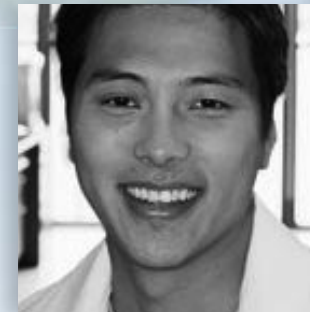
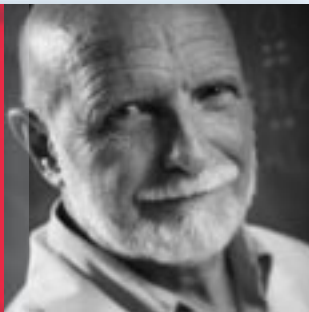




**Multiple Sclerosis Research**

# **The Effort to End MS**





## Multiple Sclerosis Research

# The Effort to End MS

**Multiple sclerosis (MS) is the most common neurological disease affecting young adults. It typically strikes people in their 20s or 30s — when they are completing their education, establishing their careers, starting a family.**

Common symptoms include fatigue, numbness, tingling, pain, muscle stiffness, weakness and difficulty with coordination. During the relapsing-remitting phase of the illness, symptoms flare up without warning and then gradually subside. These attacks, called relapses, may be frequent and debilitating. The impact of the disease — on a person's physical, personal and financial well-being — can be devastating. About 55,000 to 75,000 Canadians are currently living with MS and between 5 and 10% of those affected experienced the onset of their disease during childhood.

During the lifetime course of the illness, a majority will eventually develop progressive MS. During this phase, neurological deficits become permanent and the individual can develop a range of disabilities, such as difficulty walking, incontinence or chronic pain.

Many people living today with MS remember a time when nothing could be done to control their disease. That changed in the 1990s with the introduction of the first disease-modifying therapies (DMT) for MS. These medications — the beta-interferons, glatiramer acetate and natalizumab — have revolutionized the management of MS.

Doctors can now offer many of their MS patients a number of treatment options to reduce MS relapses and slow the progression of their disease.

“Over the past 15 years there has been an explosion of new research into what causes MS, how it develops, and why it progresses.”

The advent of DMTs has also provided important insights into the underlying disease processes at work in MS. Over the past 15 years there has been an explosion of new research into what causes MS, how it develops, and why it progresses. Canadian researchers have been in the vanguard of this research revolution, with pioneering work in genetics, pediatric MS, and stem cell research.

Since its founding in 1948, the Multiple Sclerosis Society of Canada has acted as a key partner to the MS research community. In its first 60 years, donors to the Society have made it possible to provide over \$110 million in funding for Canada's world-class researchers, enabling them to explore new ideas and participate in international clinical trials of new medications. The Society also provides vital seed money for new avenues of research, and promotes the development of the next generation of scientists and clinicians working to find a cure for MS. The MS Society now provides over \$10 million per year to MS research.

The MS Society also funds the MS Scientific Research Foundation, which supports large collaborative scientific projects. Over the next three years, the Foundation will spend another \$12 million on MS research.

This report summarizes what is now known about MS, and the important questions that Canadian researchers are now asking. Not all of the puzzle pieces are in place, but enough is now known that Canadians can glimpse the complete picture and envision the end of MS.

# The MS Disease Process

MS is believed to be an autoimmune disorder, in which the immune system attacks the body's own tissues. A prime target for this attack is myelin, the insulation that protects the delicate nerve fibres (called axons) in the central nervous system (CNS; the brain and spinal cord).



*Demyelination causes small “short circuits” in the “wiring” of the nervous system. Sensory nerves that become damaged can produce symptoms such as a tingling, burning or painful sensation. Damaged motor nerves can result in muscle weakness, spasms or spasticity.*

The autoimmune reaction is characterized by a proliferation of immune cells called T cells, which migrate to the blood-brain barrier (BBB). This layer of densely-packed cells normally screens out harmful substances from entering the CNS. However, in MS, the BBB is more porous, allowing activated T cells to pass through this barrier. Once inside the CNS, activated T cells cause inflammation and edema (swelling).

Inflammation is a normal process of the body. For example, a twisted ankle will become inflamed as the body sends specialized cells to the area to repair the damage and remove injured tissues. However, in MS, this inflammatory process doesn't “shut off”, and chronic inflammation begins to damage myelin. This process, called demyelination, causes small “short circuits” in the “wiring” of the nervous system. Sensory nerves that become damaged can produce symptoms such as a tingling, burning or painful sensation. Damaged motor nerves can result in muscle weakness, spasms or spasticity.

