

Stem Cell Research

2 contact hours: \$15

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Course Summary: Explores the unique properties of stem cells, and distinguishes between embryonic and adult cells. Potential uses for stem cells include ongoing research into treatment of Parkinson's disease and ALS.

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Course Objectives

When you finish this course, you will be able to:

- Define stem cells and identify their unique properties.
- Discuss the laboratory development of embryonic stem cells.
- List the properties of adult stem cells.
- Differentiate embryonic stem cells from adult stem cells.
- Report on the potential uses for stem cells.
- Explain the ongoing research relating stem cells to treatment of Parkinson's disease and ALS.

Stem Cells

The use of human stem cells for medical research became politically controversial in the beginning of this decade. President Bush restricted their use in 2001, but President Obama removed those barriers early in his administration. In a White House speech the new president said, “We will bring the change that so many scientists and researchers, doctors and innovators, patients and loved ones have hoped for and fought for these past eight years. We will lift the ban on federal funding for promising embryonic stem cell research” (*U.S. News and World Report*, March 9, 2009).

The executive order not only lifts the Bush administration’s federal funding restrictions on stem cell research but also changes the way the National Institutes of Health (NIH) support and conduct human cell research. President Obama’s order also revoked the Bush statement of August 9, 2001, which allowed federal funds to be awarded for research using human embryonic stem cells **only if** the cells had been derived before the Bush order, they were derived from an embryo that was created for reproductive purposes and was no longer needed, and informed consent had been obtained for the donation of the embryo without financial inducement.

Under Obama’s executive order, the Secretary for Health and Human Services (HHS) and the Director of the NIH were required to review existing guidelines on human stem cell research and issue new NIH guidelines within 120 days (NIH, 2009).

A day after the Obama order, the American Nurses Association (ANA) issued a statement supporting it: “While ANA recognizes there are opposing views on stem cell research, including within ANA, we believe the benefits to be realized for the many individuals who suffer from diseases and disabilities outweigh this dissent” (ANA, 2009).

As stem cell researchers develop new therapies to treat disease, nurses and other healthcare practitioners will be delivering these therapies and caring for the patients who receive them. Thousands of people already undergo stem cell transplants to treat cancer and other diseases, and we must provide care for these often high-risk patients. It is important for nurses to have an understanding of these therapies in order to deliver optimal care (*Medical News Today*, 2007).

What Are Stem Cells?

Stem cells are about potential. They are unspecialized cells that have the potential to develop into many different cell types and they are most active during early life and development. Stem cells can divide without limit to replenish other cells, and thus act as a sort of internal repair system.

Research on stem cells is advancing our knowledge about how an organism develops from a single cell and how healthy cells are able to replace damaged cells in adult organisms. This promising area of science is leading to the investigation of **regenerative** (reparative) **medicine**, which would use cell-based therapies to treat some of the most serious medical conditions that occur in humans. A better understanding of normal cell development will allow us to understand—and perhaps correct—the errors in cell development that cause these medical conditions.

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that can renew themselves for long periods of time through cell division. Second, under certain physiologic or experimental conditions, they can be induced to become cells with special functions, such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas.

Scientists primarily work with two kinds of stem cells from animals and humans: **embryonic stem cells** and **adult stem cells**, each of which has unique functions and characteristics. Scientists discovered ways to obtain stem cells from early mouse embryos more than twenty years ago. Many years of detailed study of the biology of mouse stem cells led to the discovery, in 1998, of how to isolate stem cells from human embryos and grow the cells in the laboratory.

These cells, called human embryonic stem cells, were first isolated by Dr. James A. Thomson, a biologist at the University of Wisconsin. The embryos used in these studies were created for infertility purposes through in vitro fertilization procedures (in an artificial environment, rather than inside a living organism) and when they were no longer needed for that purpose they were donated for research with the informed consent of the donor.

Embryonic and adult stem cells are important to living organisms for many reasons. In the 3- to 5-day-old embryo, called a **blastocyst**, stem cells in developing tissues give rise to the multiple specialized cell types that make up the heart, lung, skin, and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease. Stem cells may, at some point in the future, become the basis for treating diseases such as Parkinson's disease, diabetes, and heart disease.

Scientists want to study stem cells in the laboratory so they can learn about their essential properties and what makes them different from specialized cell types. As we learn more about stem cells, it may become possible to use the cells not only in cell-based therapies but also for screening new drugs and toxins and understanding birth defects. However, since human embryonic stem cells have only been studied since 1998, much remains to be learned. Scientists are currently focusing on the fundamental properties of stem cells. They want to:

- Determine precisely how stem cells remain unspecialized and self-renewing for many years
- Identify the signals that cause stem cells to become specialized

Unique Properties of Stem Cells

Regardless of their source, stem cells have three unique properties that make them different from other cells in the body. They are capable of dividing and renewing themselves for long periods, are unspecialized, and can give rise to specialized cell types. Scientists are trying to understand two fundamental properties of stem cells that relate to their long-term self-renewal:

- Why can embryonic stem cells proliferate for a year or more in the laboratory without differentiating, while most adult stem cells cannot?
- 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. This information would also enable scientists to grow embryonic and adult stem cells more efficiently in the laboratory.

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

Proliferation

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

It has taken many years of trial and error to learn to grow stem cells in the laboratory without spontaneous differentiation into specific cell types. For example, it was necessary to develop the conditions for growing mouse stem cells before it became possible to grow human embryonic stem cells in the laboratory, an evolution that took twenty years.

The specific factors and conditions that allow stem cells to remain unspecialized are of great interest. Researchers look to understand the signals in a mature organism that cause a stem cell population to proliferate and remain unspecialized until the cells are needed for repair of a specific tissue. Such information is critical for growing the large numbers of unspecialized stem cells that will be needed for further laboratory experimentation.

Differentiation

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

Many questions about stem cell differentiation remain. For example:

- Are the internal and external signals for cell differentiation similar for all kinds of stem cells?
- Can specific sets of signals be identified that promote differentiation into specific cell types?

Addressing these questions is critical because the answers may lead to new ways of controlling stem cell differentiation in the laboratory, thereby growing cells or tissues that can be used for specific purposes, including cell-based therapies.

