

## MS Research Program at Record Level

In March 2005, the Multiple Sclerosis Society of Canada awarded a record-breaking amount in additional research funding.

Grants were up in each category of funding: more than \$3.6 million for research projects; \$711,500 for postdoctoral fellowships and \$716,000 for studentships.

At more than \$5 million, the allocation represents the largest single amount for

research projects and scholarships ever approved by the MS Society of Canada. The funding is for 14 research projects with terms up to three years and more than 50 scholarships for young scientists.

Together, all of these projects and scholarships represent the “best of the best” – a direct result of the MS Society’s painstaking review process. Recognized scientific experts scrutinize all applications rigorously before they are recommended for approval.

### CONTENTS

<i>Repairing and Protecting Myelin</i>	2
<i>Stopping Immune System Attacks</i>	9
<i>How MS Research is Funded</i>	17
<i>MRI: Tools for Viewing MS</i>	18
<i>Managing MS Better Today</i>	20
<i>Collaboration to Speed Results</i>	23
<i>Remyelination in MS</i>	23
<i>Genetic Susceptibility</i>	24
<i>Bone Marrow Transplantation</i>	25
<i>Development of MS in Children</i>	26
<i>Programs to Attract New</i>	
<i>Scientific Talent</i>	27
<i>Glossary</i>	32

In April, the MS Scientific Research Foundation approved funding of \$2.25 million for a multi-centre collaborative study focusing on how to coax the body’s own cells to repair myelin that is damaged by MS attacks. The study is taking place at the Montreal Neurological Institute, the Hotchkiss Brain Institute in Calgary and the Mayo Clinic in Rochester, MN.

The MS Society and the related MS Scientific Research Foundation are able to continue this level of funding commitment thanks to the ongoing support of individual donors, corporate partners and MS Society chapters.

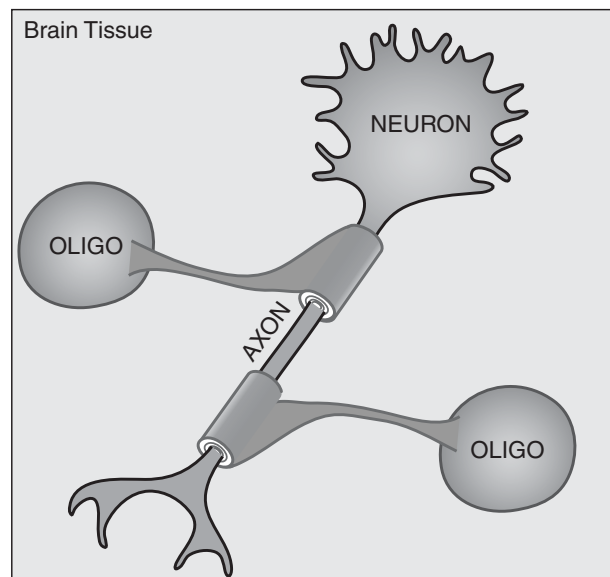
## Repairing and Protecting Myelin



The body uses myelin to cut down on the amount of space and energy it needs to transmit nerve signals. Without this essential protein, the human spinal cord would need to be

several metres wide and would rack up an unpayable energy bill to do its job. Layers of myelin are wrapped around nerve fibres (axons) forming a compact myelin sheath. In MS, the sheath is damaged and the cells making myelin can't repair it fast enough. The myelin-stripped axons have difficulty sending nerve impulses. The axons themselves are often damaged beyond repair. As the damaged myelin heals, scar tissue builds up and forms the characteristic plaques seen in MS.

All MS research has a converging aim, that is, to prevent or at least minimize the destruction to myelin in the nervous system. Scientists are striving to understand the big picture of how the specialized cells in the nervous system make the myelin sheath, and the mechanics of how it is wrapped around nerve axons. A variety of approaches from cell culture techniques, to protein and gene function analyses, to animal model studies and clinical trials should help them achieve their goal. As the processes of myelin growth (myelination) and regrowth (remyelination) are mapped out in more detail, better therapies will be available to counter the far-reaching effects of myelin damage during MS.



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

**Guillermina Almazan, PhD, and  
Walter Mushynski, PhD  
McGill University  
\$241,770 (April 1, 2003 –  
March 31, 2006)**

### **Transactivation of signalling pathways and gene expression in sensory neurons and their myelinating cells: Role of mitogen activated protein kinases (MAPK)**

Myelin architecture is the key to nerve fibres (axons) efficiently transmitting nerve impulses. In MS, an increasing number of central and peripheral nerves are stripped of their myelin sheath. This seriously affects the ability of nerve axons to do their job. Damage to myelin often goes hand in hand with irreversible damage to nerve axons, causing even more severe problems for people with MS.

Drs. Almazan and Mushynski hope to overcome some of these problems by continuing to study how to keep nerve axons covered with myelin. They know that some form of two-way communication exists between nerve axons and myelin-making

cells, (oligodendrocytes and Schwann cells). Recently, they found that p38, a member of the MAPK signalling family, is part of the two-way communication process that leads to myelin-covered axons. They are delving deeper into how p38 works, and are also studying two other members of the MAPK family, called ERK and JNK.

If researchers can identify the signals that keep nerve axons covered with myelin, they can then ask how such signals are different during MS. That information will help them to design treatments to restore normal communication patterns between axons and myelin-making cells in people with MS.

**Joan Boggs, PhD**  
**Hospital for Sick Children Research**  
**Institute, University of Toronto**  
**\$311,744 (April 1, 2005 –**  
**March 31, 2008)**

#### **Glycosphingolipid signaling domains and protein-protein associations in oligodendrocyte/myelin membranes**

Oligodendrocytes wrap their myelin-filled outer membranes many times around nerve fibres (axons) to build up the myelin sheath. The resulting sheath is like the layers of an onion surrounding the nerve axon which is at the core. Many different proteins, fats and glycolipids (fats plus a sugar) are part of the myelin sheath. In MS, oligodendrocytes cannot fully repair the damaged myelin sheath but clues about how to help them do this more effectively might come from studying the function of the proteins and glycolipids within the myelin sheath itself.

Dr. Boggs believes that glycolipids and proteins touching each other in different layers of the myelin sheath can transmit signals affecting the health of both myelin and nerve axons. Building on previous MS Society funding, she is mimicking the situation of two myelin-

filled membranes in the sheath touching each other by adding synthetic membranes containing glycolipids and proteins to oligodendrocytes. Such an approach will allow her to study the behaviour of oligodendrocytes, and to dissect the signals involved in oligodendrocyte function and communication with nerve axons.

Dr. Bogg's research could lead to new therapeutic methods for stimulating remyelination by oligodendrocytes and preventing nerve axon damage in people with MS.

**Peter Braun, PhD, and Michel**  
**Gravel, PhD**  
**McGill University**  
**\$261,710 (April 1, 2005 –**  
**March 31, 2007)**

#### **Biological assembly of myelin: role of CNP**

Myelination is a complex series of events where oligodendrocyte cells make myelin and project it from their membranes in sail-like structures. The 'myelin sails' wrap around nerve fibres (axons) many times forming a protective sheath which optimizes the conduction of nerve impulses. In MS, the myelin sheath is damaged and, for some reason, oligodendrocytes can't fully remyelinate nerve axons. Some of the nerve axons die while those remaining seem unable to function normally. Drs. Braun and Gravel are exploring the fundamental process of myelination in an effort to better understand how healthy myelin is made and maintained.

Their focus is a protein/regulatory enzyme called CNP/CNPase that may play an important role during myelination of nerve axons. In previous studies, they showed that nerve axon function decreased in animals lacking CNPase. Their recent

observations point to a role for CNP/CNPase during the process of oligodendrocytes making the 'myelin sails' and maintaining nerve axon function. They continue to explore their theory that CNP is a multi-functional protein capable of binding many oligodendrocyte proteins and RNA (ribonucleic acid) to promote myelination.

This research might point to CNP/CNPase as a future therapeutic target for improving myelination in people with MS.

**George Harauz, PhD**  
**University of Guelph**  
**\$171,394 (April 1, 2003 –**  
**March 31, 2005)**

**Interactions of myelin basic protein (MBP) with SH3-domain proteins in signalling pathways during remyelination: Effects of post-translational modifications and interferon / Vitamin B12 treatment**

The chronic form of MS is noted for cycles in which myelin is stripped from axons during demyelination, and partially added to axons during remyelination. A pivotal player during this neurological seesaw is myelin basic protein (MBP), which makes up a major part of the myelin sheath. In MS, altered forms of MBP disrupt the myelin sheath and are often an indicator of disease severity.

Dr. Harauz is measuring how changes during the assembly of MBP can affect its normal function. One such change, called methylation, might promote remyelination by enhancing the communication between MBP and signalling proteins. Once this information is collected, he will test whether current therapies for MS, such as beta interferon combined with Vitamin B12, can restore the normal function of MBP by increasing its level of methylation.

This research is doubly valuable. It not only provides much needed information on

the role of MBP in MS, but also evaluates how current therapies used in MS might work. Taken together, the results from this study will be useful in designing better therapies for people with MS.

**Timothy Kennedy, PhD**  
**McGill University**  
**\$266,370 (April 1, 2005 –**  
**March 31, 2008)**

**Netrin function in the development of axonal-oligodendroglial interactions**

The oligodendrocyte cells that make myelin in the central nervous system (CNS) are lost during diseases like MS. Understanding more about how these important cells mature and become functional is central to winning the battle against MS. To that end, Dr. Kennedy is investigating the mechanisms controlling oligodendrocyte maturation and function, with the goal of identifying ways to promote myelin regrowth.

Using animal models, Dr. Kennedy recently reported results from research funded by the MS Society that a protein called Netrin-1 is a chemical repellent that pushes immature oligodendrocytes toward axons in the embryonic CNS. The receptor for Netrin-1, called DCC, is also required for the process to occur. In an exciting find, he showed that Netrin-1 and DCC are made by different types of neurons, as well as by mature, functional oligodendrocytes in the adult CNS. From post-mortem studies of human MS plaques, Dr. Kennedy thinks that too much netrin-1 in MS lesions may inhibit myelin regrowth by preventing immature oligodendrocytes from reaching damaged axons. If Dr. Kennedy can find ways to interfere with Netrin-1 and DCC in MS lesions, he may be able to help oligodendrocytes reach stripped axons and begin the repair process.

