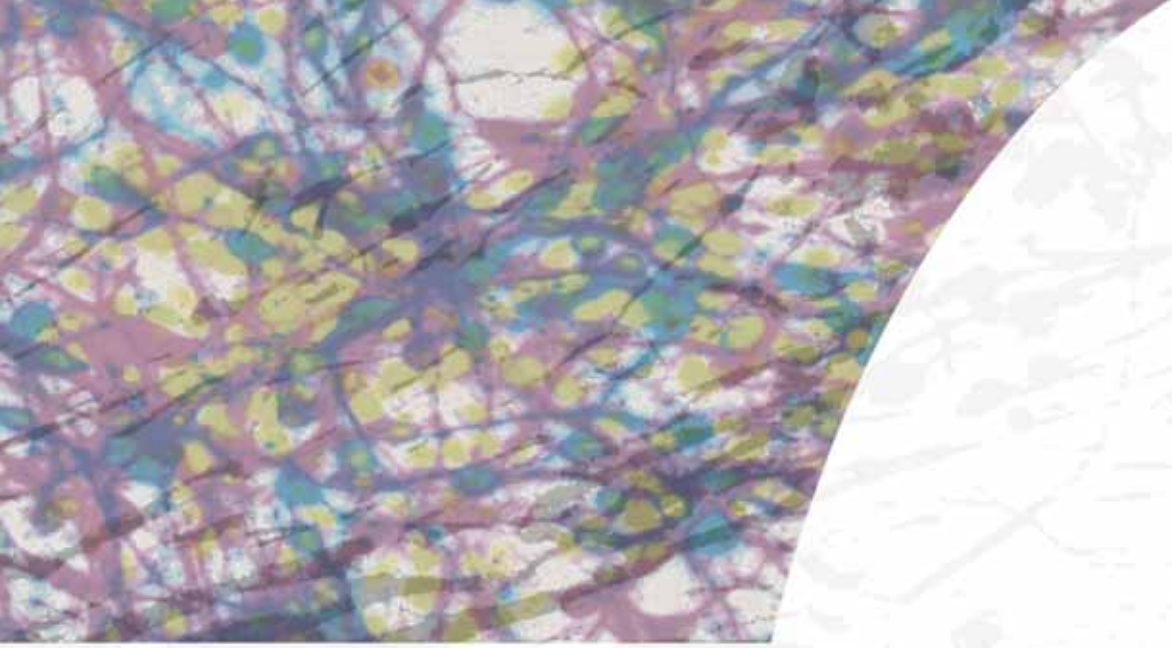
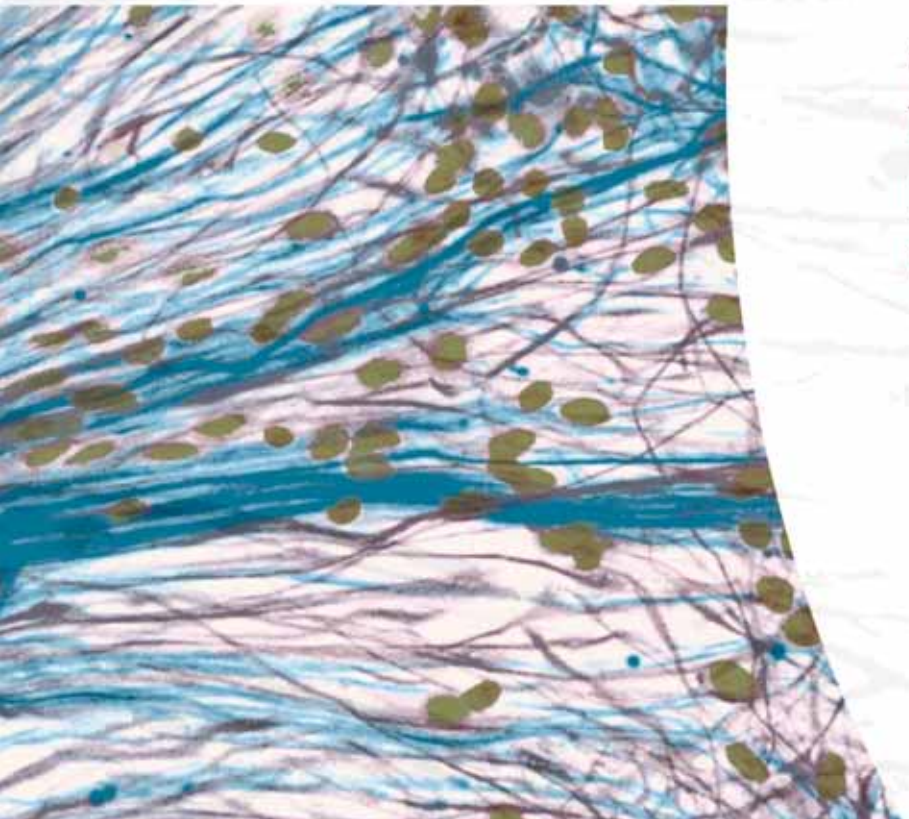


UNDERSTANDING STEM CELLS



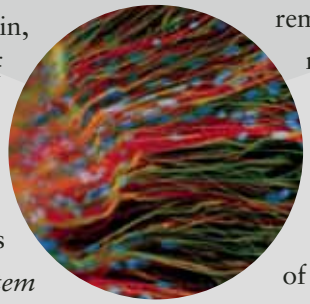
AN OVERVIEW OF THE SCIENCE AND ISSUES FROM THE NATIONAL ACADEMIES

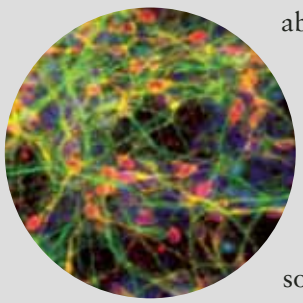
National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

IN THIS BOOKLET. . .

For centuries, scientists have known that certain animals can regenerate missing parts of their bodies. Humans actually share this ability with animals like the starfish and the newt. Although we can't replace a missing leg or a finger, our bodies are constantly regenerating blood, skin, and other tissues. The identity of the powerful cells that allow us to regenerate some tissues was first revealed when experiments with bone marrow in the 1950s established the existence of *stem cells* in our bodies and led to the development of bone marrow transplantation, a therapy now widely used in medicine. This discovery raised hope in the medical potential of regeneration. For the first time in history, it became possible for physicians to regenerate a damaged tissue with a new supply of healthy cells by drawing on the unique ability of stem cells to create many of the body's specialized cell types.



