

MS Research Summaries 2010

MS Society of Canada



CONTENTS

BIOMEDICAL RESEARCH GRANTS	3
CLINICAL AND POPULATION HEALTH RESEARCH GRANTS	22
FOUNDATION AWARDS	25
PILOT GRANTS	32
DONALD PATY CAREER DEVELOPMENT AWARDS	33
POST-DOCTORAL FELLOWSHIPS	34
STUDENTSHIPS	37

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.

Jack Antel, M.D.

McGill University, Montréal

\$236,500

(April 1, 2009 – March 31, 2011)

Cellular Immune Injury of Human Oligodendrocytes

The neurologic disorder multiple sclerosis (MS) involves injury and destruction of the myelin membranes that ensheath nerve fibers (axons) and that are required for efficient electrical conduction with the central nervous system (CNS). The nerve fibers themselves are also subject to injury even early in the disease process. Such injury is mediated by components of the immune system that enter the CNS during the disease course. Our studies are aimed at defining the basis for the injury of myelin or its cell of origin the oligodendrocyte (OLs) and of the nerve cells and their processes. Our ongoing work indicates that the properties of both the immune cells that mediate the injury and the neural cells are themselves modified by the microenvironment that exists in the inflamed CNS, resulting in novel mechanisms of neural cell injury. We will use human immune cells and CNS derived cells to help define the mechanisms underlying the injury process. We are specifically focusing on mechanisms that are associated with a component of the immune system termed the innate immune system. We hope our studies will provide insights that will lead to therapies that will protect from injury and promote tissue repair in multiple sclerosis.

Jack Antel, M.D.

McGill University, Montréal

\$233,200

(April 1, 2009 – March 31, 2011)

Microglia as Regulators of the Immune Response in the Central Nervous System

The lesions in the central nervous system (CNS) that underlie the clinical events in multiple sclerosis (MS) are caused by components of the immune system that enter the CNS and induce injury. The cells that lead this entry are the T lymphocytes of the immune system. For these cells to enter, persist, and be activated, they must receive signals from cells of another part of the immune system, termed the innate immune system. The latter include the microglia, a resident cell type within the normal CNS.

Specialized cells of the innate immune system also reside around the blood vessels of the CNS. Under conditions of inflammation as in MS, a further innate population termed macrophages enters the CNS from the blood. Our work aims to understand what capacity each of these different innate immune cells has to support immune activity that is ongoing in the CNS during MS, how their properties are influenced by signals coming from tissue injured in the MS process, and what therapeutic agents could be used to control unwanted activity. Our studies are conducted using human cells and tissues in order to make the work most relevant to understanding the MS disease process.

Nathalie Arbour, Ph.D.

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

\$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 potentiates 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

\$240,000

(April 1, 2009 – March 31, 2011)

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

\$264,350

(April 1, 2008 – March 31, 2011)

Imaging Demyelination and Remyelination in Multiple Sclerosis

Multiple Sclerosis (MS) is an inflammatory demyelinating disease in which failure of myelin repair is associated with the accumulation of neurological impairment and disability. Researchers around the world are working to find ways of enhancing the normal mechanisms of myelin repair in the body, and to develop methods for transplanting stem cells in the nervous system to generate new myelin. Development of these future therapies for use in patients with MS will require clinical trials to assess whether they work. To do this, it will be necessary to measure remyelination of MS lesions in patients.

Two of the most promising methods involve advanced MRI scans that measure either the transfer of magnetization from molecules in myelin or the amount of water trapped in myelin. However, before these techniques can be used in clinical trials, they require validation to prove that they provide reliable measures of remyelination. In the first year of this 3-year project, we have been working on speeding up these lengthy examinations. We now will start to perform these advanced MRI scans in MS patients who died and consented before death to undergo post-mortem MRI followed by pathological examination. Having both the MRI and the pathology will allow us to determine how the findings on MRI relate to the amount of myelin in the lesions.

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 has a protective effect. The protein that binds estrogen in cells (estrogen receptor) can be located in both the nucleus and the cell membrane. 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 plan to determine the effect of 17alpha-estradiol and other estrogens on the development of OLs, their rate of migration, and their rate of myelination and remyelination of nerve axons, using cultured cells and brain tissue.

Andrew Chojnacki, Ph.D.

University of 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

\$279,431

(April 1, 2008 – March 31, 2011)

Role of Prostaglandins D₂, E₂, and their Receptors in EAE

We have discovered that 4 members of a family of enzymes called phospholipase A₂ (PLA₂) play differing roles in either triggering the onset, progression or remission phases of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. This was discovered using a number of novel compounds that selectively block these PLA₂s. These compounds are currently being further developed for therapeutic use in MS. In addition to this work, PLA₂s are also known to regulate the production of prostaglandins via the cyclooxygenase-1 and 2 (COX-1 and 2) enzymes.

Prostaglandins can have either pro-inflammatory or protective effects depending on the type of receptors they bind to on the surface of cells. Currently there is no work done so far on the various prostaglandin receptors and their role in MS. This proposal is to extend our studies on PLA₂ to assess the expression and role of various prostaglandins and their receptors in EAE in mice. This work can be expected to provide important information that could lead to the development of novel compounds for the treatment of MS.

In the past year of this 3-year grant, we have carried out much of the first aim that we proposed to do, namely to study the expression of the enzymes that synthesize PGD₂ and PGE₂ as well as their various receptors (DP₁, DP₂, EP₁, EP₂, EP₃, EP₄) and the various cell types, both immune and CNS cells, that express these molecules. This work now sets the stage for the next part of this work to be done in the coming year.

