

MS Research Summaries 2011

MS Society of Canada



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Guillermina Almazan, Ph.D., and Walter Mushynski, Ph.D.

McGill University, Montréal

\$300,000

(April 1, 2009 – March 31, 2012)

Role of p38 MAPK (mitogen activated-protein kinase) Signaling Pathways in Myelination

The multilayered myelin sheath that enwraps nerve fibers serves as an insulator to facilitate nerve impulse conduction. It also maintains the integrity of associated nerve fibers through the activation of signals that affect nerve fiber structure and function. Erosion of the myelin sheath therefore causes neurological impairments such as those seen in multiple sclerosis patients. In order to better understand the process of myelination and the trophic interactions between myelin and nerve fibers, it is essential to characterize the sequence of events taking place during myelination and the molecular signals that mediate these interactions. We have identified a number of molecular targets that are important in myelination. One of these targets is a group of proteins referred to as the p38 family of protein kinases, which may play an important physiological role in myelination, but are also involved in inflammation. The objective of this grant proposal is to delineate the molecular mechanisms by which p38 regulate myelination, and to explore their function during myelination and remyelination in vivo. Identification of the specific p38 protein substrates regulating myelination is of paramount importance since these proteins are potentially important therapeutic targets for treating chronic inflammatory diseases.

Jack Antel, M.D.

McGill University, Montréal

\$219,900

(April 1, 2010 – March 31, 2012)

Promoting Remyelination in Multiple Sclerosis

Multiple sclerosis (MS) is characterized in its initial phases by recurrent relapses with variable degree of subsequent recovery. An estimated 50% of cases in the pre-therapeutic era eventually entered a secondary progressive phase. Recovery from relapses is now considered to reflect at least in part a component of remyelination. The later progressive phase can reflect both ongoing tissue injury and failure of the initial repair mechanisms. Experimental animal studies indicate that remyelination in the CNS is mediated by progenitor cells that differentiate into myelinating cells. Such progenitor cells have been identified in the adult human CNS including in the region of MS lesions.

The central goal of this proposal is to understand the signaling pathways used by human progenitor cells as part of their myelination program. With such knowledge we can then identify or develop therapeutic agents that can be used to enhance the capacity of these cells to restore myelin loss that occurs during the course of MS. For our studies, we will particularly take advantage of our access to surgically resected human CNS tissue and a post mortem tissue collection of cases of MS. Promoting repair and functional recovery is a currently unmet therapeutic need in MS.

Nathalie Arbour, Ph.D.

**Research Centre of the University of Montréal Hospital Centre (CR-CHUM) ,
Montréal**

\$330,000

(April 1, 2009 – March 31, 2012)

Detrimental Dialogue Between the Immune System and the Central Nervous System: Roles of CD8 T Lymphocytes

Multiple sclerosis is the most common disease of the brain in young adults: between 55,000 and 75,000 people are affected by this disease in Canada. Despite many years of research, the cause of this illness is still unknown. The immune system usually provides protection against microbes. However, the immune system in multiple sclerosis patients shows abnormalities and it attacks components of the brain as if they were foreign microbes. The purpose of our study is to identify molecules present in the brain of multiple sclerosis patients that are used by the immune system to attack it. A particular type of white blood cells bears the capacity to kill other cells and was observed in the brain of multiple sclerosis patients at the site of tissue destruction. The goal is to analyze these killing cells and determine what potentiate their capacity to be toxic in the brain of multiple sclerosis patients. We hope to identify new molecules and cells that could eventually be targeted by future treatments.

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.

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.

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.

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.

Andrew Chojnacki, Ph.D.
University of Calgary, Calgary
\$160,430

(April 1, 2010 – March 31, 2012)

Regulation of human oligodendrogenesis by Nodal signaling

In multiple sclerosis, the immune system attacks the brain and spinal cord. The myelin sheath covering the processes of neurons is targeted by immune attack. Neurons stripped of myelin cannot efficiently send signals used to control thoughts or movements. Some neurons missing their myelin regain their myelin sheath. This is called remyelination. Oligodendrocytes make myelin in the brain and spinal cord. Only new-born oligodendrocytes can replace lost myelin. New oligodendrocytes are made by platelet-derived growth factor-responsive neural precursor cells. Why remyelination fails in multiple sclerosis is unknown. Platelet-derived growth factor-responsive precursors may use up their ability to make new oligodendrocytes during remyelination. They may also lose their ability to make more of themselves (a processes called expansion). Understanding the factors that control expansion may help increase remyelination in multiple sclerosis. We found that by itself, Nodal increased the expansion of platelet-derived growth factor-responsive neural precursors. Nodal together with platelet-derived growth-factor increased expansion of platelet-derived growth factor-responsive neural precursors more than either factor on their own. We want to understand how Nodal on its own or with platelet-derived growth-factor increases platelet-derived growth factor responsive neural precursor expansion.

