Multiple Sclerosis Society of Canada

MS Research Summaries 2006

MS Society funds increased number of research grants and scholarships

In April, the MS Society of Canada approved more than $4.5 million to fund 13 research projects and a record-breaking number of research scholarships to attract young scientists to the MS field.

More than $2.6 million was awarded for 13 research projects, $300,000 for Dr. Donald Paty Career Development Awards, $594,500 for postdoctoral fellowships and $786,666 for studentships.

"The research projects include the best in basic laboratory research that are targeted at finding ways to repair the damage in the brain and spinal cord that MS causes and in stopping MS attacks," said Dr. William J. McIlroy, national medical advisor.

"I am particularly pleased that we are funding more than 60 research scholarships. These awards are designed to both attract and then keep young researchers working to end MS. Our scholarship program has more than doubled in less than 10 years," he added.

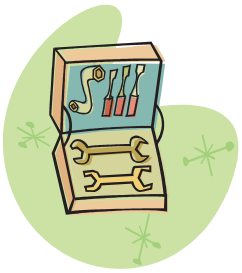
To be funded, the research projects and scholarships must meet two critical principles. The first is scientific excellence; they must be the very best of the research projects and scholarship applicants. Second, and equally important, they must be of direct relevance to MS. Both principles must be met before they are recommended for funding.

Following an exacting review process, the recommended research projects and scholarships go to the Medical Advisory Committee for a definitive overview. The final step is for the National Executive Committee to receive the recommendations and approve them based on the Society's available resources.

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.

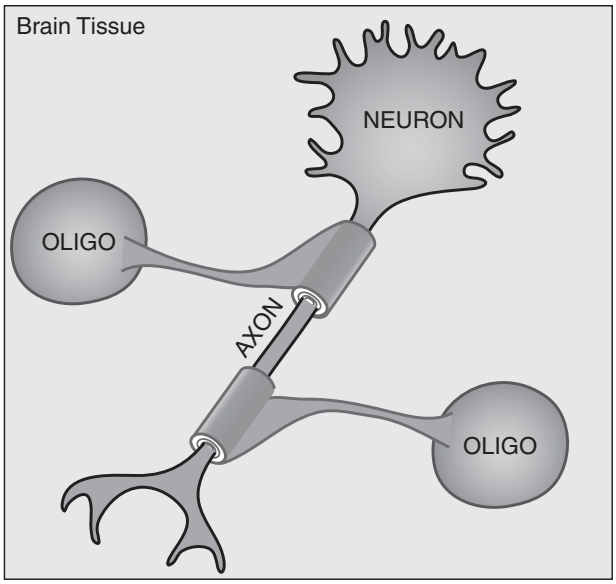
CONTENTS

Repairing Myelin and Protecting Nerves



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. The body uses myelin by wrapping it around nerve fibres (axons) to form a compact 'myelin sheath'. In MS, the myelin sheath is damaged and the cells making myelin can't repair it fast enough. Not only do the myelin-stripped axons have difficulty sending nerve impulses, but the axons themselves are also 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 scientists achieve their goal. As the processes of myelination (myelin growth) and remyelination (myelin regrowth) are mapped out in more detail, better therapies will be available to counter the far-reaching effects of myelin damage during MS.



© Maya Chaddah

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
$305,200 (April 1, 2006 – March 31, 2009)

Role of p38 MAPK (mitogen activated protein kinase) signalling pathways in myelination

Myelin is made as a membrane extension of Schwann cells in the peripheral nervous system and of oligodendrocyte cells in the central nervous system. The dominant feature of MS is the formation of large lesions where myelin is damaged. The immune system cells that attack myelin cause inflammation of the brain tissue, and the irreversible loss of nerve function that follows often goes hand in hand with axon (nerve fibre) damage. To better understand the interactions between myelin and nerve fibres, it is essential to clearly describe the sequence of events and signals that lead to normal myelination of nerve fibres.

Drs. Almazan and Mushynski are specifically looking at some of the molecular mechanisms required for the initiation and maintenance of

myelination. For their experiments, they are using mixed cultures of dorsal root ganglion neurons (nerve cells) plus either Schwann cells or oligodendrocytes. They have identified p38, a member of the MAPK family, as playing a fundamental role in the process of myelination. There are different types of p38, and one type called p38a controls the production of cytokine messengers involved in inflammation.