Shannon Dunn, Ph.D.

University of Toronto, Toronto

\$221,224

(April 1, 2009 – March 31, 2011)

PPARalpha as a Mediator of Sex Differences in Autoimmunity

Multiple Sclerosis (MS) is an autoimmune disease where the individual's own immune system goes awry and mounts attacks on myelin in the brain and spinal cord. Myelin is the protective coating on nerves that enables them to conduct signals from the brain to other parts of the body. When myelin is destroyed, nerve conduction is

disrupted, resulting in such symptoms as muscle weakness, blindness, loss of sensation, and cognitive dysfunction.

For reasons that are unclear, MS affects women three times more often than men. The goal of our research program is to determine the underlying reasons for sex-based differences in the prevalence of MS. To this end, we conduct studies using the animal model of MS, experimental autoimmune encephalomyelitis (EAE). Previous work by our group and others has revealed that sex differences in the development of EAE may relate in part to the ability of male sex hormones (androgens) to dampen the activity of myelin-reactive T cells. Additionally, we have made progress towards identifying the genes that mediate the effects of androgens on the immune response. Our studies have shown that male sex hormones induce the expression of Peroxisome Proliferator-Activated Receptor alpha (PPARalpha) in T cells and that this gene has suppressive effects on the activity of these cells.

The major objective of our research is to study in more depth the mechanism of how male sex hormones limit the activity of myelin-reactive T cells in EAE and to test the hypothesis that these hormones suppress the activity of T cells by increasing the expression of PPARalpha. This research will provide insights into why females preferentially develop MS. Moreover, elucidation of the molecular mechanism of how male sex hormones dampen the immune response may lead to the discovery of new targets for drug development.

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 how PPARs work to inhibit EAE. First we will define where (what cells) these molecules function. Next, we will investigate whether EAE gets better when the activity of PPARs is increased. Finally, we will investigate the mechanism by which these PPARs inhibit IL-12p40, a cytokine that has a known function in spurring the inflammatory response in EAE.

Eleanor Fish, Ph.D.

Toronto General Research Institute

\$252,650

(April 1, 2009 – March 31, 2011)

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

IFN- β therapy has been effective in treatment of MS, where it is clinically proven to reduce relapse rates and lesion formation. Despite a long history of efficacy, the mechanism of action of IFN- β therapy is not understood. Therefore, we used animals lacking the IFN- β gene in an experimental model of MS to further understand the role of IFN- β . IFN- β negative animals are more susceptible to the induction of MS and had higher levels of specific subsets of inflammatory cells, CD4 and CD11b cells, in their brains. This correlated with higher levels of the chemicals that recruit these cells in the serum of IFN- β negative animals. Autoreactive CD4 cells initiate MS and we observed an increase in the generation of CD4 cells in animals lacking IFN- β . Recently, a subpopulation of CD4 cells, known as Th17 cells, have been shown to initiate MS. IFN- β negative mice have higher levels of Th17 cells during MS, suggesting that IFN- β suppresses the formation of the cells that initiate disease. IFN- β treatment reduces the expression of specific cytokines and growth factors known to drive the formation of Th17 cells. Taken together, our data suggests that IFN- β therapy may not only suppress the immune system but may also suppress the formation of cells that trigger MS.

Paula Foster, Ph. D.

Robarts Research Institute, London

\$209,956

(April 1, 2009 – March 31, 2011)

The Use of Cellular MRI to Evaluate Stem Cell Transplantation in a Model of Multiple Sclerosis

Stem cell transplantation is being assessed as a potential treatment for patients with severe multiple sclerosis. There are still many questions about how these transplants should be performed to achieve the best outcome. Animal models of multiple sclerosis are being used to test this form of therapy. It is difficult to assess the fate of transplanted stem cells with the commonly used techniques, that typically look at the stem cells in the tissues, using a microscope, at the end of the study. We have developed imaging techniques which allow stem cells to be detected in live animals and monitored over time. This new form of imaging is called cellular magnetic resonance imaging (MRI). In this project we will use cellular MRI to monitor the fate of transplanted stem cells in the spinal cord of mice with a form of multiple sclerosis. Our goal is to determine the most effective stem cell transplantation protocols for promoting repair and recovery by addressing important questions such as where, when and how many stem cells to transplant.

Alyson Fournier, Ph.D.

Montréal Neurological Institute, McGill University

\$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. 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

Multiple sclerosis (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. How CD8+ T lymphocytes can induce inflammation in the nervous tissue of MS patients is largely unknown. We have generated an animal model which spontaneously develop 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 will allow us to dissect the mechanisms by which the activation of CD8+ T lymphocytes in the nervous tissue can lead to injury of the nervous tissue. This will help us to better understand MS and develop new therapeutic approaches.

Jennifer Gommerman, Ph.D.

University of Toronto

\$408,335

(April 1, 2010 – March 31, 2013)

Understanding the role of TNF super-family members in EAE/MS pathology

Multiple Sclerosis (MS) is an autoimmune disease whereby lymphocytes attack elements of the central nervous system. 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 and CD40 pathways as they represent important means of regulating dendritic cell function. In addition, we know that inhibitors of these pathways 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 to treat MS.

Tim Kennedy, Ph.D.

