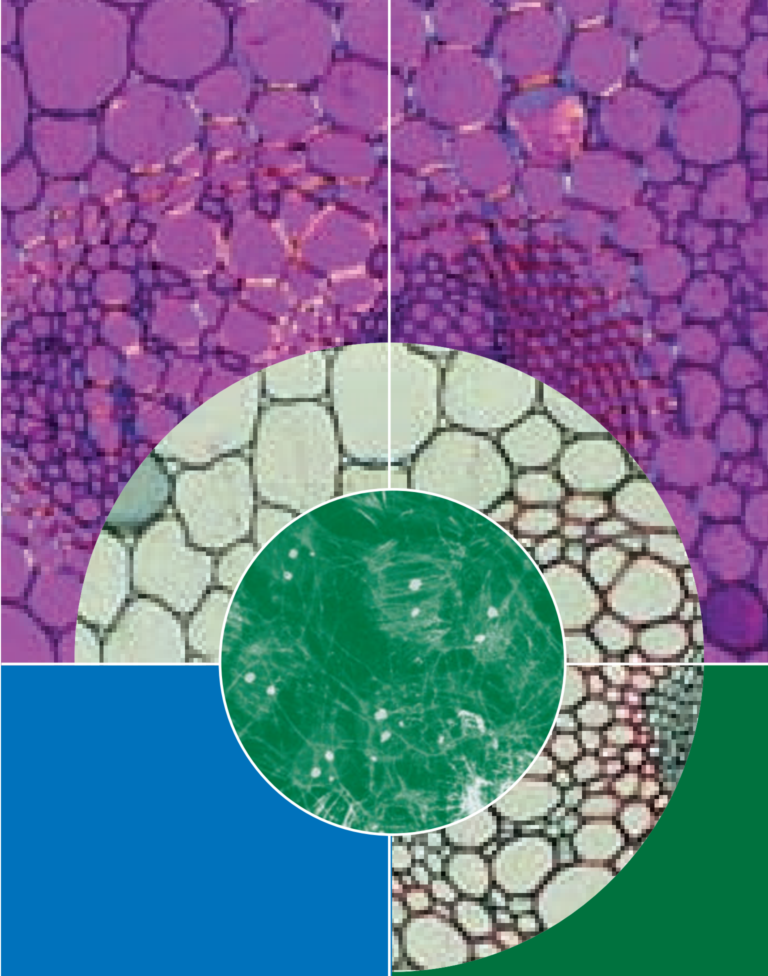


Stem Cell Facts

The next frontier?

ISSCR
International Society for Stem Cell Research

Prepared by the International Society for Stem Cell Research, an independent, nonprofit organization formed to foster the exchange of information on stem cell research.

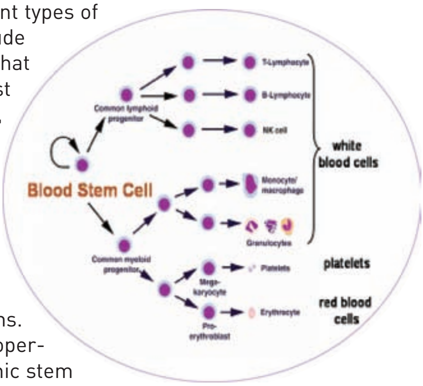
Stem Cells

Every organ and tissue in our bodies is made up of specialized cells that originally come from a pool of stem cells in the very early embryo; throughout our lives we rely on persisting stem cells to regenerate organs and tissues that are injured or lost every day, such as our skin, our hair, our blood and the lining of our gut. Thus, the study of stem cells is central to understanding not just our normal development, but also human disease and injury, and for using this knowledge to develop new therapies.

What Are Stem Cells?

Stem cells are the foundation cells for every organ and tissue in the body. They are like a blank microchip that can ultimately be programmed to perform particular tasks. Under proper conditions, stem cells begin to develop or 'differentiate' into specialized cells that carry out a specific function, such as in the skin, muscle or liver. Additionally, stem cells can 'self-renew,' that is they can divide and give rise to more stem cells.

