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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.

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 the 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 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
$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
$223,265
(April 1, 2008 – March 31, 2010)

**Glycosphingolipid Interactions and Signaling Domains in Oligodendrocytes and Myelin**

Myelin, a fatty sheath surrounding nerves, is necessary for rapid passage of signals along the nerves to muscles and organs. It contains many layers of membrane made by cells called oligodendrocytes (OLs). Myelin is destroyed in Multiple Sclerosis (MS) and adult OLs do not make much new myelin to repair this injury. In order to develop strategies to stimulate OLs to make new myelin around denuded axons in MS, we need to better understand the process of myelin formation and factors which regulate it. We are studying two different factors which may do this. One is the glycolipids (fats bearing sugar groups) in OLs and myelin, which are exposed to the outer surface and can bind to each other across apposed membranes of cells or myelin. We have shown that this binding triggers a signal which is passed into the inside of the cell by adding synthetic membranes containing myelin constituents such as glycolipids to OLs grown in vitro. This is done to mimic the signal provided when two membrane surfaces contact each other, which may affect the health of both myelin and the nerve. These studies help to understand how the myelin membranes function. Recently, we have also tested synthetic polymeric molecules bearing these sugars and shown that they have a similar effect. These polymers are simpler and better understood than the synthetic membranes used previously, and might be more useful for therapy. We now plan to determine if they stimulate or inhibit myelination when neurons are present with the OLs. If these compounds stimulate myelination, we will test them in demyelinated brain slices in culture, to determine if
they can cause remyelination. We can then test them in animals with an experimental demyelinating disease to determine if they cause remyelination and decreased paralysis in the animals. Estrogens are another factor which may affect remyelination. MS is two times more prevalent in females than males and steroid hormones may play a role. Estrogen has been found to ameliorate demyelinating disease in animals and could do this by acting on neurons and the immune system, in addition to OLs. However, we recently discovered in OLs and myelin a membranous form of the estrogen receptor, the protein which binds estrogens in cells and allows them to exert their effect, indicating estrogens could act on OLs and myelin also. We found that a form of estrogen called 17α-estradiol stimulated signaling pathways in OLs. This form is even more abundant in the brain of both sexes than the more common form, 17β-estradiol, found mainly in females, and therefore may be important for brain function. We plan to determine if it stimulates myelination of neurons and causes remyelination as described above. If it is effective, it could be used to treat both males and females, since it is normally present in both.

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.
Lillian DeBruin, Ph.D.
Wilfrid Laurier University, Waterloo
$122,040
(April 1, 2008 – March 31, 2010)
**Molecular Characterization of Myelin Rafts During Demyelination**

The myelin membrane is altered during the demyelinating process. The early events in the onset of multiple sclerosis may involve compromised signaling events in the myelin membrane. Like other plasma membranes, myelin contains specialized microdomains, in particular lipid rafts, that are paramount in cellular function. Myelin rafts, composed of specialized lipids and proteins, ensure proper development and maintenance. We hypothesize that the protein composition of these lipid rafts changes during demyelination and the function of the myelin raft is disrupted. With the use of brain tissue from control mice and a spontaneously demyelinating mouse model, we are characterizing the myelin rafts in health and during disease. We have found that protein levels and profiles are different between control and “diseased” myelin. The levels of myelin basic protein, one of the most abundant proteins, are altered. By further investigating changes to the proteome we can identify molecular targets that are affected during the demyelination process. This and other basic biochemical and cellular research will accelerate the process of developing of effective therapies for multiple sclerosis.

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.

Vincent Duronio, Ph.D., and Kelly McNagny, Ph.D.
University of British Columbia, Vancouver
$195,200
(April 1, 2008 – March 31, 2010)
Regulatory role of CXCL12 in the EAE model of Multiple Sclerosis

In a mouse model of MS, called EAE, the immune response breaks down the myelin sheath surrounding motor neurons, causing loss of mobility in the animals. We have found that this response can be completely blocked when the animals are injected with a peptide that blocks the action of one protein, referred to as CXCL12. We have also discovered a new way in which CXCL12 controls responses of T lymphocytes of our immune systems. We plan to further investigate how blocking CXCL12 in the EAE model is blocking the response – is it directly blocking activity or movement of the T cells of the immune system, and does CXCL12 act as master regulator of the entire immune response? In parallel, we plan to further investigate the actions of CXCL12 by examining its effect on T cell processes, to determine if this is how blocking CXCL12 is helping in the EAE model. We will follow up our initial exciting findings to determine if blocking CXCL12 at a stage after the EAE has been initiated (as in a real MS patient) can have a beneficial effect. Our hope is that the compounds that block CXCL12 (several drugs are being developed for this purpose) may be a promising therapy for MS patients.