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.

Shannon Dunn, Ph.D.

University Health Network, Toronto

\$211,100

(April 1, 2010 – March 31, 2012)

PPARdelta and PPARgamma as negative regulators of innate inflammation in EAE

In MS, one's own immune cells attack the myelin sheath that covers the nerves in the brain and spinal cord. The accumulation of these cells in the brain results in the formation of a lesion, the location of which determines the pattern of clinical symptoms that an MS patient may experience. For reasons that are still unclear, inflammatory lesions in MS and EAE (mouse model of MS) sometimes spontaneously resolve. Recent studies indicate that the activity of proteins called peroxisome proliferator-activated receptors (PPARs) may be involved in this process in EAE. In mice that do not have certain types of these molecules, EAE clinical signs are significantly worse and do not improve. How these molecules work and in what types of cells that they function in has not been determined. The major objective of this grant is to elucidate the cellular and molecular basis of action of PPARs in EAE. The first aim was to define where (what cells) these molecules function. To date, we have found that one of these molecules, PPARdelta, appears to play a role in the innate immune cell compartment in calming inflammation leading to disease remission. Interestingly, this protective effect is only apparent in males, suggesting a sexual dimorphism in the functioning of this molecule. We also have observed that microglia (the immune cell of the brain) taken from mice that don't have this molecule are more prone to develop inflammation. Additionally, we made the discovery that a related molecule, PPARgamma is expressed at higher levels in female T cells and that in the absence of this molecule, T cells are more prone to produce IL-17, a cytokine associated with severe inflammation in MS. In the next year, our plan is to conduct further experiments exploring the sexual dimorphism in PPARdelta and PPARgamma functioning in microglia and in T cells and to tease the respective roles of these molecules in the control of inflammation in the brain and spinal cord during EAE.

Eleanor Fish, Ph.D.

Toronto General Research Institute, Toronto

\$338,295

(April 1, 2011 – March 31, 2014)

The Role of IFN- β in the Pathogenesis of Multiple Sclerosis

IFN- β therapy is effective in the treatment of MS, yet its mechanism of action is not understood. We are using mice lacking the IFN- β gene in an experimental model of MS to understand the role of IFN- β . IFN- β 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- β 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- β may regulate these cells, thereby inhibiting MS disease onset and development. We also have evidence that IFN- β levels may contribute to the sex differences in incidence of MS: we show that female mice lacking IFN- β are at higher risk of developing MS than male mice lacking IFN- β . Our ongoing studies continue to examine the molecular events that IFN- β drives in protection against MS. In addition, we are focusing on delineating the sex-specific events that IFN- β regulates. By identifying specific targets of IFN- β , it will be possible to develop additional therapeutic interventions for MS.

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.

Sylvie Fournier, Ph.D.

McGill University, Montréal

\$178,180

(April 1, 2010 – March 31, 2012)

Pathogenic mechanisms in an animal model of CD8+ T cell-mediated demyelinating disease

To develop efficient therapeutic approaches that can cure or minimize disease and benefit the affected individuals, it is essential to identify the pathological processes

that contribute to multiple sclerosis (MS) development. MS is an inflammatory disease of the central nervous system in which T lymphocytes, a cell type of the immune system, are believed to play an important role. There are two major subsets of T lymphocytes: the CD4+ and the CD8+ T cells. Over the years, CD4+ T cells have almost exclusively been held responsible for the disease. Recent evidences suggest that the CD8+ T cells may also contribute to the initiation or propagation of MS. In active MS brain lesions, CD8+ T cells were shown to predominate over CD4+ T cells. However, the function of the expanded CD8+ T cells in MS patients is still unknown. How CD8+ T lymphocytes can induce inflammation in the nervous tissue of MS patients is also largely unknown. We have generated an animal model which spontaneously develops a neurological disease that is like MS. We have shown that the disease in these animals is caused by the activation of CD8+ T lymphocytes in the nervous tissue. The study of this animal model allowed us to identify several key aspects regarding the mechanisms by which the activation of CD8+ T lymphocytes in the nervous tissue can lead to injury of the nervous tissue and to better understand how the response of these CD8+ T lymphocytes that react against the nervous tissue is regulated.

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.

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.

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.

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.

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 formation. This is an important first step towards the development of better treatments for disorders in which this process is aberrant, such as in MS.

Steve Lacroix, Ph.D.

