Current State of Stem Cell Treatments for Cerebral Palsy:

A Guide for Patients, Families and Service Providers

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Key Points:

- Transplanting stem cells into the brain could support and/or replace deteriorating brain tissue during the process of white matter damage in cerebral palsy.

- Animal models used in research on cerebral palsy have shown that many types of stem cells can be used to reduce damage and return motor function after brain injury.

- New technological improvements make it possible for skin cells to be taken from a patient and turned into the exact cell needed to repair injured tissue, getting rid of the need for tissue donor waiting lists and anti-rejection drugs.

Potential Pitfalls:

- Once stem cells are put in, they can never be removed.

- There are no proven stem cell treatments available for patients right now, and it will take a number of years for safe and effective therapies to make it to the clinic.

- Unregulated clinics outside North America are offering stem cell transplants; however, these clinics have shown no scientific proof that their procedures offer any effect beyond placebo effects and/or normal development

- Stem cell transplantation would probably have to be performed within the window of time between the first appearance of injury and irreparable loss of neurons.

Glossary

Transplantation: a medical procedure where cells, tissues or organs are placed into the body of a recipient; in some cases the patient can be both donor and recipient. Transplantation of cells can be done by simple injection, while tissue or organ transplants typically require surgery.
Cerebral palsy: a disability resulting from damage to the brain before, during, or shortly after birth, which is outwardly shown as poor muscular coordination and/or speech disturbances.
Animal model: a living, non-human animal that can be used in medical research to study a human condition. Using these models, scientists can gain understanding of the underlying causes for numerous conditions, and can create viable treatment options as a result.
Stem cells: primitive cells that can either "self-renew" and expand by creating daughter stem cells of the same type, or create mature cells with specific functions of any organ in the body. Stem cells have varying degrees of "potency", ranging from the ability to differentiate into every cell in the body, to only a few cell types.
Placebo effect: Any improvement, actual or perceived, seen in a patient's condition that is due to the patient receiving the treatment, and not due to the effect of the treatment itself.
Tissue: a collection of cells of a similar type that are specialized to perform a particular function.
Neurons: nerve cells which make up the basic signaling units of the brain. They consist of three main parts – dendrites, which receive electrical signals from other neurons; the cell body, which acts as a processing centre, and; axons, which send electrical signals over long distances throughout the body.
Oligodendrocytes: major support cells for neurons. They provide the myelin that wraps the neurons' axons to maintain the speed and strength of the electrical signal.
Myelin: a soft white material of fat and protein that is secreted by oligodendrocytes (or Schwann cells), that forms a thick, insulating sheath around axons.
Hypoxic-ischemic insult: injury to the body caused by a lack of oxygen (hypoxic) and blood flow (ischemic) to the tissue and its cells.
Neuromotor impairment: abnormal or restricted movement caused by damage to the system that handles the brain's (neuro) control of body movement (motor).
Regenerative medicine: a type of medicine focusing on the renewal, growth, and restoration of a body part, organ, or tissue. This aims to copy and repeat the normal growth and development of the body following an injury.

Stem Cells and Cerebral Palsy

Stem cells are naturally-occurring cells found throughout development, and in adults. They can come from many sources in the body and are special because they can turn into different cell types. Large advances have been made in recent years to our knowledge of how to study and handle stem cells. From this, it is expected that we will develop ways to transplant stem cells into damaged tissues to treat and cure injury and disease. This is especially true with diseases or disorders of the nervous system, where damage and disorder often appears from the death of one specific region or cell type.

Cerebral palsy (CP) is an umbrella term that includes several forms and degrees of brain-related injury, which cause neuromotor impairment and other symptoms. The origin of this injury is often caused by many factors, and can include infection before birth, premature birth and lack of oxygen around the time of birth.

Scientists agree that the major similarity in CP is a lack of blood and oxygen to the brain during the fetal development and/or at delivery. This is known as a hypoxic-ischemic insult. Blood vessels in the regions that carry motor neuron branches (called "tracts") are fragile and are at risk of blockage and reduced blood flow. The cells most in danger of this hypoxic-ischemic insult are oligodendrocytes, the support cells that wrap neurons with a protective white fat called myelin (hence the term "white matter").