The body is able to repair some of the myelin damage, a process called remyelination. However, as time passes, as a person with MS experiences repeated bouts of CNS inflammation, this repair work cannot keep up with the

“The brain has the ability to compensate for some lost connections by re-routing the circuitry or shifting the task to another part of the brain.”

amount of damage being done. The “short circuit” results in a “blown fuse”, killing the underlying axon and destroying that connection. CNS inflammation also appears to have direct effects on axons, altering their structure and function, which ultimately leads to their destruction. Progressive axonal damage is called neurodegeneration. If there is enough axonal loss, that “circuit” can no longer function. This can result in a permanent shutting down of that nerve connection.

Not all nerve deficits will immediately translate into disability. The brain has the ability to compensate for some lost connections by re-routing the circuitry or shifting the task to another part of the brain. This process, called brain plasticity, is seen in a number of brain injury syndromes. For example, following a stroke, rehabilitation and training can teach the injured brain to re-learn how it performs tasks and the person can regain some degree of function.

However, the brain's ability to compensate for nerve damage is limited. As MS progresses, the accumulation of neurodegenerative damage results in permanent disabilities. For example, some people may develop chronic fatigue, balance, or muscle weakness problems, and may need a cane or a wheelchair to get around. As MS progresses, a variety of other physical or mental problems may also develop. ■



# MS Research

**Over the past decade, researchers have learned a great deal about MS. They have identified many of the constituents of the immune system that are involved in the autoimmune response; how activated T cells enter the CNS; and how MS lesions (or plaques) form and evolve over time.**

There have also been some practical applications of this new knowledge. By understanding how inflammation and neurodegeneration act in MS, scientists and doctors have been able to design new therapies that specifically target the source of the problem. For example, two types of MS medication — the beta-interferons and the selective adhesion molecule inhibitors (such as natalizumab) — act at the blood-brain barrier, reinforcing the barrier and preventing activated T cells from entering the CNS.

Ongoing research into the mechanisms of neurodegeneration and repair offers people new hope — especially those living with progressive forms of MS. To date, treatments have had little impact on the accumulation of disability seen in secondary- and primary-

progressive MS. But as more is learned about how progression occurs, it will be possible to intervene to halt the deterioration in nerve function and stimulate the body to repair itself. That is why the MS Society is so dedicated to funding basic scientific research: to control progressive forms of MS, manage it better and improve the lives of people with the disease, we will first have to complete the groundwork. That work is now being done in laboratories and clinics across Canada and around the world.

As you might expect, the nature of medical research is such that one answer generates a dozen new questions. The puzzle that is MS is a complex one and many pieces still need to be fitted into place. This ongoing quest for answers that will lead to a cure for MS is why the research funding provided by The MS Society and the MS Scientific Research Foundation is so vital. The following are some of the questions that Canadian researchers are asking in their quest to bring the picture of MS into focus.



## Profile: Dr. Dessa Sadovnick, Vancouver, BC

**Researcher Dessa Sadovnick has been a part of the MS community since**

**childhood. One of her earliest memories is of attending a fundraiser organized by Evelyn Opal, who had founded the Montreal chapter of the MS Society in 1947 (a year before the incorporation of the MS Society of Canada).**

Born in Montreal, Dr. Sadovnick obtained her BSc and MSc in genetics from McGill University, and her doctorate in medical genetics at the University of British Columbia. When considering her area of study, she was advised to “go with what you know” — and from an early age her curiosity had been piqued about MS. She is currently a Professor in the Department of Medical Genetics and the Faculty of Medicine, Division of Neurology, at the University of British Columbia.

Her life’s work has been the Canadian Collaborative Project on Genetic Susceptibility to MS, a landmark achievement in MS research and funded since its inception by the MS Scientific Research Foundation. The Collaborative Project is the largest database of its kind in the world and has accumulated a vast amount of information on people with MS and their families. The database now includes over 30,000 families affected by MS, and has provided crucial information on the epidemiology, genetics and clinical outcome of

MS. Dr. Sadovnick is co-principal investigator (with Dr. George Ebers, Oxford, U.K.) for the Canadian Collaborative Project.

“MS affects a whole family’s life, and we are looking at ways of easing that burden of disease.”

“MS affects a whole family’s life,” Dr. Sadovnick says, “and we are looking at ways of easing that burden of disease.”

