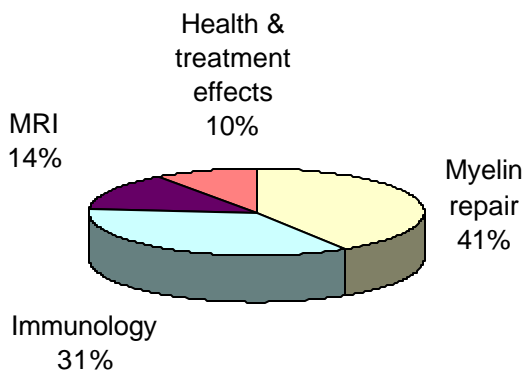


**MS Society Supported Research 2001 - 2006
29 Research Projects**



Note: Foundation-funded projects are not included in the above percentages.

Research Focus: Myelin Repair and Stopping MS Attacks

This year, the Multiple Sclerosis Society of Canada has committed an additional \$3.8 million to support 12 new and renewal multi-year research projects and research fellowships and studentships. Following rigorous review in January 2003 by volunteer committees of MS scientific experts, these projects were found to have the highest scientific merit and relevance to advancing the fight against MS.

Each year, the MS Society provides approximately \$5 – 6 million to its research program. This investment is possible because of the support by individual donors, corporate partners and MS Society chapters and units that raise funds tirelessly in their local communities.

Part of the research funding is invested in the MS Scientific Research Foundation, which supports large collaborative research projects and innovative pilot grants. It is the largest foundation in the world dedicated solely to MS research. The MS Society is the Foundation's primary funding source.

The summaries in this publication are organized into the scientific areas that currently promise the greatest opportunity to make progress: myelin investigations, immune system research, genetics, MRI tools and health research. Together, MS Society and MS Foundation funded research projects are making a significant difference in the lives of people with MS today and tomorrow as we work toward a future free of MS.

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Myelin: Undoing the damage

How does the body cut down on the amount of space and energy it needs to transmit nerve signals? The answer is myelin. This essential component is wrapped around nerve fibres, much the same way that insulation cables are wrapped around electrical wires. Without myelin the human spinal cord would have to be several metres wide and would rack up an unpayable energy bill to do its job. Myelin is not a simple structure. It is a mixture of proteins and fats, layered into a compact sheath. In MS, the myelin sheath is damaged, and the cells that normally make myelin can't replace it fast enough. When that happens, the myelin-stripped nerve fibres have difficulty sending impulses, and are often damaged beyond repair. As damaged myelin begins to heal, scar tissue builds up to form the characteristic plaques seen in MS.

All MS research has a converging aim – to prevent or at least minimize the destruction to myelin in the nervous system. Researchers are striving to understand the big picture of how specialized cells in the nervous system make the myelin sheath, and the intricacies of how myelin is wrapped around nerve axons. Many questions still need to be addressed. Which genes are involved in myelin growth? What are the interactions between myelin-making cells and nerve cells promoting myelin growth? What factors and treatments promote myelin regrowth?

Researchers are using a variety of approaches, from cell culture techniques to protein and gene function analyses to clinical trials. As myelin growth and regrowth are mapped out in more detail, researchers will be able to design new therapies to counter the far-reaching effects of myelin damage during MS.

Guillermina Almazan, PhD, and Walter Mushynski, PhD
McGill University
\$241,770 (April 1/03 – March 31/06)

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

Myelin architecture is the key to nerve fibres (axons) efficiently transmitting nerve impulses. In MS, large areas lacking myelin develop in the central and peripheral nervous systems. This seriously affects the ability of nerve axons to do their job. Damage to myelin often goes hand in hand with irreversible damage to nerve axons, causing even more severe problems for people with MS.

Drs. Almazan and Mushynski hope to overcome some of these problems by continuing to study what is needed to keep nerve axons covered with myelin. They know that some form of two-way communication exists between nerve axons and myelin-making cells, (oligodendrocytes and Schwann cells). Recently, they found that p38, a member of the MAPK signalling family, is part of the two-way communication process that leads to myelin-covered axons. They are delving deeper into how p38 works, and are also studying two other members of the MAPK family, called ERK and JNK.

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

Joan Boggs, PhD
Hospital for Sick Children, Toronto
\$283,368 (April 1/02 – March 31/05)

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

Oligodendrocyte cells maintain the myelin sheath by wrapping their myelin-filled outer membranes around nerve axons. In people with MS, the protein and lipid-rich myelin sheath is destroyed and oligodendrocytes can't totally reverse the damage. Dr. Boggs is studying how proteins in the oligodendrocyte membrane communicate to maintain the health of the myelin sheath.

Dr. Boggs thinks that glycosphingolipids and major myelin proteins (MBP, MAG, PLP) are first to receive 'myelin health messages' that come from outside the oligodendrocyte. She thinks that the glycosphingolipids and major myelin proteins pass on the message to a variety of proteins inside the oligodendrocyte. These proteins then relay the 'myelin health' message to the oligodendrocyte nucleus which decides what to do with the message. To test her hypotheses, Dr. Boggs has created artificial membranes containing glycosphingolipids and major myelin proteins. The membranes can be added to oligodendrocytes grown in culture and the protein-protein and protein-glycosphingolipid communications can be evaluated for their ability to transmit 'myelin health' messages.

The question of how oligodendrocyte proteins and glycosphingolipids communicate to convey such important messages is one that scientists will have to answer before they can effectively rebuild myelin and stop nerve damage in people with MS.

Peter Braun, PhD
McGill University
\$176,635 (April 1/01 – March 31/03)

Regulation of Myelinogenesis: Role of CNP

Myelin wraps around nerve axons and helps them to send nerve impulses. When myelin is destroyed in certain areas of the brain and spinal cord during MS, the nerve axons in that area have difficulty sending impulses. Researchers need to understand how myelination happens before they can design new therapies aimed at remyelination of axons.

Dr. Braun has isolated CNP, a protein that oligodendrocytes might use during myelination. He and his research team recently discovered that CNP could help immature oligodendrocytes become mature cells capable of making myelin. The investigators have created mice that make too much human CNP, a situation which then leads to abnormal myelin formation. Their next step is to screen the mice for genes that may be affected by too much CNP. For future studies related to CNP, Dr. Braun plans to grow oligodendrocytes from embryonic stem cells and to create mice that lack CNP.

