American Association of Neurological Surgeons

# Stem Cell Research

## Patient Information

This resource, developed by neurosurgeons, provides patients and their families trustworthy information on neurosurgical conditions and treatments.

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The proper functioning of all the human body's cells is crucial to maintaining good health. There are hundreds of different specialized cell types in the adult body. Cells perform very specific functions for the tissues or organs they comprise. In diseases like Parkinson's, the death of cells transcends the body's ability to replace them, which results in the failure of organ functions and, inevitably, death.

Stem cells have the unique ability to replace cells and regenerate tissues affected by disease, age or trauma. Stem cell research offers hope to millions of people, from Parkinson's patients whose brains have stopped producing dopamine, to people with diabetes who can no longer produce insulin, to millions of others with degenerative diseases such as ALS (amyotrophic lateral sclerosis), to people paralyzed by spinal cord injuries.

# What is a Stem Cell?

All mammals begin as two cells, the sperm and egg, which combine into a single cell. This single cell divides exponentially into specialized cells, making up various organs and systems that comprise all the tissues of a new organism.

A stem cell is an immature cell that can become a different cell or may become one of many different cells. Most stem cells also can renew themselves by dividing indefinitely. These two characteristics are what present a new pathway to repairing damage to the human body caused by trauma, degeneration and disease.

# Types of Stem Cells

Thus far, research has revealed two basic types of stem cells: embryonic and adult. Embryonic stem cells are found in embryos or in fetal tissue. Embryonic stem cells are either totipotent or pluripotent. Totipotent stem cells have the potential to become any cell in the body. Pluripotent stem cells can become any type of cell in the body except those needed to develop a fetus.

Adult stem cells, by contrast, are unspecialized cells that occur in specialized tissue. These stem cells are found in mammals that have matured past the fetal stage. Adult stem cells are called multipotent because they can become one kind of a certain type of cell, but not any type of cell. An example of a multipotent stem cell is a blood stem cell that could become a white blood cell, a red blood cell, or a platelet. It could not, however, become a nerve cell. Adult stem cells can replicate for the life of an organism, but they cannot replicate indefinitely like totipotent and pluripotent stem cells can.

# Stem Cell Development

The development of totipotent, pluripotent and multipotent stem cells is best illustrated by reviewing normal human development. The single cell created from a fertilized egg has the potential to form an entire or total organism. This single cell is therefore totipotent. In the first hours after fertilization, this single cell divides into two identical totipotent cells, either of which, if placed into a woman's uterus, may develop into a fetus. About four days after fertilization and after several cycles of cell division, these totipotent cells begin to specialize, forming a hollow sphere of cells called a blastocyst. The blastocyst is comprised of an outer layer of cells and a cluster of cells, called the inner cell mass, which is inside the hollow sphere. The outer layer of cells will form the placenta and other supporting tissues needed for development in the uterus. The cells in the inner mass will form all the cells of the organism, but by themselves, cannot form an organism, because they cannot form the placenta and supporting tissues that enable an organism to develop. The inner mass cells are pluripotent. These pluripotent cells transform into specialized multipotent stem cells at a later stage of development. Multipotent stem cells thus far have been found in several areas of the body, including in the hippocampus area of the brain and in the blood.

# Progress

A procedure known as somatic cell nuclear transfer (SCNT) produced Dolly the sheep, the world's first cloned mammal, in 1996. In SCNT, the nucleus of an unfertilized egg is replaced with the nucleus of an ordinary body cell that contains a full set of genetic information. Within a few days, this develops into a human embryo, or the beginnings of one, that contains a cluster of stem cells, which have the potential to become any type of cell in the human body.

While scientists have been studying human development for years, it is only in 1998 that they were able to isolate pluripotent stem cells from human embryos and grow them in the laboratory. Given the properties of pluripotent cells, they are able to replicate indefinitely in the laboratory to develop into almost all types of cells in the body, the 1998 findings were groundbreaking.

The recent advances in the ability to manipulate adult and embryonic stem cells have opened a whole new spectrum of potential therapies for many disorders of the human body. One example is recent research indicating that pancreatic cells implanted into the body of a person with diabetes began to produce insulin.

# Politics and Ethics

Stem cell research is controversial because embryonic stem cells (taken from the 5-to-7-day-old embryos known as blastocysts) and embryonic germ cells, taken from immature aborted fetuses, are the two most promising sources of stem cells. There are four main sources of embryonic stem cells; all are associated with moral issues and debate.

- Surplus embryos that are the by-product of in vitro fertilization
- Embryos created in the lab from donated sperm and eggs
- Embryos created through SCNT, a cloning technique
- Embryos from aborted fetuses

In August 2001, the United States government approved federal funding for research on the 60-plus stem cell lines that at that time were already created through private research. To qualify for research through federal funding, these stem cell lines must meet the following criteria:

- Been created with the informed consent of the donors
- Originated from excess embryos created for reproductive purposes only
- Been donated without financial compensation to the donors

Federal funds cannot be used with stem cell lines derived from newly destroyed embryos, the creation of any human embryos for research purposes or the cloning of human embryos. This not only restricts scientists from receiving government grants, but also requires scientists already working in federally-funded labs to replace or duplicate any equipment needed for this kind of research. All equipment, down to every test tube, must be purchased through private funding initiatives and grant programs.