To date, the Canadian Collaborative Project has contributed important insights on the changing incidence and prevalence of MS, the impact of genetics on the disease course, and has reported that primary-progressive MS is not a distinct entity but part of the heterogeneity of the disease.

“We’ve come a long way in understanding MS, which is leading to different ideas about how to treat it in the future,” Dr. Sadovnick says.

For her important contributions to MS research, Dr. Sadovnick has earned a Michael Smith Distinguished Scholar award, and the MS Society of Canada National Award of Merit. She is currently a member of the Medical Advisory Committee of the MS Society of Canada, and a board member of the MS Society’s B.C. division. ■

## ? Why does MS develop?

MS is believed to be due to a combination of genetic and environmental factors. While genetic factors play a role, this does not mean that MS is a “genetic disease” (such as cystic fibrosis or Down’s syndrome). Rather, there appear to be genetic components that may confer either a susceptibility or a resistance to developing MS.

Much of what we know about the genetics of MS comes from the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS), which is funded by the MS Scientific Research Foundation. For the past 15 years, **Dr. Dessa Sadovnick, University of British Columbia** (see *Profile*), Dr. George Ebers, Oxford University, U.K., and colleagues on the Canadian Collaborative Project have developed the largest population-based MS database in the world. Based in Vancouver, the genetic epidemiological database now includes over 30,000 people with MS, as well as information on their biological relatives. The DNA bank is located at the University of Western Ontario, London.

By integrating genetics with genetic epidemiology (the genetics of populations), Canadian researchers have determined that the inheritance pattern of MS is not due to the effects of a large number of genes. Instead, there is a key region, called the major histocompatibility complex, or MHC (or human leukocyte antigen [HLA]), that appears to be one of the keys to MS susceptibility. MHC class II molecules present antigens (proteins) to T cells, which in turn stimulate T helper cells and B cells (which produce antibodies), as part of the immune response.

This genetic dysregulation of the immune response appears to make some people more susceptible to developing MS. The Canadian Collaborative Project is now focusing on identifying the genetic and non-genetic factors underlying the development of MS.

## Why does the immune system become activated in MS?

One of the roles of the immune system is to identify foreign proteins (e.g. bacteria, viruses), which it then attacks as part of the body's immune response. The key to an effective defence is to be able to distinguish between these invader proteins (“non-self”) and the body's own proteins (“self”). In autoimmune disorders (e.g. MS, lupus, type 1 diabetes), this distinction is blurred and the body attacks its own tissues. Why does this error occur?

It has long been hypothesized that a virus may initially activate the immune system in MS. The viral proteins may be similar to the body's own myelin proteins, so the immune system mistakenly attacks myelin. However, despite numerous studies over the years, researchers have not been able to identify a virus that causes MS.

What if the foreign protein hasn't invaded but is already present in the body? Over millions of years of evolution, the human genome has incorporated a variety of viral genes into our genetic code. Indeed, an estimated 5-10% of our genetic sequence is made up of retroviruses. **Dr. Christopher Power, University of Alberta**, has discovered that a unique kind of retrovirus is made in the brains of some people with MS. Preliminary studies indicate that when these retroviral genes become activated, they contribute to the activation of the immune system and damage to myelin. Dr. Power now plans to evaluate the level of these retroviral elements in people with MS to see how they may contribute to the development and progression of MS.

A key event in the autoimmune attack is the activation of specialized white blood cells called T cells. **Dr. David Haegert, McGill University**, has recently discovered abnormalities in the body's regulation of the T cell population. He believes that in people with MS, T cells are in a state of “high alert” even before they become activated. These partially activated T cells may respond more readily and more robustly to activation signals, which could explain why some people develop

MS and others do not. By studying profiles of gene expression, he hopes to identify subgroups of people who might respond differently to MS therapies.

T cells become activated when they interact with an antigen-presenting cell (APC), which “presents” a protein fragment so it can be identified as “self” or “non-self”. This interaction occurs via receptors such as the T cell receptor (TCR) and its co-receptor, CD4, which amplifies the TCR signal.

Until recently, researchers had only investigated the CD4 T cell. However, it now appears that a second type of T cell, called CD8, may also play a role. **Dr. Sylvie Fournier, McGill University**, has shown that activation of CD8 T cells in an animal model results in a neurological disease that resembles MS. She plans to investigate how activation of CD8 T cells can contribute to tissue damage. In a separate research project, **Dr. Nathalie Arbour, Centre Hospitalier de l'Université de Montréal (CHUM)**, will analyse CD8 T cells isolated in injured CNS tissue to determine how they are involved in the process.

