

# MS Research Summaries 2008

MS Society of Canada



## BIOMEDICAL

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**Guillermina Almazan, PhD, and Walter Mushynski, PhD**

**McGill University**

(April 1, 2006 – March 31, 2009)

**Role of p38 MAPK (mitogenactivated protein kinase) signaling pathways in myelination**

The myelin that insulates nerve fibres is produced by specialized cells called oligodendrocytes (in the central nervous system, i.e. the brain and spinal cord), and Schwann cells (in the peripheral nervous system). A signalling system tell these cells when to produce myelin and ensures that the new myelin completely ensheathes the nerve fibre. The chemical signals are called mitogen-activated protein kinases (MAPK). A mitogen is a stimulus that comes from outside the cell. Drs. Guillermina Almazan, Walter Mushynski and colleagues have used cultures of Schwann cells and dorsal root ganglion neurons to demonstrate that one family of MAPKs, called p38, is essential to myelination. Inhibiting p38 interferes with the early stages of myelination, preventing the proper alignment of Schwann cells along the axon (nerve fibre). Inhibition of p38 has also been shown to block CNS myelination by oligodendrocytes. The researchers hope to identify the particular forms of p38 that might stimulate myelination in multiple sclerosis.

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**Jack Antel, MD**

**McGill University**

(April 1, 2007 – March 31, 2009)

**Cellular immune injury of human oligodendrocytes**

The MS disease course is characterized by damage to the myelin membrane that ensheathes nerve fibres (axons) and which is required for efficient electrical conduction within the central nervous system (CNS). Nerve fibres themselves are also subject to injury even early in the disease process. The damage occurs as a result of components of the immune system that enter the CNS in MS. Dr. Antel's studies are intended to define how damage occurs to myelin, its cell of origin (the oligodendrocyte), and to nerve cells. He postulates that properties of immune components present in MS lesions, or properties of the neural cells, may determine the extent of myelin and axonal injury. To date, he and his colleagues have shown that both the immune cells and the neural cells are modified by the inflammatory microenvironment seen in MS. For example, he has shown that oligodendrocytes are susceptible to injury by a highly reactive oxidant called peroxynitrite. Dr. Antel will use human immune cells and CNS-derived cells to help define the mechanisms underlying the process of myelin and axonal injury. He hypothesizes that CNS tissue injury that occurs early in the MS disease process can contribute to persistent neurologic deficits and predispose to the development of the late progressive phase of MS. These studies will provide insights that may lead to therapies that will protect myelin and axons from injury and promote tissue repair in people with MS. The results may also be used to evaluate the effect of MS therapies on immune components of MS to determine whether they exert direct positive or negative effects on neural cells.

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# MS Research Summaries 2008

**Nathalie Arbour, PhD**

**CHUM**

(April 1, 2007 – March 31, 2009)

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

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 determine immune responses of multiple sclerosis patients toward components of the brain and compare these responses to healthy people. White blood cells will be isolated from human blood and from the liquid in which the brain soaks. A particular white blood cell type with capacity to kill other cells 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 these patients. We hope to identify new molecules and cells that could eventually be targeted by future treatments.

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**Doug Arnold, MD**

**Montreal Neurological Institute**

(April 1, 2007 – March 31, 2009)

## **In Vivo Detection of Cortical MS Lesions on MRI**

Recent post-mortem studies have revealed that a substantial amount of cortical damage occurs in multiple sclerosis (MS). The vast majority of the cortical pathology in MS takes the form of band-like demyelinated lesions on the cortical surface that may span several gyri, yet still remain “invisible” to current MRI techniques. Our inability to visualize these lesions during life are a major impediment to progress in our understanding of the clinical evolution of MS and the use of MRI as a marker of MS pathology. As long as we cannot see these lesions during life, we cannot determine when in the course of MS they develop, and how they relate to clinical disability and progression (which eventually occurs independently of the focal white matter lesions, despite their suppression with current therapies). The goal of this project is to develop MRI methods to detect and quantify the cortical gray matter lesions that occur in patients with MS using a specialized form of MRI that is more specific to myelin density (magnetization transfer imaging), and advanced image processing techniques. We will validate these novel methods with respect to post-mortem histopathology, and determine how the cortical lesions relate to the clinical course of MS (including neuropsychological deficits), to white matter lesions and to brain atrophy.

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# MS Research Summaries 2008

**Doug Arnold, MD**

**Montreal Neurological Institute**

(April 1, 08 to March 31, 11)

## **Imaging demyelination and remyelination in MS**

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 into 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. This project will provide the required proof by performing 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.

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**Joan Boggs, PhD**

**Hospital for Sick Children Research Institute**

**University of Toronto**

(April 1, 2007 – March 31, 2009)

## **Functions of myelin basic protein in oligodendrocytes and myelin**

Multiple sclerosis is characterized by myelin damage, which results in disruption of nerve conduction and axonal (nerve fibre) degeneration. The second most abundant protein making up myelin is called myelin basic protein (MBP), and is the only structural protein known to be essential for myelination. Like other proteins, MBP can adapt its structure to different environments, and thus may have several different functions. Dr. Boggs' research aims to show that MBP, in addition to its generally accepted role of binding the membrane layers together to produce the myelin sheath, also interacts with the cytoskeleton, a network of proteins found inside all cells. This cytoskeleton connects the cell membrane to signalling molecules inside the cell and may also bind directly to some signalling molecules. Dr. Boggs will test this idea by reconstituting purified MBP into model membranes to determine its structure in this environment. Purified cytoskeletal and signalling proteins will then be added to determine if they bind to MBP on a membrane surface, and how they interact with each other. The goal is to determine which proteins are associated with MBP in myelin.