**Rashmi Kothary, PhD**  
**Ottawa Health Research Institute**  
**\$273,300 (April 1, 2005 –**  
**March 31, 2008)**

### **Integrin signalling pathway and CNS myelination/remyelination**

Effective treatments for MS must not only stop myelin damage but also stimulate oligodendrocyte cells to make new myelin for damaged nerves. Oligodendrocytes undergo many changes before becoming fully functional and capable of myelinating axons. It stands to reason that understanding this process in more detail will help researchers devise better treatments for MS.

With previous MS Society funding, Dr. Kothary has attacked the problem of how oligodendrocytes myelinate nerve fibres (axons) by focussing on integrins, which are proteins that span the cell membrane of oligodendrocytes. Integrins are like telephone operators who connect incoming and outgoing messages between the oligodendrocyte's exterior and interior. This two-way communication affects how and when oligodendrocytes will begin to wrap their myelin-filled membranes around nerve axons. Dr. Kothary is studying myelin loss and regrowth in transgenic mice that contain introduced genes to make different types of integrin. For his research, he is creating other transgenic mice that have a gene to make ILK, a protein inside the oligodendrocyte that carries the integrin message. The ILK-transgenic mice will help him study the role of ILK in myelination.

The long-term goal of this work is to manipulate integrin in a way that will reduce myelin destruction and promote myelin regrowth in people with MS.

**Mario Moscarello, PhD**  
**Fabrizio Mastronardi, PhD**  
**Hospital for Sick Children, Toronto**  
**\$177,730 (April 1, 2004 –**  
**March 31, 2006)**

### **Vitamin B12 in combination therapy induces remyelination**

MS is characterized by the patchy destruction of the myelin sheath surrounding nerve fibres. If myelin is not properly repaired, symptoms of MS start to develop. An effective therapy must therefore have a double action. It should stop myelin destruction while rebuilding the myelin sheath, a job that is normally done by oligodendrocyte cells.

The results from previous work funded by the MS Society convinced these researchers that combining vitamin B12 and beta interferon might be the double action therapy required. This combination of drugs was able to stop myelin loss, reduce clinical signs, and restore near to normal function in mice that develop an MS-like disease (DM20 transgenic mice and acute and chronic EAE mice). Drs. Moscarello and Mastronardi saw similar clinical results when vitamin B12 was added to paclitaxel, a well known cancer drug. They also found that vitamin B12 and beta interferon therapy alters the levels of Notch-1, Jagged-1 and Sonic hedgehog. These interestingly named molecules help immature oligodendrocytes to become mature, myelin-making cells.

With their renewed funding, they plan to study how vitamin B12 synergizes with other drugs to alleviate the clinical symptoms of MS-like disease. They hope their studies in mice can be applied to people to improve the clinical picture of multiple sclerosis.

**Adil Nazarili, PhD**  
**University of Saskatchewan**  
**\$65,506 (April 1, 2004 –**  
**March 31, 2005)**

### **Expression of homeobox genes in myelinating cells in vitro and in vivo**

Olfactory ensheathing cells (ECs) and oligodendrocyte cells are responsible for wrapping myelin around axons in the central nervous system (CNS). Both of these cells go through a process called differentiation where they change from immature cells unable to myelinate axons into mature cells capable of doing so. Currently there is little information about what controls the pivotal process that makes these cells mature and become fully functional.

Dr. Nazarali has been steadily closing the information gap with research funded by the MS Society over the past two years. He has made considerable progress towards understanding how homeobox (Hox) genes are linked to differentiation in ECs and oligodendrocytes. Hox genes code for proteins that bind to DNA and influence gene activity. He is the first to show that *Hoxa2* and *Hoxb4* genes are made by ECs and oligodendrocytes. His work also makes a strong case for *Hoxa2* being involved in myelination. With the improved methods he developed for isolating and growing mouse ECs and oligodendrocytes, he is continuing to study the link between Hox genes, and EC and oligodendrocyte maturity.

Getting at the question of what helps these cells mature to the point where they can add myelin to axons, especially damaged axons, is important for future therapies intended to reverse the CNS damage in multiple sclerosis.

**Alan Peterson, PhD**  
**McGill University**  
**\$229,020 (April 1, 2004 –**  
**March 31, 2006)**

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

In people with MS, brain lesions that lack myelin are often not repaired despite the presence of oligodendrocytes (myelin making cells) that can fix the damage. Dr. Peterson is looking for a solution to this problem by investigating the molecules that control myelin formation, maintenance and repair.

Technical advancements during the last funding period have enabled the team to better focus their efforts on the myelin basic protein (MBP) gene. They compared mouse and human genomes and found a regulatory system composed of more than 1,000 base pair sequences of DNA that controls the switch for the MBP gene. Curiously, not all parts of the regulatory system are used equally in the developing or mature nervous system. For example, the regulatory parts that control myelin regrowth are different from those used during nervous system development. With its renewed funding, the team will use the 1,000 base pairs of sequence to capture interacting proteins that are involved in normal MBP production.

Development of new therapeutic strategies capable of enhancing myelin stability and repair should become possible once the control mechanisms regulating myelin formation, maintenance and repair are known.

**Christopher Power, MD**  
**University of Calgary**  
**\$240,000 (April 1, 2003 –**  
**March 31, 2006)**

### **Purine receptor-mediated immune regulation in multiple sclerosis**

In MS, inflammation of the central nervous system (CNS) leads to myelin loss, damage to nerve fibres and often physical disability in people who have the disease. Dr. Power's approach to these problems is to study the adenosine A1 receptor, which he recently linked to brain inflammation in people with multiple sclerosis.

Adenosine A1 receptors are found on macrophages in the blood and brain. These receptors bind to adenosine, which is known to protect against some neurological diseases. In previous work, Dr. Power showed that the levels and function of adenosine A1 receptors are lower than normal in people with MS. In the present study, he is focusing on how the damage in MS is linked to having fewer adenosine A1 receptors. He is using mice lacking the adenosine A1 receptor, and blood and brain tissue of people with MS to see if the damage in MS is linked to fewer adenosine A1 receptors.

This research may lead to new therapies that would harness the protective effects of adenosine A1 receptors. Such therapies could ultimately decrease the damage from inflammation of the CNS in people with multiple sclerosis.

**Stéphane Richard, PhD**  
**Lady Davis Research Institute, Jewish**  
**General Hospital, Montreal**  
**\$291,630 (April 1, 2003 –**  
**March 31, 2006)**

### **The role of the quaking proteins in oligodendrocyte physiology**

Quaking viable mice are so named because a defect in the quaking proteins causes a tremor to develop within 10-12 days after birth. The underlying cause of these MS-like tremors is unknown, but one clue is that myelin-making cells (oligodendrocytes) are abnormal in these mice.

Dr. Richard is continuing to study the role that different types of quaking proteins play in normal oligodendrocyte development. Quaking proteins reside either in the nucleus and/or the cytoplasm of a cell. The balance of quaking proteins in these locations can tip a cell towards death or survival. Recently, Dr. Richard showed that too much of the quaking protein that lives in the cytoplasm will kill oligodendrocytes. He is the first to show that quaking proteins transport the instructions for making myelin from the nucleus to the cytoplasm of the oligodendrocyte. In future studies on *quaking viable* mice, Dr. Richard wants to show that abnormal quaking proteins cause abnormal oligodendrocytes to develop which are only able to partially cover nerve fibres with myelin.

Although closer to 'the bench' than to the 'bedside', Dr. Richard's work has shown a direct link between myelination and quaking proteins. The next step is to test whether people with MS have similar protein defects. If so, researchers will be closer to designing therapies that can restore oligodendrocyte function in people with MS.

**Valerie Anne Wallace, PhD**  
**Ottawa Health Research Institute**  
**\$74,746 (April 1, 2004 –**  
**March 31, 2006)**  
With additional funding from the Canadian  
Institutes of Health Research

### **The role of neuron-derived morphogens in optic nerve development**

A major goal in the treatment of MS is to promote the addition of new myelin (remyelination) to damaged regions of the central nervous system. In the majority of MS cases, this vital repair process is incomplete, and to date no therapy fully restores the damage. There is growing evidence that morphogens (growth stimulators) may link the cell-to-cell communications that contribute to effective remyelination of damaged nerves.

Dr. Wallace is studying the communication between nerve axons and astrocytes (support cells) in the developing rodent optic nerve. Messages from nerve axons promote astrocyte development, and Dr. Wallace is the first to show that a morphogen called Sonic hedgehog is the signal go-between. How Sonic hedgehog does this is important because astrocytes are key to the remyelination process. They make messenger proteins involved in the development of oligodendrocytes, the cells that make and maintain myelin. Garbled communication from astrocytes may be one of the reasons that nerve axons are not well remyelinated. Dr. Wallace's long-term goal is to discover the details of how Sonic hedgehog works, what its targets are and how it gets transported in neurons.

By learning more about how morphogens contribute to nerve, astrocyte and oligodendrocyte communication, new ways to promote nerve remyelination after injury due to MS may become apparent.

**V. Wee Yong, PhD**  
**University of Calgary**  
**\$352,500 (April 1, 2004 - March 31, 2007)**

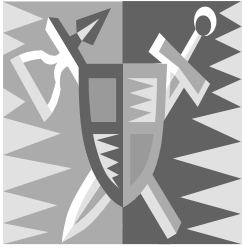
### **Beneficial roles of matrix metalloproteinases (MMPs) in myelin formation**

The myelin sheath is created from the long, slender myelin-filled membranes that radiate from oligodendrocytes. If this vital process could be enhanced and oligodendrocyte survival ensured, myelin loss might be stopped or slowed during MS. To this end, Dr. Yong is searching for ways to promote the survival and function of oligodendrocytes and is focusing on matrix metalloproteinases (MMPs). MMPs are well positioned to promote myelin regrowth as they help oligodendrocytes to develop and extend their myelin-filled membranes around nerve fibres.

In research funded by the MS Society in the last funding period, Dr. Yong found that astrocytes (support cells in the brain) interact directly with surface proteins on oligodendrocytes, sending them signals that enhance survival. He also showed that MMP-9 is made at the site of brain tissue injury during myelin regeneration in mice, and that MMP-12 levels are increased in human oligodendrocytes extending their processes. In some mice, the loss of MMP-9 and MMP-12 impairs myelin formation. With the renewed research grant, he will continue to study the need for MMP-9 and MMP-12 in myelin formation. Some MS therapies are designed to inhibit certain MMPs which help inflammation-causing white blood cells to enter the brain. Dr. Yong will assess whether chronic inhibition of MMP activity by such therapies actually impairs myelin formation in the long-term.

This study may lead to new therapies based on MMPs which would help restore the myelin sheath and promote recovery in people with MS.