Plasticity

Adult stem cells typically generate the cell types of the tissue in which they reside. A blood-forming adult stem cell in the bone marrow, for example, normally gives rise to the many types of blood cells (eg, red blood cells, white blood cells, platelets). Until recently, it had been thought that a blood-forming cell in the bone marrow—which is called a *hematopoietic* stem cell—could not give rise to the cells of a very different tissue, such as nerve cells in the brain. However, a number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as **plasticity**.

Examples of such plasticity include blood cells becoming neurons (nerve cells), liver cells that can be made to produce insulin, and hematopoietic stem cells that can develop into heart muscle. Exploring the possibility of using adult stem cells for cell-based therapies has recently become an active area of investigation.

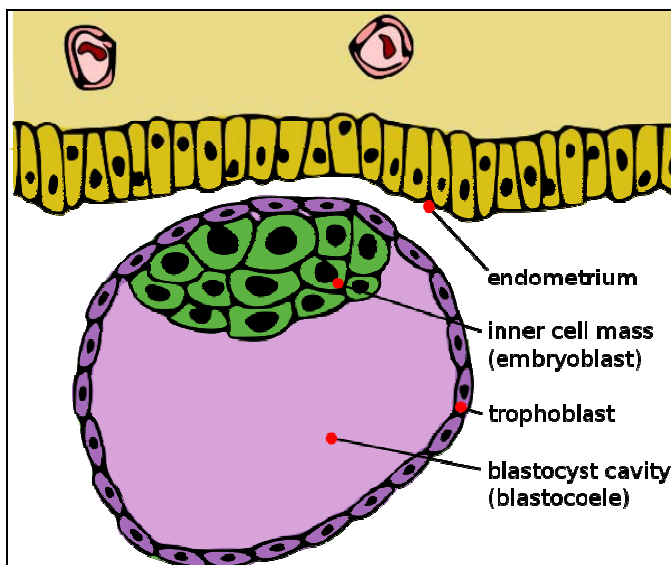
Embryonic Stem Cells

Embryonic stem cells, as their name suggests, are derived from embryos. The embryonic stem cells to be used for research are derived from embryos that develop from eggs fertilized outside of the womb—in an in vitro fertilization clinic—and then donated for research purposes with the informed consent of the donors. They are not derived from eggs fertilized in a woman's body.

The embryos from which stem cells are derived are typically 4 or 5 days old and are in the form of a hollow microscopic ball of cells called a blastocyst. The **blastocyst** includes three structures, as shown in Figure 1:

- Trophoblast, the layer of cells that surrounds the blastocyst
- Blastocoel, which is the hollow cavity inside the blastocyst
- Inner cell mass, a group of about 30 cells at one end of the blastocoel

Figure 1: Cross-section of a blastocyst showing its internal elements.



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Culturing the Cells

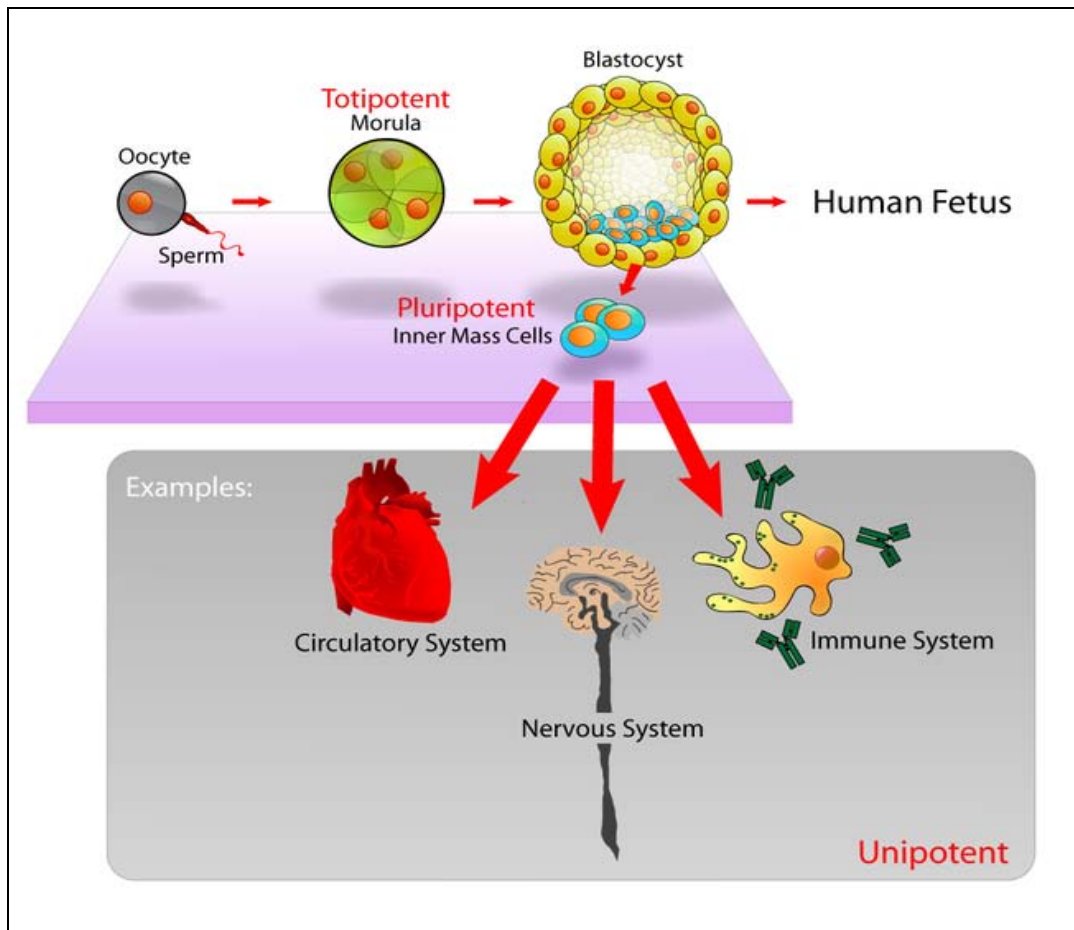
Growing cells in the laboratory is known as cell culture. Researchers isolate human embryonic stem cells by transferring the inner cell mass into a culture dish that contains a nutrient broth called the *culture medium*. The cells then divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with a feeder layer of mouse embryonic skin cells that have been treated so they will not divide. The mouse cells in the bottom of the culture dish give the inner mass cells a sticky surface to attach to.

