MS Research Summaries 2012

MS Society of Canada

Multiple Sclerosis Society of Canada

CONTENTS

BIOMEDICAL

Dr. Guillermina Almazan, Ph.D.
McGill University, Montréal
$286,214.80
(April 1, 2012 – March 31, 2015)
Trophic signaling in oligodendrocytes: Role of insulin-like growth factor 1 in myelination

A major objective in this proposal is to evaluate the roles of IGF-1 in OLG growth and myelination by identifying more specifically the signaling molecules implicated. Our hypothesis is that selective targeting of signaling molecules downstream of the IGF-1R may help in the development of therapeutic strategies to prevent oligodendrocyte death and to improve remyelination in MS. To start testing this hypothesis, we will pharmacologically target the lipid phosphatases PTEN and SHIP2, which negatively regulate PI3K/PIP3 signaling, to assess their role in myelination and remyelination.

Dr. Jack Antel, M.D.
McGill University, Montréal
$189,300
(April 1, 2012 – March 31, 2014)
Cellular immune injury of human oligodendrocytes

The neurologic deficits in multiple sclerosis (MS) are a consequence of injury and loss of myelin and its cell of origin in the central nervous system the oligodendorcyte (OL). Examination of MS lesions indicates that OL injury may result from several different mechanisms. Our work involves the use of OLs derived from surgically resected adult human CNS tissue (not from MS patients) to study how these cells may be injured by these implicated mechanisms. One postulated mechanism implicates inflammatory cells (lymphocytes) as are found in MS lesions as inducing injury OLs. In our 1st aim we will identify the basis whereby such injury occurs. A 2nd postulated mechanism is the OLs within MS lesions are subject to metabolic insults ie their environment deprives them of adequate nutrients and energy. In our 2nd aim, we will identify the molecular properties of OLs that make them vulnerable or resistant to such insults and seek means that could potentially be used therapeutically to protect the cells. In our 3rd aim we will examine whether progenitor cells responsible for remyelination are more or less vulnerable to the same insults as OLs, providing an explanation why repair may be limited in MS.

Dr. Douglas Arnold, M.D., Ph.D.
McGill University, Montréal
$238,564
(April 1, 2011 – March 31, 2013)
Imaging Inflammation in Multiple Sclerosis

Injection of a dye or contrast agent during MRI is capable of lighting up active inflammatory lesions in the brains of patients with MS. These lesions can be the cause of clinical relapses, but usually are clinically silent. The use of new, stronger MRI machines and special techniques to enhance sensitivity to lesion detection can greatly increase the numbers of active lesions that are visualized. However, the effect of this increased sensitivity may not be straightforward. Whereas, with less sensitive techniques, drugs could be evaluated on the basis of their ability to prevent new lesion formation, it may be that sufficiently sensitive techniques show that current drugs do not eliminate new lesion formation, but rather suppress inflammation in new lesions that are continuing to form, but at a reduced level. If this is true, then we would have to change the way we look at the evolution of MS and the effect of these treatments. For example, long-term disability in MS is largely determined by disease outside the visible lesions. In the past, it was assumed that there must be a different process responsible for this. However, if many new lesions are being formed that are not visible on conventional MRI scans, it may be that the process of lesion formation is more important for chronic disability than previously believed. This project would determine whether this is the case, and in so doing, provide important information about how MS evolves and how best to use MRI in the development of new drugs.

Dr. Douglas Arnold, M.D., Ph.D.
McGill University, Montréal
$183,194.20
(April 1, 2011 – March 31, 2013)
MTR for assessment of remyelinating therapies

New therapies aimed at improving remyelination in MS patients are about to enter clinical trials . The only practical way to know if these therapies are doing what they are supposed to do is to study them in clinical trials with a special MRI technique, called magnetization transfer ratio (MTR) imaging. We have already started to use MTR imaging in clinical trials, but still need to work out the final details of how best to do this. In particular we need to perfect the methods used to process the MTR data properly. We need to determine which methods are most efficient for measuring MTR changes and estimating remyelination in MS lesions, and we need to better understand the changes to be expected in relapsing remitting and progressive MS so that we can estimate how many patients will be required for these clinical trials.

Dr. Steffany Bennett, Ph.D.
University of Ottawa, Ottawa
$192,365.50
(April 1, 2011 – March 31, 2014)
Connexin-mediated control of remyelination

Successful treatment of multiple sclerosis must involve therapy designed not only to limit the extent of brain cell destruction but also to stimulate repopulation of damaged tissue. Cell-replacement strategies are key to achieving this goal. The mammalian adult brain, once thought to be completely post -mitotic, is now recognized to contain a finite number of neural stem and progenitor cells with the capacity for self-renewal and the ability to differentiate into functional brain cells. To realize the therapeutic potential of these cells, endogenous stem cells must be able to survive in injured tissue, respond to proliferative cues released by damaged brain, and yet cease division, once normal cell number and cell circuitry has been attained. Our research is designed to study functional brain repair in multiple sclerosis. Specifically, by using a unique combination of phytochemical (plant chemistry), genetic (mouse models of human disease), and molecular approaches in cells and animals, we aim to show:
(a) that changing how stem cells communicate with adjacent cells in adult brain can be used to enhance remyelination.
(b) that compounds found in specific plants can be identified and used to target this type of communication and accelerate functional cell replacement in injured brain.

Dr. Joan Boggs, Ph.D.
Hospital for Sick Children, Toronto
$332,435
(April 1, 2010 – March 31, 2013)
Function of the membrane estrogen receptor in oligodendrocytes/myelin

Myelin is destroyed in MS, and the cells that make it, called oligodendrocytes (OLs), do not remyelinate well. Estrogens have been implicated in susceptibility to MS. MS occurs two times more frequently in females than males, but pregnancy, when estrogen is at its highest, has a protective effect. The protein that binds estrogen in cells (estrogen receptor) can be located in both the nucleus and the cell membrane, including in myelin. The receptor in the nucleus is responsible for slow changes that require protein synthesis and is involved in the development of reproductive organs. The receptor in the membrane causes rapid changes that can affect cell development, migration and membrane production, all changes required for myelination. We discovered that OLs and myelin both have the membrane estrogen receptor and that estrogen added to OLs causes rapid modifications to cell proteins. A form of estrogen produced naturally in the brain of both males and females, 17alpha-estradiol, which has much less effect on the nuclear receptor, also caused these rapid changes. We are

examining the effect of 17alpha-estradiol and other estrogens on the development of OLs and their rate of myelination and remyelination of nerve axons, using cultured cells and brain tissue. We have found that estrogen causes rapid changes in a network of proteins under the cell membrane, called the cytoskeleton, which is important for myelination. Further study of the effects of estrogenic compounds on OLs may allow us to identify some which will be useful for stimulation of remyelination in both males and females.

Dr. Samuel David, Ph.D.
McGill University, Montréal
$279,059.65
(April 1, 2011 – March 31, 2014)
Dysregulation of iron homeostasis in the CNS in EAE and MS and its role in pathogenesis

Recently, there has been much interest in iron deposition in MS lesions and its contribution to MS pathology. Although there is MRI evidence suggesting accumulation of iron in MS brain lesions, there is very little information at the neuropathology level. In other words, we still do not have definite information on which cells accumulate iron, the reasons why it accumulates, and its contribution to the pathology. The proposed work is designed to study these questions in samples of MS brain tissue and in the mouse model of central nervous system autoimmune disease called experimental autoimmune encephalomyelitis (EAE). In addition, we propose to test the effects of an iron chelator (which bind and remove iron) not only on the clinical course of EAE but also its effects on EAE pathology. This work will provide much needed information on the role of iron in MS pathology.