Université Laval, Québec City

\$253,178

(April 1, 2010 – March 31, 2012)

Dichotomous actions of the IL-1 system in MS

Multiple sclerosis (MS) is a chronic demyelinating disease that afflicts approximately 350,000 and 500,000 individuals in North America and Europe, respectively. The cause or causes of MS are still unknown, although viral infection, genetic predisposition, environmental factors, and autoimmunity are all considered as contributing factors in the etiology of the disease. Most researchers agree, however, 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, the cytokine interleukin-1, may also contribute to repair of the CNS. The main goal of this research proposal is to clarify how the positive and negative effects of IL-1 are mediated during MS, and to determine whether we can preferentially inhibit the negative effects of IL-1 without suppressing its beneficial actions.

Alan Peterson, Ph.D.

McGill University, Montréal

\$205,320

(April 1, 2010 – March 31, 2012)

Generation and characterization of a conditional model of interrupted myelinogenesis

When glial cells elaborate myelin sheaths around axons they activate and coordinately up-regulate genes encoding the numerous components necessary to build and stabilize myelin. By characterizing the mechanism that controls such gene expression, we hope to understand in more depth how myelin elaboration is

controlled during both early development and repair in the mature nervous system. The specific question we are asking was suggested by our recent finding that a protein required for cell movement also plays an essential role in spiral wrapping of membrane around axons during construction of a myelin sheath. Cells lacking a protein called N-WASp are able to surround axons normally but subsequently completely fail to perform the next steps required to synthesize myelin. Despite this dramatic disruption in normal nervous system development, mice missing this protein are remarkably stable and enjoy long life spans.

In addition to the essential role played by N-WASp in cell movement and myelin synthesis, this protein also participates directly in the mechanism controlling expression of several genes. In the nerves of our mice that lack all myelin, we evaluated the expression of the major myelin protein genes and found that all were significantly down regulated. Therefore, our investigation is designed to determine if the strikingly down regulated expression program of myelin genes is a secondary consequence arising in response to arrested myelin development or rather, as a direct effect of the missing protein on the regulation of myelin genes. Regardless of the result, it is our expectation that this investigation will lead to a much deeper understanding of both the components that participate in the mechanism controlling myelin gene expression as well as their functional organization.

Christopher Power, M.D.

University of Alberta, Edmonton

\$297,858

(April 1, 2009 – March 31, 2012)

Syncytin-1 and Endoplasmic Reticulum Stress in the Pathogenesis of Multiple Sclerosis

Over the past two years, my laboratory has been focused on identifying mechanisms by which the Multiple Sclerosis disease process occurs and progresses. To this end, we have identified a protein that became part of the human genome several million years ago which now appears to be activated inappropriately in brains of patients with MS to cause disease. We have characterized this protein together with investigating its effects on the nervous system and identifying a potential therapeutic strategy. A receptor for this protein also exhibits variability in MS for which we have dissected out individual mechanisms. These studies are yielding outcomes which may have potentially important implications for the understanding and treatment of Multiple Sclerosis.

Alexandre Prat, M.D., Ph.D.

**Research Centre of the University of Montréal Hospital Centre (CR-CHUM),
Montréal**

\$374,997

(April 1, 2009 – March 31, 2012)

Origin, Regulation and Function of Perivascular Dendritic Cells in MS

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 immune cells into the brain. The abundance of immune cells and their products found in MS lesions supports the concept that MS is an autoimmune disorder. The disease pathogenesis is attributed to autoreactive T lymphocytes whose receptors recognize sequences (small parts) of myelin processed by antigen-presenting cells (APCs). Thus, trafficking of those APCs through BBB is essential for lymphocyte activation within the brain. Our work focuses on understanding the molecular mechanisms which govern the migration of APCs across a competent BBB and to study the molecules which affect the survival and the maturation of such immune cells within the human brain. Previously, we have identified a population of APCs called myeloid dendritic cells who's responsible for the inflammatory profile of T lymphocytes. Recently, we have identified a second population of APCs called plasmacytoid dendritic cells (pDCs). Those pDCs are able to induce an anti-inflammatory profile from T lymphocytes and could potentially help to reduce MS lesions caused by inflammatory events occurring in the brain. By understanding the mechanism and the molecular events leading to the migration of those pDCs, we could promote their migration to the brain in order to develop an anti-inflammatory response. In a second part of our project, we identified an important and specific role for a novel adhesion molecule, Ninjurin-1, in the recruitment of APCs across BBB. Ninjurin-1 was identified on the vascular endothelium of the BBB, and its expression increases during an inflammatory context on the endothelial cells of the BBB, on the infiltrating APCs in human MS lesions and in the brain of the murine model of MS, the mice affected with experimental autoimmune encephalomyelitis (EAE). In addition, blockade of Ninjurin-1 in EAE reduces significantly clinical signs of the disease while blocking the entry to the brain of APCs. Thus our study uncovers an important cell-specific role for Ninjurin-1 in the transmigration of APCs across the BBB and further emphasizes the importance of APCs recruitment into the brain in the development of neuroinflammatory lesions.

