cell research.

In Vitro Fertilization (IVF). IVF involves fertilizing eggs in a culture dish to be implanted into a woman's uterus. Doctors give a woman fertility drugs to stimulate her ovaries to produce multiple mature eggs and then typically fertilize all the donated eggs in order to maximize the chance of producing viable embryos to be implanted in her womb. This procedure has been subject to ethical debate because it leads to the creation of excess embryos that are either not suitable or necessary for implantation. Researchers can use most leftover embryos, including those that are not suitable for implantation owing to some genetic defect or development problem.

As of April 2002, the RAND Corporation estimated that there were approximately 400,000 embryos frozen in storage in fertility clinics across the country.[14] These include embryos that have been stored since as far back as the mid-1980s. Of the 400,000 embryos, 88.2 percent were being held for family building. Embryos are stored at the patient's expense, and when patients no longer wish to continue to store their embryos, they have three options: 1) donate them to others seeking fertility treatment who cannot produce their own viable embryos, 2) donate them to research, or 3) discard them as medical waste. At the time of RAND's research, 2.3 percent of the total embryos in storage were awaiting donation to another patient (i.e., embryo adoption), 2.8 percent were designated for research, 2.2 percent were designated to be discarded, and 4.5 percent were being held in storage for other reasons (e.g., lost contact with a patient or patient death). The question is what will be done with the 88.2 percent when they are no longer needed for family building. Results of a 2007 survey of over 1,000 fertility patients conducted by researchers at Johns Hopkins University and Duke University found that 60 percent of patients reported that they were likely to donate their left-over embryos to stem cell research once they no longer need them, whereas 22 percent of respondents were likely to donate their embryos to other patients for adoption (the percentages reflect those that responded they were somewhat or very likely to donate their embryos to stem cell research or to another couple; respondents were also given

other options, including discarding their embryos).[15] Embryos that are not suitable for implantation are not included in the 400,000 number because they are never frozen and are simply discarded or donated to research.

Embryo donation to other patients seeking fertility treatment is an option routinely provided by fertility clinics. One example of a program offering embryo adoption is the Snowflakes Frozen Embryo Adoption Program. It was founded in 1997 and has received a lot of press since the advent of embryonic stem cell research as a viable alternative to either donating excess embryos to research or discarding them. If Proposal 2008-02 passes, patients will retain the option to donate their excess embryos to other patients seeking fertility treatment.

Storing embryos permanently is not generally an option because of the fees associated with storing the embryos and uncertainty as to how long embryos can survive frozen storage. If patients have completed their family and do not wish to continue to store their embryos or put them up for adoption, then they have the choice of either donating them for research or discarding them as medical waste. Currently, Michigan researchers may not conduct research on donated embryos, but researchers in most other states can. If Proposal 2008-02 passes, it will allow Michigan scientists to conduct research on embryos with the informed, written consent of the donors. It is currently legal for fertility clinics in Michigan to discard excess embryos as medical waste and Proposal 2008-02 would not change that.

Abortion. Abortion is an issue that is often tied to embryonic stem cell research even though there is no direct link between the two. Embryonic stem cells are derived from pre-implantation embryos, not from aborted embryos or fetuses. Once an embryo has been implanted into a woman's uterus, its stem cells begin the specialization process.[16] However, the premise that life begins at conception does raise a potential ethical problem for abortion, and even some forms of contraception that prevent the implantation of fertilized eggs.

Cloning. Cloning for reproductive or research purposes is an issue that is often linked to embryonic stem cell research. In theory, therapeutic cloning could produce patient-specific stem cells. However, Proposal 2008-02 would have no effect on Michigan's law prohibiting cloning. This issue goes beyond the scope of the ballot proposal, which would not legalize therapeutic cloning and would simply allow for research on human embryos left over after fertility treatment.

Chimeras. Medical research relies on animal subjects and stem cell research is no different. Scientists implant human stem cells into animals (mainly mice) to study human cell and disease development. Organisms that contain cells or tissues from another individual of the same or a different species are called chimeras. These include mice that have been implanted with human stem cells as well as a person who has received a blood transfusion. While the creation of chimeras that contain both animal and human cells raises unique ethical issues, they are considered essential for the advancement of stem cell research because no therapy can be used in humans without first being tested in animals. The research guidelines issued by the National Academies address the creation of human-animal chimeras by prohibiting 1) the introduction of human cells into the blastocyst of a non-human primate, 2) the introduction of any animal or human cells into a human blastocyst, and 3) the breeding of human-animal chimeras in the unlikely event that any human genetic material would be contained in their reproductive cells.[17] These guidelines, while accepted by many scientists, are not legally binding.