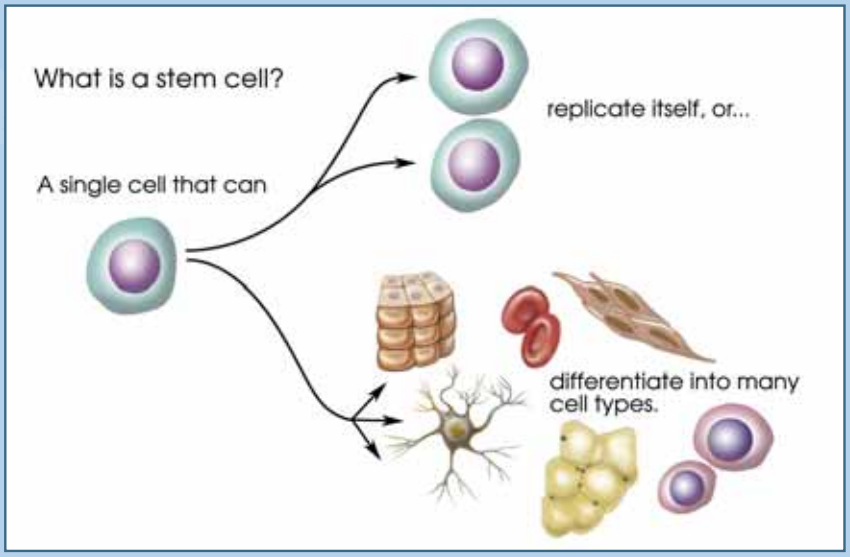


Once they had recognized the medical potential of regeneration through the success of bone marrow transplants, scientists sought to identify similar cells within the embryo. Early studies of human development had demonstrated that the cells of the embryo were capable of producing every cell type in the human body. Scientists were able to extract embryonic stem cells from mice in the 1980s, but it wasn't until 1998 that a team of scientists from the University of Wisconsin–Madison became the first group to isolate human embryonic stem cells and keep them alive in the laboratory. The team knew that they had in fact isolated stem cells because the cells could remain unspecialized for long periods of time, yet maintained the ability to transform into a variety of specialized cell types, including nerve, gut, muscle, bone, and cartilage cells.

Stem cell research is being pursued in the hope of achieving major medical breakthroughs. Scientists are striving to create therapies that rebuild or replace damaged cells with tissues grown from stem cells and offer hope to people suffering from cancer, diabetes, cardiovascular disease, spinal-cord injuries, and many other disorders. Both adult and embryonic stem cells may also provide a route for scientists to develop valuable new methods of drug discovery and testing. They are also powerful tools for doing the research that leads to a better understanding of the basic biology of the human body. By drawing on expert scientists, doctors, bioethicists, and others, the National Academies have examined the potential of stem cell technologies for medicine and provided a forum for discussing the ethical implications and moral dilemmas of stem cell research.

WHAT IS A STEM CELL?

Ultimately, every cell in the human body can be traced back to a fertilized egg that came into existence from the union of egg and sperm. But the body is made up of over 200 different types of cells, not just one. All of these cell types come from a pool of *stem cells* in the early embryo. During early development, as well as later in life, various types of stem cells give rise to the *specialized* or *differentiated* cells that carry out the specific functions of the body, such as skin, blood, muscle, and nerve cells.



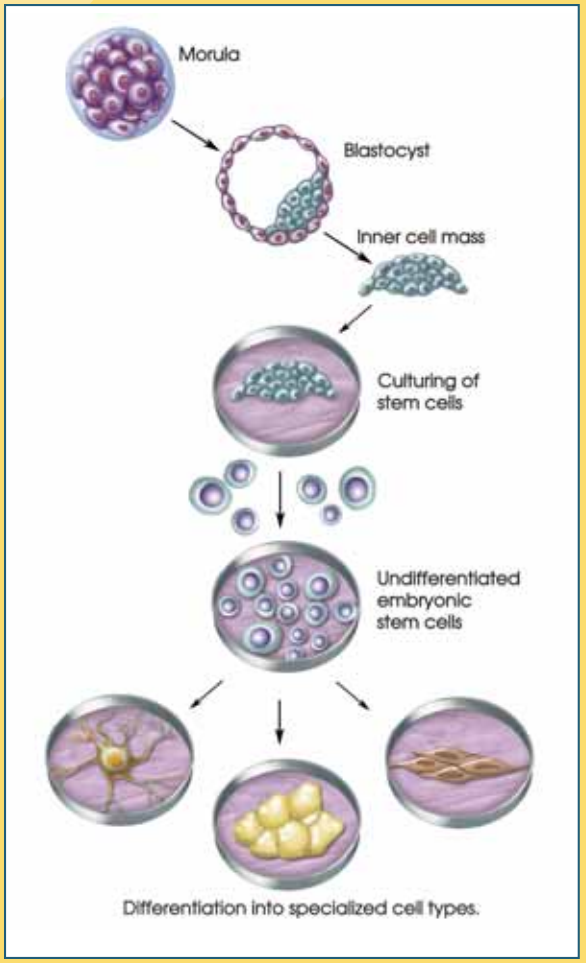
Over the past two decades, scientists have been gradually deciphering the processes by which unspecialized stem cells become the many specialized cell types in the body. Stem cells can regenerate themselves or produce specialized cell types. This property makes stem cells appealing for scientists seeking to create medical treatments that replace lost or damaged cells.

TYPES OF STEM CELLS

Stem cells are found in all of us, from the early stages of human development to the end of life. All stem cells may prove useful for medical research, but each of the different types has both promise and limitations. *Embryonic stem cells*, which can be derived from a very early stage in human development, have the potential to produce all of the body's cell types. *Adult stem cells*, which are found in certain tissues in fully developed humans, from babies to adults, may be limited to producing only certain types of specialized cells. Recently, scientists have also identified stem cells in umbilical cord blood and the placenta that can give rise to the various types of blood cells.

Embryonic Stem Cells

A *blastocyst* (BLAST-oh-sist), is a pre-implantation embryo that develops 5 days after the fertilization of an egg by a sperm. It contains all the material necessary for the development of a complete human being. The blastocyst is a mostly hollow sphere of cells that is smaller than the period at the end of this sentence. In its interior is the inner cell mass, which is composed of 30-34 cells that are referred to by scientists as *pluripotent* because they can differentiate into all of the cell types of the body. In comon usage, "embryo" can refer to all stages of development from fertilization until a somewhat ill-defined stage when it is called a fetus. Scientists use terms such as "morula" and "blastocyst" to refer to precise, specific stages of pre-implantation development. In order to be as precise as possible, this booklet uses the scientific terms when describing scientific concepts but uses the term "embryo" where more precision seemed likely to confuse rather than clarify.



Embryonic stem cells are derived from the inner cell mass of the blastocyst. In culture, they can self-replicate or produce specialized cell types.

In normal development, the blastocyst would implant in the wall of the uterus to become the embryo and continue developing into a mature organism. Its outer cells would begin to form the placenta and the inner cell mass would begin to differentiate into the progressively more specialized cell types of the body.

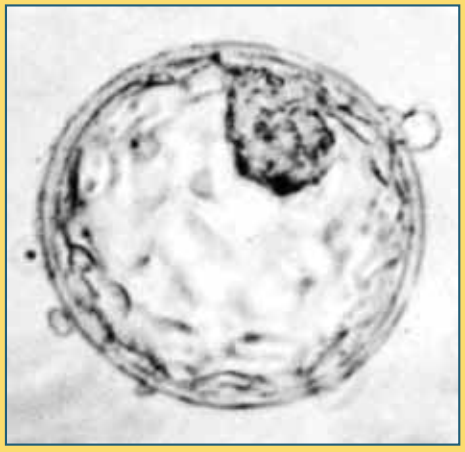
When the blastocyst is used for stem cell research, scientists remove the inner cell mass and place these cells in a culture dish with a nutrient-rich liquid where they give rise to embryonic stem cells. Embryonic stem cells seem to be more flexible than stem cells found in adults, because they have the potential to produce every cell type in the human body. They are also generally easier to collect, purify and maintain in the laboratory than adult stem cells.

