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2015 Doctoral Research Award Recipients Announced

It is with great pleasure that ALS Canada announces the 2015 recipients of our Doctoral Research Awards. As a result of continued pursuance of a better understanding of the disease and new treatments, it is imperative that promising young investigators are nurtured into a career focused on ALS research. Attracting the brightest young minds to ALS research will contribute to a succession plan for the Canadian ALS research community and will nurture the potential for younger perspectives to bring new ideas to the field.

The Doctoral Research Awards provide $25,000 per year over three years for salary to pursue a PhD in a Canadian laboratory. This funding also assists the hosting laboratory by offsetting funds that will help them to achieve their goals.

As a result, it is a wise investment that will hopefully launch the career of a future leader in the field and further secure our ability to achieve the vision of making ALS a treatable, not terminal disease.

And now, the recipients:
Maneka Chitiprolu is named the ALS Cycle of Hope Doctoral Research Award recipient. Working under the supervision of Dr. Derrick Gibbings at the University of Ottawa, Maneka will pursue a project aimed at better understanding how a particular cellular disposal mechanism called autophagy is disrupted in ALS. Most autophagy research has involved disposal of large cellular structures or proteins, whereas preliminary work in the Gibbings lab has demonstrated that RNArich clumps called stress granules, prominent features in ALS, can be degraded as well. However, this process is impaired in ALS and Maneka will attempt to determine how autophagy of stress granules occurs and fails in the healthy and diseased situation respectively with the hope that this will signal the potential for novel therapies, including autophagy activating drugs, to slow down progression of ALS. Maneka has many formidable accomplishments for someone so early in their career and she is ambitious to pursue a scientific career. In addition, Maneka will be working alongside our recent awardee of the ALS Canada Postdoctoral Fellowship, Dr. Matteo da Ros and together, we can hope that they will achieve significant progress on our understanding of autophagy in ALS under the tutelage of Dr. Gibbings. As a result of being the top ranked candidate, Maneka will also attend the ALS Cycle of Hope Kelowna Community Rides beginning in 2016, where she will experience the warm welcome of those who are supporting her award and share progress on her work. ALS Canada, with generous sponsorship from the ALS Cycle of Hope, is pleased to support another great young mind to focus their efforts on making ALS a treatable, not terminal disease.

Éric Martineau is named the ALS Canada Doctoral Research Award recipient. Working under the Supervision of Dr. Richard Robitaille at the Université de Montréal, Éric will utilize state-of-the-art techniques to analyze the contribution of specialized cells called perisynaptic schwann cells (PSC) to ALS. These cells are important for supporting the health of the motor neuron at the site where it connects to muscle (called the neuromuscular junction or NMJ). His work will examine if these PSC are impaired in their function before ALS symptoms begin to show in laboratory models of the disease. To do this, Éric will use a personally developed method to study a single NMJ in a living ALS mouse model and study the effect of PSC on NMJ disconnection, as well as its potential to be repaired or rescued. In addition, if Éric indeed discovers that PSC function is failing to keep the NMJ healthy in ALS, he will attempt a therapeutic approach to see if their abilities can be restored to better preserve the motor neuron/muscle connection. Éric has been an attendee at the ALS Canada Research Forum for the last three years, has shown enthusiasm to be a part of the ALS research community in Canada and in his application he states that he has been impacted by learning more about how ALS effects families including both the emotional and financial burden. As a result, he is very driven to find ways of making a difference and making ALS a treatable, not terminal disease in the foreseeable future and he is an exemplary young researcher for ALS Canada to be supporting.

2015 Postdoctoral Fellowship Recipients

It is with great pleasure that ALS Canada announces the two recipients of 2015 postdoctoral fellowships awarded by the ALS Canada Research Program. As a result of the continued pursuance of a better understanding of the disease and new treatments to achieve our vision, it is imperative that promising young investigators are nurtured into a career focused on ALS research. Early postdoctoral years are when critical decisions are made in determining the direction of an individual's research and academic career. Supporting the highest calibre applicants at this stage provides the best possible chance

for maintaining Canadian ALS research excellence in the future.

