= main idea
= supporting detail

STEM CELL INFORMATION

Stem Cell Basics

I. Introduction: What are stem cells, and why are they important?

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: **embryonic stem cells** and non-embryonic **"somatic" or "adult" stem cells**. The functions and characteristics of these cells will be explained in this document. Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981. The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called **human embryonic stem cells**. The embryos used in these studies were created for reproductive purposes through ***in vitro* fertilization** procedures. When they were no longer needed for that purpose, they were donated for research with the informed consent of the donor. In 2006, researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell, called **induced pluripotent stem cells (iPSCs)**, will be discussed in a later section of this document.

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a **blastocyst**, the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs 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.

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for **cell-based therapies** to treat disease, which is also referred to as **regenerative or reparative medicine**.

Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects.

Research on **stem cells** continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Stem cell research is one of the most fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

could this fix birth mutation of the body?

like what?

All around cells, multiuse
Could it fix permanent damage like burns?

I. Introduction | **Next**

Page citation: Stem Cell Basics: Introduction. In *Stem Cell Information* [World Wide Web site]. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2002 [cited Tuesday, March 18, 2014] Available at <http://stemcells.nih.gov/info/basics/pages/basics1.aspx>

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Stem Cell Basics

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 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, or **proliferate**. 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**.

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 **non-embryonic 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. Such information would also enable scientists to grow embryonic and non-embryonic stem cells more efficiently in the laboratory.

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 derive and maintain stem cells in the laboratory without them spontaneously differentiating into specific cell types. For example, it took two decades to learn how to grow **human embryonic stem cells** in the laboratory following the development of conditions for growing mouse stem cells. Therefore, understanding the signals in a mature organism that cause a stem cell population to proliferate and remain unspecialized until the cells are needed. 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 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. For example, a stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell), and it cannot carry oxygen molecules through the bloodstream (like a red blood cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

By putting a stem cell into a specific area will it correctly differentiate on its own

Stem cells can give rise to specialized cells. When unspecialized stem cells give rise to specialized cells, the process is called **differentiation**. While differentiating, the cell usually goes through several stages, becoming more specialized at each step. Scientists are just beginning to understand the signals inside and outside cells that trigger each stem of the differentiation process. The internal **signals** are controlled by a cell's **genes**, which are interspersed across long strands of DNA, and carry coded instructions for all cellular structures and functions. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the **microenvironment**. The interaction of signals during differentiation causes the cell's DNA to acquire **epigenetic** marks that restrict DNA expression in the cell and can be passed on through cell division.

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 may lead scientists to find new ways to control stem cell differentiation in the laboratory, thereby growing cells or tissues that can be used for specific purposes such as **cell-based therapies** or drug screening.

Adult stem cells typically generate the cell types of the tissue in which they reside. For example, a blood-forming adult stem cell in the bone marrow normally gives rise to the many types of blood cells. It is generally accepted that a blood-forming cell in the bone marrow—which is called a **hematopoietic stem cell**—cannot give rise to the cells of a very different tissue, such as nerve cells in the brain. Experiments over the last several years have purported to show that stem cells from one tissue may give rise to cell types of a completely different tissue. This remains an area of great debate within the research community. This controversy demonstrates the challenges of studying adult stem cells and suggests that additional research using adult stem cells is necessary to understand their full potential as future therapies.

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Stem Cell Basics

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. Most 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.

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

Growing cells in the laboratory is known as **cell culture**. Human embryonic stem cells (hESCs) are generated by transferring cells from a preimplantation-stage embryo 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 mouse cells in the bottom of the culture dish provide the cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium. Researchers have devised ways to grow embryonic stem cells without mouse feeder cells. This is a significant scientific advance because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells.

The process of generating an embryonic stem cell line is somewhat inefficient, so lines are not produced each time cells from the preimplantation-stage embryo are placed into a culture dish. However, if the plated cells survive, divide and multiply enough to crowd the dish, they are removed gently and plated into several fresh culture dishes. The process of re-plating or subculturing the cells is repeated many times and for many months. Each cycle of **subculturing** the cells is referred to as a **passage**. Once the cell line is established, the original cells yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for for a prolonged period of time without differentiating, are **pluripotent**, and have not developed genetic abnormalities are referred to as an **embryonic stem cell line**. At any stage in the process, batches of cells 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.

Scientists who study human embryonic stem cells have not yet agreed on a standard battery of tests that measure the cells' fundamental properties. However, laboratories that grow human embryonic stem cell lines use several kinds of tests, including:

- Growing and subculturing the stem cells for many months. This ensures that the cells are capable of long-term growth and 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 transcription factors that are typically produced by undifferentiated cells. Two of the most important transcription factors are Nanog and Oct4. Transcription factors help turn **genes** on and off at the right time, which is an important part of the processes of cell **differentiation** and embryonic development. In this case, both Oct 4 and Nanog are associated with maintaining the stem cells in an undifferentiated state, capable of self-renewal.
- Using specific techniques to determine the presence of paricular cell surface markers that are typically produced by undifferentiated cells.
- 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 re-grown, or subcultured, after freezing, thawing, and re-plating.
- 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 cells characteristic of the three germ layers; or 3) injecting the cells into a mouse with a suppressed immune system to test for the formation of a benign tumor called a **teratoma**. Since the mouse's immune system is suppressed, the injected human stem cells are not rejected by the mouse immune system and scientists can observe growth and differentiation of the human stem cells. 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?