Because of this myelin, neurons can send electrical signals efficiently throughout the body. Once oligodendrocytes die, the neurons are like unprotected short-circuiting wires—they eventually degrade and die. If myelin white matter could be replaced before this neuronal death, neurons could be spared and motor impairments could be minimized. Therefore, stem cells could even be effective when transplanted after the injury. Replacing neurons themselves would be like trying to rewire a giant switchboard with tens of thousands of ports and no labels, where improper connections can lead to pain. It is for this reason that the aim of many cell transplantation strategies currently being tested is to minimize damage from hypoxic-ischemic insult and replace lost oligodendrocytes.

Cell transplantation-based regenerative medicine has been studied at length in animal models of brain disease. There are three important aspects of these studies: 1) better appreciating what the injury is, 2) which cells should be used, and 3) how the cells are delivered.

For injuries to oligodendrocytes and myelin, the following cells are typically injected into the fluid-filled spaces of the brain:

Mesenchymal Stem Cells

Bone marrow and umbilical cords are rich sources of mesenchymal (from the middle layer of cells in the developing body) stem cells, which normally produce the tissues of the skeletal, muscle, and circulatory systems. Evidence from animal models suggests that umbilical cord mesenchymal stem cells (UC-MSCs) and bone marrow mesenchymal stem cells (BM-MSCs) can migrate to the brain and improve function following injury. These cells can produce neurons in a dish, but are unable to create mature, functional neurons in live

animals. Instead, their benefit comes from providing nutritional and structural support to the region of injury.

Neural Precursor Cells
Taken from a thin layer inside the brain or spinal cord, neural precursor cells (NPCs) are most capable of repairing damaged nervous tissue. These cells are able to migrate short distances through neural tissue and replace damaged cells, preferentially oligodendrocytes. Extracting these cells from a patient would be highly invasive, and currently these cells are used mainly as a research tool in animal models. Sine these cells are already present in the adult nervous system, it is possible that, eventually, a patient could be given a drug that could activate their native stem cells to repair damage after an injury.

Pluripotent Stem Cells
The term pluripotency means the capacity to differentiate into many or all the cell types of the body. Embryonic stem cells (ESCs) have been widely used in research and can easily become NPCs. The ethical objection to the destruction of an embryo, as well as the chance of rejection by the immune system, has eliminated the potential for using ESCs in the clinic. This concern was recently solved when researchers discovered how to turn skin cells into ESC-like cells, so-called induced pluripotent stem cells (iPSCs). Technology surrounding iPSCs has advanced rapidly; new methods have developed which produce patient-specific cells without additives that are known to cause tumors, moving iPSCs one step closer to human trials. Scientists think that the iPSCs will be the best candidate for use as a transplantation strategy to treat children with CP in the clinic because they can be taken directly from the patient and thus would get rid of tissue rejection issues and long donor lists.

How NeuroDevNet Is Pursuing Stem Cell Treatment for CP
As a joint effort between the laboratory of Dr. Michael Fehlings in Toronto (University of Toronto Neuroscience Program and McEwen Center for Regenerative Medicine at the Krembil Neuroscience Center, University Health Network), and Dr. Jerome Yager in Edmonton (University of Alberta), the current NeuroDevNet initiative is investigating patient-specific iPSCs in animal models of cerebral palsy. The team has access to cutting-edge stem cell technologies, as well as state-of-the-art bioengineering products and imaging centres. By first developing straightforward, reproducible means of creating CP in animal models, and then by testing iPSCs, derived in a safer way from adult cells, NeuroDevNet's research arm aims to restore myelin-producing cells and their natural environment, thereby saving neurons before or soon after CP-related damage occurs. Testing iPSCs will allow cells that are used for transplants to be derived in a safer way from adult cells without the need for donor matching.

From Mice to Humans
In some studies, use of neural stem cells was accompanied by improvement of motor function and injury sparing in animal models. Specifically, researchers have used these cells to improve the injury environment or to replace lost oligodendrocytes, thereby sparing degenerating tissue. Transplants can also induce change and reorganization, allowing the

brain to maintain its function. To date experiments with neural stem cells in animal models have been promising. For example, human stem cells were able to replace the myelin of mice that cannot make their own, normalizing motor function and extending their life span from six months to two years.