Dr. Shannon Dunn, Ph.D.
University Health Network
$285,000
(April 1, 2012 – March 31, 2015)
PPARdelta as a regulator of EAE progression

Currently, there are few treatments available to help people with primary or secondary progressive MS. In regards to these forms of MS, what we do know is that for some reason patients are losing neurons in their brain. This neuron loss has been shown to associate with the activation of a population of cells called "microglia" in the brain. Through our research, we have identified a gene, called PPARdelta, that makes microglia less inflammatory and thus less able to damage nerves. We thus believe that increasing the activity of this gene may be one way of treating progressiveMS. In our grant, we explore this possibility by using a number of approaches to increase the activity of this gene and examining the effects of these treatments in a common model of MS. Another possible reason that we do not have great drugs for progressive MS is that new drugs are often screened in animal models that resemble relapsing-remitting MS. In this proposal, we are

also trying to investigate a possible new mouse model that may be more appropriate for screening drugs for progressive MS.

Dr. Eleanor Fish, Ph.D.
Toronto General Research Institute, Toronto
$338,295
(April 1, 2011 – March 31, 2014)
The Role of IFN-ß in the Pathogenesis of Multiple Sclerosis

IFN-ß therapy is effect ive in the treatment of MS, yet its mechanism of action is not understood. We are using mice lacking the IFN-ß gene in an experimental model of MS to understand the role of IFN-ß. IFN-ß negative mice are more susceptible to MS and have higher levels of specific pro-inflammatory immune cells in their brains. These proinflammatory cells are implicated in driving the pathology in MS. Our studies are directed at understanding how IFN-ß treatment regulates the generation of these pro-inflammatory immune cells. In studies funded by the MS Society we have accumulated preliminary data that reveal how IFN-ß may regulate these cells, thereby inhibiting MS disease onset and development. We also have evidence that IFN-ß levels may contribute to the sex differences in incidence of MS: we show that female mice lacking IFN-ß are at higher risk of developing MS than male mice lacking IFN-ß. Our ongoing studies continue to examine the molecular events that IFN-ß drives in protection against MS. In addition, we are focusing on delineating the sex-specific events that IFN-ß regulates. By identifying specific targets of IFN-ß, it will be possible to develop additional therapeutic interventions for MS.

Dr. Alyson Fournier, Ph.D.
Montréal Neurological Institute, McGill University, Montréal
$399,980
(April 1, 2010 – March 31, 2013)
Immune cell influences on neuronal viability and repair

Multiple Sclerosis (MS) is characterized by demyelination and damage of neuronal processes (neurites) mediated by infiltration of activated immune cells. Sustained neurological disability is believed to be due to transection of neuronal processes within affected brain regions and subsequent failure of neuronal processes to repair themselves. Little is known about the potential impact of immune cells on neuronal process repair. We have observed that immune cells have a significant inhibitory effect on neurite outgrowth and repair. T lymphocytes and B lymphocytes impact neuronal repair when activated by a variety of stimuli. We are currently following up on the molecular mechanism of action of this inhibitory activity and on the identification of molecular and pharmacological antagonists that may promote repair. Our findings provide insights into immune-neural interactions

relevant to CNS inflammatory conditions and suggest a new avenue for the development of therapeutic strategies to promote axonal repair in MS.

Dr. Jennifer Gommerman, Ph.D.
University of Toronto, Toronto
$408,335
(April 1, 2010 – March 31, 2013)
Understanding the role of TNF super-family members in EAE/MS pathology

Lymphocytes are cells of the immune system that fight infection. In addition to recognizing foreign pathogens such as viruses, some lymphocytes may self-react to tissues in our bodies, causing inflammation. Normally the immune system maintains such lymphocytes in a state of "tolerance" so that they do not respond to these self-determinants. However, in some individuals this state of tolerance is broken, resulting in autoimmunity. It is now appreciated that interactions between lymphocytes and specialized accessory cells called Dendritic Cells within the central nervous system are important for propagating inflammation and disease. However, the nature of these interactions remain poorly characterized. Our lab is interested in the Lymphotoxin pathway as it is an important regulator of dendritic cell function. In addition, we know that inhibitors of this pathway prevent disease relapses in animal models of multiple sclerosis by inducing T cell tolerance. Our aim is to uncover how this important pathway is involved in the cellular events which cause inflammation in the central nervous system, with the ultimate goal of rationalizing the use of Lymphotoxin pathway inhibitors as well as other drugs that modulate dendritic cells, to treat MS.

Dr. Marc Horwitz, Ph.D.
The University of British Columbia, Vancouver
$341,799.55
(April 1, 2011 – March 31, 2014)
A novel mechanism revealing Epstein-Barr Virus-induced neuropathology

Viruses have often been implicated in the development of MS. Several lines of evidence have identified Epstein –Barr virus (EBV), the causative agent of infectious mononucleosis, as a potential trigger of MS. Epidemiological studies indicate that the risk of developing MS is ten fold greater in individuals who were infected by EBV during childhood and twenty fold greater in those developing mononucleosis. Additionally, EBV infected B cells have been found in the brain of MS patients. Brain vessels are composed of a specialized type of endothelial cells. These cells form the blood brain barrier (BBB) that protects the brain by blocking the passage of molecules and immune cells. If the BBB is damaged, it can become more permeable and allow the passage of inflammatory cells that can start to react and destroy the myelin sheath. An increase in permeability of the BBB is one of the primary stages in the development of MS. This project's aim is to study whether EBV is able to infect BBB endothelial cells. As a consequence of the viral infection the cells become inflamed and

this inflammation damage the BBB and allow the passage of immune cells that destroy the myelin sheath.

Dr. Tim Kennedy, Ph.D.
McGill University, Montréal
$327,812.70
(April 1, 2011 – March 31, 2014)
Netrin regulation of axonal-oligodendroglial interactions: novel mechanisms and molecular targets

We aim to identify and characterize a new biochemical mechanism that regulates the formation and stability of myelin. We have reported that mature myelinating oligodendrocytes in the healthy adult brain make a secreted protein called netrin-1, and two netrin-1 receptors, called DCC and UNC5B. These proteins are known to be absolutely essential for normal brain development, but why they are made by oligodendrocytes in the mature brain is not clear. Using cell culture studies, we have recently obtained evidence that netrin-1 and its receptor DCC promote oligodendrocyte maturation and the stability of the connections made between mature myelinating oligodendrocytes and axons. We have now generated genetically modified mice in which we can inactivate DCC function in oligodendrocytes. Using these mice we have demonstrated that DCC is essential to maintain normal myelin in the living brain. We now propose to similarly identify the consequences of disrupting the function of netrin -1 and the other netrin-1 receptor UNC5B in the brains of mice. Our studies aim to better understand how myelin is generated and maintained, with the ultimate goal of finding ways to promote remyelination by identifying novel therapeutic targets for the treatment of demyelinating diseases such as multiple sclerosis.

Dr. Stephen Kerfoot, Ph.D.
The University of Western Ontario
$271,950
(April 1, 2012 – March 31, 2015)
Characterization of the pathogenic mechanisms and potential as therapeutic targets of antigen-experienced B cells in chronic central nervous system autoimmunity

Recent trials of B cell targeting therapies in MS clearly demonstrated the critical role that these cells play in driving disease, although little is known about how they accomplish this. Following activation, B cells have the potential to differentiate into multiple different subsets, each capable of contributing to disease in different ways. Identifying and characterizing the these subsets of long-lived, "memory" B cells is at the cutting edge of B cell biology, but has yet to be applied to the context of autoimmunity. Here, I propose a series of studies to identify subsets of activated autoimmune B cells that develop in CNS autoimmunity and how they drive disease. We will employ a novel animal model of disease in which fluorescently tagged, antigen-specific B cells are used to track all of the cells that

derive from the original autoimmune response. Different subsets will be characterized for their expression of activation proteins, their anatomical location, which strongly influences mechanism and their ability to promote disease. Finally, the susceptibility of the different subsets to therapeutic intervention through CD20 and alpha4-integrin targeting drugs will be assessed, as these targets are the basis of two of the most modern and effective therapies for MS.