Scientists can induce embryonic stem cells to replicate themselves in an *undifferentiated* state for very long periods of time before stimulating them to create specialized cells. This means that just a few embryonic stem cells can build a large bank of stem cells to be used in experiments. However, such undifferentiated stem cells could not be used directly for tissue transplants because they can cause a type of tumor called a teratoma. To be used for therapies, embryonic stem cells would first need to be differentiated into specialized cell types.

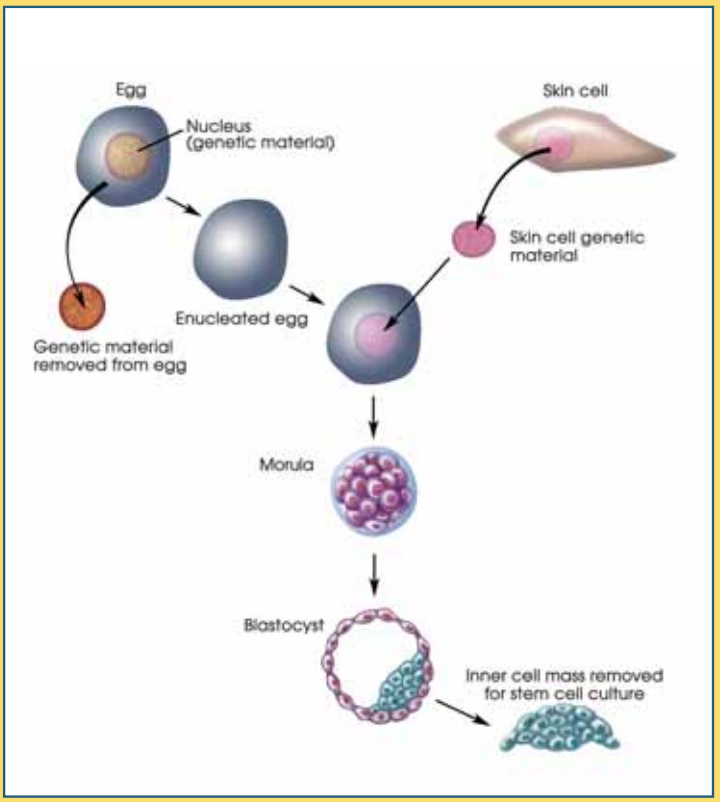
Some find embryonic stem cell research to be morally objectionable, because when scientists remove the inner cell mass, the blastocyst no longer has the potential to become a fully developed human being.

Sources of Embryonic Stem Cells

In Vitro Fertilization: The largest potential source of blastocysts for stem cell research is from in vitro fertilization (IVF) clinics. The process of IVF requires the retrieval of a woman's eggs via a surgical procedure after undergoing an intensive regimen of "fertility drugs," which stimulate her ovaries to produce multiple mature eggs. When IVF is used for reproductive purposes, doctors typically fertilize all of the donated eggs in order to maximize their chance of producing a viable blastocyst that can be implanted in the womb. Because not all the fertilized eggs are implanted, this has resulted in a large bank of "excess" blastocysts that are currently stored in freezers around the country. The blastocysts stored in IVF clinics could prove to be a major source of embryon-



A human blastocyst, which is produced about 5 days after fertilization, is smaller than the period at the end of this sentence. NIH/Mr. J. Conaghan.



Through nuclear transfer, scientists could produce a blastocyst by inserting the nucleus from an adult cell (for example, a skin cell) into an egg without a nucleus. All the stem cells derived from this blastocyst are genetically matched to the adult cell.

ic stem cells for use in medical research. However, because most of these blastocysts were created before the advent of stem cell research, most donors were not asked for their permission to use these left-over blastocysts for research.

The in vitro fertilization (IVF) technique could potentially also be used to produce blastocysts specifically for research purposes. This would facilitate the isolation of stem cells with specific genetic traits necessary for the study of particular diseases. For example, it may be possible to study the origins of an inherited disease like cystic fibrosis using stem cells made from egg and sperm donors who have this disease. The creation of stem cells specifically for research using IVF is, however, ethically problematic for some people because it involves intentionally creating a blastocyst that will never develop into a human being.

Nuclear Transfer: The process called *nuclear transfer* offers another potential way to produce embryonic stem cells. In animals, nuclear transfer has been accomplished by inserting the nucleus of an already differentiated adult cell—for example, a skin cell—into a donated egg that has had its nucleus removed. This egg, which now contains the genetic material of the skin cell, is then stimulated to form a blastocyst from which embryonic stem cells can be derived. The stem cells that are created in this way are therefore copies or "clones" of the original adult cell because their nuclear DNA matches that of the adult cell.

As of the summer of 2006, nuclear transfer has not been successful in the production of human embryonic stem cells,[1] but progress in animal research suggests that scientists may be able to use this technique to develop human stem cells in the future.

[1]Claims by Korean scientists of successful derivation of human embryonic stem cells using nuclear transfer have been found to be invalid and were retracted.

Producing Embryonic Stem Cells Using Nuclear Transfer Is Not the Same as Reproductive Cloning

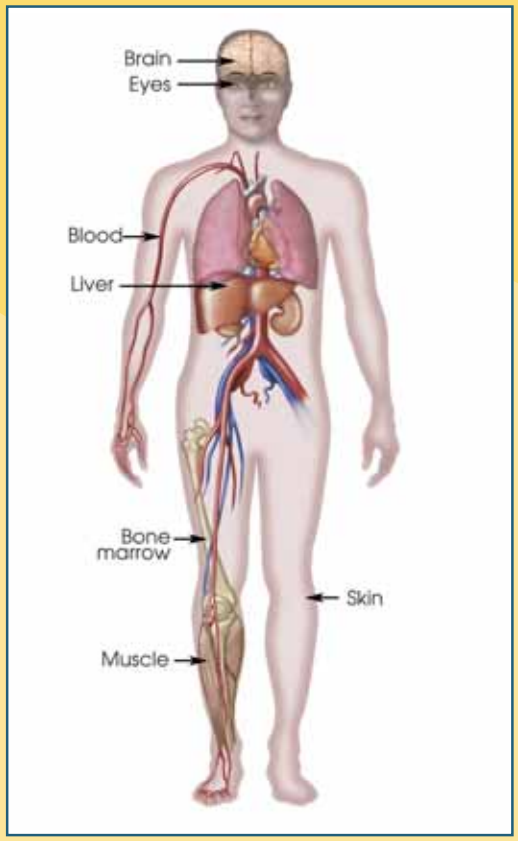
The use of nuclear transfer to develop disease-specific stem cells can be called *research cloning*, and the use of this technique for personalized tissue transplants is sometimes called *therapeutic cloning*. These terms must be carefully distinguished from *reproductive cloning*, in which the intent is to implant a cloned embryo in a female's womb and allow it to develop fully into an individual. This was the technique by which Dolly the sheep was made and is now widely used for reproductive cloning in animals. In humans, however, reproductive cloning has been actively discouraged by most in the scientific community. The National Academies concluded, "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail" in the 2002 report *Scientific and Medical Aspects of Human Reproductive Cloning*.

