

Stem Cells: A Primer

National Institutes of Health

I. INTRODUCTION

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

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

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

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

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

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

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

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

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

B. Scope of this document

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

Stem Cells for the Future Treatment of Parkinson's Disease

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

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

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

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. When cells replicate themselves many times over it is called proliferation. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal.

Scientists are trying to understand two fundamental properties of stem cells that relate to their long-term self-renewal: 1) why can *embryonic* stem cells proliferate for a year or more in the laboratory without differentiating, but most *adult* stem cells cannot; and 2) what are the factors in living organisms that normally regulate stem cell proliferation and self-renewal?

Discovering the answers to these questions may make it possible to understand how cell proliferation is regulated during normal embryonic development or during the abnormal cell division that leads to cancer. Importantly, such information would enable scientists to grow embryonic and adult stem cells more efficiently in the laboratory.

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

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

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

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

The answers to some questions about stem cells vary, depending on the source of the stem cells. For instance, if the starting stem cells are derived from the inner cell mass of the embryo, they can generate many cell types of the body derived from all three embryonic cell types: endoderm, mesoderm and ectoderm. Stem cells with this property are said to be pluripotent. Embryonic stem cells are one kind of pluripotent stem cell. Another cell type, embryonic *germ* cells are also pluripotent, but they are derived at a later stage of development.

Human embryonic stem cells are derived from the inner cell mass of a four- or five-day-old blastocyst. Human embryonic germ cells, in contrast, are derived from a five- to ten-week-old fetus.

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

III. WHAT ARE EMBRYONIC STEM CELLS?

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

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

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

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

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

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

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

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

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

- growing and subculturing the stem cells for many months. This ensures that the cells are capable of *long-term self-renewal*. Scientists inspect the cultures through a microscope to see that the cells look healthy and remain undifferentiated.
- using specific techniques to determine the presence of surface markers that are found only on undifferentiated cells. Another important test is for the presence of a protein called Oct-4, which undifferentiated cells typically make. Oct-4 is a transcription factor, meaning that it helps turn genes on and off at the right time, which is an important part of the processes of cell differentiation and embryonic development.
- examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells.
- determining whether the cells can be subcultured after freezing, thawing, and replating.
- testing whether the human embryonic stem cells are pluripotent by 1) allowing the cells to differentiate spontaneously in cell culture; 2) manipulating the cells so they will differentiate to form specific cell types; or 3) injecting the cells into an immunosuppressed mouse to test for the formation of a benign tumor called a teratoma. Teratomas typically contain a mixture of many differentiated or partly differentiated cell types – an indication that the embryonic stem cells are capable of differentiating into multiple cell types.