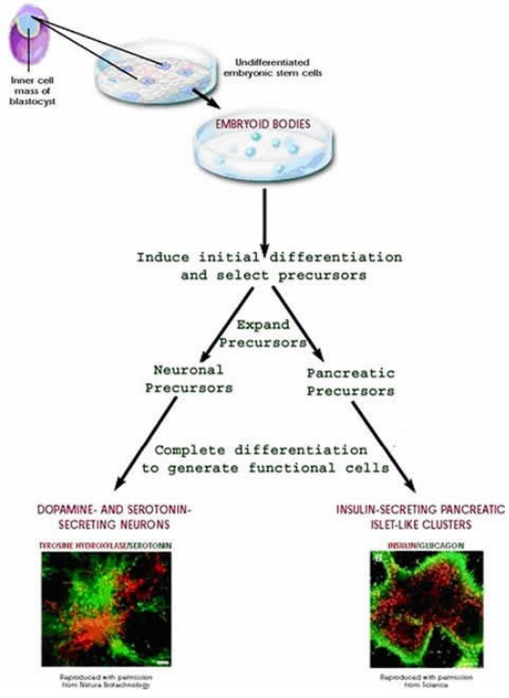

Figure 1. Directed differentiation of mouse embryonic stem cells. Click here for larger image. (© 2001 Terese Winslow)

As long as the embryonic stem cells in culture are grown under appropriate 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 additional examples of directed differentiation of embryonic stem cells, refer to the NIH stem cell reports available at /info/Regenerative_Medicine/ and /info/2001report/pages/2001report.aspx.)

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 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, Duchenne's muscular dystrophy, heart disease, and vision and hearing loss.

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Page citation: What are embryonic stem cells?. In *Stem Cell Information* [World Wide Web site]. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2010 [cited Saturday, March 22, 2014] Available at <http://stemcells.nih.gov/info/basics/pages/basics3.aspx>

Stem Cell Basics

IV. What are adult stem cells?

An adult stem cell is thought to be an **undifferentiated** cell, found among differentiated cells in a tissue or organ that can renew itself and can differentiate to yield some or all of 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. Scientists also use the term **somatic stem cell** instead of adult stem cell, where somatic refers to cells of the body (not the germ cells, sperm or eggs). Unlike embryonic stem cells, which are defined by their origin (cells from the preimplantation-stage embryo), the origin of adult stem cells in some mature tissues is still under investigation.

Research on adult stem cells has 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 researchers and clinicians to ask whether adult stem cells could be used for transplants. In fact, adult hematopoietic, or blood-forming, stem cells from bone marrow have been used in transplants for 40 years. Scientists now have evidence that stem cells exist in the brain and the heart. If the differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of transplantation-based therapies.

The history of research on adult stem cells began about 50 years ago. In the 1950s, 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 stem cells** (also called **mesenchymal stem cells**, or skeletal stem cells by some), were discovered a few years later. These non-hematopoietic stem cells make up a small proportion of the **stromal cell** population in the bone marrow, and can generate bone, cartilage, fat, cells that support the formation of blood, and fibrous connective tissue.

In the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells that ultimately become nerve cells. Despite these reports, most scientists believed that the adult brain could not generate new nerve cells. 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.

howdo other organs get repaired if this is all stem cell are in?

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

Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They are thought to reside in a specific area of each tissue (called a "stem cell niche"). In many tissues, current evidence suggests that some types of stem cells are pericytes, cells that compose the outermost layer of small blood vessels. Stem cells may remain quiescent (non-dividing) for long periods of time until they are activated by a normal need for more cells to maintain tissues, or by disease or tissue injury.

Typically, there is a very small number of stem cells in each tissue, and once removed from the body, their capacity to divide is limited, making generation of large quantities of stem cells difficult. Scientists in many laboratories are trying to find better ways to grow large quantities of adult stem cells in **cell culture** and to manipulate them to generate specific cell types so they can be used to treat injury or disease. Some examples of potential treatments include regenerating bone using cells derived from bone marrow stroma, developing insulin-producing cells for type 1 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 often use one or more of the following methods to identify adult stem cells: (1) label the cells in a living tissue with molecular markers and then determine the specialized cell types they generate; (2) remove the cells from a living animal, label them in cell culture, and transplant them back into another animal to determine whether the cells replace (or "repopulate") their tissue of origin.

Importantly, it must be demonstrated that a single adult stem cell can generate a line of genetically identical cells that then gives rise to all the appropriate differentiated cell types of the tissue. To confirm experimentally that a putative adult stem cell is indeed a stem cell, scientists tend to show either that the cell can give rise to these genetically identical cells in culture, and/or that a purified population of these candidate stem cells can repopulate or reform the tissue after transplant into an animal.

C. What is known about adult stem cell differentiation?

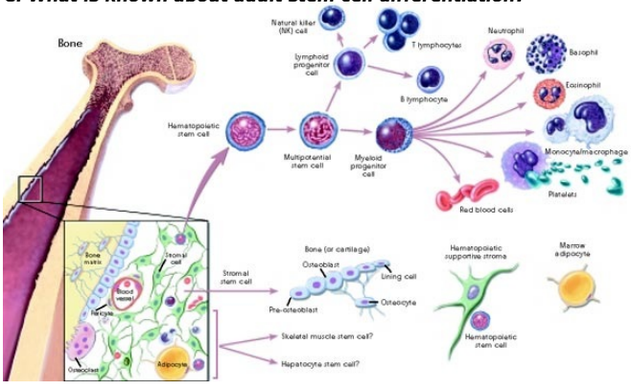

Figure 2. Hematopoietic and stromal stem cell differentiation. Click here for larger image. (© 2001 Terese Winslow)

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.

