

Originally published by the Stem Cell Network February 2012

## Amyotrophic Lateral Sclerosis (ALS)

- [About ALS](#)
- [Symptoms, Diagnosis and Treatment](#)
- [What causes ALS?](#)
- [Can stem cells help?](#)
- [iPS cells](#)
- [Pre-clinical studies using stem cells](#)
- [Canadian stem cell studies](#)
- [Looking to the future with clinical trials](#)
- [Links](#)

### About ALS

Amyotrophic lateral sclerosis (ALS) is an incurable progressive neuromuscular disease, known as Lou Gehrig's disease in North America and motor neuron disease (MND) in Australia and the United Kingdom. ALS is one of the most common neurological diseases worldwide, and if not for its fatal progression, the prevalence of disease would be similar to that of multiple sclerosis. Each year about 3000 Canadians and 30,000 Americans of all ethnic backgrounds live with this debilitating disease. Men are affected more often than women, with a lifetime risk of developing the disease in the range of 1 in 400 for men and 1 in 350 for women.

ALS attacks specialized nerve cells called motor neurons that are located in the brain and spinal cord. These motor neurons convey electrical signals from the brain and spinal cord to the muscles that control voluntary movements throughout the body. Motor neurons have a spherical cell body at one end that funnels into an elongated section called an axon, which can be as long as one metre. Nerve axons are wrapped in a protective covering, called myelin, that insulates nerves and speeds the transmission of nerve signals. Although motor neurons are the main cell type affected in ALS, one of the major findings in recent years has been the discovery that glial cells in the central nervous system also play pivotal role in perpetuating the disease. Under normal circumstances, glial cells protect and support motor neuron growth and development but, for some reason, in ALS, glial cells create a microenvironment that becomes toxic to motor neurons.

Because motor neurons in the central nervous system lack the capacity to regenerate, ALS is not reversible. As the disease progresses, motor neurons slowly waste away and are unable to transmit the crucial signals that control eating, speaking, walking and even breathing. The disease affects the entire body, usually causing death within 2-5 years.

ALS is classified as either familial or sporadic. Only 5 - 10 per cent of cases are familial, which means the disease is linked to a genetic defect that can be inherited among family members. The remaining 90 - 95 per cent of cases appear to occur sporadically, with only a few accounts of genetic defects proven to play a role. ALS can affect individuals from 40 - 70 years of age but the peak age of onset is typically 47 - 52 years for familial ALS and 58 - 63 years for sporadic ALS. There is currently no cure for either familial or sporadic forms of ALS.

### Symptoms, Diagnosis and Treatment

Symptoms of ALS vary from person to person and are usually subtle at the beginning. Diagnosing the disease is tricky and it takes time for physicians to rule out other more treatable diseases that may have similar symptoms early on.

*Research is a dynamic activity that creates new ideas. It provides a forum for generating observations and testing why they occur. Because people and diseases are so diverse, clinical trials are the ONLY WAY it is possible to test whether new ideas about how to diagnose or treat human disease will work. But the process of taking research from bench to bedside is a lengthy one and demands not only vision but also years of teamwork and dedication on the part of scientists, physicians and patients. This document presents basic information about arthritis and frames the context for the discussion that follows about how stem cells could be used to better understand and eventually treat this condition. Readers may also wish to peruse additional web resources or speak with their physicians for more information about ALS.*

Originally published by the Stem Cell Network February 2012

The progression of ALS is usually rapid and within a relatively short time, controlling the muscles in the limbs, neck, face and torso becomes more difficult. A person can experience clumsiness and unsteady gait, have muscle twitching and cramping and feel extreme fatigue. As the condition spreads, the entire body becomes paralyzed. Cognitive functions may or may not be affected and the disease proves fatal when the muscles responsible for swallowing and breathing shut down.

Research on ALS is wide ranging in its search for a cause and a cure. Although certain drugs and exercise can strengthen wasted muscles, current treatments are only able to alleviate symptoms or minimally delay the progression of disease. Riluzole is the only drug proven to treat ALS and it works by slowing disease progression, but only by 3-6 months. One promising research direction is to find biological signposts called biomarkers that can track the progression of ALS. Identifying biomarkers is key because in most cases, by the time a person is diagnosed with ALS, a significant portion of motor neurons have already died, so any opportunity to diagnose and treat the disease earlier could help to prevent further motor neuron death. In addition, biomarkers for ALS would help clinicians to test the benefit of drugs being used in clinical trials. Some of the novel therapeutic approaches being tested to treat ALS include antisense and RNAi technology. These approaches are intended to block the production of abnormal proteins found in ALS. Scientists are also on the search for new susceptibility genes that may contribute to familial or sporadic forms of ALS, and new drugs that will better treat the disease.