McGill University, Montréal

\$311,718

(April 1, 2008 – March 31, 2011)

Netrin Function in the Development of Axonal-Oligodendroglial Interactions

Oligodendrocytes make myelin in the CNS and are lost in demyelinating diseases such as multiple sclerosis. We have discovered that a protein named netrin-1 directs oligodendrocyte precursor cell migration towards axons in the embryo. Oligodendrocyte precursor cells must express a receptor for netrin-1 called DCC to respond appropriately. We also reported that netrin-1 and DCC are expressed by myelinating oligodendrocytes in the adult nervous system, leading us to think that they have an important function in the adult brain. Using cell culture, we have obtained evidence that the organization of specialized sites of contact between oligodendrocytes and axons, called paranodal junctions, are severely disrupted in the absence of netrin-1 and DCC.

The studies we propose aim to accomplish the following three goals.

1. To determine if netrin-1 and DCC are essential for axonal-oligodendroglial paranodal junctions made in the brain and spinal cord.
2. To determine if netrin-1 and DCC contribute to remyelination.
3. To identify the proteins that work with netrin-1 and DCC at axonal-oligodendroglial paranodal junctions.

These studies aim to better understand oligodendrocytes, with the goal of identifying means to promote remyelination.

Bradley Kerr, Ph.D.

University of Alberta, Edmonton

\$148,912

(April 1, 2009 – March 31, 2011)

Examining Novel Targets to Treat Neuropathic Pain in Multiple Sclerosis: The Glutamate Transporters

Chronic pain has a major effect on the quality of life of patients with MS.

"Neuropathic" pain, which arises when there is injury or disease in the nervous system, is the most prevalent and difficult to treat pain syndrome seen in MS patients. Unfortunately, there are few effective treatments to relieve neuropathic pain in MS because little is known about its underlying causes.

Two important neurotransmitters that are necessary for proper communication between cells in the nervous system are the amino acids glutamate and aspartate. If their levels are too high, cells can become overexcited which leads to errors in the way they process information. In these instances, signals from the environment such as light touch on the skin may be interpreted as painful.

Glutamate transporters are important for controlling the levels of glutamate and aspartate that are made available to a cell. Our experiments will test specific drugs that affect glutamate transporter function and assess how they influence neuropathic pain in an animal model of MS. Our studies will provide much needed insight into the underlying causes of chronic pain in MS and will assess a potentially important target for the treatment of neuropathic pain in this disease.

Rashmi Kothary, Ph.D.

Ottawa Health Research Institute

\$304,320

(April 1, 2008 – March 31, 2011)

Integrin Linked Kinase and CNS Myelination

Multiple Sclerosis 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 around the axons is

the oligodendrocyte. This cell has to undergo many changes prior to being able to myelinate the axons. Our research is directed towards understanding the molecular mechanisms involved in this process. We have focused our efforts on proteins, called integrins, at the surface of the oligodendrocytes. These proteins serve as important mediators of bidirectional signals between the extracellular milieu and the intracellular machinery. These signals will dictate when and how the oligodendrocyte will elaborate the extensive membranes necessary for proper myelination of axons. An important downstream node is the integrin linked kinase (ILK). Our goal is to determine the role that integrins and ILK play in myelination, and to uncover the specific signaling pathways implicated in this process. This is an important first step towards the development of better treatments for Multiple Sclerosis.

Steve Lacroix, Ph.D.

Université Laval, Québec

\$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.

Wayne Moore, M.D.

University of British Columbia, Vancouver

\$355,936

(April 1, 2008 – March 31, 2011)

The Pathologic Basis of Magnetic Resonance Imaging in Multiple Sclerosis

Magnetic Resonance Imaging (MRI) is a very sensitive technique for detecting the focal abnormalities (plaques) in multiple sclerosis (MS). In recent years, MRI studies have detected subtle abnormalities in the brain and spinal cord in a more widespread distribution, which may well be the basis for disease progression. It is unclear as to what changes in the brain tissue are causing these diffuse MRI abnormalities. However, our research suggests that only certain molecular components of myelin are reduced in some of these areas, in contrast to the plaque wherein all myelin components are lost. High field strength MRI scanners are showing even more detail than earlier generation machines. This project will examine brain tissue, imaged at high field strength, to define the changes in the tissue in these ill-defined regions, to determine how they are related to the formation of new plaques and how they may be responsible for the subtle diffuse changes seen on the MRI. These areas will be examined for loss of the various components of myelin, loss of axons, and disruption of blood vessel integrity. The findings will aid in understanding how and where a MS plaque develops and factors responsible for progression of the disease.

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

Myelin sheaths play an essential role in the function and integrity of the nervous system. In diseases like MS, myelin is lost in the central nervous system altering the transmission of electrical signals. Also, axons that form the essential pathways over which such signals travel can be permanently damaged. We have built and are characterizing a model in the mouse that blocks myelin formation in peripheral nerves. It is providing novel insights into changes in cell structure and gene expression programming that occur in the myelin forming cells in peripheral nerves in response to this disruption of normal development. In this proposal, we will modify specific components of this experimental system so that similar disruptions in myelin formation and maintenance can be imposed on the cells that elaborate myelin in the central nervous system. These modifications also will extend experimental control to the timing at which disrupted elaboration or maintenance of myelin occurs. It is our expectation that this new model will lead to important insights into how myelin-forming cells develop and maintain myelin sheaths. In addition, we expect this model will be valuable for testing therapeutic strategies designed to stabilize mature myelin or promote recovery following myelin loss.