D. How are embryonic stem cells stimulated to differentiate?

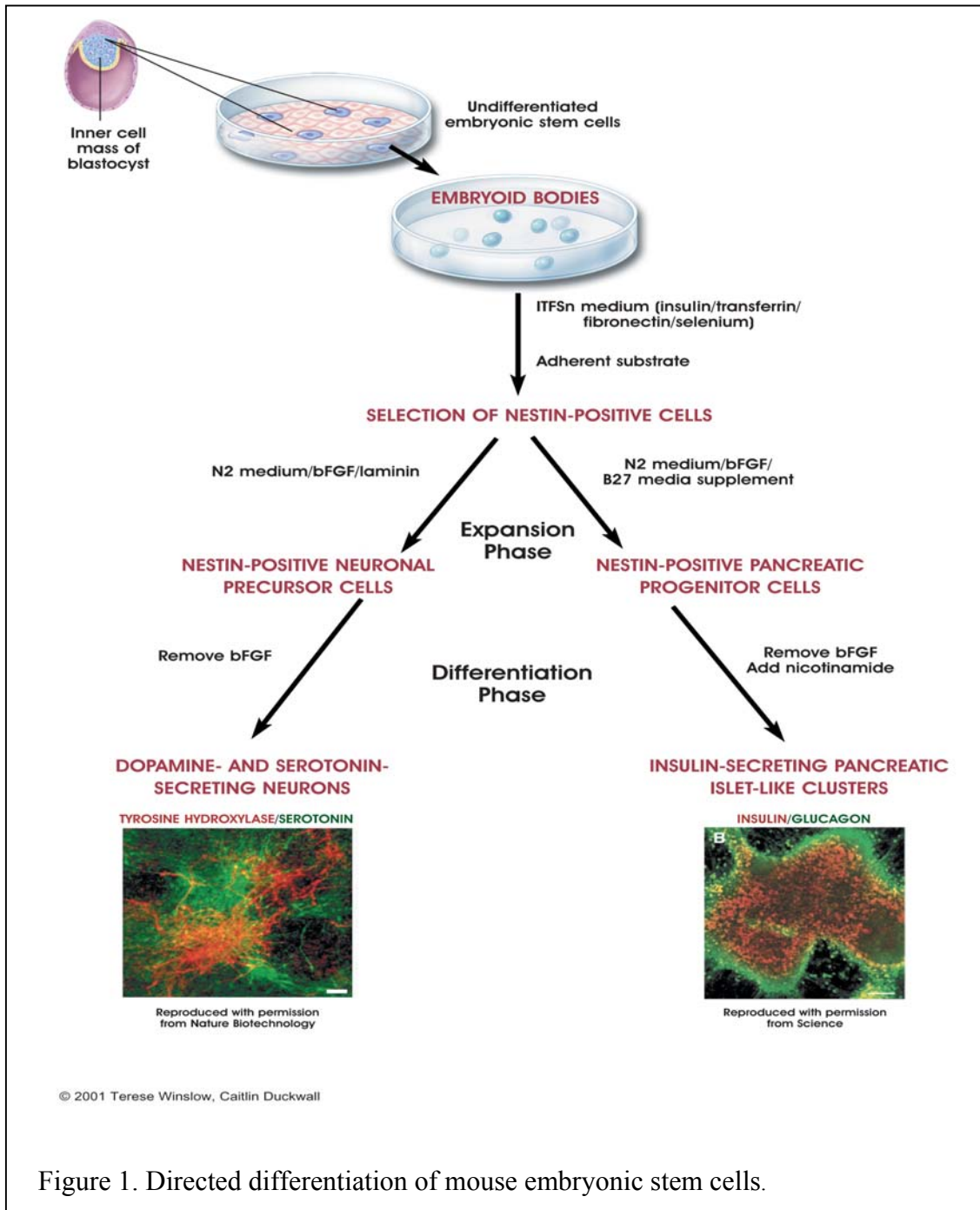


Figure 1. Directed differentiation of mouse embryonic stem cells.

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

cells, and many other cell types. Although spontaneous differentiation is a good indication that a culture of embryonic stem cells is healthy, it is not an efficient way to produce cultures of specific cell types.

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

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

IV. WHAT ARE ADULT STEM CELLS?

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

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

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

Also in the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells, which become nerve cells. Despite these reports, most scientists

believed that new nerve cells could not be generated in the adult brain. It was not until the 1990s that scientists agreed that the adult brain does contain stem cells that are able to generate the brain's three major cell types – astrocytes and oligodendrocytes, which are non-neuronal cells, and neurons or nerve cells.