The feeder cells also release nutrients into the culture medium. Recently, scientists have begun to devise ways of growing embryonic stem cells without the mouse feeder layer to address the potential risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells.

Over the course of several days, the cells of the inner cell mass proliferate and begin to crowd the culture dish. When this occurs, they are gently removed and plated into several fresh culture dishes. The process of re-plating the cells is repeated many times over many months, and is called sub-culturing. Each cycle of sub-culturing the cells is referred to as a *passage*. After six months or more, the original 30 cells of the inner cell mass have yielded millions of embryonic stem cells.

Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating are referred to as an embryonic stem cell line. These stem cells appear genetically normal and are *pluripotent*—able to differentiate into multiple distinct cell types, as shown in Figure 2. Once cell lines are established, or even before that stage, batches of them can be frozen and shipped to other laboratories for further culture and experimentation.

Figure 2: The source of pluripotent stems cells from developing embryos.



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Testing the Cells

At various points during the process of generating embryonic stem cell lines, the cells are tested 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 to measure the cells' fundamental properties. In addition, scientists acknowledge that many of the tests they do use may not be good indicators of the cells' most important biological properties and functions. Nevertheless, laboratories that grow human embryonic stem cell lines use several kinds of tests. These tests include:

- Growing and sub-culturing the stem cells for many months. This ensures that the cells are capable of long-term self-renewal. The cultures are inspected through a microscope to see that they look healthy and remain undifferentiated.
- Using specific techniques to determine the presence of surface markers that are found only on undifferentiated cells. One important test is for the presence of a protein called Oct-4, which undifferentiated cells typically make. Oct-4 is a transcription factor, meaning that it helps turn genes on and off at the right time, which is an important part of the processes of cell differentiation and embryonic development.
- Examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells.
- Determining whether the cells can be sub-cultured 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 specific cell types; or (3) injecting the cells into an immunosuppressed mouse to test for the formation of a benign tumor called a *teratoma*. Teratomas typically contain a mixture of many differentiated or partially differentiated cell types and are an indication that the embryonic stem cells are capable of differentiating into multiple cell types.

As long as the embryonic stem cells in culture are grown under certain conditions, they can remain undifferentiated (unspecialized). But if cells are allowed to clump together to form embryoid bodies, they begin to differentiate spontaneously. At this point 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.

Generating Specific Types of Cells

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.

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

Adult Stem Cells

An adult stem cell, also called a somatic stem cell, is an undifferentiated cell in a tissue or organ, which can renew itself and differentiate to yield the major specialized cell types of that 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. Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), the origin of adult stem cells in mature tissues is unknown.

Research on adult stem cells has recently generated a great deal of excitement. Scientists have found adult stem cells in many more tissues than they once thought possible. This finding has led them to ask whether adult stem cells could be used for transplants. In fact, adult blood-forming stem cells from bone marrow have been used in transplants for thirty years.

The history of research on adult stem cells began about 40 years ago. In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population, bone marrow stromal cells, was discovered a few years later. Stromal cells are a mixed cell population that generates bone, cartilage, fat, and fibrous connective tissue.

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

Location and Function

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

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

Testing the Cells

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

A single adult stem cell should be able to generate a line of genetically identical cells—known as **clones**—which then give rise to all the appropriate differentiated cell types of the tissue. Recently, by infecting adult stem cells with a virus that gives a unique identifier to each individual cell, scientists have been able to demonstrate that individual adult stem cell clones have the ability to repopulate injured tissues in a living animal.

Researchers have reported that adult stem cells occur in many tissues and that they enter normal differentiation pathways to form the specialized cell types of the tissue in which they reside. Adult stem cells may also exhibit the ability to form specialized cell types of other tissues; this is known as trans-differentiation, or plasticity.