Traditional wisdom has long held that immune cells react specifically to proteins, and the target of the T cell attack in MS is the proteins that make up myelin (e.g. myelin basic protein, or MBP). However, in the 1990s, researchers discovered that T cells can also target lipids (fats). This may have important implications for MS since lipids are the main constituent of myelin. Of particular interest to this line of research is a blood protein called apoE, which is largely produced by the liver and is involved in transporting cholesterol through the blood stream. However, apoE is also produced in the nervous system by specialized cells (e.g. microglia, astrocytes).

**Dr. Peter van den Elzen, University of British Columbia**, has recently discovered that apoE can transport fats to APCs for presentation to T cells. His research into how the immune response to fats is involved in T cell activation has several potentially important implications. Dietary modifications or therapies that alter cholesterol metabolism, such as cholesterol-lowering drugs, might prove to be beneficial in MS.

“Over millions of years of evolution, the human genome has incorporated a variety of viral genes into our genetic code.”

“Over the past decade, researchers have learned that 2-5% of people with MS are children aged 16 or younger.”

## Can MS affect children?

MS is most commonly diagnosed in people aged 20-40 years. However, over the past decade, researchers have learned that 2-5% of people with MS are children aged 16 or younger.

Canada has been at the forefront of pediatric MS research, contributing important insights on diagnosing early-onset MS, distinguishing MS symptoms from other neurological conditions, characterizing the impact of MS on cognitive and social development, and examining the effect of disease-modifying therapies in this young group of people. **Dr. Brenda Banwell, Hospital for Sick Children** (see *Profile*), is currently examining the effects of MS on cognition in children and adolescents to see if the severity of cognitive deficits increases over time, and whether key factors (such as age at first attack, MRI findings) influence the type and severity of cognitive impairments. She is also a recipient of an MS Scientific Research Foundation Award for a landmark study of clinically isolated syndrome (CIS) in children and adolescents.

## Can we defend the CNS from invasion by activated immune cells?

The blood-brain barrier (BBB) is a layer of tightly-packed cells that acts to filter out harmful substances to prevent them from entering the CNS. In MS, this barrier becomes more porous, which allows activated T cells to gain access to the brain and spinal cord.

Before an activated T cell can enter the CNS, it must first be attracted to the BBB and adhere to the barrier cells so it can squeeze past them. If this trafficking of T cells across the BBB could be prevented, it would reduce or prevent the CNS inflammation seen in MS.

Can this barrier be defended? In fact, two classes of MS medication now available act at the level of the BBB. Beta-interferons inhibit the enzymes (called matrix metalloproteinases, or MMPs) that degrade the BBB. Selective adhesion molecule inhibitors block the adhesion molecules that enable

T cells to stick to the BBB. Both classes of medication have been shown to be highly effective in reducing CNS inflammation in MS.

Can more be done to protect the CNS? **Dr. Katerina Dorovini-Zis, Vancouver General Hospital**, believes that studying endothelial cells, which form the outermost layer of the BBB, will prove to be important in our understanding of how MS develops. Thus far, Dr. Dorovini-Zis has shown that some agents, such as nitric oxide, can decrease the permeability of the BBB. She is now investigating whether endothelial cells have a role in activating T cells.

Selective adhesion molecular inhibitors (e.g. natalizumab) target one type of adhesion molecule. A second type, called activated leukocyte cell adhesion molecule (ALCAM), has been identified by **Dr. Alexandre Prat, Université de Montréal** (see *Profile* on p.8), and colleagues. ALCAM is expressed by endothelial cells of the BBB and appears to play a key role in T cell trafficking into the CNS. He is now investigating the role of ALCAM in the development of MS lesions in the CNS. In a separate project, Dr. Prat will try to determine if endothelial cells influence the development of dendritic cells. Dendritic cells trigger T cell activation and appear to be involved in the formation of inflammatory lesions in the CNS. This research will attempt to discover if BBB-associated dendritic cells contribute to and sustain the T cell attack that results in tissue damage in MS.

## How can we see into the brain to know what is happening in MS?

Magnetic resonance imaging (MRI) has been an important clinical tool for confirming a diagnosis of MS. MRI produces a powerful magnetic field that shows areas of inflammation and edema inside the CNS. While these scans give clinicians some idea of how MS lesions develop and resolve over time, they provide little information on the processes of lesion formation, axonal damage and remyelination.