These researchers hope to identify the particular forms of p38 that might become part of new therapies to treat chronic inflammatory diseases like multiple sclerosis.

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 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. Clues about how to help oligodendrocytes do their job more effectively can 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 where two myelin-filled membranes in the sheath touch 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. Boggs's research could lead to new therapeutic methods for stimulating remyelination by oligodendrocytes and for 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 cell surfaces 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 while oligodendrocytes make the 'myelin sails' and maintain nerve axon function. They are continuing to explore the 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.

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.

Dr. Kennedy recently reported promising results from research funded by the MS Society. Using animal models, he showed 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. Results from post-mortem studies of human MS plaques has led Dr. Kennedy to propose 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 damage 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 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 using transgenic mice that make different types of integrin to study myelin loss and regrowth. He is also 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
$203,570 (April 1, 2006 – March 31, 2008)

Demyelination and remyelination in MS. The role of Vitamin B12 and methylation

MS is characterized by loss of myelin surrounding axons (nerve fibres), and failure of the stripped axons to be remyelinated by oligodendrocyte cells. In addressing these two issues, Drs. Moscarello and Mastronardi found that an enzyme called PAD alters myelin basic protein, causing myelin destabilization.

In searching for reasons why this might occur, they found that the start of the PAD gene had fewer chemical groups called 'methyl groups' than normal, meaning that more PAD was made. They are currently exploring whether vitamin B12 can increase the number of methyl groups at the start of genes. They continue to study molecules such as sonic hedgehog, Notch-1 and stathmin. To date, they have shown that decreases in sonic hedgehog and increases in Notch-1 and stathmin prevent oligodendrocyte maturation. Without mature oligodendrocytes, stripped nerve axons cannot be remyelinated.

In the last period funded by the MS Society, they found that B12 in combination with beta interferon or paclitaxel dramatically improved the clinical symptoms in various animal models of MS. Given their results, Drs. Moscarello and Mastronardi have recommended that vitamin B12 be used in the treatment of people with MS.

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 Alberta
$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
$295,830 (April 1, 2006 – March 31, 2009)

The role of quaking proteins in oligodendrocyte physiology and myelination

One unusually named animal model of MS is the 'quaking viable mouse'. It gets its name from the tremors that occur shortly after birth in mice with defective quaking proteins. Dr. Richard's lab has shown that mice lacking the quaking proteins also have myelin defects. He continues to study the function of quaking proteins in an effort to tease out how they are required for the growth of myelin-making oligodendrocyte cells.

Dr. Richard has made considerable progress since his previous grant funded by the MS Society. He has published two major research papers on quaking proteins and has another manuscript in preparation. In one of the research publications, he presented unique data showing that quaking proteins 6 and 7 can cause oligodendrocyte differentiation and maturation. These oligodendrocytes can come from parent cells (neural precursors) in the brain, and also from immature oligodendrocytes in cell cultures.

With the renewed research grant, Dr. Richard is continuing to study the potential of quaking proteins to cause oligodendrocyte growth. In the future, his studies may provide a way to repair myelin by using therapies that enhance the function of quaking proteins 6 and 7.

Peter Stys, MD
University of Ottawa
$165,668 (April 1, 2006 – March 31, 2008)

Mechanisms of axon spheroid formation

MS is an autoimmune disease where the body's own immune system mistakenly attacks the brain tissue. The brain is made up of 'wires' called axons that are insulated with a material called myelin. Axons play the critical role of transmitting electrical impulses within the nervous system. When attacked by the immune system, myelin is damaged and the wire-like axons are cut. The severed axons might be the most important feature of

MS, because once cut, they degenerate and disappear forever from the brain and spinal cord. After enough axons are lost, the brain suffers permanent and progressive loss of function.

Before damaged axons are severed, they swell up in a process called spheroid formation. Although this phenomenon has been observed microscopically for over 150 years, there is still no clear idea what causes the swelling. Dr. Stys' research team has developed a tissue model mimicking axon swelling so he can visualize the process in real time with laser scanning microscopes.