Life Sciences Business Sector

Regenerative medicine is driving the life sciences business sector in Michigan, the United States, and the rest of the world. Stem cell research, including human embryonic stem cell research, is seen by many as vital to advancing regenerative medicine. According to a 2006 U.S. Department of Health & Human Services report,[18] a conservative estimate of the worldwide market for regenerative medicine by 2010 is $500 billion. The projected U.S. market is $100 billion. However, to date, there has been a lack of federal investment in regenerative medicine (as of the report, private investment was 10 times the amount of public investment). Private investment tends to focus on marketable products while public investment is essential to the fundamental building block research that is necessary to better understand cells and tissues so that

products and therapies can be developed and brought to the market.

Not only do advancements in regenerative medicine have the potential to be an economic boon for the country, but they also may lower overall health care costs, which are in excess of $2 trillion annually (16 percent of U.S. Gross Domestic Product).[19] Regenerative medicine has the potential to provide cures for many currently incurable diseases and to put an end to many chronic, and costly, diseases. However, the potential magnitude of the impact of stem cell research and regenerative medicine is speculative because it is impossible to know what will come of the current research.

While the U.S. is competing with other countries to build its life sciences industry, Michigan is competing with its fellow states for investment by the industry. It is argued by the University of Michigan that preventing Michigan scientists from participating fully in embryonic stem cell research impairs their ability to be at the forefront of the industry and to discover and deliver new therapies to patients. The University argues that other states and countries are already using Michigan's unfavorable research climate to recruit Michigan's best researchers away from the state.[20] An unfavorable research climate also may make it less likely that the life sciences industry will invest in Michigan. The eight states that are providing state funds for human embryonic stem cell research are doing so to advance the research, but also to attract further private investment and high paying jobs to their state.

Opponents of embryonic stem cell research counter that research using human embryos is just one piece of regenerative medicine and Michigan researchers are able to conduct research on human embryonic stem cells derived outside of the state and on all types of adult stem cells, including iPS cells and reprogrammed adult cells.

Embryonic Stem Cells Are Not Currently Used in Therapies

Opponents of embryonic stem cell research argue that these stem cells are not being used to treat patients. While that is true, it does not mean that they do not hold potential for use in therapies in the future. Research has been conducted on human embryonic stem cells for only the past 10 years. That is not very long when discussing biomedical research, which can take decades to lead to commonplace therapies in humans.

Adult stem cells, which have been studied since the 1950s, are used to treat some patients. However, there is debate over how many diseases are currently treated with adult stem cells. According to many scientists, both embryonic and adult stem cells have potential to provide cell-based therapies and cures for many chronic diseases and injuries. Only time, and future research, will tell what therapies are realized and which stem cells are necessary for those therapies.

Some argue that continued investment in embryonic stem cell research is important because it allows researchers to study early human cell development and it has helped lead to some advancements, including emerging research into reprogramming adult cells.

Michigan Impact

If Proposal 2008-02 passes, it will provide constitutional protection to embryonic stem cell research in Michigan. It will end the State's prohibition of research on human embryos and allow researchers to derive new human embryonic stem cell lines in Michigan. It will not alter Michigan's current law that bans human cloning for reproductive and therapeutic purposes. It does not provide state funds for embryonic stem cell research, but it would not prohibit a future proposal to provide state funds or the legislature from appropriating funds for the research.

Michigan is currently one of only three states that ban research on human embryos. This restrictive policy could influence the location decisions of scientists and biomedical companies. If the proposal passes, it will put Michigan with the other nine states that have laws to specifically permit human embryonic stem cell research. While the research is permitted in all 47 states that do not have a law prohibiting it, passage of this proposal would insert into the State Constitution the citizens' intent to allow for research on human embryos and the derivation of embryonic stem cells in the state. This may make Michigan appear more hospitable to the life sciences industry and lead to greater investment in Michigan and its universities and research institutions. The life sciences industry consists of the type of high paying jobs that Michigan is hoping to attract. However, it must be noted that Michigan already has some investment in the life sciences industry (e.g., the University of Michigan has a Center for Stem Cell Biology and an Exploratory Center for Human Embryonic Stem Cell Research). Passage of this proposal may simply make it easier to attract investment and jobs in the life sciences sector.