## What causes ALS?

The question of how ALS starts in the first place or how to reverse the damage is still a conundrum. Scientists are looking for clues that would explain where the disease begins: some hypothesize that the disease starts in motor neurons in the brain, some think it could be the muscle or the neuromuscular junction, and others propose that disease starts in both places independently. Scientists agree that a complex interaction between genes and the environment is a big part of the puzzle; however, identifying the genes and teasing out which environmental factors are the culprits pose many ongoing challenges. In general, the avenues of exploration continue to be directed at potential disease mechanisms, such as accumulation of protein aggregates or inclusions, abnormal glial cell function, inflammation, and defects in neurotransmitters, mitochondrial function, axon transport, nutrition, neurotransmitters, RNA metabolism, and protein degradation.

In trying to unravel the complexity of ALS, many groups are whole genome sequencing, in search of single nucleotide mutations in genes, while others are undertaking large exposome-wide studies measuring the myriad environmental exposures that a person receives during a lifetime. Great strides have been made in gene discovery, as demonstrated by the growing number of genes shown to have an effect in familial ALS – notably C9ORF72, SOD1, TDP-43, and FUS – and the identification of new susceptibility genes for sporadic ALS. However, the fact that some susceptibility genes are found only in small families and that finding genes involved in sporadic ALS is progressing slowly suggests to researchers that ALS might be a disease caused by multiple rare variants rather than by a common genetic variant.

In a recent discovery, researchers at the U.S. National Institutes of Health (NIH) and Mayo Clinic independently identified a mutation in a gene on chromosome 9 called C9ORF72 that results in a 'repeat expansion' of DNA – in this case an extra stretch of DNA rich in guanine-cytosine bases is inserted into the non-coding region of the gene. This defective gene is thought to be the number one cause of familial ALS as it is found in roughly 30 per cent of cases. It is also believed to play a role in sporadic ALS and has been found in four per cent of cases to date. Researchers are not sure how the defective C9ORF72 works, but they think the mutated gene makes an RNA molecule that binds to proteins and causes them to clump in the brain.

Other exciting new research from Johns Hopkins is identifying some overlap between familial and sporadic ALS. Researchers there have shown astrocytes from both familial and sporadic ALS patients are toxic to normal motor neurons and that lowering SOD1 enzyme levels in the astrocytes can lessen the toxic effect. Researchers are also finding clues as to the causes of ALS by studying other neurodegenerative diseases. Similarities among ALS, Alzheimer's, Parkinson's and Huntington's disease have been found: for example, they all display an accumulation of proteins, some of which are abnormal, and that appear to contribute to a toxic environment for neurons. For ALS, Alzheimer's and Parkinson's, there are also abnormalities in the glial cells (astrocytes and microglia) that normally secrete growth factors and detoxify neurons, as well as abnormalities in mitochondria that normally supply

Originally published by the Stem Cell Network February 2012

neurons with energy. Researchers think that the upshot is a process that triggers the death of neurons, and that drugs targeting the abnormalities could be applied to many different neurodegenerative diseases.

Previously, scientists believed that ALS did not affect nerve cells that enable other functions of the central nervous system. However, recent discoveries have shown that cognitive impairment in the region of the brain responsible for executive decision-making, behaviour and language does occur in some cases, as demonstrated by people with ALS who suffer from frontotemporal degeneration. The hunt for a “molecular signature” of cognitive impairment has implicated TDP-43, a regulatory gene, and most recently ubiquilin 2, a gene involved in protein degradation, as possible culprits contributing to neurodegeneration.

## Can Stem Cells Help?

The best of all scenarios – preventing ALS by understanding its cause – will take time, so some scientists are studying how stem cells could be used ameliorate this devastating disease. Their arsenal of stem cells includes embryonic stem cells, neural progenitor cells from embryonic or fetal tissue, adult neural stem cells, bone marrow mesenchymal stem cells, cord blood-derived stem cells, and skin-derived iPS cells. Embryonic stem cells and iPS cells are the most versatile in terms of the variety of cell types they can produce, all the different stem cells offer the possibility being used in the future to create renewable sources of healthy neural cell transplants for people with ALS.