Normal differentiation pathways of adult stem cells. In a living animal, adult stem cells are available to divide, when needed, 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) that have been demonstrated *in vitro* or *in vivo*.

- 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, and macrophages.
- **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.

Does this covers every cell type?
Yes
http://www.eurostemcell.org/factsheet/reprogramming-how-turn-any-cell-body-pluripotent-stem-cell

Transdifferentiation. A number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted lineage (i.e., brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells, and so forth). This reported phenomenon is called transdifferentiation.

Although isolated instances of transdifferentiation have been observed in some vertebrate species, whether this phenomenon actually occurs in humans is under debate by the scientific community. Instead of transdifferentiation, the observed instances may involve fusion of a donor cell with a recipient cell. Another possibility is that transplanted stem cells are secreting factors that encourage the recipient's own stem cells to begin the repair process. Even when transdifferentiation has been detected, only a very small percentage of cells undergo the process.

In a variation of transdifferentiation experiments, scientists have recently demonstrated that certain adult cell types can be "reprogrammed" into other cell types in vivo using a well-controlled process of genetic modification (see Section VI for a discussion of the principles of reprogramming). This strategy may offer a way to reprogram available cells into other cell types that have been lost or damaged due to disease. For example, one recent experiment shows how pancreatic beta cells, the insulin-producing cells that are lost or damaged in diabetes, could possibly be created by reprogramming other pancreatic cells. By "re-starting" expression of three critical beta-cell genes in differentiated adult pancreatic exocrine cells, researchers were able to create beta cell-like cells that can secrete insulin. The reprogrammed cells were similar to beta cells in appearance, size, and shape; expressed genes characteristic of beta cells; and were able to partially restore blood sugar regulation in mice whose own beta cells had been chemically destroyed. While not transdifferentiation by definition, this method for reprogramming adult cells may be used as a model for directly reprogramming other adult cell types.

In addition to reprogramming cells to become a specific cell type, it is now possible to reprogram adult somatic cells to become like embryonic stem cells (**induced pluripotent stem cells, iPSCs**) through the introduction of embryonic genes. Thus, a source of cells can be generated that are specific to the donor, thereby increasing the chance of compatibility if such cells were to be used for tissue regeneration. However, like embryonic stem cells, determination of the methods by which iPSCs can be completely and reproducibly committed to appropriate cell lineages is still under investigation.

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?
- How do adult stem cells evolve during development and how are they maintained in the adult? Are they "leftover" embryonic stem cells, or do they arise in some other way?
- Why do stem cells remain in an undifferentiated state when all the cells around them have differentiated? What are the characteristics of their “niche” that controls their behavior?
- Do adult stem cells have the capacity to transdifferentiate, and is it possible to control this process to improve its reliability and efficiency?
- If the beneficial effect of adult stem cell transplantation is a trophic effect, what are the mechanisms? Is donor cell-recipient cell contact required, secretion of factors by the donor cell, or both?
- What are the factors that control adult stem cell proliferation and differentiation?
- What are the factors that stimulate stem cells to relocate to sites of injury or damage, and how can this process be enhanced for better healing?

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Stem Cell Basics

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**. One major difference between adult and embryonic stem cells is their different abilities in the number and type of differentiated cell types they can become. **Embryonic stem cells** can become all cell types of the body because they are **pluripotent**. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin.

Embryonic stem cells can be grown relatively easily in culture. Adult stem cells are rare in mature tissues, so isolating these cells from an adult tissue is challenging, and methods to expand 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.

Scientists believe that tissues derived from embryonic and adult stem cells may differ in the likelihood of being rejected after transplantation. We don't yet know whether tissues derived from embryonic stem cells would cause transplant rejection, since the first phase 1 clinical trials testing the safety of cells derived from hESCS have only recently been approved by the United States Food and Drug Administration (FDA).

Adult stem cells, and tissues derived from them, are currently believed less likely to initiate rejection after transplantation. This is because a patient's own cells could be expanded in culture, coaxed into assuming a specific cell type (**differentiation**), and then reintroduced into the patient. The use of adult stem cells and tissues derived from the patient's own adult stem cells would mean that the cells are less likely to be rejected by the immune system. This represents a significant advantage, as immune rejection can be circumvented only by continuous administration of immunosuppressive drugs, and the drugs themselves may cause deleterious side effects

could this end up fatal?

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Stem Cell Basics

VI. What are induced pluripotent stem cells?

Induced pluripotent stem cells (iPSCs) are adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. Although these cells meet the defining criteria for pluripotent stem cells, it is not known if iPSCs and embryonic stem cells differ in clinically significant ways. Mouse iPSCs were first reported in 2006, and human iPSCs were first reported in late 2007. Mouse iPSCs demonstrate important characteristics of pluripotent stem cells, including expressing stem cell markers, forming tumors containing cells from all three germ layers, and being able to contribute to many different tissues when injected into mouse embryos at a very early stage in development. Human iPSCs also express stem cell markers and are capable of generating cells characteristic of all three **germ layers**.