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**Joan Boggs, PhD**

**Hospital for Sick Children research Institute , University of Toronto**

(April 1, 08 to March 31, 11)

### **Glycosphingolipid interactions and signaling domains in oligodendrocytes and myelin**

Myelin, a fatty sheath surrounding nerves, is necessary for rapid conduction of signals along the nerve. 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. This advancement will require determination of the functions of the myelin proteins and glycolipids (fats bearing sugar groups). The glycolipids are exposed to the outer surface and can bind to each other across apposed membranes. We believe that this binding triggers a signal which is passed into the inside of the cell. Some of the proteins are involved in receiving or transmitting these and other regulatory signals from outside the OL and from the nerve, across the membrane to proteins inside the cell. These proteins amplify the signals and regulate myelin formation and other cell functions. Since myelin contains many layers of membrane, interactions between membrane proteins and glycolipids in apposed membranes, which are in contact with each other in the myelin sheath, can also occur and may transmit signals which affect the health of both myelin and the nerve. We are testing this prediction by adding synthetic membranes containing myelin constituents such as glycolipids to OLs grown *in vitro*, to mimic the signal provided when two membrane surfaces contact each other. We are studying the effect of these synthetic membranes on the behavior of OLs and on interactions between membrane proteins and regulatory proteins inside the cell. We will determine if synthetic molecules bearing these sugars have a similar effect and determine if they can stimulate or inhibit myelination when neurons are added to the OLs. These compounds will help to understand how the myelin membranes function and may also be useful to stimulate remyelination.

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**Fiona Costello, MD**

**Ottawa Hospital**

(April 1, 2007 – March 31, 2009)

### **Comparison of Structural Biomarkers of Axonal Integrity in Optic Neuritis: Correlating VEP, MRI and Optical Coherence Tomography Measurements**

Optic neuritis (ON) is common in MS, and affects 75% of patients during the course of their disease. The visual pathway offers scientists a unique opportunity to study the effects of MS, because damage may be observed directly in the eye. The optic nerve is a structure that carries information from the eye to vision centers in the brain. When attacked by MS, the wires or “axons” within the optic nerve become damaged. As these axons splay over the retina, they make up the retinal nerve fiber layer (RNFL). A new device called optical coherence tomography (OCT) can be used to measure the thickness of the RNFL. By using this technique we can quantify axonal loss due to ON. We believe that if the damage that

occurs in optic nerve axons is the same as that which occurs in the brain, then the retina could be a “window” to look more directly at axonal damage in MS patients. This is what we aim to prove in this proposal. This will lead to the use of OCT as a measure to assess how the brain repairs itself and whether therapies are working in MS.

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**Samuel David, PhD**

**McGill University**

(April 1, 08 to March 31, 10)

**Role of Prostaglandins in the Pathogenesis of Experimental Autoimmune Encephalomyelitis**

We have discovered that 4 members of a large family of enzymes called phospholipase A<sub>2</sub> (PLA<sub>2</sub>) play different 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 PLA<sub>2</sub>s. PLA<sub>2</sub>s, however, 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. Surprisingly, no work has been done so far on the various prostaglandin receptors and their role in EAE or MS. I propose to extend our studies on PLA<sub>2</sub> to assess the expression and role of various prostaglandins and their receptors in EAE. The proposed work on prostaglandins can also be expected to provide important information that could lead to the development of additional new treatments for MS.

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**Lillian DeBruin, PhD**

**Wilfred Laurier University**

(April 1, 08 to March 31, 10)

**Molecular characterization of myelin rafts during demyelination**

Multiple sclerosis (MS) is a debilitating disease that is characterized by the active degradation of the myelin sheath. In the myelin membrane, unique regions or microdomains such as lipid rafts are functional entities involved in processes to ensure proper development and maintenance of the myelin sheath. We hypothesize that lipid rafts undergo remodeling during demyelination, and thus the function of the myelin rafts is disrupted. With a mouse model for spontaneously demyelinating disease, we will purify lipid rafts from myelin at various stages of disease progression. By identifying protein and lipid changes to the myelin rafts, we will be able to determine which functional pathways have become altered. This can provide new strategies for the development of treatments for multiple sclerosis.

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## **MS Research Summaries 2008**

**Katerina Dorovini-Zis, MD**  
**Vancouver General Hospital**  
**University of British Columbia**  
(April 1, 2006 – March 31, 2009)

### **Human cerebral endothelium lymphocyte interactions in immune-mediated CNS diseases**

During the course of MS, the blood-brain barrier (BBB) becomes more porous, allowing activated immune cells to enter the central nervous system. Endothelial cells (ECs) line all of the blood vessels in the body, including those of the BBB. Since ECs lining the BBB of the brain are the first cells to meet circulating immune system cells, Dr. Dorovini-Zis predicts that the interactions between these cell types are likely important in the pathogenesis of MS. Using an in vitro model of the BBB developed in her laboratory, previous research by Dr. Dorovini-Zis identified that some agents, such as nitric oxide (NO), can decrease BBB permeability. Dr. Dorovini-Zis now plans to study whether T cells are activated by ECs at the level of the BBB. This research may point to specific therapies that may restore normal function of ECs lining the BBB in people with MS.

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**Alyson Fournier, PhD**  
**Montreal Neurological Institute**  
(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 mediated by infiltration of activated immune cells. Sustained neurological disability is believed to be due to transection of neuronal processes within MS plaques and subsequent failure of neuronal processes to repair themselves. Little is known about the potential impact of immune cells on neuronal process repair. We demonstrate that total peripheral blood mononuclear cells (PBMCs) have a significant inhibitory effect on neurite outgrowth. T-lymphocytes and B lymphocytes impact neuronal repair when activated by a variety of stimuli. 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.