Damage to the nervous system is one of the most widely studied areas of Regenerative Medicine, and each piece learned about the repair of the brain and spinal cord helps to develop approaches to treat other diseases. Even if cell transplantation proves to be impossible, the lessons learned about how to handle stem cells that naturally exist in the body could produce therapies in the future. These advances lend hope that such basic knowledge will translate into useful therapies and drugs.

Clinical Trials in Humans

There is a huge split, however, between what can be done in a lab with a mouse or a Petri dish, and what should be done in a hospital to a human being. Clinical trials are closely monitored studies of potential medical treatments performed on patients.

Based on positive results from work done in cells and animals, a treatment is first tested on a small group of people to make sure it does not cause harm, and then on larger groups to make sure it works. This method is the foundation of evidence-based medicine, and the best way we have to determine whether a treatment is both safe and effective.

Clinical trials must first and foremost prove that a treatment is safe; this step takes time, but is absolutely essential. Equally, treatments that work perfectly in mice will often show no benefit when used in people. Mice used in research have simple, tailor-made injuries, and cannot reject transplanted cells. It is because of these differences that hype about novel treatments, such as stem cells, should be based on improvements that can be expected in humans. Individual therapies are most beneficial when used as part of a complete treatment program; therefore, stem cells will likely be combined with various other treatments to provide the best outcome.

Beyond the difficulty in moving from the laboratory bench to the bedside, injecting stem cells in people can be dangerous. The more powerful and promising the cell, the higher the risk that it will become cancer, since cancer cells also share many of the characteristics that define stem cells, such as better growth and the ability to move throughout the body. The issue for scientists will be to get stem cells that are flexible enough to grow into the numbers and cell types needed, but inflexible enough to only turn into the correct type of tissue and to target the desired area.

This is understandably quite difficult and of 125 registered clinical trials that are studying treatments for CP, there are currently only 4 evaluating stem cell transplantation. Two of these are being conducted in the United States, and use stem cells taken from the patient's own umbilical cord. Proving that this approach is safe and effective will take several years. In the meantime, researchers will continue exhausting all other ways of treatment, including transplantation of other cell types.

Being Careful: Unproven Treatments

The large demand for effective treatments has led to the creation of unregulated clinics in foreign countries that don't require proof of safety for new medical therapies. There is an increasing trend of people travelling to such clinics to receive stem cell injections. Clinics offering "Stem Cell Tourism"—located in China, India, Germany, and Central America—operate outside medical or scientific supervision. There is inherent risk to any new medical treatment, but are greatest under these circumstances. In fact, patients have developed cancer or dying after they received treatment by medical tourism.

Unregulated clinics commonly inject patient-specific bone marrow, or banked umbilical cord cells. Adult bone marrow cells do not turn into mature neurons or oligodendrocytes within the brain, and banked cord blood cells are killed by the patient's immune system. The improvements that are reported for muscle tone, etc., are most probably a result of placebo effects, the child's natural development, and ongoing rehabilitation. In addition, participating in Stem Cell Tourism would likely eliminate the possibility of enrolling in promising clinical trials in North America.

Reports of successful treatment consistently create massive demands for new procedures or therapies to become available before proper testing. Patients and their families deserve evidence showing that treatments offered are safe. When considering Stem Cell Tourism, it is a must to be a critical, informed reviewer of these clinics, and look past the amazing and unbelievable stories or videos of how their clients have had major recovery. Critically examine the information and look for total clients treated, detailed methods, clear definition of how the cells are made, where and who they are from, where they will be injected, information about results, comparison to similar patients without treatment, and long-term follow-up.

Highly reputable scientific organizations, such as the International Society for Stem Cell Research, currently provide expert analysis of these experimental procedures and specific companies offering them. Without clear, controlled evidence, anecdotal stories cannot be trusted. The truth is that it is difficult and time-consuming for researchers to prove that using stem cells is safe. It is even more difficult to prove that it is also effective. However, it is better to be patient and wait for proof that these treatments work, than to physically suffer from terrible and unproven results.