For example, the blood stem cell can produce all the cell types in the blood while also replacing itself. Bone marrow transplants can lead to long-lasting cures because the bone marrow contains blood stem cells.



There are many different types of stem cells. These include embryonic stem cells that exist only at the earliest stages of development, and various types of 'tissue-specific' (sometimes referred to as 'adult' or 'somatic') stem cells that exist in a number of different fetal and adult tissues and organs. Recently, cells with properties similar to embryonic stem cells, known as induced pluripotent stem cells (iPS cells), have been engineered from specialized cells such as adult skin cells.

Who Needs Stem Cell Research?

Stem cell research allows us to gain a fundamental understanding of how organisms develop and grow, and how tissues are maintained throughout adult life. This is knowledge that is required to work out what goes wrong during disease and injury and to ultimately understand how these conditions might be treated. Studying stem cells is helping researchers to study disease, test drugs and develop increasingly effective therapies. Scientists are pursuing stem cell research from many angles and investigating cells of various origins to address what we need to know.

The study of stem cells has led to many new insights into how cancers develop and may be treated. Many cancers contain dysfunctional cells with the properties of stem cells that propagate the cancer. These cells are known as 'cancer stem cells' and are the best target for chemotherapy.

Replacing diseased cells with healthy cells, a process called cell therapy, is another promising use of stem cells in the treatment of disease; this is similar to organ transplantation except the transplant consists of cells instead of organs. Currently, researchers are investigating the use of both tissue-specific and embryonic stem cells as a source for different cell types that might one day be used to treat many different diseases.

Tissue-specific Stem Cells

Tissue-specific stem cells (sometimes called 'adult' or 'somatic' stem cells) are found in a given tissue in our bodies and generate the mature cell types within that particular tissue or organ. They are already somewhat specialized and produce only a limited number of cell types each, and are described as 'multipotent.'

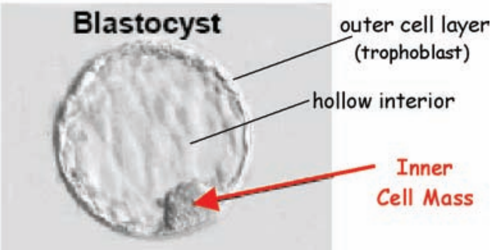
Tissue-specific stem cells have been found in several organs that continuously replenish themselves, such as the blood, skin and gut. They have also been found in other less regenerative organs such as the brain. These stem cells are rare and hidden deep within a tissue, and can be difficult to identify, isolate and grow in the laboratory.

The most readily accessible source of tissue-specific stem cells is the bone marrow located in the center of our bones. There are different types of stem cells found in the bone marrow, including blood stem cells that form blood and mesenchymal stem cells that form tissues such as bone, cartilage and fat.

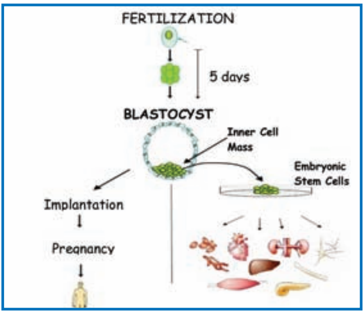
Embryonic Stem Cells

Embryonic stem cells have been derived from a variety of animals, including humans, and are described as 'pluripotent,' that is, they are capable of generating *all* cells in the body.

Embryonic stem cells can be obtained from the blastocyst, a very early stage of development, which in the human forms about five days after fertilization of an egg.



The blastocyst is a mainly hollow ball of approximately 150-200 cells, barely visible to the naked eye. At the blastocyst stage, there are no organs, not even blood. However, inside of the blastocyst is the inner cell mass from which embryonic stem cells are grown.