Therapies based on this research would focus on correcting CNP levels in oligodendrocytes. This might help to restore the ability of oligodendrocytes to remyelinate damaged axons in people with MS.

Canadian Collaborative Study on Myelin Gene Regulation

\$1.5 million over three years from the Multiple Sclerosis Scientific Research Foundation – Approved October 2000

Principal Investigator

Dr. Alan Peterson, Department of Oncology, McGill University and Royal Victoria Hospital

In MS, the central problem is the attack by immune system cells on the myelin covering that protects the nerve fibres in the central nervous system. When myelin is damaged, the nerve signals are slowed or stopped, causing many variable MS symptoms.

Dr. Alan Peterson, is the principal investigator of the myelin gene regulation project which is looking for the “switches” that turn central nervous system repair off and on. In work previously funded by the MS Society of Canada, Dr. Peterson showed that myelin production is different from myelin repair. He also found that the myelin basic protein gene has dozens of molecular ‘switches’ that may interact at different levels.

Five laboratories are studying the myelin production control system from various angles, thus making possible rapid advances in this field. Understanding which molecules are involved and how they interact could lead to treatments which turn the right switch(es) on or off and in so doing maintain myelin or repair it after it is damaged during MS.

**George Harauz, PhD
University of Guelph
\$171,394 (April 1/03 – March 31/05)**

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

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

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

This research is doubly valuable. It not only provides much needed information on the role of MBP in MS, but also evaluates how current therapies used in MS might work. Taken together, the results from this study will be useful in designing better therapies for people with MS.

Together, MS Society and MS Foundation funded research projects are making a significant difference in the lives of people with MS today and tomorrow as we work toward a future free of MS.

Timothy Kennedy, PhD
Montreal Neurological Institute
\$198,920 (April 1/02 – March 31/05)

Netrin function in the development of axonal-oligodendroglia interactions

Understanding more about how oligodendrocyte cells make myelin is central to winning the battle against MS. Dr. Kennedy is attacking this problem by looking at netrin-1 and its receptor, DCC. Netrins are proteins that help extend nerve fibres and are essential for normal nervous system function. Dr. Kennedy's goal is to determine how netrin-1 and DCC help oligodendrocytes to mature and make myelin in the adult rodent central nervous system (CNS).

Dr. Kennedy has already found that in the CNS of embryos netrin-1 and DCC chaperone immature oligodendrocytes to their proper locations. In work supported by the MS Society, he also showed that in adults netrin-1 and DCC are made by oligodendrocytes that are actively adding myelin to nerve fibres. In a recent publication, Dr. Kennedy reported that netrin-1 is made by many classes of neurons as well as by oligodendrocytes in the adult rat and mouse spinal cord. In the current study, Dr. Kennedy is using mouse models to continue to study the role of netrin-1 and DCC in oligodendrocyte migration and interaction with nerve fibres.

This study may lead to new information about how oligodendrocytes migrate, make myelin and wrap it around nerve fibres. Such information would be put to good use towards new therapies promoting myelin regrowth in people with MS.

Rashmi Kothary, PhD
Ottawa Health Research Institute
\$178,960 (April 1/03 – March 31/05)

The role of beta1 integrin in the process of CNS myelination

Effective treatments for MS must not only stop myelin damage but also promote regrowth of myelin in damaged areas. It stands to reason that gaining a better understanding of how oligodendrocyte cells wrap myelin around nerve fibres in the central nervous system (CNS) will help researchers reach this goal.

Dr. Kothary is working on beta1 integrin, a protein that spans the cell membrane of oligodendrocytes. Beta1 integrin is like a telephone operator connecting incoming and outgoing calls to and from the oligodendrocytes. These two-way calls, or signals, help oligodendrocytes to become fully capable of adding myelin to nerve fibres. For this project, Dr. Kothary has created transgenic mice that make abnormal types of beta1 integrin in oligodendrocytes. This will help him to identify how the abnormal beta1 integrins disconnect the communication pathways that oligodendrocytes need to do their job.

The long-term goal of this work is to manipulate beta1 integrin so that myelin damage is reduced and myelin regrowth is promoted in people with MS.

**Mario Moscarello, PhD, and
Fabrizio Mastronardi, PhD
Hospital for Sick Children, Toronto
\$165,660 (April 1/02 – March 31/04)**

**Vitamin B12 in combination therapy
induces remyelination**

MS is characterized by the patchy destruction of the myelin sheath surrounding nerve fibres. To treat MS effectively, therapies must not only stop the destruction of myelin but also help repair the myelin sheath. Dr. Moscarello has devoted many resources towards identifying new therapies and testing them on DM20 and EAE mice, which both develop an MS-like disease.

In his earlier studies on the DM20 mouse, Dr. Moscarello showed that the well known cancer drug, paclitaxel (Taxol) worked well to slow the signs of MS, but could not extensively repair the myelin sheath. In more recent work, he and Dr. Mastronardi showed that vitamin B12 is better at rebuilding myelin and that it works best in combination with paclitaxel or beta interferon. They think that vitamin B12 may help mature oligodendrocytes to assemble myelin and control enzymes that could damage it. While they study the details of how vitamin B12 works, they are also preparing the groundwork for a future clinical trial for people with MS receiving vitamin B12 combined with paclitaxel or beta interferon therapies.

If their theories prove correct, using vitamin B12 in combination with other therapies could greatly improve the clinical outlook for people with MS.

**Adil Nazarali, PhD
University of Saskatchewan
\$57,764 (April 1/01 – March 31/03)**

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

In the nervous system of mammals, three types of cells -- Schwann cells, olfactory ensheathing cells, and oligodendrocytes -- are capable of wrapping myelin around axons. Each of these cells must first go through a process called differentiation, which changes them from immature cells, incapable of myelinating axons, to mature and fully functioning cells. Currently, there is little information about the molecular controls that influence this process.

Dr. Nazarali and his team are attempting to bridge the information gap by examining the differentiation process of these cells more closely. They are studying Hox genes, known to be involved in the development of many other cell types, to see if they also play a role in the differentiation of oligodendrocytes and olfactory ensheathing cells. Dr. Nazarali thinks it likely that one particular Hox gene, called (Hoxa2), has to be functional for oligodendrocytes and olfactory ensheathing cells to develop into normal myelinating cells.

The question of what influences the differentiation of these cells is important to future therapies involving myelination.