Although stem cells offer tremendous promise and can be used to identify drug targets and test treatments, there are currently no stem cell treatments that are able to cure a neurodegenerative disease such as ALS. Ideally, the stem cell treatments would work to replace diseased motor neurons, increase needed cell populations, or restore the microenvironment by delivering neurotrophic factors that protect motor neurons. In reality, however, taking stem cells from bench to bedside is no trivial matter. Although scientists have managed to optimize culture conditions to grow stem cells into large quantities of motor neurons, the conditions that would promote nerve axons to grow up to one metre, the length required to replace damaged motor neurons, still elude them. Scientists are also trying to optimize other variables required for transplantation studies, such as selecting the best cell type and timing, the best delivery technique and injection sites, ensuring cell survival and that the injected cells go to the right place or connect to the right muscle. Of course, without understanding why motor neurons die in the first place, transplanted neurons might be affected by the same disease process. These and other challenges are being addressed by current research.

## iPS Cells

In the past four years, there has been considerable excitement about the potential of *induced pluripotent stem cells* (iPS) to treat ALS. The groundbreaking discovery of iPS cells 2007 enabled ALS researchers at Harvard and Columbia Universities to transform the skin cells from an ALS patient into iPS cells and then to coax them into becoming motor neurons that were genetically identical to a patient’s own neurons, in this case a patient who had the genetic form of ALS.

In a relatively short period of time, scientists have been able to use iPS technology to generate motor neuron and glial cell lines created from patients with ALS and other neurodegenerative diseases. These lines are helping them to decode the mechanisms of disease and study the gamut of disease phenotypes that exist. Because iPS cells are patient specific, they can be transplanted without the typical problems of graft rejection. This quality is what provides such hope for iPS cells being used as patient-specific transplants to regenerate damaged cells or restore the protective microenvironment.

Questions do remain, however, surrounding the long-term safety of transplanting iPS cells, whether they work as well as embryonic stem cells and whether the neural cells generated are the same as those from healthy individuals. Many research groups are striving to address the looming concerns around iPS technology by optimizing the choice of reprogramming factors and perfecting the protocols for delivering the factors.

Originally published by the Stem Cell Network February 2012

## Pre-clinical studies using stem cells

Transplantation studies in animal models of ALS are key for understanding the disease progression and identifying possible targets for future therapies. The majority of studies take place in rodent models of ALS, but other animal models – roundworm and zebrafish, and larger animals such as dogs and the mini-pig – are also proving invaluable.

In rodents, mesenchymal stem cells injected into the brain and spinal cord can grow into both neurons and astrocytes, and some of the cells even become integrated into the spinal cord. Other studies with these stem cells have shown that they can delay progression of the disease and improve the lifespan of the animals.

Studies on how the normal adult brain continues to generate neurons throughout life and integrate them into existing circuits are also of great value. In testing whether endogenous neural progenitors that normally reside in the spinal cord can be stimulated to restore damaged nervous tissue during ALS, it appears that they are capable of doing so to some extent, but the numbers simply aren't great enough to stem the tide of disease. However, researchers have found that human neural progenitors can be stimulated to produce astrocytes in high enough numbers to protect motor neurons and prolong survival in rats. Even more encouraging is the fact that some of these neural progenitor cells are able to create a functional neural circuitry in the rats by making connections with motor neurons.

## Canadian Stem Cell Studies

Scientists across Canada are advancing basic stem cell research towards understanding the mechanisms of disease and developing therapeutic to treat ALS.

Scientists at Dalhousie University are using both embryonic stem cells and iPS cells to examine motor neuron diseases and mechanism of repair. Of great interest is whether motor neurons derived from iPS cells share the same characteristics as those from embryonic stem cells: for example, can the motor neurons made from iPS cells connect to muscles or restore muscle function as well as those made from embryonic stem cells?

Stimulating the body's own stem cells to produce new motor neurons is another possible approach for trying to slow down the disease progression in ALS. One Vancouver study infused the growth factor G-CSF into eight patients with ALS and found that bone-marrow stem cells became mobilized and circulated in the body with no adverse effects to patients. Ongoing studies in mice will optimize the treatment prior to a multi-centre trial being designed to test the therapeutic benefit of this treatment.