**Dr. Doug Arnold, Montreal Neurological Institute**, is investigating specialized MRI techniques that will provide a more accurate picture of CNS remyelination. In a separate



*MRI produces a powerful magnetic field that shows areas of inflammation and edema inside the CNS.*

project, Dr. Arnold is also working to develop a novel MRI approach (called magnetization transfer imaging) that will enable researchers to visualize MS lesions that appear in unmyelinated areas of the brain, such as the cerebral cortex. These grey-matter lesions appear to have a significant impact on physical and cognitive functioning, but little is known about how they develop and progress because they are invisible to conventional MRI.

**Dr. Alex Mac Kay, University of British Columbia,** plans to

use MRI to assess the neurodegenerative processes that occur in MS. **Dr. Wayne Moore, University of British Columbia,** will employ high field-strength MRI to boost the amount of detail in MRI images in an attempt to see the type of tissue damage that occurs, such as loss of myelin components, loss of axons, and disruption of blood vessels in the CNS.

MRI is able to detect differences in tissue density, which is partially affected by the water content. **Dr. Anthony Trabousee, University of British Columbia,** will examine how the intake of liquids and medications alters brain water content, and how this affects the MRI measures currently used when assessing MS and individuals' response to treatment.

Another innovative research approach is being used by **Dr. Ross Mitchell, University of Calgary,** who is employing a technique called texture analysis. As the name suggests, this technique measures the texture of an MR image. By looking at healthy individuals and comparing their results to people with MS, Dr. Mitchell hopes to identify markers of myelin health that can be used to assess the effectiveness of MS therapies.



## Profile: Dr. Brenda Banwell, Toronto, Ontario

**Dr. Brenda Banwell has always felt a special affinity for children so**

**it was no surprise to her family and friends that she chose to specialize in pediatrics. Born in Winnipeg, Dr. Banwell obtained her medical degree from the University of Western Ontario in London, then completed residencies in pediatrics at the Children's Hospital of Western Ontario, and in pediatric neurology at the Hospital for Sick Children, Toronto. During that period she married David, and the couple now has three daughters, Emma, Kate and Sarah.**

**D**r. Banwell became interested in MS research while completing a fellowship in neuromuscular disease at the prestigious Mayo Clinic in Rochester, Minnesota. Upon her return to Canada, she was asked to oversee the care of five children with MS and decided that a formal program was needed. So she successfully founded the Pediatric MS Clinic at the Hospital for Sick Children, and currently serves as its director.

Over the past decade, Dr. Banwell has become a world leader in pediatric MS as a clinician, researcher and educator. Her many awards include the President's Prize from the Canadian Congress of Neurological Sciences, two William A. Hawke

Awards for Clinical Excellence in Teaching from the Hospital for Sick Children, the Woman Against Multiple Sclerosis Woman of the Year Award, and the Canada's Top 40 under 40 award.

Her current project is a five year study investigating clinically isolated syndromes (CIS) in children; CIS is an initial demyelinating event that often heralds the later diagnosis of MS. This groundbreaking trial, funded by the MS Scientific Research Foundation, involves 23 centres across Canada and will obtain genetic, immunological and MRI data. The key questions the investigators hope to answer are: What is the cause of MS; and What is the risk of developing MS in children with CIS?

"Pediatric patients are closest to the biological onset of the disease," Dr. Banwell says, "so we hope to identify the earliest events in the pathobiology of MS." Since the immune systems of children have experienced less exposure to environmental and other factors, it may be possible to determine key events — genetic, immunological and environmental — that contribute to the development of MS. The study may also help to identify why one-half of the children with a demyelinating event don't develop MS. This information could then be used to define predictors of MS in children and adolescents.

"This study has very exciting potential," Dr. Banwell says. "Over the next five years, we hope to obtain the information we need to better manage pediatric MS patients." ■



## Profile: Dr. Alexandre Prat, Montreal, Quebec

**A leading member of Canada's next generation of MS researchers is Dr. Alexandre**

**Prat, Director of the Neuroimmunology Laboratory at the Centre Hospitalier de l'Université de Montreal Research Centre (CRCHUM) in Montreal.**

Dr. Prat had always dreamed of being a medical researcher but he was initially turned down for medical school. Not one to give up, he completed a Bachelor's degree in biochemistry, then was accepted into an integrated program that combined medical school with a Master's degree in pharmacology.