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**Sylvie Fournier, PhD**  
**McGill University**  
(April 1, 08 to March 31, 09)

### **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.

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**Jennifer Gommerman, PhD**

**University of Toronto**

(April 1, 2007 – March 31, 2010)

### **Evaluating the Role of the Lymphotoxin Pathway in EAE**

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

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**Fabrizio Giuliani, MD**

**University of Alberta**

(April 1, 08 to March 31 10)

### **Role of Inflammation in neurodegenerative processes of Multiple Sclerosis**

Classically, Multiple Sclerosis has been described as an inflammatory disease of the central nervous system mainly characterized by myelin and oligodendrocyte destruction. More recently, it has become evident that Multiple Sclerosis has an important neurodegenerative component with neuronal and axonal injury. In the majority of cases, the disease starts with a relapsing course featured with episodes of neurological disability followed by periods of partial or complete clinical remission. Between 50 and 70 % of these patients later enter a progressive phase characterized by a steady decline in neurological function, and recent evidences strongly suggest that axonal and neuronal degeneration underlies the

development of such permanent disability. The cause of tissue loss in Multiple Sclerosis is uncertain but inflammation likely plays a role since there is good correspondence between the frequency of axonal injury and the degree of inflammation within a given lesion. I have discovered that inflammatory cells such as T lymphocytes are able to destroy human neurons in vitro. This research proposal seeks to fully establish the role of inflammation in neurodegenerative processes of Multiple Sclerosis. Overall, these studies are aimed at stopping the neurodegenerative processes of Multiple Sclerosis, thereby improving the prognosis of patients with the disease.

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**David Haegert, MD**

**McGill University**

(April 1, 2007 – March 31, 2009)

### **CD4 Subsets in RRMS: Transcriptional Profiles and Cytokine Production**

CD4 T-cells have a central role in initiating the autoimmune attack against the brain and spinal cord in MS. Recently, we found that there are abnormalities in regulation of the naive CD4 T-cells in RRMS, and that these cells proliferate to maintain the size of the naive CD4 T-cell population. We hypothesize, therefore, that naive CD4 T-cells are partly activated in some RRMS patients and respond more readily and to a greater extent to activation signals than do comparable cells from healthy controls. If correct, this would help explain why some individuals develop MS and others do not, i.e. naive CD4 T-cells from RRMS patients may respond more readily to various signals that lead to autoreactivity than do other individuals who do not develop MS. To investigate this, we will use microarray methods to study gene expression and cytokine production in freshly prepared and stimulated naive CD4 T-cells from RRMS patients and controls. Further, we will use similar methods to study memory CD4 T-cells. We believe a detailed study of naive and memory CD4 T-cells will permit us to identify subgroups of RRMS patients who have different gene expression profiles. Importantly, one or more subgroups may show a differential response to treatment and thus our work has potential treatment implications for RRMS patients.

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**Tim Kennedy**

**McGill University**

(April 1, 08 to March 31, 11)

### **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

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oligodendrocytes and axons, called paranodal junctions, are severely disrupted in the absence of netrin-1 and DCC.

The studies we propose aim 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.

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**Rashmi Kothary**

**Ottawa Health Research Institute**

(April 1, 08 to March 31, 11)

**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 bi-directional 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 Mac Kay**

**University of British Columbia**

(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

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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 in treatment. Magnetic resonance imaging give 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.

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**Ross Mitchell, PhD**

**University of Calgary**

(April 1, 2006 – March 31, 2009)

**Texture analysis of myelin sensitive MRI**

Magnetic resonance imaging (MRI) is a very sensitive diagnostic test. Although MS lesions are reliably visualized using MRI, it is often unclear how lesions relate to clinical status in people with MS. Great advances have been made in medical imaging over the last two decades, but the interpretation of this new digital data is still somewhat subjective. During the last period funded by the MS Society, Dr. Mitchell made considerable progress. In 2003, he introduced a new type of analysis to the medical imaging community, resulting in numerous high profile publications. In the current project, Dr. Mitchell builds a unique component into his new analysis; namely, the ability to measure the ‘texture’ of MR images in people with MS. Texture refers to an intuitive, yet measurable characterization of the local pattern of an MR image. Using texture analysis, Dr. Mitchell is analyzing MRI exams from normal volunteers to develop markers of myelin health throughout the normal brain. These markers can then be used to gauge how new treatments affect the brain of people with MS. Dr. Mitchell’s MRI texture analysis tool should improve the power and efficiency of clinical trials evaluating new MS therapies.

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**Wayne Moore**

**University of British Columbia**

(April 1, 08 to March 31, 11)

## **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, PhD**

**Hospital for Sick Children**

(April 1, 08 to March 31, 10)

## **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 cell 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 represent new targets for drug treatment in MS. We are studying one such molecule, 2-chloroacetamide (2CA). PAD function in our MS animal model is lowered by 2CA. The combination of vitamin B12 and 2CA enhanced 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.

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## **MS Research Summaries 2008**

**Alan Peterson, PhD**

**Royal Victoria Hospital**

(April 1, 2007 – March 31, 2009)

### **Regulation of the oligodendrocyte genome**

In the formation of myelin there is genetic expression of myelin basic protein (MBP), an essential building block of myelin. Dr. Peterson and colleagues have located the DNA switches that control myelin expression, and are working to define the individual and combined functions of these switches using artificial genes that are expressed in mice. Thus far, they have discovered that the cells repairing myelin in the mature brain are using parts of the regulatory program that are special to the repair process. The present research hopes to identify the switches and the factors they engage, thereby determining the special requirements of remyelinating cells.