Stem Cell Tourism is very expensive, which is a fact that many people are eager to accept for the promise of a useful treatment. However, no trustworthy stem cell treatment for CP currently exists. Stem cell therapies are still in the developmental stages and no legitimate, reliable company would ever make you pay for an experimental treatment. It is important to be objective and knowledgeable, and to have strong proof that potential treatments are safe and effective. Once stem cells are put in, they cannot be taken out.

Take-home Message	Explanation
Why Stem Cells?	
Stem Cells have the potential to restore lost tissue after injury	Stem cells can become specific cell types needed for repair after transplantation
Different types of stem cells can have a variety of beneficial effects	Recovering function after injury can be done by sparing dying tissue or replacing cells that have been lost
Transplantable Cells	
Mesenchymal Stem Cell (MSC): Isolated from the umbilical cord (UC-MSC) or bone marrow (BM-MSC) of the patient or a matched family member	Able to travel to and change the injured environment, increasing survival of neurons and making up for losses
Neural Precursor Cell (NPC): Exist in small numbers in the brain with great potential for regeneration	Quickly differentiate to replace supporting cells and lost myelin, and send out signals that enhance repair
Pluripotent Stem Cell: Taken from an early embryo (**ESC**) or induced from a patient's skin cell (**iPSC**)	Can be turned into any cell in the body, such as NPCs. Of these, iPSCs are the newest and least proven type, but also the most promising, as they are made completely from patient's own tissue, eliminating the need for donor lists, anti-rejection drugs and destruction of an embryo. These cells can be used most widely for many different types of injury.
Animal Studies	
Transplanting stem cells into animals has been shown to return and restore function following injuries to the nervous system	Transplanted MSCs and NPCs have been successful in replacing and supporting dying cells, which greatly spares deteriorating tissue, and recovers motor and cognitive function after stroke and traumatic brain injury
Clinical Trials	
The study of stem cell transplantation for CP is very recent, and very few clinical trials have begun	Of 4 currently ongoing clinical trials—all using MSCs—only 2 are being led at recognized clinics in North America.
Stem Cell Tourism	
Several unregulated clinics in Asia, Central America and some parts of Europe are currently offering stem cell transplants	These companies have professional-looking clinics and unbelievable success stories; unfortunately, these are only stories and are not supported by any properly-reviewed data
Companies are using patient desperation to sell unproven procedures	These services are expensive. At best, they have no additional benefit, and at worst they could be very dangerous

Stem Cell Facts: Where to Look
A number of organizations have excellent up-to-date information on stem cells and CP:

International Society for Stem Cell Research (ISSCR)
A world leader for stem cell research with 2600+ scientific members, the ISSCR produced several educational materials on stem cells, including a handbook on experimental stem cell therapies, and will contact companies on your behalf:
http://www.isscr.org/public
http://www.closerlookatstemcells.org/

Canadian Institutes of Health Research
The CIHR Stem Cell Research page provides up-to-date information on stem cell governance and legislature in Canada.
http://www.cihr-irsc.gc.ca/e/15255.html

National Institutes of Health Research
For a superb overview on diagnosis, additional symptoms, associated health concerns, treatments and research on cerebral palsy:
http://www.ninds.nih.gov/disorders/cerebral_palsy/detail_cerebral_palsy.htm

The NIH also runs a Government-sponsored initiative providing up-to-date information on stem cells in regenerative medicine:
http://stemcells.nih.gov/