Although using nuclear transfer to produce stem cells is not the same as reproductive cloning, some are concerned about the potential misapplication of the technique for reproductive cloning purposes. Other ethical considerations include egg donation, which requires informed consent, and the possible destruction of blastocysts.

Adult Stem Cells

Adult stem cells are hidden deep within organs, surrounded by millions of ordinary cells, and may help replenish some of the body's cells when needed. In fact, some adult stem cells are currently being used in therapies. They have been found in several

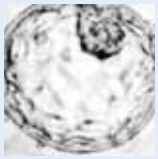
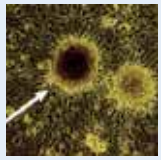
Scientists believe that if they are able to use nuclear transfer to derive human stem cells, it could allow them to study the development and progression of specific diseases by creating stem cells containing the genes responsible for certain disorders. In the future, scientists may also be able to create "personalized" stem cells that contain only the DNA of a specific patient. The embryonic stem cells created by nuclear transfer would be genetically matched to a person needing a transplant, making it far less likely that the patient's body would reject the new cells than it would be with traditional tissue transplant procedures.



Some of the known sources of adult stem cells.

organs that need a constant supply of cells, such as the blood, skin, and lining of the gut, and have also been found in surprising places like the brain, which is not known to readily replenish its cells. Unlike embryonic stem cells, adult stem cells are already somewhat specialized. For example, blood stem cells normally only give rise to the many types of blood cells, and nerve stem cells can only make the various types of brain cells. Recent research however, suggests that some adult stem cells might be more flexible than previously thought, and may be made to produce a wider variety of cell types. For example, some experiments have suggested that blood stem cells isolated from adult mice may also be able to produce liver, muscle, and skin cells, but these results are not yet proven and have not been demonstrated with human cells. Nevertheless, scientists are working on finding a way to stimulate adult stem cells, or even other types of adult cells, to be more versatile. If they succeed, it could provide another source of unspecialized stem cells.

COMPARISON OF THE DIFFERENT SOURCES OF STEM CELLS

	Embryonic Stem Cells		Adult Stem Cells
			
	In Vitro Fertilization	**Nuclear Transfer**	**Adult Tissues**
Attributes	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • large source of "excess" blastocysts from IVF clinics	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • stem cells may be genetically matched to patient	• demonstrated success in some treatments • stem cells may be genetically matched to patient
Limitations	• limited number of cell lines available for federally funded research • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• not yet achieved with human cells • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• produce limited number of cell types • not found in all tissues • difficult to identify, isolate, maintain, and grow in the laboratory
Ethical Concerns	• destruction of human blastocysts • donation of blastocysts requires informed consent	• destruction of human blastocysts • donation of eggs requires informed consent • concern about misapplication for reproductive cloning	• no major ethical concerns have been raised

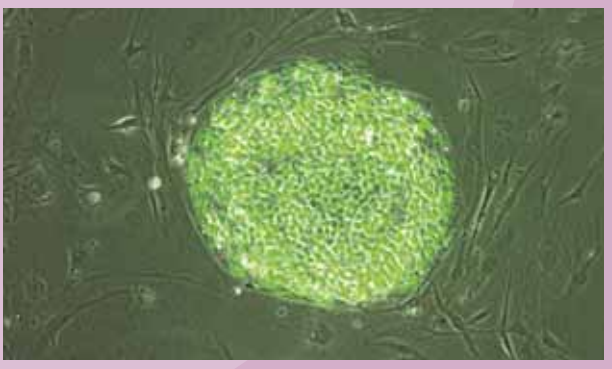
WORKING WITH STEM CELLS

The day-to-day work that goes on in the laboratories across the country studying stem cells begins with developing ways to identify stem cells, culture cell lines, and stimulate stem cells to differentiate. Once these first steps have been achieved, work on animals plays an important role in furthering basic research and developing medical applications. This work is necessary to form the foundation of knowledge that will point the way to medical advances.

Identifying Stem Cells

As early as 1961, scientists knew that adult bone marrow contained cells that could make all of the blood cell types. But it wasn't until 1988 that those stem cells were isolated as pure populations. Why did it take so long? The techniques for identifying stem cells have only recently been developed. Partly, this is because adult stem cells are, by their very nature, inconspicuous in shape, size, and function. They also tend to hide deep in tissues and are present only in very low numbers, making their identification and isolation like finding a needle in a haystack.

How do scientists know when they have found a stem cell? Every cell displays an array of proteins on its surface; different cell types have different proteins. Scientists can use these surface proteins as "markers" that characterize individual cell types—a type of "molecular ID." For example, using molecules that recognize and attach to specific surface proteins and that can fluoresce under certain wavelengths of light, scientists can visually tell the difference between a blood stem cell and a mature white blood cell. Unfortunately, not all stem cells can now be identified in this manner because scientists have not yet identified markers for all stem cell types. Scientists also identify stem cells by observing their behavior in the laboratory: stem cells must be able to remain unspecialized and self-renew for long periods of time.



Fluorescent markers can be used to identify stem cells hidden among ordinary adult cells. Here, human embryonic stem cells are recognized by the marker proteins they express (green). Courtesy of Paul J. Tesar, Laboratory of Molecular Biology, NINDS and the NIH Stem Cell Unit.

Scientists believe that there might be more types of adult stem cells than the handful that have already been identified, but finding them is a difficult process.

Culturing Cell Lines and Stimulating Stem Cells to Differentiate

Cell culture is a term that refers to the growth and maintenance of cells in a controlled environment outside of an organism. A successful stem cell culture is one that keeps the cells healthy, dividing, and unspecialized. The culturing of stem cells is the first step in establishing a stem cell line—a propagating collection of genetically identical cells. Cell lines are important because they provide a long-term supply of multiplying cells that can be shared among scientists for research and therapy development. The National Academies report *Stem Cells and the Future of Regenerative Medicine* (2001) described some of the challenges of maintaining cell lines: "Over time, all cell lines…change, typically accumulating harmful genetic mutations. There is no reason to expect stem cell lines to behave differently. While there is much that can be learned using existing stem cell lines…such concerns necessitate continued monitoring of these cells as well as the development of new stem cell lines in the future."

Once they have established a stable stem cell line, scientists start the process of causing the stem cells to differentiate into specialized cell types. The cellular environment in which stem cells naturally reside provides scientists with clues about how to make them differentiate in a culture dish. For example, in the bone marrow, where blood stem cells reside, bone cells send physical and chemical signals that tell the blood stem cells when to differentiate. Scientists are just beginning to understand these signals and have developed ways to mimic the natural processes in cell cultures. Usually, the technology involves adding certain proteins to the cell culture and, in some cases, introducing specific genes into the stem cells.