Using this unique process, Dr. Stys hopes to learn more about what triggers axon swelling, and the drugs that might be used to prevent it 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 metallo-proteinases (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 very survival and

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.

function of oligodendrocytes by focusing on matrix metalloproteinases (MMPs). MMPs are well positioned to promote myelin regrowth as they help oligodendrocytes develop and extend their myelin-filled membranes around nerve fibres.

In research previously funded by the MS Society, Dr. Yong found that astrocytes (support cells in the brain) interact directly with surface proteins on oligodendrocytes, sending them signals that enhance their 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. He is continuing 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.

Immune System Has Key Role

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 the tight seal of the blood-brain-barrier (BBB) loosens to allow white blood cells into the brain. Equally important are studies evaluating new and existing immunotherapies that can help clinicians to tailor treatments for 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 tissue. 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 can cross 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 in 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_2 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). In previous research funded by the MS Society, he showed that PLA_2 is expressed at high levels in spinal cord lesions in the relapsing-remitting form of EAE. He also found that chemical inhibitors of PLA_2 can significantly reduce the onset and progression of relapsing-remitting EAE. With continued funding from the MS Society, he plans to broaden 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_2.

Studying EAE mice will give researchers more clues about how to design treatments, such as PLA_2 inhibitors, that might block inflammation and CNS damage in people with various forms of multiple sclerosis.

Samuel David, PhD
McGill University
$84,186 (April 1, 2006 – March 31, 2008)

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

Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model of MS. Dr. David has shown that an enzyme called phospholipase A2 (PLA_2) plays an important role in the onset and progression of EAE in mice. He has identified an inhibitor compound that blocks PLA_2 and reduces the onset and progression of EAE. However, there are several different types of PLA_2, some of which have normal functions in the body. Unfortunately, the inhibitor compound blocks those forms of PLA_2 as well.

Dr. David now has evidence that four out of fourteen PLA_2 tested are increased in the spinal cord and spleen of EAE mice. His preliminary data show that these four PLA_2 may be involved in different phases of EAE. He is collaborating with a scientist in Greece who has developed specific inhibitors for the four PLA_2 enzymes. The goal of the current proposal is to find out which cells in EAE lesions produce the four different forms of PLA_2, and to assess their role by selectively blocking them with the specific inhibitors.

If successful, this novel group of inhibitors could be further developed and tested for the treatment of MS in humans.

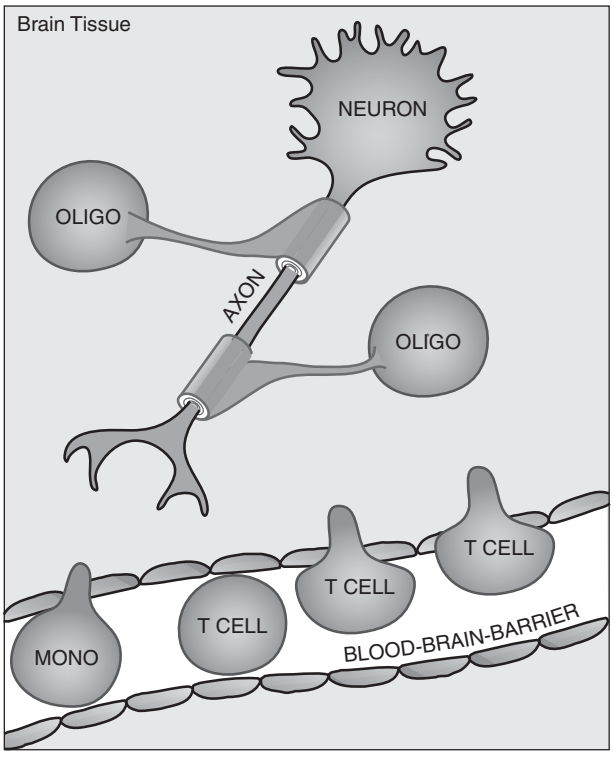
Katerina Dorovini-Zis, MD
Vancouver General Hospital
$292,890 (April 1, 2006 – March 31, 2009)

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

During MS, the blood-brain-barrier (BBB) becomes leaky and destructive immune system cells enter the brain. Endothelial cells (ECs) line all the blood vessels in the body, including those of the BBB. ECs lining the BBB of the brain are the first cells to meet circulating immune system cells. Because of that, Dr. Dorovini-Zis predicts that the interactions between these cell types are likely important for the brain damage seen in MS.

