

New Record Achieved in MS Research Funding

The Multiple Sclerosis Society of Canada is a national organization dedicated to improving the lives of people with MS through education, support and research. As part of its commitment to MS research, the MS Society funds Canadian physicians and scientists as they search for a cure.

In 2007, the MS Society surpassed its previous record for research funding. It approved over \$5.5 million in funding for new and renewed grants and personnel awards, to be paid over the next 3 years. The MS Society also provides funding to the MS Scientific Research Foundation, which currently has approved over \$17 million in grants to investigate ground-breaking initiatives, such as the Canadian Collaborative Project on Genetic Susceptibility to MS.

“The MS Society is dedicated to the idea of ending MS – stopping the onset of the disease and ending the disability that affects so many Canadians,” said Dr. William J. McIlroy, national medical advisor. “The best way to achieve that goal is to fund new and innovative research. Our researchers are investigating ways of regulating the immune system, repairing damaged myelin, restoring nerve function and improving quality of life in people living with MS.”

To be funded, research projects must achieve the highest level of scientific excellence, and they must focus exclusively on MS. Proposed projects undergo an exacting review process, then are forwarded to the Medical Advisory Committee for review. The National Executive Committee of the MS Society then discusses the recommendations and approves them based on the Society’s available resources.

The MS Society and the MS Scientific Research Foundation are able to continue this impressive level of funding because of the ongoing support of individual donors, corporate partners and MS Society chapters across Canada. Their efforts, with those of thousands of dedicated Canadian researchers, will help us achieve the goal of ending MS in our lifetime.

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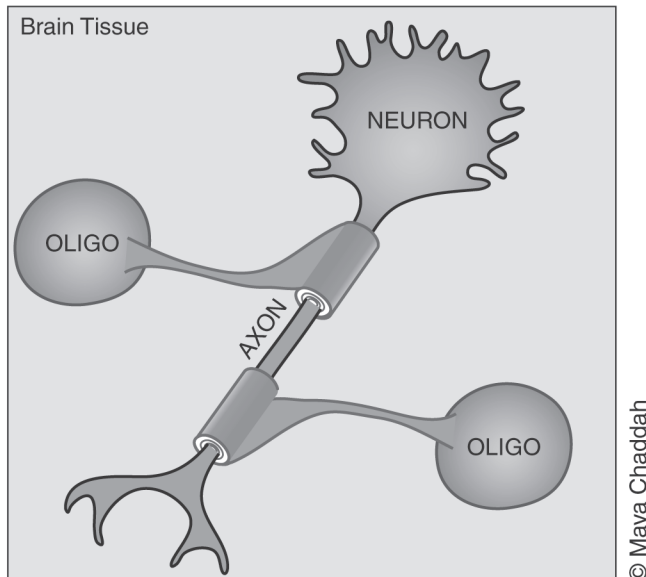
PROMOTING MYELIN

Myelin is the insulating layer that surrounds nerve fibres (axons) in the nervous system. First discovered in 1878 by Louis-Antoine Ranvier, myelin is produced by specialized glial cells. In the central nervous system (CNS), myelin is supplied by oligodendrocytes. In the peripheral nervous system, it is supplied by Schwann cells. Myelinated neurons appear white, hence the term “white matter”. “Grey matter” is composed of unmyelinated neurons.

Myelin is composed of lipids and proteins. Some of the proteins that make up myelin are myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG).

The myelin layer, or sheath, enables nerve cells to increase the speed at which they propagate nerve impulses. When the insulating layer of myelin is degraded, nerve impulses can be interrupted (a “short circuit”).

This is what occurs in multiple sclerosis. MS is characterized by an autoimmune response, in which immune cells cross the blood-brain barrier (BBB) and cause inflammation and damage to myelin in the CNS. Disruption of the myelin layer (called demyelination) results in the typical MS symptoms, such as tingling, numbness, pain and muscle weakness. If the myelin isn't fully repaired, there will be damage to the underlying axon. Over time, this process results in axonal transection (severing), axonal loss and permanent impairment of nerve function.



Oligodendrocytes (OLIGO) project their myelin-filled cell membranes, wrapping them around nerve axons to form the myelin sheath.

Protecting myelin is one of the keys to preserving nerve function and preventing disability in MS. This could be achieved by:

- Promoting the function of oligodendrocytes so they are better able to replace damaged myelin
- Enhancing the signalling that occurs between oligodendrocytes and axons
- Blocking the action of factors that inhibit remyelination.

The MS Society is funding 12 innovative research projects investigating myelin function. The goals of these efforts are to promote remyelination, protect nerve cells, and prevent the development of disability in people with MS.

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

(April 1, 2006 – March 31, 2009)

**Role of p38 MAPK (mitogen-
activated protein kinase) signalling
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.

Publications:

- Frago et al. p38 mitogen-activated protein kinase is required for central nervous system myelination. *Glia* 2007; epublihed August 29, 2007.

- Frago et al. Inhibition of p38 mitogen-activated protein kinase interferes with cell shape changes and gene expression associated with Schwann cell myelination. *Exp Neurol* 2003;183:34-46.

**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.

Publications:

- Antel J. Oligodendrocyte/myelin injury and repair as a function of the central nervous system environment. *Clin Neurol Neurosurg* 2006;108:245-259.
- Antel J, Owens T. Multiple sclerosis and immune regulatory cells. *Brain* 2004;127(pt 9):1917-1927.

Joan Boggs, PhD
Hospital for Sick Children Research Institute
University of Toronto
(April 1, 2005 –March 31, 2008)

Glycosphingolipid signalling domains and protein-protein associations in oligodendrocyte/myelin membranes

Oligodendrocytes are cells that produce myelin in the central nervous system. They wrap their myelin-filled outer membranes many times around nerve fibres (axons) to build up the myelin

sheath. The result is like the layers of an onion surrounding the axon.

In MS, oligodendrocytes cannot fully repair the damaged myelin. Clues about how to help oligodendrocytes do their job more effectively can come from studying the function of the different proteins, fats and glycolipids (a sugar bound to a fat) that make up myelin. Dr. Boggs believes that glycolipids and proteins that are in contact with each other in different layers of the myelin sheath can transmit signals that affect the viability of myelin. Building on previous MS Society funding, she is studying the behaviour of oligodendrocytes with the goal of determining the signals involved in oligodendrocyte function and oligodendrocyte-axon communication. This line of research could lead to new therapeutic approaches for stimulating remyelination by oligodendrocytes and for preventing nerve axon damage in people with MS.

Publications:

- Musse AA, et al. Deimination of membrane-bound myelin basic protein in multiple sclerosis exposes an immunodominant epitope. *Proc Natl Acad Sci USA* 2006;103:4422-4427.
- Boggs JM, et al. Effect of arginine loss in myelin basic protein, as occurs in its deiminated charge isoform, on mediation of actin polymerization and actin binding to a lipid membrane in vitro. *Biochemistry* 2005;44:3524-3534.

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.

Publications:

- Bates IR, et al. An immunodominant epitope of myelin basic protein is an amphipathic alpha-helix. *J Biol Chem* 2004;279:5757-5764.
- Bates IR, et al. Membrane-anchoring and charge effects in the interaction of myelin basic protein with lipid bilayers studied by site-directed spin labeling. *J Biol Chem* 2003;278:29041-29047.

Timothy Kennedy, PhD
McGill University

(April 1, 2005 – March 31, 2008)

Netrin function in the development of axonal-oligodendroglial interactions

Netrins are a family of proteins that are involved in guiding the development and migration of cells in the central nervous system (CNS). In research funded by the MS Society, Dr. Kennedy and colleagues have shown that one netrin, called netrin-1, is involved in regulating axon extension during embryonic development and is expressed by neurons and myelinating oligodendrocytes in the adult CNS.

In addition to this long-range role, netrins also appear to have short-range functions. Recent studies by Dr. Kennedy and colleagues have shown that netrin-1 protein and its messenger RNA (mRNA) demonstrate reduced expression at the site of spinal-cord injury. However, netrin-1 was expressed by neurons and oligodendrocytes immediately adjacent to the site of damage. The pattern of expression resembles that of known inhibitors of axon

regeneration, suggesting that netrin-1 is a myelin-associated inhibitor of axonal regeneration after spinal cord injury.

Previous work by Dr. Kennedy showed that netrin-1 is produced by different types of neurons and by mature oligodendrocytes in the adult CNS. He now plans to investigate how netrins may influence the maturation and function of oligodendrocytes in the CNS. He believes that netrins inhibit the regrowth of myelin at the site of CNS injury by preventing oligodendrocytes from reaching damaged axons. Interfering with netrin-1 may enable oligodendrocytes to migrate to the damaged axon so as to effect repair.

Publications:

- Manitt C, et al. Positioned to inhibit: netrin-1 and netrin receptor expression after spinal cord injury. *J Neurosci Res* 2006;84:1808-1820.
- Kennedy TE, et al. Axon guidance by diffusible chemoattractants: a gradient of netrin protein in the developing spinal cord. *J Neurosci* 2006;26:8866-8874.