It will be essential that scientists are sure that stem cells have fully differentiated before they can use them for medical applications. If completely undifferentiated stem cells (such as embryonic stem cells) are implanted directly into an organism, they can cause a type of tumor called a *teratoma*, which scientists have observed in experiments using mice. Semi-specialized adult stem cells and differentiated cells derived from embryonic stem cells are unlikely to cause teratomas.

The Role of Animals in Stem Cell Research

For medical research, as well as for research that explores the basic processes in the development of organisms and diseases, scientists often rely on animals. Implanting human cells into animals

Center Photo: Scientists can test whether they have successfully caused embryonic stem cells to differentiate by labeling for specific *marker proteins* found in specialized cells. Courtesy of Dr. Daniel Anderson, MIT.

such as mice has long been common practice in order to test the safety and effectiveness of new drugs, procedures, and medical devices before clinical testing in human volunteers. For stem cell research, scientists use animals to make sure the stem cells are able to incorporate into the tissue, do not cause any harmful consequences, and function in concert with the rest of the body. For example, before using stem cells to replace the pancreatic cells that are destroyed by type I diabetes in humans, scientists will transplant human stem cells into a mouse to see whether the stem cells yield healthy, insulin-producing cells. If their methods prove successful in mice, scientists may eventually apply the technology to developing treatments for diabetes in humans.

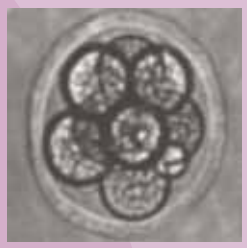
Animal studies can also reveal how human cells differentiate during normal development. For example, scientists may implant human stem cells into a developing mouse to observe the processes involved in building and organizing the different tissue types that make up the human body. Scientists can also trace the development and progression of certain diseases within an animal. By implanting human stem cells that lead to a particular disease into a mouse blastocyst, scientists can observe when and how the afflicted cells begin to show signs of disease and can test drugs that might prevent that process.

Many research mice are *chimeras* because they contain both human and mouse cells. Courtesy of Advanced Cell Technology, Inc., Alameda, CA.

Organisms that contain cells or tissues from another individual of the same or a different species are called *chimeras*. A common example of a chimera is a mouse that has been injected with some human cells so that it can be used for studying a human disease or testing a new drug. A person who has had a blood transfusion or a person who has received a heart valve transplant from a pig is technically a chimera, as well. The making of chimeras for research has unique ethical implications that have been the topic of discussions among scientists, ethicists and the public, especially when the chimeras contain both human and animal cells.

Alternatives to Using Embryos in Stem Cell Research

To address ethical concerns about the destruction of blastocysts, scientists are trying to find new ways of obtaining stem cells that behave like embryonic stem cells but that don't require harming a blastocyst. As the science progresses, ethical issues surrounding these alternatives may also arise. Some possible alternatives include:



Courtesy of Leonard I. Zon

- Cells collected from the *morula* (MOR-yoo-la), the developmental stage prior to the blastocyst. The morula, a solid ball of about 16–30 cells, seems able to sustain the loss of a few cells without developmental damage so that the remaining cells can continue to develop. Cell extraction from the morula is already being used in some clinics to screen for genetic disorders in embryos produced by in vitro fertilization. Researchers have recently shown that cells isolated from a mouse morula can give rise to embryonic stem cells while the remaining morula cells develop into a healthy mouse. However, this process may still be morally objectionable to some because of the chance of harm to the morula, and because the long-term effects of removing cells from a morula are not yet known.

- The creation of embryonic stem cells through a process called *altered nuclear transfer* (ANT). In this variation of the nuclear transfer technique, scientists create a blastocyst whose genetic material has been changed so that further development and implantation into the uterus is not possible. It aims to create embryo-like entities that are not truly embryos but that can be a source of pluripotent stem cells. ANT, so far only tested with mouse blastocysts, could allow the creation of embryonic stem cells without destroying a viable human blastocyst. Some who object to embryonic stem cell research support ANT because the resulting blastocyst could never develop into a full human being and therefore would not have the moral status of a human embryo. However, this procedure is objectionable to some because they believe that it involves the creation of an imperfect blastocyst that is designed to be destroyed.

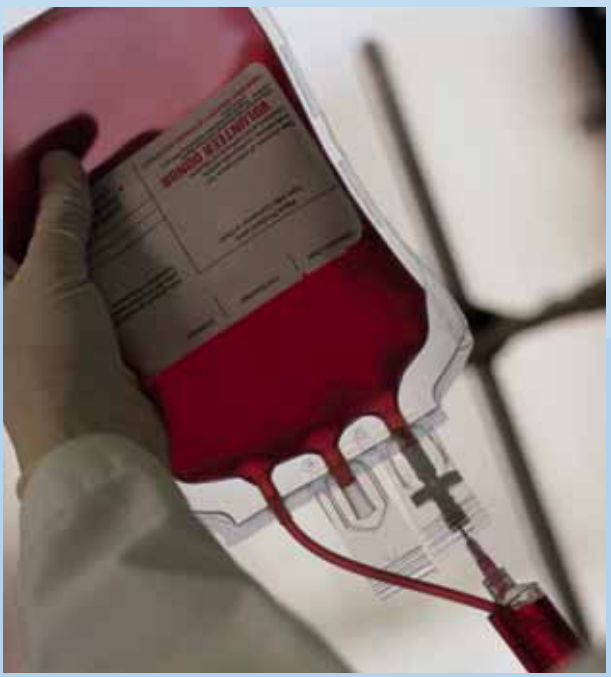
- Causing an adult cell to act like an embryonic stem cell. During development, as cells become more and more specialized, they gradually lose the ability to turn on the genes that allow embryonic stem cells to be so versatile. The silencing of these genes seems to be responsible for keeping specialized cells specialized and limiting the differentiation capacities of adult stem cells. By "reprogramming" adult stem cells so that they can turn on the genes that allow versatility, scientists hope to cause them to revert to a more flexible state. It is even possible that scientists could one day "reprogram" any cell, not only stem cells. However, research in this area is in the early stages and scientists may be many years away from making an adult cell as versatile as an embryonic stem cell.

WHY STEM CELL RESEARCH IS BEING PURSUED

Right now, only a few diseases are treatable with stem cell therapies because scientists can only regenerate a few types of tissues. However, the success of the most established stem cell-based therapies—blood and skin transplants—gives hope that someday stem cells will allow scientists to develop therapies for a variety of diseases previously thought to be incurable. Many major diseases are caused by the loss of a single type of cell or tissue. For example, type I diabetes (juvenile-onset) is caused by the loss of the insulin-producing cells of the pancreas, and its treatment is limited to merely alleviating the symptoms. Finding a cure for such diseases would be much easier if scientists could simply re-grow the missing or damaged cells and implant them into patients.