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

Multiple sclerosis is a common neurological disease that appears to be caused largely by dysregulation of the immune system leading to a range of physical disabilities. 8% of the human genome is comprised of retroviruses that have been accumulated over millions of years. My laboratory has shown that under selective immune conditions a particular retroviral protein, Syncytin-1, is highly induced in glial cells of brains from patients with MS. Indeed, we have also demonstrated Syncytin-1 contributes to immune activation and damage to myelin producing cells in cell culture as well as in an animal model. In the present proposal, we intend to define the specific form of Syncytin-1 that causes neurological disease. In addition, we will also use unique tools based on RNA interference strategies to regulate the expression of the receptor for Syncytin-1 with the long-term goal of identifying its contribution to disease progression in multiple sclerosis. Lastly, we have developed a new transgenic mouse that expresses Syncytin-1 in which we will study a novel and fundamental cellular mechanism of cellular damage termed endoplasmic reticulum (ER) stress in MS together with potential (therapeutic) modulators of ER stress. Hence, this proposal addresses a burgeoning question regarding the role of viruses in multiple sclerosis while at the same time also developing new tools to understand immune and neurological disorders.

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

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

\$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 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 inflammatory diseases directed to the brain. We intend to understand the molecular mechanisms which govern the migration of monocytes across a competent BBB and to study the molecules which affect the survival and the maturation of such immune cells within the human brain.

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

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

\$330,000

(April 1, 2008 – March 31, 2011)

Novel Adhesion Molecules of the Blood-Brain Barrier Regulating Central Nervous System Inflammation

Immune cells travel from the blood to local inflammatory sites where they initiate and maintain tissue-specific immune responses. 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 the central nervous system (CNS) disorder multiple sclerosis (MS), a large number of immune cells known as TH1 and TH17 lymphocytes readily cross the BBB to infiltrate the brain and eventually lead to the formation of lesions. The movement of immune cells from the blood to the CNS is orchestrated by many factors, including cell adhesion molecules (CAMs) that enable immune cells to adhere and cross over the BBB. We have identified ALCAM (for Activated Leukocyte Cell Adhesion Molecule) 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, second only to trauma as the most debilitating. Given only partially effective current therapies, those with immunomodulatory and neuroprotective capabilities have the greatest promise in treating disease. TEMPOL is a multifunctional antioxidant able to scavenge and protect against numerous oxidative stresses, including free radicals identified as major players during immune-mediated tissue damage in MS. We have shown that TEMPOL limits the incidence and reduces the severity of disease in animal models of MS. This proposal investigates several mechanisms whereby TEMPOL may limit disease: preventing or reducing the generation of pathogenic T cells; limiting blood-brain barrier alterations and entry of immune cells to the central nervous system (CNS); or scavenging free radicals to limit tissue damage. The proposed studies characterize the potential for TEMPOL to

reduce damage and enhance repair as a novel therapy to treat MS, as well as contributing to our understanding of reactive processes in the inflamed CNS.

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

\$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.

George Robertson, Ph.D.

Dalhousie University, Halifax

\$244,050

(April 1, 2009 – March 31, 2011)

Modulation of Apoptotic Signaling 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.

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 recently identified a new population of monocytic precursor cells that patrol the cerebral blood vessels by crawling on their interior surface and that can penetrate the brain to give rise to mononuclear phagocytes, which are known to play essential roles in the development of MS. Our goal is to clarify how these cells are recruited into the brain. In this project, we will test the hypothesis that their adhesion to the vessels can be enhanced by a mechanism that involves the proinflammatory cytokine interleukin-6, the chemoattractive protein CX3CL1, and the adhesion

molecule $\alpha 4\beta 7$. We will attempt to validate this mechanism using a simple model, that of the pertussis toxin, because this bacterial product is commonly used to induce experimental autoimmune encephalomyelitis, a more complex model of MS. By clarifying the molecular mechanism by which mononuclear phagocytes are recruited at the bloodbrain interface in response to pertussis toxin, this study should help not only to understand how environmental toxins can influence the development of MS, but also to identify potential drug targets for this devastating disease.

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

Magnetic Resonance Imaging (MRI) has been used to visualize the brain in multiple sclerosis (MS) for many years. However, MRI findings often do not relate to the actual physical symptoms of the patient. Here, we introduce new MRI approaches to gain a greater understanding of MS in patients. The new methods focus on two main areas of MS that need further investigation: lesion detection, and brain iron content. The methods introduce a living iron "stain" to determine relative iron content, and a new "microscope" that enables visualization of previously invisible lesions. Most of the methods used are "quantitative" since they supply an absolute measure that can be used to follow disease over time. The methods are performed on a triple-strength

MRI system that is three times stronger than the standard clinical field strength. Higher strength MRI's are much more sensitive to iron changes and offer more signal to enable higher resolving power. To gain new insight into MS, we apply the methods in two ways: 1) a time course study of MS lesion evolution, and 2) an assessment of changes to deep grey matter in patients versus healthy controls.

V. Wee Yong, Ph.D.

University of 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.

Lenora Brown, M.D.