Dr. Dorovini-Zis has made considerable progress since the last granting term funded by the MS Society. She has published seven research papers, and currently has several other manuscripts in preparation. These papers explore the role of ECs in stimulating immune system cells to cross the BBB. With these details firmly in hand, Dr. Dorovini-Zis pushes forward to study whether the immune system T cell (which enters the brain to damage myelin) is activated by ECs at the BBB. The artificial model of the BBB pioneered in her lab is still the major tool she uses to observe the EC-immune system cell interactions under closely controlled conditions.

This research may point to specific therapies targeted at restoring the normal function of ECs lining the BBB in people with MS.



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

Alexander Easton, MBBS, PhD
Chunahi Hao, MD, PhD
Dalhousie University
$129,343 (April 1, 2006 – March 31, 2008)

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

During MS, myelin is attacked by activated T cells, immune system cells that ordinarily protect the body. Activated T cells do not normally reside in the brain. For them to damage myelin, they must first leave the blood and enter the brain tissue by interacting with endothelial cells lining the blood vessels of the brain. Brain endothelial cells create a blood-brain-barrier (BBB) which restricts the entry of cells and substances from the blood into the brain. During the inflammatory process that occurs in MS, the tight seal of the BBB is broken. This process occurs in part because of the activity of cellular messengers called cytokines, particularly tumor necrosis factor (TNF).

Drs. Easton and Hao are studying two members of the TNF family, called Fas ligand and TRAIL. Their role in endothelial cell activation is unclear, but the researchers have discovered already that Fas ligand promotes the activation of brain endothelial cells while TRAIL inhibits it. In cell culture models of the BBB, Fas ligand increases T lymphocyte adhesion and permeability, while TRAIL reduces permeability without promoting adhesion. This means that Fas ligand might increase the movement of T cells across the BBB, while TRAIL might reduce it.

With the new operating grant, the researchers hope to confirm their initial findings and explore the various signals involved. If TRAIL reduces inflammation, it may have an exciting therapeutic potential in 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 be regenerated. 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. The researchers are building on their findings to decipher the role of Nogo A 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.

Sylvie Fournier, PhD
McGill University
$181,264 (April 1, 2006 – March 31, 2008)

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

Multiple sclerosis is an inflammatory disease of the central nervous system (brain and spinal cord) where immune system T cells play an important role. There are two major types of T cells: CD4+ T cells and CD8+ T cells. Over the years, CD4+ T cells have been held almost exclusively responsible for MS. Recent evidence, however, suggests that CD8+ T cells may also contribute to starting and continuing the disease process. How these cells might cause inflammation in the nervous system is largely unknown.

Dr. Fournier has generated a new model of MS in which mice spontaneously develop a neurological disease similar to MS in humans. She has shown that the MS-like disease is caused by the activation of CD8+ T cells in the nervous system. Further study of this animal model should allow her to dissect the steps by which CD8+ cells are triggered, leading to inflammation and injury of the nervous system.

Aside from broadening the understanding of MS, this research might also lead to the development of new therapeutic approaches to prevent CD8+ T cells from causing the nerve damage so devastating in MS.

Fabrizio Giuliani, MD
University of Alberta
$172,000 (April 1, 2006– March 31, 2008)

Role of inflammation in neurodegenerative processes of multiple sclerosis

MS typically displays a relapsing course marked by episodes of neurological disability. Such episodes are followed by periods of partial or complete remission. Axon and neuron (nerve cell) damage can lead to permanent disability, and severe axon (nerve fibre) damage might even be responsible for turning relapsing-remitting MS to the secondary-progressive form.

The cause of tissue damage in MS is uncertain, but inflammation likely plays a role since axon damage increases as inflammation worsens within a lesion. Dr. Fabrizio has determined that human neurons are extremely vulnerable to injury by T cells, immune system cells that normally protect the body. He has focused his research on learning how T cells and other immune system cells cause inflammation, neuron and axon damage.