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
$344,610
(April 1, 2007 – March 31, 2010)
Inhibitory Effects of Immune Cells on Neurite Outgrowth

Multiple sclerosis (MS) is characterized by demyelination and damage of neuronal processes (neuritis) 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
$182,764
(April 1, 2008 – March 31, 2010)
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 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 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
$362,956
(April 1, 2007 – March 31, 2010)
Evaluating the Role of the Lymphotoxin Pathway in Experimental Auto-immune Encephalomyelitis (EAE)

Multiples 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 remains 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 in these pathways prevent disease relapse 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.

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Alex MacKay, Ph.D.
University of British Columbia, Vancouver
$354,953
(April 1, 2007 – March 31, 2010)

**In Vivo Measurement of MS Pathology by Magnetic Resonance Imaging**

Multiple Sclerosis (MS) is a complex disease in which damage to the central nervous system is manifested in most people through attacks (relapses) to vision, sensation, coordination and strength, either temporarily or permanently. MS attacks the myelin covering of nerve fibers in white matter, causing inflammation and often destroying the myelin in patches which results in an interruption of normal nerve impulse flow. Much of what we know about the mechanisms of damage in MS is based on examination of the brain and spinal cord after death. Since the average duration of the disease is 35 years, we do not have much insight into what happens earlier. It would be valuable to study MS in the early stages of disease, as this would allow researchers to better understand the mechanisms of damage, which may in turn aid treatment. Magnetic resonance imaging gives us the ability to follow physical and chemical changes in the brains of people living with MS.

The goal of this study is to use magnetic resonance imaging to follow the neurodegenerative processes which occur in multiple sclerosis. We shall focus on three particular magnetic resonance techniques: T2 relaxation, diffusion tensor imaging and perfusion imaging which enable us to measure different properties of brain tissue at the cellular level. A particular emphasis will be to understand the process of myelin destruction and regrowth in lesions, as well as in normal appearing white matter. We shall also investigate the presence or absence of pools of extracellular water which can increase in some lesions, and also in other white matter areas. Gaining in vivo insight into the pathological processes which occur in MS will aid in the diagnosis and management of people living with multiple sclerosis and may also help define techniques for assessing new treatments.

We found that most MS lesions have already undergone demyelination by the time they are first visible on MR scans. One half of all new lesions exhibited some remyelination during the next few months. This work provides important natural history data which can be compared to future data acquired from subjects undergoing novel new therapies designed to promote remyelination.

Using two magnetic resonance techniques, $T_2$ relaxation and diffusion tensor imaging, we identified a particular sub-type of MS lesions which we believe have a specific pathology known as isomorphic fibrillary gliosis. While further research will be required to validate this interpretation, if our hypothesis holds, this represents an important advance in the capabilities of MR to measure neuropathology.
**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.

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**Mario Moscarello, Ph.D.**  
**Hospital for Sick Children, Toronto**  
**$200,000**  
**(April 1, 2008 – March 31, 2010)**  
*Demyelination and remyelination in MS, the Role of Vitamin B12 and Methylation*

Multiple Sclerosis (MS) is the most common “demyelinating” disease of the human brain. Demyelination involves loss of myelin (the fatty substance which surrounds nerves, essential for nerve function). Our research is to understand changes that occur before MS development. This can only be done in animal models but the data can be extrapolated to human MS. Previously we showed that changes in one of the major myelin proteins, myelin basic protein, was associated with the loss of myelin interactions. These changes were attributed to a molecule called peptidylarginine deiminase (PAD). In this research proposal we hypothesize that PAD leads to damage in MS brains. In the brain, if the effects of PAD are kept unchecked, this may result in disruptions leading to injury and death of cells. PAD function thus represents new targets for drug treatment in MS. We are studying one such molecule, 2-chloracetamide (2CA). PAD function in our MS animal model is lowered by 2CA. The combination of vitamin B12 and 2CA enhanced our myelin repair and reduced signs of
MS very significantly in comparison with 2CA alone. Our studies suggest that addition of vitamin B12 to treat MS should be considered.