University of Calgary

\$42,580.45

(April 1, 2010 – March 31, 2011)

Measures of Corpus Callosum Function in MS: Development of an Outcome Measure

Multiple sclerosis (MS) has detrimental effects on the functioning of different regions in the brain. A real problem in clinical trials is that we currently do not have an effective method to measure treatment benefits of drug therapies that have the potential to provide protection or ability to repair damage. The corpus callosum is a brain region that is frequently damaged by MS. The corpus callosum is the main structure that transfers information from one cerebral hemisphere to the other hemisphere. In this study we will employ tests that require the functioning of this brain structure. One of the tests that I employ in my MS research is a tactile stimulation test that delivers harmless stimulations to fingertips and the individual makes judgments about the timing of the stimulations. This test relies on the corpus callosum (i.e., damage to this structure will negatively affect performance). Our preliminary work has shown that performance on this test is associated with damage that has occurred in the corpus callosum of MS patients, which indicates that further investigation of this measure may have scientific and clinical value in measuring treatment benefits.

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 will affect more than half of all MS patients. To assess cognition, MS patients should have access to a neuropsychology service. However, there are few neuropsychologists working with MS patients which means that many patients cannot be assessed. The present proposal aims to address this by developing a computerized battery of cognitive tests. These tests are easy to administer and can be given to MS patients by a clinic nurse or occupational therapist or research assistant. The study aims to show that such an approach is comparable to the testing carried out by a neuropsychologist. If successful, the study has the ability to make cognitive testing more widely available to the MS community thereby improving quality of care for patients.

Ruth Ann Marrie, M.D., Ph.D.
University of Manitoba, Winnipeg
\$111,288

(April 1, 2009 – March 31, 2011)

Frequency of Comorbidity in Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic disabling disease affecting more than 50,000 Canadians. In other chronic diseases, comorbidity adversely affects many health outcomes. Using administrative claims data from Manitoba Health, this study will identify the type and frequency of comorbidities which occur in MS, determine how these are changing over time, and how this differs from the general population. Once we know which comorbidities are common in MS, and those which are increasing in frequency, the next phase of the research can be focused on those comorbidities most likely to affect outcomes at the population level. The next phase of the research program will evaluate the influence of comorbidity on a range of health outcomes in MS.

Anthony Traboulee, Ph.D.
University of British Columbia, Vancouver
\$92,768

(April 1, 2009 – March 31, 2011)

Improving Safety Monitoring and Design of Future Multiple Sclerosis Clinical Trials Using Historical MRI Data

MS results in areas of inflammation throughout the brain and other parts of the central nervous system, 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 centers 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. With data from tens of thousands of MRIs, we will develop new statistical methods that will allow us to improve the design of MS clinical trials. Our goal is to minimize the number of patients exposed to unproven therapies, as well as the number of MRI scans needed during the trial. We will develop guidelines to better detect potential safety risks of unproven therapies. Our research will aid in the development of better therapies through more efficient and safer clinical trial design. We believe that this will be an important tool in the search for a cure for MS.

Daria Trojan, Ph.D.

McGill University, Montréal

\$201,670

(April 1, 2009 – March 31, 2011)

Sleep Abnormalities in Multiple Sclerosis: Potential Benefits of Treatment and Effect on Neurodegeneration

Most people with multiple sclerosis (MS) have fatigue, which is usually the most disabling symptom. In our previous study we found that people with MS have poor sleep, and that poor sleep is related to fatigue. The purpose of this study is to

- 1) Evaluate sleep and its abnormalities in MS,
- 2) Determine if there is an association between sleep study results and fatigue in MS patients,
- 3) Determine the relationship between sleep study results and sleepiness during the day and quality of life, and
- 4) Evaluate the ability of a sleep quality questionnaire to predict sleep study results in MS.

60 MS patients and 30 normal controls will participate in this study. Study subjects will be evaluated by a physician, undergo overnight sleep studies followed by a sleepiness test, have blood tests to measure immunologic and hormonal factors, and complete a questionnaire on fatigue, sleep quality, sleepiness, restless legs syndrome, depression, stress, and quality of life. This study will provide important new information on sleep difficulties in MS, and on their importance in determining clinical symptoms in MS. It may result in the identification of an easily administered questionnaire to assess sleep difficulties in MS. We expect that this study will result in improved management of MS patients and a reduction in the important symptom of fatigue.

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.

George Ebers, M.D., University of Oxford

Dessa Sadovnick, Ph.D., University of British Columbia, Vancouver

\$4, 453,477

**Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) –
Molecular Genetics**

There have been several major developments in the granting period of the last 12 months. One of the enduring mysteries of MS has been the pattern of inheritance. There are now several insights into this.

Firstly let's start with the major histocompatibility complex (MHC), the gene region known to be associated with MS for a very long time. Its true impact has only become apparent in the last 2 years with the discovery of 2 new concepts, namely "epistasis" (gene-gene interaction), and "epigenetics" (changes in DNA structure but not sequence which are typically brought about by the environment and are temporary, perhaps lasting for a generation or two). It now emerges that the role of this gene region is much larger than we thought and the greatly increased additional influence occurs via these 2 mechanisms.

MS risk is actually determined by the interaction of the 2 parental gene MHC regions but this is not like recessive inheritance. There are protective forms of this gene region and susceptibility forms. The protective form, if inherited from one parent, overrides any susceptible form inherited from the other. So risk is determined by what pairing of this gene region one has received and the way in which these interact together is termed "epistasis". Think of it as a complicated form of blood group compatibility.