As a young physician, Dr. Prat's first area of interest was brain inflammation. After training in internal medicine, he joined Dr. Jack Antel at the Montreal Neurological Institute to research how immune cells enter the brain. He completed a PhD and neurology training at the MNI, then was hired by the CHUM as an MS researcher and clinician.

His plan was to investigate the blood-brain barrier (BBB), the layer of cells that screens substances from entering the central nervous system (CNS). "My first grant to open our lab came from the MS Society of Canada," Dr. Prat says. "The Society's support has been critically important. Their open-minded approach has

enabled Canadian researchers to investigate the immunological and biological processes of MS."

The start-up funding has already borne fruit. With Dr. Sam David and other researchers at McGill University and the Université de Montréal, Dr. Prat has discovered molecules produced by BBB endothelial cells that regulate the trafficking of cells into the CNS.

One of these molecules is ALCAM (activated leukocyte cell adhesion molecule; or CD166), which enables one type of T cell (called CD4) to cross the BBB. But it isn't involved with trafficking CD8 T cells, which help protect the body from viruses. Some adhesion molecule inhibitors, such as natalizumab (Tysabri), also block CD8 T cells. This has been associated with reactivation of the JC virus, which results in PML (progressive multifocal leukoencephalopathy). An ALCAM blocker might avoid this problem, but further research is needed.

Dr. Prat's team has also discovered ninjurin-1, which regulates the migration of monocytes into the CNS. Monocytes are involved in the reactivation of T cells in the CNS, which results in myelin and nerve damage. So blocking this adhesion molecule may prove to be beneficial to MS patients.

For his pioneering research, Dr. Prat has been awarded the prestigious S. Weir Mitchell award from the American Academy of Neurology, and the Donald Paty Career Development Award from the MS Society of Canada. ■

## ? Can we stimulate remyelination and protect neurons?

The MS disease process is characterized by an erosion of the myelin sheath, which exposes the delicate nerve fibres (called axons) to neurotoxic constituents of the CNS microenvironment. The body is able to reverse some of this damage through remyelination. However, during the course of the illness, remyelination is insufficient to keep up with the amount of damage being done, or the process fails altogether. In either case, the result is widespread destruction of axons throughout the CNS and a gradual accumulation of nerve deficits or disabilities.

Why does remyelination fail? If this question could be answered, scientists might be able to develop methods to stimulate remyelination and prevent nerve damage and disability. Because of the urgent need to understand this process, a majority of research projects funded by the MS Society of Canada are investigating remyelination.

The starting point for remyelination is a specialized cell called an oligodendrocyte, which produces myelin. **Dr. Jack Antel, McGill University**, has found that inflammation can directly damage oligodendrocytes and he is now investigating how this occurs.

When myelin damage occurs, a chemical signal is sent to the oligodendrocyte to produce new myelin. These chemical signals are called mitogen-activated protein kinases (MAPK); a "mitogen" is a stimulus that comes from outside the cell. **Drs. Guillermina Almazan and Walter Mushynski, McGill University**, have shown that one family of MAPKs (called p38) is essential to remyelination. If p38 is blocked, the oligodendrocyte can no longer remyelinate the axon. The researchers are now working to identify the precise type of p38 that will stimulate remyelination.

“Why does remyelination fail? If this question could be answered, scientists might be able to develop methods to stimulate remyelination and prevent nerve damage and disability.”

**Dr. Joan Boggs, Hospital for Sick Children Research Institute**, is also investigating the signalling mechanisms in remyelination. Dr. Boggs believes that as different components of myelin are bound together, this binding triggers a signal that acts to regulate how and when myelination will occur. In a separate project, Dr. Boggs also plans to study how myelin proteins such as MBP interact with the structural proteins inside cells (called the cytoskeleton), and how the cytoskeleton in turn interacts with signalling molecules involved in myelin formation.

Another key protein involved in remyelination is netrin-1, which directs oligodendrocyte precursor cells to migrate to the area where remyelination is to occur. **Dr. Tim Kennedy, McGill University**, has discovered that netrin-1 and its receptor, DCC, are expressed by myelinating oligodendrocytes in the adult CNS. Moreover, when netrin-1 and DCC are absent, there is a disruption in the normal contact between oligodendrocytes and axons.

