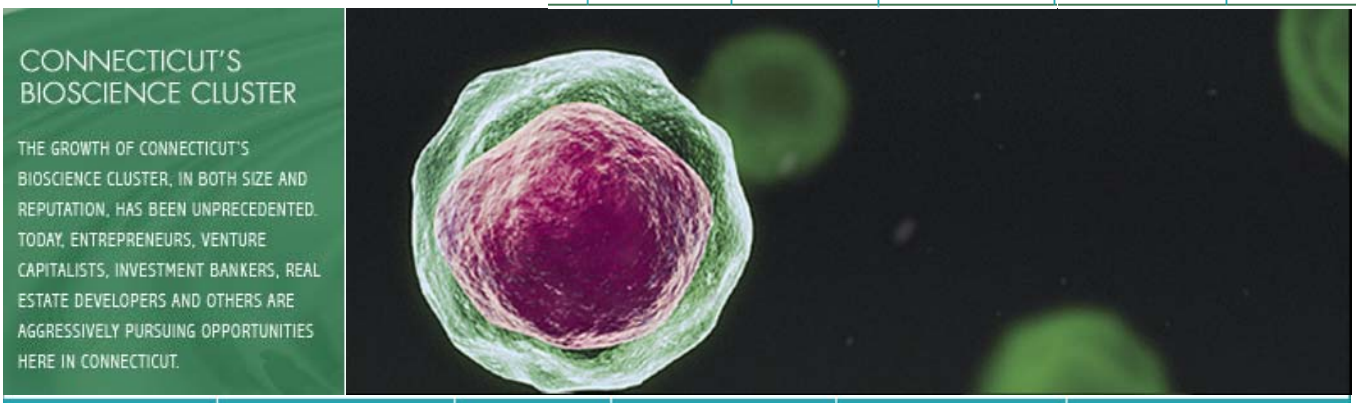
Connecticut United for Research Excellence, Inc.
The Center of Connecticut's BioScience Cluster

Background Information
Connecticut Stem Cell Research

Compiled March 15, 2006

CURE (http://www.curenet.org) is a statewide coalition of over 100 educational and research institutions, biotechnology and pharmaceutical companies and other supporting businesses. It is dedicated to promoting the growth and increasing public understanding of biomedical research and science in Connecticut.



CURE CALENDAR

3/14 3:30 p.m. - 6:00 p.m.
Yale BioHaven Entrepreneurship Seminar featuring VaxInnate, Inc. The Anlyan Center auditorium, Yale School of Medicine, New Haven ... more

3/24 9:00 a.m. - 5:15 p.m.
Healthcare Conference 2006. New Haven Lawn Club New Haven ... more

4/5 8:15 a.m. - 4:00 p.m.
BioScience Competition & Event. Hosted by CT SBIR. UConn Health Center, Farmington ... more

4/9-12
BIO 2006.Chicago, IL. Housing requests now being accepted ... more

5/2-3
Crossroads Venture Fair. The Westin, Stamford ... more

6/7
Entrepreneurs from UConn's TIP and R&D Corp companies. Farmington. Watch for further details.

6/12-14
BIO Venture Forum East. Jersey City, NJ ... more

STEM CELL RESEARCH

On June 15, 2005, Connecticut's Governor M. Jodi Rell signed into law "An Act Permitting Stem Cell Research and Banning the Cloning of Human Beings" This landmark legislation appropriated the sum of $100 million over ten years for the purpose of grants-in-aid for conducting embryonic or human adult stem cell research.

Passage of the act positioned Connecticut as just the third state in the nation in providing public funding in support of embryonic and human adult stem cell research. CURE was a major supporter of the legislation and instrumental in securing its passage.

"This is a great day for Connecticut bioscience. It marks a significant step forward for those suffering from a host of diseases and conditions. It is also a further step toward attracting substantial investment and high-paying jobs to Connecticut," said Paul R. Pescatello, president and CEO of CURE, when the act was passed.

News Flash

The University of Connecticut has named Dr. Ren-He Xu, a developmental biologist and expert in growing human embryonic stem cells lines, director of UConn's new human embryonic stem cell core laboratory. Xu will also become a faculty member of the Department of Genetics and Developmental Biology at the Health Center, with a joint appointment at the Center for Regenerative Biology in Storrs. ***Read more***

Connecticut will be hosting a major international stem cell conference in March 27-28 2007. Watch this space for further details.

Implementation of the Act

The act established a Connecticut Stem Cell Research Advisory and Peer Review Committee, with the Commissioner of Public Health as chair. Implementation of the Act is being achieved through the development of collaborative relationships among the Department of Public Health and members of the local, national and international stem cell research community, including scientists, policy makers, advocates and consumers.

In addition to CURE, major partners in the Connecticut stem cell effort include Connecticut Innovations, the Connecticut Stem Cell Research Coalition, and academic research institutions, Including The University of Connecticut, Wesleyan University, and Yale University.

Connecticut is committed to getting public dollars into the hands of its very talented and very passionate stem cell research community. The state is also committed to leveraging public dollars to attract new researchers, to improve and promote for-profit and not-for-profit embryonic and human stem cell and related research, to identify additional public and private funding resources to support such research, and to recruit new scientists, researchers and businesses to Connecticut.

The Department of Public Health maintains a stem cell research web page with more information and further links on the progress of stem cell research in Connecticut. The text of the act is available here.

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For immediate release

Contact
Bill Kelly 203-375-2696
bill@harveymalis.com

Connecticut Governor M. Jodi Rell Signs Stem Cell Bill Into Law

New Haven, Conn., June 15, 2005 – Governor Jodi M. Rell of Connecticut signed into law today legislation supporting embryonic stem cell research and earmarking $100 million in funding for such research. Paul R. Pescatello, president and chief executive office of CURE (Connecticut United for Research Excellence) issued the following remarks at the signing ceremony:

"This is a great day for Connecticut bioscience. Enactment of this legislation marks a significant step forward for those suffering from a host of diseases and conditions. It is also a further step toward attracting substantial investment and high-paying jobs to Connecticut.

"With President Bush set to veto any expansion of federally funded embryonic stem cell research, it will be up to the states and to private investors to fund additional research in the area. By signing this bill into law, Governor Rell has catapulted Connecticut into the vanguard as a state that not only welcomes embryonic stem cell research but supports it financially.

"CURE was an important resource in researching and drafting the legislation and the catalyst that brought together the coalition that worked for its passage. I'm proud to represent bioscience in a state where the Governor and legislators on both sides of the aisle are so willing to work together to do the right thing."

CURE (http://www.curenet.org) is a statewide coalition of over 100 educational and research institutions, biotechnology and pharmaceutical companies and other supporting businesses. It is dedicated to promoting the growth and increasing public understanding of biomedical research and science in Connecticut.

CURE
Connecticut United for Research Excellence, Inc.

300 George Street, Suite 561
New Haven, CT 06511
Tel 203-777-8747
Fax 203-777-8754
e-mail: cure@curenet.org
www.curenet.org

The Center of Connecticut's BioScience Cluster

About *An Act Concerning Embryonic Stem Cell Research and Banning Cloning of Human Beings*

What the Bill Does

Research involving embryonic stem cells will lead to treatments and cures for a host of diseases and conditions, including Parkinson's disease, Alzheimer's disease, multiple sclerosis, ALS (Lou Gehrig's disease) and spinal cord injury. The proposed *An Act Concerning Embryonic Stem Cell Research and Banning Cloning of Human Beings* (the "Act") is intended to make clear to doctors and research scientists that Connecticut is hospitable to embryonic stem cell research, to provide regulation of such research where none now exists and to ban the cloning of human beings (which is not now barred under Connecticut law).

Why Embryonic Stem Cells Hold Unique Promise

Embryonic stem cells are cells which are undifferentiated – that is, they are uniquely malleable and can be used to build any type of tissue, from skin to brain cells. It is this flexibility that makes embryonic stem cells so promising and revolutionary in a therapeutic sense. Rather than simply attempting to halt or contain disease, embryonic stem cells offer the possibility of replacing diseased or damaged tissues with new cells.

Why Proponents of Embryonic Stem Cell Research Do Not Consider Embryonic Stem Cells a Human Being

Embryonic stem cells are cells that occur at the earliest stage of cell division when embryos are between four and fourteen days old. These cells take on a spherical shape that resembles a hollow ball. Again, embryonic stem cells are undifferentiated and it is impossible to identify them as anything other than embryonic stem cells. They cannot be identified as, for example, liver or bone cells.

As with the end of life, the beginning of life may be defined by the presence or absence of neurological activity. Embryonic stem cells do not constitute life because neurological activity does not occur within or about them. Indeed, there is not even a scaffold upon which neurological activity could take place.