Rashmi Kothary, PhD

Ottawa Health Research Institute

(April 1, 2005 –March 31, 2008)

Integrin signalling pathway and CNS myelination/remyelination

Integrins are receptors on the surface of cells that act as a communications link across the cell membrane. Previous work by Dr. Kothary and colleagues funded by the MS Society has shown the importance of one integrin, called beta-1 integrin, in the maturation of

oligodendrocytes. Defects in beta-1 integrin are accompanied by disruption of mitogen-activated protein kinase (MAPK) signalling. MAPK is known to be essential to proper remyelination.

Dr. Kothary is using transgenic mice that make different types of integrins to study myelin loss and regrowth. He is also creating other transgenic mice that have a gene to make integrin-linked kinase (ILK), a protein inside oligodendrocytes that is associated with cell migration, proliferation and signalling. The goal of this research is to manipulate integrin in a way that will reduce myelin destruction and promote myelin regrowth in people with MS.

Publications:

- Lee KK, et al. Dominant-negative beta1 integrin mice have region-specific myelin defects accompanied by alterations in MAPK activity. *Glia* 2006;53:836-844.
- Saulnier R, et al. Alterations in myelination in the central nervous system of dystonia musculorum mice. *J Neurosci Res* 2002;69:233-242.

Mario Moscarello, PhD and Fabrizio

Mastronardi, PhD

Hospital for Sick Children

(April 1, 2006 –March 31, 2008)

Demyelination and remyelination in MS: the role of vitamin B12 and methylation

Arginine is an amino acid that is broken down by enzymes to form citrulline. The enzymes involved are peptidyl arginine deiminases (PADs). In their previous

work, Drs. Moscarello and Mastronardi have shown that enhanced formation of citrulline in myelin basic protein (MBP) contributes to destabilization of the myelin membrane in the central nervous system of people with MS. Furthermore, Drs. Moscarello and Mastronardi have demonstrated that the amount of PAD (specifically PAD-2) appears to be increased in the normal-appearing white matter (NAWM) of the brain in people with MS. The mechanism for this increase is hypomethylation of the promoter region of the PAD-2 gene. This means that this part of the gene lacks methyl groups (CH₃). In contrast, excess PAD-2 does not appear to occur in other neurological diseases, such as Alzheimer's, Parkinson's and Huntington's disease. In consequence, Drs. Moscarello and Mastronardi have proposed that citrullinated MBP, the result of elevated PAD-2 levels, may be an important pathway in the MS disease process.

The current research will examine whether vitamin B12 can increase the number of methyl groups at the PAD-2 gene promoter. The goal is to reduce the amount of PAD-2 and prevent the destabilization of myelin in the central nervous system. Previous work by Drs. Moscarello and Mastronardi has reported that vitamin B12, in combination with beta-interferon or paclitaxel, reduces MS symptoms in animal models. These studies were funded by the MS Society.

Publications:

- Moscarello MA, et al. The role of citrullinated proteins suggests a novel mechanism in the pathogenesis of multiple sclerosis. *Neurochem Res* 2007;32:251-256.

- Mastronardi FG, et al. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. *J Neurosci Res* 2007;85:2006-2016.

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.

Publications:

- Yin X, et al. Evolution of a neuroprotective function of central nervous system myelin. *J Cell Biol* 2006;172:469-478.
- Forghani R, et al. A distal upstream enhancer from the myelin basic protein gene regulates expression in myelin-forming Schwann cells. *J Neurosci* 2001;21:3780-3787.

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.

Publications:

- Larocque D, Richard S. QUAKING KH domain proteins as regulators of glial

cell fate and myelination. *RNA Biol* 2005;2:37-40.

- Galarneau S, Richard S. Target RNA motif and target mRNAs of the Quaking STAR protein. *Nat Struct Mol Biol* 2005;12:691-698.

Peter Stys, MD
University of Calgary

(April 1, 2006 –March 31, 2008)

Mechanisms of axon spheroid formation

The destruction of myelin and the degeneration of nerve fibres (axons) seen in MS results in axonal transection, in which the axons are severed and can no longer transmit electrical impulses. As more and more axons are lost, there is progressive and permanent loss of nerve function, resulting in the range of disabilities seen in MS.

Before an axon is severed, it swells up in a process called spheroid formation. Although this phenomenon has been observed microscopically for over 150 years, there is still no clear idea what causes the swelling. Dr. Stys and colleagues have developed a tissue model that mimics axonal swelling to visualize the process in real time with laser scanning microscopes. The goal of this research project is to determine what triggers axonal swelling. This may lead to medications that might be used to prevent spheroid formation and axonal transection in people with MS.

Publications:

- Stys PK. Sodium channel blockers as neuroprotectants in neuroinflammatory

disease: a double-edged sword.
Ann Neurol 2007;62:3-5.

- Micu I, et al. Real-time measurement of free Ca²⁺ changes in CNS myelin by two-photon microscopy. *Nat Med* 2007;13:874-879.

V. Wee Yong, PhD
University of Calgary

(April 1, 2004 -March 31, 2007)

Beneficial roles of matrix metalloproteinases (MMPs) in myelin formation

Matrix metalloproteinases (MMPs) are enzymes that degrade the blood-brain barrier in MS, enabling activated T cells to enter the central nervous system. However, in recent years Dr. Yong and colleagues have shown that MMPs may also have beneficial effects in MS. In animal models, MMP-9 at the site of a demyelinating lesion of the spinal cord has been shown to facilitate remyelination. During myelin formation, two MMPs, MMP-9 and -12, are upregulated, and mice deficient in MMP-9 and -12 display deficient myelination.

Dr. Yong continues to explore the role of metalloproteinases in regulating myelin formation and axonal growth. Some MS therapies act by inhibiting selected MMPs, and Dr. Yong will also research if chronic inhibition of MMP activity actually impairs myelin formation. This research may lead to new therapies based on MMPs that could help restore the myelin sheath and promote recovery in people with MS.

Publications:

- Larsen PH, et al. Myelin formation during development of the CNS is delayed in matrix metalloproteinase-9 and -12 null mice. *J Neurosci* 2006;26:2207-2214.
- Yong VW. Metalloproteinases: mediators of pathology and regeneration in the CNS. *Nat Rev Neurosci* 2005;6:931-944.

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.

Publications:

- Yong VW, et al. Elevation of matrix metalloproteinases (MMPs) in multiple sclerosis and impact of immunomodulators. *J Neurol Sci* 2007;259(1-2):79-84.
- Yong VW, et al. Experimental models of neuroprotection relevant to multiple sclerosis. *Neurology* 2007;68(22 suppl 3):S32-S37.

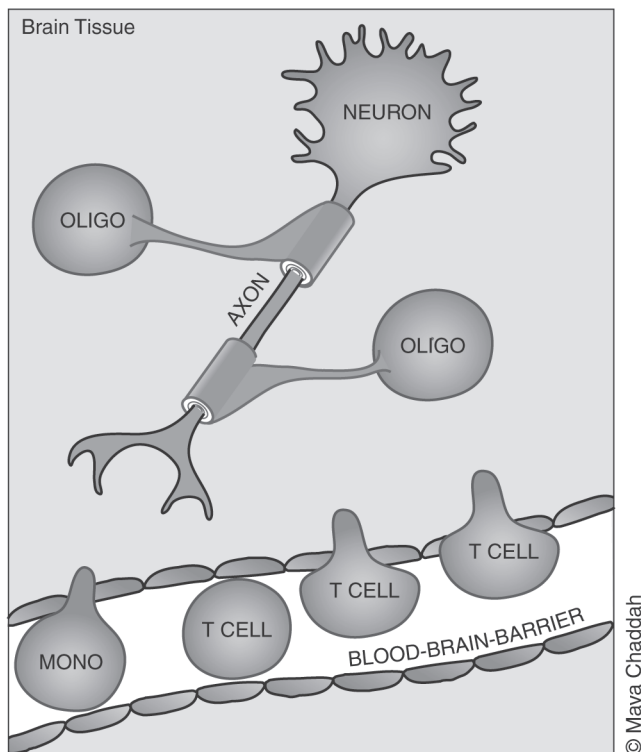
UNDERSTANDING THE IMMUNE RESPONSE

MS is characterized by an abnormal autoimmune response in which the body's immune system attacks its own tissues. Activated T cells cross the blood-brain barrier (BBB) and cause inflammation and damage to the central nervous system. A chief target of this T cell attack is myelin basic protein (MBP), a major component of myelin. During inflammatory episodes, myelin is degraded (demyelinated) and the underlying neuron can become damaged or destroyed.

The immune response is highly complex and a great deal of research is needed to understand:

- How are T cells activated?
- What factors are involved in trafficking T cells across the BBB and are there factors that could enhance the integrity of the BBB?
- How does inflammation result in damage to the myelin and axons?
- How are inflammatory lesions formed in the CNS?