Dr. Fabrizio is also exploring new anti-inflammatory combination treatments and their potential to reduce inflammation in EAE mice with an MS-like disease. His results are so promising that they have prompted a Phase II clinical trial on 40 people with MS at the University of Calgary. The long-term goal of the trial is to identify new anti-inflammatory therapies that might lessen inflammation in MS lesions, and also prevent people with MS from transitioning to the progressive phase of the disease.

MS Research Commitments at a Glance

Total MS Society-funded research projects	37
Total Foundation-funded collaborative projects	4
Total MS Society-funded scholarships	61
Donald Paty Career Development Awards	6
Postdoctoral Fellowships	15
Research Studentships	40
Total Foundation-funded Pilot Research Projects	3

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 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 believes that an inhibitor of the lymphotoxin pathway might be involved in the process, and prove to be a good 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

Immune system T cells are made in the bone marrow and travel to the thymus where they mature before being released into the blood. This process is tightly controlled 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. Lower numbers of T cells in people with MS may also be linked to additional T cell abnormalities.

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 precurser 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 causing inflammation which leads 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 is assessing 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.

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

Immune-glial 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 tissue 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 nerve fibres (axons) in the brain causes resident support cells, called glial cells, to make chemokines. These are messenger molecules that attract immune system cells 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's results should contribute to a better understanding of MS and help to control the immune response in people with this often disabling disease.

Alexandre Prat, MD, PhD
Montreal University
$295,491 (April 1, 2006 – March 31, 2009)

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

The presence of dendritic cells (DCs) in human and mouse brains has been a controversial topic for more than a decade. DCs have the pivotal role of triggering T cells in the immune system. Several independent investigators have found that DCs associated with the blood brain barrier (BBB) are important for the formation of lesions in EAE, an animal model of MS. The BBB is a network of blood vessels that nourishes the brain and is lined by endothelial cells.

To aid his research, Dr. Prat has developed a human model of the BBB. In his current proposal, he is investigating whether endothelial cells lining the BBB make cytokine messengers that influence the development of DCs. Because these DCs are associated with BBB endothelial cells, Dr. Prat calls them 'eDCs'. He is curious whether eDCs can trigger or halt the activation of different types of T cells that might be present in MS lesions. To confirm his findings, Dr. Prat will take advantage of his substantial bank of MS brain specimens.

This proposal offers the potential to discover how eDCs are formed and whether they sustain or counteract the damage that T cells cause during MS.

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

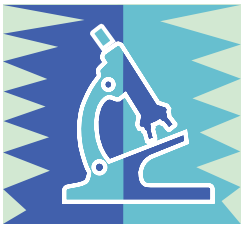
Regulation of cerebral macrophage genesis in a murine model of multiple sclerosis

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.

Looking at Viruses



The idea that viruses play a role in autoimmune diseases such as MS is gaining credibility. Over the past 60 years almost 24 viruses, including rabies virus, coronavirus, herpesviruses, measles virus, and retroviruses, have been isolated from brain tissue of people with MS. Although a person may be infected with one of these viruses, he or she may not necessarily go on to develop MS. This observation suggests that viruses do not cause MS directly but may be linked to its development in susceptible people.

Scientists are striving to discover the connection between viruses and MS. Some scientists suspect that virus fragments resemble certain body fragments. This theory is called 'molecular mimicry' and leads to the immune system mistakenly attacking the body fragments while it is attacking the virus. Other scientists believe that virus infections ramp up dendritic cells of the immune system that can trigger 'autoreactive' T cells, which are pre-armed to attack the body for some reason. This theory is called 'bystander activation of autoreactive T cells'. Another theory is that 'persistent viral infections' prolong the immune system attack on virally infected tissues, resulting in inflammation and tissue damage.

Whatever the scenario, the story is far from straightforward because some viruses can also protect people from overzealous immune systems that cause inflammation during autoimmune diseases like MS. Future research will take advantage of many new and existing technologies in order to evaluate how one's history of viral infection combines with genetics and environmental influences to increase the risk of MS.