Blood Stem Cells

After scraping a knee or donating blood, the body replenishes the blood cells that are lost by drawing on a small number of semi-specialized *hematopoietic* (heem-AT-oh-poh-EH-tik) stem cells contained in the blood and bone marrow. For decades, scientists have been using this type of adult stem cell to treat patients with diseases such as leukemia, sickle cell anemia, bone marrow damage, and some metabolic disorders and immunodeficiencies where the body has lost its ability to replenish its own set of healthy blood cells. Hematopoietic stem cells give rise to all the blood cell types, from infection-fighting white blood cells to blood-clotting platelets. Preliminary results have suggested that they may also be able to produce other cell types not found in blood, but this is not yet proven.



In the past, the only way to use hematopoietic stem cells for therapies was through bone marrow transplants. Extracting bone marrow is an uncomfortable and invasive procedure, and in order for a transplant to work, the donor and recipient must be genetically similar. If they are too genetically different, the blood cells produced from the transplanted marrow may recognize the patient's body as foreign and fight against the patient's own cells and organs. Additionally, the patient's immune system may reject the transplant, causing a dangerous "war" within the patient's body.

More recently, scientists have developed ways to derive hematopoietic stem cells from the blood contained in the umbilical cord and placenta at birth. The stem cells isolated from a person's own umbilical cord blood and placenta, if used for therapies later in life, would be less likely to cause an "internal war" within the recipient's body. They are also more accessible than the stem cells in bone marrow because the extraction of this blood poses no risk to the mother or infant.

The Changed Face of Skin Grafts

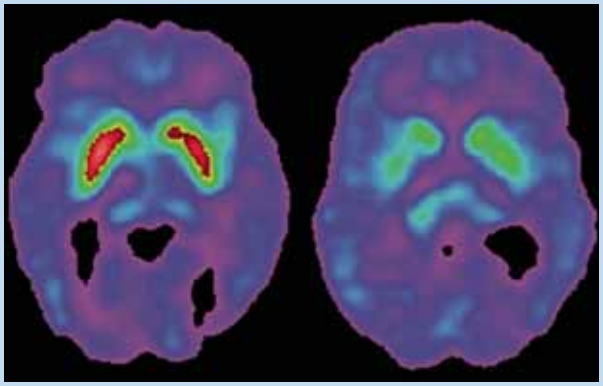
For many years, scientists have been harnessing the regenerative capabilities of human skin to treat victims of severe burns using skin transplants. Skin transplants are possible because of the existence of stem cells located just under the top layer of skin. Every day, thousands of new skin cells are produced to replace those that have been shed. When someone suffers severe burns that destroy the source of these stem cells, their skin can no longer regenerate on its own. Traditionally, doctors treated severe burns by transplanting sections of skin from undamaged areas of the body onto the burned areas, but if doctors could not find enough unharmed skin to cover the burned areas, the patient could die. Now, scientists can grow vast sheets of new skin by culturing the stem cells from small pieces of healthy skin. This practice, which is a type of tissue engineering, has become routine for treating burn victims over the past 20 years. Recently, scientists have identified other types of stem cells in hair follicles and deeper layers of the skin. The inclusion of these new stem cells into engineered skin should help create more natural-looking skin transplants in the future.

Stem Cells Found in Umbilical Cord Blood

In 2005, the National Academies issued a report, *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*, which recommended that a national cord blood "bank" be established to harness the medical potential of this source of stem cells. Such a bank would not only benefit the people from whom the blood was collected but anyone in need of blood transplants. As with blood banks for blood transfusions, scientists could screen the bank to find the best match for each patient, providing a safer, more personalized living-cell therapy.

Possible Future Treatment for Parkinson's Disease?

When most people reach for a pen, their body acts in one smooth and controlled movement. This is because the instant a person thinks of grabbing the pen, a series of nerve cells fire in an orchestrated symphony from the brain to the muscles responsible for that action. For the movement to be precise and smooth, all the nerve cells in the "grabbing-the-pen network" must function properly, including cells that tell unneeded muscles to stay still. In Parkinson's disease, the brain cells responsible for keeping unneeded muscles from moving degenerate and die. This results in progressively more dramatic and uncontrolled movements, tremors, and spasms. To date, there is no cure for Parkinson's disease because no one has figured out a way to bring back the specialized nerve cells that have died.



Parkinson's disease is caused by the loss of a single type of nerve cell. These brain scans show the difference between a normal brain (left) and the brain of a Parkinson's patient (right). Courtesy of Dr. David A. Rottenberg, Professor of Neurology and Radiology, University of Minnesota.

Are the Promises of Stem Cell Therapies Realistic?

The list of medical achievements stem cells could offer seems to be expanding at an incredible pace. The role of stem cells in medicine is already very real, but there is a danger of exaggerating the promise of new medical developments. What tend to be "over-promised" are not only the potential outcomes of both embryonic and adult stem cell research, but also the time scales that are involved. The basic research needed to develop viable therapeutic options is a lengthy process that may extend over many years and decades. Even after science has moved from basic research to developing medical applications, it still takes many years to thoroughly test those applications and demonstrate that they are safe to prescribe for patients. This is true for all medical treatments, including the development of new drugs, procedures, and medical equipment, and is not specific to the living cell therapies made possible by stem cell research.

There are also many legal and social questions that must be addressed before stem cell-based therapies become clinically available. Legal issues that will affect stem cell applications include how to address intellectual property concerns and how to apply and enforce diverse and sometimes conflicting state and national laws. Social issues include concerns about the destruction of embryos, the distribution of the benefits of the research, and the protection of both physical and privacy interests of egg and sperm donors and clinical research subjects.

Because Parkinson's disease results from the loss of one specific type of nerve cell, stem cells offer a very tangible possibility for treatment. Researchers have recently learned how to differentiate embryonic stem cells into the specific type of brain cell that is lost in Parkinson's disease. They have also successfully transplanted adult nerve stem cells into rat brains. When this technique is proven to be effective and safe, transplantation of stem cells into the brains of patients may one day allow doctors to reverse the burden of Parkinson's disease and restore control of movement. Another strategy currently under study is the addition of chemicals or growth factors that aim to induce the patient's own stem cells to repair the damaged nerves without needing to grow and transplant stem cells.

Possible Fix for Diabetes?

In people who suffer from type I diabetes, the beta cells of the pancreas that normally produce insulin are destroyed by the patient's overactive immune system. Without insulin, the cells of the body cannot take up glucose and they starve. Patients with type I diabetes

STEM CELL TIMELINE

1956

First successful bone marrow transplant

1981

Embryonic stem cells are isolated from mouse blastocysts

1988

Hematopoietic (blood) stem cells from adult mice are purified and characterized

1992

Stem cells are identified in the adult human brain

1998

The first human embryonic stem cells are isolated

require insulin injections several times a day for their entire lives. The only current cure is a pancreatic transplant from a recently deceased donor, but the demand for transplants far outweighs the supply. While adult stem cells have not yet been found in the pancreas, scientists have made progress transforming embryonic stem cells into insulin-producing cells. Combining beta-cell transplants with methods to "fix" the patient's immune system—including chemotherapy to destroy malfunctioning immune-system cells and blood transplants to replenish healthy white blood cells—could offer great hope for the many Americans suffering with type I diabetes.