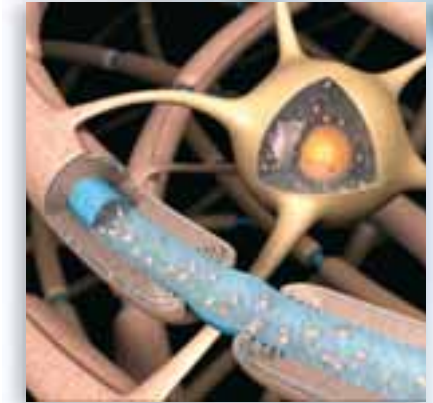
**Dr. Rashmi Kothary, Ottawa Health Research Institute**, is researching another chemical signal, called integrin-linked kinase (ILK), which interacts with a receptor (called an integrin) on the surface of the oligodendrocyte. ILK is believed to be involved in telling the oligodendrocyte how to properly remyelinate axons.

The structure and function of myelin itself are also being studied. The myelin membrane comprises a variety of different regions that are distinct in terms of their composition, structure and function. **Dr. Lillian DeBruin, Wilfrid Laurier University**, hypothesizes that myelin components undergo remodelling during demyelination, and is now investigating which functional pathways become altered.

**Dr. Mario Moscarello, Hospital for Sick Children Research Institute**, has found that the myelin structure can become destabilized in the presence of key chemicals. One such chemical is citrulline, which is synthesized in myelin proteins through the actions of a family of enzymes called PADs (for peptidylarginine deiminases). Myelin obtained from persons with MS has been found to have an elevated level of PADs, which Dr. Moscarello believes leads to cell damage during the MS disease process. He is now investigating the potential benefits of combining vitamin B12 and a chemical called 2CA (2-chloroacetamide). In animal studies, this combination has been shown to enhance myelin repair and reduce the signs of neurological damage.

Substances in the microenvironment of the MS lesion, called extracellular matrix molecules (ECMs), may also impair the body's ability to repair myelin. For the past decade, **Dr. V. Wee Yong, University of Calgary**, has been investigating the role of a family of enzymes called matrix metalloproteinases (MMPs). MMPs are known to regulate ECMs, and Dr. Yong will explore if these enzymes can remove ECMs to allow remyelination to occur.

These research projects will try to determine where the many pieces fit in the complex machinery of remyelination. Another approach is to find the “master switch” that will regulate oligodendrocyte function. In fact, **Dr. Alan Peterson, Royal Victoria Hospital**, and colleagues have located the DNA switches that control myelin expression by oligodendrocytes. Dr. Peterson now hopes to identify how these switches work in the remyelination of axons.

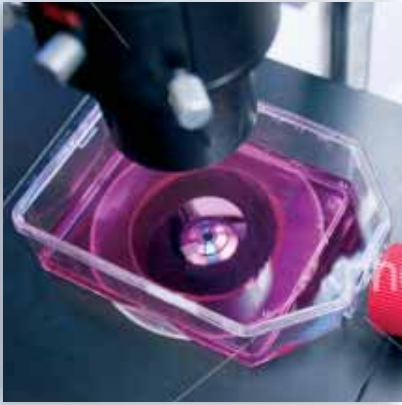


*These research projects will try to determine where the many pieces fit in the complex machinery of remyelination. Another approach is to find the “master switch” that will regulate oligodendrocyte function.*

Researchers are also studying genetic defects in animals to provide clues to remyelination. One example is the quaking viable mouse (qk(v), which develops tremors shortly after birth. These tremors are caused by demyelination resulting from a defect in a key protein (called quaking RNA binding protein) needed for oligodendrocyte development.

**Dr. Stéphane Richard, Jewish General Hospital**, is using this animal model to determine if enhancing the function of quaking proteins will stimulate the differentiation and maturation of oligodendrocytes able to repair myelin.

It has been speculated that remyelination may fail in some MS cases due to an inadequate number of functioning oligodendrocytes. During the course of the disease, oligodendrocytes may malfunction or may die off. A potential solution to the problem is to transplant cells to replace oligodendrocytes. Stem cells are cells with the ability to divide and differentiate into a wide range of specialized cell types. **Dr. Charles Tator, University of Toronto**, is experimenting with one type of stem cell, called neural stem progenitor cells (NSPC). NSPCs are found in the adult spinal cord. Laboratory studies performed thus far have shown that when transplanted, NSPCs can differentiate into oligodendrocyte precursors, which then develop into functioning oligodendrocytes. See *Stem Cells and MS* for another application of this technology.