Although additional research is needed, iPSCs are already useful tools for drug development and modeling of diseases, and scientists hope to use them in transplantation medicine. Viruses are currently used to introduce the reprogramming factors into adult cells, and this process must be carefully controlled and tested before the technique can lead to useful treatments for humans. In animal studies, the virus used to introduce the stem cell factors sometimes causes cancers. Researchers are currently investigating non-viral delivery strategies. In any case, this breakthrough discovery has created a powerful new way to "de-differentiate" cells whose developmental fates had been previously assumed to be determined. In addition, tissues derived from iPSCs will be a nearly identical match to the cell donor and thus probably avoid rejection by the immune system. The iPSC strategy creates pluripotent stem cells that, together with studies of other types of pluripotent stem cells, will help researchers learn how to reprogram cells to repair damaged tissues in the human body.

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Stem Cell Basics

VII. 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 research and the clinic. Studies of **human embryonic stem cells** will 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 the differentiated cells that form the tissues and organs. 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 more complete understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. Predictably controlling cell proliferation and differentiation requires additional basic research on the molecular and genetic signals that regulate cell division and specialization. While recent developments with iPS cells suggest some of the specific factors that may be involved, techniques must be devised to introduce these factors safely into the cells and control the processes that are induced by these factors.

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. 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 falls short of being able to mimic these conditions precisely to generate pure populations of 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 Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

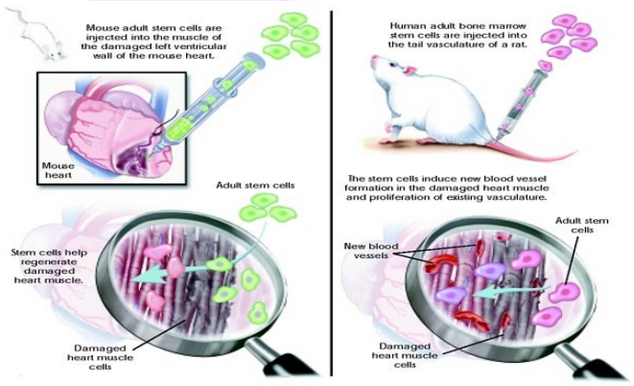

Figure 3. Strategies to repair heart muscle with adult stem cells.
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For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Preliminary research in mice and other animals indicates that bone marrow stromal cells, transplanted into a damaged heart, can have beneficial effects. Whether these cells can generate heart muscle cells or stimulate the growth of new blood vessels that repopulate the heart tissue, or help via some other mechanism is actively under investigation. For example, injected cells may accomplish repair by secreting growth factors, rather than actually incorporating into the heart. Promising results from animal studies have served as the basis for a small number of exploratory studies in humans (for discussion, see call-out box, "Can Stem Cells Mend a Broken Heart?"). 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 3).

would injecting too much of this cause overgrowth of organ

Can Stem Cells Mend a Broken Heart?: Stem Cells for the Future Treatment of Heart Disease

Cardiovascular disease (CVD), which includes hypertension, coronary heart disease, stroke, and congestive heart failure, has ranked as the number one cause of death in the United States every year since 1900 except 1918, when the nation struggled with an influenza epidemic. Nearly 2600 Americans die of CVD each day, roughly one person every 34 seconds. Given the aging of the population and the relatively dramatic recent increases in the prevalence of cardiovascular risk factors such as obesity and type 2 diabetes, CVD will be a significant health concern well into the 21st century.

Cardiovascular disease can deprive heart tissue of oxygen, thereby killing cardiac muscle cells (cardiomyocytes). This loss triggers a cascade of detrimental events, including formation of scar tissue, an overload of blood flow and pressure capacity, the overstretching of viable cardiac cells attempting to sustain cardiac output, leading to heart failure, and eventual death. Restoring damaged heart muscle tissue, through repair or regeneration, is therefore a potentially new strategy to treat heart failure.

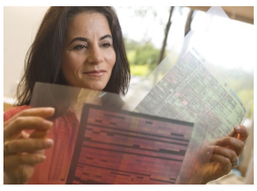
The use of embryonic and adult-derived stem cells for cardiac repair is an active area of research. A number of stem cell types, including embryonic stem (ES) cells, cardiac stem cells that naturally reside within the heart, myoblasts (muscle stem cells), adult bone marrow-derived cells including mesenchymal cells (bone marrow-derived cells that give rise to tissues such as muscle, bone, tendons, ligaments, and adipose tissue), endothelial progenitor cells (cells that give rise to the endothelium, the interior lining of blood vessels), and umbilical cord blood cells, have been investigated as possible sources for regenerating damaged heart tissue. All have been explored in mouse or rat models, and some have been tested in larger animal models, such as pigs.

A few small studies have also been carried out in humans, usually in patients who are undergoing open-heart surgery. Several of these have demonstrated that stem cells that are injected into the circulation or directly into the injured heart tissue appear to improve cardiac function and/or induce the formation of new capillaries. The mechanism for this repair remains controversial, and the stem cells likely regenerate heart tissue through several pathways. However, the stem cell populations that have been tested in these experiments vary widely, as do the conditions of their purification and application. Although much more research is needed to assess the safety and improve the efficacy of this approach, these preliminary clinical experiments show how stem cells may one day be used to repair damaged heart tissue, thereby reducing the burden of cardiovascular disease.

In people who suffer from type 1 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 persons with diabetes.

could this work for all cells? x and are they have

To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able to 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 control to



Dennise Dalma-Weiszhausz, PhD

Stem Cell Applications

From Alzheimer's to arthritis, blindness, burns, cancer, diabetes, heart disease, liver disorders, multiple sclerosis, Parkinson's, spinal cord injury, stroke… Stem cells have been proposed as candidates to treat diseases and disorders of every organ of the human body.