"Epigenetics" is the second new concept coming from the Canadian Collaborative Study on Genetic Susceptibility to MS (CCPGSMS). For a long time, it was thought impossible for the environment to alter the genes temporarily or in the short term. However, this is exactly what happens in MS. The past year has finally seen yielding of the old "nature vs. nurture" argument to the realization that an integration of the genetics with the environment and epigenetics is the key way in which this happens and how MS risk is determined.

Three ways in which the environment specifically interacts with genes all funnel towards the MHC. This now makes clear that this region determines almost all the genetic risk in MS. The first way in which the environment integrated with the genetics was the finding that the month of birth (mob) effect only occurs in those who have particular forms of this gene region. This is the first mob effect for any disease which has been localized to a specific gene region. The second is the evidence for epigenetic modification in the MS risk region. Here it was possible to show that this region undergoes a chemical modification – temporary for a

generation or two or three - and that this change is critical for risk. The third piece is that this occurs in mothers consequent to an environmental exposure. Vitamin D is a candidate for this because the critical gene region of the MHC in MS risk is regulated by vitamin D. There is present in this region a stretch of DNA to which vitamin D binds and is thus able to control the expression of this region.

Returning to the inheritance pattern, we rarely see MS in 3 generations and virtually never in four. This appears to be because the epigenetic mark placed by interaction between the environment and the genetics is temporary. The leading candidate is methylation of DNA and this modification has been engineered by nature to be temporary. Thus, it may disappear in one or two generations and therefore is not passed on further than this.

There is much to do now in terms of taking advantage of these developments for the best interests of MS families. Our CCPGSMS projects are working towards predictive and prevention studies in MS.

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.

Dessa Sadovnick, Ph.D., University of British Columbia, Vancouver

George Ebers, M.D., University of Oxford

\$4,502,164

Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) –Phase 5: Genetic Epidemiology & Databases, including DNA Bank

MS is the most common neurological disease affecting young adults. The CCPGSMS identifies MS cases through the MS Clinics located across Canada. This CCPGSMS database contains information on over 30,000 families with at least 1 person having MS and has been responsible for several milestone studies in MS.

The CCPGSMS has the most complete and unique database for complex traits of any kind for reasons including:

- Living database (not static in one point in time);
- Longitudinal nature;
- Ongoing contact with families & ability to update both clinically and biological samples;
- Family cooperation;
- Clinical & molecular information on affected & unaffected, including various degrees of affected individuals & intervening relatives;
- Spouse controls;
- Sib controls;
- Many individuals past “risk age range” for MS;
- Ethnic diversity;
- Essentially “equal access” to clinics, thus wide range of socioeconomic status (SES).

The CCPGSMS has assembled several unique resources, which have taken over 2 decades of organization, dedication, and cooperation:

1. A clinical database now includes the great majority of ambulatory patients in the country;

2. A DNA bank and database which is unique compared to others as it includes DNA from unaffected and affected individuals within the same family for a variety of rarer relationships, in addition to sib pairs and multiplex families, including affected first-cousin pairs & intervening relatives; affected aunt/uncle-niece/nephew and intervening relative pairs, trios and quartets from non-multiplex families (e.g. affected individual and both unaffected parents; affected individual, both unaffected parents, and one unaffected sibling);
3. The establishment of clear recurrence risks for a variety of relatives of affected individuals in the same generation of the index cases;
4. The most comprehensive natural history database.

Together, these resources provide a solid foundation for continued studies on the prevalence, pathogenesis and natural history of MS. From the perspective of the MS population, including both affected individuals and their family members, the Canadian Study has bridged the gap that often exists between research and patient/clinical services. Some of the issues we can now address with MS patients and their families include:

- Can I catch MS through sexual contact from my partner with MS?
- Can my children catch MS through normal family contact, such as hugs, kisses, sharing an ice cream cone, etc.?
- What are potential high risk groups for getting MS to whom primary prevention approaches should be targeted?
- Is life expectancy altered by MS?
- From what do most persons with MS die?
- What is the relationship between MS and other common diseases (e.g. cancer, cardiovascular disease) and how does this information affect my routine medical care?
- What are the chances that my biological relatives will develop MS, i.e. genetic counselling?
- Does the type of MS (age of onset, clinical course, time to progressive stage, etc.) “run true” in families?
- Is the age of onset of MS under any genetic control?
- What factors must be considered in the decision-making process about having children when one parent (or both parents) has MS, i.e. Reproductive counseling?
- What is known about the safety of disease modifying therapies during pregnancy and breast-feeding?

- Can I do anything to prevent or reduce my risk (or my child's risk) to develop MS?

From a research point of view, the CCPGSMS is “cutting edge”. Peer-reviewed research papers have been published in high impact general medical journals (e.g. Lancet, Nature Genetics, New England Journal of Medicine, as well as in leading neurology, genetics, and general scientific publications including the prestigious Proceeds of the National Academy of Sciences (PNAS). Significantly, over the past few years, several editorials have been written on specific findings of the CCPGSMS. “Cutting edge” research from the CCPGSMS includes:

- Redefinition of the Role of HLA (human leukocyte antigens) complex;
- Gender Influences;
- Importance of Environmental Factors;
- Environmental Factors are Population-Based, Not Family-Specific;
- Genes and Outcome;
- Nature of the Temporal Change in the Prevalence of MS;
- Gene-Environment interactions.

Some may ask why the Canadian Study is ongoing, especially as we have reported progress at the conclusion of each Phase. It is in fact the longitudinal nature of this study that has provided unique insights into the etiology of MS, including the role of gender and the implications for epigenetic factors.