Current information on registered clinical trials:
http://clinicaltrials.gov/

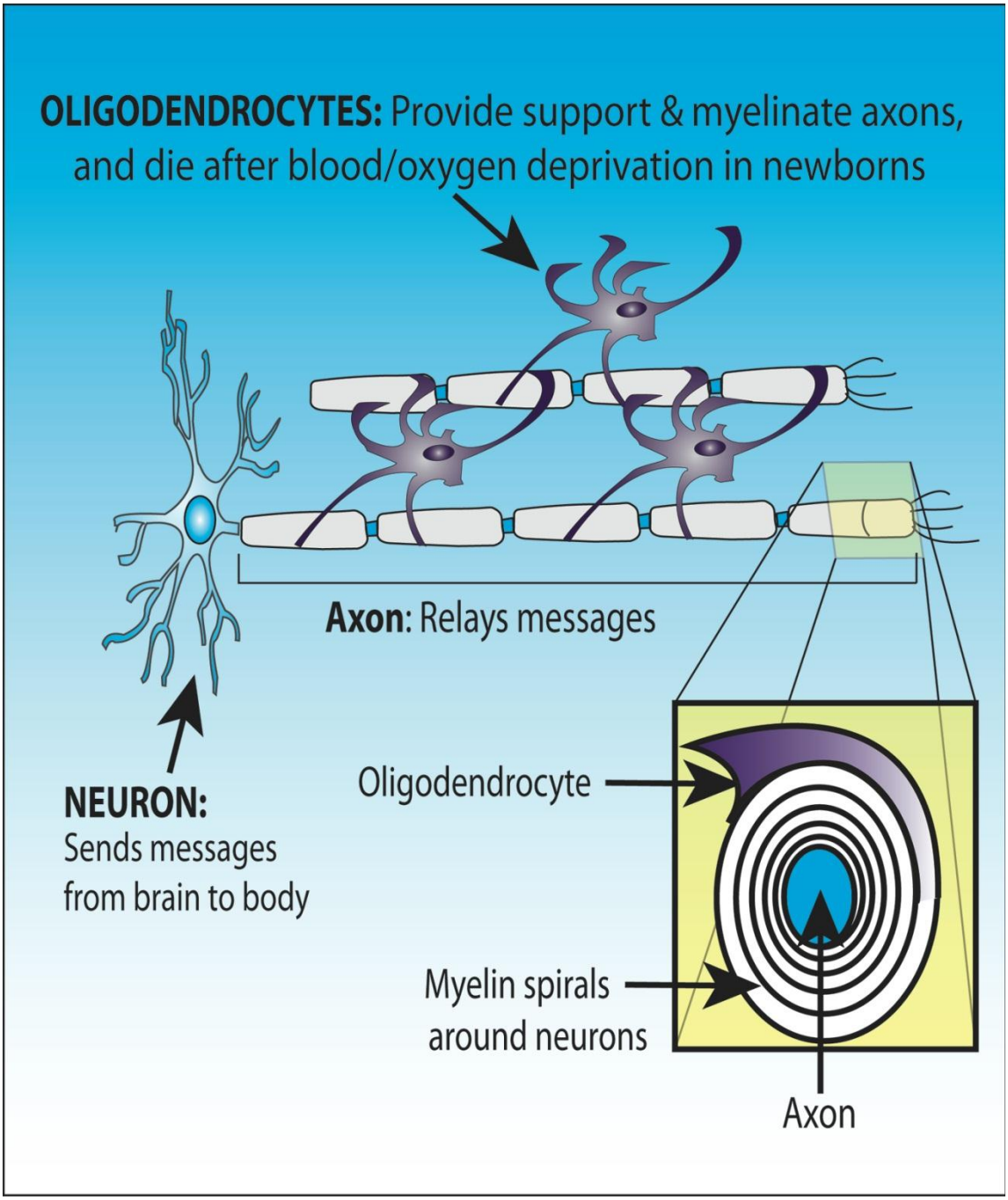

Figure 1: In the brain, nerve cells or neurons are surrounded by special cells called oligodendrocytes, which provide structural and chemical support. They also wrap axons (fibers which extend from neurons) in an insulating layer called myelin. After perinatal injury (during pregnancy or around the time of childbirth), neurons and oligodendrocytes die and myelin is degraded. Without functioning myelin, the relay of messages along axons is blocked.