Cell-based Therapies

Historically, donated organs have been transplanted and medical devices implanted to replace failing systems. In the case of the former, the need far outweighs the available supply and, in both cases, the risks and costs are high. Side effects may limit the effectiveness or feasibility of d radiation or surgical interventions. Advances in biotechnology have led to the identification and replication of specific substances — such as sugars, amino acids, neurotransmitters and hormones — that are deficient in some degenerative diseases. While administering these substances medication can overcome some of the limitations of more traditional pharmaceutical products, such as lack of specificity, there is no synthetic technology that can deliver them to the precise sites of action under the appropriate physiological regulation and dosage, or for the duration req cure the condition. Cells, however, do this naturally.

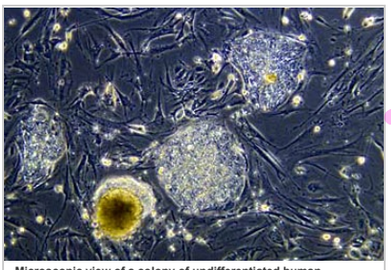
The concept of cell-based therapy (or simply cell therapy, as it is sometimes called) is to repair, replace or supplement damaged or diseased cells with healthy cells. The work of StemCells scientists has already generated the means to supply stem cells, which upon transplantation, can differentiate into healthy new cells or tissues, and which may thereby be capable of alleviating or potentially even curing a broad array of intractable conditions.

The introduction of healthy cells has been shown to protect remaining functionality, as in the company's preclinical studies of the effects of neural stem cell transplantation in an animal model of AMD. Transplanted neural stem cells appear to be able to replace dysfunctional cells, such a oligodendrocytes needed to alleviate myelination disorders, such as PMD. Where impaired cellular function is associated with the progressive decline commonly seen in degenerative diseases like NCL, stem cells can deliver specialized cells that secrete, metabolize or regulate essentia substances. Stem cells may even be able to help make gene therapy a reality by delivering the truly long-term gene expression necessary for successful treatment of genetic disorders. The therapeutic programs currently underway and, in some cases, already in clinical trials at StemCe are paving the way for a variety of promising new cell-based therapies.

How Stem Cells Work

by Stephanie Watson and Craig Freudenrich, Ph.D.

Browse the article **How Stem Cells Work**



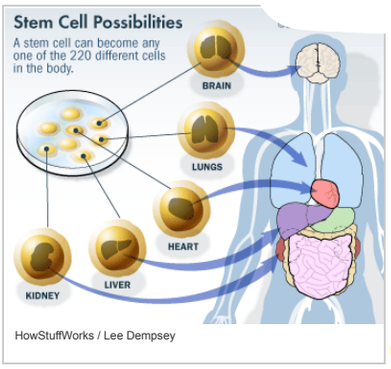
Microscopic view of a colony of undifferentiated human embryonic stem cells being studied in developmental biologist James Thomson's research lab at the University of Wisconsin-Madison.
Photo courtesy University of Wisconsin-Madison

Introduction to How Stem Cells Work

Many diseases kill cells within organs, claiming lives or impairing a person's ability to live a normal life. For example, about 5.8 million Americans have heart failure and 670,000 people are diagnosed with it each year [source: Centers for Disease Control]. In heart failure, much of the heart muscle itself dies, so the heart cannot sufficiently pump blood.

Similarly, about 23.6 million Americans have diabetes [source: NIDDK, NIH]. Five to 10 percent of these people have Type I diabetes in which the insulin-producing cells of the pancreas are dead. Finally, about 1 million Americans live with Parkinson's disease [source: Parkinson's Disease Foundation]. In this disease, cells that make the neurotransmitter dopamine, which helps control movement, die. Patients with Parkinson's disease have tremors and uncontrollable movements. But what if these dead cells could be replaced with fresh cells? Could the patients be treated and live normal lives? That's the goal of stem cell research.

In this article, we'll look at stem cells, starting with the accompanying picture above. In the photo, the embryonic stem cell colonies are the rounded, dense masses of cells. The flat elongated cells are fibroblasts used as "feeder cells." We'll also find out how stem cells work, discover their potential to treat disease and get inside the ongoing debate surrounding their research and use. But first, let's cover some basics.



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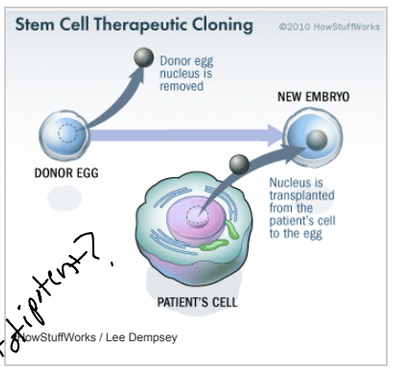
A stem cell is essentially the **building block of the human body**. Stem cells are capable of dividing for long periods of time, are unspecialized, but can develop into specialized cells. The earliest stem cells in the human body are those found in the human embryo. The stem cells inside an embryo will eventually give rise to every cell, tissue and organ in the fetus's body. Unlike a regular cell, which can only replicate to create more of its own kind of cell, a stem cell is **pluripotent**. When it divides, it can make any one of the **220 different cells** in the human body. Stem cells also have the capability to **self-renew** -- they can reproduce themselves many times over.