Christopher Power, MD
University of Alberta
$294,000 (April 1, 2006 – March 31, 2009)

Pathogenic interactions between human retroelements and neuroinflammation in MS

How viruses affect the immune system during MS is still unclear. Interestingly, 5-10% of the human genome is made up of viruses called 'retroviruses'. These viruses have been incorporated into the human genome over millions of years of evolution. Dr. Power has found that a group of unique retroviruses are made in the brains of some people with MS. Moreover, he has found an abundance of a particular retrovirus gene in the brains of people with MS. This gene contributes to the activation of the immune system and damage to myelin in cell cultures and in animal models.

Dr. Power is combining unique microarray technology with new transgenic mice and other detection tools to evaluate the level of different retroviruses in people with MS. The long-term goal of this project is to identify the contribution that such retroviruses might make to the progression of MS. He has also developed a new retrovirus-containing transgenic mouse which he can use to study myelin damage and the effects of novel therapies for MS.

Taken together, this research should address the growing question of the role of viruses in MS, and also provide new therapeutic opportunities for its treatment.

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, virology, MRI technology, health and treatment effects.

MRI: Window into 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. Better imaging tools will improve diagnosis, monitoring and management of clinical symptoms, and treatments for people with MS.

Douglas Arnold, MD, and
Bruce 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, regrowth and changes in 'normal appearing' white matter of the brain.

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

Ross Mitchell, PhD
University of Calgary
$244,451 (April 1, 2006 – March 31, 2009)

Texture analysis of myelin sensitive MRI

Magnetic resonance imaging (MRI) is a very sensitive diagnostic test. Although MS lesions are reliably visualized using MRI, it is often unclear how lesions relate to clinical status in people with MS. Great advances have been made in medical imaging over the last two decades, but the interpretation of this new digital data is still somewhat subjective.

During the last period funded by the MS Society, Dr. Mitchell made considerable progress. In 2003, he introduced a new type of analysis to the medical imaging community, resulting in numerous high profile publications. In the current project, Dr. Mitchell builds a unique component into his new analysis; namely, the ability to measure the 'texture' of MR images in people with MS. Texture refers to an intuitive, yet measurable characterization of the local pattern of an MR image. Using texture analysis, Dr. Mitchell is analyzing MRI exams from normal volunteers to develop markers of myelin health throughout the normal brain. These markers can then be used to gauge how new treatments affect the brain of people with MS.

Dr. Mitchell's MRI texture analysis tool should improve the power and efficiency of clinical trials evaluating new MS therapies.

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 DWM, suggesting that it 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. The researchers 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 the disease for a long time.

Health research projects investigate problems that people with MS encounter during daily life. 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.

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, the researchers are performing MRIs and DTIs on people with MS who either do or do not suffer from mood changes.

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.

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.

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.

**Reinhold Vieth, PhD,
University of Toronto;
A. Dessa Sadovnick, PhD, University of British Columbia; and George Ebers, MD, University of Oxford**
$276,000 (April 1, 2006 – March 31, 2008)

Vitamin D levels in MS patients and their families

There is growing evidence that the interplay between genes and the environment determines susceptibility to MS. One very striking clue about a role for the environment is that MS increases the farther away one lives from the equator. In Australia, the incidence of MS in temperate Tasmania is five times greater than in subtropical Queensland, despite the similar ethnic origins of the inhabitants. Very few foods contain vitamin D so geographical location would definitely influence vitamin D levels because people living further away from the equator don't get enough sunlight (UVB) for the skin to make vitamin D during winter months.

The focus of the research is to compare vitamin D levels in people with and without a risk for MS. The researchers are measuring the levels of vitamin D in identical and fraternal twins, in people with MS and their families (3,500 individuals in total), and in mothers with multiple children having MS. Improving vitamin D nutrition could be implemented fairly easily and safely, and in a cost-effective way.

If they find a link between vitamin D and MS, then the research may provide the evidence needed to begin clinical studies of vitamin D-based strategies to prevent MS.

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. Currently, the MS Scientific Research Foundation is funding four flagship collaborative research initiatives. It also funds small pilot research projects which allow investigators to pursue new innovative approaches to MS research.

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 stem cell 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 stem cell progenitors 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 stem cell progenitors that have already been located within the body and uses various proteins and hormones to entice them to the damaged parts of the brain and spinal cord that need remyelination.

The researchers have also pioneered new ways of using magnetic resonance imaging to non-invasively measure 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.

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:

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

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.