Adult Stem Cells Do Not Offer the Research Potential of Embryonic Stem Cells

Embryonic stem cells are distinct from adult stem cells. Adult stem cells have been identified in only a few – certainly not all – tissues. To the extent adult stem cells exist they are partially but not fully undifferentiated. Bone marrow stem cells, for example, are destined to become only blood cells, not brain or kidney cells.

It is important to underscore that cells derived from fetal or umbilical cord tissue are *adult* stem cells. Embryonic stem cell research therefore does not involve the use of fetal tissue.

Embryonic Stem Cells are Derived from Fertility Procedures

Embryonic stem cells are created in the laboratory in Petri dishes, generally as part of a variety of fertility procedures. In order to maximize the possibility of success, such procedures typically involve the creation of numerous embryos. Embryos remaining after a course of fertility treatment are either discarded or made available for research.

There are over 400,000 such excess embryos in existence in the United States today. The women and men who participated in the fertility procedures from which the embryos were derived often express a desire that any excess embryos not be destroyed and, instead, be used for embryonic stem cell research. The Act specifically requires health care providers to provide persons undergoing fertility treatments four options concerning disposition of embryos – donation for research purposes, donation to another person, further storage or destruction.

Embryos For Stem Cell Research Must Be Donated – The Act Bars Payment for Embryos

Though it is unlikely given the sheer number of embryos available for research that much incentive would exist for significant monetary payments for embryos, the Act also specifically bars payment for embryos.

Nuclear Transfer and Therapeutic Cloning Have Nothing To Do with Radioactive Material or Human Cloning

Embryonic stem cells may also be derived through a process sometimes referred to as "nuclear transfer" or "therapeutic cloning." These highly charged labels are unfortunate because the process has nothing to do with either nuclear/radioactive material or human cloning.

Nuclear transfer means the replacement of an egg's nucleus with the nucleus of another cell, such as a skin cell. The embryonic stem cells derived from such embryos are perfectly matched to the donor of the nucleus. Therapeutically, this means that use of embryonic stem cells created through nuclear transfer will not be rejected when used in the donor and that the donor will not require a lifelong regimen of immunosuppressant drugs (which themselves reduce longevity).

Nuclear transfer is not human cloning because it is used only to create embryonic stem cells. And the Act specifically bars embryos used in embryonic stem cell research from being implanted in a uterus of any kind – that is, a woman's uterus or any artificial uterus in the unlikely event that such an enormously complex device is created.

Justin Ide/Harvard News Office

From the CT Department of Public Health Website

http://www.dph.state.ct.us/StemCell/index.htm

Stem Cell Research Program

Welcome to the new State of Connecticut, Department of Public Health Stem Cell Research web page.

Public Act 05-149, “An Act Permitting Stem Cell Research and Banning the Cloning of Human Beings” (the Act), was approved by the General Assembly and signed by Governor M. Jodi Rell on June 15, 2005. Passage of the Act positioned Connecticut as just the third state in the nation in providing public funding in support of embryonic and human adult stem cell research.

Within the Department of Public Health, the Office of Research and Development is responsible for managing all aspects of the Act, including working out committee appointments, conducting and coordinating internal and external meetings, and establishing and fostering collaborative relationships with members of the Connecticut Stem Cell Research Committee, advocates, and policy makers. One of the guiding and continuing principles of the Office of Research and Development is the commitment to transparency, and we are proud to offer this web page as an important vehicle in maintaining open and transparent lines of communication with residents of Connecticut and members of the national and international stem cell research community.

On behalf of the Office or Research and Development, we invite you to use this site to learn more about stem cells and stem cell research, to link to other helpful stem cell research web pages, to find out more about Connecticut’s Stem Cell Research Program, to keep track of the State’s progress in terms of the granting of public dollars to support research, and to access information on the activities and proceedings of the Stem Cell Research Advisory and Peer Review Committees. As always, we invite your comments and suggestions regarding any aspect of this web page. Thanks, and enjoy!!!

Stem Cell Bill Committee Duties/Conduct Parameters

Stem Cell Research Advisory Committee (SCRAC) – Nine members

1. Commissioner of Public Health, Chair
2. by Governor – nationally recognized stem cell investigator/researcher
3. by Governor – bioethicist
4. by Senate President Pro Tempore – private sector stem cell researcher
5. by House Speaker – private sector stem cell researcher
6. by Senate majority leader – academic researcher
7. by House majority leader – academic researcher
8. by Senate minority leader – public or private stem cell research and development or related research fields including embryology, genetics, or cellular biology
9. by House minority leader – business and financial investments

Duties: To advance embryonic and human adult stem cell research

Conflicts: No participation in Committee affairs regarding grant-in-aid where person has financial interest

Committee duties:

1. Donated egg/embryo program
2. Ways to improve and promote for-profit and not-for-profit embryonic and human adult stem cell research
3. Establishing grants-in-aid program
4. Monitoring stem cell research as funded

Stem Cell Research Peer Review Committee

- 5 members
- Appointed by Commissioner of Public Health
- Experience in field
- Work to advance embryonic and adult stem cell research
- No participation where financial or business, employment, transaction, or professional activity
- Makes *recommendations* to SCRAC

Biomedical Research Trust Fund = Tobacco Settlement Fund $ + public or private gifts

Biomedical Research Trust Fund grants in aid to eligible institutions (via Commissioner of Public Health upon direction of SCRAC) for embryonic or adult stem cell research.

Eligible institutions:

- Nonprofit tax exempt institution of higher education
- Hospitals that conduct biomedical research
- Any entities (non and for profit) that conduct biomedical research

Applications to conduct stem cell research include:

- complete description of organization
- plans for research – research protocol
- proposed funding from sources other than the state of Connecticut
- arrangements regarding patent/royalty including from research

Substitute Senate Bill No. 934

Public Act No. 05-149

AN ACT PERMITTING STEM CELL RESEARCH AND BANNING THE CLONING OF HUMAN BEINGS.

Be it enacted by the Senate and House of Representatives in General Assembly convened:

Section 1. (NEW) (*Effective from passage*) (a) As used in sections 1 to 4, inclusive, of this act and section 4-28e of the general statutes, as amended by this act:

(1) "Institutional review committee" means the local institutional review committee specified in 21 USC 360j(g)(3)(A)(i), as amended from time to time, and, when applicable, an institutional review board established in accordance with the requirements of 45 CFR 46, Subpart A, as amended from time to time.

(2) "Cloning of a human being" means inducing or permitting a replicate of a living human being's complete set of genetic material to develop after gastrulation commences.

(3) "Gastrulation" means the process immediately following the blastula state when the hollow ball of cells representing the early embryo undergoes a complex and coordinated series of movements that results in the formation of the three primary germ layers, the ectoderm, mesoderm and endoderm.

(4) "Embryonic stem cells" means cells created through the joining of a human egg and sperm or through nuclear transfer that are sufficiently undifferentiated such that they cannot be identified as components of any specialized cell type.

(5) "Nuclear transfer" means the replacement of the nucleus of a human egg with a nucleus from another human cell.

(6) "Eligible institution" means (A) a nonprofit, tax-exempt academic institution of higher education, (B) a hospital that conducts biomedical research, or (C) any entity that conducts biomedical research or embryonic or human adult stem cell research.

(b) No person shall knowingly (1) engage or assist, directly or indirectly, in the cloning of a human being, (2) implant human embryos created by nuclear transfer into a uterus or a device similar to a uterus, or (3) facilitate human reproduction through clinical or other use of human embryos created by nuclear transfer. Any person who violates the provisions of this subsection shall be fined not more than one hundred thousand dollars or imprisoned not more than ten years, or both.

Each violation of this subsection shall be a separate and distinct offense.

(c) (1) A physician or other health care provider who is treating a patient for infertility shall provide the patient with timely, relevant and appropriate information sufficient to allow that person to make an informed and voluntary choice regarding the disposition of any embryos or embryonic stem cells remaining following an infertility treatment.

(2) A patient to whom information is provided pursuant to subdivision (1) of this subsection shall be presented with the option of storing, donating to another person, donating for research purposes, or otherwise disposing of any unused embryos or embryonic stem cells.

(3) A person who elects to donate for stem cell research purposes any human embryos or embryonic stem cells remaining after receiving infertility treatment, or unfertilized human eggs or human sperm shall provide written consent for that donation and shall not receive direct or indirect payment for such human embryos, embryonic stem cells, unfertilized human eggs or human sperm.

(4) Any person who violates the provisions of this subsection shall be fined not more than fifty thousand dollars or imprisoned not more than five years, or both. Each violation of this subsection shall be a separate and distinct offense.