Thus, in conclusion, the CCPGSMS results to date have implications not only for understanding the relative roles of genes and environment in the cause of MS (our original goal) but also critical insights into other key areas including:

- Role of gender;
- Maternal effects;
- Impact of genetics on disease outcome;
- Clues to the changing prevalence of MS;
- Clues to the changing MS rates in migrants;
- Heterogeneity of the MS;
- Evidence that primary progressive MS is not a distinct entity;
- Environmental impact on susceptibility and disease course;
- Role for epigenetics (i.e. non-genetic factors cause genes to express themselves differently, particularly HLA haplotypes in MS).

PILOT GRANTS

Dr. Andrew Emili

University of Toronto

\$35,000

(January 1, 2010 – December 31, 2010)

A neuroproteomics assessment of multiple sclerosis

Dr. Anthony Feinstein

Sunnybrook Health Sciences Centre

\$35,000

(January 1, 2010 – December 31, 2010)

Validation and feasibility of an internet-based approach to cognitive assessment

Dr. Stacey Hart

Ryerson University

\$30,250

(January 1, 2010 – December 31, 2010)

Illness uncertainty, relationship dynamics, and distress in couples facing MS

Dr. Margaret Schneider

Wilfrid Laurier University

\$21,605

(January 1, 2010 – December 31, 2010)

Physical Activity Participation and Access Among Individuals Living with MS in Ontario

Dr. Maria Vrontakis

University of Manitoba

\$35,000

(January 1, 2010 – December 31, 2010)

Role of Galanin on CNS remyelination in a cuprizone model of MS

DONALD PATY CAREER DEVELOPMENT AWARDS

Dr. Nathalie Arbour

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

\$150,000

(July 1, 2008 – June 30, 2011)

Dr. Bradley Kerr

University of Alberta

\$150,000

(July 1, 2009 – June 30, 2012)

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	University of British Columbia	A North American Multiple Sclerosis Pregnancy Registry
Dr. Joseph Antony	Dr. Shannon Dunn	The Hospital for Sick Children	To study the role of PPARs as negative regulators of innate neuroinflammation
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. Benoit Barrette	Dr. Klaus-Armin Nave	Max-Planck Institute	Characterization of the inflammatory response in the CNS of Cnp1Cre*Pex5 mice presenting a peroxisome oligodendroglial defect
Dr. Jayasree Basivireddy	Dr. Jacqueline Quandt	University of British Columbia	A novel role of SPARC in multiple sclerosis regenerative therapies
Dr. Zhihong Chen	Dr. Bruce Trapp	Cleveland Clinic	Neuroprotective effect of LPS-preconditioned microglia
Dr. Ajit Singh Dhaunchak	Dr. David Coleman	McGill University	Role of tmem10 and tmeff2 in myelination and CNS development
Dr. Axinia Samentha Doering	Dr. Wee Yong	University of Calgary	Promoting remyelination in demyelinating models
Dr. Lama Fawaz	Dr. Amit Bar-Or	McGill University	B cell effector responses in Pediatric ADS and other autoimmune diseases
Dr. Debra Fulton	Dr. Alan Peterson	The University of British Columbia	Identification and validation of the transcription factor binding sites and

Dr. Georgina Galicia Rosas Dr. Steve Gendron	Dr. Jennifer Gommerman Dr. Alexandre Prat	University of Toronto Centre de recherche du Chum	transcription factor cooperativity relationships that control expression of myelin-associated genes in oligodendrocytes Evaluating the mechanism of action of LTBR-Ig in EAE Role of integrin alpha8beta1 and semaphorin/plexin in multiple sclerosis
Dr. Denis Gris	Dr. Jenny Ting	University of North Carolina at Chapel Hill	Role of Nlrs in multiple sclerosis
Dr. Dong Han	Dr. Timothy Kennedy	McGill University	Mechanisms Regulating the Formation and Maintenance of CNS Myelin
Dr. Andrew Jarjour	Dr. Charles Ffrench-Constant	University of Edinburgh	Investigating the role of polarity complex in oligodendrocyte development, myelination, and remyeliation
Dr. Sukhdev Singh Kamboj	Dr. Sam David	McGill University	Role of prostaglandin D2, E2 and their Receptors in Experimental Autoimmune Encephalomyelitis
Dr. Elaine Kingwell	Dr. Helen Tremlett	University of British Columbia	Survival and predictors of mortality in the British Columbian Multiple Sclerosis Population
Dr. Shannon Kolind	Drs. Heidi Johansen-Berg and Sean Deoni	University of Oxford	Correlating Magnetic Resonance Changes with Clinical Multiple Sclerosis Symptoms: Whole Brain Multi-Component Relaxation along Specific Fibre Pathways
Dr. Sébastien Lévesque Dr. Samantha Lloyd-Burton	Dr. Steve Lacroix Dr. Jane Roskams	Université Laval University of British Columbia	Dichotomous actions of the IL-1 system in MS The role of the matricellular protein SPARC in the regulation of microglial processes during