These are among the many research questions that are now being investigated in 15 MS Society-funded projects. The goals of this research are to identify ways to modulate the immune response, protect the CNS from inflammation, and make the immune attack on CNS tissues less damaging.



T cells and monocytes (MONO) enter the brain tissue by squeezing through endothelial cells that line the blood brain barrier.

Nathalie Arbour, PhD **Centre Hospitalier de l'Université de Montréal**

(April 1, 2007 – March 31, 2009)

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

The immune system in multiple sclerosis demonstrates abnormalities in T cell activation resulting in tissue destruction in the central nervous system. Previous research by Arbour and colleagues has shown that environmental signals, such as DNA damage and inflammation, can induce the expression of an activating or coactivating receptor (NKG2D) on human natural killer (NK) cells and CD8+ T cells. Disruption of the NKG2D- ligand interaction in vitro significantly inhibited

killing of oligodendrocytes by activated NK cells and self-reactive CD8+ T cells.

Dr. Arbour plans to compare the immune responses of MS patients with healthy controls. The goal is to analyse the function of NK and CD8+ T cells to determine what potentiates their capacity to be injurious to CNS tissues in MS patients. This research may lead to the identification of new potential targets for future treatments.

Publications:

- Saikali P, et al. NKG2D-mediated cytotoxicity toward oligodendrocytes suggests a mechanism for tissue injury in multiple sclerosis. *J Neurosci* 2007;27:1220-1228.
- Arbour N, et al. A new clinically relevant approach to expand myelin specific T cells. *J Immunol Methods* 2006;310(1-2):53-61.

Samuel David, PhD **McGill University**

(April 1, 2006 – March 31, 2008)

Selective roles for different members of the phospholipase A2 family in EAE

Phospholipase A2 (PLA2) is an enzyme that produces products that can induce the breakdown of myelin and stimulate the inflammatory response. In an animal model of MS, called experimental autoimmune encephalomyelitis (EAE), PLA2 has been shown to play an important role in the onset and progression of EAE. In one experiment, blocking cytosolic PLA2 in the transected sciatic nerve slowed myelin degradation and axonal deterioration in the distal nerve segment. Deterioration distal

to the site of injury is called Wallerian degeneration, and PLA2 appears to play a direct role.

Dr. David now has evidence that four of fourteen PLA2 tested are increased in the spinal cord and spleen of EAE mice. His preliminary data show that these four PLA2 may be involved in different phases of EAE. He is currently working on developing specific inhibitors for these four PLA2 enzymes. The goal is to determine which cells in EAE lesions produce the different forms of PLA2, and to assess their role by selectively blocking them with the specific inhibitors.

Publications:

- Kalyvas A, David S. Cytosolic phospholipase A2 plays a key role in the pathogenesis of multiple sclerosis-like disease. *Neuron* 2004;41:323-335.
- De S, et al. Phospholipase A2 plays an important role in myelin breakdown and phagocytosis during Wallerian degeneration. *Mol Cell Neurosci* 2003;24:753-765.

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 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.

Publications:

- Wong D, et al. Adhesion and migration of polymorphonuclear leukocytes across human brain microvessel endothelial cells are differentially regulated by endothelial cell adhesion molecules and modulate monolayer permeability. *J Neuroimmunol* 2007;184(1-2):136-148.
- Wong D, et al. Cytokines, nitric oxide, and cGMP modulate the permeability of an in vitro model of the human blood-brain barrier. *Exp Neurol* 2004;190:446-455.

Katerina Dorovini-Zis
Vancouver General Hospital
University of British Columbia
(April 1, 2007 – March 31, 2008)

Entry of monocytes and dendritic cells into the brain: regulation by adhesion molecules and chemokines

The two most important features of autoimmune inflammatory diseases of the central nervous system are the

infiltration of circulating white blood cells (WBC), and an early increase in the permeability of the blood-brain barrier (BBB). The objective of the proposed studies is to characterize the role of an important group of molecules, called endothelial cell (EC) adhesion molecules, and a family of inflammatory mediators, the chemokines, in the recruitment of certain WBC subsets. Previous research by Dr. Dorovini-Zis and colleagues identified the importance of beta-chemokines, which mediate inflammation, in regulating the traffic of recently activated T cells.

Dr. Dorovini-Zis will also investigate the molecular mechanisms that mediate the permeability of the BBB during WBC transmigration using an in vitro model of the BBB developed in her laboratory. The studies will focus on two WBC subtypes: the monocytes, and the dendritic cells (DC). Both play important roles in CNS inflammation and autoimmunity.

This research will provide insight into the factors that regulate the traffic of monocytes and DCs across the BBB and the mechanisms of BBB dysfunction during inflammation. The results may lead to new therapeutic interventions in CNS inflammation, such as treatment with antibodies against adhesion molecules, integrins or chemokine receptors, or administration of modified chemokines that would block the influx of WBCs into the CNS.

Publications:

- Quandt J, Dorovini-Zis K. The beta chemokines CCL4 and CCL5 enhance adhesion of specific CD4+ T cell

subsets to human brain endothelial cells. *J Neuropathol Exp Neurol* 2004;63:350-362.

- Dorovini-Zis K, et al. Isolation and characterization of human brain endothelial cells. *Methods Mol Med* 2003;89:325-336.

Alexander Easton, MBBS, PhD and Chunahi Hao, MD, PhD Dalhousie University

(April 1, 2006 –March 31, 2008)

Inflammatory modulation of the blood-brain barrier by Fas ligand and TRAIL

A key aspect of the MS disease process is the increased permeability of the blood-brain barrier (BBB), which normally restricts the passage of substances into the central nervous system (CNS). In MS, inflammation disrupts the BBB, allowing activated T cells to enter the CNS, where they cause tissue damage. This process occurs, in part, because of the activity of cellular messengers called cytokines. Of particular interest is one type of cytokine called tumour necrosis factor (TNF).

Drs. Easton and Hao are studying two members of the TNF family, called Fas ligand and TRAIL (TNF-related apoptosis-inducing ligand). Their role in endothelial cell activation is unclear but to date, the researchers have discovered that Fas ligand promotes the activation of brain endothelial cells while TRAIL inhibits it. In cell culture models of the BBB, Fas ligand has been shown to increase T lymphocyte adhesion and permeability, indicating that Fas ligand may increase

the movement of T cells across the BBB. Conversely, TRAIL reduces permeability without promoting adhesion, suggesting that TRAIL may reduce the transmigration of T cells across the BBB. With the new operating grant, the researchers hope to confirm their initial findings and explore the various signals involved. If TRAIL can be demonstrated to reduce T cell entry into the CNS, it may have potential as a therapy to reduce CNS inflammation in MS.

Publications:

- Hu DE, et al. TRPV1 activation results in disruption of the blood-brain barrier in the rat. *Br J Pharmacol* 2005;146:576-584.
- Alladina SJ, et al. TRAIL-induced apoptosis in human vascular endothelium is regulated by phosphatidylinositol 3-kinase/Akt through the short form of cellular FLIP and Bcl-2. *J Vasc Res* 2005;42:337-347.

**Sylvie Fournier, PhD
McGill University**

\$181,264 (April 1, 2006 – March 31, 2008)

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

Multiple sclerosis is an inflammatory disease of the central nervous system (brain and spinal cord) in which immune system T cells play an important role. There are two major types of T cells: CD4+ and CD8+ T cells. In the past, research has focused almost exclusively on the role of CD4+ T cells in MS. However, recent evidence suggests that CD8+ T cells may also contribute to starting and

continuing the disease process.

In past studies, Dr. Fournier and colleagues have generated a new model of MS in which mice spontaneously develop a T cell-mediated demyelinating disease similar to MS. She has shown that this demyelinating disease occurs as a result of an inflammatory response initiated through the activation of CNS-specific CD8+ T cells. These findings indicate that autoreactive CD8+ T cells may have a direct role in the development of MS.

Dr. Fournier now plans additional studies using this animal model to identify the process by which CD8+ T cells become activated, and how this activation leads to inflammation and tissue damage in the CNS.

Publications:

- Brisebois M, et al. A pathogenic role for CD8+ T cells in a spontaneous model of demyelinating disease. *J Immunol* 2006;177:2403-2411.
- Zehntner SP, et al. Constitutive expression of a costimulatory ligand on antigen-presenting cells in the nervous system drives demyelinating disease. *FASEB J* 2003;17:1910-1912.

**Alyson Fournier, PhD
Montreal Neurological Institute**
(April 1, 2007 – March 31, 2010)

Inhibitory effects of immune cells on neurite outgrowth

Multiple sclerosis is characterized by demyelination and neuronal damage as a result of infiltration of activated immune cells into the central nervous system. Sustained neurological disability is

believed to be due to axonal transection within MS inflammatory plaques and subsequent failure of the neurons to repair themselves. Little is known about the potential impact of immune cells on neuronal repair.