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 inflammation 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 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.

Jacqueline Quandt, Ph.D.

University of British Columbia, Vancouver

\$210,660

(April 1, 2010 – March 31, 2012)

Anti-inflammatory and neuroprotective effects of TEMPOL in models of multiple sclerosis

Multiple sclerosis (MS) is the most common neurological disease of young adults in Canada. This disease is second only to trauma as the most debilitating. MS can cause loss of balance, impaired vision or speech, extreme fatigue and paralysis. However, disease presentation and course are largely unpredictable and may vary for each individual. Given only partially effective current therapies, therapies with immunomodulatory and neuroprotective capabilities have the greatest promise in treating and preventing this disease. Free radicals have been identified as major players during immune-mediated tissue damage in MS. TEMPOL is a multifunctional antioxidant able to scavenge and protect against free radical damage. We have shown that TEMPOL limits the incidence and reduces the severity of animal models of MS. TEMPOL may limit disease via a number of mechanisms, and we believe that TEMPOL may be acting to limit disease by influencing one of the following steps in the disease process:

1. preventing or reducing the generation of disease-causing cells
-

2. limiting blood-brain barrier alterations and entry of immune cells to the central nervous system (CNS); or
3. scavenging free radicals to limit tissue damage when given after the onset of clinical disease .

The proposed studies characterize the potential for TEMPOL to reduce tissue damage and enhance repair of tissues damaged by free radicals. These methods are novel therapies to treat MS. As well these studies will contribute to our understanding of free radical processes in the inflamed CNS.

To date we have shown that TEMPOL, when given orally, reduces the severity of an MS-like disease in animal models and can both prevent as well as treat established disease. TEMPOL does not interfere with the generation of myelin-reactive T cells in an animal model of MS. However, the ability of these cells to produce proteins including antibodies that are important in causing disease is indeed altered and is influencing their ability to cause damage. We have found that TEMPOL does not reduce the generation of antibodies to myelin proteins, however, the type of antibody which is generated is associated with an immunosuppressive response in animals rather than the disease-associated profile seen in control animals. Analysis of immune cells in cell culture shows TEMPOL at doses the same as those associated with therapeutic benefit reduces the ability of immune cells to respond and divide, however this response is not observed in all classes of immune cells. We have shown that TEMPOL is safe in vivo and also for both immune cells as well as cells which form blood vessels at the doses being studied. Importantly, TEMPOL reduces the entry of immune cells into the nervous system in a model of MS and also lessens the degree of damage to axons of nerve cells and in this regard is serving as a neuroprotectant. We continue to explore the anti-inflammatory and neuroprotective properties of TEMPOL as a novel therapeutic in several models of MS to better understand its mechanism of action.

Stéphane Richard, Ph.D.

Lady Davis Research Institute, Jewish General Hospital, Montréal

\$319,080

(April 1, 2009 – March 31, 2012)

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 progenitor 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.

Serge Rivest, Ph.D.

Université Laval, Québec City

\$203,914

(April 1, 2010 – March 31, 2012)

Therapeutic potential of a new subset of macrophages in animal models of MS.

Macrophages are important cells of the innate immune system, which essentially phagocyte bacteria and toxic elements from the organism. Despite having the same origin, circulating monocytes and tissue macrophages encompass a wide range of phenotypically and functionally distinct sub-populations. The project proposed here builds on results obtained by our group showing that these immune cells can be driven into new subpopulations of macrophages with neuroprotective properties. When transplanted into a mouse model of MS, these cells were found to decrease disease severity. Our general hypothesis is that monocytes, when exposed to specific cytokines, cells, and/or drugs, can be driven into macrophage subsets with a specific genetic profile that allows these cells to be immunosuppressive and neuroprotective in models of demyelinating disease such as MS/EAE. We therefore propose to further characterize these immune cell subsets and identify the cellular and molecular mechanisms that these cells employ to prevent demyelination and/or improve remyelination. These experiments will be undertaken to test the therapeutic potential of these cells in different models of MS and generate important data for their potential therapeutic applications.