Dr. Veronique Miron	Dr. Charles Ffrench-Constant	University of Edinburgh	MS pathogenesis Identification of inflammatory cytokines that promote oligodendrocyte-mediated myelination and remyelination: implications for multiple sclerosis
Dr. Danette Nicolay	Dr. Wendy Macklin	University of Colorado Denver	Retinoic acid signalling in oligodendrocyte development
Dr. Jiwon Oh	Dr. Peter Calabresi	University of Toronto	7-Tesla MRI Correlates of Cognitive Dysfunction in Multiple Sclerosis (MS)
Dr. Scott Ryan	Dr. Rashmi Kothary	Ottawa Health Research Institute	Organelle specific dysfunction in a mouse model of MS
Dr. Raphael Schneider	Dr. Nathalie Arbour	Centre de Recherche du CHUM	Modulation of CD8 T cell functions by IL-27 and IL-15 in the context of multiple sclerosis
Dr. Emilie Viel	Dr. Nathalie Arbour	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
Dr. Jing Wang	Dr. Freda Miller	The Hospital for Sick Children	The atypical PKC-CBP pathway and oligodendrocyte genesis
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
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
Sarah-Jane Bull	Dr. Timothy Kennedy	Montreal Neurological Institute	The role of DCC in paranodal junctions and myelin maintenance
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
Danielle Culp	Dr. Stacey Hart	Ryerson University	Sexual Dysfunction and Sexual Satisfaction among those with Multiple Sclerosis: How Can the Illness Intrusiveness Model Help Explain the Relationship?
Miguel De Avila	Dr. George Harauz	University of Guelph	Myelin basic protein interactions with SH3 domains
Marcio Luiz 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. Doug Arnold	McGill	MRI measures of brain

Alan Gillett	Dr. Tomas Olsson	University Karolinska Institutet	injury in Children with MS Genetic and Functional Mechanisms Regulating Neuroinflammation
Yoko Ishigami	Dr. Raymond Klein	Dalhousie University	Measuring the components of attention in ms patients using the Attention Network Test (ANT)
Saeed Kalantari	Dr. Alex MacKay	University of British Columbia	Myelin Water Measurements in Multiple Sclerosis: The Role of Water Exchange
Allison Kraus	Dr. Marek Michalak	University of Alberta	Dysmyelination in the Calnexin-Deficient Mouse
Ayse Kuspinar	Dr. Nancy Mayo	McGill University	Physical, mental and immunomodulatory effects of exercise in persons with multiple sclerosis
Dina Lafoyiannis	Drs. Brenda Banwell and Mary Desrocher	The Hospital for Sick Children	Optical Coherence Tomography, MRI outcomes and Cognition in Pediatric Multiple Sclerosis
Catherine Larochelle, M.D.	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
Ashleigh McLean	Dr. Steffany Bennett	University of Ottawa	Examining the role of Cx32 in demyelination following EAE disease induction
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
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

Camille Pittet	Dr. Nathalie Arbour	Centre hospitalier de l'université de Montréal	versus relapsing EAE Potential immunoregulatory roles of programmed-cell death-1 ligands in human central nervous system
Katrin Schulz	Dr. Samuel David	McGill University	Iron efflux mechanism in CNS glia cells
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
Pei-Shan Wang	Dr. Catherine Pallen	University of British Columbia	The role of protein tyrosine phosphatase α (PTP α) in CNS 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

M.Sc. Studentship

RECIPIENT	SUPERVISOR	INSTITUTION	PROJECT TITLE
Nadine Akbar	Dr. Anthony Feinstein	Sunnybrook Health Sciences Centre	Validation of an internet version of the multiple sclerosis neuropsychological questionnaire
Mark Akins	Dr. Steffany Bennett	University of Ottawa	Targeting connexin32 (Cx32) to promote remyelination of damaged optic tract and corpus callosum
Haim Ben Ami	Dr. Roger Tam	The University of British Columbia	Accurate and Reproducible Methods for MRI Morphometry of the

Jochen Fahr	Dr. Michael Kallos	University of Calgary	Corpus Callosum in Multiple Sclerosis Patients Protein Production and Purification using Murine Embryonic Stem Cells – Process Engineering and Evaluation using a Target Protein for the Treatment of Multiple Sclerosis
Kimia Honarmand	Dr. Anthony Feinstein	Sunnybrook Health Sciences Centre	Cannabis use in multiple sclerosis: A cognitive and neuroimaging study
Michael Keough	Dr. Wee Yong	University of Calgary	Altering the Microenvironment to Promote Remyelination
Antonia Kobert	Dr. Amit Bar-Or	McGill University	Effects of Inflammatory Glial-Cell Derived Factors on B-Cell Activation of T Cells in MS
Shruti Krishnamoorthy	Dr. Paula Foster	The University of Western Ontario	The use of Cellular MRI to Evaluate Stem Cell Transplantation in a Model of Multiple Sclerosis
Marc-André Lécuyer	Dr. Alexandre Prat	Université de Montréal	The Role of ALCAM in the Murine Model of Multiple Sclerosis EAE (Experimental Autoimmune Encephalomyelitis)
Joshua Lee	Dr. Dessa Sadovnick	University of British Columbia	Canadian Asians with multiple sclerosis (CAMS) study
Ellen Meng-I Lu	Dr. Helen Tremlett	The University of British Columbia	Adverse Pregnancy-Related and Birth Outcomes in Multiple Sclerosis
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
Amy Styles	Dr. Christina Wolfson	McGill University	Environmental and lifestyle risk factors for multiple

Raphael Turcotte

Dr. Daniel Côté

Université
Laval

Fatma Zaguia

Dr. Jack Antel

McGill
University

sclerosis: An international
study

Quantitative Imaging of
water transport in the CNS

Role of HLA-E expression
by oligodendrocytes in MS
pathogenesis