There are several types of stem cells, including:

- **Embryonic stem cells** - Embryonic stem cells include those found within the embryo, the fetus or the umbilical cord blood. Depending upon when they are harvested, embryonic stem cells can give rise to just about any cell in the human body.
- **Adult stem cells** - Adult stem cells can be found in infants, children and adults. They reside in already developed tissues such as those of the heart, brain and kidney. They usually give rise to cells within their resident organs.
- **Induced pluripotent stem cells (IPSC)**- These stem cells are adult, differentiated cells that have been experimentally "reprogrammed" into a stem cell-like state.

So how do all these types of stem cells work? And what are their potential uses? Let's find out -- starting with embryonic stem cells.



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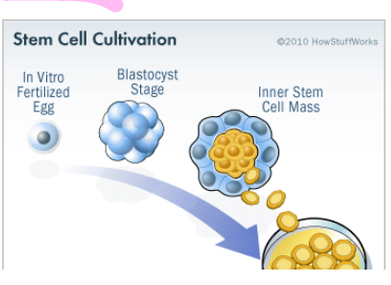
Embryonic Stem Cells

Once an egg cell is fertilized by a sperm, it will divide and become an embryo. In the embryo, there are stem cells that are capable of becoming all of the various cell types of the human body. For research, scientists get embryos in two ways. Many couples conceive by the process of in vitro fertilization. In this process, a couple's sperm and eggs are fertilized in a culture dish. The eggs develop into embryos, which are then implanted in the female. However, more embryos are made than can be implanted. So, these embryos are usually frozen. Many couples donate their unused embryos for stem cell research.

The second way in which scientists get embryos is **therapeutic cloning.** This technique merges a cell (from the patient who needs the stem cell therapy) with a donor egg. The nucleus is removed from the egg and replaced with the nucleus of the patient's cell. (For a detailed look at the process, see How Cloning Works) This egg is stimulated to divide either chemically or with electricity, and the resulting embryo carries the patient's genetic material, which significantly reduces the risk that his or her body will reject the stem cells once they are implanted.

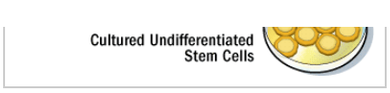
Both methods -- using existing fertilized embryos and creating new embryos specifically for research purposes -- are controversial. But before we get into the controversy, let's find out how scientists get stem cells to replicate in a laboratory setting in order to study them.

When an embryo contains about eight cells, the stem cells are **totipotent** - they can develop into all cell types. At three to five days, the embryo develops into a ball of cells called a **blastocyst**. A blastocyst contains about 100 cells total and the stem cells are inside. At this stage, the stem cells are **pluripotent** - they can develop into almost any cell type.



To grow the stem cells, scientists remove them from the blastocyst and culture them (grow them in a nutrient-rich solution) in a Petri dish in the laboratory. The stem cells divide several times and scientists divide the population into other dishes. After several months, there are millions of stem cells. If the cells continue to grow without differentiating, then the scientists have a **stem cell line**. Cell lines can be frozen and shared between laboratories. As we will see later, stem cell lines are necessary for developing therapies.

Today, many expectant mothers are asked about umbilical cord banking -- the process of storing umbilical cord blood after giving birth. Why would someone want to do that? Once a mother gives birth, the umbilical cord and remaining blood are often discarded. However, this blood also contains stem cells from the fetus. Umbilical cord blood can be harvested and the embryonic stem cells grown in culture. Unlike embryonic stem cells from earlier in development, fetal stem cells from



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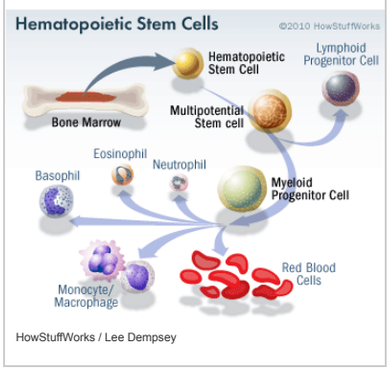
umbilical cord blood are **multipotent** - they can develop into a limited number of cell types.

Now that you have a better understanding of embryonic stem cells, let's look at adult stem cells.



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Adult Stem Cells

You can think of adult stem cells as our built-in repair kits, regenerating cells damaged by disease, injury and everyday wear and tear. These undifferentiated cells reside among other differentiated cells in a tissue or organ; they divide and become specialized to repair or replace the surrounding differentiated cells. A common example of adult stem cells is **hemopoietic stem cells**, which are found in red bone marrow. These stem cells differentiate into various blood cells (red blood cells, lymphocytes, platelets-- see How Blood Works for more information). For example, red blood cells are not capable of reproducing and survive for about 28 days. To replace worn-out red blood cells, hemopoietic stem cells in the bone marrow divide and differentiate into new red blood cells.

Bone marrow also contains a second type of adult stem cell known as a **stromal** or **mesenchymal stem cell**. Stromal stem cells become bone, cartilage, fat and connective tissues found in bone. Adult stem cells have also been found in many other tissues such as the brain, skeletal muscle, blood vessels, skin, liver, teeth and the heart. Regardless of the source, adult stem cells are **multipotent** - they can develop into a limited number of cell types.