(d) A person may conduct research involving embryonic stem cells, provided (1) the research is conducted with full consideration for the ethical and medical implications of such research, (2) the research is conducted before gastrulation occurs, (3) prior to conducting such research, the person provides to the Commissioner of Public Health documentation verifying that any human embryos, embryonic stem cells, unfertilized human eggs or human sperm used in such research have been donated voluntarily in accordance with the provisions of subsection (c) of this section, on a form and in the manner prescribed by the Commissioner of Public Health, (4) the general research program under which such research is conducted is reviewed and approved by an institutional review committee, as required under federal law, and (5) the specific protocol used to derive stem cells from an embryo is reviewed and approved by an institutional review committee.

(e) The Commissioner of Public Health shall enforce the provisions of this section and may adopt regulations, in accordance with the provisions of chapter 54 of the general statutes, relating to the administration and enforcement of this section. The commissioner may request the Attorney General to petition the Superior Court for such order as may be appropriate to enforce the provisions of this section.

Sec. 2. (NEW) (*Effective from passage*) (a) There is established the "Stem Cell Research Fund" which shall be a separate, nonlapsing account within the General Fund. The fund may contain any moneys required or permitted by law to be deposited in the fund and any funds received from any public or private contributions, gifts, grants, donations, bequests or devises to the fund. The Commissioner of Public Health may make grants-in-aid from the fund in accordance with the provisions of subsection (b) of this section.

(b) Not later than June 30, 2006, the Stem Cell Research Advisory Committee established pursuant to section 3 of this act shall develop an application for grants-in-aid under this section for the purpose of conducting embryonic or human adult stem cell research and may receive applications from eligible institutions for such grants-in-aid on and after said date. The Stem Cell Research

Advisory Committee shall require any applicant for a grant-in-aid under this section to conduct stem cell research to submit (1) a complete description of the applicant's organization, (2) the applicant's plans for stem cell research and proposed funding for such research from sources other than the state of Connecticut, and (3) proposed arrangements concerning financial benefits to the state of Connecticut as a result of any patent, royalty payment or similar rights developing from any stem cell research made possible by the awarding of such grant-in-aid. Said committee shall direct the Commissioner of Public Health with respect to the awarding of such grants-in-aid after considering recommendations from the Stem Cell Research Peer Review Committee established pursuant to section 4 of this act.

(c) Commencing with the fiscal year ending June 30, 2006, and for each of the nine consecutive fiscal years thereafter, until the fiscal year ending June 30, 2015, not less than ten million dollars shall be available from the Stem Cell Research Fund for grants-in-aid to eligible institutions for the purpose of conducting embryonic or human adult stem cell research, as directed by the Stem Cell Research Advisory Committee established pursuant to section 3 of this act. Any balance of such amount not used for such grants-in-aid during a fiscal year shall be carried forward for the fiscal year next succeeding for such grants-in-aid.

Sec. 3. (NEW) (*Effective from passage*) (a) There is established a Stem Cell Research Advisory Committee. The committee shall consist of the Commissioner of Public Health and eight members who shall be appointed as follows: Two by the Governor, one of whom shall be nationally recognized as an active investigator in the field of stem cell research and one of whom shall have background and experience in the field of bioethics; one each by the president pro tempore of the Senate and the speaker of the House of Representative, who shall have background and experience in private sector stem cell research and development; one each by the majority leaders of the Senate and House of Representatives, who shall be academic researchers specializing in stem cell research; one by the minority leader of the Senate, who shall have background and experience in either private or public sector stem cell research and development or related research fields, including, but not limited to, embryology, genetics or cellular biology; and one by the minority leader of the House of Representatives, who shall have background and experience in business or financial investments. Members shall serve for a term of four years commencing on October first, except that members first appointed by the Governor and the majority leaders of the Senate and House of Representatives shall serve for a term of two years. No member may serve for more than two consecutive four-year terms and no member may serve concurrently on the Stem Cell Research Peer Review Committee established pursuant to section 4 of this act. All initial appointments to the committee shall be made by October 1, 2005. Any vacancy shall be filled by the appointing authority.

(b) The Commissioner of Public Health shall serve as the chairperson of the committee and shall schedule the first meeting of the committee, which shall be held no later than December 1, 2005.

(c) All members appointed to the committee shall work to advance embryonic and human adult stem cell research. Any member who fails to attend three consecutive meetings or who fails to attend fifty per cent of all meetings held during any calendar year shall be deemed to have resigned from the committee.

(d) All members shall be deemed public officials and shall adhere to the code of ethics for public officials set forth in chapter 10 of the general statutes. No member shall participate in the affairs of the committee with respect to the review or consideration of any grant-in-aid application filed by

such member or by any eligible institution in which such member has a financial interest, or with whom such member engages in any business, employment, transaction or professional activity.

(e) The Stem Cell Research Advisory Committee shall (1) develop, in consultation with the Commissioner of Public Health, a donated funds program to encourage the development of funds other than state appropriations for embryonic and human adult stem cell research in this state, (2) examine and identify specific ways to improve and promote for-profit and not-for-profit embryonic and human adult stem cell and related research in the state, including, but not limited to, identifying both public and private funding sources for such research, maintaining existing embryonic and human adult stem cell related businesses, recruiting new embryonic and human adult stem cell related businesses to the state and recruiting scientists and researchers in such field to the state, (3) establish and administer, in consultation with the Commissioner of Public Health, a stem cell research grant program which shall provide grants-in-aid to eligible institutions for the advancement of embryonic or human adult stem cell research in this state pursuant to section 2 of this act, and (4) monitor the stem cell research conducted by eligible institutions that receive such grants-in-aid.

(f) Connecticut Innovations, Incorporated shall serve as administrative staff of the committee and shall assist the committee in (1) developing the application for the grants-in-aid authorized under subsection (e) of this section, (2) reviewing such applications, (3) preparing and executing any assistance agreements or other agreements in connection with the awarding of such grants-in-aid, and (4) performing such other administrative duties as the committee deems necessary.

(g) Not later than June 30, 2007, and annually thereafter until June 30, 2015, the Stem Cell Research Advisory Committee shall report, in accordance with section 11-4a of the general statutes, to the Governor and the General Assembly on (1) the amount of grants-in-aid awarded to eligible institutions from the Stem Cell Research Fund pursuant to section 2 of this act, (2) the recipients of such grants-in-aid, and (3) the current status of stem cell research in the state.

Sec. 4. (NEW) (*Effective from passage*) (a) There is established a Stem Cell Research Peer Review Committee. The committee shall consist of five members appointed by the Commissioner of Public Health. All members appointed to the committee shall (1) have demonstrated knowledge and understanding of the ethical and medical implications of embryonic and human adult stem cell research or related research fields, including, but not limited to, embryology, genetics or cellular biology, (2) have practical research experience in human adult or embryonic stem cell research or related research fields, including, but not limited to, embryology, genetics or cellular biology, and (3) work to advance embryonic and human adult stem cell research. Members shall serve for a term of four years commencing on October first, except that three members first appointed by the Commissioner of Public Health shall serve for a term of two years. No member may serve for more than two consecutive four-year terms and no member may serve concurrently on the Stem Cell Research Advisory Committee established pursuant to section 3 of this act. All initial appointments to the committee shall be made by October 1, 2005. Any member who fails to attend three consecutive meetings or who fails to attend fifty per cent of all meetings held during any calendar year shall be deemed to have resigned from the committee.

(b) All members shall be deemed public officials and shall adhere to the code of ethics for public officials set forth in chapter 10 of the general statutes. No member shall participate in the affairs of the committee with respect to the review or consideration of any grant-in-aid application filed by such member or by any eligible institution with whom such member has a financial interest in, or

engages in any business, employment, transaction or professional activity.

(c) Prior to the awarding of any grants-in-aid for embryonic or human adult stem cell research pursuant to section 2 of this act, the Stem Cell Research Peer Review Committee shall review all applications submitted by eligible institutions for such grants-in-aid and make recommendations to the Commissioner of Public Health and the Stem Cell Research Advisory Committee established pursuant to section 3 of this act with respect to the ethical and scientific merit of each application.

(d) The Peer Review Committee shall establish guidelines for the rating and scoring of such applications by the Stem Cell Research Peer Review Committee.

(e) All members of the committee shall become and remain fully cognizant of the National Academies Guidelines For Human Embryonic Stem Cell Research, as from time to time amended, and the committee may make recommendations to the Stem Cell Research Advisory Committee and the Commissioner of Public Health concerning the adoption of said guidelines, in whole or in part, in the form of regulations adopted pursuant to chapter 54 of the general statutes.