## Stopping Immune System Attacks



Cells of the immune system are constantly battling to defend the body against invading viruses, bacteria and other threats. Since the immune system normally protects the body from

such dangers, it is puzzling that it should turn its deadly arsenal against myelin and the cells that make it during MS. Some scientists believe that infectious agents can act as catalysts to “trigger” the immune system attack in susceptible individuals. The term “autoimmunity” has been coined to describe how the immune system unwittingly attacks the body in the same way that it fights off an infection.

Although scientists are making constant headway, there is still a long way to go before they fully understand the immune system attack during MS. Much of the research effort focuses on determining the role of white blood cells (T cells, B cells, macrophages, mast cells, etc.) during inflammation in MS, and discovering how cell-cell communications loosen the tight seal of the blood-brain-barrier (BBB) allowing the white blood cells to enter the brain. Equally important are studies evaluating new and existing immunotherapies that can help clinicians tailor treatments to specifically suit people with different forms of MS. As more and more pieces of the immunological puzzle surrounding MS are discovered, researchers will be able to design new treatments aimed at bringing the immune system back onside.

**Jack Antel, MD**  
**Montreal Neurological Institute,**  
**McGill University**  
**\$306,000 (April 1, 2004 –**  
**March 31, 2007)**

### **The systemic immune response in multiple sclerosis and effects of therapy**

The initial lesions in MS are caused by immune cells called lymphocytes that leave the blood vessels and cross the blood-brain-barrier (BBB). This barrier is made of lines of endothelial cells that normally prevent lymphocytes from squeezing into the brain. Dr. Antel has developed an artificial model of the BBB to study how dangerous lymphocytes manage to breach the tight seal of the BBB.

During the previous granting period, Dr. Antel used his artificial model to show that immune cells called microglia make factors that enhance the tight seal of the BBB. He also showed that lymphocytes from people with active MS crossed the artificial BBB faster than lymphocytes from people with stable MS. His current work revolves around how interactions between lymphocytes and BBB endothelial cells alter each of these cell types and set the stage for the progression of MS. Dr. Antel is also continuing his studies on beta interferon and its ability to alter T cells which in turn might have positive or negative effects on BBB endothelial cells.

These studies will get directly at the question of how lymphocytes cross the BBB. In the future, Dr. Antel’s results may help identify particular aspects of lymphocyte-endothelial cell interactions that could serve as new therapeutic targets for people with MS.

**Jack Antel, MD and Amit Bar-Or, MD**  
**Montreal Neurological Institute,**  
**McGill University**  
**\$180,000 (April 1, 2004 –**  
**March 31, 2006)**

**Microglia as regulators and effectors of the immune response in the central nervous system**

MS most often follows an initial relapsing-remitting course and then evolves into a more progressive phase. Drs. Antel and Bar-Or think that front-line immune cells called microglia and monocytes are central to each phase of the disease. Microglia are cells that reside in the brain and are a first line of defence against invaders. Monocytes migrate from the blood to the brain and are found in active MS lesions. Both cells 'eat' cellular debris and stimulate immune responses. Drs. Antel and Bar-Or think that microglia and monocytes contribute to tissue injury and repair in the brain during MS.

To tackle their research, they are taking advantage of access to human adult central nervous system tissue as a source of microglia. They are using peripheral blood from volunteers and people with MS, including those receiving disease-modifying therapies, as the source of monocytes and other immune cells relevant to MS. The researchers have developed MS-like conditions in cell cultures to test a variety of processes implicated in disease progression. First on their list is to determine how signals from immune cells, oligodendrocytes (myelin-making cells) and myelin impact on microglia and monocytes. Then they will check how receptors found on microglia and monocytes direct microglia and monocyte responses.

These studies should enhance the understanding of MS and suggest therapies which downplay the pro-injury actions and encourage the repair actions of microglia and monocytes.

**Amit Bar-Or, MD**  
**Montreal Neurological Institute,**  
**McGill University**  
**\$44,679 (April 1, 2003 –**  
**March 31, 2006)**  
With additional funding from the Canadian Institutes of Health Research

**Human B cell subsets: Immune regulatory properties and role in multiple sclerosis**

Most MS research to date has focused on how immune system T cells cause tissue damage in the central nervous system. It is becoming clear that another type of immune cell, the B cell, may also be involved. B cells normally protect the body by making antibodies to fight infections. For some reason, B cells can also cause considerable damage for certain people with MS.

Dr. Bar-Or recently identified a particular type of memory (long-lived) B cell that can trigger T cells and make an abundance of antibodies. He finds high levels of these memory B cells in people with progressive MS. Samples collected from blood and cerebral spinal fluid (CSF) in people with and without MS will help him to narrow down who is most likely to have the memory B cells. He is also testing if the memory B cells can make antibodies against myelin and how they might be triggering T cells. Another important question to address is how easy it is for the memory B cells to cross the blood-brain-barrier.

Dr. Bar-Or's study will help form the foundation for new therapies specifically tailored for people who are most likely to develop these destructive memory B cells.

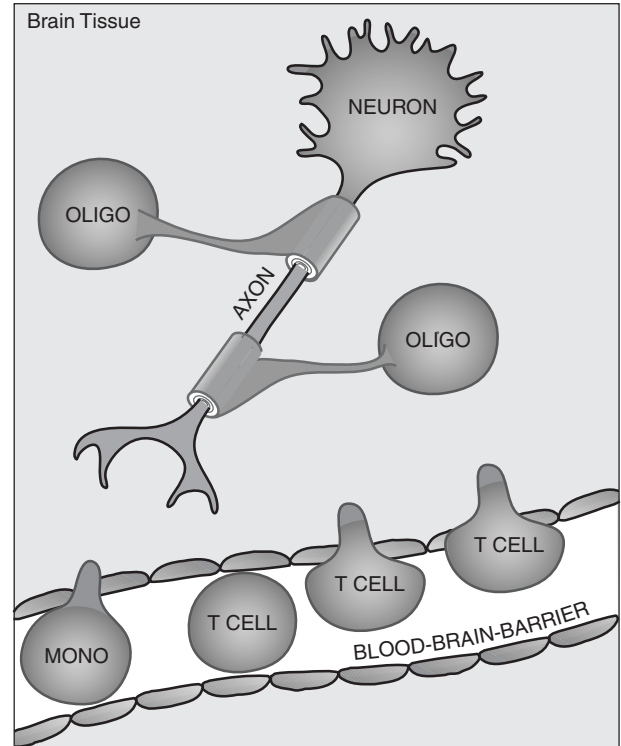
**Samuel David, PhD**  
**McGill University**  
**\$239,921 (April 1, 2004 –**  
**March 31, 2007)**

**Pathogenesis and treatment of chronic experimental autoimmune encephalomyelitis**

MS is an inflammatory disease of the central nervous system (CNS) that can result in myelin loss, sensory loss and even paralysis. The clinical course of MS varies from person to person and includes relapsing-remitting and chronic (progressive) forms. Although a variety of factors likely trigger MS in susceptible individuals, those that promote inflammation and damage to myelin are good candidates to study. For this reason, Dr. David is focusing on the enzyme PLA<sub>2</sub> whose by-products can dissolve myelin and cause inflammation.

Dr. David's studies take place in mice that develop an MS-like disease called experimental autoimmune encephalomyelitis (EAE). He made notable progress during the last period funded by the MS Society. In particular, he showed that PLA<sub>2</sub> is expressed at high levels in spinal cord lesions in the relapsing-remitting form of EAE. He also found that chemical inhibitors of PLA<sub>2</sub> significantly reduce the onset and progression of relapsing-remitting EAE. With new funding from the MS Society he plans to extend his studies to include a mouse model of chronic EAE. The changes in inflammation and nerve damage in the spinal cord at various stages of chronic EAE will be studied, as will the role of PLA<sub>2</sub>.

Studying EAE mice will give researchers more clues about how to design treatments, such as PLA<sub>2</sub> inhibitors, that might block inflammation and CNS damage in people with various forms of multiple sclerosis.



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

**Katerina Dorovini-Zis, MD**  
**Vancouver General Hospital**  
**\$158,892 (April 1, 2005 –**  
**March 31, 2007)**

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

During MS, the blood-brain-barrier (BBB) becomes leaky and encourages white blood cells to enter the central nervous system (CNS) where they damage nerve axons and myelin. Endothelial cells (ECs) forming the BBB are the first CNS cells to encounter circulating white blood cells. Because of this, Dr. Dorovini-Zis predicts that interactions between ECs and white blood cells may explain how white blood cells are able to get into the brain.

Using an artificial BBB pioneered in her laboratory with funding from the MS Society, Dr. Dorovini-Zis is studying the

interactions between endothelial cells and two types of white blood cells, called monocytes and dendritic cells. Monocytes are often seen in large numbers in MS lesions. Dendritic cells are not normally detected in the brain but have recently been found in the central nervous system of mice with an MS-like disease. Dr. Dorovini-Zis is using a variety of techniques to measure the role of endothelial cell adhesion molecules and endothelial cell messenger molecules called chemokines in promoting the leakiness of the BBB.

Therapeutic interventions stemming from this work might be treatment with antibodies to block adhesion molecules and administration of modified chemokines that block the influx of white blood cells into the brains of people with MS.

**Alyson Fournier, PhD, and  
Amit Bar-Or, MD  
McGill University  
\$219,740 (April 1, 2005 –  
March 31, 2007)**

### **Myelin inhibitory molecules and the neuro-immune interface**

The influx of activated immune system cells across the endothelial cells lining the blood-brain-barrier (BBB), myelin loss and nerve fibre (axonal) injury are all hallmarks of MS. Axonal injury is now recognized as the major instigator of sustained neurological disability. Drs. Fournier and Bar-Or's research focus is to study the mechanisms that limit axon regeneration.

When the myelin sheath is damaged during MS, several myelin proteins that are normally embedded in the sheath become exposed. These proteins, the most potent of which is called Nogo A, are known to inhibit the ability of axons to regenerate. Nogo A binds to the Nogo A receptor (NgR) on axons and leads to their

collapse. Some studies show that blocking Nogo in an EAE animal model of MS leads to better axon regeneration and recovery. Dr. Fournier recently discovered that Nogo A is found on activated human immune system cells, and that NgR is found on endothelial cells lining the human BBB. She and Dr. Bar-Or are building on these findings to uncover the role Nogo A plays during the MS disease process.

Therapies arising from the work on Nogo A would be aimed at optimizing axonal repair and minimizing the accumulation of disability in people with MS.