This year, we are fortunate to provide two fellowships at $55,000 per year for three years. These funds provide the salary for these talented individuals and ultimately assist the hosting lab and supervisor to better flourish in their contribution to the field of ALS research. Postdocs are the key implementers of the lab's vision and not only contribute to the direction of their work, but also execute the work to achieve results. The fellowship program is a fantastic investment and an important part of the ALS Canada Research Program that has previously nurtured individuals who are now global contributors to the field of ALS research as independent principal investigators.

And the recipients are…
Dr. Jacquelyn Cragg is the 2015 recipient of the Tim E. Noël Postdoctoral Fellowship. Under the co-supervision of Dr. Neil Cashman at the University of British Columbia and Dr. Marc Weisskopf at Harvard University, Dr. Cragg will pursue a project focused on epidemiological research in ALS. Through an impressive collaboration between mentors with expertise in epidemiology and ALS, she will examine how military service, trauma and prescription drug use affect risk of ALS using data from the entire Canadian population. Dr. Cragg is a focused, ambitious and extremely accomplished young researcher with a desire to utilize her expertise to fill a niche in Canadian ALS research that does not currently exist. Her vision to become a permanent contributor to our research community aligns perfectly with the goal of the fellowship program and this represents a new step for ALS Canada and the provincial Societies in supporting epidemiological expertise that will hopefully play a unique role in the process of making ALS a treatable, not terminal disease.

Dr. Matteo Da Ros is the 2015 recipient of the ALS Canada Postdoctoral Fellowship. Under the supervision of Dr. Derrick Gibbings at the University of Ottawa, Dr. Da Ros will be working on better understanding the role of specialized structures called stress granules in ALS. These structures are formed in our cells when they are under stress and are believed to protect RNA (genetic information that moves around in cells) from damage during the cellular stress. However, in ALS it is believed that stress granules fail to disassemble properly and may contribute to the disease process. Not only are proteins made by key ALS genes found abnormally in stress granules in the disease, but others may be responsible for their impaired breakdown. In this fellowship, Dr. Da Ros will first examine the content of stress granules caused in cells making the ALS mutant gene FUS, and then will study the ability of a specialized disposal mechanism called autophagy to break them down. His work will hopefully give us a better understanding of how ALS occurs and gather knowledge about the potential for autophagy stimulating therapeutics to be beneficial in ALS. Dr. Da Ros has recently completed a PhD studying similar cellular functions as they relate to spermatogenesis. Supporting young researchers like Dr. Da Ros to come from other fields and focus their expertise on problems in ALS is something ALS Canada and the provincial Societies are proud of and we look forward to welcoming him into the Canadian ALS research community with hope that he and his work will be valuable contributors as we strive to make ALS both understandable and someday treatable. We look forward to engaging with these young researchers and watching them progress in their careers.

Arthur J. Hudson Translational Team Grant Recipients

The Arthur J. Hudson Translational Team Grant was first announced on May 3, 2014 at the ALS Canada Research Forum and the inaugural competition deadline was July 1, 2014. This new grant program is designed to fund teams of Canadian researchers to accelerate the movement of ideas out of the laboratory and into the clinic with the hope of assisting development of new therapeutics for ALS. It is the cornerstone of our ALS Canada Research Program designed to emphasize bench-to-bedside translation. For the first time ever, ALS Canada, in partnership with Brain Canada, have utilized an International Peer Review Panel consisting of seven European and American ALS experts, spanning the basic to clinical spectrum, who convened in Toronto in November to determine the top project amongst strong competition.

It is a great pleasure to announce that the recipient of the first Arthur J. Hudson Translational Team Grant is a team led by Dr. Lawrence Korngut, MD at the University of Calgary and also includes Dr. Lorne Zinman, MD from Sunnybrook Health Sciences Centre and University of Toronto. Together, they will pursue “A randomized controlled trial of pimozide in subjects with ALS”; a Phase II study involving 100 participants across 8 ALS clinics across Canada.