Cancer: Getting to the Root of the Problem

Why are some cancers so hard to eliminate, even after many rounds of chemotherapy? The answer may lie in a few abnormal stem cells. Cancerous stem cells were first identified in 1997 when a research group from the University of Toronto transferred a few blood stem cells from human leukemia patients into mice and watched leukemia develop in the mice. Stem cell-like cells have also recently been found in breast and brain tumors. Like normal stem cells, tumor stem cells exist in very low numbers, but they can replicate and give rise to a multitude of cells. Unlike normal stem cells, however, cancerous stem cells lack the controls that tell them when to stop dividing. Traditional chemotherapy kills off the majority of the tumor cells, but if any of the cancerous stem cells survive the treatment, the cancer may return. Research into the differences in gene expression between normal and tumor stem cells may lead to treatments where the root of the problem—the cancer stem cell—is targeted.

2001

Mouse embryonic stem cells are created by nuclear transfer

2002

Pancreatic cells derived from mouse embryonic stem cells cure diabetes in mice

2004

The type of nerve cell lost in Parkinson's disease is produced from human embryonic stem cells

Stem cell research continues to advance. Preliminary results from recent studies support the promise of stem cells for conducting basic research that may eventually lead to medical achievements. For example, in 2005, human embryonic stem cells were shown to differentiate into active functioning nerve cells when placed in mouse brains. Scientists also made significant progess in deriving pancreatic cells from adult stem cells. In 2006, scientists were able to derive embryonic stem cells from the morula of a mouse, and embryonic stem cells were first grown without animal products in the culture. Results of these and other recent experiments must be replicated and consistently demonstrated by other researchers before they become generally accepted by the scientific community.

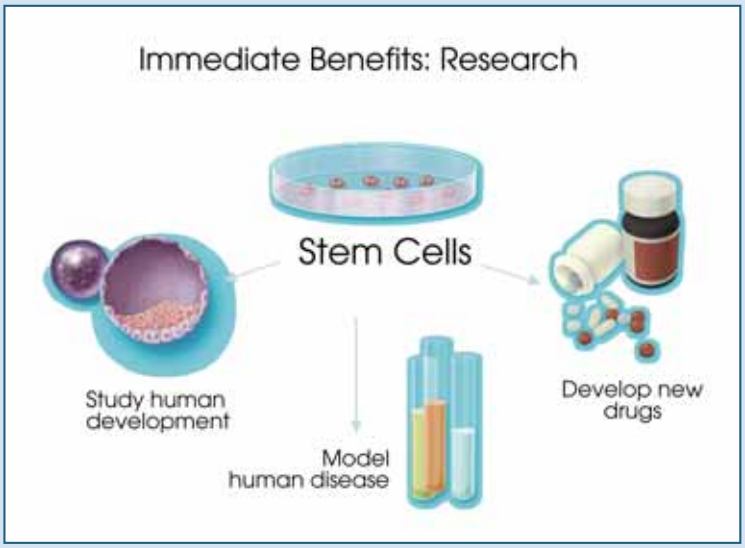
The Role of Stem Cells in Basic Research

Stem cells offer opportunities for scientific advances that go far beyond regenerative medicine. They offer a window for addressing many of biology's most fundamental questions. Watching embryonic stem cells give rise to specialized cells is like peeking into the earliest development of the many tissues and organs of the human body. Stem cell research may help clarify the role genes play in human development and how genetic mutations affect normal processes. They can be used to study how infectious agents invade and attack human cells, to investigate the genetic and environmental factors that are involved in cancer and other diseases, and to decipher what happens during aging.

Stem cells may also revolutionize traditional chemical medicine. Because embryonic stem cells can continue to divide for long periods of time and produce a variety of cell types, they could provide a valuable source of human cells for testing drugs or measuring the effects of toxins on normal tissues without risking the health of a single human volunteer. In the future, thousands of compounds could be quickly tested on a wide assortment of cell types derived from stem cells, making drug discovery more efficient and cost effective.

Using nuclear transfer to produce stem cells could be particularly useful for testing drugs for disorders that are of genetic origin. For example, it is difficult to study the progression of Alzheimer's and Parkinson's diseases in the brains of live patients—but by using the cells of an Alzheimer's patient to create stem cell lines with nuclear transfer, scientists could trace the development of the disease in a culture dish and test drugs that regenerate lost nerve cells with no danger to the patient.

Stem cells may also help scientists calculate the effects of toxic substances in drugs, food, and the environment.



Courtesy of Dr. Leonard I. Zon.

ETHICS, MORAL VALUES, AND U.S. LAW

Scientists and society as a whole must consider the ethical implications of stem cell research. As discussed throughout this booklet, different ethical issues are raised by the wide range of stem cell research activities. In 2005, the National Academies published guidelines for scientists who do research with human embryonic stem cells to encourage responsible and ethically sensitive conduct in their work. Although the guidelines are not expressly legally binding, many researchers have voluntarily adopted them as a guide to what constitutes appropriate conduct in human embryonic stem cell research. Yet for some people, such guidelines are inadequate because they aim to govern a practice that they see as intrinsically unethical.

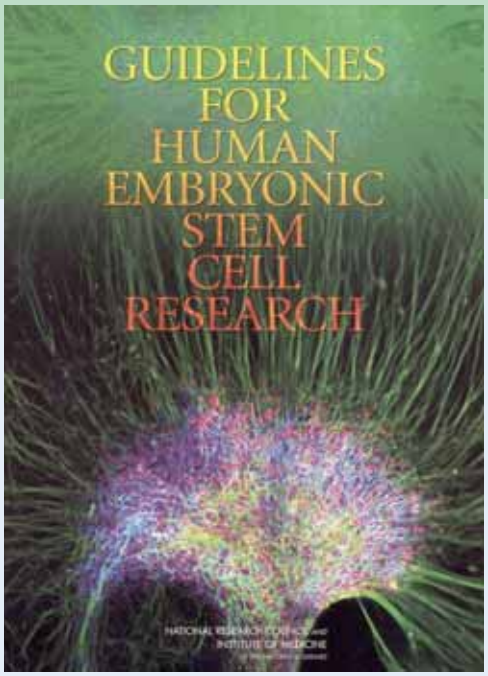
As the science advances, it is essential that scientists; religious, moral, and political leaders; and society as a whole continue to evaluate and communicate about the ethical implications of stem cell research.

The National Academies published the *Guidelines for Human Embryonic Stem Cell Research* in 2005. Here, members of the committee present at a report briefing.

Is an Embryo a Person?