Dr. Bradley Kerr, Ph.D.
University of Alberta, Edmonton
$236,092.10
(April 1, 2011 – March 31, 2014)
Examining the underlying mechanisms of neuropathic pain in Multiple Sclerosis

Chronic pain has a major effect on the quality of life of patients with MS. "Neuropathic" pain occurs when there is an injury or disease in the nervous system and is the most prevalent and difficult to treat pain syndrome seen in MS patients. Unfortunately, there are few effective treatments to relieve this pain because very little is known about its underlying causes. Proteins called glutamate transporters are important for controlling pain signals in the nervous system. My research will test the hypothesis that in MS, glutamate transporter function is impaired leading to neuropathic pain. Using a mouse model of MS, we will identify the areas of the brain and spinal cord where glutamate transporters are affected. We will examine how cells in these areas respond to painful and non-painful stimuli to better understand how the disease affects the responses of cells to sensory stimulation. We will then test whether a specific drug that restores glutamate transporter function can prevent neuropathic pain. Finally, we will examine how a clinical treatment that reduces inflammation affects neuropathic pain and determine if it has any effects on glutamate transporters in our model for MS.

Dr. Rashmi Kothary, Ph.D.
Ottawa Health Research Institute, Ottawa
$360,240
(April 1, 2011 – March 31, 2014)
Cell extrinsic mechanisms in oligodendrocyte biology and CNS myelination – the role of the integrin pathway

MS is a disease in which the insulation around the nerves, known as myelin, is damaged by the immune system, resulting in loss of muscle control and partial paralysis. The cell type that produces the myelin sheath (analogous to a jelly roll) around the nerve fibers is called the oligodendrocyte. This cell has to undergo morphological changes prior to being able to wrap around the nerve fibers. Our research is directed towards understanding the molecular mechanisms involved in the steps leading to the morphological changes. We study proteins, called integrins that reside at the surface of the oligodendrocytes. These proteins serve as

important mediators of communication signals between the extracellular milieu and the intracellular machinery. These signals will dictate when and how the oligodendrocyte will elaborate extensive membranes necessary for proper wrapping of nerve fibers. An important downstream node in this signaling cascade is a protein known to associate with integrins, called the integrin linked kinase (ILK). Our goal is to determine the role that integrins and ILK plays in myelin format ion. This is an important first step towards the development of better treatments for disorders in which this process is aberrant, such as in MS.

Dr. Steve Lacroix, Ph.D.
Université Laval
$285,000
(April 1, 2012 – March 31, 2015)
Dichotomous actions of the IL-1 system in MS

Most researchers agree that MS results in the breakdown of the blood-brain barrier and the attack of brain and spinal cord cells by autoaggressive immune cells that invade the central nervous system (CNS); causing damage to sheaths (termed myelin) that cover nerves (axons) and loss of motor, sensory, and autonomic functions. Importantly, MS is not only characterized by extensive demyelination of CNS white matter but also by remyelination periods. Recent evidence obtained in our laboratory has demonstrated that a key molecule involved in the regulation of autoimmunity is the proinflammatory cytokine interleukin (IL)-1ß. In a murine disease model of MS, experimental autoimmune encephalomyelitis (EAE), neutralization of IL-1ß or blockade of its receptor prevents mice from developing EAE. Like TNF, however, IL-1ß could exert paradoxical effects during MS, a theory supported by earlier conflicting reports on the role of IL-1ß in CNS remyelination. The main objectives of this research proposal are therefore: 1) to clarify whether the IL-1 system may exert both detrimental and beneficial actions during MS, 2) to understand how these effects are mediated, and 3) to verify whether we can preferentially inhibit the negative effects of IL-1ß without suppressing its beneficial actions.

Dr. Fang Liu, M.D., Ph.D.
Centre for Addiction and Mental Health
$285,000.00
(April 1, 2012 – March 31, 2015)
Novel Therapeutics targeting protein-protein interactions for Multiple Sclerosis

Treatments for multiple sclerosis need improvement, since current approaches offer incomplete symptom control and do not substantially alter disease outcomes. Most research into multiple sclerosis has focused on the immune system and current treatments are primarily focused on suppressing immunological function to reduce the severity of MS.

We wish to investigate a new approach to treating MS, involving an emerging technique that uses a small peptide (protein fragment) that interferes with the binding of two other proteins. One of these two interacting proteins is a receptor for glutamate, which has been known for a long time to be involved in cell death in many different contexts and diseases. Glutamate toxicity may also be killing nerve cells in MS, and our peptide seems to be able to block this in our preliminary experiments with animal models of MS. Our preliminary experiments also show that our peptide can prevent the progression of paralysis in conjunction with protecting neurons and other spinal cord cells from damage. We propose to confirm and expand on these promising early results, with the hope of generating enough evidence to eventually test this treatment in the clinic.

Dr. Alex Mackay, DPhil.
The University of British Columbia
$277,312.35
(April 1, 2012 – March 31, 2015)
Anatomical and Functional MRI correlates of Cognitive Dysfunction in Multiple Sclerosis

Cognitive impairment (CI) affects between 45 and 65% of people with MS, and has a significant impact on quality of life in terms of activities of daily living, socialization, and ability to remain in the workplace. Although MS lesions can appear in any part of the brain, the types of CI seen in MS are similar for different people. Therefore, we believe that the integrity of complete brain networks is required for normal brain function. MS lesions occurring anywhere along a network can cause it to become dysfunctional. Complete neuropsychological assessment of MS subjects is typically lengthy and often unavailable during routine clinical visits. Using magnetic resonance (MR) imaging, we will apply two new techniques to look at brain networks and compare the MR results to results from cognitive tests. Myelin water imaging measures brain myelin content; loss of myelin causes slowing of nerve signals, leading to impaired brain function. Resting state fMRI measures the strength of connectivity across different brain networks; low connectivity strength also indicates impaired brain function. If this study is successful, these MR techniques will not only identify MS subjects more at risk for developing CI but also enable assessment of the effects of disease-modifying therapies.

Dr. George Robert Wayne Moore, MD, CM, FRCPC, FRCPath.
The University of British Columbia
$283,760.40
(April 1, 2012 – March 31, 2015)
The Pathologic Basis of Magnetic Resonance Imaging in Multiple Sclerosis

This project seeks to determine the changes in the brain responsible for the findings seen with magnetic resonance imaging (MRI) of multiple sclerosis (MS), a disorder characterized by loss of the insulating sheath (myelin) around the electrical cables (axons) of the brain and

spinal cord. MRI changes consist of focal regions of damage termed plaques, which show complete loss of myelin and some loss of axons, and abnormalities outside of these plaques. Some regions outside plaques appear normal on routine MRI scans, and are therefore termed normal-appearing white matter (NAWM), but do show abnormalities with sophisticated non-conventional MRI techniques. Other non-plaque regions show subtle abnormalities on routine MRI imaging, which are referred to as diffusely-abnormal white matter (DAWM). The presence of DAWM may play an important role in MS progression. Our studies have shown that there is an abnormality of fatty (lipid) compounds but relatively normal proteins in the myelin sheath in DAWM and this is associated with some degree of axonal loss. We intend to further characterize these DAWM abnormalities and to determine their possible causes. These studies should lead to significant insights into how myelin and axons are lost in MS.

Dr. Catherine Pallen, Ph.D.
The University of British Columbia
$275,998.50
(April 1, 2012 – March 31, 2015)
Role of PTP Alpha in Oligodendrocyte Maturation and Myelination/Re-Myelination

In MS, attack by the immune system destroys myelin, the protective coating of nerves. The accumulating damage results in the debilitating loss of neurological functions, including movement. A major goal in MS treatment is to find therapies that stimulate myelin repair (re-myelination) to reverse or limit myelin destruction. Currently this is hindered by our meager knowledge not only of the re-myelination process, but also of its similarities and differences with the process of myelination that occurs during normal development.
For many years, we have studied a molecule called PTPa that is present in high amounts in brain. We find that mice that do not produce PTPa have defective myelination, and we have shown that PTPa is required for the normal growth and maturation of myelin-producing cells. In the proposed research, we will investigate this in more detail to identify how PTPa may help transmit signals into cells to direct them to mature and make myelin. We will also determine, using experimental models of myelin destruction, if PTPa is required for myelin repair. Our results will improve our knowledge of the molecular control of these intricate processes and may enhance the rational design of therapies to treat MS.