Alan Peterson, PhD
McGill University
\$228,000 (April 1/01 – March 31/04)

Regulation of the oligodendrocyte genome

In people with MS, brain lesions that lack myelin are often not repaired despite the presence of cells that can fix the damage. Dr. Peterson heads a research team that is looking for a solution to this problem. They are trying to identify some of the mechanisms that control how myelin is made by oligodendrocytes in the central nervous system.

The research team is focussing on MBP (myelin basic protein), one of a family of myelin specific proteins. They have already located what they think is the major DNA control switch for the MBP gene. When this switch is flipped on, the production of MBP in oligodendrocytes is ramped up. Using a variety of methods, they plan to use the DNA control switch to trap other proteins that might also help oligodendrocytes make MBP.

Dr. Peterson and his colleagues believe their work will uncover ways to control the MBP gene, and perhaps other important myelin genes as well. Their ultimate goal would be to use such information to design new therapies that would help oligodendrocytes rebuild myelin in people with MS.

Christopher Power, MD
University of Calgary
\$240,000 (April 1/03 – March 31/06)

Purine receptor-mediated immune regulation in multiple sclerosis

In MS, inflammation of the central nervous system (CNS) leads to myelin being stripped from nerve fibres, 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 MS.

Adenosine A1 receptors are found on macrophages in the blood and brain. These receptors bind to adenosine, which is known to have protective qualities against some neurological diseases. In his previous work, Dr. Power showed that the levels and function of adenosine A1 receptors are lower than normal in people with MS. These receptors bind to adenosine, which is known to have protective qualities against some neurological diseases. In the present study, he is focussing on how the damage in MS is linked to having fewer adenosine A1 receptors. His information will be collected from mice lacking the adenosine A1 receptor, and from the blood and brain tissue of people with MS.

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 MS.

**Remyelination in Multiple Sclerosis:
Neural precursor-based repair**

**\$3.5 million over three years from the
Multiple Sclerosis Scientific Research
Foundation – Approved July 2001**

Principal Investigator
Dr. Jack Antel, McGill University

Co-Investigators
Dr. Mark Noble, University of Rochester (NY)
Dr. Moses Rodriguez, Mayo Clinic,
Rochester, Minn.
Dr. Derek van der Kooy, University of
Toronto
Dr. Samuel Weiss, University of Calgary

A large, collaborative research project, funded by the Multiple Sclerosis Scientific Research Foundation, is underway to find out if the body's own cells can be transformed into a cellular repair team to mend damage caused by multiple sclerosis. Coordinated by Dr. Jack Antel of McGill University, leading researchers at centres in Canada and the United States are tackling one of the central problems in multiple sclerosis. When the disease strikes, 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.

The goal of this project is to use immature cells called stem cells and turn them into the right kind of cell that will produce myelin where it is needed. There are two basic ways to approach this challenge. One is to find ways to turn stem cells that already exist in the adult nervous system into myelin-making cells. The second is to introduce stem cells from an external source using surgical or transplantation techniques.

The scientists involved in this project have chosen to use the body's own stem cells from the adult central nervous system. This avoids invasive surgical procedures and should overcome the limitations in the numbers of cells available for transplantation and the problem of directing the cells to the sites of injury. This multi-disciplinary team of neurologists and basic scientists believe the approach of using the body's own cells to repair myelin damage is particularly applicable in a disease in which injury can occur in any part of the central nervous system. If successful, this work should lead to specific strategies for myelin repair.

Stéphane Richard, PhD
Lady Davis Research Institute, Jewish
General Hospital, Montreal
\$291,630 (April 1/03 – March 31/06)

The role of the quaking proteins in oligodendrocyte physiology

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

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

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

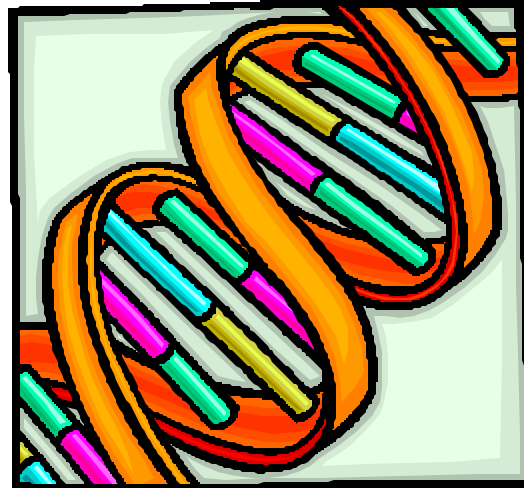
Voon Wee Yong, PhD
University of Calgary
\$304,703 (April 1/01 – March 31/04)

Matrix metalloproteinases in process extension and myelin formation by oligodendrocytes

The myelin sheath that surrounds nerve fibres in the central nervous system (CNS) is damaged during MS. The myelin sheath is created from the long, slender myelin-filled membranes that radiate from oligodendrocytes, the myelin-making cells. One way to stop myelin loss during MS might be to enhance the first step of myelin sheath formation -- the extension of myelin-filled membranes from oligodendrocytes.

Dr. Yong and his team are studying a group of enzymes, called matrix metalloproteinases (MMPs). They have shown that many MMPs are active in oligodendrocytes. In fact, oligodendrocytes may use MMP-9 to extend their myelin-filled membranes. Dr. Yong's research on adult mouse brain has shown that although MMP-9 is critical for early membrane extension, it is not solely responsible for it. In fact, they discovered that MMP-12 may be even more important than MMP-9. In future work, the team will continue to probe the role of MMP-9 and MMP-12 during the formation of the myelin sheath by oligodendrocytes.

The process of oligodendrocyte membrane extension is crucial for the normal development of the myelin sheath and function of nerve fibres. This study may lead to new therapies based on MMPs which would help to restore the myelin sheath in people with MS.



Genetics: The link to MS

Multiple sclerosis is not an inherited disease, but it does occur more often in families where other members are affected. Women are 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 (the hereditary pieces of DNA that control life) making the members more likely to get MS.

The focus of genetic research is to find the genes that make a person more susceptible to MS. It is just as important for researchers to compare susceptibility genes in people with MS, and to figure out what those genes normally do in a healthy body. Not surprisingly, genes chosen for study are often those with obvious links to myelin growth, like the myelin basic protein gene, oligodendrocyte and immune cell genes and cytokine messenger genes. Much of the information acquired from genetic studies is obtained by looking at special groups of people, like twins, siblings, half-siblings and adoptees. The knowledge gained from genetic research is absolutely essential for designing new therapies to control susceptibility genes in people with MS.

Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis – Phase III

\$5.1 million over three years from the Multiple Sclerosis Scientific Research Foundation – Approved May 2002

Principal Investigators

George Ebers, MD, University of Oxford and University of Western Ontario

A. Dessa Sadovnick, PhD, University of British Columbia

Co-Investigator

Neil Risch, PhD, Stanford University, California

Since the initial study began in 1993, much progress has been made in the understanding of the relative roles of genetic (inherited) and environmental (non-genetic) factors both in the overall cause of MS and the increased numbers of MS cases among family members of an affected individual. This unprecedented cooperative study involves more than 19,000 people with MS registered at 18 MS clinics across Canada. This study looks at the molecular genetics, clinical genetics, genetic epidemiology and environmental factors which may play a role in causing MS. Dr. Ebers heads the molecular genetic part of the study, and Dr. Sadovnick directs the genetic epidemiological portion.

The 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 and II.

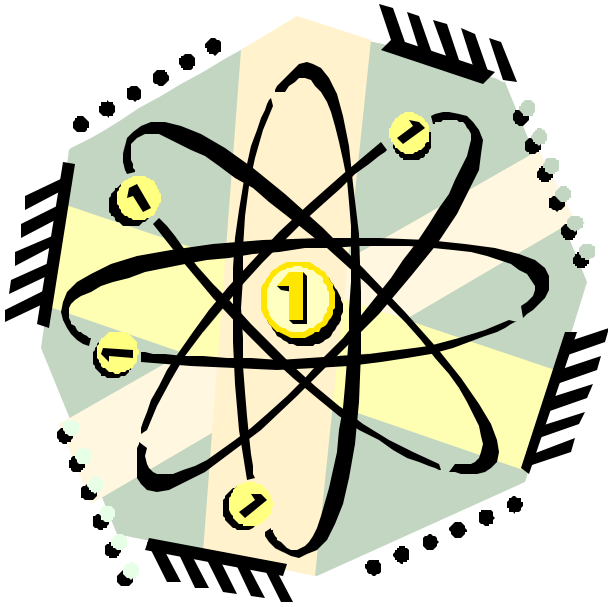
- It has been clearly shown that the increase of MS among relatives of affected individuals is because they share genetic material (DNA) and not because they share a common family environment.
- Studies of affected sibling pairs and their parents have suggested that some families may have more genetic 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 are focusing 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.

Information gained from Phase I and II is being used for genetic and reproductive counselling services for people with MS.



Immunology: Stopping MS attacks

Every second of the day, cells of the immune system battle to defend the body against invading viruses, bacteria and other threats. Since the immune system normally protects the body from these dangers, it is a puzzle as to why – when MS occurs – its deadly arsenal should be directed at myelin and the cells that make it. Some scientists believe that bits of infectious agents act as catalysts that somehow ‘trigger’ the immune system attack in susceptible individuals. Researchers have coined the term ‘autoimmunity’ 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 1) identifying the different players (T cells, B cells, macrophages etc.), 2) learning how the tight seal of the blood-brain-barrier is breached by dangerous immune cells and 3) how and why normally protective immune cells

coordinate the attack on myelin and 4) how the immune system attack during MS varies from person to person. Equally important are studies evaluating new and existing therapies, keeping in mind the goal of tailoring treatments to suit different people with MS. The answers to many of these questions will help fill in the missing pieces of the immunological puzzle underlying MS. As more and more pieces are found, researchers will be able to design new therapies bringing the immune system back onside.

Jack Antel, MD
McGill University, Montreal Neurological Institute
\$261,951 (April 1/01 – March 31/04)

Systemic immune response in multiple sclerosis and effects of therapy

During MS, damage to the central nervous system begins when immune cell lymphocytes leave the circulatory system to enter the brain. Lymphocytes can enter the brain only by crossing the blood-brain-barrier (BBB). This barrier is made up of endothelial cells which are so tightly spaced that there is no way for most cells to squeeze their way into the brain. Dr. Antel has developed an artificial model of the BBB that will help him to study how dangerous lymphocytes manage to cross the BBB.

Dr. Antel is taking lymphocyte samples from healthy volunteers and from people with MS and adding them to the artificial BBB. He will then compare the differences between the two groups of lymphocytes as they cross the BBB. He is also asking whether any of the current or experimental MS therapies can slow or stop lymphocytes from crossing the BBB. Finally, he will check to see if any of the lymphocytes used in the study can make molecules that protect the brain or promote recovery from injury during MS.

This study promises to shed some light on how destructive lymphocytes cross the BBB. With this information researchers may be able to refine existing therapies, or design new ones to effectively counter the entry of these cells into the brain during the first phase of MS.

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

\$44,679 (April 1/03 – March 31/06)

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.

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

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

The Multiple Sclerosis Scientific Research Foundation is funding a multi-centre project to determine definitively 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, it has been noted that their MS 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 MS.

Equally important, should the procedure not fully stop the disease process, is that the researchers hope to gain information about what triggers are present and what changes to the immune system occur at the beginning of disease activity. They will monitor 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 the tracking of certain immune-related genetic changes in the hope of unveiling particular genes that might contribute to genetic susceptibility.

Samuel David, PhD
Montreal General Hospital Research Institute
\$156,336 (April 1/02 – March 31/04)

Role of phospholipase A2 in the pathogenesis of experimental allergic encephalomyelitis and its expression in MS

MS is an inflammatory disease of the central nervous system (CNS), resulting in demyelination, sensory loss and even paralysis. Although many factors likely cause MS, those promoting inflammation of MS lesions are good candidates to study. Dr. David's research focuses on the enzyme PLA₂ whose by-products can provoke inflammation and trigger immune cells to enter the CNS. For this study, Dr. David is using EAE mice which develop an MS-like disease, along with tissue samples from people with MS.

Previously, Dr. David showed that PLA₂ increases in lesions from EAE mice that also have a mutation in a major form of PLA₂. He

is currently studying PLA₂ levels in MS tissue samples. He is very interested in how much PLA₂ is found in CNS cells of these mice. Dr. David thinks that PLA₂ might be produced by cells at or near the site of lesions in both MS tissue and these mice. If his theory is correct, he will test for chemicals that block PLA₂. Some of the early results show that blocking PLA₂ can delay the onset, and perhaps even lessen the severity of EAE.

Studying the EAE mouse model will give researchers more clues about what to look for in people with MS. This in turn may lead to new treatments, perhaps based on blocking PLA₂, which might minimize the damage due to inflammation during MS.