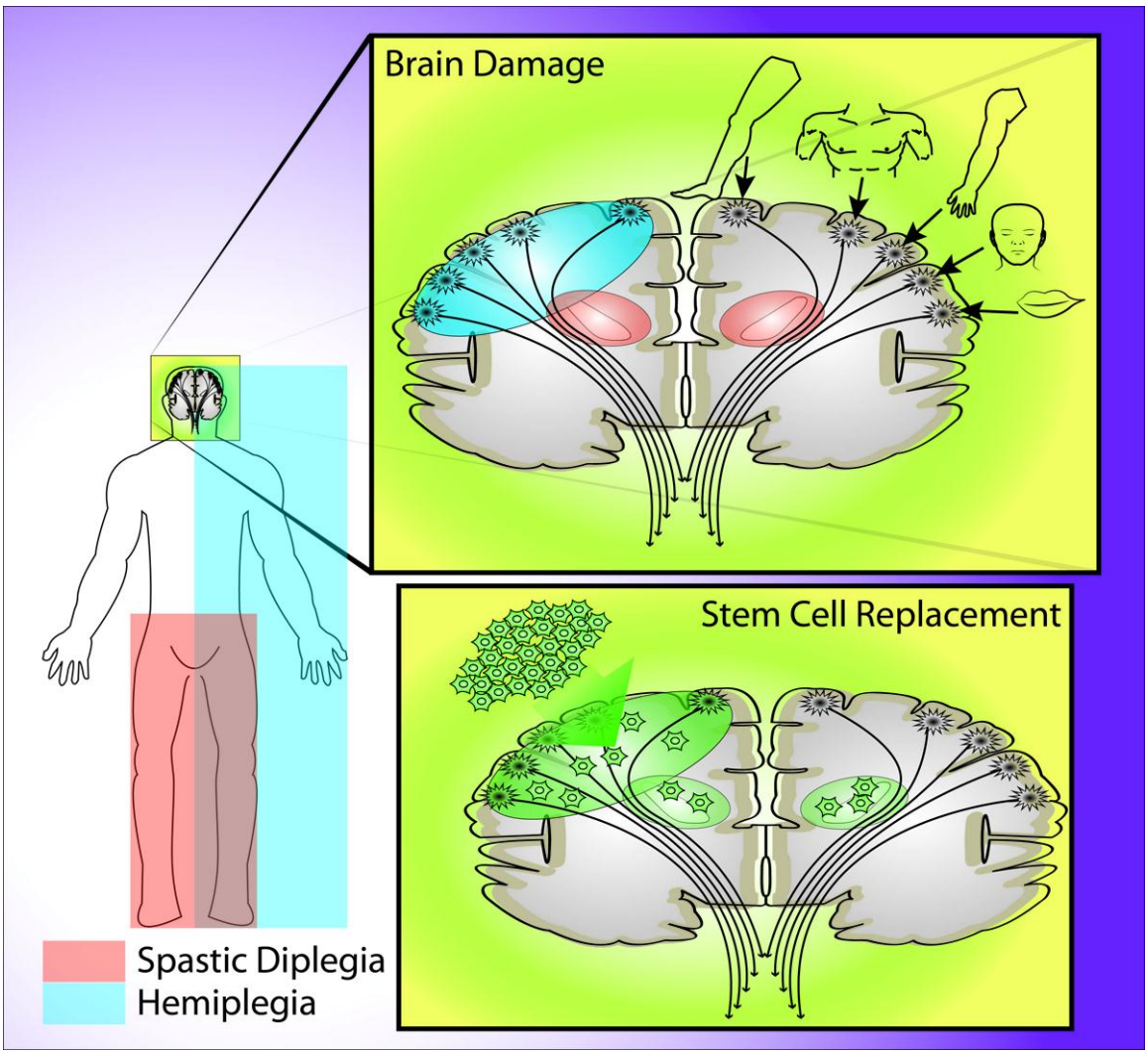

Figure 2: Neurons are arranged in tracts that relay messages from the brain down to the rest of the body. Death of neurons in "motor tracts" that control movement leads to the clinical presentation (symptoms) of CP. The two most common motor deficits in CP are spastic diplegia and hemiplegia. Spastic Diplegia (muscle weakness and stiffness in the legs) results from tissue damage near both tracts containing leg motor fibers – an area of the brain called the ventricles – and hemiplegia (muscle weakness on one side of the body) results from oxygen deprivation to only one side of the brain. Stem cells can replace lost oligodendrocytes and provide chemical and structural support for neurons.