Normal Differentiation Pathways

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

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

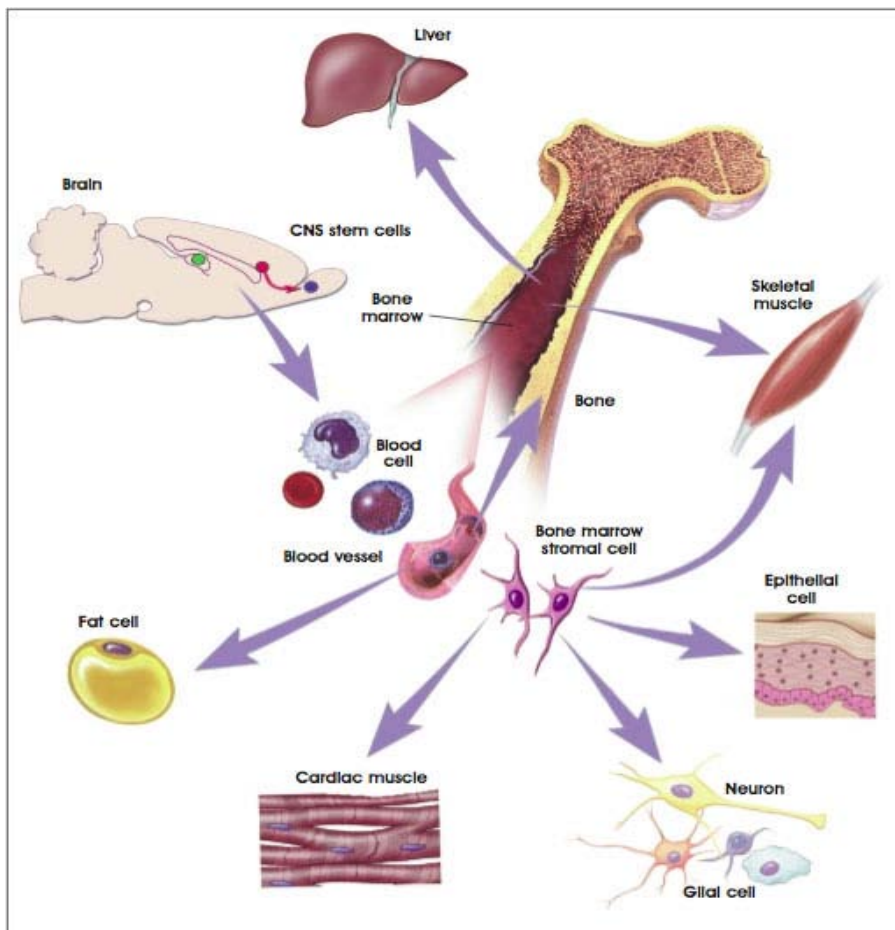
Plasticity and Trans-Differentiation

A number of experiments have suggested that certain adult stem cell types are *pluripotent*, or able to differentiate into multiple distinct cell types. As stated earlier, the ability of an adult stem cell to form specialized cell types of different tissues is called *plasticity*, or *trans-differentiation*. The following list offers examples of adult stem cell plasticity that have been reported during the past few years.

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

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

Figure 3: Preliminary evidence of plasticity among nonhuman adult stem cells.



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Embryonic vs. Adult Stem Cells

Both human embryonic and adult stem cells have advantages and disadvantages for cell-based regenerative therapies. Of course, adult and embryonic stem cells differ in the number and type of cells they can become. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are generally limited to the cell types of their tissue of origin; however, as previously mentioned, evidence suggests that adult stem cell plasticity may exist, increasing the number of cell types a given adult stem cell can become.

A potential advantage of using stem cells from an adult is that the patient's own cells could be expanded in culture and then re-introduced into the patient. The use of the patient's own adult stem cells would mean that the cells would not be rejected by the immune system. This represents a significant advantage because immune rejection is a difficult problem that requires the use of immunosuppressive drugs. However, it has not yet been determined in human experiments if embryonic stem cell recipients would reject donor embryonic stem cells.

Although it is relatively easy to grow large numbers of embryonic stem cells in culture, adult stem cells are rare in mature tissues and methods for expanding their numbers in cell culture have not yet been worked out. This is an important distinction, as large numbers of cells are needed for stem cell replacement therapies.

Potential Uses and Obstacles

Human stem cells have enormous potential for use in basic research and in clinical research. However, there are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research.

Controlling Abnormal Cell Division

Studies of human embryonic stem cells may yield information about the complex events that occur during human development. A primary goal of this work is to identify how undifferentiated stem cells become differentiated; turning genes on and off is central to this process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation.

A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. A significant hurdle to this use, and most uses, of stem cells is that scientists do not yet fully understand the signals that turn specific genes on and off to influence the differentiation of the stem cell.

Testing New Medications

Human stem cells could 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. Increased availability of pluripotent stem cells would allow drug testing over a wider range of cell types. However, in order to screen drugs effectively, the conditions must be identical when comparing drugs. For this reason, scientists must 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 that control differentiation fall well short of being able to precisely and consistently create identical cells for each drug being tested.

Devising Cell-Based Therapies

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

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

Embryonic and adult stem cells have been investigated to regenerate damaged heart tissue in animal models and in a limited number of clinical studies. Because embryonic stem cells (ES) are pluripotent, they can potentially give rise to the variety of cell types that can regenerate damaged myocardium, including cardiomyocytes (heart muscle tissue), endothelial cells, and smooth muscle cells.

Mouse and human ES cells have been shown to differentiate spontaneously to form endothelial and smooth muscle cells both in vitro and in vivo, and human ES cells have been shown to differentiate into myocytes (contractile muscle cells) with the structural and functional properties of cardiomyocytes. Moreover, ES cells that were transplanted into ischemically injured myocardium in rats differentiated into normal myocardial cells that remained viable for up to 4 months, suggesting that these cells may be candidates for regenerative therapy in humans (Panchision, 2008).

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

Necessary Steps to Cell-Based Treatments

To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able easily and reproducibly 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 precisely control to bring such treatments to the clinic:

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

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

Repairing the Nervous System with Stem Cells

Material in this section on Parkinson's disease is taken from a report issued by the National Institutes of Health in 2006. See Panchision in the References at the end of this course.

Diseases of the nervous system, including congenital disorders, cancers, and degenerative diseases, affect millions of people of all ages. Congenital disorders occur when the brain or spinal cord does not form correctly during development. Cancers of the nervous system result from the uncontrolled spread of aberrant cells. Degenerative diseases occur when the nervous system loses functioning of nerve cells.

Most of the advances in stem cell research have been directed at treating degenerative diseases. While many treatments aim to limit the damage of these diseases, scientists believe that in some cases, damage can be reversed by replacing lost cells with new nerve cells derived from neural stem cells. Research that uses stem cells to treat nervous system disorders remains an area of great promise. Scientists hope to demonstrate that cell-replacement therapy can restore lost function.

Parkinson's Disease

The intensive research aimed at curing Parkinson's disease with stem cells is a good example for the various strategies, successful results, and remaining challenges of stem cell-based brain repair. Parkinson's disease is a progressive disorder of motor control that affects roughly 2% of people 65 years and older.

Triggered by the death of neurons in a brain region called the *substantia nigra*, Parkinson's disease begins with minor tremors that progress to limb and body rigidity and difficulty initiating movement. These neurons connect via long axons to another region called the *striatum*, composed of sub-regions called the *caudate nucleus* and the *putamen*.

These neurons that reach from the substantia nigra to the striatum release the chemical transmitter dopamine onto their target neurons in the striatum. One of dopamine's major roles is to regulate the nerves that control body movement. As these cells die, less dopamine is produced, leading to the movement difficulties characteristic of Parkinson's disease. Why these neurons die is not yet understood.

For many years, people who have Parkinson's disease have been treated with the drug **levodopa** (L-dopa), which the brain converts into dopamine. Although the drug works well initially, levodopa eventually loses its effectiveness, and side effects increase. Ultimately, many doctors and patients find themselves fighting a losing battle. For this reason, a major effort is under way to develop new treatments, including growth factors that help the remaining dopamine neurons survive and transplantation procedures to replace those that have died.

