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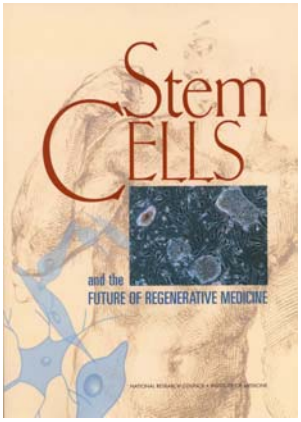

THE PROMISE OF STEM CELLS

FROM RESEARCH TO MEDICAL THERAPIES

As scientists search for treatments for disease, they often benefit from breakthroughs in understanding the basic biology of the cell. The discovery in the late 1800s of how enzymes work in cells, for instance, laid the groundwork that led to eventual treatments for some types of cancer. The sequence of the human genome, released in 2001, has introduced exciting possibilities for tackling the root causes of a wide array of diseases and inherited disorders.

Stem cells hold particular promise for unlocking life-saving secrets of the cell because of two important characteristics: 1) they are the primitive cells that give rise to different kinds of tissues in the body, and 2) they are "self-renewing" in the body and in the laboratory so that large quantities can be produced for medical purposes. Researchers hope that by harnessing the capabilities of stem cells they can generate specific tissues, such as heart, lung, or kidney tissue, which could then help repair damaged and diseased organs or provide alternatives to organ transplants. Stem cell therapy could offer hope for the millions who suffer from spinal-cord injuries, cardiovascular disease, autoimmune disease, diabetes, osteoporosis, cancer, Alzheimer's disease, Parkinson's disease and other disorders.

Stem cells are found in embryos during early stages of development, in fetal tissue and in some adult tissues. While some types of stem cells have been studied for many years, public awareness of stem cell research rose dramatically in 1998 when a team of scientists at the University of Wisconsin isolated the first human embryonic stem cells. Scientists believe that, because of their versatility, these cells could provide the fastest route to medical therapies. However, ethical issues concerning the use of early embryos have called the future of stem cell research into question.

What are the concerns about the various sources of stem cells? What are the characteristics of different stem cells? How do we proceed most responsibly from our current understanding to medical therapies?

To answer these and other fundamental questions, the National Academies formed the Committee on the Biological and Biomedical Applications of Stem Cell Research. The committee convened a workshop in June 2001 to hear from leading scientists engaged in stem cell research and from policy-makers, ethicists and legal experts. The committee report, *Stem Cells and the Future of Regenerative Medicine,* summarizes the workshop and the scientific and public policy concerns that present both opportunities and barriers to progress in this field.

Potential US Patient Populations for Stem Cell-Based Therapies.
High incidence of the following conditions suggests that stem cell research could potentially help millions of Americans.

Condition	Number of Patients
Cardiovascular disease	58 million
Autoimmune diseases	30 million
Diabetes	16 million
Osteoporosis	10 million
Cancers	8.2 million
Alzheimer's disease	5.5 million
Parkinson's disease	5.5 million
Burns (severe)	0.3 million
Spinal-cord injuries	0.25 million
Birth defects (per year)	0.15 million

Sources of Stem Cells: Possibilities and Limitations

Adult Stem Cells

The hope that many diseases may someday be treated with stem cell therapy is inspired by the historical success in using stem cells from bone marrow to treat patients with leukemia and other cancers, inherited blood disorders, and diseases of the immune system. The blood stem cells found in bone marrow, also known as hematopoietic stem cells, were discovered almost 40 years ago and are still among the few adult stem cells to be successfully isolated.

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Adult stem cells renew themselves continuously in some organs of the body, providing a source of new cells for those organs. Blood stem cells, for example, replenish the full complement of blood and immune system cells. Researchers continue to find new ways to take advantage of this characteristic. Since this report was produced, for example, French researchers announced in April 2002 success in treating a fatal inherited immune disorder by replacing a faulty gene in the patients' blood stem cells, which, when reintroduced into the patient, began generating normal healthy blood and immune system cells.

