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A Primer on Stem Cells

A Primer on Stem Cells
By Lucie Bruijn, PhD, The ALS Association's Senior Vice President of Research and Development
What are stem cells?
Stem cells are cells that have the ability to divide for indefinite periods in culture and give rise to multiple specialized cell types. They can develop into blood, bone, brain, muscle, skin and other organs. Embryonic stem cells are undifferentiated cells that have the ability to form any adult cell.

Where do embryonic stem cells come from?
(see Figure 1)

Human embryonic stem cells are derived from fertilized embryos less than a week old. When a sperm fertilizes an egg and creates a single cell, this cell has the potential to form a complete organism and is called totipotent. In the first hours after fertilization, this cell divides into identical totipotent cells. After approximately four days, the cells start to specialize and form a hollow sphere of cells called a blastocyst. The blastocyst has an outer layer of cells and inside the hollow sphere there is a cluster of cells called the inner cell mass. Cells from the inner cell mass can be used to develop pluripotent stem cell lines. Embryonic stem (ES) cells lines are considered to be pluripotent as they can develop into any of the tissues that form the body. Earlier studies focused on mouse ES cells (see Figure 2) , however recently scientists have shown that they are able to isolate and propagate human embryonic stem cells in culture. (see Figure 3) Pluripotent stem cells undergo further specialization into multipotent stem cells that give rise to cells with a particular function. For example, multipotent stem cells in the brain give rise to different neuronal cell types and glia (Figure 2A and Figure 3).

The discovery that human embryonic stem cells can be isolated and propagated in culture with the potential of developing into all tissues of the body is a major medical breakthrough. However it has raised a great deal of ethical questions.

What are the potential applications for stem cells?
Insult to the adult central nervous system is devastating because of the inability of central neurons to regenerate and form appropriate connections to restore function. The consequences of insults to the brain and spinal cord are not just a break in communication between healthy neurons and their target, but a cascade of events that can lead to cell death. The discovery of stem cells that can differentiate into neurons has opened up new doors for potential brain "repair" either through stimulation of stem cells resident in adult brain, endogenous stem cells, or through transplantation methods. The promise of these cells for cellular therapy is driving this explosive field of research.

Human stem cell research could also dramatically change the way we develop drugs and test them for safety. New medications could initially be tested using human cell lines prior to going into clinical trials. In addition, human stem cells can be used to develop assays to screen novel chemical compounds. Using these cell lines, scientists can discover the molecular cues necessary to differentiate stem cells into various specialized cells.

Adult stem cells vs. embryonic stem cells
While stem cells are important in early human development, they persist into adulthood. Their function in adulthood is less clear. The presence of bone marrow stem cells in adults has been known for a long time. These stem cells give rise to all cells of the blood system. More recently, stem cells have been discovered in the adult

brain and spinal cord. There are several approaches now in human clinical trails that utilize adult stem cells (such as blood forming cells and cartilage forming cells). However, because adult cells are already specialized, their potential to regenerate damaged tissue is more limited. Another limitation is their inability to proliferate in culture. Therefore, obtaining clinically significant amounts of adult stem cells may prove to be difficult.

An intriguing discovery is that bone marrow cells (which are able to develop into all the cells of the blood system) transplanted into mice can migrate into the brain and develop into cells that appear to be neurons. These studies suggest that bone marrow may be a readily available source of neural cells with the potential for treating neurological disorders that would overcome the ethical issues. In addition cord blood as a source of stem cells for transplantation has been proposed and studies have been published using this approach in animal models. However these results are still somewhat controversial and further research needs to be done to determine whether these sources of stem cells will indeed be useful for therapeutic approaches in diseases such as ALS.

Adult stem cell research is important and should be done alongside embryonic stem cell research as both will provide valuable insights. Only through exploration of all types of stem cell research will scientists find the most efficient and effective ways to treat diseases.

The presence of endogenous stem cells in the adult brain and spinal cord may provide an alternative to transplantation, eliminating the issues of tissue rejection. If there were a way to stimulate resident stem cells to replace dying cells the limitations of transplantation could be overcome. Small biotech companies are pursuing this direction in the hope of finding therapeutic compounds that will do this. Further research into molecules and genes that govern cell division, migration and specialization is needed, ultimately leading to new drug targets and therapies for ALS.

What are the challenges facing "stem cell therapy" in ALS?

Despite encouraging data that transplanted fetal cells can survive over long periods of time in the damaged area, few studies have shown functional recovery of neurons (neurons making appropriate contact with their target). A recent report demonstrating that modified embryonic stem cells can generate a large number of dopaminergic neurons (the neurons missing in Parkinson's disease) and show some functional recovery in an animal model of Parkinson's is very encouraging. However, unlike Parkinson's disease where functional improvement is less dependent on appropriate neuronal connections, motor neurons have a huge challenge to form connections with their target (muscle) over a very long distance, in adults up to a meter (about 3 feet) in length.

The mechanism of motor neuron death in ALS remains unclear. It is not certain that transplanted stem cells would be resistant to the same source(s) of damage that causes motor neurons to die and stem cells may need to be modified to protect against the toxic environment. There is also the potential that cultured stem cells used in transplant medicine could face rejection by the body's immune system.

Current research efforts

In the last several months there has been an escalation of publications in the stem cell field. For selected references see below. Whether adult stem cells are similar to embryonic stem cells in their ability to differentiate into the required cell types in desirable quantities remains hotly debated with claims that published results cannot be replicated. In contrast, what may have appeared to be impossible several years ago and of particular relevance to ALS is whether stem cells can be directed to generate motor neurons. Research in Dr. Tom Jessell's laboratory demonstrates that mouse embryonic stem cells can indeed be differentiated into motor neurons and when introduced into the spinal cord of embryonic chicks, motor axons form contacts with skeletal muscle. This promising research demonstrates the progress that has recently been made. Scientists acknowledge that the leap from an embryonic chick to a human adult is huge and currently an unobtainable goal. However, the promise of stem cells as vehicles for trophic support for dying neurons is possibly a more feasible goal and many studies are focusing on this approach. Several studies have shown that embryonic stem cells in culture can be genetically modified. Using this technology, stem cells can be modified to deliver genes and other factors to dying motor neurons. More research is needed in this area.

What about clinical trials?
There are currently no clinical trials however a few unpublished efforts have been disclosed using bone marrow and cord blood stem cells in humans and are in very early stages. With all the excitement and possibilities stem cells have to offer as a therapy, it is critical that scientists and clinicians are cautious, plan rigorous studies and most importantly focus on key laboratory experiments that will provide answers to the many challenges that still face this therapeutic approach. For this therapy to be safe and have potential in the clinic, it is critical that the appropriate studies are conducted to learn more about the properties and complexities of the various stem cells.