Katerina Dorovini-Zis, MD
University of British Columbia
\$321,379 (April 1/03– March 31/06)

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

The specialized cells that line the blood vessels of the brain are called endothelial cells. These cells normally form a tight blood-brain barrier (BBB) preventing most immune cells from gaining access to the brain. Early during MS, the BBB becomes leaky, letting in immune system T cells that can cause tissue damage. Dr. Dorovini-Zis thinks that the communication between endothelial cells and T cells sets the stage for the resulting damage in MS.

Dr. Dorovini-Zis has pioneered the creation of an artificial BBB. With this laboratory version of the blood-brain-barrier she can test if messages passing between endothelial cells and T cells increase the BBB leakiness. She is also testing her theory that endothelial cells stick pieces of myelin with "display" proteins onto their surfaces. T cells that can bind to the

myelin/display proteins might be triggered, cross the leaky blood-brain-barrier and go on to attack myelin in the brain.

This work is important for researchers to understand how endothelial cells let T cells cross the barrier. A major achievement would be to design therapies to tighten the BBB and block triggered T cells from entering the brain in the first place.

**Lionel Filion, PhD, and
Mark Freedman, MD**
University of Ottawa
\$137,594 (April 1/01 – March 31/03)

Immunological determinants of disease progression in response to therapy

Four therapies are available in Canada to treat MS. They all decrease the number and severity of MS attacks, but how they work is not totally understood. Drs. Filion and Freedman's work should provide more insight.

In MS, immune system cells called T cells and macrophages contribute to inflammation within the central nervous system which can lead to MS attacks and permanent damage. This inflammatory process may be initiated by the interaction of a number of signalling molecules which are found on the surfaces of T cells and macrophages. Signalling molecules include cytokines and cytokine receptors. Certain cytokines make MS worse by encouraging the development of a group of T cells called Th1. In contrast, current MS therapies encourage the development of other T cells called Th2 which help prevent inflammation and MS attacks. Drs. Filion and Freedman think the current MS therapies are successful because they affect the signalling molecules at work between T cells and macrophages.

The researchers have noted a significant difference between people in the relapsing stage compared to those in the secondary progressive phase of MS. In particular, the levels of the macrophage surface protein CD86, and the cytokine IL-12 were much higher in the progressive stage. They also found that beta interferon therapy reduces these levels in people with MS. Drs. Filion and Freedman are now examining these observations in more detail and are extending their studies to include glatiramer acetate (Copaxone) therapy.

The overall goal of this work is to find markers that might predict disease changes in MS and/or responses to current therapies.

Mark Freedman, MD
University of Ottawa
\$173,870 (April 1/02 – March 31/04)

The role of gamma-delta T cells in MS: Friends, foes or both?

Gamma-delta T cells are specialized immune cells. They normally form the first line of defense against invaders until other more specialized immune cells reach the scene. Dr. Freedman thinks that gamma-delta T cells may become part of the problem in MS by driving the specialized immune cells to attack myelin, or by failing to turn them off once they have been triggered.

In the EAE mouse, which mimics MS, removing gamma-delta T cells worsens the disease. However, Dr. Freedman has also shown that gamma-delta T cells can kill laboratory grown oligodendrocytes faster than any other immune cell. It appears then, that gamma-delta T cells teeter-totter between being beneficial and destructive during the disease. Using his own special technique for growing gamma-delta T cells indefinitely, Dr. Freedman will determine the role gamma-delta T cells play at any given

stage of disease and whether they are in the central nervous system or in the bloodstream. He then plans to compare the function of gamma-delta T cells over time in people with MS before and after intervention with various treatments.

Once Dr. Freedman establishes whether gamma-delta T cells are “friends, foes or both”, he will be able to choose drugs that tip the balance in favour of the protective aspects of these cells.

**David Haegert, MD, McGill University
Veerabhadra Gadag, PhD, Memorial University
\$177,773 (April 1/03 – March 31/05)**

Alterations of the T-cell receptor repertoire in MS

A group of T cells, called CD4 T cells, are thought to begin the attack against myelin in MS. Another group of T cells, called CD8 T cells, might also contribute to myelin injury during the disease. Drs. Haegert and Gadag believe that the T cell receptors on the surface of CD4 and CD8 T cells are altered in people with MS. They think that changes to the T cell receptors happen before myelin damage begins, and make a person more likely to get MS.

To test their ideas, Drs. Haegert and Gadag are studying T cell receptors in healthy identical twins and in identical twins where one or both twins has MS. Interestingly, they have found that identical twins where one twin has MS and the other is healthy, both have major changes in CD4 T cell receptors cells as compared with those in healthy identical twin pairs. This means that non-genetic factors are contributing to the changes in CD4 T cell receptors. Drs. Haegert and Gadag are looking at this phenomenon more closely, and are

extending their studies to include CD8 T cells as well.

This study promises to yield new information about how the attack in MS is started, and who is most likely to get the disease.

**Stephen J. Karlik, PhD
University of Western Ontario
\$136,012 (April 1/03 – March 31/05)**

Angiogenesis in chronic neuroinflammation

Angiogenesis is the process of growing new blood vessels. It is a natural part of wound healing, and many other bodily processes. New blood vessels also form during many diseases, including cancer, heart disease and rheumatoid arthritis. Recently, Dr. Karlik found that angiogenesis also takes place in guinea pigs that develop MS-like lesions. Dr. Karlik thinks that the new blood vessels that form are the highway along which vital nutrients and cells travel, helping the lesions grow.

Dr. Karlik is testing his unique idea on guinea pigs that develop a chronic, progressive MS-like disease. Both conventional and new MS drugs will be given to the guinea pigs in effort to stop new blood vessels from growing, which in turn, might shrink the lesions. Dr. Karlik is using a new type of MRI to track angiogenesis in the guinea pigs and to gauge how well the various treatments are working.

These studies provide an exciting new possibility for future therapies. If the blood vessel highway along which nutrients and destructive cells travel could be blocked, then there may be a way of controlling the growth of lesions in people with MS.

Michael Mayne, PhD
University of Manitoba
\$170,000 (April 1/03 – March 31/05)

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

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

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

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

Trevor Owens, PhD
McGill University / Montreal Neurological Institute
\$276,030 (April 1/02 – March 31/05)

Immune-glia interactions in CNS inflammation and demyelinating disease

During MS, immune system cells invade the brain and together with messenger molecules called chemokines contribute to myelin loss. At some point during the course of MS, nerve damage also occurs. It is not clear, however, how nerve damage is connected with the invasion of immune cells during MS.