Dr. Fournier and colleagues have demonstrated that peripheral blood mononuclear cells (PBMCs), such as lymphocytes, have a significant inhibitory effect on neurite outgrowth. Small lymphocytes, such as T lymphocytes and B lymphocytes, can influence neuronal repair when activated by a variety of stimuli. Ongoing research will clarify immune-neural interactions relevant to CNS inflammatory conditions and may lead to new avenues for promoting axonal repair in MS.

Publications:

- Niino M, et al. Natalizumab effects on immune cell responses in multiple sclerosis. *Ann Neurol* 2006;59:748-754.
- Fournier AE, et al. Rho kinase inhibition enhances axonal regeneration in the injured CNS *J Neurosci* 2003;23:1416-1423.

**Fabrizio Giuliani, MD
University of Alberta**

(April 1, 2006–March 31, 2008)

Role of inflammation in neurodegenerative processes of multiple sclerosis

The inflammatory episodes seen in MS are believed to result in damage to neurons (nerve cells) and axons (nerve fibres). Axonal damage has been shown to be increased during periods when

inflammation worsens within MS lesions.

In his previous research, Dr. Giuliani determined that human neurons are extremely vulnerable to injury. His in vitro studies have shown that activated T cells align along the axons and cell bodies of cultured human neurons, which leads to neuronal death. Dr. Giuliani is also exploring new anti-inflammatory combination treatments and their potential to reduce inflammation in a mouse model of MS. These results have led to a phase II clinical trial involving 40 people with MS at the University of Calgary. The long-term goal of the trial is to identify new anti-inflammatory therapies that might lessen inflammation in MS lesions and prevent the transition to the progressive phases of MS.

Publications:

- Kebir H, et al. Human T(H)17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med* 2007;epublished September 9, 2007.
- Giuliani F, et al. Vulnerability of human neurons to T cell-mediated cytotoxicity. *J Immunol* 2003;171:368-379.

**Jennifer Gommerman, PhD
University of Toronto**

(April 1, 2007 – March 31, 2010)

Evaluating the role of the lymphotoxin pathway in EAE

Lymphocytes are a type of white blood cell (WBC) that are involved in fighting infection. In addition to recognizing foreign pathogens (e.g. viruses), some lymphocytes may self-

react to tissues in our bodies and cause inflammation. Normally the immune system maintains such lymphocytes in a state of tolerance so that they do not respond to 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 (DC) within the central nervous system are important for propagating inflammation and disease. However, the nature of these interactions remains poorly characterized.

Dr. Gommerman's area of interest is the lymphotoxin pathway. Lymphotoxin is a cytokine that is an important regulator of DC function. Previous research has shown that inhibitors of the lymphotoxin pathway can reduce disease activity in a variety of laboratory models of autoimmune disease. For example, inhibitors of this pathway have been shown to prevent disease relapses in EAE (an animal model of MS) by inducing T cell tolerance. Dr. Gommerman plans to investigate the lymphotoxin pathway to determine how it is involved in the cellular events that cause inflammation in the CNS. For her research, she will use a new type of EAE mouse that has been genetically altered so that it develops both spontaneous and induced EAE. With this model, she will be able to track the fate of the lymphocytes attacking the CNS in parallel with inhibitors of the lymphotoxin pathway.

Publications:

- Summers-DeLuca LE, et al. Expression of lymphotoxin-alpha on antigen-

specific T cells is required for DC function. *J Exp Med* 2007;204:1071-1081.

- Gommerman JL, Browning JL. Lymphotoxin/light, lymphoid microenvironments and autoimmune disease. *Nat Rev Immunol* 2003;3: 642-655.

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, Dr. Haegert and colleagues found that there are abnormalities in the regulation of naive CD4 T cells in relapsing-remitting MS, and that these cells proliferate to maintain the size of the naive CD4 T cell population.

Dr. Haegert hypothesizes that naive CD4 T cells are partly activated in some RRMS patients. These CD4 T cells respond more readily and significantly to activation signals than do comparable cells from healthy controls. This abnormal response to various signals may result in autoreactivity. This might explain why some individuals develop MS and others do not.

To investigate this, Dr. Haegert will use microarray methods to compare gene expression and cytokine production in naive CD4 T cells and memory CD4 T cells from MS patients and controls. A detailed study of naive and memory CD4 T cells may be able to identify subgroups

of relapsing-remitting MS patients who have different gene expression profiles. As one or more subgroups may show a differential response to treatment, the findings may ultimately guide clinicians in selecting treatment for MS.

Publications:

- Duszczyszyn DA, et al. Altered naive CD4 and CD8 T cell homeostasis in patients with relapsing-remitting multiple sclerosis: thymic versus peripheral (non-thymic) mechanisms. *Clin Exp Immunol* 2006;143:305-313.
- Haegert DG, et al. Does a shift in the T-cell receptor repertoire precede the onset of MS? *Neurology* 1999;53: 485-490.

**David George Haegert, MD, and Veerabhadra Gadag, PhD
McGill University**

(April 1, 2005 –March 31, 2008)

Altered naive T-cell homeostasis in multiple sclerosis

T cells of the immune system are made in the bone marrow and travel to the thymus where they mature before being released into the blood. Building on work previously supported by the MS Society, Drs. Haegert and Gadag propose that people with MS have fewer T cells than healthy individuals, and that a reduced T cell population may be linked to additional T cell abnormalities.

To date, Drs. Haegert and Gadag have identified a marker that measures the number of naive (untriggered) T cells made by the thymus. They now plan to test for this marker in people with relapsing-remitting MS, primary-

progressive MS, and clinically isolated syndrome (a single demyelinating event). They will also analyse factors influencing T cell regulation in these groups.

If it can be established that MS patients have a reduced number of T cells, this finding would have important implications. An abnormality in T cell production could precede the onset of MS and help explain why some individuals develop the disease. In people with precursor lesions resulting from a single demyelinating event, identifying lower numbers of naive T cells might help to predict who will go on to develop clinically definite MS. These higher-risk individuals would be candidates for early treatment to prevent the onset of MS.

Publications:

- Haegert DG, et al. Identical twins discordant for multiple sclerosis have a shift in their T-cell receptor repertoires. *Clin Exp Immunol* 2003;134:532-537.
- Daniel ES, et al. Method of data analysis that elucidates contributions to the T-cell receptor repertoire. *Biotechniques* 1997;23:78-82.

Trevor Owens, PhD
McGill University

(April 1, 2005 –March 31, 2008)

Immune-glia interactions in CNS inflammation and demyelinating disease

Toll-like receptors (TLR) are initiators of the immune system's response to pathogens. In recent years, TLRs have been shown to play a role in the central nervous system, regulating neuroinflammation and the outgrowth of neurites (projections from nerve cells, i.e. axons and dendrites).

In research funded by the MS Society, Dr. Owens has shown that damage to nerve fibres (axons) in the brain causes glial cells (support cells) to produce chemokines. These are messenger molecules that attract immune cells to the chemokine source. He also showed that TLRs are critical for T cell entry into the CNS, and can control how cytokine messenger molecules respond to injury.

Dr. Owens is using genetically modified mice to explore how TLRs, cytokines and chemokines influence the entry of T cells and macrophages into the brain. He believes that not all immune cells entering the brain cause damage and will investigate how to control the outcome of macrophage and T cell entry into the CNS.

Publications:

- Babcock AA, et al. Toll-like receptor 2 signaling in response to brain injury: an innate bridge to neuroinflammation. *J Neurosci* 2006;26:12826-12837.
- Owens T, et al. Cytokine and chemokine inter-regulation in the inflamed or injured CNS. *Brain Res Rev* 2005;48:178-184.

Alexandre Prat, MD, PhD
Montreal University

(April 1, 2006 –March 31, 2009)

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

Dendritic cells (DCs) have the pivotal role of triggering T cells as part of the immune system response. Several investigators have found that DCs associated with the blood-brain barrier (BBB) are important for the formation of lesions in EAE (experimental autoimmune encephalomyelitis), an animal model of MS.

Dr. Prat is investigating whether endothelial cells lining the BBB (dubbed "eDCs") make cytokine messengers that influence the development of DCs. He plans to investigate whether eDCs can trigger or halt the activation of different types of T cells that might be present in MS lesions. The goal is to discover how eDCs are formed and whether they sustain or counteract the damage that T cells cause during MS. To aid his research, Dr. Prat has developed a human model of the BBB and will employ tissue from his substantial bank of MS brain specimens.

Publications:

- Kebir H, et al. Human T(H)17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med* 2007;epublished September 9, 2007.
- Jack CS, et al. Th1 polarization of CD4+ T cells by toll-like receptor 3-activated human microglia. *J Neuropathol Exp Neurol* 2007;66:848-859.