Dr. Alan Peterson, Ph.D.
McGill University
$158,688.00
(April 1, 2012 – March 31, 2014)
Cre-expressing transgenes targeted to the oligodendroglial lineage: A Resource

The ongoing investigations in my laboratory are designed to illuminate and characterize the regulatory mechanisms that oligodendrocytes use to control myelin synthesis in the central

nervous system. To advance on that objective we use mouse models in which DNA regulatory sequence is attached to a gene that encodes an easily detectable product. Through these investigations we have obtained unique insight into the structure of DNA sequences that target expression to oligodendrocytes at specific stages of maturation. In this investigation, we propose to take advantage of that insight and use such characterized sequences to develop new experimental tools. These will provide improved control in experiments that using gene targeting to probe oligodendrocyte development and regenerative capacity. As we expect these new tools to greatly improve both the efficiency and resolution of ongoing and future investigations across a wide front of investigations focusing on oligodendrocyte biology, we will assure that they are readily available and distributed throughout the research community.

Dr. Christopher Power, M.D., FRCPC
University of Alberta
$285,000.00
(April 1, 2012 – March 31, 2015)
The inflammasome and its regulation by neurosteroids in multiple sclerosis

Inflammation is a key cause of the disease process in neurological diseases such as multiple sclerosis (MS). The underlying cellular and molecular mechanisms of brain inflammation are currently unclear, although we have recently reported that certain steroids synthesized within the brain exert protective effects by regulating immune pathways. Herein, we will investigate the role of the brain's inflammatory machinery in the context of MS and the effects of the brain's intrinsic steroids (neurosteroids) on neuroinflammation. A combined approach will be used in which clinical samples, an animal model and the actions of neurosteroids will be analysed based on existing assays in our laboratories. We expect that different elements of the brain's inflammatory machinery will be selectively regulated by specific neurosteroids, leading to new preventative and/or therapeutic options for MS.

Dr. Alexandre Prat, M.D., Ph.D.
Université de Montréal
$280,787.13
(April 1, 2012 – March 31, 2015)
Ninjurin-1 in CNS inflammation

The Blood-brain barrier (BBB) restricts the passage of cells and molecules from the peripheral blood to the brain. In the disease multiple sclerosis (MS), the BBB fails to prevent the migration of aggressive leukocytes into the brain. These leukocytes are thought to be the effectors of damage to brain cells. Our work focuses on both the intact and damaged BBB and its role in the development of aggressive dendritic cells which attack myelin and axons. We intend to understand the molecular mechanisms which govern the

migration of dendritic cells across the BBB and to study the molecules which affect the survival and the maturation of these aggressive dendritic cells within the human brain.

Dr. Alexandre Prat, M.D., Ph.D.
Research Centre of the University of Montréal Hospital Centre (CR-CHUM), Montréal
$431,775
(April 1, 2011 – March 31, 2014)
ALCAM expression in brain vasculature and its role in neuroinflammation

White blood cells travel from the blood to local sites of inflammat ion where they initiate and maintain defensive immune responses against infections. Normally, the brain is not easily accessible to cells of the immune system due to the presence of the endothelial blood-brain barrier (BBB). However, in brain disease such as multiple sclerosis (MS), an abnormally large number of white blood cells cells readily cross the BBB, infiltrate the brain which eventually lead to the formation of MS lesions. The movement of immune cells from the blood to the CNS is orchestrated by many factors, including adhesion molecules (CAMs) that enable immune cells to cross over the BBB. We have identified ALCAM as a novel CAM expressed by endothelial cells of the BBB, and found it to play a critical role in the migration of immune cells into the CNS. For that reason, ALCAM is an attractive target in the development of novel therapies for the treatment of MS. Our research will focus on this newly discovered route used by immune cells to enter the brain and its role in the development of MS lesions.

Dr. Stéphane Richard, Ph.D.
McGill University
$285,000.00
(April 1, 2012 – March 31, 2015)
The role of the quaking proteins in oligodendrocyte physiology and myelination

My laboratory studies the quaking proteins in myelination and we have shown that the absence of these proteins causes myelination defects in mice. By understanding how the quaking proteins function we are able to tease out the molecular details that are required for oligodendrocyte differentiation. Importantly, we have shown that the QKI-6/7 isoforms can induce oligodendrocyte maturation from neural progenitors in vivo and from oligodendrocyte precursors in vitro. These studies define a new mode of regulating oligodendrocyte differentiation. Our studies are focused on further understanding the ability of QKI-6/7 in myelin maintenance and myelination. As these QKI proteins are quite potent oligodendrocyte differentiation factors, these studies may provide a means to repair the myelin sheath by using therapies that enhance QKI-6/7 function.

Dr. George Robertson, Ph.D.
Dalhousie University, Halifax
$255,739.05
(April 1, 2011 – March 31, 2014)
Apoptotic regulation of B cell activity in experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is an animal model of multiple sclerosis (MS) that, like MS, is characterized by paralysis resulting from destruction of the myelin sheath. The myelin sheath surrounds the electrically conductive branch of a nerve cell called the axon. Loss of the myelin sheath (demyelination) therefore interferes with communication between nerve cells in the brain resulting in the clinical features of EAE and MS. Both are autoimmune diseases in which white blood cells known as T lymphocytes attack the myelin sheath. Accumulating evidence indicates that immune cells responsible for demyelination are resistant to death or apoptotic signals that normally eliminate them from the body. We have shown that this increased resistance to apoptosis may be endowed by altered expression of members of the inhibitor of apoptosis (IAP) family. The purpose of the present proposal is to investigate the distinct roles played by two well known members of this family (XIAP and cIAP2) in EAE. This will be done using genetically engineered mice in which the expression of XIAP or cIAP2 has been altered to establish their respective roles in immune function following induction of EAE. The roles of cIAP1 and cIAP2 in EAE will be further established by systemic administration of a new type of drug called a SMAC mimetic that selectively reduces levels of these anti-apoptotic proteins. These studies will therefore determine if drugs that modulate apoptosis signaling may have benefit in the treatment of MS.

Dr. Fabio Rossi, Ph.D.
The University of British Columbia, Vancouver
$284,489.85
(April 1, 2011 – March 31, 2014)
Role of circulating monocytes in EAE progression

In MS, entry of circulating monocytes (white blood cells) in the central nervous system (CNS) is associated with active lesion, but whether the incoming cells play an active role in causing the damage or are just attracted to clean the debris created by the damage is controversial. Here we will us a novel experimental strategy based on surgically joining two mice in a way that leads to their blood to be shared, to address this question. As this approach also allow us to completely replace white blood cells in a mouse without affecting the cells that are already present in the CNS, it will also allow us to easily distinguish the "incoming" from the resident cells and therefore identify specific roles for each of these. In addition, we will study whether the increase in vessel leakiness observed prior to clear

symptoms in MS has a role in determining where and when circulating cells can enter the CNS.

Dr. Wolfram Tetzlaff, Ph.D.
The University of British Columbia, Vancouver
$187,241.20
(April 1, 2011 – March 31, 2013)
Oligodendrocyte maturation: a potential target to promote white matter repair

Loss of myelin (insulating material of our nerve fibers) is a hallmark of MS and reformation of myelin (remyelination) is inefficient due to a hypothesized block in the maturation of oligodendrocyte precursors (OPCs) the cells that give rise to myelin forming cells. This maturation of OPCs is inhibited by myelin debris as it accumulates in a MS lesion. In our preliminary work we found that stimulation of the mTOR pathway overcomes this inhibition. Hence, we propose a series of experiments to understand this pathway in cell cultures. In addition, we will use a mouse model that allows us to cell-specifically delete several genes that normally inhibits mTOR – i.e. we propose take the brakes off this maturation block and test the outcome in several models of demyelination. These experiments provide the proof of principle that stimulating the mTOR pathway is beneficial for myelin repair and will open the door to research into novel MS treatments. The second project will address the longstanding question whether demyelination is a direct mediator of axonal death and how long demyelinated axons can survive (the axon is the conducting part of the nerve fibre). Here we use a similar genetic approach in mice.