Human embryonic stem cells have been derived primarily from blastocysts created by *in vitro* fertilization (IVF) for assisted reproduction, that were no longer needed.

Why Are Embryonic Stem Cells So Valuable?

Embryonic stem cell lines can, under the right conditions, be grown and expanded indefinitely. Importantly, these cells can retain their ability to form all the different, specialized cell types of the body if they are removed from the conditions that keep them in an undifferentiated, or unspecialized, state.

Mouse embryonic stem cells, first isolated in 1981, are the most widely studied. They have taught us a great deal about how pluripotent cells grow and specialize, and how organisms and diseases develop. Indeed, mouse embryonic stem cells have proven an invaluable tool for biology and medical research. They have led to the discovery of many genes associated with different diseases, allowed us to model human diseases, and they have been used to treat certain human disorders in animal models.

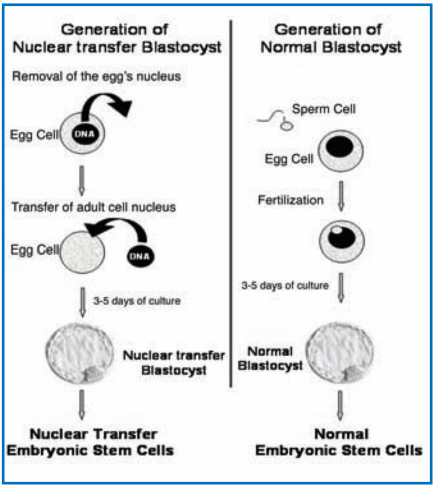
Human embryonic stem cells were isolated in 1998. They are more difficult to work with than their mouse counterparts and currently less is known about them. However, researchers are making remarkable progress, learning about early human developmental processes that they otherwise can't access, modeling disease and establishing strategies that could ultimately lead to therapies to replace or restore damaged tissues.

Disease-specific or Patient-specific Pluripotent Stem Cells

The development of pluripotent stem cells specific to a patient or disease has great promise: first, these stem cells could provide a powerful new tool for studying the basis of the particular human disease and then for discovering and testing drugs for a cure. Second, if patient-specific cells are used in a cell therapy, they would be recognized as 'self,' thereby avoiding the serious problems of rejection and immunosuppression that often occur with transplants from unrelated donors.

Nuclear Transfer to Generate Embryonic Stem Cells

One way that patient- or disease-specific embryonic stem cells could be created is by a technique called nuclear transfer. In nuclear transfer, an egg has its original nucleus including its genetic material removed and replaced with that of a donor cell. The egg is then coaxed into developing as if it had been fertilized, dividing to the blastocyst stage from which embryonic stem cells can be derived. This method has been shown to work for certain animals such as mice but has proven extremely difficult in humans.



As long as a nuclear transfer blastocyst is not implanted into a uterus, it cannot develop further into a living organism. If a nuclear transfer blastocyst were to be implanted, it is possible that a live offspring could be born, a process referred to as reproductive cloning. Based on animal models, reproductive cloning is not only very inefficient but also highly unsafe. The ISSCR does not support reproductive cloning for humans.

'Induced Pluripotent Cells' or iPS Cells

Producing 'induced pluripotent cells' or iPS cells is another way to create patient- or disease-specific pluripotent stem cells.

This strategy also starts from adult cells but rather than transferring the nucleus of these cells into an egg, the cells themselves are engineered ('induced') to become pluripotent, that is, able to form all cell types of the body. In other words, a cell with a specialized function (for example, a skin cell) was 'reprogrammed' to an unspecialized state similar to that of an embryonic stem cell.

Embryonic stem cells and iPS cells share many characteristics including the ability to give rise to the cells of all organs and tissues, but they are not identical.

The generation of human iPS cells was first reported by several groups at the end of 2007. These iPS cells were produced by inserting extra copies of three to four genes known to be important in embryonic stem cells into the genome of the specialized adult cells using viruses. It is not yet completely understood how each of these 'reprogramming' genes restores pluripotency; ongoing research is addressing this question.