In a collaboration with US researchers, a scientist from Dalhousie has contributed to an exciting new discovery showing that it is possible to sidestep the iPS cell stage to make an induced motor neurons directly from embryonic and adult mouse fibroblasts. Although there are many different types of motor neurons, the motor neurons produced in this way specifically become spinal motor neurons. Their characteristics may prove very valuable for studying ALS because they can migrate to the spinal cord when transplanted and send out axons, connect to muscle and cause it to contract, and are sensitive to the toxic microenvironment created by mutant glial cells.

## Looking to the Future with Clinical Trials

There are research teams around the world that are actively investigating how stem cells might be used to treat ALS. Some of their research is being moved forward into clinical trials by groups poised to test the feasibility and tolerability of various stem cell treatments. Common to all the trials are the numerous challenges involved in transplantation: understanding how to confine the beneficial effects of the transplant to the area most in need, optimizing the number and spacing of the injections, controlling rejection in cases where the cells do not originate from the patient, and the high costs of clinical trials. Some of the current trials underway are profiled below.

In the first FDA-approved human stem cell trial for ALS, Neuralstem is performing a phase I safety trial by transplanting up to 18 patients with human fetal spinal cord stem cells. Researchers from Emory University who are involved in the study have created an innovative device that delivers the cells directly into the lumbar region of the spinal cord of patients and buffers the movement of the spinal cord while the patient is breathing. So far, none of the first 12 patients have suffered any major adverse effects. Based on these promising results, the FDA has allowed the trial to begin

Originally published by the Stem Cell Network February 2012

injecting the stem cells directly into the cervical region of the spine as well. Their long-term hope is that the transplanted cells will be neuroprotective, either by making new neurons, trophic factors, or by creating a microenvironment conducive to the survival of motor neurons.

A different type of stem cell is being tested by BrainStorm Cell Therapeutics, which recently received approval for a phase I clinical trial to inject mesenchymal stem cells into the brain or spinal cord of early stage ALS patients. They have perfected a process for turning the bone marrow-derived mesenchymal stem cells into glial-like cells that secrete neurotrophic factors which they hope will protect the neurons in the trial participants.

Despite the many challenges of translating the benefits of stem cell therapies, many research groups and drug development companies are forming partnerships to facilitate a more aggressive approach to translating stem cell technology into possible ALS therapeutics. For example, iPierian is generating iPS cells from ALS patients in order to identify lead compounds for drug development and Pfizer is developing a bank of compounds that may be useful for screening iPS cells for drug targets.

Scientists around the world have made great progress in understanding basic stem cell biology and are working intensely to find ways to translate that knowledge into practical therapies for patients. Although there is still much work to be done, the collaborative model for scientific discovery is lending momentum and direction to the lofty goal of developing stem cell therapies for treating people with ALS.

## Links

### General Information

- The ALS Society of Canada: [www.als.ca](http://www.als.ca)
- The ALS Association: [www.alsa.org](http://www.alsa.org)
- The Motor Neurone Disease Association: [www.mndassociation.org](http://www.mndassociation.org)
- The Packard Center (Johns Hopkins University): [www.packardcenter.org](http://www.packardcenter.org)
- EuroStemCell's Motor Neurone Disease summary: <http://www.eurostemcell.org/factsheet/motor-neurone-disease-how-could-stem-cells-help>

### Research

- [www.alsa.org/research/stem\\_cells.cfm?CFID=225433&CFTOKEN=30953959](http://www.alsa.org/research/stem_cells.cfm?CFID=225433&CFTOKEN=30953959)

### Canada

- <http://www.als.ca/en/node/141/research-newsletter>
- <http://www.als.ca/en/node/434/clinical-trials/current-clinical-trials>

### United States

- <http://www.alsa.org/research/about-als-research/>
- [www.ucsfhealth.org/adult/medical\\_services/neuro/lou\\_gehrigs\\_disease/index.html](http://www.ucsfhealth.org/adult/medical_services/neuro/lou_gehrigs_disease/index.html)
- <http://www.neuralstem.com>
- <http://www.brainstorm-cell.com/>

### United Kingdom

- [www.mndassociation.org/](http://www.mndassociation.org/)