Endnotes

[1] Public Act 368 of 1978 (Public Health Code), MCL 333.2685, 2692.

[2] Public Act 368 of 1978 (Public Health Code), MCL 333.16274.

[3] Public Act 368 of 1978 (Public Health Code), MCL 333.2691.

[4] Public Act 328 of 1931 (The Michigan Penal Code), MCL 750.430a.

[5] National Institutes of Health. *NIH Funding of Research Using Specified Existing Human Embryonic Stem Cells*, NOT-OD-01-058. 23.Aug.01.

[6] Research Q&A. In *Center for Stem Cell Biology* (World Wide Website). University of Michigan: Life Sciences Institute, 2006 (cited 15.Sep.08). Available at www.lsi.umich.edu/facultyresearch/centers/stemcellbiology/researchqa.

[7] Information on regenerative medicine and stem cells was gathered from a multitude of sources: National Institutes of Health, *Stem Cell Basics*; The National Academies, *Understanding Stem Cells: An Overview of the Science and Issues from the National Academies*; University of Michigan, Stem Cell Research and Life Sciences Institute, Center for Stem Cell Biology; International Society for Stem Cell Research; WiCell Research Institute; University of Wisconsin-Madison Stem Cell and Regenerative Medicine Center.

[8] The National Academies consist of committees of experts in all areas of scientific and technological endeavor that address critical national issues and give advice to the federal government and public.

[9] A joint project between the Academies' National Research Council and the Institute of Medicine.

[10] National Research Council and Institute of Medicine. *2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research*. National Academy of Sciences, 2008.

[11] California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York and Wisconsin.

[12] Vestal, Christine. "Embryonic Stem Cell Research Divides States." *Stateline.org*, 21.Jun.07 (cited 2.Sep.08). Available at www.stateline.org/live/printable/story?contentId=218416.

[13] "Bioethics." *Dictionary.com*, 2008 (cited 5.Sep.08). Available at dictionary.reference.com/browse/bioethics.

[14] RAND Law & Health Research Brief. *How Many Frozen Human Embryos Are Available for Research?*, 2003 (cited 15.Sep.08). Available at www.rand.org/pubs/research_briefs/RB9038/RB9038.pdf.

[15] Lyerly, Anne Drapkin and Faden, Ruth R. "Willingness to Donate Frozen Embryos for Stem Cell Research." Science, Vol. 317, 6.Jul.07 (cited 16.Sep.08). Available at www.sciencemag.org/cgi/reprint/317/5834/46.pdf (supporting online material published 21.Jun.07, available at www.sciencemag.org/cgi/content/full/1145067/DC1).

[16] Research Q&A. In *Center for Stem Cell Biology* (World Wide Website). University of Michigan: Life Sciences Institute, 2006 (cited 15.Sep.08). Available at www.lsi.umich.edu/facultyresearch/centers/stemcellbiology/researchqa.

[17] The National Academies. *Understanding Stem Cells: An Overview of the Science and Issues from the National Academies*. Available at dels.nas.edu/dels/rpt_briefs/Understanding_Stem_Cells.pdf (cited 15.Sep.08).

[18] U.S. Department of Health & Human Services. *2020: A New Vision – A Future for Regenerative Medicine*, 28.Mar.06 (cited 9.Sep.08). Available at www.hhs.gov/reference/newfuture.shtml.

[19] Zerhouni, Elias (Director, National Institutes of Health). "FY2008 Director's Budget Request Statement," testimony March 19, 2007 before the U.S. Senate Subcommittee on Labor—HHS—Education Appropriations. Available at www.nih.gov/about/director/budgetrequest/fy2008directorssenatebudgetrequest.htm (cited 10.Sep.08).

[20] Research Q&A. In *Center for Stem Cell Biology* (World Wide Website). University of Michigan, 2006 (cited 10.Sep.08). Available at www.lsi.umich.edu/facultyresearch/centers/stemcellbiology/researchqa#top.