Adult stem cells have also been found in the eye, the brain, skeletal muscle, dental pulp, liver, skin, the lining of the gastrointestinal tract, and the pancreas. Animal studies suggest that at least some adult stem cells may be "plastic," or capable of becoming types of tissues other than those of the organ with which they are associated, although more conclusive evidence is needed.

Despite success in using adult stem cells to treat disease, several limitations hinder progress. Adult stem cells are present only in minute quantities, and isolating them is very difficult. Multiplying them outside the body is not yet possible in most cases. There is only preliminary evidence that stem cells obtained from an adult organ can be coaxed into becoming different tissue types, and it is not yet proven that adult stem cells give rise to fully functional cells. In addition, adult stem cells may contain DNA abnormalities from aging and accumulated mutations.

Embryonic Stem Cells

Embryonic stem cells (ESCs) are in many ways the ultimate stem cells for researchers. They are capable of becoming almost any type of cell or tissue (they are multipotent) and are easy to isolate and grow in laboratories. ESCs are found in embryos at about 5 - 6 days after fertilization when the embryo becomes a hollow sphere called a

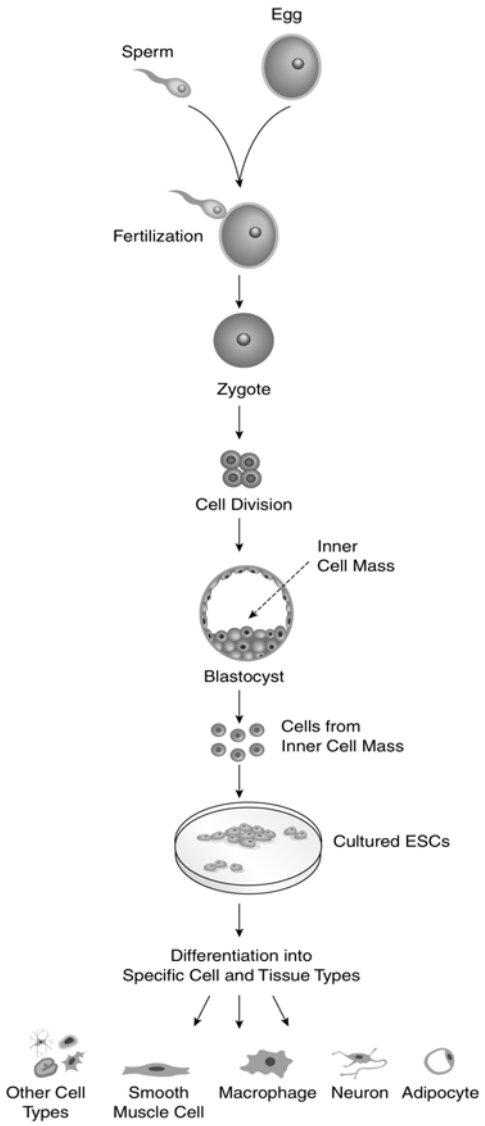

Figure 1. Isolation and culture of human ESCs by in vitro fertilization.

"blastocyst," which contains about 200 stem cells. Stem cells are removed from the blastocyst and put into a culture dish to produce a stem cell "line" (see Figure 1). Stem cell lines grow rapidly in the laboratory, sometimes through 300-400 population-doubling cycles, and they maintain a stable and normal complement of chromosomes.

Although human ESCs have only recently become available, scientists have learned a lot about ESCs through studies with animals conducted over the last 2 decades. These studies have shown some promising results for developing medical therapies. For example, transplanted embryonic stem cells from mice have restored some insulin regulation ability in mice with diabetes, relieved symptoms of Parkinson's disease in rodents, and partially restored neural function in animals with spinal-cord injuries. The research has also provided critical data on how stem cells differentiate into other types of cells. Mouse embryonic stem cells have been spurred to become fat cells, various brain and nervous system cells, insulin-producing cells, bone cells, blood cells, muscle cells, and others.

While mouse studies are important, scientists are especially interested in human embryonic stem cells because they potentially offer the fastest route to therapies for humans.