We previously demonstrated that bone marrow-derived monocytes/macrophages (BMDM) have neuroprotective and neuroregenerative effects in mouse models of Alzheimer's disease (AD), brain cancer, amyotrophic lateral sclerosis (ALS), and peripheral nerve and spinal cord injury (SCI). We recently found that intravenous delivery of a new subset of macrophages, called IFN-gamma-stimulated monocyte-derived cells (IFN- γ -M ϕ C) decreased disease severity in EAE mice. Further studies using these cells revealed that IFN- γ -M ϕ C preferentially migrate to inflammatory sites and suppress inflammation. Notably, IFN- γ -M ϕ C have the ability to polarize naive T cells into CD4⁺CD25⁺Foxp3⁺ T regulatory cells (Tregs). The importance of Tregs in limiting neuronal damage has also been well documented in MS and its EAE animal model. Also of particular relevance to the present proposal is the recent demonstration that transplantation of macrophages treated with the FDA-approved drug glatiramer acetate (GA) has the ability to reverse established EAE by inducing the formation of M2-like macrophages that produced anti-inflammatory cytokines and polarized T cells toward Th2 and Tregs. Together, these results suggest that it

may be possible to drive monocytes toward potentially beneficial macrophage subsets and be used as a new treatment for MS.

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.

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 use 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 allows 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.

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.

Luc Vallières, Ph.D.

Université Laval, Québec

\$221,460

(April 1, 2010 – March 31, 2012)

Recruitment of monocytes into the brain: regulation by pertussis toxin

We have identified a new population of leukocytes that patrol the cerebral blood vessels by crawling on their interior surface. These cells are recruited in greater numbers when stimulated with the bacterial toxin lipopolysaccharide (LPS) through a mechanism involving a protein called angiopoietin-2. In the present project, we found that the population of crawling leukocytes, consisting mainly of granulocytes, is also increased in the brains of mice suffering from experimental autoimmune encephalomyelitis (EAE) or injected with pertussis toxin (PTX), which is commonly used to induce EAE. However, this recruitment occurs through an alternative

mechanism, independent of angiopoietin-2. In a series of experiments, we found that PTX acts indirectly on blood vessels in part through the signalling molecule interleukin-6, which is essential for increasing the levels of the adhesion molecule ICAM1 and a chemokine. We also found that granulocytes adhere to brain blood vessels through the interaction of integrin alphaM with ICAM1. Remarkably, blocking the chemokine with a neutralizing antibody delays and reduces the clinical symptoms of EAE. In conclusion, this study supports the concepts that granulocytes play a previously unsuspected role in EAE and that environmental toxins might promote multiple sclerosis, at least in part, by inducing vascular changes necessary for the recruitment of these cells. By clarifying the molecular mechanism by which granulocytes are recruited at the blood-brain interface, this study led to the identification of a chemokine as a new potential therapeutic target for multiple sclerosis.

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.

Alan Wilman, Ph.D.

University of Alberta, Edmonton

\$193,256

(April 1, 2010 – March 31, 2012)

Application of High Field MRI to Multiple Sclerosis

MRI, or Magnetic Resonance Imaging, has been used in Multiple Sclerosis (MS) for many years. However, the relationship between what is seen on MRI and clinical symptoms of the patient is not particularly strong. There is a need to develop more

specific MRI methods that target new and evolving theories of MS. Traditional MRI methods and traditional thinking on MS need to be augmented with active research into new MRI methods and new understanding of the MS disease process. Our research grant funded by the MS Society uses new highly-resolved and iron-sensitive quantitative MRI methods to provide a new window of visibility into the MS brain. The advanced MRI methods have been developed on a special triple-strength MRI scanner. We are applying these methods in three ways: first, to visualize previously MRI-invisible lesions, second, to determine the iron dependence in deep grey matter and third, to validate the methods in postmortem studies.

In the first year of this grant, we have focused on acquiring the MRI scans on different patient groups. For the study of deep grey matter, 25 MS patients with early relapsing-remitting MS and 25 age and sex matched healthy control subjects have been studied. In this study we are comparing the iron content in deep grey matter by making individual measurements in each functional area using 3 separate MRI methods that provide independent measures of tissue iron. Analysis from this study finds that key areas deep in the brain including the thalamus and putamen exhibit higher iron content in early relapsing-remitting MS patients than in healthy controls. This is an intriguing finding that suggests substantial changes in the deep grey matter in the early phases of MS.

For the study of MS lesions, to date we have been following 13 MS patients with monthly or bimonthly MRI scans in order to track the evolution of MS lesions using both standard and our new advanced MRI techniques. In this study we build on our past work that demonstrated that a number of MS lesions previously invisible to MRI can be seen with new advanced MRI methods. Our purpose now is to relate changes in these newly visible lesions to patient symptoms in order to determine the importance of these lesions in quantifying the clinical status of the patient.