Although adult stem cells exist in many tissues, their numbers are small, perhaps one adult stem cell for every 100,000 surrounding cells. These stem cells look like the surrounding cells, so it's difficult to tell them apart. But researchers have developed an interesting way to identify them by "lighting them up." All cells have unique proteins on their surface called **receptor**s. Receptors bind chemical messages from other cells as part of cell-to-cell communication. Researchers use these receptors -- or **markers** -- to identify and isolate adult stem cells by "tagging" the chemical messages that bind to those specific receptors on the stem cell with fluorescent molecules. Once the fluorescent chemical message binds to the receptor on the surface of the stem cell, the stem cell will "light up" under fluorescent light. The "lighted" stem cell can then be identified and isolated.

Like embryonic stem cells, adult stem cells can be grown in culture to establish stem cell lines.

Adult stem cells were once believed to be more limited than embryonic stem cells, only giving rise to the same type of tissue from which they originated. But new research suggests that adult stem cells may have the potential to generate other types of cells, as well. For example, liver cells may be coaxed to produce insulin, which is normally made by the pancreas. This capability is known as **plasticity** or **transdifferentiation**

It used to be believed that there were only two types of stem cells -- embryonic and adult -- but there's another kid on the stem cell block. Keep reading to learn about this "new" type: the induced pluripotent stem cell.

SAVE THOSE TEETH

Dentists usually discard wisdom teeth after they've been extracted -- but maybe they should start saving them; they just might be useful in make stem cells. Recently, a group of Japanese scientists made induced pluripotent stem cells (IPSCs) from the tooth pulp of extracted wisdom teeth. They used viruses to deliver stem cell factors to mesenchymal stromal cells isolated from the pulp of third molars. The resulting IPSCs were similar to embryonic stem cells.

In 2003, an NIH researcher, Sangtao Shi, extracted stem cells from his daughter's baby teeth. The stem cells grew in culture and could form bone when implanted into mice. Potentially, you could bank stem cells from your teeth for future use, but it would be an expensive process.

Maybe that's what the tooth fairy does with all those teeth?

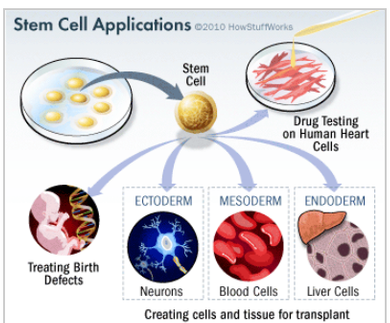
Induced Pluripotent Stem Cells (IPSCs)

Whether from embryos or adult tissues, stem cells are few. But many are needed for cell therapies. There have been ethical and political problems with using embryonic stem cells -- so if there were a way to get more stem cells from adults, it might be less controversial. Enter the IPSC.

Every cell in the body has the same genetic instructions. So what makes a heart cell different from a liver cell? The two cells express different sets of genes. Likewise, a stem cell turns on specific sets of genes to differentiate into another cell. So, is it possible to reprogram a differentiated cell so that it reverts back to a stem cell? In 2006, scientists did just that. They used a virus to deliver four stem cell factors into skin cells. The factors caused the differentiated stem cells to go into an embryonic-stem-cell-like state. The resulting cells, called **induced pluripotent stem cells** (IPSCs), shared many characteristics with human embryonic stem cells. The structures of IPSCs were similar, they expressed the same markers and genes, and they grew the same. And the researchers were able to grow the IPSCs into cell lines.

There are many more differentiated cells in the human body than stem cells, embryonic or adult. So, vast amounts of stem cells could be made from a patient's own differentiated cells, like skin cells. Making IPSCs does not involve embryos, so this would circumvent the ethical and political issues involved in stem cell research. However, making ISPSCs is a recent development, so scientists need to do more research before they can be used for therapies. First, we need to understand the "reprogramming" process better. And then we need to investigate whether IPSCs are just similar enough or are actually identical to embryonic stem cells. Current research is focused on these questions, but reprogramming cells to make IPSCs has great potential.

Now that you have a good idea of what stems cells are and how they work, let's see how they can be used to treat diseases.



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Using Stem Cells to Treat Disease

The first step in using stem cells for disease treatment is to establish stem cell lines, which researchers have accomplished. Next, scientists must be able to turn on specific genes within the stem cells so that the stem cells will differentiate into any cell they wish. But scientists have not learned how to do this yet; so, studying stem cell differentiation is an active area of research. Once scientists can create differentiated cells from stem cells, then there are many possibilities for their use, such as drug testing and cell-based therapies. For example, let's say you want to test new drugs to treat heart diseases. Currently, new drugs must be tested on animals. The data from animal research must be interpreted and then extrapolated to humans prior to human clinical trials. But suppose you could test them directly on human heart cells. To do this, human stem cell lines could be treated to differentiate into human heart cells in a dish. The potential drugs could be tested on those cells and the data would be directly applicable to humans. This use could save vast amounts of time and money in bringing new drugs to market.

Stem-cell-based therapies are not new. The first stem-cell-based therapy was a bone marrow transplant used to treat leukemia. In this procedure, the patient's existing bone marrow is destroyed by radiation and/or chemotherapy. Donor bone marrow is injected into the patient and the bone marrow stem cells establish themselves in the patient's bones. The donor bone marrow cells differentiate into blood cells that the patient needs. Often, the patient must take drugs to prevent his or her immune system from rejecting the new bone marrow. But this procedure uses existing hemopoietic stem cells. How would you use stem cell lines? Let's look at how stem cells might be used to treat heart failure.

Ideally, to treat a failing heart, scientists could stimulate stem cells to differentiate into heart cells and inject them into the patient's damaged heart. There, the new heart cells could grow and repair the damaged tissue. Although scientists cannot yet direct stem cells to differentiate into heart cells, they have tested this idea in mice. They have injected stem cells (adult, embryonic) into mice with damaged hearts. The cells grew in the damaged heart cells and the mice showed improved heart function and blood flow.