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

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

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

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

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

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

C. What is known about adult stem cell differentiation?

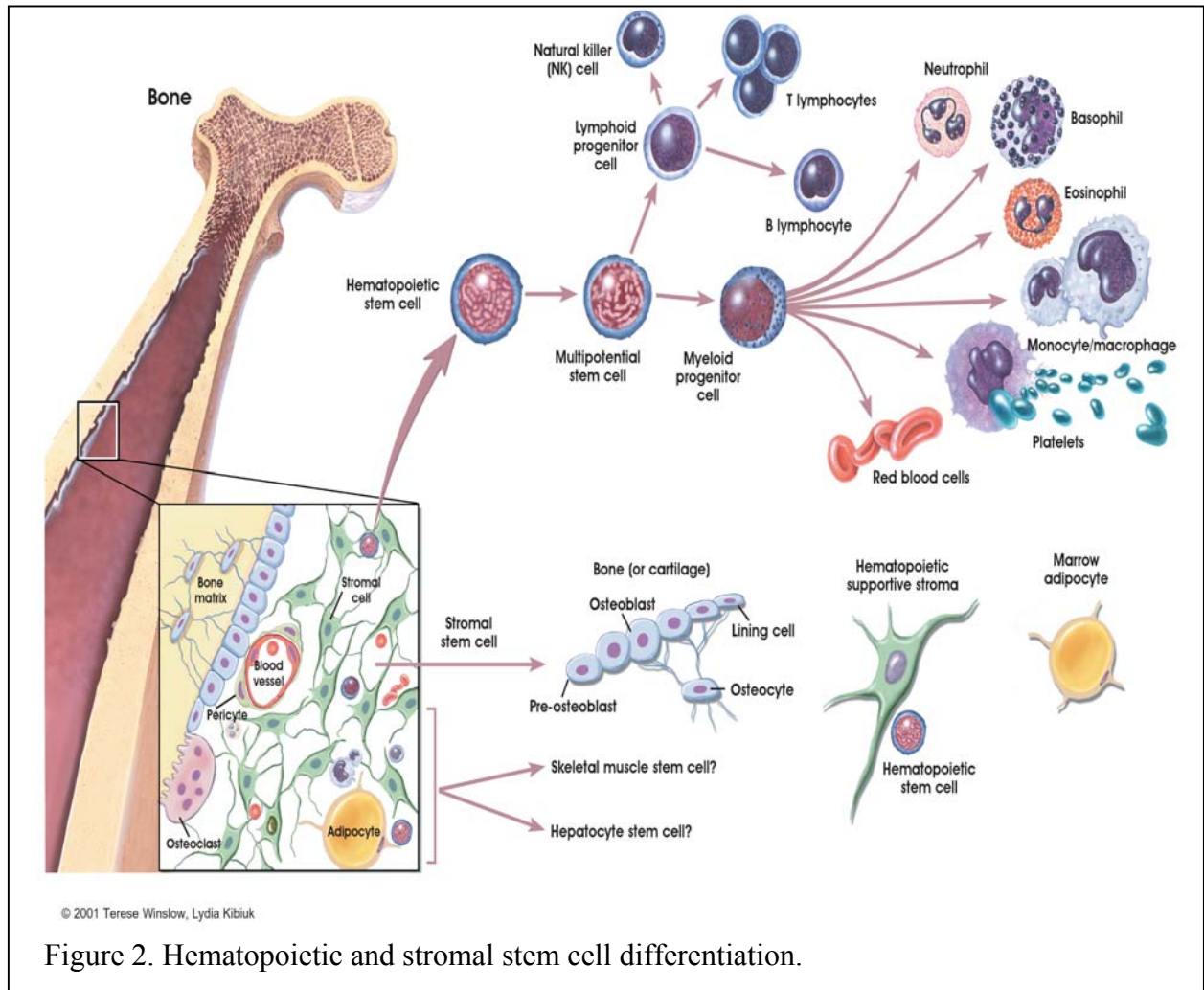


Figure 2. Hematopoietic and stromal stem cell differentiation.

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

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

- Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, macrophages, and platelets.
- Bone marrow stromal cells (mesenchymal stem cells) give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

- Neural stem cells in the brain give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells – astrocytes and oligodendrocytes.
- Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.
- Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the hair follicle and to the epidermis.