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

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

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

  The study has three pillars: clinical and genetic epidemiology, pathobiology and neuroimaging.

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

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

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

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.

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: $900,000

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. Fabrizio Giuliani
University of Alberta
Category: Immunology
New: $50,000 for each of three years
Beginning July 1, 2006

Dr. Ross Mitchell
University of Calgary
Category: MRI techniques
Renewal: $50,000 for each of three years beginning July 1, 2006

Dr. 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: $594,500

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

Smriti Mona Agrawal, PhD
University of Calgary
Supervisor: Dr. V. Wee Yong
New: $39,000

Claudia Calder, PhD
Montreal Neurological Institute
Supervisor: Dr. Amit Bar-Or
New: $39,000

Peter Darlington, PhD
McGill University
Supervisor: Dr. Timothy Kennedy
Renewal: $39,000

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

Yunfei Gao, PhD
University of Toronto
Supervisor: Dr. Jennifer Gommerman
New: $39,000

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

Andrea Hebb, PhD
Dalhousie University
Supervisor: Dr. George Robertson
Renewal: $39,000

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

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

Madeline Pool, PhD
Ottawa Health Research Institute
Supervisor: Dr. Alyson
Fournier
Renewal: $39,000

Dafni Reiss, PhD
BC Cancer Research Agency, Vancouver
Supervisor: Dr. Dixie Mager
New: $39,000

Viktor Skihar, MD, PhD
University of Calgary
Supervisor: Dr. V. Wee Yong
Renewal: $48,500

Nicolas P. Turrin, PhD
CREMO, Montreal
Supervisor: Dr. Serge Rivest
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: $786,666

Azadeh Arjmandi
University of British Columbia
Supervisor: Dr. Katarina Dorovini-Zis
New: $20,000

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

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

Jennifer Beveridge
University of Ottawa
Supervisor: Dr. Mark Freedman
New: $20,000

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

Thor Bjarnason
University of Calgary
Supervisor: Dr. Ross Mitchell
Renewal: $20,000

Michelle Brucal
Wayne State University,
Detroit, MI (USA)
Supervisor: Dr. John Kamholz
Renewal: $20,000

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

Zhihong Chen
University of Ottawa
Supervisor: Dr. Mark Freedman
New: $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
Renewal: $20,000

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

Farnaz Forghani
McGill University
Supervisor: Dr. Alan Peterson
Renewal: $20,000

Ebrima Gibbs
University of British Columbia
Supervisor: Dr. Jöel Oger
New: $20,000

Elizabeth Girolami
McGill University
Supervisor: Dr. Samuel David
New: $20,000

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

Jeffrey Haines
McGill University
Supervisor: Dr. Guillemina Almazan
New: $18,000

Shireen Hossain
McGill University
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

Hania Kébir
University of Montreal
Supervisor: Dr. Alexandre Prat
New: $20,000

Melissa Kehler
University of Regina
Supervisor: Dr. Heather Hadjistravropolous
New: $18,000

Samantha Kimball
University of Toronto
Supervisor: Dr. Reinhold Vieth
New: $18,000

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

Kaveh Koochesfahani
University of British Columbia
Supervisor: Dr. Katarina Dorovini-Zis
New: $20,000

Antonia Kuznetsova
Dalhousie University
Supervisor: Dr. John Fisk
Renewal: $20,000

Genevieve Lacroix
McGill University
Supervisor: Dr. Stéphane Richard
New: $20,000

Lorraine Lau
University of Calgary
Supervisor: Dr. V. Wee Yong
New: $20,000

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

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

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

Craig Moore
Dalhousie University
Supervisor: Dr. George Robertson
Renewal: $20,000

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

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

Sathyanath Rajasekharan
McGill University
Supervisor: Dr. Timothy Kennedy
Renewal: $20,000

Debra Robson
University of Guelph
Supervisor: Dr. George Harauz
New: $20,000

Philippe Saikali
Montreal Neurological Institute
Supervisor: Dr. Jack Antel
New: $20,000

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

Nazi Torabi
McGill University
Supervisor: Dr. Stéphane Richard
Renewal: $20,000

Melissa Welsh
University of Western Ontario
Supervisor: Dr. Stephen Karlik
New: $16,666

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.