Fetal Tissue Transplants

Using new cells to replace lost ones is not a new idea. Surgeons first attempted to transplant dopamine-releasing cells from a patient's own adrenal glands in the 1980s. Although one of these studies did report a dramatic improvement in the patients' conditions, U.S. surgeons were only able to achieve modest and temporary improvement, insufficient to outweigh the risks of such a procedure. As a result, these human studies were abandoned.

Another strategy was attempted in the 1970s, in which cells derived from fetal mouse substantia nigra were transplanted into the adult rat eye and found to develop into mature dopamine neurons. In the 1980s, several experiments showed that transplantation of this type of tissue could reverse Parkinson's-like symptoms in rats and monkeys when placed in the damaged areas. The success of the animal studies led to several human trials beginning in the mid 1980s. In some cases, patients showed a lessening of their symptoms; also, researchers could measure an increase in dopamine neuron function in the striatum of these patients by using positron emission tomography (PET) scans.

The NIH has funded two large and well-controlled clinical trials in the past 15 years in which tissue from aborted fetuses was transplanted into the striatum of patients with Parkinson's disease. These studies, performed in Colorado and New York, included controls where patients received "sham" surgery (no tissue was implanted), and neither the patients nor the scientists who evaluated their progress knew which patients received the implants.

The patients' progress was followed for up to 8 years. Unfortunately, both studies showed that the transplants offered little benefit to the patients as a group. While some patients showed improvement, others began to suffer from dyskinesias, jerky involuntary movements that are often side effects of long-term L-dopa treatment. This effect occurred in 15% of the patients in the Colorado study and more than half of the patients in the New York study. Additionally, the New York study showed evidence that some patients' immune systems were attacking the grafts.

However, promising findings did emerge from these studies. Younger and milder Parkinson's patients responded relatively well to the grafts, and PET scans of patients showed that some of the transplanted dopamine neurons survived and matured. Additionally, autopsies on three patients who died of unrelated causes, years after the surgeries, indicated the presence of dopamine neurons from the graft. These cells appeared to have matured in the same way as normal dopamine neurons, which suggested that they were acting normally in the brain.

Researchers in Sweden followed the severity of dyskinesia in patients for 11 years after neural transplantation and found that the severity was typically mild or moderate. These results suggested that dyskinesias were due to effects distinct from the beneficial effects of the grafts and that dyskinesias may therefore be related to the ways that transplantation disturbs other cells in the brain and thus may be minimized by future improvements in therapy.

Another study that involved the grafting of cells both into the striatum (the target of dopamine neurons) and the substantia nigra (where dopamine neurons normally reside) of three patients showed no adverse effects and some modest improvement in patient movement. To determine the full extent of therapeutic benefits from such a procedure and confirm the reliability of these results, this study will need to be repeated with a larger patient population that includes the appropriate controls.

The limited success of these studies may reflect variations in the fetal tissue used for transplantation, which is of limited quantity and cannot be standardized or well characterized. The full complement of cells in these fetal tissue samples is not known at present. As a result, the tissue remains the greatest source of uncertainty in patient outcome following transplantation.

Transplantation of Neurons

The major goal for Parkinson's investigators is to generate a source of cells that can be grown in large supply, maintained indefinitely in the laboratory, and differentiated efficiently into dopamine neurons that work when transplanted into the brain of a Parkinson's patient. Scientists have investigated the behavior of stem cells in culture and the mechanisms that govern dopamine neuron production during development in their attempts to identify optimal culture conditions that allow stem cells to turn into dopamine-producing neurons.

Preliminary studies have been carried out using immature stem cell–like precursors from the rodent ventral midbrain, the region that normally gives rise to these dopamine neurons. In one study, these precursors were turned into functional dopamine neurons, which were then grafted into rats previously treated with 6-hydroxy-dopamine (6-OHDA) to kill the dopamine neurons in their substantia nigra and induce Parkinson-like symptoms. Even though the percentage of surviving dopamine neurons was low following transplantation, it was sufficient to relieve the Parkinson's-like symptoms. Unfortunately, these fetal cells cannot be maintained in culture for very long before they lose the ability to differentiate into dopamine neurons.

Cells with features of neural stem cells have been derived from embryonic stem cells, fetal brain tissue, brain tissue from neurosurgery, and brain tissue that was obtained after a person's death. There is controversy about whether other organ stem cell populations, such as hematopoietic stem cells, either contain or give rise to neural stem cells.

Many researchers believe that the more primitive ES cells may be an excellent source of dopamine neurons because ES cells can be grown indefinitely in a laboratory dish and can differentiate into any cell type, even after long periods in culture. Mouse ES cells injected directly into 6-OHDA–treated rat brains led to relief of Parkinson-like symptoms. Further investigation showed that these ES cells had differentiated into both dopamine and serotonin neurons. This latter type of neuron is generated in an adjacent region of the brain and may complicate the response to transplantation.

Since ES cells can generate all cell types in the body, unwanted cell types such as muscle or bone could theoretically also be introduced into the brain. As a result, a great deal of effort is being put into finding the right “recipe” for turning ES cells into dopamine neurons—and only dopamine neurons—to treat Parkinson's disease. Researchers strive to learn more about normal brain development to help emulate the natural progression of ES cells toward dopamine neurons in the culture dish.

The recent availability of human ES cells has led to further studies on their potential for differentiation, and dopamine neurons have now been generated from human ES cells. One research group used a special type of companion cell, along with specific growth factors, to promote the differentiation of the ES cells through several stages into dopamine neurons. These neurons showed many of the characteristic properties of normal dopamine neurons. Furthermore, recent evidence of more direct neuronal differentiation methods from mouse ES cells fuels hope that scientists can refine and streamline the production of transplantable human dopamine neurons.

One method with great therapeutic potential is nuclear transfer. This method fuses the genetic material from one individual donor with a recipient egg cell that has had its nucleus removed. The early embryo that develops from this fusion is a genetic match for the donor. This process is sometimes called *therapeutic cloning* and is regarded by some to be ethically questionable. However, mouse ES cells have been differentiated successfully in this way into dopamine neurons that corrected Parkinsonian symptoms when transplanted into 6-OHDA-treated rats. Similar results have been obtained using parthenogenetic primate stem cells, which are cells that are genetic matches from a female donor with no contribution from a male donor. These approaches may offer the possibility of treating patients with genetically matched cells without triggering graft rejection.