**Jennifer Gommerman, PhD  
University of Toronto  
\$218,039 (April 1, 2005 –  
March 31, 2007)**

### **Evaluating the role of the lymphotoxin pathway in EAE**

Lymphocytes are immune system cells that fight infections in our body. During MS, the body's own lymphocytes can also attack parts of the central nervous system (CNS). Before the lymphocytes can attack the CNS, they must first be activated in the lymph nodes and from there migrate to the CNS. Understanding this process will help researchers to develop better therapies for treating MS.

Dr. Gommerman is studying an inhibitor of the lymphotoxin pathway as a candidate therapy for MS. This lymphotoxin pathway is made up of cytokine messenger molecules and other signalling molecules that are involved in the developing and adult immune system. In previous studies, the lymphotoxin pathway inhibitor prevented EAE, an MS-like disease in rodents. However, the EAE rodents used did not provide useful information about the lymphocytes causing CNS damage. Dr. Gommerman is using 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 CNS-attacking lymphocytes and study the lymphotoxin pathway inhibitors in parallel.

Putting this information together will lead to a better understanding of how lymphotoxin inhibitors prevent EAE, and whether or not they might have therapeutic value in people with MS.

**David George Haegert, MD,  
and Veerabhadra Gadag, PhD  
McGill University  
\$310,956 (April 1, 2005 –  
March 31, 2008)**

### **Altered naïve T-cell homeostasis in multiple sclerosis**

The production of immune system T cells developing in the thymus is normally tightly regulated in healthy people. Based on their recent findings supported by previous MS Society funding, Drs. Haegert and Gadag are proposing that people with MS have fewer T cells. T cells are normally made in the bone marrow and travel to the thymus where they mature before being released into the blood. Lower numbers of T cells in people with MS may also be linked to additional abnormalities in T cell regulation.

The scientists have identified a marker that measures the number of naïve (untriggered) T cells made by the thymus. Drs. Haegert and Gadag are testing for the marker in people with relapsing-remitting MS and primary-progressive MS, as well as in people with clinically isolated syndrome (a single demyelinating event). They are also studying factors influencing T cell regulation in these groups.

Showing reduced numbers of T cells made by the thymus in people with MS would be important in three ways. First, an

abnormality in T cell production might precede the onset of MS, and help explain why some individuals develop the disease. Second, identifying lower numbers of naïve T cells in people with precursor lesions (those that result because of a single demyelinating event) might help to predict who will go on to develop MS. Third, the marker of T cell production may identify people with precursor lesions who need early treatment to prevent the development of clinically definite MS.

**Stephen Karlik, PhD  
University of Western Ontario  
\$217,956 (April 1, 2005 –  
March 31, 2007)**

### **Angiogenesis in chronic EAE**

Chronic inflammation outside the central nervous system depends in part on angiogenesis, the process of growing new blood vessels from existing ones. The new blood vessels that form are like a highway along which nutrients and immune system cells can travel to the tissues to promote inflammation, leading to damage. Angiogenesis is known to contribute to chronic inflammatory diseases like rheumatoid arthritis and psoriasis, but its contribution to MS is still unknown.

Dr. Karlik recently found that angiogenesis occurs in the spinal cord of mice and guinea pigs with EAE, an MS-like disease. Increased levels of VEGF, a molecule that promotes angiogenesis, can be found in the animals. He also found that interfering with HIF-1, a molecule that controls VEGF, exposes the animals to high oxygen levels and dramatically alters the course of inflammation. Dr. Karlik is examining the role of VEGF by blocking its action with a vaccine or with safe thalidomide derivatives. He is also investigating why breathing higher oxygen levels can decrease inflammation.

By studying the connection between angiogenesis, VEGF and HIF-1, Dr. Karlik hopes to identify ways to block angiogenesis in animals with EAE, and provide new possibilities for treating people with MS.

**Paul Kubes, PhD**  
**University of Calgary**  
**\$176,352 (April 1, 2004 –**  
**March 31, 2006)**

**The role of TLR4 and mast cells in the development of CNS autoimmune disease**

Why some people develop MS and others do not is an unresolved question. Most research focuses on the role that T cells play in MS. It is clear however, that T cells able to attack myelin in people with MS are not the whole story because healthy individuals have such T cells as well. Researchers think that environmental factors, including early exposure to some infectious agents, likely play a critical role in starting MS. How this might happen is still a mystery.

Dr. Kubes has identified the TLR4 receptor, which binds invading infectious agents, as a possible mediator of environmental factors involved in MS. TLR4 is found on many immune cells, but one in particular – the mast cell – is a good candidate for this study. It resides in tissues exposed to the environment, accumulates around MS lesions and makes factors that lead to inflammation and stimulate immune responses. Dr. Kubes plans to assess the role of mast cell TLR4 in an animal model of MS. He also hopes to discover how and why mast cells accumulate in the brain during the course of MS, and how exactly such cells contribute to disease development in MS.

This innovative research may show that mast cells are the interface for the environmental influences that initiate MS. If this proves to be correct, mast cells and

mast cell TLR4 might be two new therapeutic targets for the treatment and prevention of MS.

**Michael Mayne, PhD**  
**University of Prince Edward Island**  
**\$170,000 (April 1, 2003 –**  
**March 31, 2005)**

**Role of Rac-1 and CYFIP1 in T cell activation in multiple sclerosis patients**

A hallmark of MS is the movement of CD4 T cells into the brain. When triggered CD4 T cells enter the brain, they can cause tissue damage and early lesion formation. CD8 T cells are also present in lesions, but their role is still unclear. In this project, which developed from an initial Pilot Research Grant, Dr. Mayne wants to determine the steps that lead to CD4 and CD8 T cell triggering and movement into the brain.

A technique called genome array, where the activity of thousands of genes can be assessed at once, has given Dr. Mayne a clue. He found two proteins, Rac-1 and CYFIP1 that interact with each other and are overactive in CD4 T cells from people with MS. Rac-1's job is to trigger the moving machinery in many cells, including T cells, but the function of CYFIP1 is still unknown. Dr. Mayne continues to explore the function of Rac-1/CYFIP1 in people with MS. He also has some preliminary data on therapies, such as beta interferon and rolipram that might alter the role of Rac-1. Rolipram is an anti-depressant that also decreases the levels of some destructive enzymes in animal models of MS.

Dr. Mayne hopes that this study will generate new MS therapies that target Rac-1. The goal would be to slow down or stop the moving machinery in T cells and prevent them from entering the brain.

**Trevor Owens, PhD**  
**McGill University**  
**\$309,480 (April 1, 2005 –**  
**March 31, 2008)**

**Immune-glia interactions in  
CNS inflammation and  
demyelinating disease**

Inflammation is characteristic of MS and is associated with the entry of immune system cells into the brain. These cells mainly include T cells, many of which can attack myelin, and macrophages, which can contribute to the inflammation. The point at which macrophages and T cells enter the brain marks a pivotal step in the cascade of events that lead to MS. Dissecting the cascade is critical for controlling this disease.

In previous MS Society funded research, Dr. Owens showed that damage to axons in the brain causes resident support cells, called glial cells, to make chemokines. These are messenger molecules that attract immune system cell to the chemokine source. He also showed that Toll-like receptors, which normally bind parts of invading organisms in front-line immune responses can control how cytokine messenger molecules respond to injury. Toll-like receptors are also critical for T cell entry into the brain. Dr. Owens is using genetically modified mice to further explore how Toll-like receptors, cytokines and chemokines influence macrophage and T cell entry into the brain. He believes that not all immune system cells entering the brain cause damage and wants to learn how to control the outcome of macrophage and T cell entry into the brain.

Taken together, Dr. Owens' results should contribute to a better understanding of MS and help to control the immune response in people with this often disabling disease.

**Trevor Owens, PhD**  
**McGill University / Montreal**  
**Neurological Institute**  
**\$55,052 (April 1, 2003 –**  
**March 31, 2005)**  
**With additional funding from the Canadian**  
**Institutes of Health Research**

**The role of interferon-gamma in  
central nervous system inflammation**

The T cell attack on myelin in the brain results in inflammation (tissue damage) during MS. Many cytokines (message molecules) contributing to inflammation are made by brain cells. Others, like interferon-gamma, are made by cells that travel to the brain. Interferon-gamma seems to be a double-edged sword when it comes to MS. For example, when interferon-gamma is injected into people with MS, the disease worsens. When it is lacking in mice with an MS-like disease, the disease also worsens.

Dr. Owens' challenge is to understand when interferon-gamma is beneficial and when it is harmful. He thinks that interferon-gamma might control brain cells that can minimize T cell damage. Interferon-gamma might also communicate with chemokines (beacon molecules) that control immune cell entry into the brain, and the extent of myelin loss. Dr. Owens is trying to locate the source of the beacon molecules and to identify the ones that control interferon-gamma. To test his theories, Dr. Owens is using mice with an MS-like disease that lack interferon-gamma or other cytokines.

These experiments will tease apart the complexities of brain inflammation during MS. Understanding the destructive versus beneficial effects of interferon-gamma will help researchers to design better anti-inflammatory therapies.

**Alexandre Prat, MD, PhD**  
**Montreal University**  
**\$200,000 (April 1, 2004 –**  
**March 31, 2006)**

**Role and function of human endothelial cells during CNS inflammation**

The brain is an immunologically privileged site, meaning that immune responses in this location are muted compared to those that occur elsewhere in the body. This may be because monocytes (one of the group of glial cells) in the brain don't stimulate full immune responses. It turns out this is a good thing because vigorous immune responses in the brain can damage delicate brain tissue. Under normal circumstances, the tight junctions between the endothelial cells that line the blood vessels in the brain restrict the movement of circulating immune cells into the brain. In MS, the tight seal of the blood-brain-barrier (BBB) is broken and white blood cells, like lymphocytes and monocytes, get into the brain. These cells are thought to spearhead the attack on myelin.

A broad array of cell culture and other laboratory techniques will help Dr. Prat to compare the intact BBB with the leaky BBB to get a better idea of how MS starts. He wants to know whether glial cell signals maintain the tight seal between endothelial cells. He is very curious to see if BBB endothelial cells send signals that turn monocytes into better stimulators of immune responses in the brain. If so, such monocytes may play a significant role in contributing to the damage seen in MS.

Depending upon the outcome of this research, Dr. Prat could manipulate the BBB to allow anti-inflammatory drugs to pass into the brain. Such treatments could have a significant benefit for the thousands of Canadians with MS.