For the post-mortem validation studies, we have studied 3 MS patients after death, where we compare the MRI findings to histological measures. These studies enable us to validate the MRI measures because the MRI is directly compared to the physical observation by a pathologist. Our findings to date indicate that the new MRI measure called phase susceptibility is sensitive to both iron and myelin in lesions, and is dominated by iron in deep grey matter. In summary, in our first year of funding, we are making advances in the use of advanced MRI methods to gain a greater understanding of MS lesions and deep grey matter changes in MS patients.

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.

Anthony Feinstein, Ph.D.

Sunnybrook Health Sciences Centre, Toronto

\$134,929.50

(April 1, 2010 – March 31, 2012)

Detecting cognitive dysfunction in patients with Multiple Sclerosis: assessing the validity of a computerized battery

Cognitive dysfunction affects 40-60% of MS patients and exerts a negative effect on employment, social relationships and quality of life. Many MS patients are not tested for cognition given limited resources, particularly neuropsychological expertise. The aim of the present study is to develop a computerized battery of cognitive tests that can be easily administered by clinic staff, i.e. nurses, occupational therapists etc and to demonstrate that these tests are both valid indicators of cognitive impairment. If successful, these computerized tests will be made available to MS clinics throughout Canada.

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.

Anthony Traboulee, Ph.D.
University of British Columbia, Vancouver

\$51,775

(April 1, 2011 – March 31, 2012)

Improving Safety Monitoring and Design of Future Multiple Sclerosis Clinical Trials

MS results in areas of inflammation throughout the brain and spinal cord, causing damage and scarring (lesions). Often this damage occurs without symptoms but can be easily detected with magnetic resonance imaging (MRI). Repeated contrast-enhanced MRI allows researchers and clinicians to routinely monitor the brain for evidence of ongoing inflammation. This approach is used in clinical trials (drug studies) to determine if a new therapy is effective and safe. MRI studies are costly and have limited availability at many centres across Canada. At the UBC MS/MRI Research Group, we have been collecting information about new MS lesion development from MRI studies for the past 20 years. We are continually developing new statistical tools to analyze data from tens of thousands of MRIs. These tools will allow us to develop better protocols to detect potential safety risks of unproven therapies, minimize the number of patients exposed to unproven therapies, and reduce the number of MRI scans needed during the trial. Our research aids in the development of better therapies through more efficient and safer clinical trial design. We believe that this will be an important contribution to the search for a cure for MS.

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 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.

FOUNDATION AWARDS

Brenda Banwell, M.D., Hospital for Sick Children, Toronto
Amit Bar-Or, M.D., Montreal Neurological Institute, Montreal
Dessa Sadovnick, Ph.D., University of British Columbia, Vancouver
Douglas Arnold, M.D. , Montreal Neurological Institute, Montreal
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.

Mark Freedman, M.D., Ottawa Hospital Research Institute, Ottawa
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.

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.

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, 2009 – June 30, 2012)

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, 2009 – June 30, 2012)

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 FELLOWSHIPS

RECIPIENT	SUPERVISOR	INSTITUTION	PROJECT TITLE
Dr. Sura Alwan	Dr. Dessa Sadovnick	The University of British Columbia	A North American multiple sclerosis pregnancy registry
Dr. Vladimir Bamm	Dr. George Harauz	University of Guelph	Interrelationships between phosphorylation and citrullination in 18.5 kDa MBP and their effect on calmodulin binding and on interactions with actin, tubulin and divalent metal cations
Dr. Lindsay Berrigan	Dr. John Fisk	Dalhousie University	An investigation of the impact of mental health comorbidity on cognitive functioning and health outcomes in MS
Dr. Robert Brown	Dr. Douglas Arnold	McGill University	Longitudinal analysis of demyelination and remyelination in multiple sclerosis
Dr. Zhihong Chen	Dr. Bruce Trapp	Cleveland Clinic	Neuroprotective effect of LPS-preconditioned microglia
Dr. Ajit Dhaunchak	Dr. David Coleman	McGill University	Role of tmem10 and tmeff2 in myelination and CNS development
Dr. Debra Fulton	Dr. Alan Peterson	McGill University	Identification and validation of the transcription factor binding sites and transcription factor cooperativity relationships that control expression of myelin-associated genes in