Cell Repair

Scientists are also studying the possibility that the brain may be able to repair itself with therapeutic support. This avenue of study is in its early stages but may involve administering drugs that stimulate the birth of new neurons from the brain's own stem cells. The concept is based on research showing that new nerve cells are born in the adult brains of humans. The phenomenon occurs in a brain region called the dentate gyrus of the hippocampus. While it is not yet clear how these new neurons contribute to normal brain function, their presence suggests that stem cells in the adult brain may have the potential to re-wire dysfunctional neuronal circuitry.

The adult brain's capacity for self-repair has been studied by investigating how the adult rat brain responds to **transforming growth factor alpha (TGFA)**, a protein important for early brain development that is expressed in limited quantities in adults. Injection of TGFA into a healthy rat brain causes stem cells to divide for several days before ceasing division.

In 6-OHDA-treated (Parkinsonian) rats, however, the cells proliferated and migrated to the damaged areas. Surprisingly, the TGFA-treated rats showed few of the behavioral problems associated with untreated Parkinsonian rats. Additionally, in 2002 and 2003, two research groups isolated small numbers of dividing cells in the substantia nigra of adult rodents.

These findings suggest that the brain can repair itself, as long as the repair process is triggered sufficiently. It is not clear, though, whether stem cells are responsible for this repair or if the TGFA activates a different repair mechanism.

Potential for Other Applications of Stem Cell Therapies

Many other diseases that affect the nervous system hold the potential for being treated with stem cells. Experimental therapies for chronic diseases of the nervous system, such as Alzheimer's disease, ALS (Lou Gehrig's disease), or Huntington's disease, and for acute injuries, such as spinal cord and brain trauma or stroke, are being currently developed and tested. These diverse disorders must be investigated within the contexts of their unique disease processes and treated accordingly with highly adapted cell-based approaches.

Although severe spinal cord injury is an area of intense research, the therapeutic targets are not as clear-cut as in Parkinson's disease. Spinal cord trauma destroys numerous cell types, including the neurons that carry messages between the brain and the rest of the body. In many spinal injuries the cord is not actually severed, and at least some of the signal-carrying neuronal axons remain intact. However, the surviving axons no longer carry messages because oligodendrocytes, which make the axons' insulating myelin sheath, are lost.

Researchers have recently made progress in replenishing these lost myelin-producing cells. In one study, scientists cultured human ES cells through several steps to make mixed cultures that contained oligodendrocytes. When they injected these cells into the spinal cords of chemically demyelinated rats, the treated rats regained limited use of their hind limbs compared with ungrafted rats. Researchers are not certain, however, whether the limited increase in function observed in rats is actually due to the remyelination or to an unidentified effect of the treatment.

Getting neurons to grow new axons through the injury site to reconnect with their targets is alluring but even more challenging. While myelin promotes normal neuronal function, it also inhibits the growth of new axons following spinal injury. In a recent study to attempt post-trauma axonal growth in adult rats with spinal cord injuries, the rats were injected with ES cells that had been treated with a combination of factors known to promote motor neuron differentiation. While many of these cells survived and differentiated into neurons, they did not send out axons unless the researchers also added drugs that interfered with the inhibitory effects of myelin.

The growth effect was modest, and the researchers have not yet seen evidence of functional neuron connections. However, the results of this study raise the possibility that signals can be turned on and off in the correct order to allow neurons to reconnect and function properly. Researchers on spinal injury emphasize that much more work must be done before they can attempt human trials using stem cell therapies to repair the trauma-damaged nervous system.

Since myelin loss is at the heart of many other degenerative diseases, oligodendrocytes made from ES cells may be useful to treat these conditions as well. For example, scientists recently cultured human ES cells with a combination of growth factors to generate a population of myelinating oligodendrocyte precursors. These cells were then tested in a genetically mutated mouse that did not produce myelin properly. When these ES cells were transplanted into affected mice, the cells migrated and differentiated into mature oligodendrocytes that made myelin sheaths around neighboring axons.

The researchers were able to show subsequently that these cells matured and improved movement when grafted in rats with spinal cord injury. Improved movement only occurred when grafting was completed soon after injury, suggesting that some post-injury responses may interfere with the grafted cells. However, these results are sufficiently encouraging to plan further clinical trials.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is characterized by a progressive destruction of motor neurons in the spinal cord. Patients with ALS develop increasing muscle weakness over time, which ultimately leads to paralysis and death. The cause of ALS is largely unknown, and there are no effective treatments.

Researchers recently have used different sources of stem cells in rat models of ALS to test for possible nerve cell–restoring properties. In one study, researchers injected cell clusters made from embryonic germ (EG) cells into the spinal cord fluid of the partially paralyzed rats. Three months after the injections, many of the treated rats were able to move their hind limbs and walk with difficulty, while the rats that did not receive cell injections remained paralyzed. Moreover, the transplanted cells had migrated throughout the spinal fluid and developed into cells that displayed molecular characteristics of mature motor neurons.

However, too few cells matured in this way to account for the recovery, and there was no evidence that the transplanted cells formed functional connections with muscles. The researchers suggest that the transplanted cells may be promoting recovery with the use of trophic factors (regulatory molecules that play important roles in the development, maintenance, and survival of a wide variety of cells) or helper molecules.

This possibility was addressed in a second study, in which scientists grew human fetal CNS (central nervous system) stem cells in culture and genetically modified them to produce a trophic factor that promotes the survival of cells that are lost in ALS. When grafted into the spinal cords of the ALS-like rats, these cells secreted the desired growth factor and promoted the survival of the neurons that are normally lost in the ALS-like rats. While promising, these results highlight the need for additional basic research into ALS.

Stroke affects about 750,000 patients per year in the United States and is the most common cause of disability in adults. A stroke occurs when blood flow to the brain is disrupted, causing cells in affected brain regions to die from insufficient amounts of oxygen. The treatment of stroke with anti-clotting drugs has dramatically improved the odds of patient recovery.