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**Christopher Power, MD**

**University of Alberta**

(April 1, 2006 – March 31, 2009)

### **Pathogenic interactions between human retroelements and neuroinflammation in MS**

How viruses affect the immune system during MS is still unclear. Interestingly, 5-10% of the human genome is made up of viruses called 'retroviruses'. These viruses have been incorporated into the human genome over millions of years of evolution. Dr. Power has found that a group of unique retroviruses are made in the brains of some people with MS. Moreover, he has found an abundance of a particular retrovirus gene in the brains of people with MS. This gene contributes to the activation of the immune system and damage to myelin in cell cultures and in animal models. Dr. Power is combining unique microarray technology with new transgenic mice and other detection tools to evaluate the level of different retroviruses in people with MS. The long-term goal of this project is to identify the contribution that such retroviruses might make to the progression of MS. He has also developed a new retrovirus-containing transgenic mouse which he can use to study myelin damage and the effects of novel therapies for MS. Taken together, this research should address the growing question of the role of viruses in MS, and also provide new therapeutic opportunities for its treatment.

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**Alexandre Prat, MD, PhD**

**Montreal University**

(April 1, 2006 – March 31, 2009)

### **Origin, regulation and function of brain perivascular dendritic cells in MS**

The presence of dendritic cells (DCs) in human and mouse brains has been a controversial topic for more than a decade. DCs have the pivotal role of triggering T cells in the immune system. Several independent investigators have found that DCs associated with the blood

brain barrier (BBB) are important for the formation of lesions in EAE, an animal model of MS. The BBB is a network of blood vessels that nourishes the brain and is lined by endothelial cells. To aid his research, Dr. Prat has developed a human model of the BBB. In his current proposal, he is investigating whether endothelial cells lining the BBB make cytokine messengers that influence the development of DCs. Because these DCs are associated with BBB endothelial cells, Dr. Prat calls them 'eDCs'. He is curious whether eDCs can trigger or halt the activation of different types of T cells that might be present in MS lesions. To confirm his findings, Dr. Prat will take advantage of his substantial bank of MS brain specimens. This proposal offers the potential to discover how eDCs are formed and whether they sustain or counteract the damage that T cells cause during MS.

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**Alexandre Prat, MD**

**University of Montreal**

(April 1, 08 to March 31, 11)

**Novel Adhesion Molecules of the Blood-Brain Barrier Regulating CNS 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.

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**Stéphane Richard, PhD**

**Lady Davis Research Institute Jewish General Hospital**

(April 1, 2006 – March 31, 2009)

**The role of quaking proteins in oligodendrocyte physiology and myelination**

An animal model of MS that is used in the laboratory is the quaking viable mouse (qk(v)), which develops characteristic tremors shortly after birth. Tremors in mice with defective quaking proteins are due to demyelination, making this animal an important model for MS research. Demyelination is the result of a failure in qk(v) mice to develop mature oligodendrocytes. A genetic defect prevents the expression of a type of quaking RNA binding protein. Thus, the qk(v) mouse model enables researchers to link RNA binding

proteins with defects in oligodendrocyte development and myelination. Since receiving a previous grant from the MS Society, Dr. Richard and colleagues have investigated how quaking proteins are required for oligodendrocyte development. A recent study showed that two quaking proteins can cause oligodendrocyte differentiation and maturation. These oligodendrocytes can come from parent cells (precursors) in the brain, as well as immature oligodendrocytes in cell cultures. The hope is that this research will lead to ways of repairing myelin by enhancing the function of quaking proteins.

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**Charles Tator, MD, PhD**

**University of Toronto**

(April 1, 08 to March 31, 10)

**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 both in 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.

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**Anthony Traboulsee, MD**

**University of British Columbia**

(April 1, 08 to March 31, 10)

**Pseudo-atrophy of the brain in multiple sclerosis**

Despite a vast amount of research in MS, the relationship between tissue degeneration and clinical disability is still not well understood, and the correlation between MRI biomarkers and clinical symptoms is modest at best. For this reason, precision and accuracy are of utmost importance when performing studies to evaluate treatments, and potentially confounding factors such as pseudo-atrophy and hydration status need to be understood. This knowledge will lead to better designed clinical trials and more efficient development of effective new treatments. Canada has a large population of people with MS who stand to benefit from the

proposed research. We expect the results of this study to significantly increase the understanding of how liquid intake and medications affect brain water content, and how water content impacts the MR measures used in developing and monitoring new MS therapies. This knowledge will be directly useful for clinicians and researchers using MRI to quantitatively monitor the progression of MS and evaluate therapeutic efficacy. Clinical researchers can use this information to amend MRI protocols to reduce confounding factors in their studies. The knowledge gained from this study will also help researchers interpret the results of therapeutic studies, especially those in which the treatment used affects brain water content.

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**Luc Vallieres, PhD**

**Laval University**

(April 1, 08 to March 31, 11)

**Regulation of macrophage in a model of multiple sclerosis**

Multiple sclerosis is the most common cause of neurological disability in young adults. Cells of the immune system known as macrophages are thought to play essential roles in its pathogenesis. Blockade of macrophage activation is regarded as a promising therapeutic strategy, but developing an inhibitor that would achieve this goal without causing major side-effects has so far proved elusive. The long-term goal of our laboratory is to elucidate molecular mechanisms that govern the activity of macrophages and thereby assist in the rational design of safer and more effective immunosuppressors. In this project, we will test the hypothesis that a newly discovered signaling molecule called GPR84 is involved in the activation of macrophages and the propagation of the inflammatory response throughout the brain and spinal cord in an animal model of multiple sclerosis. The hope is that GPR84 can be a target of choice for a new class of anti-inflammatory drugs intended for the treatment of neuroinflammatory diseases. Such agents could prove more selective and less compromising than the broad-rang immunosuppressants commonly used today.