Sec. 5. Subsection (c) of section 4-28e of the general statutes is repealed and the following is substituted in lieu thereof (*Effective from passage*):

(c) (1) For the fiscal year ending June 30, 2001, disbursements from the Tobacco Settlement Fund shall be made as follows: (A) To the General Fund in the amount identified as "Transfer from Tobacco Settlement Fund" in the General Fund revenue schedule adopted by the General Assembly; (B) to the Department of Mental Health and Addiction Services for a grant to the regional action councils in the amount of five hundred thousand dollars; and (C) to the Tobacco and Health Trust Fund in an amount equal to nineteen million five hundred thousand dollars.

(2) For the fiscal year ending June 30, 2002, and each fiscal year thereafter, disbursements from the Tobacco Settlement Fund shall be made as follows: (A) To the Tobacco and Health Trust Fund in an amount equal to twelve million dollars; (B) to the Biomedical Research Trust Fund in an amount equal to four million dollars; (C) to the General Fund in the amount identified as "Transfer from Tobacco Settlement Fund" in the General Fund revenue schedule adopted by the General Assembly; and (D) any remainder to the Tobacco and Health Trust Fund.

(3) For each of the fiscal years ending June 30, 2008, to June 30, 2015, inclusive, the sum of ten million dollars shall be disbursed from the Tobacco Settlement Fund to the Stem Cell Research Fund established by section 2 of this act, for grants-in-aid to eligible institutions for the purpose of conducting embryonic or human adult stem cell research.

Sec. 6. (*Effective from passage*) The sum of twenty million dollars is appropriated to the Stem Cell Research Fund established by section 2 of this act, from the General Fund, for the fiscal year ending June 30, 2005.

Approved June 15, 2005

Stem Cell Basics

I. Introduction

Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as regenerative or reparative medicine.

Stem cells are one of the most fascinating areas of biology today. But like many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

The NIH developed this primer to help readers understand the answers to questions such as: What are stem cells? What different types of stem cells are there and where do they come from? What is the potential for new medical treatments using stem cells? What research is needed to make such treatments a reality?

A. What are stem cells and why are they important?

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under certain physiologic or experimental conditions, 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.

Scientists primarily work with two kinds of stem cells from animals and humans: embryonic stem cells and adult stem cells, which have different functions and characteristics that will be explained in this document. Scientists discovered ways to obtain or derive stem cells from early *mouse* embryos more than 20 years ago. Many years of detailed study of the biology of mouse stem cells led to the discovery, in 1998, of how to isolate stem cells from *human* embryos and grow the cells in the laboratory. These are called human embryonic stem cells. The embryos used in these studies were created for infertility purposes through in vitro fertilization procedures and when they were no longer needed for that purpose, they were donated for research with the informed consent of the donor.

Stem cells are important for living organisms for many reasons. In the 3 to 5 day old embryo, called a blastocyst, a small group of about 30 cells called the inner cell mass gives rise to the hundreds of highly specialized cells needed to make up an adult organism. In the developing fetus, stem cells in developing tissues give rise to the multiple specialized cell types that make up the heart, lung, skin, and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease.

It has been hypothesized by scientists that stem cells may, at some point in the future, become the basis for treating diseases such as Parkinson's disease, diabetes, and heart disease.

Scientists want to study stem cells in the laboratory so they can learn about their essential properties and what makes them different from specialized cell types. As scientists learn more about stem cells, it may become possible to use the cells not just in cell-based therapies, but also for screening new drugs and toxins and understanding birth defects. However, as mentioned above, human embryonic stem cells have only been studied since 1998. Therefore, in order to develop such treatments scientists are intensively studying the fundamental properties of stem cells, which include:
1) determining precisely how stem cells remain unspecialized and self renewing for many years; and 2) identifying the signals that cause stem cells to become specialized cells.

B. Scope of this document

This primer on stem cells is intended for anyone who wishes to learn more about the biological properties of stem cells, the important questions about stem cells that are the focus of scientific research, and the potential use of stem cells in research and in treating disease. The primer includes information about stem cells derived from the embryo and adult. Much of the information included here is about stem cells derived from human tissues, but some studies of animal-derived stem cells are also described.

II. What are the unique properties of all stem cells?

Stem cells differ from other kinds of cells in the body. All stem cells — regardless of their source — have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized; and they can give rise to specialized cell types.

Stem Cells for the Future Treatment of Parkinson's Disease

Parkinson's disease (PD) is a very common neurodegenerative disorder that affects more than 2% of the population over 65 years of age. PD is caused by a progressive degeneration and loss of dopamine (DA)-producing neurons, which leads to tremor, rigidity, and hypokinesia (abnormally decreased mobility). It is thought that PD may be the first disease to be amenable to treatment using stem cell transplantation. Factors that support this notion include the knowledge of the specific cell type (DA neurons) needed to relieve the symptoms of the disease. In addition, several laboratories have been successful in developing methods to induce embryonic stem cells to differentiate into cells with many of the functions of DA neurons.

In a recent study, scientists directed mouse embryonic stem cells to differentiate into DA neurons by introducing the gene Nurr1. When transplanted into the brains of a rat model of PD, these stem cell-derived DA neurons reinnervated the brains of the rat Parkinson model, released dopamine and improved motor function.

Regarding human stem cell therapy, scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease. The successful generation of an unlimited supply of dopamine neurons could make neurotransplantation widely available for Parkinson's patients at some point in the future.

Information Center
- Stem Cell Basics
- Scientific Progress & Future Directions
- Clinical Trials
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Scientists are trying to understand two fundamental properties of stem cells that relate to their long-term self-renewal: 1) why can *embryonic* stem cells proliferate for a year or more in the laboratory without differentiating, but most *adult* stem cells cannot; and 2) what are the factors in living organisms that normally regulate stem cell proliferation and self-renewal? Discovering the answers to these questions may make it possible to understand how cell proliferation is regulated during normal embryonic development or during the abnormal cell division that leads to cancer. Importantly, such information would enable scientists to grow embryonic and adult stem cells more efficiently in the laboratory.

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Stem cells are unspecialized. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell); it cannot carry molecules of oxygen through the bloodstream (like a red blood cell); and it cannot fire electrochemical signals to other cells that allow the body to move or speak (like a nerve cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

Stem cells are capable of dividing and renewing themselves for long periods. Unlike muscle cells, blood cells, or nerve cells — which do not normally replicate themselves — stem cells may replicate many times. When cells replicate themselves many times over it is called proliferation. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal.

The specific factors and conditions that allow stem cells to remain unspecialized are of great interest to scientists. It has taken scientists many years of trial and error to learn to grow stem cells in the laboratory without them spontaneously differentiating into specific cell types. For example, it took 20 years to learn how to grow human embryonic stem cells in the laboratory following the development of conditions for growing mouse stem cells. Therefore, an important area of research is understanding the signals in a mature organism that cause a stem cell population to proliferate and remain unspecialized until the cells are needed for repair of a specific tissue. Such information is critical for scientists to be able to grow large numbers of unspecialized stem cells in the laboratory for further experimentation.

Stem cells can give rise to specialized cells. When unspecialized stem cells give rise to specialized cells, the process is called differentiation. Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The internal signals are controlled by a cell's genes, which are interspersed across long strands of DNA, and carry coded instructions for all the structures and functions of a cell. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the microenvironment.

Therefore, many questions about stem cell differentiation remain. For example, are the internal and external signals for cell differentiation similar for all kinds of stem cells? Can specific sets of signals be identified that promote differentiation into specific cell types? Addressing these questions is critical because the answers may lead scientists to find new ways of controlling stem cell differentiation in the laboratory, thereby growing cells or tissues that can be used for specific purposes including cell-based therapies.

Adult stem cells typically generate the cell types of the tissue in which they reside. A blood-forming adult stem cell in the bone marrow, for example, normally gives rise to the many types of blood cells such as red blood cells, white blood cells and platelets. Until recently, it had been thought that a blood-forming cell in the bone marrow — which is called a hematopoietic stem cell — could not give rise to the cells of a very different tissue, such as nerve cells in the brain. However, a number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as plasticity. Examples of such plasticity include blood cells becoming neurons, liver cells that can be made to produce insulin, and hematopoietic stem cells that can develop into heart muscle. Therefore, exploring the possibility of using adult stem cells for cell-based therapies has become a very active area of investigation by researchers.

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III. What are embryonic stem cells?

A. What stages of early embryonic development are important for generating embryonic stem cells?

Embryonic stem cells, as their name suggests, are derived from embryos. Specifically, embryonic stem cells are derived from embryos that develop from eggs that have been fertilized *in vitro* — in an *in vitro* fertilization clinic — and then donated for research purposes with informed consent of the donors. They are *not* derived from eggs fertilized in a woman's body. The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of cells called the blastocyst. The blastocyst includes three structures: the trophoblast, which is the layer of cells that surrounds the blastocyst; the blastocoel, which is the hollow cavity inside the blastocyst; and the inner cell mass, which is a group of approximately 30 cells at one end of the blastocoel.