Christopher Power, MD

University of Alberta

(April 1, 2006 – March 31, 2009)

Pathogenic interactions between human retroelements and neuroinflammation in MS

An estimated 5-10% of the human genome is made up of viruses called retroviruses, which have been incorporated into the human genome over millions of years of evolution. In his prior research, Dr. Power and colleagues have shown that there is increased activity of the human endogenous retrovirus (HERV) gene in human glial cells. Moreover, syncytin-1, an envelope protein produced by HERV, has been shown to be upregulated in glial cells inside the acute demyelinating lesions of MS patients. Thus, HERV gene expression in the central nervous system of people with MS contributes to activation of the immune system and damage to myelin.

Dr. Power plans to evaluate the level of different retroviruses present in people with MS. The long-term goal of his 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 will use to study myelin damage and the effects of novel therapies for MS.

Publications:

- Antony JM, et al. The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum

chaperones in astrocytes. *J Immunol* 2007;179:1210-1224.

- Antony JM, et al. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. *Nat Neurosci* 2004;7:1088-1095.

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 myelin sheath, a fatty insulation that covers nerve cells in the brain and spinal cord. A distinguishing feature of myelin is its high fat concentration, which makes up 70% of its total content. Myelin destruction in MS is believed to be caused by aberrant immune system activity, which mistakenly targets myelin. The reasons for this are unknown.

Coordinating this attack are T cells, which recognize myelin components presented to them by specialized antigen-presenting cells (APC). While considerable progress has been made in understanding how T cells recognize the protein components of myelin, it was only recently discovered that fats can be targeted by T cells in a similar manner to proteins. Prior research by Dr. van den Elzen and colleagues showed that lipid antigens presented by APCs are bound by CD1 molecules to lipid-reactive T cells. Apolipoproteins, which mediate lipid transport, are involved in this process. Their recent work demonstrated that

ApoE binds lipid antigens and delivers them into endosomal compartments containing CD1 in APCs. ApoE was previously thought to be involved only in cholesterol transport and metabolism.

Dr. van den Elzen plans to study the immune responses to the fat components of the myelin sheath, which appear to play an important role in the overall immune recognition of myelin. The connection between apoE and the immune system recognition of fats is likely to be of great importance in our understanding of how the immune system attacks the myelin sheath. Therapies and drugs that target this pathway, such as the cholesterol-lowering drugs, hold great promise. Future treatment plans to address this pathway could include modulation of dietary fats or other approaches that would be important to all MS patients.

Publications:

- van den Elzen P, et al. Apolipoprotein-mediated pathways of lipid antigen presentation. *Nature* 2005;437:906-910.
- Hava DL, et al. CD1 assembly and the formation of CD1-antigen complexes. *Curr Opin Immunol* 2005;17:88-94.

MRI: PROVIDING PICTURES OF MS

Magnetic resonance imaging (MRI) is a highly useful tool that allows doctors and scientists to take pictures inside the body. An MRI can detect differences in tissue density through the use of powerful magnetic fields. Areas of inflammation show up as discrete spots, indicating that edema (fluid) and tissue destruction have occurred.

The presence of inflammatory plaques (lesions) in the central nervous system, accompanied by certain neurological signs and symptoms, is highly suggestive of MS. So MRI is now routinely used to confirm the diagnosis. During the clinical course of MS, serial MRIs can record changes that are occurring as lesions develop, remyelinate or progress.

MRI has led to the development of other imaging techniques used in clinical research, such as magnetic resonance spectroscopy (MRS), which provides detailed information on biochemical changes in the CNS (such as destruction of myelin); and diffusion tensor imaging (DTI), which measures water diffusion in tissues to enable researchers to construct a map of the brain.

The MS Society is currently funding six MRI research projects. The hope is that if doctors can "see" MS more clearly during the course of disease, they will be in a better position to treat it more effectively.

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 of MS patients have revealed that a substantial amount of damage occurs in the cerebral cortex (the “grey matter”). The majority of this pathology in MS takes the form of band-like demyelinated lesions on the cortical surface that may span several gyri (ridges), yet still remain “invisible” to current MRI techniques. Our inability to visualize these lesions in living subjects is a major impediment to progress in understanding the clinical evolution of MS and the use of MRI as a marker of MS pathology. As long as we cannot see these lesions, we cannot determine when they develop and how they relate to clinical disability and progression. This is important since progression will eventually occur independently of focal white matter lesions despite their suppression with current therapies.

Dr. Arnold plans to develop MRI methods that will detect and quantify the cortical gray matter lesions that occur in MS patients. His approach will be to use magnetization transfer imaging (MTI), a specialized form of MRI that is more specific to myelin density, and advanced image-processing techniques. These novel methods will be validated with respect to post-mortem histopathology. The goal is to determine how cortical lesions affect the clinical course of MS, their association with neuropsychological

deficits, and their relationship to white matter lesions and brain atrophy.

Publications:

- Chen JT, et al. Relating neocortical pathology to disability progression in multiple sclerosis using MRI. *Neuroimage* 2004;23:1168-1175.
- Antel SB, et al. Computational models of MRI characteristics of focal cortical dysplasia improve lesion detection. *Neuroimage* 2002;17:1755-1760.

Douglas Arnold, MD, and Bruce Pike, PhD McGill University
(April 1, 2005 – March 31, 2008)

Imaging demyelination and remyelination in MS

During MS, the myelin insulation surrounding nerve fibres (axons) is damaged. Short-term myelin loss can cause acute symptoms of relapse while prolonged myelin loss may cause the death of axons, leading to permanent disability. The relationship between myelin loss, axonal injury and disability can be investigated by using imaging techniques that measure myelin loss and repair. Damage to the brain during MS can be seen as white spots on conventional magnetic resonance images (MRI). Unfortunately, these findings are difficult to interpret and cannot be correlated with the degree of brain injury or to the clinical symptoms that develop.

Drs. Arnold and Pike are investigating better imaging methods to measure myelin loss and repair over time in acute MS lesions. Magnetization transfer imaging (MTI) is a newer MRI technique

that is superior to MRI in that it gives specific information about myelin damage. To date, Drs. Arnold and Pike have used MTI to clarify the timeline of myelin loss in chronic and acute MS lesions. Their ongoing research should be able to demonstrate whether MTI can be successfully used to monitor the effect of future therapies aimed at promoting myelin regrowth in people with MS.

Publications:

- Chen JT, et al. Voxel-based analysis of the evolution of magnetization transfer ratio to quantify remyelination and demyelination with histopathological validation in a multiple sclerosis lesion. *Neuroimage* 2007;36:1152-1158.
- Arnold DL. Evidence for neuroprotection and remyelination using imaging techniques. *Neurology* 2007;68(22 suppl 3):S83-S90.

Fiona Costello, MD

University of Calgary

(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, affecting 75% of patients during the course of their disease. The visual pathway offers scientists a unique opportunity to study the effects of MS, because nerve damage can be observed directly in the eye. The optic nerve is a structure that carries information from the eye to vision centres in the brain. When attacked by MS, the axons (nerve

fibres) within the optic nerve become damaged.

As these axons splay over the retina, they make up the retinal nerve fibre layer (RNFL). A new device called optical coherence tomography (OCT) can be used to measure the thickness of the RNFL. This technique can be employed to quantify axonal loss due to ON. Dr. Costello hypothesizes that if the damage that occurs in optic nerve axons is the same as that which occurs in the brain, the retina could be a window through which clinicians could look more directly at axonal damage in MS patients. Dr. Costello's investigation of OCT could lead to the use of this technology to evaluate how the brain repairs itself and whether therapies are effective in MS.

Publications:

- Frohman E, et al. Optical coherence tomography in multiple sclerosis. *Lancet Neurol* 2006;5 :853-863.
- Costello F, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. *Ann Neurol* 2006;59:963-969.

Alex MacKay, MD, and David Li, MD

University of British Columbia

(April 1, 2004 – March 31, 2007)

In vivo serial studies of pathology in multiple sclerosis integrating the results from several magnetic resonance techniques

In MS, damage to myelin may result in relapses in which vision, sensation, coordination and strength are temporarily or permanently lost. With the development of magnetic resonance (MR)

techniques, researchers are no longer confined to post-mortem observation but can follow physical and chemical changes to myelin in people living with MS.

Drs. MacKay and Li are using a variety of different MR techniques to pinpoint when myelin loss occurs in MS lesions. With past funding from the MS Society, the researchers developed a better MR technique that takes advantage of water trapped in the myelin layers to generate a very high-resolution myelin map. Their new magnetic resonance spectroscopy (MRS) scanner also provides higher quality two-dimensional images than those obtained in previous years.

With their new and improved MR techniques, Drs. MacKay and Li are using a number of markers to gauge myelin loss, regrowth and changes in normal-appearing white matter of the brain. By relating clinical disability with the observed physical and chemical changes to myelin, they hope to be able to predict some of the factors that contribute to functional loss in people living with MS.