Dr. Luc Vallières, Ph.D.
Université Laval
$285,000.00
(April 1, 2012 – March 31, 2015)
Mechanism of leukocyte recruitment at the blood-brain interface

Multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), are inflammatory diseases that can be influenced by environmental factors, such as microbes and their toxins. Our goal is to understand how microbial agents affect leukocyte traffic in the cerebrospinal vasculature. In this project, we will study the mechanism of action of pertussis toxin (PTX), which is commonly used to induce EAE. We will test the hypothesis that PTX activates the NLRP6 inflammasome, which would induce inflammatory mediators such as IL-6 and IL-33. This study should help to understand how microbial agents influence the course of MS and to identify potential therapeutic target.

Dr. Peter van den Elzen, M.D.
University of British Columbia, Vancouver
$165,000
(April 1, 2010 – March 31, 2013)
Lipid Antigen Presentation by B cells and EBV-infected B cells in MS

MS involves an immune attack on myelin, which is the fatty insulating sheath coating axons, where nerve signals are transmitted. Since myelin is primarily composed of fats (a.k.a. lipids), it is vital to understand how the immune system responds to lipid molecules. We have been studying how the immune system recognizes lipids, including myelin lipids, and the role this may have in MS. Our work has led to the discovery of a role for a lipid transport protein, apoE, in the immune response to lipids. ApoE has been linked to MS, and thus the connection between apoE and immunity to lipids suggests that lipids carried by apoE may be targeted in MS. We have also found that a particular class of lipid-responsive cell may also be involved in responding to EBV, and we are thus investigating how EBV affects lipid recognition by the immune system. Our work has the potential to uncover new therapies that are based on lipids in the treatment of MS.

Robin Yates, Ph.D.
University of Calgary, Calgary
$215,420.10
(April 1, 2011 – March 31, 2013)
Exploring the mechanisms of myelin antigen processing within the endosomal systems of macrophages and dendritic cells

MS is a disease where immune cells (T-cells), mistakenly react to their own proteins present in the myelin sheath of nerves, resulting in neurologic impairment. While autoimmune T-cells trigger the inflammation seen in the disease, it is the antigen presenting cells (APCs) that engulf myelin debris that are responsible for activating the T-cells in the first place. APCs engulf these proteins and digest them in compartments within the cell called phagosomes and endosomes. Some of the protein fragments resulting from this digestion are then shown to T-cells, activating them to cause demyelination. We have exciting new evidence that chemical reactions (reflecting the balance between cellular oxidants and anti-oxidants) within phagosomes and endosomes, can alter protein digestion, and this is critical in determining whether the disease-causing T cells will become activated. The research we are proposing will investigate the details of how APCs digest myelin proteins and we will also be testing several drugs and supplements for their ability to "reprogram" the digestive process by testing in cell culture and in a mouse model of MS. By modifying the way APCs digest protein, but not stopping it altogether, it may eventually be possible control MS disease while maintaining beneficial immune responses.

V. Wee Yong, Ph.D.
University of Calgary, Calgary
$394,662
(April 1, 2010 – March 31, 2013)
Promoting remyelination by overcoming an inhibitory microenvironment

Repair of myelin is a desirable goal in MS. This repair (remyelination) is enabled by oligodendrocyte precursor cells that mature into oligodendrocytes that then send out processes to contact and surround axons to form new myelin. The milieu surrounding an MS lesion is composed to several factors that serve to retard remyelination. Strategies to overcome these negative factors could lead to improved repair in MS. We have understood further the conditions that impair repair, or which lead to successful remyelination. In particular, we have discovered that a family of proteins, referred to as chondroitin sulfate proteoglycans (CSPGs), is deposited in the injury site soon after demyelination, and that they retard attempts at repair. Proteases are expressed physiologically to remove the inhibitory CSPGs, and this is aided by the deposition of a protein that helps repair, laminin. Here we wish to discover whether we can deliver safe proteases (ADAMTS4) pharmacologically to the lesion site to help clear CSPGs, and whether this then leads to repair. These findings are important to help explain the causes of why repair sometimes fails in MS, and they may lead to the identification of a potential therapeutic agent for repair, ADAMTS4.

CLINICAL AND POPULATION HEALTH RESEARCH

Dr. Michelle Driedger, Ph.D.
University of Manitoba
$279,700.55
(April 1, 2012 – March 31, 2015)
Improving health policy decision making in the face of uncertainty: A case study of endovascular treatment for multiple sclerosis

Health policy makers must often make decisions in an environment of uncertainty. The controversial CCSVI hypothesis and "Liberation Therapy" treatment for multiple sclerosis offer a timely opportunity to study health policy making under these conditions. Scientific evidence about the CCSVI hypothesis and the effectiveness and safety of the treatment remains unclear, but policy makers face pressure from intense patient demand fueled by media coverage and the advanced networking opportunities provided by social media tools like Facebook and Twitter. The study's objectives are to (1) identify types and sources of uncertainty health policy decision-makers face, (2) identify the impacts that uncertainty has on decision-making, (3) identify strategies to help decision-makers manage and mitigate uncertainty, and (4) develop an instrument to measure uncertainty. These objectives will be addressed with a mixed-method strategy consisting of (1) a media analysis of newspaper coverage and social media discourses, (2) interviews with policy makers and clinicians, (3) focus groups with MS patients, and (4) test construction. Our research will address an important gap in the MS community, create new knowledge to advance the scientific understanding of uncertainty, and develop practical tools to help policy makers make better decisions about MS.

***** *Recipient of the Manitoba Health Research Council and MS Society of Canada Partnership*

Anthony Feinstein, Ph.D.
Sunnybrook Health Sciences Centre, Toronto
$126,210.83
(April 1, 2011 – March 31, 2013)
The effects of cannabis on information processing speed in MS: a fMRI study

Cognitive dysfunction affects 40-60% of MS patients. Patients experiencing cognitive impairment tend to have greater difficulties at work, in recreational pursuits and maintaining relationships. Studies using Magnetic Resonance Imaging (MRI) have linked cognitive impairments to structural brain abnormalities in MS patients. Of note is that functional MRI (fMRI) studies have demonstrated that in MS patients, additional brain regions are activated during performance of cognitive tasks, presumably to compensate for the structural abnormalities of the brain. MS patients

use cannabis for many reasons, most commonly in response to pain and spasticity. Previous work from our group has shown that MS patients who smoke cannabis may have additional cognitive deficits in information processing speed as measured by the Symbol-Digit-Modality Test (SDMT). The proposed study will investigate how inhaled cannabis may affect cognitive function and fMRI activation patterns while patients undergo the SDMT. This study will determine whether and to what degree inhaled cannabis alters compensatory brain activation in MS patients and determine the relationship between the putative negative effects of cannabis and brain function. Knowledge of the full range of effects of cannabis would be of considerable benefit to patients and healthcare professionals in making decisions regarding the management of MS symptoms.

Dr. Ruth Ann Marrie, M.D., Ph.D.
University of Manitoba
$155,593.55
(April 1, 2012 – March 31, 2015)
The Impact of Comorbidity and Secular Time on Hospitalizations and Mortality in MS

Multiple sclerosis (MS) affects 70,000 Canadians, many of whom also face co-existing (comorbid) health conditions, and the prospect of reduced survival. We do not know much about the relationships between multiple sclerosis and comorbid conditions. The long-term goal of our research program is to shed light on the interactions between MS and comorbid conditions in order to reduce morbidity and mortality due to the combined presence of MS and comorbidity. We will compare hospitalizations and survival in the MS and general populations. We will describe the frequency of hospitalizations, reasons for hospitalization, and causes of death in MS. Also, we will look at how hospitalizations and survival are changing over time, and how they are affected by comorbid conditions. We will do this by using health claims data. Findings from our study will help clinicians to give accurate prognostic information to persons with MS. Our study will also provide information that policymakers need to make decisions about health services. Finally, this study will take an important step toward identifying the comorbid conditions which have the biggest impact on hospitalizations and survival in MS; so that we can develop interventions to reduce their impact.