The technology used to generate iPS cells holds great promise for creating patient- and disease-specific cell lines for research purposes. However, a great deal of work remains before these methods can be used to generate iPS cells suitable for safe and effective therapies.

Stem Cells in the Clinic

Blood stem cells are currently the most frequently used stem cells for therapy. Doctors have been transferring blood stem cells by bone marrow transplant for more than 50 years. Advanced techniques for collecting blood stem cells are now used to treat leukemia, lymphoma and several inherited blood disorders. Umbilical cord blood, like bone marrow, is often collected as a source of blood stem cells and is being used in certain cases as an alternative to bone marrow in transplantation.

Some bone, skin and corneal diseases or injuries can be treated with grafting of tissue that depends upon stem cells from these organs. These therapies have also been shown to be safe and effective.

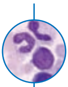
Other stem cell treatments are still at very early experimental stages and have not yet been shown to have a clear-cut advantage over existing therapies, are not considered a standard of care for any condition and do not have regulatory approval for the routine treatment of any disease.

The research, however, is very promising. For example, the mesenchymal stem cell, also found in the bone marrow, can become bone, cartilage, fat, and possibly muscle, and it has some ability to modify immune function in certain experimental models. It has therefore become a cell of great interest for treating a range of musculoskeletal abnormalities, cardiac disease and some abnormalities of immunity (such as graft-versus-host disease after bone marrow transplant).

Despite these successes, there are some big challenges that need to be addressed in order to use stem cells in treating a wider range of diseases in many patients.

First, an abundant source of stem cells must be found. The process of identifying, isolating and growing the right kind of stem cell, a rare cell in adult tissues, is painstaking. Pluripotent stem cells, such as embryonic stem cells, can be grown indefinitely in culture and have the potential to become any cell in the body (including tissue-specific stem cells), but this process is very complex and must be tightly controlled. Much work needs to be done to ensure this can be performed safely and routinely.

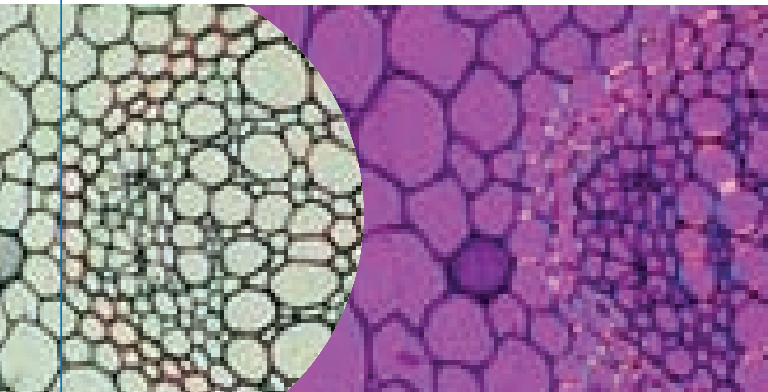
Second, just as in organ transplants, a close match of donor tissue to the recipient is very important. The more closely the tissue matches the recipient, the lower the risk of rejection. It would also be a tremendous advantage to avoid the life-long use of immunosuppressants. Several different avenues are being explored to create patient-specific pluripotent stem cell lines (see above) that could be developed into a needed cell type, and would avoid the problems of rejection and immunosuppression that occur with transplants from unrelated donors.



Third, a system that delivers the cells to the right part of the body must be developed. Once there, the new cells must be encouraged to integrate and function in concert with the body's other cells.

Stem Cells: Challenges for Clinical Use

- **Need many cells to transplant**
- **Transplanted cells must be safe**
- **Maximize tissue compatibility**
- **Transplanted cells must integrate and function properly**



Stem Cell Glossary

Blastocyst

A very early embryo that has the shape of a ball and consists of approximately 150-200 cells. It contains the inner cell mass, from which embryonic stem cells are derived, and an outer layer of cells called the trophoblast that forms the placenta.