Publications:

- Brief EE, et al. Proton T1 relaxation times of cerebral metabolites differ within and between regions of normal human brain. *NMR Biomed* 2003;16:503-509.
- MacKay A, et al. In vivo visualization of myelin water in brain by magnetic resonance. *Magn Reson Med* 1994;31:673-677.

Alex MacKay

University of British Columbia

(April 1, 2007 – March 31, 2010)

In vivo measurement of MS pathology by magnetic resonance imaging

Much of what we know about the mechanisms of myelin and axonal 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, little is known about the pathological changes that occur earlier in the disease process. It would be invaluable to study MS in the early stages of disease, as this would allow researchers to better understand the mechanisms of damage.

Magnetic resonance imaging enables us to follow the physical and chemical changes in the brains of people living with MS. The goal of this study is to use MRI to follow the neurodegenerative processes that occur in MS. Dr. MacKay will focus on three particular magnetic resonance techniques – T2 relaxation, diffusion tensor imaging and perfusion imaging – to measure different properties of brain tissue at the cellular level. One goal will be to understand the process of myelin destruction and regrowth in lesions, as well as in normal-appearing white matter. Dr. MacKay will also investigate the presence or absence of pools of extracellular water, which can increase in some lesions and in other white matter areas. Gaining insight into the pathological processes that occur will aid in the diagnosis and management of people living with MS.

Publications:

- MacKay A, et al. Insights into brain microstructure from the T2 distribution. *Magn Reson Imaging* 2006;24:515-525.
- Larsson HB, et al. Nuclear magnetic resonance relaxation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998;64(suppl 1):S70-S76.

J. Ross Mitchell, PhD

University of Calgary

(April 1, 2006 –March 31, 2009)

Texture analysis of myelin sensitive MRI

Magnetic resonance imaging (MRI) is a reliable method of visualizing MS lesions but it is often unclear how lesions relate to clinical status in people. Despite advances in medical imaging over the last two decades, the interpretation of MRIs is still somewhat subjective.

During the last period funded by the MS Society, Dr. Mitchell introduced a new type of MRI analysis, called multiscale localized image texture analysis. Texture refers to a measurable characterization of the local pattern of an MR image and provides a sensitive and precise indication of disease activity.

Dr. Mitchell will employ texture analysis to study MRIs 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.

Publications:

- Zhang Y, et al. A novel MRI texture analysis of demyelination and inflammation in relapsing-remitting experimental allergic encephalomyelitis. *Med Image Comput Assist Interv Int* 2006;9(pt 1):760-767.
- Zhu H, et al. A new local multiscale Fourier analysis for medical imaging. *Med Phys* 2003;30:1134-1141.

IMPROVING QUALITY OF LIFE

MS results in a number of disabling symptoms, such as fatigue, chronic pain and sleep disorders, that can have a major impact on patients' ability to work and on their quality of life.

Fatigue is a factor in the daily life of most people living with MS, and many people say that it is their worst MS symptom. Fatigue is commonly cited as the reason why an individual with MS can no longer work.

People with MS are also at high risk of developing clinical depression because of the physical and psychosocial changes that come from living with the disease.

The MS Society is funding three research projects on MS symptoms and dietary factors. The goals are to enable people with MS to cope with their illness and improve their daily quality of life.

Anthony Feinstein, PhD

University of Toronto

(April 1, 2007-March 31, 2008)

MS and depression: an MRI diffusion tensor imaging study

Depression contributes significantly to the disability associated with MS. Almost one in two MS patients will experience clinically significant depression during the course of their lives. The reason why so many MS patients become depressed is unclear

Dr. Feinstein and colleagues have previously shown that lesions and shrinkage in certain brain regions leave MS patients at risk for developing depression. These results could explain less than one-half the reasons why depression first began, perhaps due to the limitations of MRI technology. However, newer MRI techniques are allowing researchers to probe the brain in greater detail, looking not just at anatomy, but also at microscopic indices of brain pathology. One such technique is diffusion tensor imaging (DTI).

Dr. Feinstein plans to use conventional MRI and DTI to identify brain correlates of mood change. Specifically, he will compare MS patients with and without depression. Both groups will undergo brain MRI. He hypothesizes that the depressed group will have more lesions, more brain shrinkage and greater DTI abnormalities. The constellation of these various changes would help to explain why depression occurs so often in MS patients.

Publications:

- Feinstein A. Neuropsychiatric syndromes associated with multiple sclerosis. *J Neurol* 2007;254(suppl 2):II73-II76.
- Ghaffar O, Feinstein A. The neuropsychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry* 2007;20:278-285.

Daria Trojan, PhD

McGill University

(April 1 2007-March 31, 2009)

Sleep abnormalities in MS: association with fatigue, sleepiness and quality of life

Most MS patients experience fatigue, which is often the most disabling symptom. Previous research by Dr. Trojan and colleagues found that fatigue correlates with poor sleep quality in people with MS.

Dr. Trojan plans to evaluate sleep quality and abnormalities, determine if there is an association between sleep study results and fatigue, examine the relationship between sleep study results, sleepiness during the day and quality of life, and evaluate the ability of a sleep quality questionnaire to predict sleep study results in MS patients. The planned study will enroll 60 MS patients and 30 normal controls. 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 will complete questionnaires on fatigue, sleep quality, sleepiness, restless legs syndrome, depression,

stress, and quality of life.

Dr. Trojan believes that this study will provide important new information on sleep difficulties in MS, and their role in contributing to clinical symptoms in MS. The study may also result in the identification of an easily-administered questionnaire to assess sleep difficulties in MS.

Publications:

- Trojan DA, et al. Fatigue in multiple sclerosis: association with disease-related, behavioural and psychosocial factors. *Mult Scler* 2007;epublished April 27, 2007.

Reinhold Vieth, PhD, University of Toronto, A. Dessa Sadovnick, PhD, University of British Columbia, and George Ebers, MD, Oxford University
(April 1, 2006 –March 31, 2008)

Vitamin D levels in MS patients and their families

There is growing evidence that the interplay between genes and the environment determines susceptibility to MS. The incidence of MS becomes higher with increasing distance from the equator, suggesting that geographical location can influence the development of MS. This may be due to vitamin D, which is manufactured by the skin upon exposure to sunlight. It has been suggested that people living farther from the equator do not get sufficient sunlight (ultraviolet-B) during the winter months to manufacture vitamin D.

Drs. Veith, Sadovnick and Ebers will compare vitamin D levels in people

with and without a risk of MS. Vitamin D levels will be measured in identical and fraternal twins, in people with MS and their families, and in mothers with more than one child with MS. If MS risk is associated with vitamin D deficiency, improving vitamin D nutrition could be implemented easily and safely in a cost-effective manner. If they discover a link between vitamin D and MS, these findings could provide the evidence needed to begin clinical studies of vitamin D-based strategies to prevent MS.

Publications:

- Kimball SM, Vieth R. A comparison of automated methods for the quantitation of serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. *Clin Biochem* 2007;epublished August 11, 2007.
- Ebers GC, Sadovnick AD, Veith R. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;63:939.

Funding MS Research

The MS Society of Canada is a principal supporter of MS research, raising over \$9 million annually to fund important and innovative scientific projects. Funding is provided through the MS Society's operating grants and personnel awards programs, and through the MS Scientific Research Foundation pilot grants and collaborative grants.

Operating grants run for 2-3 years and are typically about \$100,000 per year. Funding for these projects is recommended by the Biomedical Grants Review Committee chaired by Dr. Rashmi Kothary, and by the Clinical and Population Health Grants Review Committee chaired by Dr. Christina Wolfson.

Personnel awards fund the work of individual researchers and include studentships, postdoctoral fellowships,

which run for one year, and the Donald Paty Career Development Awards, which are for a three-year term. These are adjudicated by the Society's Grants Review Committees.

The MS Scientific Research Foundation provides pilot grants to stimulate research in new areas. Its collaborative grants are intended to fund large, multicentre projects that are attempting to answer some of the big questions about MS. What are the genetics of MS? What is the role of bone marrow transplant in treatment? What can pediatric MS teach us about the development of the disease? These are some of the questions the MS Society and the MS Scientific Research Foundation hope to answer.

The key principles guiding the MS Society research program are simple ones: excellence and relevance to MS. The MS Society only supports the best ideas, the best projects and the best scientists in MS research today.

MS Scientific Research Foundation Grants

The MS Scientific Research Foundation was established in 1973 with an initial investment of \$1,000. Over the years, with funding from the MS Society of Canada, the Foundation has become one of the world's largest funding bodies dedicated to MS research.

The MS Scientific Research Foundation is funding the five unique and innovative collaborative projects listed below. All are truly ground-breaking efforts to address key issues in MS. The Foundation also serves as a stimulus for new ideas, funding small pilot research projects that allow investigators to pursue new approaches in MS research.

**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, well-tolerated, 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.