Dr. Neil Rector, Ph.D, C.Psych.
Sunnybrook Research Institute
$263,305.30
(April 1, 2012 – March 31, 2015)
A Randomized Controlled Trial Testing the Additive Benefits of CBT and Exercise For Depression and Cognitive Dysfunction in MS

Multiple sclerosis is a disease that affects not only physical functioning. Depression and cognitive deficits affect at least half or more of all patients over the course of their lives with

MS. While cognitive deficits can occur in the absence of depression there is evidence that depression may worsen the cognitive burden. What is not yet known is whether treating the depression can in turn lead to cognitive improvement. This question forms the gist of our study. Studies have already shown that a particular form of therapy, namely Cognitive Behavior Therapy (CBT), is effective in successfully treating depression. CBT is just as effective as antidepressant medication and does not have side effects. Studies have also shown that exercise is beneficial to mood and cognitive function. We therefore propose undertaking a study investigating the effects of CBT, Exercise, and CBT plus exercise compared to waitlist controls on indices of depression and neuropsychological functioning. While we hypothesize that all active treatments will produce significant improvements, we further hypothesize that the combined CBT and exercise package will be more effective than lone treatments.

Dr. Daria Trojan, M.D., MSc, B.A.
McGill University
$284,712.15
(April 1, 2012 – March 31, 2015)
A Randomized, Controlled, Clinical Trial of Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea-Hypopnea in Multiple Sclerosis

We found in a recent study funded by the MS Society of Canada that obstructive sleep apnea-hypopnea (OSAH) is the most common sleep abnormality in multiple sclerosis (MS) patients. We also found a relationship between OSAH and higher fatigue scores in our MS patients. Our preliminary work from this group of subjects shows that treatment of sleep disorders (mostly OSAH) can markedly improve fatigue and other symptoms in some MS patients. However, we now need to systemically test the effect of OSAH treatment in a scientifically rigorous study, to be sure that it really does improve fatigue and other symptoms. The best treatment for OSAH in the general population is continuous positive airway pressure (CPAP). This treatment has been well tolerated by most of our MS patients who have used the device. This project will be a randomized, controlled, clinical trial of CPAP in MS patients with OSAH. The effects of six months of CPAP treatment on fatigue as well as sleep quality, somnolence, pain, disability, and quality of life will be studied.

Dr. Christina Wolfson, Ph.D.
McGill University, Montréal
$188,891.35
(April 1, 2011 – March 31, 2013)
A population study of risk factors for Multiple Sclerosis: the Canadian contribution to an international study

The cause of Multiple Sclerosis remains unknown despite more than 100 years of research. There are, however, a few promising individual risk factors including infectious agents,

smoking and vitamin D exposure through diet and sunlight. However there have been no studies large enough to examine how these possible risk factors act together. A team of MS researchers from Europe and Canada are conducting a study including participants from 5 countries with differing MS risk that is large enough to examine how the factors work together. The International case-control study on Environmental factors In Multiple Sclerosis (EnvIMS) has been launched in Norway, Italy, Sweden and Serbia and the focus of the current proposal is the Canadian component of this 5 country study. An important feature is that a common methodology is being applied and a common questionnaire is being be used to collect information on early life infections, smoking, and vitamin D exposure through diet and sunlight. The questionnaire has been adapted to ensure that sources of vitamin D exposure through diet are appropriate for each country and that other questions take into account cultural variability. Once completed this case control will be the largest MS risk factor study ever conducted.

Dr. Brenda Banwell, M.D., Hospital for Sick Children, Toronto
Dr. Amit Bar-Or, M.D., Montreal Neurological Institute, Montreal
Dr. Dessa Sadovnick, Ph.D., University of British Columbia, Vancouver
Dr. Douglas Arnold, M.D. , Montreal Neurological Institute, Montreal
Dr. Ruth Ann Marrie, M.D., Ph.D., University of Manitoba, Winnipeg
$4,300,000

Prospective Study of the Clinical Epidemiology, Pathobiology, & Neuroimaging Features of Canadian Children with Acquired Demyelinating Syndromes

Demyelinating disease of the nervous system represents a serious illness that is increasingly diagnosed in children and adolescents. Symptoms include loss of vision (optic neuritis), inability to walk (transverse myelitis), numbness, impaired sense of balance, and even coma. Some children will completely recover from an attack of demyelination, while others will experience further attacks that characterize the chronic disease, Multiple Sclerosis (MS).

Our work is designed to better understand the symptoms of demyelination in children, to visualize the appearance of demyelination in brain using magnetic resonance imaging (MRI), to explore whether genes (the instructions inside every cell) influence risk, and to investigate why the immune cells (cells that normally fight infection) attack the brain and spine. Twenty-three centers across Canada participate in this study, with a goal of offering inclusion to every child with demyelination in Canada. All children are followed carefully, for up to 8 years, in order to recognize those children who develop new attacks confirming a diagnosis of MS, and of equal importance, to evaluate those children who recover. All children and their families will be asked to tell us how demyelination has impacted their quality of life, so that we might better appreciate the consequences of this illness on child and youth health. Finally, given that demyelination in children occurs in the still developing brain and during the period of core academic study, we will also evaluate the impact of demyelination on learning.

By comparing the features of children diagnosed with MS to the features of children who experience a full recovery, we hope to learn important information about the causes of MS. The ability to predict MS in patients at risk will also allow earlier treatment to reduce attack, and may identify opportunities to reduce risk.

Dr. Mark Freedman, M.D., Ottawa Hospital Research Institute, Ottawa
Dr. Harold Atkins, M.D., Ottawa Hospital Research Institute, Ottawa
$2,419,701

Long Term Outcomes Following Immunoablative Therapy and Autologous Stem Cell Transplant for Poor Prognosis MS

In 2000, the Multiple Sclerosis Scientific Research Foundation funded a multi-centre project entitled Targeting Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoablative Therapy and Immunological Reconstitution to determine definitively whether transplanting bone marrow stem cells in people with MS can stop the disease. The study involved 25 people with rapidly progressing multiple sclerosis who were likely to become severely disabled. Twenty-four of the participants received bone marrow transplantation (BMT) while two participants with the same kind of MS but who did not wish to have the procedure were enrolled in the control group. Recruitment began in October 2000 and the first transplant was completed in October 2001. Follow-up of the patients now ranges from 1 month to 8 years.

To date, all patients post BMT remain relapse and MRI- free of new disease activity. Several patients showed unexpected recovery of function and all remain off of disease modifying drugs.

In order to establish whether immunoablative therapy will induce a long lasting MS progression free state, long term follow-up is essential. Furthermore, to better understand the recovery observed in the primary study the investigators added a number of new investigations including new MRI studies, assessments of visual pathways and cognitive studies. The Multiple Sclerosis Scientific Research Foundation is funding the project Long Term Outcomes Following Immunoablative Therapy and Autologous Stem Cell Transplant for Poor Prognosis MS. Any patient with MS who had a bone marrow transplant is eligible to enrol in the study. Comprehensive clinical, MRI and immunological studies will be performed on study participants from 2007 through 2012.

Dr. Luanne Metz, M.D., University of Calgary
$4,047,255

Phase III double-blind, randomized, placebo-controlled trial of minocycline in clinically isolated syndromes (CIS)

This phase III clinical trial, funded by the MS Society of Canada, will determine if minocycline can prevent or delay further disease activity in people with suspected MS compared to placebo. It is ongoing across the country. Sites involved include the MS Clinics in Vancouver, Burnaby,

Edmonton, Toronto-Sunnybrook, London, Kingston, Ottawa, Montreal, Quebec, Greenfield Park, and Halifax.

Clinical trials take a long time to complete so results are not expected for about 5 years. Minocycline however continues to show promise as a potential therapy for MS. Results of other studies will also become available over the next few years and together all of these trials will help us to determine the role of minocycline in MS. A recently completed Canadian study of minocycline plus Copaxone suggests that this combination therapy may be beneficial and that further study of the combination is warranted. Minocycline is also being investigated in two other ongoing clinical trials including a combination trial of minocycline with Rebif in Europe and an optic neuritis trial to determine if minocycline is neuroprotective in Calgary.