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**Peter van den Elzen, MD**

**University of British Columbia**

(April 1, 2007 – March 31, 2009)

**Autoimmunity to Myelin Lipids: Apolipoproteins, T cells and B cells**

MS is caused by damage to the fatty insulation that covers nerve cells in the brain and spinal cord, known as the myelin sheath. A distinguishing feature of myelin is its high fat content, which makes up 70% of its total content. Myelin destruction in MS is believed to be caused by aberrant immune activity, which mistakenly seems to target myelin for unknown reasons. The primary players in the immune system that coordinate this attack are T cells, which recognize components of myelin presented to them by specialized antigen presenting cells, or APC. A great deal of progress has been made to understand how T cells recognize the protein components of myelin, although proteins are only a minority of the total tissue composition.

Only recently, in the early 1990's, did we come to realize that fats can be targeted by T cells in a similar manner to proteins. This grant proposal aims to study the almost completely unexplored area of immune responses to the fatty components of the myelin sheath. Intriguing evidence already exists that this is an important part of the overall immune recognition of myelin. We have recently found that a part of this new pathway of immunology involves the express delivery of fats to APC by a well-known blood protein (apoE) which previously was thought to play a role only in metabolism and cholesterol transport. Importantly, apoE is known to be involved in MS, thus the connection we have made between apoE and the immune recognition of fats is likely to be of great importance in our understanding of how the immune system targets the myelin sheath. Therapies and drugs which target this pathway, such as the cholesterol-lowering drugs hold great promise in light of these critical connections. Also, the design of therapies to target this pathway could include modulations of fats in the diet, or other therapies which could apply to all MS patients.

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**V. Wee Yong, PhD**

**University of Calgary**

(April 1, 2007 – March 31, 2010)

**The microenvironment in remyelination: MMPs, extracellular matrix and inflammation**

An important objective of MS treatment is to develop therapies that will enhance innate repair mechanisms and induce remyelination. However, considerable research is needed to understand the impediments to successful remyelination in MS. Dr. Yong and colleagues postulate that the microenvironment of MS lesions contains molecules that impede the process of repair. Specifically, they hypothesize that the deposition of extracellular matrix molecules (ECM) retards remyelination. Dr. Yong will explore whether the use of matrix metalloproteinases (MMPs), which are known to be physiological regulators of ECM biology, will remove inhibitory ECM molecules and allow natural repair process to occur. This research will advance the understanding of the process of myelin repair and may lead to novel medications that will enhance remyelination in MS.

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## CLINICAL and POPULATION HEALTH

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**Brenda Banwell, MD**

**Hospital for Sick Children**

(April 1, 08 to March 31, 10)

### **Clinical & neuroimaging correlates of cognitive decline in children and adolescents with MS**

Multiple sclerosis (MS) also occurs in children. Cognitive dysfunction and impaired school performance have been shown to be an important manifestation of pediatric MS, but it is not known whether the likelihood and severity of cognitive deficits increases over time, whether deficits are influenced by MRI evidence of new areas of injury (lesions) or by loss of brain volume or structure (implying a degenerative aspect of the disease), or whether cognitive impairment is influenced by age at first attack, frequency of MS relapses, or the development of physical disability. We will perform detailed studies of cognition and MRI analyses of MS lesion volume, brain volume, and structural integrity of specific brain pathways in 30 children with MS and 30 age-matched healthy children. These studies will be repeated 12 months apart to determine whether MS patients decline over time. Our study will provide urgently needed information for future studies aimed at improving cognitive outcomes in children with MS. MRI evidence of loss of brain volume or structure in very young MS patients will also support emerging concerns that the degenerative aspects of MS occur as an early aspect of the disease. Such information will further catalyze the search for neuroprotective medications- an important treatment advance for all MS patients.

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**Daria Trojan, PhD**

**McGill University**

(April 1 2007-March 31, 2009)

### **Sleep Abnormalities in MS: Association with Fatigue, Sleepiness and Quality of Life**

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 questionnaires 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.

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Lisa Walker, PhD

The Ottawa Hospital

(April 1, 08 to March 31, 10)

**A New Clinical Test for Measuring Information Processing in MS patients: The Computerized Tests of Information Processing (CTIP)**

MS patients often comment as to how the disease affects their ability to think. More specifically, they mention 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 Tests 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 traditionally have been used. The first goal is to determine if the new tests are sensitive to cognitive deficits when patients are initially evaluated. The second goal is to assess the ability of the tests to track the progressive effects of MS over a three year period. It is anticipated that results will offer clinicians a more effective technique for determining the cognitive effects of MS and assessing the therapeutic effects that various types of drugs have on the ability of patients to process information more efficiently.

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## FOUNDATION AWARDS

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**Dr. Brenda Banwell, Hospital for Sick Children, Toronto**  
**Dr. Douglas Arnold, Montreal Neurological Institute, Montreal**  
**Dr. Amit Bar-Or, Montreal Neurological Institute, Montreal**  
**Dr. Dessa Sadovnick, University of British Columbia, Vancouver**  
**\$4,300,000**

### **Development of MS in Children: Prospective Study of the Clinical Epidemiology, Pathobiology and Neuroimaging Features of Canadian Children with Clinically Isolated Demyelinating Syndromes**

This ground-breaking Canadian study will examine children who have experienced an initial attack suggestive of MS, also known as clinically isolated syndrome (CIS). This five-year, prospective paediatric MS study has 22 Canadian centres participating in 17 cities, including: Victoria, Vancouver, Edmonton, Calgary, Saskatoon, Winnipeg, London, Hamilton, Windsor, Toronto, Kingston, Ottawa, Sherbrooke, Montreal, Saint John, Halifax and St. John's. Paediatric CIS has never before been examined in such detail. The study is possible through the development of the Paediatric Demyelinating Disease Network, an extensive Canada-wide network of physicians and scientists.