However, in many patients the damage cannot be prevented, and the patient may permanently lose the functions of affected areas of the brain. For these patients, researchers are now considering stem cells as a way to repair the damaged brain regions. This problem is made more challenging because the damage in stroke may be widespread and may affect many cell types and connections.

Researchers from Sweden recently observed that strokes in rats cause the brain's own stem cells to divide and give rise to new neurons. But these neurons, which survived only a couple of weeks, are few in number. A group from the University of Tokyo added a growth factor, bFGF, into the brains of rats after stroke and showed that the hippocampus was able to generate large numbers of new neurons. The researchers found evidence that these new neurons were actually making connections with other neurons. These and other results suggest that future stroke treatments may be able to coax the brain's own stem cells to make replacement neurons.

Another group of researchers attempted transplantation as a means to treat the loss of brain mass after a severe stroke. By adding stem cells onto a polymer scaffold that they implanted into the stroke-damaged brains of mice, the researchers demonstrated that the transplanted stem cells differentiated into neurons and that the polymer scaffold reduced scarring. In two independent studies, human fetal cells were transplanted into the brains of stroke-affected rodents. These stem cells not only survived but also migrated to the damaged areas of the brain.

There is increasing evidence from numerous animal disease models that stem cells are actively drawn to brain damage. Once they reach these damaged areas, they have been shown to exert beneficial effects, such as reducing brain inflammation or supporting nerve cells. It is hoped that, once these mechanisms are better understood, this stem cell recruitment can potentially be exploited to mobilize a patient's own stem cells.

Similar research is being considered with other disorders such as Huntington's disease and with certain congenital defects. While much attention has been given to the treatment of Alzheimer's disease, it is still not clear if stem cells hold the key to its treatment. But despite the fact that much basic work remains and many fundamental questions are yet to be answered, researchers are hopeful that repair for once-incurable nervous system disorders may be amenable to stem cell-based therapies.

Considerable progress has been made over the last few years in our understanding of stem cell biology and devising sources of cells for transplantation. New methods are also being developed for cell delivery and targeting affected areas of the body. These advances have fueled optimism that new treatments will come for millions of persons who suffer from neurologic disorders. But it is the current task of scientists to bring these methods from the laboratory to the clinic in a scientifically sound and ethically acceptable fashion (Panchision, 2006).

Ethical Considerations

While stem cell research has the potential to provide major medical advances, including cures for many diseases, it remains controversial. Despite the exciting potential for stem cell therapies, scientists have faced great opposition to their research and have been provided with limited government funding. In November of 1998, the first embryonic stem cells were isolated by James A. Thompson, a biologist at the University of Wisconsin, Madison. However, Thompson's work was not eligible for federal funding from the NIH—the government's primary sponsor of biomedical research—because of a 1995 Congressional ban on human embryonic research (AAAS Policy Brief, 2009).

In January 1999, the Department of Health and Human Services (DHHS) changed its policy to allow public funding of human stem cell research as long as the derivation of the cells was paid for with private funding (AAAS, 2009). Then, on August 9, 2001, President Bush issued a statement that allowed government funding of research on 21 embryonic cell lines that were already in existence, giving the rationale that the decision on these stem cell lines had already been made.

Until this time, no government funding had been provided for human embryonic stem cell research. However, no further research could be carried out using government money on any embryos that were destroyed after this date and, therefore, no new stem cell lines could be created (AAAS, 2009).

On March 9, 2009, President Obama partly reversed the Bush policy, removing barriers to federal funding for the creation of new stem cell lines. Obama's executive order did not provide ethical guidelines but directed that new guidelines be developed by DHHS and NIH.

The use of human stem cells for scientific research has been a source of controversy since the cells were first isolated in 1998. Opponents of human stem cell research say that life begins as soon as an egg is fertilized; they view the fertilized egg as a potential human being who has rights and interests that must be protected.

Those who support stem cell research point out that the fertilized eggs and embryos used for research purposes were not grown inside a uterus and were donated with the consent of the couple from whom they came. They point out that the donated embryos would otherwise be destroyed and therefore do not have the potential to become human beings. Fertilized eggs have never been created specifically for stem cell research (*MedlinePlus*, NIH 2007).

Conclusion

Stem cells have the remarkable potential to develop into many different cell types during early life and growth. Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Stem cells offer great potential for treating diseases like Parkinson's, diabetes, and heart disease, and are already being used 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. Stem cells offer exciting promise for future therapies, but significant technical hurdles remain that will only be overcome through years of intensive research (*Stem Cell Basics*, NIH 2009).

(References on next page)

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(Post Test begins on next page)

Post Test

Use the Answer Sheet following the test to record your answers.

1. President Obama's executive order changed the rules regarding stem cell research by:
 - a. Allowing federal funding of research on already existing stem cells.
 - b. Allowing private funding of stem cell research without restriction.
 - c. Calling on government agencies to issue new guidelines within 120 days.
 - d. Removing all restrictions for both federal and private funding.
2. Stem cells are specialized cells that can divide without limit.
 - a. True
 - b. False
3. Cells created by in vitro fertilization are called:
 - a. Adult stem cells.
 - b. Hematopoietic cells.
 - c. Human embryonic stem cells.
 - d. Blastocytes.
4. One of the fundamental properties of stem cells is that they:
 - a. Are specialized and can give rise to many cell types.
 - b. Contain tissue-specific structures that allow them to perform specialized functions.
 - c. Are unspecialized and can give rise to specialized cell types.
 - d. Cannot divide and renew themselves.
5. When cells replicate themselves many times the process is called:
 - a. Specialization.
 - b. Replication.
 - c. Differentiation.
 - d. Proliferation.
6. Differentiation is a process in which:
 - a. Stem cells divide and renew themselves for long periods of time.
 - b. A blood-forming cell may develop into a nerve cell.
 - c. A blastocyte becomes a trophoblast.
 - d. Unspecialized stem cells can give rise to specialized cells.
7. Recent experiments showed that adult stem cells from one tissue may be able to give rise to cell types of a completely different tissue. This phenomenon is called:
 - a. Differentiation.
 - b. Plasticity.
 - c. Specialization.
 - d. Replication.
8. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating are referred to as:
 - a. Adult stem cells.
 - b. Pluripotent cells.
 - c. An embryonic stem cell line.
 - d. A blastocyst.