**Luc Vallières, PhD**  
**CHUL Research Centre, Quebec City**  
**\$63,000 (April 1, 2004 –**  
**March 31, 2006)**

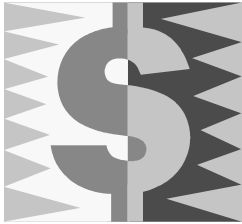
**Regulation of cerebral macrophage genesis in a murine model of multiple sclerosis**

Microglia and other brain macrophages stimulate immune responses within the central nervous system. The verdict is still out, however, as to whether these cells play a helpful or harmful role in MS. While these macrophages repair neural damage by 'eating' cellular debris, they also produce soluble messengers that promote inflammation which can lead to secondary tissue damage.

The main goal of this research is to discover the signals that promote the development of brain macrophages with the view of designing more effective anti-inflammatory therapies. Dr. Vallières's starting point is to better understand the role of tumor necrosis factor (TNF), a soluble messenger made by macrophages and other immune cells. Anti-TNF has recently been approved for therapeutic use in rheumatoid arthritis and may be useful for treating MS as well. However, some studies show that inhibiting TNF can promote myelin loss. In fact, Dr. Vallières's work in mice underscores this. He finds that too many microglia form after nerve axon damage in mice that lack TNF. Using a mouse model of MS, Dr. Vallières will follow macrophage formation and test whether TNF plays both inflammatory and suppressive roles during immune responses in the brain.

This research may lead to the development of more selective anti-TNF treatments aimed at slowing the progression of multiple sclerosis.

## How MS Research Is Funded



The MS Society funds a large and respected MS research program that totals between \$6 and \$7 million annually.

It provides funding to researchers carrying out a wide variety of approaches to solve the MS problem and also supports young scientists with career development awards, postdoctoral fellowships and studentships to get them started in a career in MS research.

The key principles guiding the MS Society research program are: **excellence** and **relevance to MS**. The MS Society will support **only the best** research projects and the best young scientists.

The research projects must also have **direct relevance to MS**. If a project is excellent, but has nothing to do with multiple sclerosis, it will not be funded. Currently, MS research is in these major areas: myelin repair, genetic susceptibility, immunology, MRI technology, health and treatment effects.

On October 1 of each year, nearly 100 applications for research grants, career development awards, fellowships and studentships arrive at the MS Society. Over the next few months, each application is assigned several scientific reviewers and the rigorous process of determining the best begins.

Each reviewer, who must be familiar with the research field, has to commit to many hours of work of reading and critiquing the proposal including work done by the applicant and by others, the proposed methodology (is it likely to be successful) and the budget (is it too large or too small)?

In January, the Biomedical Research Review Committee and the Health Research Review Committee meet to carefully consider each research project, discuss the critiques from the internal and external reviewers and then rank each project on its scientific excellence and relevance to MS. Budgets are scrutinized to ensure they are appropriate for the project.

The committees have clear rules about conflict of interest, which means that researchers from the same university or hospital as an applicant leave the room during the discussion and ranking of that project. The project is then ranked with each committee member voting on a scale that goes from: 0 (not acceptable) to 5 (excellent). Typically, MS Society funded research projects are in the "very good" and "excellent" categories.

At the end of two days of intense work, the review committees complete their review of the research project applications as well as career development awards, postdoctoral fellowships and studentships. Attracting new and talented young scientists to the MS research field is a challenge that the MS Society takes very seriously, and the various personnel support awards are a major incentive to students and just-graduated researchers.

The following day, the recommendations for funding go to the Medical Advisory Committee (MAC), which looks at the overall review process to ensure it was complete and fair. The MAC adds its recommendations for funding which then go to the Executive Committee of the National Board of Directors for final review and approval.

The final step is for all applicants to be notified whether they were successful or not. Those who were successful then turn their attention to gearing up their research project so they can start on April 1 for research projects or July 1 for personnel grants and to their part to solve the MS problem.

## MRI: Tools for Viewing MS



Scientists use many tools to take snapshots of what is happening in the brain during MS. One of the most sensitive of these tools is magnetic resonance imaging (MRI)

which generates two-dimensional images of the body's internal structures. MRI contrasts white matter (myelin) from grey matter and cerebral spinal fluid, and is so sensitive that it can distinguish between healthy brain tissue and lesions in a person with MS. Magnetic resonance spectroscopy (MRS) is also a useful imaging tool which compiles chemical information about healthy and diseased tissues.

As non-invasive techniques, MRI and MRS can be routinely used to follow individuals with MS on an ongoing basis. In combination, these techniques form a powerful way to monitor how MS lesions respond to different therapies. Scientists are constantly devising new and improved MRI and MRS techniques with the goal of capturing more detailed snapshots of what happens at different stages of MS. With better imaging tools will come improved diagnosis, monitoring and management of clinical symptoms, and treatments for people with MS.

***The key principles guiding the MS Society research program are: excellence and relevance to MS. The MS Society will support only the best research projects and the best young scientists.***

**Douglas Arnold, MD, and  
Gilbert Pike, PhD  
McGill University  
\$342,383 (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 lead to the death of nerve axons, causing permanent disability. The relationship between myelin loss, nerve axon 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, MRI spots are difficult to interpret as they still can't be matched with the degree of injury to the brain or to the clinical symptoms that develop. Drs. Arnold and Pike's research goal is to develop better magnetic resonance imaging techniques which measure myelin loss and repair over time in acute MS lesions. Magnetization transfer imaging (MTI) is a newer magnetic resonance imaging technique that is superior to MRI in that it gives specific information about damage to myelin. Using MTI, Drs. Arnold and Pike have already been able to clarify the timeline of myelin loss in chronic and, to a lesser extent, in acute MS lesions.

Their continued research efforts should be able to show whether MTI can be successfully used to monitor future therapies aimed at promoting myelin regrowth in people with MS.

**Alex MacKay, MD and David Li, MD**  
**University of British Columbia**  
**\$276,810 (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 cause attacks (relapses) where 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 after the blood-brain-barrier becomes leaky, allowing immune system cells into the brain and spinal cord. They made some good technical progress during the last period funded by 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 of a single slice in the brain. They also have a new magnetic resonance spectroscopy (MRS) scanner that gives higher quality 2D images than those obtained in previous years. With their new and improved MR techniques, they are using a number of markers to gauge myelin loss, myelin regrowth, and myelin changes in 'normal appearing' white matter of the brain.

By relating clinical disability with the observed physical and chemical changes to myelin, they should be able to predict some of the factors that contribute to functional loss in people living with MS.

**Ross Mitchell, PhD and**  
**Ursula Tuor, PhD,**  
**University of Calgary**  
**\$259,010 (April 1, 2003 –**  
**March 31, 2006)**

**Myelin-sensitive MRI: From bench to bedside**

Although magnetic resonance imaging (MRI) is a widespread tool used to monitor people with MS, there is still no clinical MRI exam that can capture whole-brain myelin health in people living with MS. Unfortunately, very few centres have access to the most up-to-date MRI scanners, image processing and analysis tools needed to measure whole-brain biological changes in people with MS.

In this study, Drs. Mitchell and Tuor are taking advantage of the outstanding facilities at the University of Calgary. Not only does the university have state-of-the-art animal and clinical MRI facilities, but it also boasts a large interdisciplinary group of scientists studying MS, from 'bench to bedside'. This unique combination of people and facilities drive the testing and implementation of a clinical whole-brain myelin-sensitive MRI exam. Drs. Mitchell and Tuor hope the exam will link MRI outputs to lesion composition, and provide methods for evaluating new therapies and identifying new targets for future preventive therapies.

Long-term, this research may accelerate clinical trials and connect MRI to disease pathology in a way that would guide future research directions.

**Wayne Moore, MD, Stanley Hashimoto, MD, David Li, MD, Robert Nugent, MD, and Alex MacKay, PhD**  
**University of British Columbia**  
**\$247,680 (April 1, 2005 – March 31, 2007)**

**The pathological basis of magnetic resonance imaging in multiple sclerosis**

Magnetic resonance imaging (MRI) is a very sensitive technique for detecting plaques in MS. In recent years, MRI studies have also detected other abnormalities in widespread areas of the brain and spinal cord. It is unclear what changes in the brain tissue might bring about these diffuse abnormalities and how such changes relate to new lesion formation.

Dr. Moore and his colleagues continue to study this phenomenon by examining MRI-detected changes in dirty-appearing white matter (DWM) and normal-appearing white matter (NAWM), both of which are regions of white matter without MS lesions. Since their last MS Society grant, this research team has made considerable progress. They noted a tendency for demyelinated plaques to occur in dirty-appearing white matter, suggesting that DWM is the area where white matter plaques develop. They are investigating DWM in more detail and comparing DWM and NAWM for myelin loss, lipid abnormalities, nerve fibre loss, and blood vessel integrity. They are also looking to see if there is a breakdown of the blood-brain-barrier in DWM, thereby allowing a way for circulating cells and other substances to enter the DWM and cause damage.

These findings will aid in understanding how and where an MS plaque develops and point to the factors responsible for the progression of disease.

# Managing MS Better Today



Multiple sclerosis typically affects young adults in the prime of life, between 15 and 40 years of age. The majority of people with MS start out with a relapsing-remitting form of the disease and go on to develop a more progressive form. Regardless of the type of MS an individual has, he or she must live with it for a long time.

Health research projects investigate problems that people with MS encounter in their daily lives. They focus on a number of areas including health economics, population health, and psychosocial and behavioural issues. Rather than investigating the causes of MS, health-related research measures the impact of MS on all aspects of health, and strives to improve the quality of life for people living with the disease.

<b>MS Research Commitments at a Glance</b>	
Total MS Society-funded research projects	36
Total Foundation-funded collaborative projects	4
Total MS Society-funded scholarships	60
Donald Paty Career Development Awards	5
Postdoctoral Fellowships	19
Research Studentships	36
Total Foundation-funded Pilot Research Projects	5

**Anthony Feinstein, MD, PhD,  
Danielle Tisserand, PhD, and  
Paul O'Connor, MD  
St. Michael's Hospital,  
University of Toronto  
\$144,340 (April 1, 2005 –  
March 31, 2007)**

**Multiple sclerosis and depression:  
An MRI diffusion tensor imaging study**

Almost 50% of people with MS experience clinically significant depression during the course of their lives. The reason for this is still unclear. Using MRI, Dr. Feinstein's team previously showed that MS lesions and shrinkage in certain regions of the brain increase the risk of depression. However, these MRI results do not always predict who will develop depression, suggesting inherent limitations in conventional MRI techniques.

Dr. Feinstein and his colleagues are adding diffusion tensor imaging (DTI) to their detection arsenal to help address the issue of depression in MS. They are using both conventional MRI and the newer DTI technique to look for brain factors associated with mood change. To do this, they are performing MRIs and DTIs on people with MS who suffer from mood changes, and on those who don't.