- The goal of the study is to answer two important questions: what is the cause of MS and what is the risk of MS after an initial attack of CIS.
- The cause of MS: By studying paediatric patients, who are closest to the biological onset of the disease, researchers hope to identify the factors most important in disease initiation – the earliest events in MS pathobiology.
- The risk of MS after a first attack: By carefully following children who have experienced an initial attack (known as clinically isolated syndrome – CIS), researchers hope to understand why some patients have a single attack (CIS) and never progress to MS, while others have multiple attacks leading to the diagnosis of MS. The study has three pillars: clinical and genetic epidemiology, pathobiology and neuroimaging.

#### **1) Clinical and genetic epidemiology**

- To identify predictors of the disease, the researchers will define the clinical features, demographics and genetic epidemiology of children with CIS, and of those who progress to MS. Currently, there are no childhood predictors for MS.
- To increase awareness of childhood onset MS and facilitate prompt diagnosis the researchers will identify the features of MS in children, and characteristics predictive of MS risk following a first (CIS) attack.

### 2) Pathobiology

- To define the earliest immunological events that occur at the time of the first (CIS) attack, investigators will strive to identify both the triggers and initial targets of the immune cell response.
- To define those immune responses associated with, or predictive of, the risk for further attacks leading to the diagnosis of MS.

### 3) Neuroimaging

- MRI (magnetic resonance imaging) is currently available to assist in MS diagnosis, and in the prediction of MS risk following CIS in adults. By studying MRI characteristics in the paediatric study population, the researchers will:
  - Create diagnostic MRI criteria for MS in children, facilitating diagnosis.
  - Determine if particular MRI features are predictive of MS risk in children with CIS.
  - Utilize newer MRI technologies to explore whether there are fundamental differences in the brain white matter (myelin) of children destined for MS.

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**Drs. George Ebers, University of Oxford, Dessa Sadovnick, University of British Columbia, Julian Knight, University of Oxford and Alexandre Montpetit, McGill University**

**\$4,453,477**

#### **Molecular genetics of multiple sclerosis**

This proposal has been made possible by the initiation, collaboration, coherence and execution of studies carried out within the Canadian network system of MS clinics. Since the first published study from this nascent MS clinic network group in 1982 (1), the network has grown steadily. Since 1993, network MS clinics have collaborated in the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) funded by the Canadian MS Society of Canada Scientific Research Foundation. At each renewal of CCPGMS grant funding, it has been possible to point specifically to advances which have been not only unique but also dependent on the accumulated size of the database and pool of multigenerational Canadian families

The Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS) has the largest longitudinal, population-based MS database in the world with nearly 30,000 Canadian patients enrolled. A substantial proportion of what we know about the genetics and genetic epidemiology of MS has come from the CCPGMS. It has utilised its size, population base and ascertainment advantages to carry out investigations which have not been otherwise possible. These include definitive studies of adoptees, ½ sibs, conjugals, offspring of consanguineous matings, twins, intrafamilial migration, birth order and offspring risk in matings between susceptible and non-susceptible populations. Many of these studies have no parallel in either other autoimmune diseases or even the much more prevalent chronic diseases.

The DNA collection of over 15,000 samples from nearly 2500 MS families having more than one case of MS is by far the largest such in the world and substantially exceeds the pooled published resources of the International Consortium which pools many sites. Furthermore the integration of the genetic epidemiology and genetics is unique for any complex human trait.

In the last phase, several important things have been learned:

1. The rate of MS is increasing in Canada, and this is mainly due to an increase in the number of affected females.
2. The inheritance pattern of susceptibility has been studied in detail and does not appear to fit the widely believed idea that risk results from many small genes. It now seems that complexity of inheritance centres around the region of the major histocompatibility complex (MHC), the importance of which has been known for many years.

However, what is new is that most, if not all, of the genetic susceptibility comes from this MHC region. The reason this has taken so long to determine is because the interactions in this region have proven to be improbably complex and it has taken the resources of the CCPGSMS to unravel much of the detail.

3. In addition, it has been possible to identify, for the first time, a gene which influences outcome.

These findings have immense practical significance both in identifying individuals at risk and also for putting up targets for treatment.

4. Finally, considerable focus has been placed on the environment, the finding of a strong maternal parent-of-origin effect appears to be critical for MS risk and this now appears to be a gene-environment interaction via the maternal inter-uterine milieu. It is possible that both maternal and offspring genes are involved.

The present application is for the CCPGSMS Phase: Molecular Genetics. This proposal tackles, in a comprehensive way, the underlying basis for genetic susceptibility and outcome. The DNA in the small known region of susceptibility needs to be sequenced in several individuals, since it appears likely that susceptibility is determined by an interaction between the DRB1 gene and its regulatory segments. These studies will require the full resources of the CCPGSMS and the continued excellent cooperation of the MS clinics throughout Canada.

The size of the studies, the clinical and family resources and the integration of the genetic epidemiology (currently in progress in Phase 5 and funded separately from the present application by the MS Society of Canada Scientific Research Foundation) with molecular genetics (the objective of the current application) are powerful tools which are unique worldwide. The applicants feel strongly that they are in the home stretch of unraveling the underlying causes of this disease.