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 disregulation 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 damage 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.

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.

Peter Rieckmann, M.D.
University of British Columbia, Vancouver
$161,238
(April 1, 2009 – March 31, 2010)
**Molecular and Functional Aspects of Recovery from Acute Motor Relapse**

Multiple sclerosis (MS) is one of the most frequent chronic diseases of the central nervous system and a leading cause of premature disability in young adults. Canada’s prevalence with 1 case in 500 persons is one of the highest in the world. Over 40% of young MS patients go into early retirement after an average disease duration of only 10 years. Accumulated annual cost of the disease is the second highest among all brain diseases. MS mainly starts with the relapsing-remitting course (80%) but disabling motor symptoms may persist in 20% of patients due to severe attack or reduced ability for recovery. Many clinical studies currently aim at reducing disease activity of MS, but there is little known about the mechanisms involved in recovery from the acute attacks. Resolution of inflammation, functional adaptation or regeneration of central nervous tissue are potential candidates.

In this project we want to identify factors which can predict recovery from acute MS attacks with motor disabilities. To attain this objective we will use specific blood tests, advanced magnetic resonance imaging technology and modern electrophysiology. Patients who do not recover from the relapse will be offered an established “Fitness And Mobility Exercise” program. This has been shown to be a very efficient strategy for restoration of clinical function in other brain diseases, like stroke.

Using this approach we will be able to establish new tests, which in the future can hopefully predict, whether a patient has a good potential for recovery or may need more intensive rehabilitation or drug therapies. It will also allow us to identify new molecules or pathways associated with recovery from acute MS attacks. These could then be targets for innovative treatment strategies also in other chronic progressive brain diseases.

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.

Charles Tator, MD, Ph.D.
University Health Network, University of Toronto
$188,499
(April 1, 2008 – March 31, 2010)

Neural Stem/Progenitor Cells for Remyelination and Recovery in Multiple Sclerosis

Multiple Sclerosis (MS) is the most common disease of the central nervous system affecting young adults. The body’s immune system mistakenly attacks the protective sheath (myelin) around nerve fibers (axons) resulting in a loss of myelin and neurological dysfunction. At present, treatment for most MS patients is only partially effective. One promising approach is the transplantation of myelin-producing cells for remyelination and neuroprotection. We propose to enhance functional recovery in two different experimental models in rats by transplanting neural stem progenitor cells (NSPC) derived from the periventricular region of the adult spinal cord. The models are focal demyelination produced by a chemical (EB) and X-irradiation (X-EB) and chronic-relapsing experimental autoimmune encephalomyelitis (CR-EAE). Our previous work has shown that NSPC are multipotent and generate a high proportion of oligodendrocyte precursors, and that these cells remyelinate axons in both X-EB lesions and in the shiverer mouse spinal cord that lacks myelin. In the present proposal, we aim to extend these studies by examining functional recovery and mechanisms of action after NSPC transplantation in these two models via a minimally invasive lumbar puncture. Knowledge gained in this study of enhancing repair and remyelination will increase the possibility of effective therapy for MS.
Pseudoatrophy of the Brain in Multiple Sclerosis

Magnetic Resonance Imaging (MRI) is one of the most important clinical and research tools available for the diagnosis and monitoring of MS in Canada and worldwide. Clinicians and researchers are increasingly dependent on quantitative measurements derived from MRI data both for the development of new therapies and monitoring their impact on the overall disease course. Over time, the cumulative damage caused by MS leads to a gradual decrease in brain tissue known as atrophy. This can be easily monitored with MRI. However, disease modifying therapies for MS also cause a decrease in brain size by reducing swelling caused by inflammation. This pseudo-atrophy prevents us from detecting if a medication also prevents brain damage (atrophy). Our research uses advanced imaging techniques available at the University of BC to monitor the effect of MS therapies on the water content of the brain that is responsible for pseudo-atrophy. A better understanding of pseudo-atrophy will allow researchers to determine if therapies prevent future brain atrophy that we believe is related to long term disability, both physical and cognitive (memory). This will allow us to design better clinical trials to determine if treatments can protect the nervous system from degeneration as well as prevent inflammation.