In these experiments, exactly how the stem cells improved heart function remains controversial. They may have directly regenerated new muscle cells. Alternatively, they may have stimulated the formation of new blood vessels into the damaged areas. And the new blood flow may have stimulated existing heart stem cells to differentiate into new heart muscle cells. These experiments are currently being evaluated.

One major obstacle in stem cell use is the problem of **rejection**. If a patient is injected with stem cells taken from a donated embryo, his or her immune system may see the cells as foreign invaders and launch an attack against them. Using adult stem cells or IPSCs could overcome this problem somewhat, since stem cells taken from the patient would not be rejected by his or her immune system. But adult stem cells are less flexible than embryonic stem cells and are harder to manipulate in the lab. And IPSC technology is too new for transplantation work.

Finally, by studying how stem cells differentiate into specialized cells, the information gained can be used to understand how birth defects occur and possibly, how to treat them.

So, if there's so much potential in stem cell research, why all the controversy? Let's investigate the current ethical and political issues.

STEM CELL RESEARCH ADVOCATES

Since 1991, when he was diagnosed with Parkinson's disease (a degenerative brain disorder that affects movement), actor Michael J. Fox has been a vocal proponent for stem cell research. His foundation has donated more than $205 million to help fund Parkinson's research [source: Michael J. Fox Foundation]. Fox and his foundation are hoping that scientists will one day be able to coax stem cells into producing dopamine, a chemical in the body that is deficient in patients with Parkinson's disease.

Former first lady Nancy Reagan also became an advocate for stem cell research when her husband, former President Ronald Reagan, was stricken with Alzheimer's, another degenerative brain disease. He died of Alzheimer's in the summer of 2004.

Stem Cell Research Controversy

Stem cell research has become one of the biggest issues dividing the scientific and religious communities around the world. At the core of the issue is one central question: When does life begin? At this time, to get stem cells that are reliable, scientists either have to use an embryo that has already been conceived or else clone an embryo using a cell from a patient's body and a donated egg. Either way, to harvest an embryo's stem cells, scientists must destroy it. Although that embryo may only contain four or five cells, some religious leaders say that destroying it is the equivalent of taking a human life. Inevitably, this issue entered the political arena.

In 1996, Congress passed a rider to the federal appropriations bill called the **Dickey-Wicker amendment**. Representatives Jay Dickey and Roger Wicker proposed banning the use of federal monies for any research in which a human embryo is created or destroyed. Federal monies are a primary source of funding for stem cell research. The amendment has been renewed every year since that time.

In 2001, President George W. Bush further restricted federal stem cell research. In an executive order, Bush stated that federal funds could only be used for research on human embryonic stem cell lines that had already been established (only 22 cell lines). This prevented researchers from creating more embryonic stem cell lines for research.

In 2009, President Barack Obama issued an executive order to expand embryonic stem cell research. Obama's administration allowed federal funding of embryonic stem cell research if the following conditions applied:

- The cell line was one of the 22 in existence during the Bush administration or was created from embryos that had been discarded after in vitro fertilization procedures.
- The donors of the embryos were not paid in any way.
- The donors clearly knew that the embryos would be used for research purposes prior to giving consent.

According to the administration, the new policy did not violate the Dickey-Wicker amendment because the money did not finance the creation of new embryos (they had already been created by private means) and did not finance the destruction of them.

In 2009, two researchers from Boston, Dr. James Sherley of the Boston Biomedical Research Institute and Dr. Theresa Deisher of the Ava Maria Biotechnology Company, and other agencies filed a lawsuit against the government. Initially, the lawsuit was dismissed because the judge ruled that the plaintiffs had no legal standing (i.e. they were not affected materially by the new rules). However, a court of appeals overturned the initial ruling. The two scientists remained plaintiffs. The scientists claimed that, because they used adult stem cells exclusively in their research, the new rules would increase competition for federal research dollars, thereby affecting their ability to obtain funding. Federal Judge Royce Lamberth upheld the appeals court ruling. He placed an injunction preventing the new rules from going into place. He claimed that the rules violated the Dickey-Wicker amendment because embryos must be destroyed in the process of creating embryonic stem cell lines.

In September 2010, The New York Times reported that the U.S. Court of Appeals ruled that federal funding of embryonic stem cell research could continue under the new rules while the court considers Judge Lamberth's ruling [source: New York Times]. This ruling allows researchers to continue feeding embryonic stem cell cultures, experimenting with mice, and other research activities until this court rules, the U.S. Supreme Court weighs in, or Congress passes legislation that clarifies the issues. In the meantime, stem cell research and the careers of stem cell researchers hang on a legal roller coaster. Although stem cells have great potential for treating diseases, much work on the science, ethical and legal fronts remains.

For more on stem cells, investigate the links on the following page.

Lots More Information

Related HowStuffWorks Articles

- How Your Heart Works
- How Diabetes Works
- How Parkinson's Disease Works
- How Your Brain Works
- How Cloning Works
- How Sex Works
- How Blood Works
- How In Vitro Fertilization Works

More Great Links

- NIH Stem Cell Information
- University of Utah Genetic Science Learning Center: Stem Cells
- The New York Times: Stem Cells
- Stem Cell Basics (NIH)
- Regenerative Medicine (NIH Stem Cell Report)

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