			oligodendrocytes
Dr. Georgina Galicia-Rosas	Dr. Jennifer Gommerman	University of Toronto	Evaluating the mechanism of action of LTBR-Ig in EAE
Dr. Steve Gendron	Dr. Alexandre Prat	Centre de recherche du CHUM	Role of integrin alpha8beta1 and semaphorin/plexin in multiple sclerosis
Dr. Alan Gillett	Dr. Peter van den Elzen	The University of British Columbia	The effect of apoE variants on lipid antigen presentation and T cell activation in multiple sclerosis
Dr. Jeffery Haines	Dr. Patrizia Casaccia	Mount Sinai School of Medicine	Roles of n-cofilin, LIM kinase and slingshot phosphatase in oligodendrocyte myelination and remyelination
Dr. Dong Han	Dr. Timothy Kennedy	McGill University	Mechanisms regulating the formation and maintenance of CNS myelin
Dr. Sarah Haylock-Jacobs	Dr. V. Wee Yong	University of Calgary	Expression, immunologic functions and pro-repair properties of chondroitin sulfate proteoglycans in EAE and MS
Dr. Andrew Jarjour	Dr. Charles ffrench-Constant	University of Edinburgh	Investigating the role of polarity complex in oligodendrocyte development, myelination, and remyelination
Dr. Elaine Kingwell	Dr. Helen Tremlett	The University of British Columbia	Survival and predictors of mortality in the British Columbian multiple sclerosis population

Dr. Soo Yuen Leong	Dr. Jack Antel	McGill University	Characterisation and functional analysis of pre-myelinating O4(+) oligodendrocyte progenitor cells from human brain
Dr. Sébastien Lévesque	Dr. Steve Lacroix	Université Laval	Dichotomous actions of the IL-1 system in MS
Dr. Veronique Miron	Dr. Charles ffrench-Constant	University of Edinburgh	Identification of inflammatory cytokines that promote oligodendrocyte-mediated myelination and remyelination: implications for multiple sclerosis
Dr. Lyndsay Murray	Dr. Rashmi Kothary	University of Ottawa	MicroRNA regulation of remyelination
Dr. Jiwon Oh	Dr. Peter Calabresi	John Hopkins University	7-Tesla MRI correlates of cognitive dysfunction in multiple sclerosis (MS)
Dr. Olga Rojas	Dr. Jennifer Gommerman	University of Toronto	Evaluating novel B cell effector functions in EAE/MS
Dr. Afsaneh Shirani	Dr. Helen Tremlett	The University of British Columbia	Temporal changes in disability progression and demographics in multiple sclerosis
Dr. Kenrick Vassall	Dr. George Harauz	University of Guelph	Proline isomerization and misincorporation in myelin proteins
Dr. Emilie Viel	Dr. Nathalie Arbour	Centre hospitalier de l'Université de Montréal	The intracellular functions of CD146 in immune cells in the context of MS

Dr. Yunling Wang

Dr. Stéphane
Richard

McGill
University

Characterizing the link
between miRNAs and the
QKI proteins in
oligodendrocytes.

RESEARCH STUDENTSHIPS

Ph.D. Studentship

RECIPIENT	SUPERVISOR	INSTITUTION	PROJECT TITLE
Bravina Balachandar	Dr. Christine Till	York University	Neural correlates of cognitive impairment in childhood acute disseminated encephalomyelitis (ADEM)
Erik Bélanger	Dr. Daniel Côté	Université Laval	In vivo evaluation of MS-like lesions with nonlinear microscopy
Elodie Brison	Dr. Pierre Talbot	INRS-Institut Armand-Frappier	From respiratory disease to multiple sclerosis-like disability: importance of the spike protein of human respiratory coronavirus OC43
Zografos Caramanos	Dr. Douglas Arnold	McGill University	The use and utility of quantitative magnetic resonance imaging at describing neuropathology and predicting future disability in patients with multiple sclerosis
Chelsea Davidson	Dr. Deborah Burshtyn	University of Alberta	Potential role of LILRB2 and LILRB1 immune receptors in disease progression of MS
Miguel De Avila	Dr. George Harauz	University of Guelph	Myelin basic protein interactions with SH3 domains
Marcio De Paula	Dr. Guillermina Almazan	McGill University	Role of IGF-1 signalling in oligodendrocyte development, myelination and remyelination