Dr. Owens thinks that inflammation and nerve damage are two central components in MS worthy of studying. He has already shown that nerve damage alerts the roving security force of microglial cells. These cells normally 'eat' cellular debris, waste and foreign entities in the brain. Once alerted, microglial cells also make beacon molecules, called chemokines, which attract immune cells to the site of damage. Using magnetic resonance imaging, Dr. Owens sees that nerve damage sometimes occurs before immune cells invade the brain. In his present work, he is studying whether different types nerve damage can predict the immune cell response that follows, and also if microglial cells can still do their job after immune cells invade the brain.

If his experiments could help pinpoint when immune cell invasion occurs in response to nerve damaging signals, then Dr. Owens might be able to intervene and prevent immune cells entry and damage to myelin and nerves in MS.

Trevor Owens, PhD
McGill University / Montreal Neurological Institute

\$55,052 (April 1/03 – March 31/05)

With additional funding from the Canadian Institutes of Health Research

The role of interferon-gamma in central nervous system inflammation

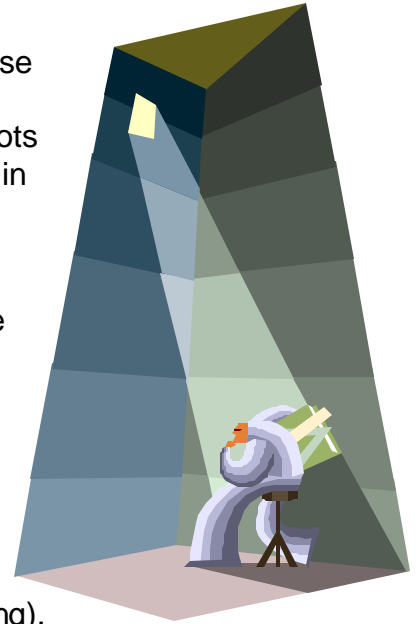
The T cell attack on myelin in the brain results in inflammation (tissue damage) during MS. Many cytokines (message molecules) contributing to inflammation are made by brain cells. Others, like interferon-gamma, are made by cells that travel to the brain. Interferon-gamma seems to be a double-edged sword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

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

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

MRI: Providing a window into MS

Scientists must use many tools to generate snapshots of what happens in the brain of a person with MS. One of the most sensitive of these is an imaging technique that became widely available in the mid-1980s, called MRI (magnetic resonance imaging).



MRI contrasts white matter (myelin) from grey matter and cerebral spinal fluid, and generates two-dimensional images of the body's internal structures. MRI is so sensitive that scientists use it to distinguish between healthy brain tissue and lesions in a person with MS. Another valuable and more recent imaging tool is MRS (magnetic resonance spectroscopy). MRS is similar to MRI but provides chemical rather than structural information about brain lesions.

Because MRI and MRS are non-invasive techniques, they can be used to follow individuals with MS on an ongoing basis. Combinations of MRI and MRS are used to monitor how MS lesions respond to different therapies. Scientists are always looking for ways to improve the capabilities of MRI and MRS and get clearer pictures of what is going on at different stages of MS. The ultimate goal of this research is to refine and develop better imaging tools that can be used for improved diagnosis and management of symptoms and treatments in people with MS.

Douglas Arnold, MD
McGill University / Montreal Neurological
Institute
\$251,896 (April 1/02 - March 31/05)

**Imaging demyelination and remyelination
in MS**

The myelin covering on nerve fibres is attacked during MS. Myelin is essential for nerve fibres to efficiently conduct electrical impulses, but it may also be needed for the long-term survival of nerve fibres. The overall goal of Dr. Arnold's work is to determine the extent of myelin loss and myelin regrowth that occurs over time in MS lesions. This information is vital for understanding the progression of nerve damage in MS.

Building on his previous research, Dr. Arnold has developed an MRI scanning method that measures the amount of myelin in MS plaques. These new scans will help him to test for myelin regrowth in plaques from people at different stages of relapsing-remitting and secondary-progressive MS. As well, his new MRI scanning method may capture whether there is ongoing damage to myelin in old plaques, and whether such damage is going undetected by older scanning methods.

Dr. Arnold's study should generate new information about myelin regrowth in MS, and also help researchers to monitor myelin loss in chronic lesions over time. Taken together, such a wealth of data should make it possible to assess the success of future therapies directed at myelin repair and controlling nerve damage in MS.

Alex MacKay, MD, David Li, MD, and
Donald Paty, MD
University of British Columbia
\$203,748 (April 1/01 – March 31/04)

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

MS is a complex disease in which damage to myelin in the nervous system may cause attacks (relapses) where vision, sensation, coordination and strength are lost, either temporarily or permanently. When destructive immune cells cross the blood-brain-barrier and enter the brain, they cause tissue inflammation which leads to the patchy destruction of myelin. This interrupts the normal flow of nerve impulses.

Until the development of magnetic resonance imaging techniques, much of what researchers knew about damage in MS was from examining the brain and spinal cord after death. By combining three magnetic resonance techniques, (relaxation, diffusion and spectroscopy) Drs. MacKay, Li and Paty can now follow the physical and chemical changes in the brains of people who are living with MS. They hope to identify the point in time at which myelin loss occurs after the blood-brain-barrier becomes leaky. They are also trying to pinpoint when myelin regrowth occurs during the disease process.

By having more precise magnetic resonance information, the researchers will be better able to relate the degree of myelin destruction in the brain with the level of disability in people with MS.

**Ross Mitchell, PhD and Ursula Tuor, PhD,
University of Western Ontario
\$259,010 (April 1/03 – March 31/06)**

Myelin-Sensitive MRI: From Bench to Bedside

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

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

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

**Wayne Moore, MD, Donald Paty, MD,
Stanley Hashimoto, MD, David Li, MD,
Robert Nugent, MD, Alex
MacKay, MD**

**University of British Columbia
\$249,739 (April 1/02 – March 31/05)**

The pathologic basis of magnetic resonance imaging in multiple sclerosis

Conventional magnetic resonance imaging (MRI) can clearly show the plaques present in the brains of people with MS. Recently, newer MRI techniques show that areas of the brain outside plaques are also abnormal. These damaged areas are called 'dirty white matter'. Researchers still don't know if dirty white matter stems from MS plaques or is caused by something else.