The controversy over embryonic stem cell research touches on some of the same fundamental questions that society has grappled with in the debates over contraception, abortion, and in vitro fertilization. The questions at the center of the controversy concern the nature of early human life and the legal and moral status of the human embryo. Embryonic stem cell research often involves removing the inner cell mass from "excess" blastocysts that are unneeded by couples who have completed their fertility treatment. This prevents those blastocysts from continuing to develop. Although such blastocysts would likely be discarded (and thus destroyed) by the clinics in any case, some believe that this does not make it morally acceptable

to use them for research or therapeutic purposes. They believe that the life of a human being begins at the moment of conception and that society undermines a commitment to human equality and to the protection of vulnerable individuals if blastocysts are used for such purposes. Some cultures and religious traditions oppose the use of human life as a means to some other end, no matter how noble that end might be. Other traditions support embryonic stem cell research because they believe that the embryo gains the moral status of a human being only after a few weeks or months of development. Many traditions emphasize obligations to heal the sick and ease suffering—goals for which embryonic stem cell research holds great potential—and favor embryonic stem cell research for this reason. Several religious groups are currently involved in internal discussions about the status of the human embryo and have not yet established official opinions on the matter. Public opinion polls suggest that the majority of both religious and non-religious



The National Academies' Guidelines for Human Embryonic Stem Cell Research

In order to provide all scientists—those working in universities and private companies and with both public and private funding—with a common set of scientific and ethical guidelines, the National Academies published the *Guidelines for Human Embryonic Stem Cell Research* in 2005. The report outlines the need for institutional oversight mechanisms for monitoring all human embryonic stem cell research and provides specific guidance regarding the derivation of new stem cell lines. Under the guidelines, certain activities, such as experimenting on human embryos by inserting stem cells into them, are not permitted. The guidelines also require that all egg, sperm, and blastocyst donations follow appropriate informed consent and confidentiality procedures. Because the ethical and technical questions associated with human embryonic stem cell research are likely to change as science advances, in 2006, the National Academies established a panel of experts to monitor and review scientific developments and changing ethical, legal, and policy issues and to prepare periodic reports to update the guidelines as needed. For more information on the guidelines, please visit www.nationalacademies.org/stemcells.

Americans support embryonic stem cell research, although public opinion seems divided about the creation or use of human blastocysts solely for research.

The Relationship of Stem Cell Research to Reproductive Cloning

Although cloning and stem cell research are often lumped together in the context of ethical debates, the goals and results of the two are very different. The common factor between current attempts at reproductive cloning and stem cell research is a laboratory technique called *nuclear transfer*. Using nuclear transfer, scientists can create blastocysts containing stem cells that are "clones" of a single adult cell by inserting the genetic material from an adult cell (for example, a skin cell) into an egg whose nucleus has been removed (this process is described in more detail on page 6). Scientists hope that they could derive stem cells from the cells inside such blastocysts and grow replacement tissues that are genetically matched to specific patients, thus offering patients a safer alternative to traditional tissue transplants.

Reproductive cloning, such as the process that was used to create Dolly the sheep, also uses the nuclear transfer technique. However, instead of removing the inner cell mass to derive a stem cell line, the blastocyst is implanted into the uterus and allowed to develop fully. In 2002, the National Academies issued the report *Scientific and Medical Aspects of Human Reproductive Cloning*, which concluded "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail."

"Human reproductive cloning should not now be practiced. It is dangerous and likely to fail."

—*Scientific and Medical Aspects of Human Reproductive Cloning,* National Academies Press, 2005

The Ethics of Human-Animal Chimeras

Chimeras are organisms composed of cells or tissues from more than one individual. Chimeras have been produced for research for many years, but when human and animal cells are mixed in the laboratory, there is a clear need for heightened ethical consideration. Cells from different organisms can be combined either in the early developmental stages (for example, introducing human cells into a mouse blastocyst to observe certain developmental processes) or after an individual is fully developed (for example, implanting

human stem cell-derived pancreatic cells into a mouse to test their ability to function in a living body). Chimeras are considered essential for advancing stem cell research to viable therapies, since no therapy can be tested in humans without research in animals first.

Some people believe that the creation of chimeras involving human cells for medical research is morally acceptable as long as the chimera has no level of human consciousness. Therefore, research in which it is possible for human stem cells to produce part of an animal's brain should be conducted with great care. The National Academies' guidelines prohibit the introduction of human cells into the blastocyst of a non-human primate, or the introduction of any animal or human cells into a human blastocyst. The guidelines also prohibit the breeding of human-animal chimeras in the unlikely event that any human genetic material would be contained in their reproductive cells.

Is it legal?

Currently, all forms of stem cell research in the U.S. are legal at the federal level. That is, it is not illegal to make or work with new embryonic stem cell lines. However, the use of federal funds for human embryonic stem cell research is restricted to the cell lines that were available as of August 9, 2001. Therefore, the derivation of new embryonic stem cell lines can only occur when scientists are working with non-federal funding. Some states and private foundations have been supporting this work. Some requirements of federal law, such as human subjects protections, apply to state- and privately funded stem cell research. For a complete discussion of the mechanisms for oversight of stem cell research, see the National Academies' report *Guidelines for Human Embryonic Stem Cell Research*.

It is legal to conduct research using blastocysts and to derive new cell lines in most states, with some exceptions. Because stem cell legislation is an area of active debate, please visit the National Conference of State Legislatures at http://www.ncsl.org/programs/health/genetics/embfet.htm to learn about the laws in a particular state.

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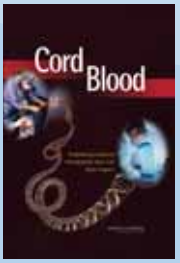
RELATED REPORTS FROM THE NATIONAL ACADEMIES

Stem Cells and the Future of Regenerative Medicine (2001).
http://www.nap.edu/catalog/10195.html

Scientific and Medical Aspects of Human Reproductive Cloning (2002).
http://www.nap.edu/catalog/10285.html

Guidelines for Human Embryonic Stem Cell Research (2005).
http://www.nap.edu/catalog/11278.html
(free download is available)



Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program (2005).
http://www.nap.edu/catalog/11269.html

These and other National Academies reports are available from the National Academies Press, 500 Fifth Street, NW, Washington, DC 20001; 800-624-6242; http://www.nap.edu. Reports are available online in a fully searchable format.

This booklet and other information about activities related to stem cells at the National Academies are available at www.nationalacademies.org/stemcells.

For more information, contact the Board on Life Sciences at bls@nas.edu or visit www.nationalacademies.org/bls. This brochure was prepared by National Research Council staff Anne Jurkowski, Giovanna Guerrero, Fran Sharples, and Adam Fagen in collaboration with Bruce Altevogt and Andrew Pope of the Institute of Medicine's Health Sciences Policy Board. It was designed by Michele de la Menardiere.

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Page 2: (left and right) Nerve cells derived from human embryonic stem cells. PNAS 101(34):12543, Copyright 2004, National Academy of Sciences, U.S.A. (middle) Nerve cells derived from human embryonic stem cells in the laboratory of Professor Su-Chun Zhang at the University of Wisconsin–Madison. Used with permission from the University of Wisconsin's Board of Regents.

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Over the past decade, stem cells have gained a place in most Americans' vocabularies—discussions of them appear on TV and radio news programs, in newspapers and magazines, and even in political campaigns across the country. As stem cells have come to the forefront of medical research, the ethical controversies over embryonic stem cells have become prominent. This booklet is designed to provide basic knowledge to facilitate thinking about and understanding the scientific and ethical issues surrounding stem cells. It is intended to help readers more easily interpret news about stem cells, as the science advances or new controversies develop.

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