Trisha Finlay	Dr. Shalina Ousman	University of Calgary	The role of alphaB-crystallin in oligodendrocyte function.
Rezwan Ghassemi	Dr. Douglas Arnold	McGill University	MRI measures of brain injury in children with MS
Nicolas Guizard	Dr. Louis Collins	Montreal Neurological Institute	Brain atrophy quantification and trajectory in MS patients
Lamia Naouel Hachehouche	Dr. Alexandre Prat	Centre hospitalier de l'Université de Montréal	IL-26 and IL-26R in multiple sclerosis
Constantina Lafoyiannis	Dr. Brenda Banwell	The Hospital for Sick Children	Optical coherence tomography, MRI outcomes and cognition in pediatric multiple sclerosis
Dr. Catherine Larochelle	Dr. Alexandre Prat	Centre hospitalier de l'Université de Montréal	MCAM implication in blood-brain barrier endothelial cells activation and interaction with immune cells in the context of MS
Joshua Lee	Dr. Dessa Sadovnick	The University of British Columbia	Multiple sclerosis in Asians: the genetic, environmental, and epigenetic determinants of variable clinical profile and susceptibility to MS
Ellen Meng-I Lu	Dr. Helen Tremlett	The University of British Columbia	Adverse obstetric and neonatal outcomes in multiple sclerosis
John-Paul Michalski	Dr. Rashmi Kothary	Ottawa Health Research Institute	A role for integrin-linked kinase in oligodendrocyte mediated myelination of the central nervous system

Camille Olechowski	Dr. Bradley Kerr	University of Alberta	Dysregulated glutamate transporter function as an underlying cause for neuropathic pain in multiple sclerosis
Ryan O'Meara	Dr. Rashmi Kothary	Ottawa Health Research Institute	The role of integrin-linked kinase in oligodendrocyte development
Natalia Pikor	Dr. Jennifer Gommerman	University of Toronto	Dissecting immune function and gene alterations in chronic versus relapsing EAE
Camille Pittet	Dr. Nathalie Arbour	Centre hospitalier de l'Université de Montréal	Potential immunoregulatory roles of programmed cell death-1 ligands in human central nervous system
Matthew Quinn	Dr. Ravi Menon	The University of Western Ontario	Towards detection of grey matter lesions in multiple sclerosis using high-field magnetic resonance imaging techniques
Jean-François Richard	Dr. Luc Vallières	Université Laval	Role of the granulocytes recruitment in a mouse model of multiple sclerosis
Monica Roy	Dr. Luc Vallières	Université Laval	Identification of chemokines involved in the intracerebral recruitment of leukocytes
Bretta Russell-Schulz	Dr. Alex MacKay	The University of British Columbia	Relationship between myelin water fraction and electrophysiology of white matter within the corpus callosum and the corticospinal tract in MS patients

Graham Smith	Dr. George Harauz	University of Guelph	Investigating cytoskeletal interactions of myelin basic protein in developing oligodendrocyte cells
Wulin Teo	Dr. Peter Stys	University of Calgary	Cellular and molecular mechanisms of axon spheroid formation in an ex-vivo model of axonal injury
Jonathan Thiessen	Dr. Melanie Martin	University of Manitoba	Correlation of myelin content to quantitative magnetic resonance imaging parameters
Li-Chun Wang	Dr. Guillermina Almazan	McGill University	Role of Cdo in p38alpha/beta MAPK regulation of oligodendrocytes differentiation and myelination
Magdalena Wojtowicz	Dr. John Fisk	Dalhousie University	Functional and structural neural correlates of cognitive functioning in multiple sclerosis
Xiaojun Xie	Dr. Vanessa Auld	The University of British Columbia	Characterization of integrins in Drosophila glial cells
Monan (Angela) Zhang	Dr. Shannon Dunn	University of Toronto	Understanding sex differences in multiple sclerosis (MS): Sexually dimorphic role for peroxisome proliferator-activated receptor alpha (PPAR α) in dampening pathogenic T helper 1 (Th1) responses in humans and mice

M.Sc. Studentship

RECIPIENT	SUPERVISOR	INSTITUTION	PROJECT TITLE
Michael Keough	Dr. V. Wee Yong	University of Calgary	Altering the microenvironment to promote remyelination
Antonia Kobert	Dr. Amit Bar-Or	McGill University	Effects of glial-cell derived factors on MS-relevant B-cell responses
Alma Mohebiany	Dr. Nathalie Arbour	Centre hospitalier de l'Université de Montréal	Establishing the in vivo contribution of interleukin-15 to the pathogenesis of multiple sclerosis and its animal models
Sarah Neil	Dr. Jacqueline Quandt	The University of British Columbia	Characterizing the anti-inflammatory effects of TEMPOL in an animal model of multiple sclerosis
Alexandre Paré	Dr. Steve Lacroix	Université Laval	Role of neurotrophin-producing immune cells in animal model of MS
Marina Sonkin	Dr. Brenda Banwell	The Hospital for Sick Children	The role of diffusion tensor MRI in improving differentiation between multiple sclerosis and ADEM in pediatrics
Afiqah Yusuf	Dr. Lisa Koski	McGill University	Linking cortical excitability with fatigue using a multimodal approach
Fatma Zaguia	Dr. Jack Antel	McGill University	Role of HLA-E expression by oligodendrocytes in MS pathogenesis