This group of researchers published papers in *Neurology* and *Multiple Sclerosis* showing that MRI scans of chemically fixed brains from autopsy material yield valuable information about myelin distribution and areas of myelin loss. In their current study, they are connecting the abnormalities in plaques and dirty white matter with the changes in brain tissue over time. They plan to use a variety of new and existing MRI techniques combined with the traditional approach of viewing post-mortem tissue under the microscope. As well, different tissue stains will help them to visualize nerve fibres, the myelin sheath, oligodendrocyte cells that make myelin, and the cells that attack myelin.

The MRI techniques employed in this study will help researchers to identify the tissue changes associated with ongoing damage in MS.



Health Research: Focusing on today

Multiple sclerosis typically affects young adults in the prime of life, between 20 and 40 years of age. The majority of people with MS start out with a relapsing-remitting form of the disease. However, after a number of years they often go on to develop a more progressive form of MS. Regardless of the type of MS an individual has, he or she must live with the symptoms for a long time. Because of this, healthcare professionals dedicate many resources to understanding how to improve the quality of life for people with MS.

The Health Research Committee reviews grants that deal with the many problems people with MS encounter in their daily lives. Health research uses a number of approaches including: health economics (effectiveness and policy), population health (epidemiology, determinants of health and environment) and psychosocial and behavioral issues (health education, health promotion sociology and communications). Rather than investigating the cause of MS, health-related research focuses on the life-issues that people with MS must deal with on an ongoing basis.

**Donald Brunet, MD, Michael Singer, MD,
and Wilma Hopman, MA**
Queen's University
\$124,313 (April 1/00 – March 31/03)

MS and changes in health-related quality of life

The health status of individuals with MS is traditionally determined by measuring neurological impairment. It is becoming clear, however, that this measurement alone cannot accurately predict the health status of a person with MS. For one thing, perceived health status does not always correspond with the degree of neurological impairment, and for another, measures of neurological impairment are not always a good indication of other problems experienced by people with MS (e.g. fatigue).

The concept of health status in MS has recently broadened to include health-related quality of life (HRQL), based on an individual's perception of his/her abilities and well-being. Dr. Brunet and his team are using a quality of life measurement tool called the Multiple Sclerosis Quality of Life Inventory (MSQLI). During a 30-minute survey, people with MS evaluate many HRQL factors, including physical functioning, bodily pain, vitality, emotional problems, fatigue, sexual satisfaction and bladder control. Dr. Brunet has already shown that people with MS score significantly lower than the general population on several measures of HRQL. The present study involves tracking the HRQL for a larger number of people with MS over a three-year time period.

This project should assist health care professionals to better counsel people with MS and to evaluate the effects of clinical interventions such as therapy, rehabilitation and counselling on a variety of HRQL factors.

John Fisk, PhD
Queen Elizabeth II Health Sciences
Centre, Halifax
\$30,250 (April 1/02 – March 31/05)

With additional funding from Health Canada

Effectiveness and Cost-Effectiveness of New Multiple Sclerosis Drugs in the “Real World”

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

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

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

Daria Trojan, MD
McGill University
\$261,360 (April 1/02 – March 31/05)

Brainstem neuronal dysfunction and central fatigue in multiple sclerosis

General fatigue is one of the most common and debilitating symptoms of MS. Many factors may contribute to fatigue in MS, including injury to the brainstem, disease duration and type, breathing difficulties, physical activity, sleep disturbance, immunological abnormalities, depression, stress and pain. Although a number of studies about fatigue in people with MS have been completed, the exact causes are still unknown.

Dr. Trojan’s study is the first to include biopsychosocial factors to measure the potential causes of fatigue in MS. The control group for the study will be made up of people with post-polio syndrome (PPS) who, like those with MS, also have a slow, progressive neurological disorder characterized by fatigue. During the course of the study, 65 people with MS and 65 people with PPS will be examined by a physician and undergo blood and lung testing. Study participants will fill out a questionnaire to assess fatigue, pain, stress, sleep quality, depression, physical activity and self-ability. Imaging techniques will be used to measure lesions to the brainstem (the area which controls wakefulness) and surrounding areas.

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

Programs to Attract New Scientific Talent

Dr. Donald Paty Career Development Awards

The Multiple Sclerosis Society provides a limited number of Dr. Donald Paty Career Development Awards for individuals holding a doctorate degree and who have demonstrated a commitment to a career in MS research. Successful applicants have already completed their research training and are capable of carrying out independent research relevant to MS in a full-time basis in a Canadian school of medicine. The university must confirm that 75% of the researcher's time will be protected for research activities. In addition, successful applicants must have an operating grant, either from the MS Society of Canada or another funding agency.

Total approved for Awards: \$ 300,000

Dr. Amit Bar-Or
McGill University
Category: Immunology
Three-year award
\$150,000 (April 1/01 – March 31/04)

Dr. Ross Mitchell
University of Calgary
Category: Magnetic Resonance
Techniques
Three-year award
\$150,000 (April 1/03 - March 31/06)

Postdoctoral Fellowships

The Multiple Sclerosis Society provides funding for investigators who hold M.D. or Ph.D. 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:
\$390,000

Lenora Brown, PhD
University of Calgary
Supervisor: Dr. Luanne Metz
One year: Renewal \$39,000

Douchebe Dakubo, PhD
Ottawa Health Research Institute
Supervisor: Dr. Valerie Wallace
One year: New \$39,000

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

Awa Dicko, PhD
Hospital for Sick Children
Supervisor: Dr. Joan Boggs
One year: Renewal \$39,000

Yanping Gong, PhD
Hospital for Sick Children
Supervisor: Dr. Joan Boggs
One year: New \$39,000

Elizabeth Jane Fry, PhD
McGill University
Supervisor: Dr. Samuel David
One year: New \$39,000

Helen Tremlett, PhD
University of British Columbia
Supervisor: Drs. Donald Paty and Joël
Oger
One year: Renewal \$39,000

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

Rachel Wheeler, PhD
Montreal Neurological Institute
Supervisor: Dr. Trevor Owens
One year: Renewal \$39,000

Rana Zabad, MD
University of Calgary
Supervisors: Drs. Luanne Metz and V. Wee
Yong
One year: New \$48,500

Simone Zehntner, PhD
Montreal Neurological Institute
Supervisor: Dr. Trevor Owens
One year: Renewal \$39,000