The results of this research will have valuable clinical impact. If depression can be more firmly linked to brain abnormalities, clinicians will more confidently choose drug intervention as the best treatment option. On the other hand, if brain abnormalities detected by MRI and DTI explain only a minority of the cases where depression occurs, clinicians can proceed with psychosocial treatment options.

**John Fisk, PhD  
Queen Elizabeth II Health Sciences  
Centre, Halifax  
\$30,250 (April 1, 2002 –  
March 31, 2005)  
With additional funding from Health  
Canada**

**Effectiveness and cost-effectiveness  
of new multiple sclerosis drugs in the  
"real world"**

Government funding for new MS treatments is a hotly debated topic. The controversy arises in large part because the direct health care costs for MS are substantial and it is unclear whether new treatments are cost-effective. Dr. Fisk believes that the potential to curtail such costs exists with treatments that slow the progression of disability in MS. The difficulty lies in predicting the extent to which the high costs associated with the treatment of acute MS symptoms might be offset by new treatments that slow the progression of MS.

This study is testing new drugs for their ability to slow the progression of disability using (1) five years of data from Nova Scotia's MS Special Therapy Program (2) MS natural history data from the Nova Scotia Multiple Sclerosis Integrated Database and other sources and (3) measurements of disability and health-related quality of life in treated and untreated people with MS. Dr. Fisk has developed new computer-generated mathematical models to integrate and assess the information he collects.

Dr. Fisk's models will provide the first Canadian-focused estimates of the cost-effectiveness of new treatments that slow the progression of disability in MS. The estimates should help policy decision makers in many countries make more informed and better decisions for funding new MS treatments.

**Helen Tremlett, PhD, and  
Joël Oger, MD  
University of British Columbia  
\$70,360 (April 1, 2004 –  
March 31, 2006)**

**The impact of beta-interferon therapy  
on multiple sclerosis: effectiveness  
and toxicity**

MS is a chronic disease of the brain and spinal cord and one of the most common reasons for severe disability in young adults. Although there is still no cure, beta interferon therapies are available to treat MS. During a post-doctoral fellowship at UBC funded by the MS Society, Dr. Tremlett observed that one participant in a clinical trial of beta interferon developed liver failure and needed a transplant. This person was also taking other medications at the same time. Such observations led Drs. Tremlett and Oger to focus their current research on the effectiveness of beta interferon and its potential for liver toxicity in people with MS.

Because people with MS frequently use multiple medications, Drs. Tremlett and Oger are investigating the risk of liver toxicity from combining different medicines with beta interferon. They are also assessing how often people with MS, not taking beta interferon, show abnormal liver test results. Another question is whether the existence of other diseases also increases the likelihood of abnormal liver tests in people with MS. Finally, the researchers plan to monitor how long-term use (over three years) of beta interferon affects disability in people with MS.

The goal of this research is to provide better counselling and monitoring of people with MS. Ultimately, Drs. Tremlett and Oger hope to reduce the number of people having to stop treatment because of abnormal liver tests.

**Daria Trojan, MD  
McGill University  
\$261,360 (April 1, 2002 –  
March 31, 2005)**

**Brainstem neuronal dysfunction and  
central fatigue in multiple sclerosis**

General fatigue is one of the most common and debilitating symptoms of MS. Many factors may contribute to fatigue in MS, including injury to the brainstem, disease duration and type, breathing difficulties, physical activity, sleep disturbance, immunological abnormalities, depression, stress and pain. Although a number of studies about fatigue in people with MS exist, Dr. Trojan is specifically focusing on biopsychosocial factors to measure the potential causes of fatigue in MS.

The control group for this study is made up of people with post-polio syndrome (PPS) who, like those with MS, also have a slow, progressive neurological disorder characterized by fatigue. During the course of the study, 65 people with MS and 65 people with PPS are being examined by a physician and undergo blood and lung testing. Study participants fill out a questionnaire to assess fatigue, pain, stress, sleep quality, depression, physical activity and self-ability. Imaging techniques are being used to measure lesions to the brainstem (the area controlling wakefulness) and surrounding areas.

Dr. Trojan's study may clarify the complex causes of fatigue and lead to a diagnostic test for fatigue in people with MS, PPS and other chronic illnesses.

# Collaboration to Speed Results

## Multiple Sclerosis Scientific Research Foundation Research 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 the largest funder in the world dedicated strictly to MS research. The Foundation supports large cooperative, multi-disciplinary research projects beyond the scope of the MS Society of Canada's regular granting program and to plan for and fund future needs and opportunities. It also funds small pilot research projects which allow investigators to pursue new innovative approaches to MS research where there is insufficient data for them to apply to the regular grants program. Currently, the MS Scientific Research Foundation is funding four flagship collaborative research initiatives.

***The MS Society and the related MS Scientific Research Foundation are able to continue this level of funding commitment thanks to the ongoing support of individual donors, corporate partners and MS Society chapters.***

## Remyelination in Multiple Sclerosis: Enhancing Intrinsic Repair

**Phase II:** \$2.25 million over three years from the Multiple Sclerosis Scientific Research Foundation – Approved April 2005

### Principal Investigators

Jack Antel, MD, Montreal Neurological Institute, McGill University  
Samuel Weiss, PhD, Hotchkiss Brain Institute, University of Calgary  
Moses Rodriguez, MD, Mayo Clinic, Rochester, MN.

Destruction of myelin in the brain and spinal cord is a major feature in multiple sclerosis. Cells from the immune system attack myelin, the substance that surrounds and protects nerve fibres in the central nervous system. 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 multiple sclerosis. The cells the researchers are targeting are called progenitor cells. They are cells within the body that have yet to become fully specialized, so the goal with 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 progenitor cells from the adult central nervous system. This avoids invasive surgical procedures and should overcome the limitations in the numbers 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 believe the approach 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 central

nervous system. The research is targeting progenitor cells that have already been located within the body and are using various proteins and hormones to entice them to the damaged parts of the brain and spinal cord that need remyelination.

The researchers also have pioneered new ways of using magnetic resonance imaging to measure, non-invasively, the production of new myelin and the rate of recovery from MS attacks. The ability to generate myelin and measure whether the new myelin is wrapping effectively around nerve fibres is key to reducing disability caused by MS.

Essentially, 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.

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### **Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis – Phase IV**

**Phase IV:** \$3.16 million over three years from the Multiple Sclerosis Scientific Research Foundation – Approved April 2004

#### **Principal Investigators**

A. Dessa Sadovnick, PhD, University of British Columbia  
George Ebers, MD, University of Oxford

#### **Co-Investigator**

Neil Risch, PhD, Stanford University, California

Multiple sclerosis is not an inherited disease, but it does tend to occur more often in families where other members are affected.

Women are more than twice as likely to develop MS as men. Although symptoms vary greatly, even between identical twins, more and more research shows that families may share common genes making them more susceptible to MS.

Much of the information acquired from genetic studies is obtained by looking at special groups of people, like twins, siblings, half-siblings and adoptees. Within these groups, scientists are identifying susceptibility genes and uncovering the normal function of those genes. Good candidate genes for study are those controlling myelin growth and cell-to-cell communications. Taken together, the knowledge gained from genetic studies is helping researchers design therapies that might be capable of controlling susceptibility genes in people with MS.

Since the initial study began in 1993, much progress has been made in understanding the relative roles of genetic (inherited) and environmental (non-genetic) factors, both in the overall cause of MS and the predisposition to MS among family members. This unprecedented cooperative study involves more than 21,000 people with MS registered at 18 MS clinics across Canada.

The Canadian Collaborative Genetic Susceptibility Study has confirmed that MS is a complex disease. Several genes are involved in causing MS and often interact with each other. Environmental factors are also important and act at a population level to strongly influence whether people who are genetically susceptible will develop MS.

The study has provided a number of important insights from Phases I, II and III.

- It has been clearly shown that the increase of MS among relatives of affected individuals is because they share genetic material (DNA) and

not because they share a common family environment.

- Studies of affected sibling pairs and their parents have suggested that some families may have more genetic factors involved in causing MS compared to other families.
- Studies of partners who both have MS support the impression that MS is not an infectious disease since the occurrence of both partners having the disease does not happen more often than expected based on general population data.

Molecular genetic studies are continuing. Some specific candidate genes have been eliminated and others are still being investigated.

In Phase III, the researchers looked at the molecular genetics, clinical genetics, genetic epidemiology and environmental factors which may play a role in causing MS. They specifically focused on:

- Environmental factors including early life events and diseases, exposure to sunlight, patterns of migration, birth order and month of birth.
- Continued genome screening and the search for "candidate" genes. This process is accelerating quickly with access to data from the Human Genome Project and new technology for screening for genes in populations.

Phase IV is developing further the genetic epidemiology and environmental factors and, at the same time, directly applying knowledge gained to date for people with MS and their families through genetic counselling. A study geared towards prevention of MS may grow out of Phase IV.

In Phase IV, the researchers are pursuing increasingly practical applications, specifically:

- Extend knowledge of the role of genetics and carefully examine environmental factors;
- Examine the incidence of MS over time;
- Use this knowledge as the basis of a Canadian prevention study in MS, which would be the first of its kind in the world.

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### **Bone Marrow Transplantation Project**

**Full title: Targeting Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoablative Therapy and Immunological Reconstitution – A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS**

\$4 million over six years from the Multiple Sclerosis Scientific Research Foundation – Approved August 2000

#### **Principal Investigators**

Harold Atkins, MD, Bone Marrow Transplantation Program, Ottawa Hospital – General Campus  
Mark Freedman, MD, MS Research Clinic, Ottawa Hospital – General Campus

The Multiple Sclerosis Scientific Research Foundation is funding a multi-centre project to determine whether transplanting bone marrow stem cells in people with MS can stop the disease. Led by Dr. Mark Freedman (MS neurologist) and Dr. Harold Atkins (bone marrow transplant physician), both at the University of Ottawa, the study will involve 36 people with rapidly progressing multiple sclerosis who are likely to become severely disabled. Twenty-four of the participants will receive bone marrow transplantation while 12 other people with

the same kind of MS but who do not wish to have the procedure will be the control group. Recruitment began in October 2000. Treatment centres for the study are located in Ottawa, Toronto and Montreal.

Bone marrow transplantation is used frequently to treat leukemia. In a very small number of people who have both MS and leukemia, MS symptoms improved following the bone marrow stem cell transplant. This project should allow investigators to determine if bone marrow transplantation is an effective treatment in a group of closely matched people with multiple sclerosis.