## MS Research Summaries 2008

Dr. Mark Freedman and Dr. Harold Atkins,  
Ottawa Hospital

\$2,419,701

### **Long term outcomes following immunoablative therapy and autologous stem cell transplant for poor-prognosis multiple sclerosis.**

MS is believed to be a disease in which the immune system attacks components of the nervous system, which ultimately results in permanent damage to the brain and spinal cord. The accumulation of the damage results in the disabilities experienced by MS patients. Drs. Freedman and Atkins hypothesize that removing the malfunctioning immune system from an MS patient will stop further damage to the nervous system. A new immune system can be grown from transplanted purified stem cells. To date, they have treated 15 patients using high doses of chemotherapy and antibodies to eradicate the malfunctioning immune system. Purified stem cells, collected from the patient prior to the chemotherapy, are transplanted back. Like patients receiving a bone marrow transplant for leukemia, MS patients experience significant side effects from the chemotherapy but generally recover in the three months following treatment. The first patient received her transplant more than five years ago. None of the patients have experienced further MS relapses following the transplant and most patients remain at the same or better level of functioning following the transplant. These results support the idea that the inexorable deterioration in function experienced by MS patients can be halted.

In-depth studies are examining the changes in brain structures with repeated MRI scans. Other laboratory studies are looking at the changes in the immune system that are associated with these outcomes. Drs. Freedman and Atkins are particularly interested in those patients that have improved following stem cell transplant. Their ongoing studies, funded by a new grant from the MS Scientific Research Foundation, will look for the mechanisms associated with this improvement.

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Dr. Luanne Metz,  
University of Calgary

\$4,047,255

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

Multiple sclerosis is a serious and costly disease but current therapies are only partially effective, are only moderately tolerable, require frequent injections, and are very expensive. Evidence suggests that treating MS very early, even after the first symptom when the diagnosis cannot yet be confirmed, may be the best way to prevent brain injury and resulting disability. Current therapies started at this time can only modestly delay a second relapse. Minocycline is an inexpensive, welltolerated, oral antibiotic that is often used to treat chronic acne. Previous research by Dr Metz and her team has demonstrated that minocycline delays disease onset and reduces disease severity in an animal model of multiple sclerosis. It also markedly reduces MRI gadolinium-enhancing activity on monthly MRI scans in people with relapsing-remitting MS. Reduced gadolinium enhancing MRI activity is known to predict reduced relapses. Levels of an enzyme, matrix metalloproteinase-9 (MMP-9), are known to be increased in people with MS, especially during a relapse. Dr. Metz has shown that this enzyme has reduced activity in the blood of patients after treatment with minocycline compared to before treatment. This further supports minocycline as a potential treatment for relapsing-remitting MS.

This study will seek to determine if minocycline is more effective than placebo in reducing the risk of developing clinically-definite MS in people with a first attack of demyelination. MS will be detected by the occurrence of a relapse or change on brain MRI scans. During the two-year study period, people who develop MS will be permitted to add an approved disease-modifying therapy and will continue in this study. Evidence that minocycline delays the onset of MS would provide patients with an inexpensive, safe, oral treatment option.

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# MS Research Summaries 2008

Dr. Dessa Sadovnick, University of British Columbia, and Dr. George Ebers,  
University of Oxford

\$4,502,164

## Canadian collaborative project on genetic susceptibility to MS (CCPGSMS) (Phase 5)

MS is the most common neurological disease affecting young adults. The CCPGSMS identifies MS cases through the MS clinics across Canada. The CCPGSMS database contains information on over 29,000 families with at least one 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:

- Living database (not static in one point in time)
- Longitudinal nature
- Ongoing contact with families and ability to update both clinical and biological samples
- Family cooperation
- Clinical and molecular information on affected and unaffected subjects, including various degrees of affected individuals and intervening relatives
- Spouse controls
- Sibling controls
- Many individuals past “risk age range” for MS
- Ethnic diversity
- “Equal access” to clinics, thereby obtaining data from a broad spectrum of socioeconomic status.

These resources provide a solid foundation for continued studies on the prevalence, pathogenesis and natural history of MS. Some of the issues that can now be addressed 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 the potential high-risk MS groups that should be targeted with primary prevention approaches?
- What are the main causes of death among people with MS?
- What is the relationship between MS and other common diseases (e.g. cancer, cardiovascular disease) and how does this information affect routine medical care?
- What are the chances that biological relatives will develop MS, and what is the need for genetic counselling?
- Does the type of MS (age of onset, clinical course, time to progressive stage, etc.) “run true” in families?

## MS Research Summaries 2008

- When one or both prospective parents has MS, what factors must be considered in the decision-making process about having children (reproductive counselling)?
- What is known about the safety of disease-modifying therapies during pregnancy and breast-feeding?