- **Trevor Owens, PhD**, McGill University
  Biomedical Research – Role of Inhibitors of Apoptosis (IAPs) in autoimmune demyelienating 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 degenarative disease, vanishing white matter
  $35,000 – Approved: June 2005

Glossary 2006

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 (activated 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; makes scars on damaged tissue during MS.

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

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

Blood brain barrier (BBB) – A blood vessel barrier lined with tightly connected endothelial cells; prevents most large molecules and cells found in the blood from entering the brain tissue.

Central nervous system (CNS) – The region composed of the brain and the spinal cord; all parts of the CNS can be affected by multiple sclerosis.

Cerebral spinal fluid (CSF) – The fluid bathing the surfaces of the central nervous system.

Chemokine – A type of cytokine that acts as a beacon to attract white blood cells from the circulation into an injured or infected site.

Cytokine – A protein 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 – The process during which myelin is stripped from nerve fibres.

Dendritic cells – A white blood cell that is bone-marrow derived and specializes in presenting (displaying) 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.

Endothelial cell – A type of cell that lines the heart and blood vessels of the circulatory and immune systems; endothelial cells lining the blood vessels of the brain form the blood brain barrier (BBB).

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

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

Gene – A stretch of DNA that contains the genetic code for making body proteins; located on chromosomes.

Glial cell – A support cell in the nervous system; e.g. oligodendrocytes, astrocytes and microglial cells in the central nervous system and Schwann cells in the peripheral nervous system.

Health Related Quality of Life (HRQL) – A measurement of the 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 – The normally protective local immune response to infection or physical/chemical injury leading to tissue damage; characterized by swelling, redness, heat and pain, and accumulation of fluid, white blood cells and plasma proteins; loss of function may occur.

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 infections. Gamma interferon makes MS worse.

Lipid – A molecule, such as a fat, fatty acid or soap; also refers to the ability of molecules to be fat soluble.

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

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

Magnetic resonance imaging (MRI) – A technological tool that detects energy released from hydrogen atoms to create anatomical images. MR images of soft tissue of the 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 an anatomical information. MRS is most useful when evaluating trials of new treatments by measuring disease severity and progression.

Mast cell – A white blood cell that originates in the bone marrow; involved in allergic responses.

Memory B cell – A type of B cell that lives in the body for long periods of time; can be triggered to make antibodies.

Microglia – A macrophage-like cell that resides in the brain; 'eats' cellular debris and stimulates immune responses.

Monocyte – A type of white blood cell that is called a monocyte while in the blood, and a macrophage upon entering the tissues.

Morphogen – A diffusable substance that influences movement and organization of cells during development.

Multiple Sclerosis Quality of Life Inventory (MSQLI) – A questionnaire designed to evaluate the burden of disease experienced by people with MS.

Myelin basic protein (MBP) – One of the main proteins found in myelin.

Myelin – A collection of proteins and lipids forming the myelin sheath; speeds transmission of signals along nerve fibres.

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

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

Nerve fibre – The slender, long branch extending from a neuron cell body, and carrying nerve impulses to adjacent nerve cells throughout the body. Most nerve fibres are surrounded by the myelin sheath; also called nerve axon.

Neuroglial cell – A type of glial cell that is a supporting, non-impulse generating cell of the nervous system (e.g. astrocyte and oligodendrocyte).

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

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

Oligodendrocyte – A 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) – The region of the nervous system in the body outside the brain and spinal cord. The PNS can be affected by MS.

Perivascular DC – A type of dendritic cell that is located around blood vessels.

Plaque – An area of myelin loss that is characteristic of multiple sclerosis.

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

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

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) – A cytokine made by macrophages and some T cells that is toxic to tumor cells and plays role in inflammatory responses. Two types are TNF alpha and TNF beta.

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

INDEX

Summaries written by: Maya Chaddah. M.Sc., Immunology
Editorial Advisor: Deanna Groetzinger, M.A.

Multiple Sclerosis Society of Canada
National Research Department
700-175 Bloor St. E, North Tower
Toronto, ON M4W 3R8

Telephone: (416) 922-6065
Toll-free: 1-866-922-6065
E-mail: info@mssociety.ca
Website: www.mssociety.ca

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.

Multiple Sclerosis Society of Canada