The Microenvironment in Remyelination: MMPs, ECM and Inflammation

We have unraveled further details of the milieu surrounding a demyelinating plaque, and 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. We have discovered also that we can deliver safe proteases (ADAMTS4) pharmacologically to the lesion site to help clear CSPGs, and that this then leads to repair. These findings are important to help explain the causes of why repair sometimes fails in MS, and they have also led to the identification of a potential therapeutic agent for repair, ADAMTS4.
Clinical and Neuroimaging Correlates of Cognitive Decline in Children and Adolescents with Multiple Sclerosis

The onset of Multiple Sclerosis (MS) during childhood or adolescence has the potential to severely impact learning and school performance. We are currently evaluating the severity of learning and thinking impairments in children and teens with MS, and are evaluating how these impairments relate to the MS disease process visible through magnetic resonance images (MRI) of the brain. MRI provides a very detailed look at how the brain is developing, growing, and can provide measurement of the degree of MS-related brain injury.

So far, 34 children with MS and 21 healthy volunteers have undergone tests of their thinking and learning, as well as MRI pictures of their brain. By the end of our study, we will have at least 30 children in each group, and will test everyone at least twice, with one year between each test.

In the first year of our work, we have confirmed that about 1/3 children with MS has trouble with thinking, and that they are most likely to have trouble with tasks that require thinking quickly, paying close attention to detail, and to tasks that require using visual information. Children who were the youngest when their MS started seem to have the most difficulty. Children with the greatest difficulties on the learning tests also tended to have more disease seen on the MRI pictures of their brain, suggesting that MS-related damage seen on MRI is an important component of the disease. Our finding that MS has an even greater impact in the youngest patients suggests that the common belief of greater resiliency in youth does not hold true for MS. We will now evaluate whether the severity of cognitive deficits seen in children with MS increases over time and whether sophisticated MRI techniques can further explain the impact of MS in the brain of affected children. Through an in-depth understanding of the impact of MS in children, we hope to develop neurorehabilitative strategies to reduce the burden of disease in children living with MS.
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 Traboulsee, 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.

Lisa Walker, Ph.D.
The Ottawa Hospital
$69,289
(April 1, 2008 – March 31, 2010)
A New Clinical Test for Measuring Information Processing in MS patients: The Computerized Test of Information Processing (CTIP)

People with MS often comment as to how the disease affects their ability to think. More specifically, they mentioned that they "think slower" or experience difficulty in processing information as quickly as they used to. Unfortunately, clinical assessment of deficits in the speed of information processing is hampered by the fact that relatively few neuropsychological tests effectively measure this cognitive ability. Preliminary results with a series of newly developed computerized tests (Computerized Test of Information Processing) suggest that these tests offer considerable promise in detecting the presence of slowed information processing. The current study seeks to determine whether these new tests can provide a more adequate assessment of cognitive deficits than the neuropsychological tests that have been used traditionally. The first goal is to determine if the new tests are sensitive to cognitive deficits when people are initially evaluated. The second goal is to assess the ability of the tests to detect any change in performance due to MS over a three-year period. It is anticipated that the findings may offer clinicians a more
effective technique for determining the cognitive effects of MS and for assessing whether or not various medications have an impact on information processing speed. We are making excellent progress in recruitment of study participants and look forward to the day when we can begin to analyze our findings. We are fortunate to be working within an MS clinic with a strong research focus. More importantly, we find that the people with MS with whom we work are keen to contribute to research initiatives such as ours by donating their time and significant effort. We are humbled by their perseverance and altruism. It is a privilege to be working with them.
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 Proceedings 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 genets 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).
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. Helen Tremlett**  
University of British Columbia  
$150,000  
(July 1, 2007 – June 30, 2010)
# POSTDOCTORAL FELLOWSHIPS

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