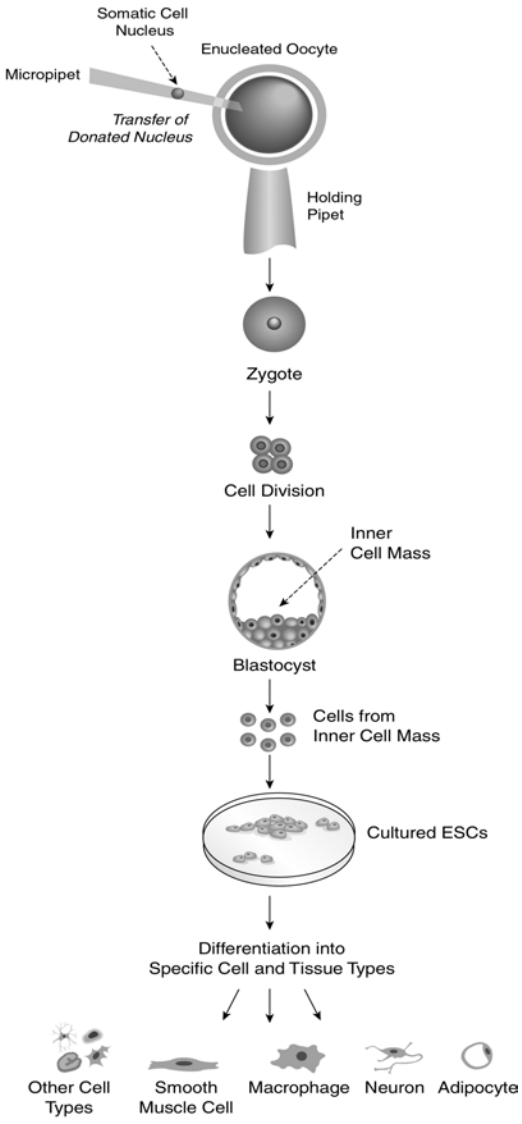

Figure 2. Isolation and culture of ESCs by nuclear transplantation.

Mouse studies are important, but scientists are especially interested in human embryonic stem cells because they potentially offer the fastest route to therapies for humans. Sources of human stem cells that can be cultured in vitro (in a laboratory dish) may be the most critical need of investigators. Many more experiments can be completed in the same amount of time with cultured cells than with living organisms, and these studies can also help scientists design better experiments on living organisms.

Stem Cells from Nuclear Transplantation

Whenever tissue transplantation takes place, there is a risk that the body's immune system will reject the new biological material. Just as with transplanted organs, transplanted tissues generated from stem cells could be rejected by the recipient. Scientists have begun to investigate whether a technique called nuclear transplantation can be used to create stem cells that are a genetic match to a patient.

The technique involves replacing the DNA of an unfertilized egg cell with the DNA from a patient's somatic (body) cell, often a skin cell, and then triggering the egg to divide to form a blastocyst. The stem cells derived from such a blastocyst would contain the patient's DNA (see Figure 2). As of June 2002, scientists have not conclusively demonstrated the ability to perform nuclear transplantation in human cells. Eggs with the new genetic material have not yet divided normally or yielded a blastocyst.

The committee concluded that stem cell research on approaches that might prevent immune rejection of stem cells, including nuclear transplantation, should be actively pursued. However, because scientists have also used the term "therapeutic cloning" to describe nuclear transplantation, much confusion has arisen in the public as to its purpose.

Cloning is a shorthand term that refers to producing a copy of some biological entity – a gene, a cell or an organism. The intent of using nuclear transplantation techniques in stem cell research has never been to clone a human being, but rather to create stem cells that may reduce the possibility of tissue rejection by the human immune system.

Informing the Ethical Debate: Where Do We Go From Here?

Stem cell research touches on some of the most fundamental issues with which society has grappled over the centuries, including the definition of human life and the moral and legal status of the human embryo.

Human embryonic stem cells hold promise for treating the world's most debilitating diseases, but research with them raises ethical and legal concerns. Stem cell research touches on some of the most fundamental issues with which society has grappled over the centuries, including the definition of human life and the moral and legal status of the human embryo. The June 2001 workshop provided an opportunity for the committee to hear about the ethical issues surrounding ESC research.