Hong-Mei Zhu, PhD
University of Calgary
Supervisor: Dr. Ross Mitchell
One year: Renewal \$39,000

Studentships

The Multiple Sclerosis Society provides funding for students who are working toward M.Sc., Ph.D. 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: \$594,000

Joseph Anthony
University of Calgary
Supervisor: Dr. Christopher Power
One year: New \$20,000

Edmund Au
University of British Columbia
Supervisor: Dr. Jane Roskams
One year: Renewal \$20,000

Alicia Babcock
McGill University
Supervisor: Dr. Trevor Owens
One year: New \$20,000

Saoussen Bamri
McGill University
Supervisor: Dr. Peter Braun
One year: New \$18,000

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

Marcel Brisebois
McGill University
Supervisor: Dr. Sylvie Fournier
One year: Renewal \$20,000

Kimberly Carcary
University of Calgary
Supervisor: Dr. Aaron Tubman
One year: Renewal \$18,000

Arnaud Charil
McGill University
Supervisor: Dr. Alain Dagher
One year: New \$20,000

Carol Anne Chénard
Lady Davis Research Institute, Jewish
General Hospital, Montreal
Supervisor: Dr. Stéphane Richard
One year: New \$18,000

Lisa Cook
University of Western Ontario
Supervisor: Dr. Steve Karlik
One year: Renewal \$20,000

Qiaoling Cui
McGill University
Supervisor: Dr. Guillermina Almazan
One year: Renewal \$20,000

Gabriele DeLuca
University of Oxford
Supervisor: Margaret Esiri
One year: Renewal \$20,000

Nancy Dionne
McGill University
Supervisor: Dr. Alan Peterson
One year: Renewal \$20,000

Danielle Duszczyszyn
McGill University
Supervisor: Dr. David Haegert
One year: New \$18,000

Greg Gillespie
University of Victoria
Supervisor: Dr. Nancy Sherwood
One year: Renewal \$20,000

Melanie Green
Ottawa Hospital Research Institute
Supervisor: Dr. Mark Freedman
One year: Renewal \$20,000

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

Shireen Hossain
McGill University
Supervisor: Dr. Guillermina Almazan
One year: New \$20,000

Igal Ifergan
McGill University
Supervisor: Dr. Amit Bar-Or
One year: New \$20,000

Andrew Jarjour
McGill University
Supervisor: Dr. Tim Kennedy
One year: Renewal \$20,000

Athena Kalyvas
McGill University
Supervisor: Dr. Samuel David
One year: New \$20,000

Jyothi Kumaran
University of Toronto
Supervisor: Dr. David Rose
One-year: Renewal \$20,000

Peter Larsen
University of Calgary
Supervisor: Dr. V. Wee Yong
One-year: New \$20,000

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

Gregory Mayer
University of Calgary
Supervisor: Dr. Ross Mitchell
One year: Renewal \$18,000

Jason Millward
McGill University
Supervisor: Dr. Trevor Owens
One year: New \$20,000

Minwoo Park
McGill University
Supervisor: Dr. Peter Braun
One year: Renewal \$20,000

Madeline Pool
Ottawa Health Research Institute
Supervisor: Dr. Rashmi Kothary
One year: Renewal \$20,000

Viktor Skihar
University of Saskatchewan
Supervisor: Dr. Ronald Doucette
One year: Renewal \$20,000

Rusia Anne Springer
University of Calgary
Supervisor: Dr. Marlene Reimer
One year: New \$18,000

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

Karolina Wosik
Montreal Neurological Institute
Supervisor: Dr. Jack Antel
One year: Renewal \$20,000

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.

- **Michael Mayne, PhD**, University of Manitoba
Biomedical Research – "Role of intracellular calcium in regulating pro-inflammatory gene expressions in MS patients"

\$35,000 – Start date: May 2002
- **Peter Stys, MD, and Mark Freedman, MD**, University of Ottawa
Biomedical Research – "A novel *in vitro* model of immune-induced demyelination"

\$34,917 – Start date: July 2002
- **Paul Kubes, PhD**, University of Calgary
Biomedical Research – "Mechanisms of leukocyte recruitment to the central nervous system in experimental autoimmune encephalomyelitis"

\$34,867 – Start date: November 2002
- **Christopher Brown, MD**, University of Calgary
Biomedical Research – Therapeutic potential of a soluble GM-CSF receptor in EAE"

\$35,000 – Start date: November 2002

- **Ann Cranney, MD**, Queen's University
Health Research – “The effect of MS on bone mass”

\$34,976 – Start date: December 2002

- **Jean-Françoise Gauchat, PhD**, University of Montreal
Biomedical Research – “Cardiotrophin-like cytokine in experimental autoimmune encephalitis”

\$34,998 – Start date: February 2003

- **Murray Brown, PhD**, Dalhousie University
Health Research – “Is it feasible to apply net benefit regression model methods when evaluating effectiveness and cost-effectiveness of new disease-modifying therapies for MS in the ‘real world’”

\$35,000 – Start date: March 2003

Glossary 2003

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

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

Angiogenesis – The formation of new blood vessels.

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

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

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

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

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

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

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

Demyelination – Process during which myelin is stripped from nerve fibres.

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 life of every individual. DNA is shaped as a double helix and is made up of nucleic acid-sugar complexes loosely bound to proteins.

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

Endothelial cell – Cell that lines the heart and blood vessels of the circulatory and immune systems; forms the blood-brain-barrier (BBB).

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

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

Glial cell – Oligodendrocytes, astrocytes and microglial cells in the central nervous system and Schwann cells in the peripheral nervous system; supports nerve cells.

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

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

Inflammation – Physical injury, infection or a local immune response leading to tissue damage where fluid, white blood cells and plasma proteins accumulate.

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

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

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

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

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

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

Memory B cells – B cells that can be triggered to make antibody after living in the body for long periods of time.

Microglia – Macrophages that reside in the brain.

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

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

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

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

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

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

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

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

Oligodendrocyte – The cell in the CNS that makes and maintains myelin.

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

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

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

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

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

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

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

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

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

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Summaries by: Maya Chaddah. M.Sc.
Translator: Andrée Maisonneuve

Edited and produced annually by:
Communications and Social Action Dept.
Multiple Sclerosis Society of Canada
250 Bloor Street East, Suite 1000
Toronto, Ontario
M4W 3P9

Tel: (416) 922-6065
Fax: (416) 922-7538
E-mail: info@mssociety.ca
Web site: www.mssociety.ca

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