Publications:

- Zabad RK, et al. The clinical response to minocycline in multiple sclerosis is accompanied by beneficial immune changes: a pilot study. *Mult Scler* 2007;13:517-526.
- Giuliani F, et al. Effective combination of minocycline and interferon-beta in a model of multiple sclerosis. *J Neuroimmunol* 2005;165:83-91.
- Metz LM, et al. Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann Neurol* 2004;55:756.

Drs. Mark Freedman and 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.

Publications:

- Freedman MS. Bone marrow transplantation: does it stop MS progression? *J Neurol Sci* 2007;259: 85-89.
- Atkins H, Freedman M. Immunoablative therapy as a treatment aggressive multiple sclerosis. *Neurol Clin* 2005;23:273-300.

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

\$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?
- 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.

Publications:

- Herrera BM, et al. Parental transmission of MS in a population-based Canadian cohort. *Neurology* 2007;69:1208-1212.
- Ramagopalan SV, et al. Autoimmune disease in families with multiple sclerosis: a population-based study. *Lancet Neurol* 2007;6:604-610.
- Orton SM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurol* 2006;5:932-936.

Drs. Jack Antel, Montreal Neurological Institute, Samuel Weiss, University of Calgary, and Moses Rodriguez, Mayo Clinic
\$2,250,000

Remyelination in multiple sclerosis: enhancing intrinsic repair – Phase II

Destruction of myelin in the brain and spinal cord is a major feature in MS. Cells from the immune system attack myelin, the substance that surrounds and protects nerve fibres in the central nervous system (CNS). Myelin damage is often severe, leaving people with long-term disability. Myelin repair and replacement does occur but the extent is limited.

Phase II of this large, collaborative research project is seeking ways to find out if there are cells in the body's own central nervous system that can be transformed into a cellular repair team to mend damage to myelin caused by MS. The cells the researchers are targeting are called stem cell progenitor cells. These are cells within the body that have yet to become fully specialized, so the goal of this project is to stimulate them to become oligodendrocytes, the cells that make myelin.

Drs. Antel, Weiss and Rodriguez have chosen to use the body's own stem cell progenitors from the adult CNS. The trial targets stem cell progenitors that have already been located within the body and uses various proteins and hormones to entice them to the damaged parts of the brain and spinal cord that need remyelination. This technique avoids invasive surgical procedures, and should overcome the limitation in the number of cells available for transplantation and the problem of directing the cells to the sites of injury. This multi-disciplinary team of neurologists and basic scientists believes the strategy of using the body's own cells to repair myelin damage is particularly applicable in a disease in which injury can occur in any part of the CNS.

The researchers have also pioneered new ways of using MRI to non-invasively measure the production of new myelin and the rate of recovery from MS attacks. The ability to generate myelin and have the new myelin wrap effectively around nerve fibres are the keys to reducing disability caused by MS. The

research teams at the three centres are looking for an “on” switch that can kick-start the remyelination process. If successful, they hope to identify specific strategies for myelin repair and turn their findings into

clinical trials to determine whether remyelination will lead to an actual decrease in disability in people with MS.

Publications:

- Ruffini F, et al. Immunobiology of oligodendrocytes in multiple sclerosis. *Adv Neurol* 2006;98:47-63.
- Gregg C, et al. White matter plasticity and enhanced remyelination in the maternal CNS. *J Neurosci* 2007;27:1812-1823.

Drs. Brenda Banwell, Hospital for Sick Children, Douglas Arnold, Montreal Neurological Institute, Amit Bar-Or, Montreal Neurological Institute, and Dessa Sadovnick, University of British Columbia
\$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). It is a five-year, prospective pediatric MS study involving 22 Canadian centres in Victoria, Vancouver, Edmonton,

Calgary, Saskatoon, Winnipeg, London, Hamilton, Windsor, Toronto, Kingston, Ottawa, Montreal, Sherbrooke, Saint John, Halifax and St. John’s.

The study is possible due to 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? By studying pediatric 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 the pathobiology of MS.
- What is the risk of MS after an initial attack of CIS? By carefully following children who have experienced an initial neurological attack (CIS), researchers hope to understand why some CIS patients never progress to MS, while others have multiple attacks leading to the diagnosis of MS.

Central to the study are clinical and genetic epidemiology, pathobiology and neuroimaging.

- **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.

- **Pathobiology:** To define the earliest immunological events that occur at the time of the first attack (CIS), investigators will strive to identify both the triggers and initial targets of the immune cell response.
- **Neuroimaging:** MRI is currently available to assist in the diagnosis of MS, and in the prediction of MS risk following a single demyelinating episode in adults. By examining MRI characteristics in the pediatric study population, the researchers will create MRI diagnostic criteria for MS in children, and determine if particular MRI features are predictive of MS risk in children with CIS. With newer MRI technologies, the researchers will explore whether there are fundamental differences in the myelinated regions of the brain in children who go on to develop clinically definite MS.

Donald Paty Career Development Awards

Dr. Donald Paty had a long and distinguished career in Canada as an MS neurologist and researcher. He headed the MS clinics at the University of Western Ontario and the University of British Columbia. His leadership in patient care, clinical trials and MRI research inspired his colleagues around the world.

The Multiple Sclerosis Society provides a limited number of career development awards for individuals holding a doctorate degree and who have demonstrated commitment to a career in MS research.

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

Postdoctoral Fellowships

The Multiple Sclerosis Society provides funding for investigators who hold MD or PhD degrees to pursue additional study in an MS-related area. The grants are for one year with an opportunity for renewal.

Recipient	Supervisor	Institution
Smriti Agrawal, PhD	Dr. V. Wee Yong	University of Calgary
Peter Darlington, PhD	Dr. Timothy Kennedy	McGill University
Shannon Dunn, PhD	Dr. Lawrence Steinman	UCLA
Yunfei Gao, PhD	Dr. Jennifer Gommerman	University of Toronto
Andrea Hebb, PhD	Dr. George Robertson	Dalhousie University
Yukie Hirahara, PhD	Dr. Joan Boggs	Hospital for Sick Children
Madeline Pool, PhD	Dr. Alyson Fournier	Montreal Neurological Institute
Viktor Skihar, MD, PhD	Dr. V. Wee Yong	University of Calgary
Patrick Cafferty, PhD	Dr. Vanessa Auld	University of British Columbia
Manu Rangachari, PhD	Dr. Vijay Kuchroo	Brigham and Women's Hospital
Jami Bennett, PhD	Dr. Kelly McNagny	University of British Columbia
Nicole Welch, PhD	Dr. Peter Stys	University of Calgary
Lopamudra Chaudhuri, PhD	Dr. Joan Boggs	Hospital for Sick Children
Tarik Touil, PhD	Dr. Amit Bar-Or	Montreal Neurological Institute
Qiao Ling Cui, PhD	Dr. Jack Antel	Montreal Neurological Institute
Dafni Reiss, PhD	Dr. Dixie Mager	British Columbia Research Institute
Christel Renoux MD	Drs. Samy Suissa & Jack Antel	McGill University

Research Studentships

The MS Society provides funding for students who are working toward an MSc, PhD or related degrees in areas relevant to MS research. The studentships are designed to encourage young scientists to consider a career in MS research. The grants are for 1 year with an opportunity for renewal.

Recipient	Supervisor	Institution
Azadeh Arjmandi	Dr. Katerina Dorovini-Zis	Vancouver General Hospital
Jennifer Berard	Dr. Sam David	McGill University
Shawn Beug	Dr. Valerie Wallace	Ottawa Health Research Institute
Jennifer Beveridge	Dr. Mark Freedman	University of Ottawa
Zhihong Chen	Dr. Mark Freedman	University of Ottawa
Rowena Cua	Dr. V. Wee Yong	University of Calgary
Farnaz Forghani	Dr. Alan Peterson	McGill University
Ebrima Gibbs	Dr. Joel Oger	University of British Columbia
Elizabeth Girolami	Dr. Sam David	McGill University
Angelika Goncalves DaSilva	Dr. V. Wee Yong	University of Calgary
Jeffery Haines	Dr. Guillermina Almazan	McGill University
Hania Kebir	Dr. Alexandre Prat	Hôpital Notre-Dame
James Knight	Dr. Rashmi Kothary	Ottawa Health Research Institute
Kaveh Koochesfahani	Dr. Katerina Dorovini-Zis	University of British Columbia
Lorraine Lau	Dr. V. Wee Yong	University of Calgary
Karen Lee	Dr. Rashmi Kothary	Ottawa Health Research Institute
Abdi Musse	Dr. George Harauz	University of Guelph
Craig Moore	Dr. George Robertson	Dalhousie University