A key debate for the use of human ESCs is about when life begins. Some religious traditions suggest that life begins several weeks or even months after conception. Others consider life to begin at conception; in this case, a human embryo is a human life with all the rights of an adult.

Acceptability of human ESCs for research is also influenced by the source of cells. Some accept the use of new cell lines as long as the cells are derived from embryos produced in fertility clinics that are no longer needed for reproductive purposes. Others accept the use of stem cells derived from embryos created specifically for research from eggs and sperm donated by volunteers who are unrelated to each other and have no reproductive intent.

In August 2001, as the committee was completing its report, President Bush announced that he would allow federal financial support for research that uses embryonic stem cells already being cultured in laboratories around the world but would prohibit funding for the development of new lines that involve the creation or destruction of additional embryos.

International Public Policy Perspective on Human ESC Research

France: Permits the use of human ESCs and their derivation from superfluous embryos not needed by the genetic parents for reproduction. (Ethical advisory committees in Canada, Japan, and Germany have also recommended this approach.)

Germany: Prohibits the derivation and use of human ESCs from blastocysts.

United Kingdom: Permits the use of human ESCs and their derivation from leftover embryos not needed by the genetic parents for reproduction, from embryos created for research purposed by in vitro fertilization, and from embryos created with the nuclear transplantation technique. (The last option is being considered in Italy, France, Australia, Israel and Holland.)

United States: As articulated by President Bush on August 9, 2001, permits federal funding only for research using cells from about 60 stem cell lines identified by the National Institutes of Health as having been derived from excess human embryos before the August 9 announcement. There is currently no federal law or policy that prohibits the private sector from creating stem cells by in vitro fertilization or by nuclear transplantation for the purpose of research, but as this document went to print, legislative prohibitions were under consideration. The policies of most individual states also currently permit private funding for the development and use of human ESCs derived from excess in vitro fertilization embryos, embryos created by in vitro fertilization for the purposes of research, and embryos created by nuclear transplantation, although a few states have banned some of these.

The committee concluded that, although there is much to learn from existing cell lines, concerns about potential changes in the genetic and biological properties of these lines call for the development of new stem cell lines in the future. Over time, all cell lines in tissue culture change, and there is no reason to expect stem cell lines not to change. Harmful genetic mutations may accumulate in the cell lines, and the fact that non-human (animal) serum has been used to culture the existing stem cells could also pose human health risks.

The Road To New Therapies: Multiple Avenues of Research

Most experts agree that medical therapies based on stem cells are still several years away. However, the opportunity to develop them is before us. Many fundamental questions still remain. What cues do cells use to tell them when to start or stop dividing? What genetic and environmental factors affect the ability of stem cells to transform into other types of tissues? How does newly generated tissue become integrated into existing organs? Finding the answers to these and other questions will require much basic research.

The committee's primary message is clear: keeping as many avenues of research open as possible – including studies on both adult and embryonic stem cells from both animals and humans, and the use of nuclear transplantation – paves the way to therapeutic advances.

Without public funding of basic research on stem cells, progress toward medical therapies is likely to be hindered.

Public vs. Private Funding

Without public funding of basic research on stem cells, progress toward medical therapies is likely to be hindered. Ample federal funding would speed progress by increasing the number of studies and also the number of scientists who participate in the research. Public sponsorship of basic research helps ensure that many scientists can pursue a variety of research questions and that their results are made widely accessible in scientific journals.

The publicly funded National Institutes of Health (NIH) is the primary sponsor of basic biomedical research in the United States. Although private, nonprofit entities, such as the Howard Hughes Medical Institute, also support basic research, most private-sector funding comes from companies with an interest in research that will yield commercial applications, such as new drugs, diagnostic tools, and medical devices. These private companies, which need to satisfy shareholders with commercial results, may be reluctant to invest in basic research on stem cells because it could take years to yield therapeutic products. In addition, in contrast to publicly funded research, results from privately funded research are often considered proprietary and not openly exchanged.