If you already have MS, or had onset of a clinically isolated syndrome (CIS) more than a few weeks ago, you are not eligible for this trial. Only people who are enrolled within several weeks of their first symptom of suspected MS are eligible to participate. In this trial of minocycline we are comparing minocycline to placebo to determine if minocycline increases the chance of the diagnosis remaining CIS. While there are other therapies (interferon and glatiramer acetate) that can have this effect, minocycline is a pill rather than an injection so would likely be preferred by most people.

Most people are not familiar with the term CIS. What is it? Sometimes, despite the occurrence of a typical neurological event that suggests MS, there is not enough evidence to confirm a diagnosis of MS, and yet the neurologist can find no other reason for the symptoms. If this is the case, a person may be told that they have suspected or probable MS. The term sometimes used to describe this early situation when MS cannot be diagnosed but MS is suspected is Clinically Isolated Syndrome (CIS). This is because there has been an isolated (single) event rather than multiple events like happens in multiple sclerosis. In such cases, to establish a diagnosis, time and further follow up are required. A brain MRI may be repeated in several months. In about 70 to 80% of people with CIS, MS becomes clear within about two years because either changes appear on MRI, or a second episode of new clinical symptoms occurs. The chance of having another episode after 2 years is much lower.

Dr. Peter Stys, M.D., University of Calgary
$3,800,000

<u>Pathobiology of MS: complex interplay between degeneration and inflammation</u>

MS is a relentless disease that has features of both brain inflammation and degeneration. While we do not yet know what the root cause is, it is apparent that a vicious cycle of degeneration and attack my inflammatory cells drives tissue damage and patient disability, despite our best drug treatments. Through pathological examination, we've known for over a century that nerve fibers die in MS, but to this day we do not know why. This team project will study the molecular mechanisms of how nerve fibers are permanently injured in the

brain and spinal cord of MS patients. We will also research which immune cells are most responsible for further propagating this relentless cellular injury. Finally, sophisticated magnetic resonance imaging studies on patients with MS will endeavor to better understand what happens in the earliest phases of this disease, and how better to predict the evolution of brain lesions and eventual permanent disability.

DONALD PATY CAREER DEVELOPMENT AWARDS

Dr. Shannon Dunn
University Health Network
$150,000
(July 1, 2011 – June 30, 2014)

Dr. Bradley Kerr
University of Alberta
$150,000
(July 1, 2012 – June 30, 2015)

Dr. Ruth Ann Marrie
University of Manitoba
$150,000
(July 1, 2011 – June 30, 2014)

Dr. Shalina Ousman
University of Calgary
$150,000
(July 1, 2012 – June 30, 2015)

Dr. Jacqueline Quandt
University of British Columbia
$150,000
(July 1, 2010 – June 30, 2013)

Dr. Helen Tremlett
University of British Columbia
$150,000
(July 1, 2010 – June 30, 2013)

POSTDOCTORAL FELLOWSHIP AWARDS

Dr. Lindsay Berrigan
Supervised by Dr. John Fisk
Dalhousie University
$39,000
(July 1, 2012-June 30, 2013)
An Investigation of the Impact of Mental Health Comorbidity on Cognitive Functioning and Health Outcomes in MS

Dr. Robert Brown
Supervised by Dr. Douglas Arnold
McGill University
$39,000
(July 1, 2012-June 30, 2013)
Longitudinal Analysis of Demyelination and Remyelination in Multiple Sclerosis

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Dr. Debra Fulton
Supervised by Dr. Alan Peterson
McGill University
$39,000
(July 1, 2012-June 30, 2013)
Identification and validation of the transcription factors and transcription factor cooperativity relationships that control expression of myelin-associated genes in oligodendrocytes

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Dr. Steve Gendron
Supervised by Dr, Alexandre Prat
Centre de recherche du Chum
$39,000
(July 1, 2012-June 30, 2013)
Role of integrin alpha8beta1 and semaphorin/plexin in multiple sclerosis

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Dr. Jeffery Haines
Supervised by Dr. Patrizia Casaccia
Mount Sinai School of Medicine
$39,000
(July 1, 2012-June 30, 2013)
Roles of n-cofilin, LIM kinase and slingshot phosphatase in oligodendrocyte myelination and remyelination

*****Recipient of the Fonds de recherche Santé du Québec and the Multiple Sclerosis Society of Canada Postdoctoral Fellowship*

Dr. Dong Han
Supervised by Dr. Timothy Kennedy
McGill University
$39,000
(July 1, 2012-June 30, 2013)
Mechanisms Regulating the Formation and Maintenance of CNS Myelin

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Dr. Soo Yuen Leong
Supervised by Dr. Jack Antel
McGill University
$39,000
(July 1, 2012-June 30, 2013)
Characterisation and functional analysis of pre-myelinating O4(+) oligodendrocyte progenitor cells from human brain

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Dr. Sébastien Lévesque
Supervised by Dr. Steve Lacroix
Université Laval
$39,000
(April 1, 2012-March 30, 2013)
Dichotomous actions of the IL-1 system in MS

Dr. Veronique Miron
Supervised by Dr. Charles ffrench-Constant
The University of Edinburgh
$39,000
(July 1, 2012-June 30, 2013)
Identification of inflammatory conditions that promote oligodendrocyte-mediated myelination and remyelination: implications for multiple sclerosis

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Dr. Lyndsay Murray
Supervised by Dr. Rashmi Kothary
University of Ottawa
$39,000
(July 1, 2012-June 30, 2013)
MicroRNA regulation of remyelination

Dr. Laura Pilutti
Supervised by Dr. Robert Motti
University of Illinois
$39,000
(July 1, 2012-June 30, 2013)
Increasing physical activity behaviour in individuals with multiple sclerosis

---

Dr. Stacey Reinke
Supervised by Dr. Christopher Power and Dr. David Broadhurst
University of Alberta
$39,000
(July 1, 2012-June 30, 2013)
Using metabolomics to establish diagnostic and prognostic biomarkers of Multiple Sclerosis and to gain insight into the molecular mechanisms of the disease

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Dr. Olga Rojas
Supervised Dr. Jennifer Gommerman
University of Toronto
$39,000
(July 1, 2012-June 30, 2013)
Evaluating novel B cell effector functions in EAE/MS

Dr. Dalia Rotstein
Supervised by Dr. Tanuja Chitnis
Brigham and Women's Hospital
$48,500
(July 1, 2012-June 30, 2013)
Predictors of Treatment Response in Multiple Sclerosis Patients

---

Dr. Scott Ryan
Supervised by Dr. Stuart Lipton
Sanford-Burnham Medical Research Institute
$39,000
(July 1, 2012-June 30, 2013)
Targeting myelination as a therapeutic for Multiple Sclerosis
***Recipient of the Asad Wali MS Society of Canada Postdoctoral Fellowship*

Dr. Afsaneh Shirani
Supervised by Dr. Helen Tremlett
University of British Columbia
$48,500
(July 1, 2012-June 30, 2013)
Temporal changes in disability progression and demographics in multiple sclerosis

---

Dr. Kenrick Vassall
Supervised by Dr. George Harauz
University of Guelph
$39,000
(July 1, 2012-June 30, 2013)
Analysis of the conformational transitions of myelin basic protein

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STUDENTSHIP AWARDS

Ph.D. STUDENTSHIP

Nadine Akbar
Supervised by Dr. Banwell
University of Toronto
$20,000
(July 1, 2012-June 30, 2013)
Functional magnetic resonance imaging correlates of cognitive dysfunction in pediatric multiple sclerosis

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Euan Allan
Supervised by Dr. Robin Yates
University of Calgary
$20,000
(July 1, 2012-June 30, 2013)
Modulation of antigen processing of myelin oligodendrocyte glycoprotein by the alteration of redox balance in the phagosome

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Bravina Balachandar
Supervised by Dr. Christine Till
York University
$20,000
(July 1, 2012-June 30, 2013)
Working memory training for patients with pediatric-onset MS: Effects across multiple domains of cognitive functioning

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Erik Bélanger
Supervised by Dr. Daniel Côté
Centre de Recherche Université Laval Robert-Giff ard (CRULRG)
$20,000
(July 1, 2012-June 30, 2013)
In vivo evaluation of MS-like lesions with nonlinear microscopy