B. How are embryonic stem cells grown in the laboratory?

Growing cells in the laboratory is known as cell culture. Human embryonic stem cells are isolated by transferring the inner cell mass into a plastic laboratory culture dish that contains a nutrient broth known as culture medium. The cells divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they will not divide. This coating layer of cells is called a feeder layer. The reason for having the mouse cells in the bottom of the culture dish is to give the inner cell mass cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium. Recently, scientists have begun to devise ways of growing embryonic stem cells without the mouse feeder cells. This is a significant scientific advancement because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells.

Over the course of several days, the cells of the inner cell mass proliferate and begin to crowd the culture dish. When this occurs, they are removed gently and plated into several fresh culture dishes. The process of replating the cells is repeated many times and for many months, and is called subculturing. Each cycle of subculturing the cells is referred to as a passage. After six months or more, the original 30 cells of the inner cell mass yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating, are pluripotent, and appear genetically normal, are referred to as an embryonic stem cell line.

Once cell lines are established, or even before that stage, batches of them can be frozen and shipped to other laboratories for further culture and experimentation.

C. What laboratory tests are used to identify embryonic stem cells?

At various points during the process of generating embryonic stem cell lines, scientists test the cells to see whether they exhibit the fundamental properties that make them embryonic stem cells. This process is called characterization.

As yet, scientists who study human embryonic stem cells have not agreed on a standard battery of tests that measure the cells' fundamental properties. Also, scientists acknowledge that many of the tests they do use may not be good indicators of the cells' most important biological properties and functions. Nevertheless, laboratories that grow human embryonic stem cell lines use several kinds of tests. These tests include:

- growing and subculturing the stem cells for many months. This ensures that the cells are capable of long-term self-renewal. Scientists inspect the cultures through a microscope to see that the cells look healthy and remain undifferentiated.
- using specific techniques to determine the presence of surface markers that are found only on undifferentiated cells. Another important test is for the presence of a protein called Oct-4, which undifferentiated cells typically make. Oct-4 is a transcription factor, meaning that it helps turn genes on and off at the right time, which is an important part of the processes of cell differentiation

and embryonic development.

- examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells.
- determining whether the cells can be subcultured after freezing, thawing, and replating.
- testing whether the human embryonic stem cells are pluripotent by 1) allowing the cells to differentiate spontaneously in cell culture; 2) manipulating the cells so they will differentiate to form specific cell types; or 3) injecting the cells into an immunosuppressed mouse to test for the formation of a benign tumor called a teratoma. Teratomas typically contain a mixture of many differentiated or partly differentiated cell types — an indication that the embryonic stem cells are capable of differentiating into multiple cell types.

D. How are embryonic stem cells stimulated to differentiate?

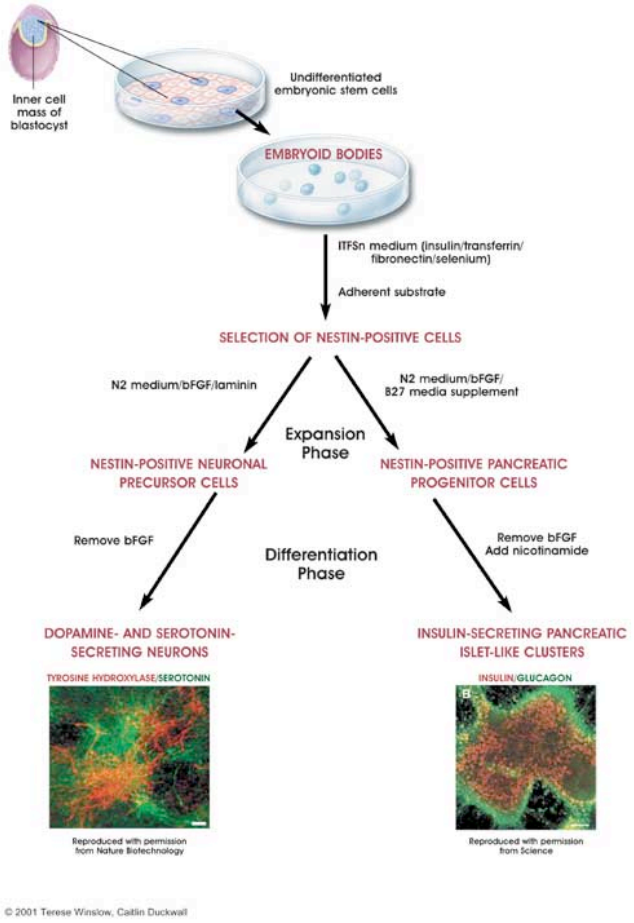

Figure 1. Directed differentiation of mouse embryonic stem cells. Click here for larger image.

As long as the embryonic stem cells in culture are grown under certain conditions, they can remain undifferentiated (unspecialized). But if cells are allowed to clump together to form embryoid bodies, they begin to differentiate spontaneously. They can form muscle cells, nerve cells, and many other cell types. Although spontaneous differentiation is a good indication that a culture of embryonic stem cells is healthy, it is not an efficient way to produce cultures of specific cell types.

So, to generate cultures of specific types of differentiated cells — heart muscle cells, blood cells, or nerve cells, for example — scientists try to control the differentiation of embryonic stem cells. They change the chemical composition of the culture medium, alter the surface of the culture dish, or modify the cells by inserting specific genes. Through years of experimentation scientists have established some basic protocols or "recipes" for the directed differentiation of embryonic stem cells into some specific cell types (Figure 1). (For more examples of directed differentiation of embryonic stem cells, see Chapters 5-9 and Appendices B and C of the NIH report "Stem Cells: Scientific Progress and Future Research Directions" go to http://stemcells.nih.gov/stemcell/scireport.asp)

If scientists can reliably direct the differentiation of embryonic stem cells into specific cell types, they may be able to use the resulting, differentiated cells to treat certain diseases at some point in the future. Diseases that might be treated by transplanting cells generated from human embryonic stem cells include Parkinson's disease, diabetes, traumatic spinal cord injury, Purkinje cell degeneration, Duchenne's muscular dystrophy, heart disease, and vision and hearing loss.

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IV. What are adult stem cells?

An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ, can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. Some scientists now use the term somatic stem cell instead of adult stem cell. Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), the origin of adult stem cells in mature tissues is unknown.

Research on adult stem cells has recently generated a great deal of excitement. Scientists have found adult stem cells in many more tissues than they once thought possible. This finding has led scientists to ask whether adult stem cells could be used for transplants. In fact, adult blood forming stem cells from bone marrow have been used in transplants for 30 years. Certain kinds of adult stem cells seem to have the ability to differentiate into a number of different cell types, given the right conditions. If this differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of therapies for many serious common diseases.

The history of research on adult stem cells began about 40 years ago. In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population, called bone

marrow stromal cells was discovered a few years later. Stromal cells are a mixed cell population that generates bone, cartilage, fat, and fibrous connective tissue.

Also in the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells, which become nerve cells. Despite these reports, most scientists believed that new nerve cells could not be generated in the adult brain. It was not until the 1990s that scientists agreed that the adult brain does contain stem cells that are able to generate the brain's three major cell types — astrocytes and oligodendrocytes, which are non-neuronal cells, and neurons or nerve cells.

A. Where are adult stem cells found and what do they normally do?

Adult stem cells have been identified in many organs and tissues. One important point to understand about adult stem cells is that there are a very small number of stem cells in each tissue. Stem cells are thought to reside in a specific area of each tissue where they may remain quiescent (non-dividing) for many years until they are activated by disease or tissue injury. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin and liver.

Scientists in many laboratories are trying to find ways to grow adult stem cells in cell culture and manipulate them to generate specific cell types so they can be used to treat injury or disease. Some examples of potential treatments include replacing the dopamine-producing cells in the brains of Parkinson's patients, developing insulin-producing cells for type I diabetes and repairing damaged heart muscle following a heart attack with cardiac muscle cells.

B. What tests are used for identifying adult stem cells?

Scientists do not agree on the criteria that should be used to identify and test adult stem cells. However, they often use one or more of the following three methods: (1) labeling the cells in a living tissue with molecular markers and then determining the specialized cell types they generate; (2) removing the cells from a living animal, labeling them in cell culture, and transplanting them back into another animal to determine whether the cells repopulate their tissue of origin; and (3) isolating the cells, growing them in cell culture, and manipulating them, often by adding growth factors or introducing new genes, to determine what differentiated cells types they can become.