# Umbilical Cord Blood

Cord blood, also known as "placental blood," is the blood that remains in the umbilical cord and placenta following birth and after the cord is cut. It is usually discarded with the placenta and umbilical cord: it is a rich source of stem cells. About three to four ounces may be taken from a mother's placenta shortly after childbirth for possible transplantation.

Many families are now choosing to bank these genetically unique cord blood stem cells for the future health of their loved ones. A case in point would be a family with a baby boy born with sickle cell anemia. When the mother became pregnant with her second child, the blood was found to be a perfect match. After giving birth, the blood was taken and transplanted in the son affected by sickle cell anemia. When treatment is successful, the stem cells from the cord blood will survive in a patient's bone marrow and produce healthy white blood cells.

Many experts believe that cord blood transplants have distinct advantages over more traditional bone marrow transplants in stimulating the growth of healthy white blood cells. The collection of cord blood is simple and painless, whereas bone marrow donors must undergo general anesthesia. Further, cord blood from an unrelated donor doesn't require the extremely close tissue-type matching of bone marrow transplants. However, there are some risks, because the patient is susceptible to infection and the body may reject the donated cells.

# Adult Stem Cells

While pluripotent stem cells still seem to offer the most promise for human therapies, research on adult stem cells offers some potential. It may seem easier to obtain adult stem cells and avoid some of the ethical issues associated with embryonic stem cells, yet there are challenges involved with adult stem cells as well. Adult stem cells have not yet been identified in every part of the body, they are multipotent and they are difficult to identify, isolate and purify.

There has been some success with adult stem cells from the bone marrow, umbilical cord blood and in the hippocampus region of the brain. Adult stem cells, such as blood-forming stem cells in bone marrow (called hematopoietic stem cells, or HSCs), are currently the only type of stem cell used widely to treat human diseases. HSCs have been transferred in bone marrow transplants for more than 40 years. More advanced techniques of harvesting HSCs are now used to treat leukemia, lymphoma and several inherited blood disorders.

A notable drawback to utilizing adult stem cells in therapies is that there are insufficient numbers of cells available for transplantation because in a culture dish they are unable to replicate over extended periods of time. Researchers have been unsuccessful in directing these cells to become functional as specialized cells. Recent research has revealed the property of plasticity in adult stem cells. Some adult stem cells have been shown to be capable of generating the specialized cell type of another tissue. A reported example of plasticity involved adult stem cells from bone marrow that generated cells resembling neurons, the functional units of the nervous system found in the brain and spinal cord.

# Progenitor Cells

A progenitor (or precursor) cell, found in both adult and fetal tissues, is a partially specialized cell that can form more progenitor cells or two specialized cells when it divides. In contrast, when a stem cell divides, one of the two new cells can replicate itself again. Progenitor cells can replace cells that are damaged in the nervous system (where they are called neural progenitor cells) and elsewhere.

Many early studies reported successfully obtaining progenitor cells from various regions of the brain (primarily the subventricular zone), growing them in the laboratory and transforming them into functional neurons. One challenge is to better identify these cells and to understand their mechanisms of growth and specialization from embryonic stem cells. Both fetal and adult neural progenitor cells show much promise in brain repair. In recent experiments, they have been shown to survive and specialize in the diseased animal brain after injury. It appears that the host brain receiving the cells may influence how the new cells behave. The potential in this area of research is immense.

Neuronal cells derived from a cancer cell line (teratocarcinoma) have been well studied and now tested in humans. Research in normal animals and in animals after injury showed that the cells behaved well and were associated with some recovery of neurological deficits. The initial human trials in patients with small strokes that have caused paralysis are continuing.

# Stem Cell Applications for Neurosurgery

Modern restorative neurosurgery began about 30 years ago when neurosurgeons and neurobiologists envisioned the possibility of replacing degenerating neurons in patients who had diseases like Parkinson's and Huntington's. At the time it was believed that neurons could not regenerate, a theory that was disproved in the 1990s. Therefore, early clinical trials were based first on a direct approach, targeting the replacement of missing specific brain chemicals (neurotransmitters) rather than regenerating the damaged neuronal circuitry. More recently, with the advent of treatment strategies developed from experimental work with stem and progenitor cells, there is hope that the final goal of reconstructing neuronal pathways may be achieved. The goals of this field can be summarized as replacement, release and regeneration. That is, dead neurons have to be replaced, the grafts have to be able to release neurotransmitters and circuits have to be rebuilt. Of course, these goals can be fulfilled only if scientists' understanding of the mechanisms of disease keeps up with the pace of development of new bioengineering strategies.

Currently grafts from fetal tissue, tumor lines and stem cells have been transplanted. Successes in animal models have led to transplant trials in the human population to treat Parkinson's disease, Huntington's disease, spinal cord injury and stroke. As research on animal models progresses, transplant trials may be initiated for the treatment of multiple sclerosis, traumatic brain injury, cerebral palsy, ALS, Alzheimer's disease and other disorders.

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