This trial, led by the Principal Investigator of the Canadian Neuromuscular Disease Registry (CNDR) and the Chair of the Canadian ALS Research Network (CALS) will examine whether pimozide, a drug already approved by Health Canada for use in psychoses like schizophrenia and Tourette’s syndrome, might slow progression of ALS. Pimozide is particularly effective at stabilizing neuromuscular function, which means it can strengthen the connection where the motor neuron meets the muscle (called the neuromuscular junction or NMJ). It is hoped that by strengthening this connection, there will be preservation of transmission of signals from the brain to the muscle and slowing of paralysis in ALS.

This Hudson Grant will also fund the validation of an exciting new potential biomarker. Biomarkers are ways of monitoring the body (eg. looking for something in blood or doing a particular physical examination) to either diagnose ALS earlier, select individuals for a trial or monitor effectiveness of a treatment. In recent years, ALS researchers have placed great emphasis on clinical trial biomarkers that ensure the drug is doing the action it is intended to in humans. Without knowing this, it is impossible to determine if an experimental ALS treatment worked or didn’t work as a result of affecting the body function scientists think it was targeting. For example, it was believed that the Biogen drug dexpramipexole, which was tested in a Phase III clinical trial in 2012, improved the function of energy producing machinery in cells called mitochondria.

When dexpramipexole failed to slow down ALS progression, there was no biomarker used to determine if this failure was a result of mitochondrial function or not because it was not tested.

In ALS clinics, neurologists utilize a procedure where they can stimulate an individual's motor neurons to examine their ability to trigger muscle function. For decades, neurologists have observed that repetitive stimulation of motor neurons can lead to decreased response of muscles in many people living with ALS (called decremental response) and it is hypothesized that this may be a result of poor NMJ connectivity and transmission as motor neurons degenerate. Since pimozide strengthens or restores the NMJ, Dr. Korngut's team will measure whether this decremental response can be a biomarker to recruit individuals likely to benefit from pimozide, but also to monitor whether pimozide is acting as hypothesized so a positive or negative result on ALS can be properly interpreted. This means if pimozide does slow ALS progression, we will know whether or not it is a result of NMJ connectivity.
"What is most exciting about this portion of the project is that Dr. Korngut will examine the effectiveness of this biomarker in a small pimozide human trial that is already underway at the University of Calgary," said Dr. David Taylor, Director of Research for ALS Canada. "Should it work, the biomarker can also be used to recruit individuals with the highest likelihood to respond to pimozide treatment for the Hudson Grant funded, 100 participant clinical trial across the country."

This project will also highlight the exceptional infrastructure of the Canadian ALS research community. The CNDR, led by Dr. Korngut, is an innovative platform for organizing patient information to facilitate clinical research and is routinely recognized as one of the best organized ALS registries in the world. In this trial, the CNDR will allow for more efficient recruitment of participants, better data management and improved monitoring of participants following the trial.

Furthermore, CALS, led by Dr. Zinman, is the incorporated network of 15 academic ALS multidisciplinary clinics across Canada. Working together the CNDR and CALS are utilizing optimal infrastructure to initiate and execute clinical trials in a manner that is unique to Canada.

Testing pimozide in the clinic is the next step in a series of projects that have taken several years to develop. Pimozide was first discovered as a potential treatment for ALS in the Canadian labs of Drs. Pierre Drapeau, Alex Parker and Richard Robitaille at Université de Montréal working with zebrafish, worm and mouse genetic models. These individuals are pioneers of the translational team concept in Canada and ALS Canada/Brain Canada are fortunate to have the opportunity to support the first large clinical study produced by this visionary pipeline. We look forward to watching the progress of this study with great excitement. ALS Canada is committed to increasing the opportunity for Canadians living with ALS to participate in clinical trials of exciting new experimental therapeutics. The first Arthur J. Hudson Translational Team Grant will provide this opportunity and lay further groundwork for future clinical trials in 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, (co-PI, Dr. Fabio Rossi)
"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 (co-PI, Dr. Jesse McLean)
"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 nonmutant 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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