Also, a single adult stem cell should be able to generate a line of genetically identical cells — known as a clone — which then gives rise to all the appropriate differentiated cell types of the tissue. Scientists tend to show either that a stem cell can give rise to a clone of cells in cell culture, or that a purified population of candidate stem cells can repopulate the tissue after transplant into an animal. Recently, by infecting adult stem cells with a virus that gives a unique identifier to each individual cell, scientists have been able to demonstrate that individual adult stem cell clones have the ability to repopulate injured tissues in a living animal.

C. What is known about adult stem cell differentiation?

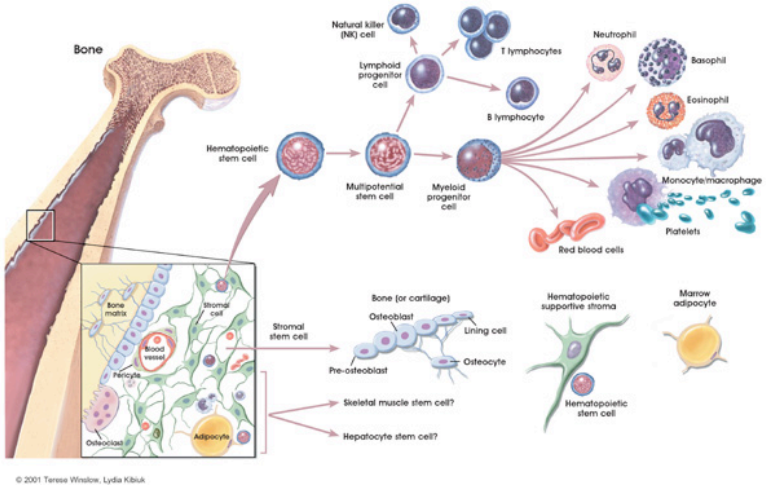

Figure 2. Hematopoietic and stromal stem cell differentiation. Click here for larger image.

As indicated above, scientists have reported that adult stem cells occur in many tissues and that they enter normal differentiation pathways to form the specialized cell types of the tissue in which they reside. Adult stem cells may also exhibit the ability to form specialized cell types of other tissues, which is known as transdifferentiation or plasticity.

Normal differentiation pathways of adult stem cells. In a living animal, adult stem cells can divide for a long period and can give rise to mature cell types that have characteristic shapes and specialized structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells (Figure 2).

- Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, macrophages, and platelets.
- Bone marrow stromal cells (mesenchymal stem cells) give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.
- Neural stem cells in the brain give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells — astrocytes and oligodendrocytes.
- Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.
- Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the hair follicle and to the epidermis.

Adult stem cell plasticity and transdifferentiation. A number of experiments have suggested that certain adult stem cell types are pluripotent. This ability to differentiate into multiple cell types is called plasticity or transdifferentiation. The following list offers examples of adult stem cell plasticity that have been reported during the past few years.

- Hematopoietic stem cells may differentiate into: three major types of brain cells (neurons, oligodendrocytes, and astrocytes); skeletal muscle cells; cardiac muscle cells; and liver cells.
- Bone marrow stromal cells may differentiate into: cardiac muscle cells and skeletal muscle cells.
- Brain stem cells may differentiate into: blood cells and skeletal muscle cells.

Current research is aimed at determining the mechanisms that underlie adult stem cell plasticity. If such mechanisms can be identified and controlled, existing stem cells from a healthy tissue might be induced to repopulate and repair a diseased tissue (Figure 3).

D. What are the key questions about adult stem cells?

Many important questions about adult stem cells remain to be answered. They include:

- How many kinds of adult stem cells exist, and in which tissues do they exist?
- What are the sources of adult stem cells in the body? Are they "leftover" embryonic stem cells, or do they arise in some other way? Why do they remain in an undifferentiated state when all the cells around them have differentiated?
- Do adult stem cells normally exhibit plasticity, or do they only transdifferentiate when scientists manipulate them experimentally? What are the signals that regulate the proliferation and differentiation of stem cells that demonstrate plasticity?
- Is it possible to manipulate adult stem cells to enhance their proliferation so that sufficient tissue for transplants can be produced?
- Does a single type of stem cell exist — possibly in the bone marrow or circulating in the blood — that can generate the cells of any organ or tissue?
- What are the factors that stimulate stem cells to relocate to sites of injury or damage?

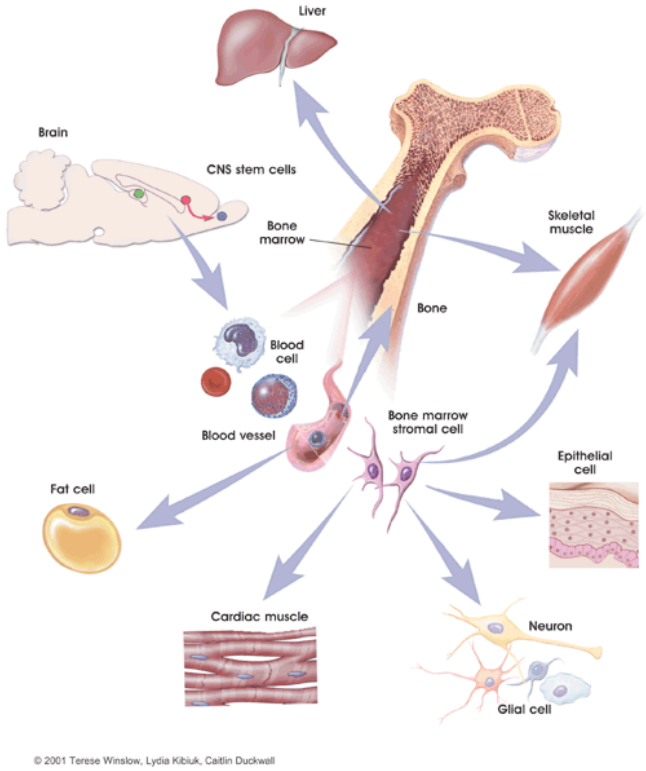

Figure 3. Plasticity of adult stem cells. Click here for larger image.

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V. What are the similarities and differences between embryonic and adult stem cells?

Human embryonic and adult stem cells each have advantages and disadvantages regarding potential use for cell-based regenerative therapies. Of course, adult and embryonic stem cells differ in the number and type of differentiated cells types they can become. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are generally limited to differentiating into different cell types of their tissue of origin. However, some evidence suggests that adult stem cell plasticity may exist, increasing the number of cell types a given adult stem cell can become.

Large numbers of embryonic stem cells can be relatively easily grown in culture, while adult stem cells are rare in mature tissues and methods for expanding their numbers in cell culture have not yet been worked out. This is an important distinction, as large numbers of cells are needed for stem cell replacement therapies.

A potential advantage of using stem cells from an adult is that the patient's own cells could be expanded in culture and then reintroduced into the patient. The use of the patient's own adult stem cells would mean that the cells would not be rejected by the immune system. This represents a significant advantage as immune rejection is a difficult problem that can only be circumvented with immunosuppressive drugs.

Embryonic stem cells from a donor introduced into a patient could cause transplant rejection. However, whether the recipient would reject donor embryonic stem cells has not been determined in human experiments.

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VI. What are the potential uses of human stem cells and the obstacles that must be overcome before these potential uses will be realized?

There are many ways in which human stem cells can be used in basic research and in clinical research. However, there are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research.

Studies of human embryonic stem cells may yield information about the complex events that occur during human development. A primary goal of this work is to identify how undifferentiated stem cells become differentiated. Scientists know that turning genes on and off is central to this process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. A significant hurdle to this use and most uses of stem cells is that scientists do not yet fully understand the signals that turn specific genes on and off to influence the differentiation of the stem cell.

Human stem cells could also be used to test new drugs. For example, new medications could be tested for safety on differentiated cells generated from human pluripotent cell lines. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to screen potential anti-tumor drugs. But, the availability of pluripotent stem cells would allow drug testing in a wider range of cell types. However, to screen drugs effectively, the conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into the specific cell type on which drugs will be tested. Current knowledge of the signals controlling differentiation fall well short of being able to mimic these conditions precisely to consistently have identical differentiated cells for each drug being tested.