Cell line

Cells that can be maintained and grown in culture and can reproduce themselves

Differentiation

The process of development with an increase in the level of organization or complexity of a cell or tissue, accompanied by a more specialized function

Embryo

The developing organism; this term denotes the period of development between the fertilized egg and the fetal stage.

Embryonic stem cell

Embryonic stem cells are cells derived from the inner cell mass of a developing blastocyst. These cells are self-renewing (can replicate themselves) and pluripotent (can form all cell types found in the body).

Induced pluripotent stem (iPS) cell

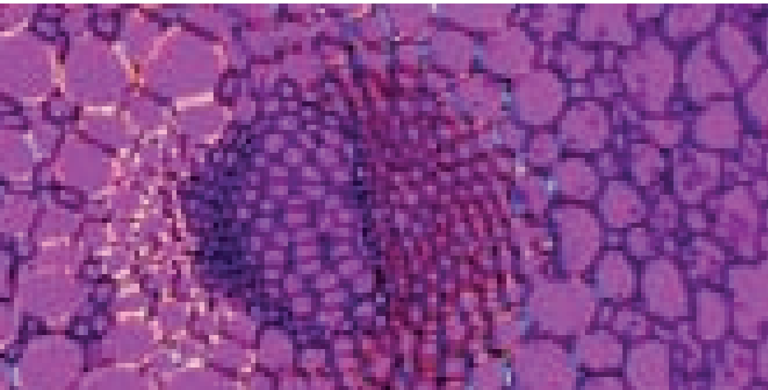
Induced pluripotent cells (iPS cells) are stem cells that were engineered ('induced') from non-pluripotent cells to become pluripotent. In other words, a cell with a specialized function (for example, a skin cell) that has been 'reprogrammed' to an unspecialized state similar to that of an embryonic stem cell.

In vitro fertilization

A procedure where an egg cell and sperm cells are brought together in a dish so that a sperm cell can fertilize the egg. The fertilized egg will start dividing and after a several divisions, forms the embryo that can be implanted into the womb of a woman and give rise to pregnancy.

Mesenchymal stem cell

Mesenchymal stem cells are rare cells, mainly found in the bone marrow, which can give rise to a large number of connective tissue types such as bone, cartilage and fat.



Multipotent stem cells
A stem cell that can give rise to several different types of specialized cells, but in contrast to a pluripotent stem cell, are restricted to a certain organ or tissue types. For example, blood stem cells are multipotent cells that can produce all the different cell types that make up the blood but not the cells of other organs such as the liver or brain.

Nuclear transfer
A technique in which an egg has its original nucleus removed and exchanged for the nucleus of a donor cell. The egg now has the same nuclear DNA, or genetic material, as the donor cell.

Nucleus
A part of the cell that contains the DNA (the genetic, inherited material of cells) surrounded by a specialized membrane

Pluripotent stem cells
Stem cells that can become all the cell types that are found in an implanted embryo, fetus or developed organism

Reproductive cloning
Production of a fetus and delivery of a live offspring from an embryo derived by nuclear transfer, and thus genetically identical to the donor of the transferred nucleus

Self-renewal
The process by which a cell divides and replaces itself with another cell that has the same potential

Stem cells
Cells that have both the capacity to self-renew (make more stem cells by cell division) and to differentiate into mature, specialized cells

Tissue-specific stem cells (also known as adult or somatic stem cells)
Stem cells found in different tissues of the developed organism that remain in an undifferentiated, or unspecialized, state. These stem cells can give rise to specialized cell types of the tissue from which they came, i.e., blood stem cell can give rise to all the cells that make up the blood but not the cells of other organs such as the liver or brain.

www.isscr.org/public www.closerlookatstemcells.org

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