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Elodie Brison
Supervised by Dr. Pierre Talbot
INRS-Institut Armand-Frappier
$20,000
(July 1, 2012-June 30, 2013)
From respiratory disease to multiple sclerosis-like disability: importance of the spike protein of human respiratory coronavirus OC43

Zografos Caramanos
Supervised by Dr. Douglas Arnold
McGill University
$20,000
(July 1, 2012-June 30, 2013)
The Use and Utility of Quantitative Magnetic Resonance Imaging at Describing Neuropathology and Predicting Future Disability in Patients with Multiple Sclerosis

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Jacquelyn Cragg
Supervised by Dr. Matt Ramer and Dr. Jaimie Borisoff
University of British Columbia
$20,000
(July 1, 2012-June 30, 2013)
Plasticity and spasticity: the Renshaw cell and spinal reflex modulation
***Recipient of the Dr. McIlroy MS Society of Canada PhD Studentship*

Miguel De Avila
Supervised by Dr. George Harauz
University of Guelph
$20,000
(July 1, 2012-June 30, 2013)
Myelin basic protein interactions with SH3 domains

Marcio DePaula
Supervised by Dr. Guillermina Almazan
McGill University
$20,000
(July 1, 2012-June 30, 2013)
Role of IGF-1 signaling in oligodendrocyte development, myelination and remyelination

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Gregory Duncan
Supervised by Dr. Wolfram Tetzlaff
International Collaboration on Repair Discoveries (ICORD)
$20,000
(July 1, 2012-June 30, 2013)
The Role of Remyelination in Protecting Demyelinated Axons from Degradation

---

Nicolas Guizard
Supervised by Dr. Louis Collins
Montreal Neurological Institute
$20,000
(July 1, 2012-June 30, 2013)
Brain Atrophy Quantification and Trajectory in MS Patients

Lamia Naouel Hachehouche
Supervised by Dr. Alexandre Prat
Centre hospitalier de l'université de Montréal
$20,000
(July 1, 2012-June 30, 2013)
IL-26 and IL-26R in Multiple sclerosis
***Recipient of the Fonds de recherche Santé du Québec and the Multiple Sclerosis Society of Canada Postdoctoral Fellowship*

Mohammad Karim
Supervised by Dr. Paul Gustafson and Dr. John Petkau
University of British Columbia
$20,000
(July 1, 2012-June 30, 2013)
Causal Inference with Observational Multiple Sclerosis Data
***Recipient of the National Bank Financial Group MS Society of Canada PhD Studentship*

Michael Keough
Supervised by Dr. Wee Yong
University of Calgary
$20,000
(July 1, 2012-June 30, 2013)
Altering the Inhibitory Microenvironment to Promote Oligodendrocyte Maturation and Remyelination
*** Recipient of the Waugh MS Society of Canada Research Fellowships*

Catherine Larochelle
Supervised by Dr. Alexandre Prat
Centre hospitalier de l'université de Montréal
$20,000
(July 1, 2012-June 30, 2013)
MCAM implication in blood-brain barrier endothelial cells and lymphocytes activation and interaction in the context of MS

Joshua Lee
Supervised by Dr. Dessa Sadovnick
University of British Columbia
$20,000
(July 1, 2012-June 30, 2013)
Multiple sclerosis in Asians: The genetic, environmental, and epigenetic determinants of variable clinical profile and susceptibility

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Camille Olechowski
Supervised by Dr. Bradley Kerr
University of Alberta
$20,000
(July 1, 2012-June 30, 2013)
Dysregulated glutamate transporter function as an underlying cause for neuropathic pain in Multiple Sclerosis

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Natalia Pikor
Supervised by Dr. Jennifer Gommerman
University of Toronto
$20,000
(July 1, 2012-June 30, 2013)
Dissecting immune function and gene alterations in chronic versus relapsing EAE

Camille Pittet
Supervised by Dr. Nathalie Arbour
Centre hospitalier de l'université de Montréa
$20,000
(July 1, 2012-June 30, 2013)
Potential Immunoregulatory Roles of Programmed Cell DEATH-1 Ligands in Human Central Nervous System

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Neda Razaz-Rahmati
Supervised by Dr. Helen Tremlett and Dr. Clyde Hertzman
University of British Columbia
$20,000
(July 1, 2012-June 30, 2013)
Children of Multiple Sclerosis: impact of chronic disease in parents on early development

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Jean-François Richard
Supervised by Dr. Luc Vallières
Université Laval
$20,000
(July 1, 2012-June 30, 2013)
Mechanism of leukocyte recruitment at the blood-brain interface

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Li-Chun Wang
Supervised by Dr. Guillermina Almazan
McGill University
$20,000
(July 1, 2012-June 30, 2013)

Role of Cdo in p38alpha/beta MAPK regulation of oligodendrocytes differentiation and myelination

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Magdalena Wojtowicz
Supervised by Dr. John Fisk
Dalhousie University
$20,000
(July 1, 2012-June 30, 2013)
Functional and Structural Neural Correlates of Cognitive Functioning in Multiple Sclerosis

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Xiaojun Xie
Supervised by Dr. Vanessa Auld
University of British Columbia
$20,000
(July 1, 2012-June 30, 2013)
Characterizaiton of integrins in Drosophila glial cells

Monan (Angela) Zhang
Supervised by Dr. Shannon Dunn
University of Toronto
$20,000
(July 1, 2012-June 30, 2013)
Understanding Sex Differences in Multiple Sclerosis (MS): Sexually Dimorphic Role for Peroxisome Proliferator-Activated Receptor Alpha (PPARa) in Dampening Pathogenic T Helper 1 (Th1) Responses in Humans and Mice

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Fei Zhao
Supervised by Dr. Shannon Dunn
University of Toronto
$20,000
(Sept 1, 2012-June 30, 2013)
The Role of PPARdelta in Limiting Pathogenic T Helper Cells in EAE
***Recipient of the Co-operators MS Society of Canada PhD Fellowship*

MSc. STUDENTSHIP

Emilie Chamma
Supervised by Dr. Daniel Côté
Université Laval
$18,000
(July 1, 2012-June 30, 2013)
Measurements of blood-brain barrier integrity and endothelial cells activation in vivo using optical microscopy in a multiple sclerosis animal model

---

Paulina Drohomyrecky
Supervised by Dr. Shannon Dunn
University of Toronto
$18,000
(July 1, 2012-June 30, 2013)
Evaluation of the role of peroxisome-proliferator activated receptor delta (PPARd) in microglial responses during experimental autoimmune encephalomyelitis (EAE)

Camille Juzwik
Supervised by Dr. Alyson Fournier
McGill University
$18,000
(July 1, 2012-June 30, 2013)
Immune cell influences on neuronal viability, repair and morphology in multiple sclerosis

---

Antonia Kobert
Supervised by Dr. Amit Bar-Or
McGill University
$18,000
(July 1, 2012-June 30, 2013)
Effects of HBEC-Soluble Factors on MS-Relevant B-Cell Responses

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Magdalena Lysenko
Supervised by Dr. Christine Till
York University
$18,000
(July 1, 2012-June 30, 2013)

Functional MRI activation of executive control networks in adolescents and young adults with multiple sclerosis (MS)
***Recipient of the Alistair Fraser MS Society of Canada MSc Studentship*

Sarah Neil
Supervised by Dr. Jacqueline Quandt
University of British
Characterizing the anti-inflammatory effects of TEMPOL in an animal model of Multiple Sclerosis
$18,000
(July 1, 2012-June 30, 2013)

Alexandre Paré
Supervised by Dr. Steve Lacroix
Université Laval
$18,000
(July 1, 2012-June 30, 2013)
Role of neurotrophin-producing immune cells in animal model of MS

Olivia Saint-Laurent
Supervised by Dr. Alexandre Prat
Centre hospitalier de l'université de Montréal
$18,000
(July 1, 2012-June 30, 2013)
Characterization of the changes occurring at the blood brain barrier of spontaneous relapsing remitting experimental autoimmune encephalomyelitis mice

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