Perhaps the most important potential application of human stem cells is the generation of cells and tissues

that could be used for cell-based therapies. Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

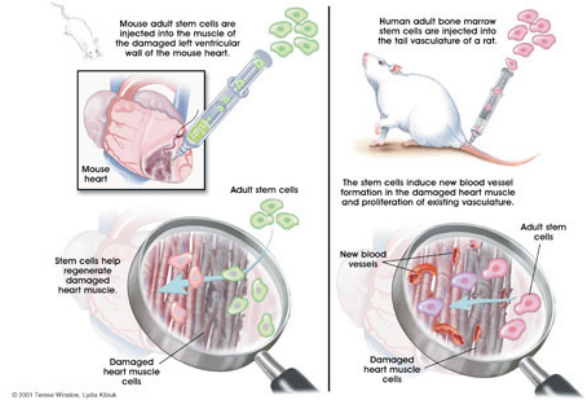

Figure 4. Heart muscle repair with adult stem cells. Click here for larger image.

For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Preliminary research in mice and other animals indicates that bone marrow stem cells, transplanted into a damaged heart, can generate heart muscle cells and successfully repopulate the heart tissue. Other recent studies in cell culture systems indicate that it may be possible to direct the differentiation of embryonic stem cells or adult bone marrow cells into heart muscle cells (Figure 4).

In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics.

To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able to easily and reproducibly manipulate stem cells so that they possess the necessary characteristics for successful differentiation, transplantation and engraftment. The following is a list of steps in successful cell-based treatments that scientists will have to learn to precisely control to bring such treatments to the clinic. To be useful for transplant purposes, stem cells must be reproducibly made to:

- Proliferate extensively and generate sufficient quantities of tissue.
- Differentiate into the desired cell type(s).
- Survive in the recipient after transplant.
- Integrate into the surrounding tissue after transplant.
- Function appropriately for the duration of the recipient's life.
- Avoid harming the recipient in any way.

Also, to avoid the problem of immune rejection, scientists are experimenting with different research strategies to generate tissues that will not be rejected.

To summarize, the promise of stem cell therapies is an exciting one, but significant technical hurdles remain that will only be overcome through years of intensive research.

The NIH has a wide array of new scientific programs designed to support research that uses embryonic stem cell lines.

VII. Where can I get more information?

The following Web sites contain information about stem cells. NIH is responsible only for the content of its own Web site.

1. http://stemcells.nih.gov/
A listing of all the information about stem cells on the NIH Web site.

2. http://www.news.wisc.edu/packages/stemcells/
The University of Wisconsin's Web site about stem cells, written for general audiences.

3. http://www.eurekalert.org/
EurekAlert! is a publicly accessible science news site run by the American Association for the Advancement of Sciences. Search for "stem cells."

4. http://scitechdaily.com/
A site that offers a range of news articles, features, and commentaries about science and technology topics. Search for "stem cells."

5. http://www.sciam.com/index.cfm
The Web site for Scientific American. Search for "stem cells."

6. http://www.reuters.com/news.jhtml?type=science
The Reuters news site for stories about science. Search for "stem cells" and select "News and Pictures."

7. http://www.stemcellresearchnews.com/
A commercial, online newsletter that features stories about stem cells of all types.

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VIII. Glossary

Adult stem cell — An undifferentiated cell found in a differentiated tissue that can renew itself and (with certain limitations) differentiate to yield all the specialized cell types of the tissue from which it originated.

Astrocyte — One of the large neuroglia cells of neural tissues.

Blastocoel — The cavity in the blastula of the developing embryo.

Blastocyst — A preimplantation embryo of about 150 cells. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the

In vitro — Literally, "in glass"; in a laboratory dish or test tube; an artificial environment.

In vitro fertilization — An assisted reproduction technique in which fertilization is accomplished outside the body.

Inner cell mass — The cluster of cells inside the blastocyst. These cells give rise to the embryonic disk of the later embryo and, ultimately, the fetus.

Long-term self-renewal — The ability of stem cells to renew themselves by dividing into the same non-specialized cell type over long periods (many months to years) depending on the specific type of stem cell.

blastocoel), and a cluster of cells on the interior (the inner cell mass).

Bone marrow stromal cells — A stem cell found in bone marrow that generates bone, cartilage, fat, and fibrous connective tissue.

Cell division — Method by which a single cell divides to create two cells. This continuous process allows a population of cells to increase in number or maintain its numbers.

Cell-based therapies — treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or depleted adult cell populations or tissues.

Cell culture — Growth of cells in vitro on an artificial medium for experimental research.

Clone — A line of cells that is genetically identical to the originating cell; in this case, a stem cell.

Culture medium — The broth that covers cells in a culture dish, which contains nutrients to feed the cells as well as other growth factors that may be added to direct desired changes in the cells.

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

Directed differentiation — Manipulating stem cell culture conditions to induce differentiation into a particular cell type.

DNA — Deoxyribonucleic acid, a chemical found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.

Ectoderm — Upper, outermost layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise to skin nerves and brain.

Embryo — In humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.

Embryoid bodies — Clumps of cellular structures that arise when embryonic stem cells are cultured.

Embryonic germ cells — Cells found in a specific part of the embryo/fetus called the gonadal ridge that normally develop into mature gametes.

Embryonic stem cells — Primitive (undifferentiated) cells from the embryo that have the potential to becomea wide variety of specialized cell types.

Embryonic stem cell line — Embryonic stem cells, which have been cultured under in vitro conditions that allow proliferation without differentiation for months to years.

Endoderm — Lower layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise tolungs and digestive organs.

Feeder layer — Cells used in co-culture to maintain pluripotent stem cells. Cells usually consist of mouse embryonic fibroblasts.

Fertilization — The process whereby male and female gametes unite.

Fetus — A developing human from usually two months after conception to birth.

Gene — A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene directs the formation of an enzyme or other protein.

Hematopoietic stem cell — A stem cell from which all red and white blood cells develop.

Human embryonic stem cell — A type of pluripotent stem cell derived from the inner cell mass of the blastocyst.

Mesenchymal stem cells — Cells from the immature embryonic connective tissue. A number of celltypes come from mesenchymal stem cells, includingchondrocytes, which produce cartilage.

Mesoderm — Middle layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise tobone, muscle, and connective tissue.

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 are important in determining the characteristicsof the cell.

Neural stem cell — A stem cell found in adult neural tissue that can give rise to neurons, astrocytes, and oligodendrocytes.

Neurons — Nerve cells, the structural and functional unit of the nervous system. A neuron consists of a cell body and its processes, an axon, and one or more dendrites. Neurons function by the initiation and conduction of impulses and transmit impulses to other neurons or cells by releasing neurotransmitters at synapses.

Oligodendrocyte — A cell that provides insulation to nerve cells by forming a myelin sheath around axons.

Passage — A round of cell growth and proliferationin cell culture.

Plasticity — The ability of stem cells from one adult tissue to generate the differentiated cell types of another tissue.

Pluripotent — Ability of a single stem cell to develop into many different cell types of the body.

Proliferation — Expansion of a population of cells by the continuous division of single cells into two identical daughter cells.

Regenerative or reparative medicine — A treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or depleted adult cell populations or tissues.

Signals — Internal and external factors that control changes in cell structure and function.

Somatic stem cells — Another name for adult stem cells.

Stem cells — Cells with the ability to divide for indefinite periods in culture and to give rise to specialized cells.

Stromal cells — Non-blood cells derived fromblood organs, such as bone marrow or fetal liver, whichare capable of supporting growth of blood cells in vitro. Stromal cells that make this matrix within the bone marrow are also derived from mesenchymal stem cells.

Subculturing — The process of growing and replating cells in tissue culture for many months.

Surface markers — Surface proteins that are unique to certain cell types, which are visualized using antibodies or other detection methods.

Teratoma — A tumor composed of tissues from the three embryonic germ layers. Usually found in ovary and testis. Produced experimentally in animals by injectingpluripotent stem cells, in order to determine the stem cells' abilities to differentiate into various types of tissues.

Transdifferentiation — The observation that stem cells from one tissue may be able to differentiate into cells of another tissue.

Trophoblast — The extraembryonic tissue responsible for implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Undifferentiated — Not having changed to become a specialized cell type.

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By JENNIFER BROOKS
News Journal Washington Bureau

WASHINGTON - Economics is joining ethics at the heart of the debate over embryonic stem cell research.

Scientists believe that stem cells - harvested from days-old human embryos and capable of growing into nerves, organs or any other cell in the body - may someday hold the key to curing diseases and repairing crippling injuries. And while scientists search for cures, states hope to cash in on the nation's multibillion-dollar biotechnology boom.

But most of the embryonic stem cell research in the United States today is going ahead without support from the federal government. President Bush cut off most embryonic stem cell funding five years ago because he opposed the idea of destroying a human embryo for medical research.

A growing number of states are offering their own research grants or considering rewriting their laws in hopes of attracting biotech jobs and research dollars.