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

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

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

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

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

- How many kinds of adult stem cells exist, and in which tissues do they exist?
- What are the sources of adult stem cells in the body? Are they “leftover” embryonic stem cells, or do they arise in some other way? Why do they remain in an undifferentiated state when all the cells around them have differentiated?
- Do adult stem cells normally exhibit plasticity, or do they only transdifferentiate when scientists manipulate them experimentally? What are the signals that regulate the proliferation and differentiation of stem cells that demonstrate plasticity?
- Is it possible to manipulate adult stem cells to enhance their proliferation so that sufficient tissue for transplants can be produced?

- Does a single type of stem cell exist – possibly in the bone marrow or circulating in the blood – that can generate the cells of any organ or tissue?
- What are the factors that stimulate stem cells to relocate to sites of injury or damage?

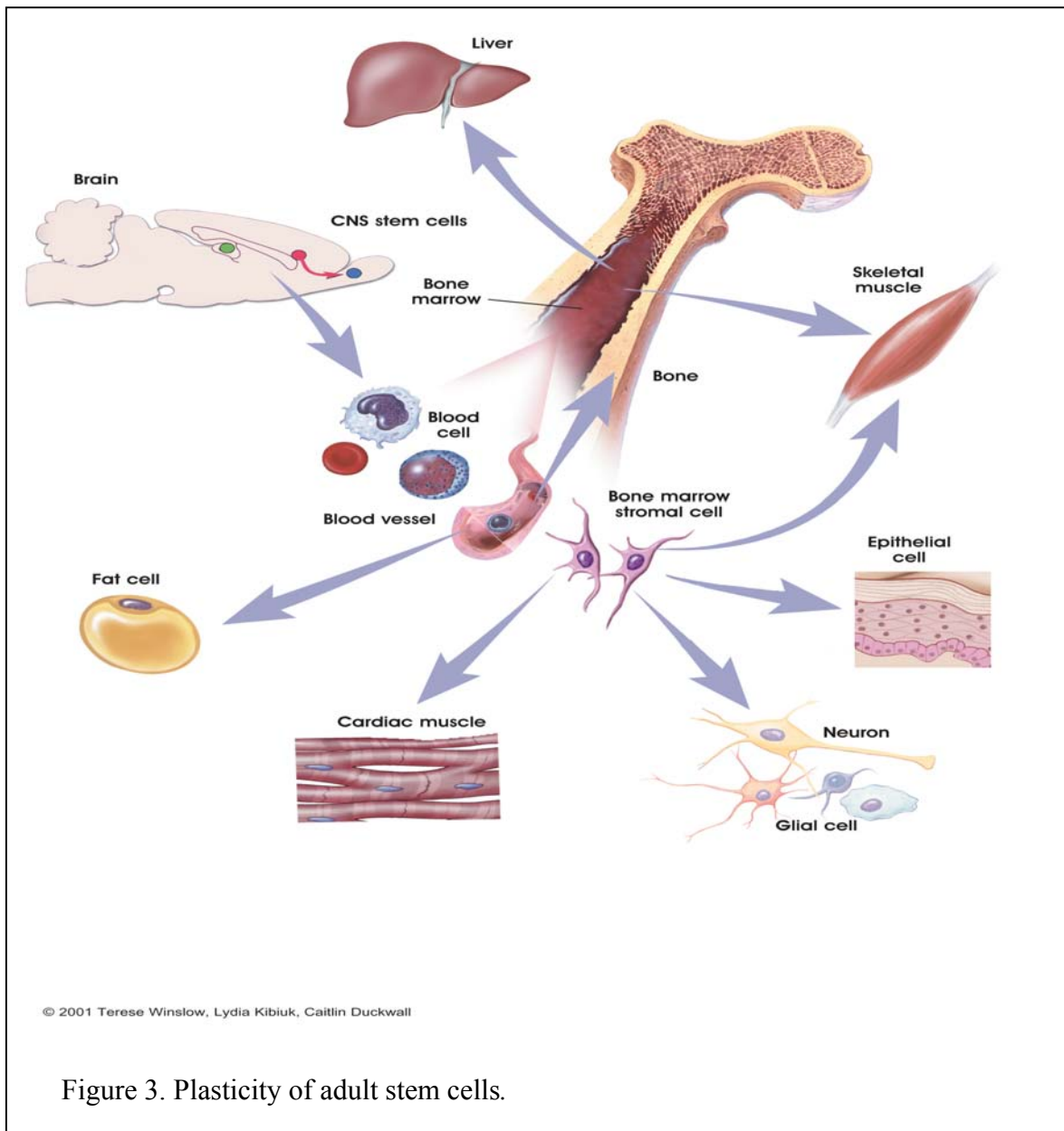


Figure 3. Plasticity of adult stem cells.

V. WHAT ARE THE SIMILARITIES AND DIFFERENCES BETWEEN EMBRYONIC AND ADULT STEM CELLS?

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

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

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

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

VI. WHAT ARE THE POTENTIAL USES OF HUMAN STEM CELLS AND THE OBSTACLES THAT MUST BE OVERCOME BEFORE THESE POTENTIAL USES WILL BE REALIZED?

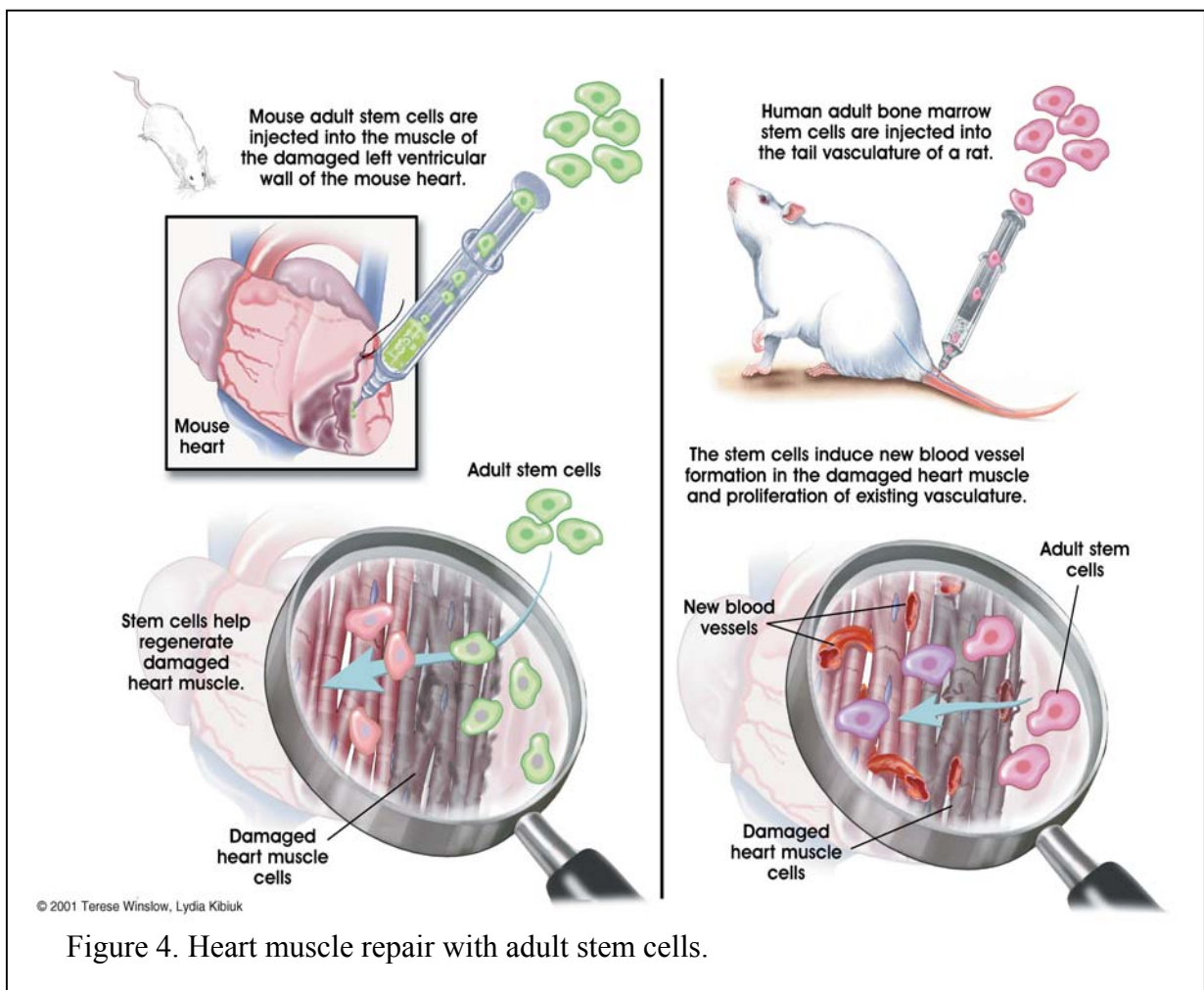
There are many ways in which human stem cells can be used in basic research and in clinical research. However, there are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research.