Equally important, should the procedure not fully stop the disease process, is gaining information about what triggers are present and what changes to the immune system occur at the beginning of disease activity. The researchers are monitoring closely for signs of disease activity in the participants at all stages of the procedure from enrolment to the end of the study. Monitoring will include complex immune system tests and tracking of certain immune-related genetic changes in the hope of unveiling particular genes that might contribute to genetic susceptibility.

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## Development of MS in Children

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

\$4.3 million over five years from the Multiple Sclerosis Scientific Research Foundation – Approved April 2004

#### **Principal Investigators**

Brenda Banwell, MD, Hospital for Sick Children, Toronto

Douglas Arnold, MD, Montreal Neurological Institute, Montreal

Amit Bar-Or, MD, Montreal Neurological Institute, Montreal

A. Dessa Sadovnick, PhD, University of British Columbia, Vancouver

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 paediatric MS study with 22 Canadian centres participating in 17 cities, including: Victoria, Vancouver, Edmonton, Calgary, Saskatoon, Winnipeg, London, Hamilton, Windsor, Toronto, Kingston, Ottawa, Sherbrooke, Montreal, Saint John, Halifax and St. John's. Paediatric CIS has never before been examined in such detail. This study is possible through the development of the Paediatric Demyelinating Disease Network, an extensive Canada-wide network of physicians and scientists.

The goal of the study is to answer two important questions: what is the cause of MS and what is the risk of MS after an initial attack of CIS.

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

The study has three pillars: clinical and

genetic epidemiology, pathobiology and neuroimaging.

1) Clinical and genetic epidemiology

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

2) Pathobiology

- By defining 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.
- In doing so, the study will define those immune responses associated with, or predictive of, the risk for further attacks leading to the diagnosis of MS.

3) Neuroimaging

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

## Programs to Attract New Scientific Talent

### Dr. Donald Paty Career Development Awards



The Multiple Sclerosis Society provides a limited number of Dr. Donald Paty Career Development Awards for individuals holding a doctorate degree and who have

demonstrated a commitment to a career in MS research. Successful applicants have already completed their research training and are capable of carrying out independent research relevant to MS in a full-time basis in a Canadian school of medicine. The university must confirm that 75% of the researcher's time will be protected for research activities. In addition, successful applicants must have an operating grant, either from the MS Society of Canada or another funding agency.

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 have inspired his colleagues around the world.

Total approved for Awards: \$750,000

Dr. Amit Bar-Or

Montreal Neurological Institute

Category: Immunology

Renewal: \$50,000 for each of three years beginning July 1, 2004

Dr. Paula Foster

Robarts Research Institute, London ON  
Category: MRI techniques

New: \$50,000 for each of three years beginning July 1, 2004

Dr. Ross Mitchell  
University of Calgary  
Category: MRI techniques  
Renewal: \$50,000 for each of three years  
beginning July 1, 2003

Dr. Alexandre Prat  
Hôpital Notre-Dame, Montreal  
Category: Immunology  
New: \$50,000 for each of three years  
beginning July 1, 2004

Dr. Helen Tremlett  
University of British Columbia  
Category: Health research  
New: \$50,000 for each of three years  
beginning July 1, 2004

### **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.

Total approved for Postdoctoral Fellowships: \$780,000

Fatemeh Afifiyan, PhD  
Hospital for Sick Children, Toronto  
Supervisor: Dr. Hans-Michael Dosch  
New: \$39,000

Peter Darlington, PhD  
McGill University  
Supervisor: Dr. Timothy E. Kennedy  
New: \$39,000

Lillian DeBruin, PhD  
University of Guelph  
Supervisor: Dr. George Harauz  
Renewal: \$39,000

Shannon Dunn, PhD  
Stanford University (California, USA)  
Supervisor: Dr. Lawrence Steinman  
Renewal: \$39,000

Julie Fotheringham, PhD  
National Institute of Health (Bethesda, MD, USA)  
Supervisor: Dr. Steven Jacobson  
Renewal: \$39,000

Elizabeth Jane Fry, PhD  
Montreal General Hospital Research Institute  
Supervisor: Dr. Samuel David  
Renewal: \$39,000

Isaias Glezer, PhD  
Laval University  
Supervisor: Dr. Serge Rivest  
Renewal: \$39,000

Andrea Hebb, PhD  
Dalhousie University, Halifax  
Supervisor: Dr. George Robertson  
New: \$39,000

Yukie Hirahara-Wada, PhD  
Hospital for Sick Children, Toronto  
Supervisor: Dr. Joan Boggs  
New: \$39,000

Bradley Kerr, PhD  
McGill University  
Supervisor: Dr. Samuel David  
Renewal: \$39,000

Bianca Kramer, PhD  
Hospital for Sick Children, Toronto  
Supervisor: Dr. Freda Miller  
New: \$39,000

Shalina Ousman, PhD  
Stanford University, (California, USA)  
Supervisor: Dr. Lawrence Steinman  
Renewal: \$39,000

Madeline Pool, PhD  
Ottawa Health Research Institute  
Supervisor: Dr. Stéphane Richard  
New: \$39,000

Victor Skihar, PhD  
University of Calgary  
Supervisor: Dr. V. Wee Yong  
New: \$39,000

Nicolas P. Turrin, PhD  
CREMO, Montreal  
Supervisor: Dr. Serge Rivest  
New: \$39,000

Shigeki Tsutsui, PhD  
University of Calgary  
Supervisor: Dr. Christopher Power  
Renewal: \$39,000

Karolina Wosik, PhD  
Hôpital Notre-Dame, Montreal  
Supervisor: Dr. Alexandre Prat  
Renewal: \$39,000

### Research Studentships

The MS Society provides funding for students who are working toward 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 one year with an opportunity for renewal.

Total approved for Studentships:  
\$716,000.

Joseph Antony  
University of Calgary  
Supervisor: Dr. Christopher Power  
Renewal: \$20,000

Alicia Babcock  
Montreal Neurological Institute  
Supervisor: Dr. Trevor Owens  
Renewal: \$20,000

Jennifer Berard  
McGill University, Montreal  
Supervisor: Dr. Samuel David  
Renewal: \$20,000

Shawn Beug  
Ottawa Health Research Institute  
Supervisor: Dr. Valerie Wallace  
New: \$20,000

Thor Bjarnason  
University of British Columbia  
Supervisor: Dr. Alex MacKay  
Renewal: \$20,000

Olivia Bibollet-Bahena  
McGill University, Montreal  
Supervisor: Dr. Guillermina Almazan  
New: \$20,000

Michelle Brucal, Ph. D.  
Wayne State University, Detroit, MI  
Supervisor: Dr. John Kamholz  
New: \$20,000

Katia Charland  
McGill University, Montreal  
Supervisor: Dr. Christina Wolfson  
Renewal: \$20,000

Arnaud Charil  
Montreal Neurological Institute  
Supervisor: Dr. Alain Dagher  
Renewal: \$20,000

Carol Anne Chénard  
Lady Davis Research Institute, Montreal  
Supervisor: Dr. Stéphane Richard  
Renewal: \$20,000

Rowena Cua  
University of Calgary  
Supervisor: Dr. V. Wee Yong  
New: \$20,000

Danielle Duszczyszyn  
McGill University, Montreal  
Supervisor: Dr. David Haegart  
Renewal: \$20,000

Farnaz Forghani  
Royal Victoria Hospital, Montreal  
Supervisor: Dr. Alan Peterson  
Renewal: \$20,000

Angelika Goncalves DaSilva  
University of Calgary  
Supervisor: Dr. V. Wee Yong  
Renewal: \$20,000

Sandy Hemdan  
McGill University, Montreal  
Supervisor: Dr. Guillermina Almazan  
Renewal: \$20,000

Shireen Hossain  
McGill University, Montreal  
Supervisor: Dr. Guillermina Almazan  
Renewal: \$20,000

Igal Ifergan  
Notre-Dame Hospital, Montreal  
Supervisor: Dr. Alexandre Prat  
Renewal: \$20,000

Carolyn Jack  
Montreal Neurological Institute  
Supervisor: Dr. Jack Antel  
Renewal: \$20,000

James Knight  
Ottawa Hospital Research Institute  
Supervisor: Dr. Rashmi Kothary  
New: \$18,000

Shannon Kolind  
University of British Columbia  
Supervisor: Dr. Alex MacKay  
New: \$20,000

Antonia Kuznetsova  
Dalhousie University, Halifax  
Supervisor: Dr. John Fisk  
New: \$20,000

Karen Lee  
Ottawa Health Research Institute  
Supervisor: Dr. Rashmi Kothary  
New: \$20,000

Matthew Lincoln  
University of Oxford  
Supervisor: Dr. George Ebers  
Renewal: \$20,000

Kenneth Liu  
University of British Columbia  
Supervisor: Dr. Katerina Dorovini-Zis  
Renewal: \$20,000

Marie Lune-Simard  
McGill University, Montreal  
Supervisor: Dr. Amit Bar-Or  
New: \$20,000

Andre Luiz Mendes Matos  
Montreal Neurological Institute  
Supervisor: Dr. Douglas Arnold  
New: \$20,000

Jason Millward  
Montreal Neurological Institute  
Supervisor: Dr. Trevor Owens  
Renewal: \$20,000

Craig Moore  
Dalhousie University, Halifax  
Supervisor: Dr. George Robertson  
New: \$20,000

Abdi Musse  
University of Guelph  
Supervisor: Dr. George Harauz  
Renewal: \$20,000

Ayman Oweida  
University of Western Ontario, London  
Supervisor: Dr. Paula Foster  
New: \$18,000

Sathyanath Rajasekharan  
McGill University  
Supervisor: Dr. Tim Kennedy  
New: \$20,000

Leah Remington  
McGill University  
Supervisor: Dr. Trevor Owens  
New: \$20,000

Leslie Summers DeLuca  
University of Toronto  
Supervisor: Dr. Jennifer Gommerman  
New: \$20,000

Henrik Toft-Hansen  
Montreal Neurological Institute  
Supervisor: Dr. Trevor Owens  
Renewal: \$20,000

Nazi Torabi  
McGill University, Montreal  
Supervisor: Dr. Stéphane Richard  
New: \$20,000

Melissa Wright  
McGill University, Montreal  
Supervisor: Drs. Alyson Fournier and Amit Bar-Or  
New: \$20,000

## Pilot Research Grants

Pilot Research Grants Pilot research grants are available to fund small, innovative research projects. They are targeted at quickly looking 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.