More than 180 stem cell bills were introduced in state legislatures last year, up from just 60 bills drafted in 2004, according to the National Conference of State Legislatures. But the bills are a conflicting mishmash. Some bills would encourage stem cell research, others would criminalize it. Often, legislatures juggle competing stem cell legislation in a single year.

California has pledged to spend $3 billion over the next decade to turn the state into a hub for stem cell research. New Jersey already has begun awarding state-funded stem cell research grants.

On the other side, Louisiana and South Dakota have passed laws prohibiting embryonic research. Nebraska and Arizona limit the use of state funds for such studies.

"Our states are now passing their own laws. They're not waiting around for us to do something," said U.S. Rep. Mike Castle, R-Del., author of a bill that would lift the federal funding limits on embryonic stem cell research. The bill passed the House last year and is expected to pass the Senate if brought to the floor. President Bush has threatened a veto.

California estimates its $3 billion stem cell investment could pay off with $10 billion in job growth and economic development. Rust Belt states such as Ohio and Michigan are courting biotechnology firms in

hopes of replacing lost blue-collar factory jobs with white lab-coat jobs.

The biotech industry is following the state stem cell debates closely. "We're looking for good science- and research-friendly environments," said Christopher Sampson, spokesman for pharmaceutical giant AstraZeneca, which has its U.S. headquarters in Fairfax.

Although the company is not engaged in stem cell research, it may do so in the future, he said. Biotech-friendly legislation could tip the balance for research companies trying to decide where to open a new lab, he said.

Some states are considering stem cell legislation just to keep their neighbors from poaching their researchers.

Last summer, Illinois Democratic Gov. Rod Blagojevich sent a letter to the head of Missouri's celebrated Stowers Institute for Medical Research, which has a $2 billion research endowment. Its plans to expand were put on hold after the Missouri Legislature tried to restrict embryonic stem cell research.

Blagojevich invited the institute to pull up stakes and move 200 miles across the border to stem cell-friendly Illinois.
Missouri's Republican Gov. Matt Blunt responded by throwing his support behind a November ballot initiative that would not only encourage embryonic stem-cell research, but also allow cloning of human embryos for research purposes. For Blunt, it was a choice between alienating his political allies or risking the loss of Missouri's prized biomedical research hub.

Also expected to push legislation supportive of embryonic stem cell research this year are Republican Govs. Bob Taft of Ohio and Robert Ehrlich of Maryland and Democrats Jim Doyle of Wisconsin and Jennifer Granholm of Michigan.

The state initiatives have outraged opponents of abortion and embryonic research.

The Missouri Right to Life coalition has labeled the cloning ballot initiative "clone and kill" and accused the governor of knuckling under to the Chamber of Commerce. The Catholic Bishops of Illinois described Blagojevich's stem cell grants as "betraying his own office, both morally and politically."

Contact Jennifer Brooks at (202) 906-8117 or jabrooks@gns.gannett.com.

VARYING RULES
States have a confusing array of regulations on whether, when and how research can be conducted on embryonic stem cells.
About half of all states restrict the sale of fetuses or embryos.
Louisiana is the only state that bans all research on embryos.
Illinois and Michigan prohibit research on live embryos.
Arkansas, Indiana, Iowa, Michigan, North Dakota and South Dakota prohibit research on cloned embryos. Virginia's law also may ban research on cloned embryos, but the statute may leave room for interpretation.

California, Connecticut, Massachusetts, New Jersey and Rhode Island prohibit reproductive cloning, but allow embryonic cloning for research.
Arizona prohibits the use of public funds for reproductive or therapeutic cloning. Nebraska limits the use of state funds for embryonic stem-cell research.
New Jersey, California, Connecticut and Illinois have authorized state funding of embryonic stem-cell research, although only New Jersey has actually awarded any research funds. Massachusetts is considering a similar fund. Ohio, Indiana and Virginia created funds for adult stem-cell research, but not embryonic.
Source: National Conference of State Legislatures
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>From courant.com

UConn Advances Stem Cell Capabilities

By WILLIAM HATHAWAY
Courant Staff Writer

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The University of Connecticut Health Center has hired an expert on human embryonic stem cells and also has reached a tentative agreement to lease a Farmington building as headquarters of its new stem cell institute, university officials said Wednesday.

As soon as April, UConn scientists will be ready to work with human stem cell lines, including those ineligible to receive federal funding.

Overseeing the human stem cell effort will be Dr. Ren-He Xu, a senior scientist at the WiCell Research Institute, a private laboratory affiliated with the University of Wisconsin. WiCell creates human embryonic stem cell lines and distributes them to scientists nationally.

Xu, who will also hold an appointment at the Center for Regenerative Biology in Storrs, will start work in April. The university has begun efforts to acquire human embryonic stem cell lines, said Marc Lalande, chairman of the department of genetics and developmental biology at UConn.

"We're ready to go," Lalande said.

Under guidelines ordered by President Bush, human embryonic cells created after August 2001 are ineligible for federal funding. The funding restrictions prompted Connecticut to become the third state to approve funding for human embryonic research. Lalande said the hiring of Xu puts UConn in a strong position to apply for funding from the state, which is expected to make $20 million available this spring.

The federal funding restrictions also forced institutions such as UConn and Yale University that want to conduct research with human embryonic cells to search out lab space and equipment that were not built or purchased with federal dollars.

UConn has tentatively agreed to enter into a 20-year lease of the Farmtech building, a 108,000-square-foot building near the health center campus. The deal requires approval of the trustees of both the health center and university, said Bruce Carlson, chief of staff at the health center, who negotiated the deal.

Carlson declined to disclose financial terms of the lease but said the building is big enough to house stem cell laboratories and companies that might want to commercialize scientific discoveries.

Lalande said many UConn scientists at both the Farmington and Storrs campuses have expressed interest in human embryonic stem cell research. He said the university has already contacted both Harvard University

and Xu's former employer, WiCell, to obtain human embryonic stem cell lines.

In addition, Xiangzhong "Jerry" Yang, director of the Center for Regenerative Biology in Storrs, has proposed creating new embryonic stem cell lines through cloning. The procedure would create new cell lines by fusing DNA from a skin cell of a patient and an egg with its nucleus removed, to create embryonic cells genetically identical to donor DNA.

Stem Cell Panel Issues Decision

By WILLIAM HATHAWAY
Courant Staff Writer

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First dibs on $20 million in state stem cell funds should go to scientists working with human embryonic cells that are ineligible for federal funding, the state stem cell research advisory committee decided Tuesday.

The committee also decided it would consider research proposals made by individual scientists - not just large proposals submitted by major research institutions such as Yale University and the University of Connecticut.

Academic administrators and Connecticut scientists have been waiting for the committee to issue guidelines about how to apply for $100 million in stem cell funds that are scheduled to be made available over the next 10 years.

The committee, which hopes to begin distributing two-year grants worth $20 million later this spring, did not specify how much money should go to laboratory research and how much should be used for capital investments on new facilities.

While scientists who work on stem cells in animals will be able to apply for funds, most committee members endorsed the idea that priority for funds should go to scientists working with human embryonic cell lines that are not approved for federal funding.

"This was clearly not intended to be a global source of funds for research," said Dr. J. Robert Galvin, the state public health commissioner and chairman of the committee.

Under guidelines issued by President Bush, no federal research money can fund research using human embryonic stem cells created after August 2001. Academic institutions that receive federal research funds have taken that to mean that in order to avoid violating federal prohibitions, they may need to create whole new laboratories and purchase new equipment in order to conduct research using newer embryonic cell lines.

Some scientists and administrators at both Yale and UConn had assumed each school would submit a single proposal encompassing research efforts of many of their scientists. However, a tentative proposal to limit grants to individual UConn researchers to $100,000 appeared to rule out an ambitious and controversial plan by Xiangzhong "Jerry" Yang, director of UConn's Center of Regenerative Biology in Storrs, to clone human embryos to create embryonic cells that would be a genetic match to individual patients.

The committee Tuesday decided it will also consider individual grant applications from established individual researchers like Yang and set aside up to 10 percent of available funds for less established scientists.

Yang, who is a member of the stem cell advisory committee, said the actions were "a good start" to promoting stem cell research in Connecticut.

Less satisfied was a contingent from Yale who attended Tuesday's meeting. Diane Krause, acting director of the stem cell research program at Yale, called the committee's actions "confusing." For instance, the committee did not address whether state money could be used to offset costs of hiring a new stem cell director at Yale, she said.

It was also unclear how much of the state money would be set aside to create new laboratory space where human stem cell research could be conducted. UConn has identified a site near the UConn Health Center in Farmington while Yale has proposed setting aside one floor in a new research building to conduct such research.

Yang floated the idea of funding a single stem cell research center where all interested Connecticut scientists could conduct stem cell research.