9. Testing to see if new stem cells exhibit the fundamental properties of embryonic stem cells is called:
 - a. Characterization.
 - b. Differentiation.
 - c. Immunosuppression.
 - d. Pluripotency.
10. Adult stem cells:
 - a. Are differentiated cells.
 - b. Are found only in bone marrow.
 - c. Maintain and repair the tissue in which they are found.
 - d. Are embryonic stem cells more than one year old.
11. Adult stem cells are thought to reside in a specific area of each tissue, where they may remain quiescent for many years until they are activated by disease or tissue injury.
 - a. True.
 - b. False.
12. Adult stem cells may be able to form specialized cell types of other tissues, a process known as:
 - a. Repopulation.
 - b. Specialization.
 - c. Trans-differentiation or plasticity.
 - d. Stromal pathways.
13. In a living animal, adult stem cells can divide for long periods and give rise to mature cell types that have the characteristic shapes, specialized structures, and functions of a particular tissue. This is known as a:
 - a. Plasticity pathway.
 - b. Normal differentiation pathway.
 - c. Stem cell line.
 - d. Somatic cell line.
14. The ability of a stem cell to become all cell types of the body is called:
 - a. Differentiation.
 - b. Plasticity.
 - c. Immunosuppression.
 - d. Pluripotency.
15. Intensive research aimed at curing Parkinson's disease using cell-based therapy is currently underway. Parkinson's disease is:
 - a. Caused by a gradual buildup of plaque in veins that eventually blocks blood flow to major organs.
 - b. Triggered by the death of neurons in the brain's substantia nigra causing decreased dopamine production and difficulties with body movement.
 - c. Caused by a virus that destroys the body's immune system.
 - d. Easily cured by the administration of levodopa.

16. A method of producing transplantable human dopamine neurons by fusing genetic material from one donor to a recipient egg cell with its nucleus removed is called:
- Neuronal differentiation.
 - Nuclear transfer or therapeutic cloning.
 - Dyskinesia.
 - Parthenogenetic transfer.
17. The dentate gyrus of the hippocampus region of the brain:
- Is responsible for dopamine production.
 - Has been successfully transplanted in mice to cure Alzheimer's disease.
 - Has been shown to generate new nerve cells in the adult brains of humans.
 - Is the only area of the brain that does not contain stem cells.
18. The use of stem cells to treat spinal cord injuries:
- Has proven to have more clear-cut therapeutic targets than Parkinson's disease.
 - Is no longer being investigated because scientists believe it is not possible to create new nerve cells.
 - Has already been used successfully in humans.
 - Is very challenging because of the numerous cell types that carry messages between the brain and the rest of the body.
19. Researchers believe they may be able to get the stem cells in brains of stroke patients to make replacement neurons.
- True
 - False
20. Stem cells that are actively drawn to brain damage:
- Attack the plaque that causes Alzheimer's disease.
 - Have been shown to reduce inflammation and support nerve cells.
 - Become inactive and die.
 - Begin to replicate uncontrollably.

(Answer sheet on next page)

Answer Sheet

Stem Cell Research

Name (Please print your name): _____

Date: _____

Passing score is 80%

- 1. _____
- 2. _____
- 3. _____
- 4. _____
- 5. _____
- 6. _____
- 7. _____
- 8. _____
- 9. _____
- 10. _____
- 11. _____
- 12. _____
- 13. _____
- 14. _____
- 15. _____
- 16. _____
- 17. _____
- 18. _____
- 19. _____
- 20. _____

Course Evaluation

Please use this scale for your course evaluation. Items with asterisks (*) are required.

- 5 = Strongly agree
- 4 = Agree
- 3 = Neutral
- 2 = Disagree
- 1 = Strongly disagree

*1. Upon completion of the course, I was able to:

a. Define stem cells and identify their unique properties.

5 4 3 2 1

b. Discuss the laboratory development of embryonic stem cells.

5 4 3 2 1

c. List the properties of adult stem cells.

5 4 3 2 1

d. Differentiate embryonic stem cells from adult stem cells.

5 4 3 2 1

e. Report on the potential uses for stem cells.

5 4 3 2 1

f. Explain the ongoing research relating stem cells to treatment of Parkinson's disease and ALS.

5 4 3 2 1

(continued on next page)

*2. The course was written in a way that facilitated my learning.

5 4 3 2 1

*3. This course was free from commercial bias.

5 4 3 2 1

*4. The course met my continuing education needs.

5 4 3 2 1

*5. The material presented was supported by evidence.

5 4 3 2 1

*6. The author avoided the use of anecdotal information as the main source of material.

5 4 3 2 1

*7. The course was free of product promotion.

Yes No**

** If you answered no, please answer #8.

8. Was product promotion the sole purpose of the presentation?

Yes No

* 9. It took me 60 minutes per contact hour to complete the course, test, and evaluation.

Yes No**

** If your answer was no, how long did it take? _____

(continued on next page)

Registration Information

Please answer all of the following questions (*required).

* Name: _____

* Address: _____

* City: _____ State: _____ Zip: _____

* Phone: _____

* Professional Designation: _____

* License Number and State: _____

Please e-mail my certificate: Yes No

Email (required if you want your certificate sent by email): _____

(Note: If you request an email certificate we will not send a copy of your certificate by US Mail.)

Payment Options

You may pay by credit card or by check. Fill out this section only if you are **paying by credit card**.

2 contact hours: \$15

Credit card information:

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Address (if different from above): _____

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Card type: Visa MC American Express Discover

Card number _____

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Test Completion and Mailing Instructions

1. Complete all forms:

Answer Sheet

Evaluation Learning Activity

Registration Form (this page)

2. If you are **paying by check**, prepare a check for \$15 made out to ATrain Education, Inc.

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When we receive your forms and payment, we will mail or email your certificate. Please call if you have questions or email Sharon@ATrainCEU.com. And thanks for taking the ATrain!