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

Human stem cells could also be used to test new drugs. For example, new medications could be tested for safety on differentiated cells generated from human pluripotent cell lines. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to

screen potential anti-tumor drugs. But, the availability of pluripotent stem cells would allow drug testing in a wider range of cell types. However, to screen drugs effectively, the conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into the specific cell type on which drugs will be tested. Current knowledge of the signals controlling differentiation fall well short of being able to mimic these conditions precisely to consistently have identical differentiated cells for each drug being tested.

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



For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Preliminary research in

mice and other animals indicates that bone marrow stem cells, transplanted into a damaged heart, can generate heart muscle cells and successfully repopulate the heart tissue. Other recent studies in cell culture systems indicate that it may be possible to direct the differentiation of embryonic stem cells or adult bone marrow cells into heart muscle cells (Figure 4).

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

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

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

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

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

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

VII. WHERE CAN I GET MORE INFORMATION?

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

1. <http://www.nih.gov/news/stemcell/index.htm>
A listing of all the information about stem cells on the NIH Web site.

2. <http://www.news.wisc.edu/packages/stemcells/>
The University of Wisconsin's Web site about stem cells, written for general audiences.
3. <http://www.eurekalert.org/>
EurekaAlert! is a publicly accessible science news site run by the American Association for the Advancement of Sciences. Search for "stem cells."
4. <http://scitechdaily.com/>
A site that offers a range of news articles, features, and commentaries about science and technology topics. Search for "stem cells."
5. <http://www.sciam.com/index.cfm>
The Web site for *Scientific American*. Search for "stem cells."
6. <http://www.reuters.com/news.jhtml?type=science>
The Reuters news site for stories about science. Search for "stem cells" and select "News and Pictures."
7. <http://www.stemcellresearchnews.com/>
A commercial, online newsletter that features stories about stem cells of all types.

VIII. GLOSSARY

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

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

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

Blastocyst – A preimplantation embryo of about 150 cells. The blastocyst consists of a sphere made up of an outer layer of cells (the trophoctoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Fertilization – The process whereby male and female gametes unite.

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

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

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

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

In vitro – Literally, “in glass;” in a laboratory dish or test tube; an artificial environment.

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

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

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

Mesenchymal stem cells – Cells from the immature embryonic connective tissue. A number of cell types come from mesenchymal stem cells, including chondrocytes, which produce cartilage.

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

Microenvironment – The molecules and compounds such as nutrients and growth factors surrounding a cell in an organism or in the laboratory, which are important in determining the characteristics of the cell.

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

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

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

Passage – A round of cell growth and proliferation in cell culture.

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

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

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

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

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

Somatic stem cells – Another name for adult stem cells.

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

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

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

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

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

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

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

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

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