The progress achieved during this project has been reported periodically. The project is ongoing because the longitudinal nature of this study has provided unique insights into the etiology of MS. The CCPGSMS results to date have implications not only for understanding the relative roles of genetics and environment in the cause of MS, but have also provided critical insights into other key areas:

- Role of gender
  - Maternal effects
  - Impact of genetics on disease outcome
  - Clues to changing the prevalence of MS
  - Clues to changing MS rates in immigrants
  - Heterogeneity of MS
  - Evidence that primary-progressive MS is not a distinct entity.
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## DON PATY CAREER DEVELOPMENT AWARDS

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### **Dr. Fabrizio Giuliani**

University of Alberta

Category: Immunology

New: \$50,000 for each of three years

Beginning July 1, 2006

### **Dr. Ross Mitchell**

University of Calgary

Category: MRI techniques

Renewal: \$50,000 for each of three years

Beginning July 1, 2006

### **Dr. Helen Tremlett**

University of British Columbia

Category: Health research

Renewal: \$50,000 for each of three years

Beginning July 1, 2007

### **Dr. Peter van den Elzen**

University of British Columbia

Category: Clinical and population health

New: \$50,000 for each of three years

Beginning July 1, 2007

### **Dr. Nathalie Arbour**

University of Montreal

Category: Biomedical

New - \$50,000 for each of three years

Start: July 1, 2008

## POST DOCTORAL AWARDS

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<b>RECIPIENT</b>	<b>SUPERVISOR</b>	<b>INSTITUTION</b>
Smriti Agrawal , PhD	Dr. Wee Yong	University of Calgary
Benoit Barrett, PhD	Dr. Klaus-Armin Navé	Max Planck Institute, Germany
Jami Bennett, PhD	Dr.Kelly McNagny	University of British Columbia
Delphine Bouhy, PhD	Dr. Sam David	Montreal Neurological Institute
Patrick Cafferty, PhD	Dr. Vanessa Auld	University of British Columbia
Qiao Ling Cui, PhD	Dr. Jack Antel	McGill University
Axinia Doring, PhD	Dr. Wee Yong	University of Calgary
Lama Fawaz, PhD	Dr. Amit Bar-Or	Montreal Neurological Institute
Yunfei Gao, PhD	Dr. Jennifer Gommerman	University of Toronto
Lopamudra Homchaudhuri, PhD	Dr. Joan Boggs	Hospital for Sick Children, Toronto
Shannon Kolind, PhD	Dr. Heidi Johansen-Berg	University of Oxford, UK
Danette Nicolay, PhD	Dr. Wendy Macklin	Cleveland Clinic Foundation
Manu Rangachari , PhD	Dr. Vijay Kuchroo	Brigham & Women's Hospital, Boston
Christel Renoux, MD	Dr. Samy Suissa	McGill University
Scott Sloka, MD	Drs. Wee Yong and Luanne Metz	University of Calgary
Jing Wang, PhD	Drs. Freda Miller and Scott Patten	University of Toronto
Yunyan Zhang , MD	Drs. David Li and Anthony Traboulsee	University of British Columbia

## RESEARCH STUDENTSHIPS

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<b>RECIPIENT</b>	<b>SUPERVISOR</b>	<b>INSTITUTION</b>
Shawn Beug, PhD	Dr. Valerie Wallace	Ottawa Health Research Institute
Jennifer Beveridge, PhD	Dr. Mark Freedman	University of Ottawa
Sarah Bull, PhD	Dr. Tim Kennedy	Montreal Neurological Institute
Romain Cayrol, PhD	Dr. Alex Prat	University of Montreal
Zhihong Chen, PhD	Dr. Mark Freedman	Ottawa General Hospital
Rowena Cua, PhD	Dr. Wee Yong	University of Calgary
Aurore Dodolet-Devillers, MSc	Dr. Alex Prat	University of Montreal
Evgueni Doukhanine, MSc	Dr. Stephané Richard	McGill University
Leslie Fitz-Gerald, MSc	Dr. David Haegert	McGill University
Christina Gavino, MSc	Dr. Stephané Richard	McGill University
Alan Gillett, PhD	Dr. Tomas Olsson	Karolinska Institute, Sweden
Rezwan Ghassemi, PhD	Dr. Doug Arnold	McGill University
Elizabeth Girolami PhD	Dr. Sam David	Montreal Neurological Institute
Jeffrey Haines, PhD	Dr. Guillermina Almazan	McGill University
Jennifer Hahn, PhD	Dr. Frank Jirik	University of Calgary
Hau Yee Hung, MSc	Dr. Sylvie Fournier	McGill University
Saeed Kalantari, PhD	Dr. Alex MacKay	University of British Columbia
Melissa Kehler, PhD	Dr. Heather Hadjistavropoulos	University of Regina
James Knight, PhD	Dr. Rashmi Kothary	Ottawa Hospital Research Institute
Kaveh Koochesfahani, PhD	Dr. Katerina Dorovini-Zis	University of British Columbia
Allison Kraus, PhD	Dr. Marek Michalak	University of Alberta

## MS Research Summaries 2008

Dina Lafoyiannis, PhD	Dr. Mary Desrocher	Hospital for Sick Children
Lorraine Lau, PhD	Dr. Wee Yong	University of Calgary
Karen Lee, PhD	Dr. Rashmi Kothary	Ottawa Hospital Research Institute
Emilie Mackie, MSc	Dr. David Li	University of British Columbia
John-Paul Michalski, MSc	Dr. Rashmi Kothary	Ottawa Health Research Institute
Marie Ndiaye PhD	Dr. Sylvie Fournier	McGill University
Antonina Omisade, PhD	Dr. John Fisk	Dalhousie University
Cornelia Podjaski, PhD	Drs. Jack Antel and	Montreal Neurological Institute
Ali Rastikerdar, PhD	Drs. Alan Peterson and Tim Kennedy	McGill University
Aja Reiger, MSc	Dr. Amit Bar-Or	Montreal Neurological Institute
James Rowland, MSc	Dr. Michael Fehlings	University of Toronto
Carole Scherling, PhD	Dr. Andra Smith	University of Ottawa
Katrin Schulz, PhD	Dr. Sam David	Montreal Neurological Institute
Graham Smith, PhD	Dr. George Harauz	University of Guelph
Pei-Shan Wang, PhD	Dr. Catherine Pallen	University of British Columbia