Need for Oversight

The committee concluded that research conducted under established standards of open scientific exchange, peer review, and public oversight offers the most efficient and responsible means to achieve medical breakthroughs. To address the many ethical dilemmas and scientific uncertainties raised by stem cell research, the committee called for the creation of a national advisory board made up of outstanding scientists, ethicists, and other stakeholders to be established at NIH. The board could ensure that proposals for federal funding to work on embryonic stem cells are justified on scientific grounds and that they meet current and future federally mandated ethical guidelines.

The use of embryonic stem cells is not the first biomedical research activity to raise ethical and social issues among the public. The committee noted that in the past, NIH had set up similar watchdog panels, such as the Recombinant DNA Advisory Committee, which oversees once-controversial genetic engineering research. This advisory committee

established safety standards and benchmarks for review of research proposals, considering both technical and ethical issues.

Committee Recommendations

Stem cell research offers unprecedented opportunities for developing new treatments for debilitating diseases for which there are few or no cures. Stem cells also make possible a new way to explore fundamental questions of biology, such as how tissues develop and specialize. Society's diverse views about the morality of using early embryos for research challenge the development of consensus on how to proceed most responsibly. The committee looked at conflicting claims about the biology and biomedical potential of stem cell research and examined them in light of findings from recent stem cell experiments. The following recommendations constitute the result of the committee's deliberations:

1. Studies with *human stem cells* are essential to make progress in the development of treatments for human diseases, and this research should continue.
2. Although stem cell research is on the cutting edge of biological science today, it is still in its infancy. Studies of both embryonic and adult human stem cells will be required to most efficiently advance the scientific and therapeutic potential of regenerative medicine. Research on both adult and embryonic human stem cells should be pursued.
3. While there is much that can be learned using existing stem cell lines if they are made widely available for research, concerns about changing genetic and biological properties of these stem cell lines necessitate continued monitoring, as well as the development of new stem cell lines in the future.
4. Human stem cell research that is publicly funded and conducted under established standards of open scientific exchange, peer review, and public oversight offers the most efficient and responsible means to fulfill the promise of stem cells to meet the need for regenerative medical therapies.
5. If the federal government chooses to fund human stem cell research, proposals to work on human embryonic stem cells should be required to justify the decision on scientific grounds and should be strictly scrutinized for compliance with existing and future federally mandated ethical guidelines.
6. A national advisory group composed of exceptional researchers, ethicists and other stakeholders should be established at NIH to oversee research on human embryonic stem cells. The group should include leading experts in the most current scientific knowledge relevant to stem cell research who can evaluate the technical merit of any proposed research on human embryonic stem cells. Other roles for the group could include evaluation of potential risks to research subjects and ensuring compliance with all legal requirements and ethical standards.
7. In conjunction with research on stem cell biology and the development of potential stem cell therapies, research on approaches that prevent immune rejection of stem cells and stem cell-derived tissues should be actively pursued. These scientific efforts include the use of a number of techniques to manipulate the genetic makeup of stem cells, including nuclear transplantation.

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For More Information…

Copies of *Stem Cells and the Future of Regenerative Medicine* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at **www.nap.edu.** The full text of this report is available online at **www.nap.edu/catalog/10195.html.**

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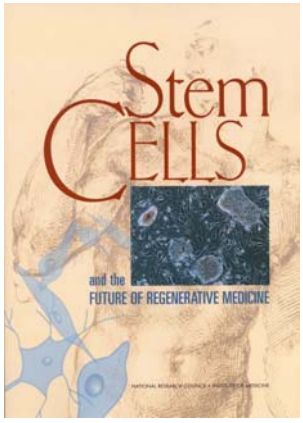
Stem Cells and the Future of Regenerative Medicine provides an exploration of the biological, ethical, and funding questions prompted by stem cell research and its potential for developing therapies for the world's most debilitating diseases. In terms accessible to lay readers, the book summarizes what we know about adult and embryonic stem cells and discusses how to most re-



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