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## ALS Canada Announces Funding for 2014 Discovery Grants

The ALS Canada Research program was established to fund the top ALS research in Canada to meet ALS Canada's strategic vision to find a treatment for ALS. Thanks to your support, we are pleased to announce the recipients of the 2014 ALS Canada-Brain Canada Discovery Grants.

This announcement marks the first grants named in the partnership with Brain Canada. As part of the ALS community, we are tremendously excited about that this partnership is able to fund world class projects that will ultimately move the field of ALS research forward.

### About The Discovery Grant Program

The Discovery Grant program began in 2008 and is designed to provide \$100,000 for funding highly novel research in ALS. By providing initial funds for high quality ideas that would otherwise have difficulty obtaining funding from traditional sources (like The Canadian Institutes of Health Research), researchers can build a foundation of results that will boost their future applications to multi-year opportunities. Each recipient receives a one-time grant to pursue new and promising avenues in ALS research.

This year, ALS Canada received 18 applications. The successful researchers awarded were reviewed by ALS Canada's International Peer Review Panel: a group of seven ALS experts from the United States and Europe.

### Background for Project Summaries

Every organ or tissue in our body is made up of microscopic living compartments called cells. Each cell has a command centre compartment within called the nucleus. The nucleus contains our DNA or genes, which provide the code for us to live. This DNA code is translated into proteins that do all of the actions in our cells required for us to perform all of our life functions. When a mutant gene is said to cause ALS in some hereditary cases, that means there is a small change in a particular gene that translates to a small change in the protein, giving it either an altered function or removing its ability to function and causing consequences that result in ALS at the cellular level. A motor neuron, which degenerates in ALS, is a type of cell in our brain and spinal cord.

### 2014 ALS Canada – Brain Canada Discovery Grant Recipients



Dr. Heather Durham, Montreal Neurological Institute, McGill University  
"Epigenetic mechanisms underlying dendritic atrophy in ALS"

Synopsis: Motor neurons are made up of three distinct regions. The top of the neuron is composed of branches like a tree called dendrites that receive information to transmit. The middle part of the neuron is called the cell body where the majority of the life processes occur and the bottom consists of a single long wire, called an axon that connects the neuron to the next neuron in the chain or to the muscle for movement. Electrical signals in the brain are received in the dendrites of upper motor neurons, transmitted along the neuron to the connection between its axon and the dendrites of the lower motor neuron, and then transmitted along the lower motor neuron to the muscle, causing it to contract. In ALS, these connections are broken when motor neurons degenerate and the brain can no longer signal the muscles, leading to paralysis. Most research has focused on the cell body and the axon, but the dendrites also play an important role in ALS and they have been demonstrated to shrink during disease. In this study, Dr. Durham's lab will examine why dendrites shrink in ALS and attempt to identify ways to prevent it. Dr. Durham's lab specializes in recreating ALS-like conditions in motor neurons living in a dish (cell culture) by giving them abnormal genes that cause the disease in humans. Preliminary findings in these motor neurons suggest a specific genetic pathway that might be affecting dendrite health. Determining if this pathway is important will not only provide an important addition to our understanding of ALS, but also a potential target for treating the disease.



Dr. Charles Krieger, Simon Fraser University  
"Use of bone marrow cells to deliver single chain antibodies in ALS"

Synopsis: This project will use cells found in bone marrow as a potential means of delivering treatments to the diseased area in brain and spinal cord. One of the biggest hurdles in treating ALS is that even if something was developed to slow down or stop the disease, the brain and spinal cord are very difficult regions to access. Our bodies have a natural boundary to protect these areas called the blood-brain barrier that only permits certain substances (like oxygen and nutrients) to cross. In this way, it not only prevents many toxins and potentially harmful chemicals from entering these delicate regions, but also many drugs or potentially helpful chemicals. Most cells circulating in our bloodstream are unable to get past the blood-brain barrier, but Dr. Krieger's team has determined that specific bone marrow cells are summoned to the brain and spinal cord during ALS progression and can cross through the blood-brain barrier. Using specialized laboratory techniques, Dr. Krieger's group can remove these special cells from the bone marrow and give them capabilities that can provide treatment to the diseased area. By then transplanting them back into the bone marrow, they will be ready to deliver this treatment when called to the diseased site by the body. This Discovery Grant will examine the ability to provide these cells with specialized substances called nanobodies that can bind to and reduce levels of a toxic form of mutant superoxide dismutase (SOD1), which is known to cause ALS in a small percentage of hereditary cases and possibly affect sporadic cases as well. The technique will be attempted in mice and if successful, it will provide proof-of-principle for this novel delivery method. Such proof would then drive optimization of this protocol for delivery of SOD1 nanobodies or other potential treatments in humans.



Dr. Alex Parker, Université de Montréal

"Investigation of the innate immune system and motor neuron degeneration in genetic models of ALS"

Synopsis: In recent years, it was discovered that a microscopic worm called *C. elegans* could mimic some of the aspects of human ALS when they were engineered to have abnormal (mutant) genes that cause the disease. Not only do they have motor neuron degeneration like humans, but the worms experience paralysis. The ability of these worms to model ALS makes them a great tool to test drugs that might relieve these effects, but also to study the disease in a very efficient manner that might take more time and expense in more evolutionarily advanced animals like mice and rats. Through examination of these *C. elegans* ALS models, Dr. Parker has discovered that there is an abnormal increase in an immediate immune response that would typically be related to infection. Further work demonstrated that blocking this response actually reduced motor neuron degeneration in ALS model worms. In this study, Dr. Parker's lab will attempt to understand how this immune response (called innate immunity) is activated by making mutant ALS genes and to further understand how it causes motor neurons to die. Identifying the pieces of this response that are crucial to disease in these

worms will lead to further investigation in more advanced animal models of ALS and could provide new treatment targets to someday slow down the disease in humans.



Dr. Janice Robertson, University of Toronto

"Characterizing the C9ORF72 protein interactome for identifying novel pathogenic pathways in ALS"

Synopsis: In late 2011, a landmark discovery was made which identified that abnormalities (mutation) in a gene called C9ORF72 were responsible for the highest percentage of hereditary ALS and frontotemporal dementia cases. Since then, a lot of work has been done to understand how these mutations cause disease. In particular, researchers are still trying to understand the normal function of the C9ORF72 protein that is coded by this gene and a grasp on its importance to cells like motor neurons might provide important clues about ALS and how to treat it. In this project, Dr. Robertson's group will utilize cutting-edge techniques and novel, specially designed biological tools to examine what other proteins interact with C9ORF72 protein in a way never been done before. By determining which proteins interact with the mutant and/or non-mutant form, new processes will be identified that are important to C9ORF72's normal function and will shed light on what processes might be disrupted in

ALS so that they may be targeted for therapy.



Dr. Melanie Woodin, University of Toronto

"Synaptic inhibition in the motor cortex of an ALS mouse model"

Synopsis: ALS is a disease characterized by degeneration of both upper and lower motor neurons. Upper motor neurons are located in a region of the brain called the motor cortex and have been far less extensively studied than lower motor neurons in the spinal cord. One of the earliest detectable abnormalities in mouse models of ALS is differences in electrical activity at the motor cortex where upper motor neurons are firing signals excessively. As a result, some hypothesize that this excessive firing (called hyperexcitability), might cause the disease. Dr. Woodin is an experienced neurophysiologist who will utilize her expertise to study the underlying causes of this hyperexcitability and to then attempt a novel method for rescuing the effect. Not only will this grant usher Dr. Woodin's lab into the ALS community, but the results form the potential to discover a new therapeutic avenue for the disease.

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