Recipient	Supervisor	Institution
Leslie Summers-DeLuca	Dr. Jennifer Gommerman	University of Toronto
Rameeza Allie	Dr. Amit Bar-Or	Montreal Neurological Institute
Sarah Jane Bull	Dr. Timothy Kennedy	McGill University
Romain Cayrol	Dr. Alexandre Prat	Hôpital Notre-Dame
Gurdip Daffu	Dr. John Kamholz	Wayne State
Aurore Dodelet-Devillers	Dr. Alexandre Prat	Hôpital Notre-Dame
Allan Gillet	Dr. Tomas Olsson	Karolinska Institute
Jennifer Nancy Hahn	Dr. Frank Jirik	University of Calgary
Hau Yee Hung	Dr. Sylvie Fournier	McGill University
Shannon Kolind	Dr. Alex MacKay	University of British Columbia
Allison Kraus	Dr. Marek Michalak	University of Alberta
Gabriel Marceau	Dr. Pierre Talbot	Institut Armand-Frappier
Cornelia Podjaski	Dr. Jack Antel	Montreal Neurological Institute
Aja Rieger	Dr. Amit Bar-Or	Montreal Neurological Institute
James Rowland	Dr. Michael Fehlings	University of Toronto
Sandrin Vautrin	Dr. Keith Murai	Montreal General Hospital
Melissa Kehler	Dr. Heather Hadjistavropoulos	University of Regina
Samantha Kimball	Dr. Reinhold Vieth Dr. Jodie Burton	University of Toronto
Antonia Kuznetsova	Dr. John Fisk	Dalhousie University
Sathyanath Rajasekharan	Dr. Timothy Kennedy	McGill University
Pavan Ahulwalia	Dr. Luanne Metz	University of Calgary
Allison Bethune	Dr. Brenda Banwell	Hospital for Sick Children
Jennifer Thannhauser	Dr. Kevin Alderson	University of Calgary

Pilot Research Grants

Pilot Research Grants are available to fund small, innovative research projects. They are intended to look at new, untested ideas to gain preliminary data that can then be used for a full research project application. The pilot

research program is supported by the MS Scientific Research Foundation, which is related to the MS Society of Canada.

At the time of this printing, the adjudication of this year's pilot grants has not been completed due to an abundance of applications.

Glossary 2007

Adhesion molecule – A protein that promotes the binding of one cell to another. Adhesion molecules enable activated T cells to attach to the blood-brain barrier and gain entry into the central nervous system.

Amino acid – The building block of proteins. A chain of amino acids is called a peptide. Cells use about 20 different amino acids to manufacture proteins.

Antibody – A protein made by a plasma cell (activated B cell) that protects the body against foreign invaders, such as bacteria and viruses.

Antigen – A substance that is bound by antibodies.

Antigen presenting cell – A specialized cell that engulfs antigens for presentation to the immune cells. The main APCs are dendritic cells, macrophages and B cells.

Apolipoprotein – A binding protein found in the blood that binds to lipids. Its principal role is to transport lipids consumed in the diet from the intestine to the liver. The five main types are labelled A through E.

Axon – The long slender nerve fibre extending from a neuron cell body. Synonymous with nerve fibre.

Axonal transection – Irreversible severing of an axon. A severed axon can no longer transmit electrical impulses.

B cell – A lymphocyte (white blood cell) originating in the bone marrow that makes antibodies.

Blood brain barrier (BBB) – A tightly-packed layer of endothelial cells lining blood vessels that prevents most large molecules and cells in the bloodstream from entering the central nervous system.

Central nervous system (CNS) – The brain, spinal cord and optic nerve. All parts of the CNS can be affected by multiple sclerosis.

Chemokine – A type of cytokine that attracts white blood cells from the circulation to the site of injury or infection.

Cytokine – A protein messenger molecule that influences the actions of immune system cells; also called a lymphokine or interleukin (IL). The different types of cytokines act only on cells that have receptors for that cytokine.

Demyelination – The process during which myelin is stripped from nerve fibres.

Dendritic cells (DC) – A type of white blood cell. Its primary role is to act as an antigen-presenting cell, displaying antigens to T cells.

Deoxyribonucleic acid (DNA) – A substance that contains all of the genetic instructions for living organisms. DNA stores information needed to construct cell components, such as RNA molecules, proteins, etc.

Endothelial cell – A type of cell that lines the heart and blood vessels. Endothelial cells lining the blood vessels of the CNS form the blood-brain barrier (BBB).

Experimental allergic encephalomyelitis (EAE) – An MS-like disease created in laboratory mice after they are injected with either CNS tissue or a derivative of myelin basic protein. It is used as an animal model of MS for research purposes.

Glial cell – A support cell in the nervous system. In the CNS, glial cells include oligodendrocytes, astrocytes and microglial cells. In the peripheral nervous system, glial cells are called Schwann cells. Oligodendrocytes and Schwann cells produce myelin.

Histopathology – The examination of tissue samples to determine the effects of disease.

Inflammation – The local immune response to infection or physical/chemical injury characterized by edema (swelling), pain, and accumulation of white blood cells and other blood constituents. The CNS inflammation in MS is seen on MRI as plaques (lesions).

Lipid – A fat or fatty acid.

Lymphocytes – White blood cells (B cells, T cells and natural killer cells) of the immune system that fight infection.

Macrophage – A white blood cell that is among the first immune system cells to respond to infection. It also acts as an antigen-presenting cell. Macrophages are called different names depending where they are found in the body (e.g. microglial cells in the brain).

Magnetic resonance imaging (MRI) – An imaging device that uses a powerful magnetic field to provide produce images of the inside of the body. In MS, MRI detects inflammatory lesions in the CNS and is used to confirm the diagnosis and to assess pathological changes during the disease course.

Magnetic resonance spectroscopy (MRS) – An imaging device that is similar to MRI. It uses a powerful magnetic field to detect chemical rather than anatomical differences. MRS is used as a research tool and has been able to quantify myelin damage and other biochemical changes in MS.

Matrix metalloproteinase (MMP) – An enzyme that degrades extracellular matrix proteins. Involved in activating/inactivating chemokines, as well as cell proliferation, migration and adhesion. MMPs are believed to degrade the BBB in MS, enabling activated T cells to enter the CNS and cause damage. Some MS therapies, such as the beta-interferons, block the action of MMPs as part of their mechanism of action.

Messenger RNA (mRNA) – A molecule of ribonucleic acid (RNA) that transcribes a blueprint for a protein from a DNA template. mRNA transports

this information to the site of protein synthesis within the cell.

Microglia – A macrophage in the CNS that consumes (phagocytoses) cellular debris and stimulates immune responses.

Monocyte – A type of white blood cell found in the blood. When a monocyte enters the tissues it is called a macrophage.

Myelin – A collection of proteins and lipids that forms a protective sheath around nerve fibres.

Myelination – The process during which oligodendrocytes and Schwann cells add new myelin to nerve fibres (axons).

Myelin basic protein (MBP) – One of the main proteins that makes up myelin.

Myelin sheath – A covering of 1-200 layers of myelin that surrounds nerve fibres in the central and peripheral nervous systems.

Natural Killer (NK) cell – A type of lymphocyte (not T or B cells) that can kill infected or defective cells.

Neurites – A projection from a nerve cell; includes axons and dendrites.

Neuron – A cell within the nervous system that consists of a cell body and membrane extensions, called axons and dendrites. Nerve impulses travel along nerve fibres (axons).

Oligodendrocyte – A specialized cell in the CNS that produces myelin and ensheathes axons.

Optic neuritis – Inflammation of the optic nerve resulting in visual impairments. It is a common herald of MS and the most frequent presenting symptom of MS.

Peripheral nervous system (PNS) – The part of the nervous system in the body outside the brain, spinal cord and optic nerve.

Plaque – An inflammatory lesion in the CNS characterized by edema, myelin loss and axonal damage.

PLP (Proteolipid Protein) – The principal protein component of myelin.

Post-mortem – After death (Latin). A post-mortem examination is an autopsy.

Remyelination – The process during which myelin is restored to demyelinated axons by oligodendrocytes or Schwann cells.

Retrovirus – A virus of the Retroviridae family. Their genome is RNA (rather than DNA), and perform a reverse transcription of its genome into DNA. The Human Immunodeficiency Virus (HIV) is a retrovirus.

Schwann cell – The cell in the peripheral nervous system that makes and maintains myelin.

T cell – A type of immune system cell that fights infection. Categories include alpha-beta and gamma-delta T cells. Alpha-beta subsets include helper T cells (CD4+) and killer T cells (CD8+).

Tumour necrosis factor (TNF) – A cytokine produced by macrophages and some T cells that is toxic to tumour cells and plays a role in the inflammatory response.

Transgenic mice – Mice that contain genes from another source (animal or human); derives from 'trans' (other) and 'genic' (genes). Summaries written by: Maya Chaddah. M.Sc., Immunology

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This document is also available
on the MS Society of Canada website
in the MS Research section
under Current Research Projects.

(Disponible en français)

The Multiple Sclerosis Society of Canada thanks the thousands of individual donors, corporations and companies, and MS Society chapters and units for their dedicated support of MS research. Together, we are making a difference.

Our Mission

To be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.