- **Paul O'Connor, MD, and Melanie Ursell, St. Michael's Hospital, Toronto**  
**Biomedical Research** – A phase 1 dose escalation study of Vitamin D3 with calcium supplementation in patients with MS  
\$35,000 – Approved: May 2004
- **Alyson Fournier, PhD, and Amit Bar-Or, MD, Montreal Neurological Institute**  
**Biomedical Research** – Role of myelin-associated inhibitor at neuro-immune interface  
\$35,000 – Approved: September 2004
- **John Fisk, PhD, Capital Health, Dalhousie University**  
**Health Research** – A pilot study of quantitative neuroimaging correlates of cognitive dysfunction in MS  
\$35,000 – Approved: October 2004

- **Jack Hay, PhD, University of Toronto**  
**Biomedical Research** – New approaches to define the exit of immune cells from the brain  
\$18,823 – Approved: December 2004
- **Trevor Owens, PhD, McGill University**  
**Biomedical Research** – Role of Inhibitors of Apoptosis (IAPs) in autoimmune demyelinating disease  
\$35,000 – Approved: February 2005
- **Tom Tombaugh, Carleton University**  
**Health Research** – Detecting cognitive impairments using the computerized test of information processing  
\$13,600 – Approved: June 2005
- **Chris Proud, University of British Columbia**  
**Biomedical Research** – Targeted transgenic mouse model for a degenerative disease, vanishing white matter  
\$35,000 – Approved: June 2005

*Attracting new and talented young scientists to the MS research field is a challenge that the MS Society takes very seriously, and the various personnel support awards are a major incentive to students and just-graduated researchers.*

## Glossary 2005

**Adhesion molecule** - A protein that promotes the binding of one cell to another or to the extracellular matrix.

**Antibody** - A protein made by a plasma cell (mature B cell) that protects the body against foreign invaders like bacteria and viruses.

**Antigen** - A substance that is bound by antibodies. The name 'antigen' arises from the ability to **generate antibodies**. Viral and bacterial molecules and even the body's own molecules can be antigens.

**Angiogenesis** - The formation of new blood vessels.

**Antigen presenting cell** - A specialized cell that sticks pieces of antigen combined with self 'display' molecules on its surface for passing immune cells to survey. Dendritic cells, macrophages and B cells are the main antigen-presenting cells.

**Astrocyte** - A support cell in the central nervous system (CNS) that attaches to both nerve cells and blood vessels; provides metabolic, nutritional and physical support. Astrocytes make the scars on damaged tissue during MS.

**B cell** - An antibody-making lymphocyte (white blood cell) originating in the bone marrow.

**Blood brain barrier (BBB)** - A barrier formed by a continuous layer of tightly connected endothelial cells; prevents most large molecules and cells found in the blood from entering the brain tissue.

**Central nervous system (CNS)** - The brain and the spinal cord; all parts can be affected by multiple sclerosis.

**Cerebral spinal fluid (CSF)** - The fluid that bathes the surfaces of the central nervous system.

**Chemokine** - A protein beacon that attracts white blood cells bearing a receptor for the chemokine.

**Cytokine** - A small messenger molecule that influences the actions of immune system cells; also called a lymphokine or interleukin (IL). There are many different cytokines, each acting only on cells that have receptors for that cytokine.

**Demyelination** - Process during which myelin is stripped from nerve fibres.

**Dendritic cells** - A white blood cell that is bone-marrow derived and specializes in presenting antigen to T cells.

**Differentiation** - A series of steps that cells go through to reach their mature state.

**DNA (deoxyribonucleic acid)** - The code of genetic instructions that shapes the development of every individual. DNA is shaped as a double helix and is made up of nucleic acid-sugar complexes loosely bound to proteins.

**EDSS** - Expanded Disability Status Score is a test for measuring the disability level of a person with MS; also known as the Kurtzke Scale after, Dr. John Kurtzke.

**Endothelial cell** - Lines the heart and blood vessels of the circulatory and immune systems; forms the blood brain barrier (BBB).

**Experimental autoimmune encephalomyelitis (EAE)** - An MS-like disease created in laboratory mice after they are injected with CNS tissue or a derivative of myelin basic protein.

**Gene** - Pieces of DNA that include the genetic code for making body proteins; located on chromosomes.

**Glial cell** – Support cells in the nervous system; oligodendrocytes, astrocytes and microglial cells in the central nervous system and Schwann cells in the peripheral nervous system.

**HRQL (Health Related Quality of Life)** - Quality of life of people with MS based on patient-perceived functional status and well-being.

**Immunoglobulin** - The membrane-bound version of antibody that binds antigens and signals the B cell to secrete antibodies.

**Inflammation** – Normally protective response to physical/chemical injury, infection or a local immune response leading to tissue damage where loss of function may accompany swelling, redness, heat and pain; fluid, white blood cells and plasma proteins accumulate.

**Interferons (IFN)** - Cytokines that help cells to fight viruses. Alpha interferon and beta interferon are made by white blood cells, fibroblasts and other cells. (Manufactured versions are useful as MS treatments.) Gamma interferon is produced by inflammatory T cells and natural killer cells and its main action is to trigger macrophages to help fight infection. Gamma interferon makes MS worse.

**Lipid** - Fat soluble. A term describing the ability of molecules, such as fats, fatty acids and soaps, to dissolve in fat.

**Lymphocytes** - White blood cells (B cells, T cells and NK cells) of the immune system that fight specific infections.

**Macrophage** - An immune cell that is among the first line of defence against invaders; also acts as antigen presenting cells. Macrophages are called different names depending where they are found in the body (e.g. microglial cells in the brain).

**Magnetic resonance imaging (MRI)** - A technological tool that detects energy released from hydrogen atoms to create anatomical images. MR images of soft tissues of the body including the brain and spinal cord clearly show MS lesions and may be used to track disease progress.

**Magnetic resonance spectroscopy (MRS)** - A technological tool similar to magnetic resonance imaging but providing chemical rather than anatomical information. MRS is most useful when evaluating trials of new treatments by measuring disease severity and progression.

**Mast cell** - Originates in the bone marrow; involved in allergic responses.

**Memory B cells** - B cells living in the body for long periods of time; can be triggered to make antibodies.

**Microglia** - Macrophage-like cells that reside in the brain; 'eat' cellular debris and stimulate immune responses.

**Monocyte** - A white blood cell that resides only in the blood. Once it migrates into the tissues, a monocyte is called a macrophage.

**Morphogen** - Diffusible substance that influences movement and organization of cells during development.

**MSQLI** - The Multiple Sclerosis Quality of Life Inventory is a questionnaire designed to evaluate the burden of disease experienced by people with MS.

**Myelin basic protein (MBP)** - One of the principal proteins found in myelin.

**Myelin** - A collection of proteins and lipids that make up the myelin sheath; speeds transmission of signals along nerve fibres.

**Myelin sheath** - 1-200 insulating layers of myelin surrounding nerve fibres in the central and peripheral nervous system.

**Nerve fibre (axon)** - The slender, long branch extending from a nerve cell that carries nerve impulses to adjacent nerve cells throughout the body. Most nerve fibres are surrounded by 1-200 layers of myelin.

**Neuroglia (glial cells)** - Supporting, non-impulse generating cells of the nervous system (e.g. astrocytes and oligodendrocytes).

**Neuron** - A cell within the nervous system that consists of a cell body and the associated membrane extensions, called dendrites when highly branched, or axons when minimally branched. Nerve impulses travel along nerve axons.

**NK cells** - Natural Killer cells are a group of lymphocytes (not T or B cells) that can kill some virally infected and tumor cells.

**Oligodendrocyte** - The cell in the CNS that makes and maintains myelin; wraps its myelin-filled membranes around nerve fibres (axons).

**Peptide** - A chain of amino acid building blocks strung together. The chain can be two (di-) amino acids, three (tri-) amino acids, or more (poly-) amino acids in length.

**Peripheral nervous system (PNS)** - Nervous system in the body aside from the brain and spinal cord. The PNS can be affected by MS.

**Plaque** - An area of myelin loss characteristic of multiple sclerosis.

**PLP (Proteolipid Protein)** - One of the major proteins found in the myelin sheath.

**Remyelination** - Process during which myelin is re-added to nerve fibres by oligodendrocytes or Schwann cells.

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

**T cell** - Immune cells that fight infections. Two broad categories are alpha-beta and gamma-delta T cells. Alpha-beta subsets include helper T cells (CD4<sup>+</sup>) and killer T cells (CD8<sup>+</sup>).

**T cell receptor (TCR)** - A protein found on the surface of T cells. Alpha-beta TCR binds to bits of foreign peptides (or sometimes body peptides, like myelin) attached to cell surface 'display' proteins on antigen presenting cells.

**Tumor necrosis factor (TNF)** - TNF alpha and TNF beta; cytokine made by macrophages and some T cells; toxic to tumor cells; plays role in inflammatory responses.

**Transgenic mice** - Mice that contain genes from another source (animal or human); derives from 'trans' (other) and 'genic' (genes).

# INDEX

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<b>MS research program at record level</b>	<b>1</b>	<b>MRI: Tools for viewing MS</b>	<b>18</b>
<b>Repairing and Protecting Myelin</b>	<b>2</b>	Arnold and Pike	18
Almazan and Mushynski	2	MacKay and Li	19
Boggs	3	Mitchell and Tuor	19
Braun and Gravel	3	Moore, Hashimoto, Li, Nugent and MacKay	20
Harauz	4	<b>Managing MS Better Today</b>	<b>20</b>
Kennedy	4	Feinstein, Tisserand and O'Connor	21
Kothary	5	Fisk	21
Moscarello and Mastronardi	5	Tremlett and Oger	22
Nazarali	6	Trojan	22
Peterson	6	<b>Collaboration to speed results</b>	<b>23</b>
Power	7	Remyelination in Multiple Sclerosis: Enhancing Intrinsic Repair	23
Richard	7	Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis – Phase IV	24
Wallace	8	Bone Marrow Transplantation Project	25
Yong	8	Prospective Study of the Clinical Epidemiology, Pathobiology and Neuroimaging Features of Canadian Children with Clinically Isolated Demyelinating Syndromes	26
<b>Stopping Immune System Attacks</b>	<b>9</b>	<b>Programs to Attract New Scientific Talent</b>	<b>27</b>
Antel	9, 10	Dr. Donald Paty Career Development Awards	27
Bar-Or	10, 12	Postdoctoral Fellowships	28
David	11	Research Studentships	29
Dorovini-Zis	11	Pilot Research Grants	31
Fournier	12	<b>Glossary 2005</b>	<b>32</b>
Gommerman	12		
Haegert and Gadag	13		
Karlik	13		
Kubes	14		
Mayne	14		
Owens	15		
Prat	16		
Vallières	16		
<b>How MS Research is Funded</b>	<b>17</b>		

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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.*