*A potential solution to oligodendrocytes malfunction is to transplant cells to replace oligodendrocytes. Stem cells are cells with the ability to divide and differentiate into a wide range of specialized cell types.*

“**Damaged neurons have the potential to repair themselves but a number of substances in the CNS microenvironment can impede regrowth.**”



### **Can we reduce or prevent nerve damage in MS?**

**A**s the protective myelin sheath is eroded, the underlying nerve fibre (axon) is left exposed to the neurotoxic effects of the inflammatory microenvironment. As axons are destroyed, there is a progressive accumulation of nerve deficits, which often culminates in the disabilities seen in MS.

Is there a way to make inflammation less toxic to axons, or is there a way to stimulate regrowth of nerve cells? Both of these approaches are currently being studied.

**Dr. Samuel David, McGill University**, is investigating the role of an enzyme called cytosolic phospholipase A2 (cPLA2). Like all enzymes, cPLA2 breaks down substances in the body to form new substances. In the case of cPLA2, one of its metabolic products promotes inflammation while another induces the breakdown of myelin. In an animal model of MS, Dr. David has shown that cPLA2 is highly expressed in CNS lesions and that blocking the enzyme significantly reduces the onset and progression of disease.

# Stem Cells and MS

**In recent years, stem cell research has attracted a great deal of attention because of the potential benefits of this technology for a wide range of illnesses.**



What makes stem cells so attractive is their ability to grow and differentiate into a wide range of tissues. In the developing embryo, embryonic stem cells are the source of all the cell types

that will make up the human body. This ability is referred to as pluripotency. However, the use of embryonic stem cells is controversial since it requires the destruction of the embryo.

The use of adult stem cells is less controversial. In children and adults, stem cells are generally more specialized so they can only differentiate into a limited number of cell types (called multipotency). An exception to the rule is umbilical cord blood, which is pluripotent and can be used to generate a virtually unlimited range of cell types.

Adult stem cells are currently used in a number of areas. For example, hematopoietic stem cells found in bone marrow will differentiate into different types of blood cells, such as red blood cells or white blood cells. Bone marrow transplants are now routinely performed in people with certain blood disorders, such as leukemia.

cPLA2 also has a second role in regulating prostaglandins, a group of lipid compounds derived from fatty acids. Prostaglandins are found throughout the body and will bind to various receptors to produce different effects. In the CNS, they can either promote inflammation or be neuroprotective. Dr. David plans to study the different prostaglandin receptors in animals to determine their role in the development of neuronal damage and repair. The hope is that this information will lead to the development of novel treatments for MS.

Damaged neurons have the potential to repair themselves but a number of substances in the CNS microenvironment can impede regrowth. For example, blocking the effects of key enzymes (e.g. Rho GTPase) has been shown in animal studies to allow for axonal regrowth. **Dr. Alyson Fournier, Montreal Neurological Institute**, and colleagues have recently found that immune cells (T and B cells) can affect neuronal repair and regrowth when activated by a variety of stimuli. This discovery indicates an important link between immune cells and nerve cells, and could provide a new approach to the development of new medications that promote nerve growth in MS and other neurodegenerative conditions.

The MS Society also funds projects to improve the day-to-day functioning of people living with MS. Over the years, a great deal of important research has been completed on the causes and treatment of MS symptoms such as fatigue, depression, and cognitive problems. By managing these symptoms more effectively, people with MS are better able to cope with their illness, are more likely to remain active and employed, and can enjoy an improved quality of life. ■

The MS Society of Canada has demonstrated its commitment to stem cell research through a Foundation Award to **Drs. Mark Freedman and Harold Atkins, Ottawa Hospital**. These researchers are investigating the potential benefits of stem cell transplantation in people with MS with a poor prognosis.

MS is believed to be an autoimmune disorder in which a dysfunctional immune response results in tissue destruction in the CNS. Drs. Freedman and Atkins hypothesize that if the immune system were removed and rebuilt from scratch (“rebooted”), the new immune system might be free of the errors that resulted in the autoimmune response.

Their approach is to obtain stem cells from individuals with MS (called “autologous” since they come from the affected individuals themselves rather than from a donor). These stem cells are then purified and maintained in the lab. Once the stem cells are obtained, the person’s immune system is eliminated with potent chemotherapy agents and antibodies (called immunoablative therapy). The purified stem cells are then transplanted back into the individual, where they grow and differentiate into a new immune system.

This procedure has risks so it is currently being limited to people with rapidly progressing MS who have a very poor prognosis. To date, Drs. Freedman and Atkins have employed this technique in a small number of people with MS. None of these individuals have had MS relapses following the procedure and most have not deteriorated further. These preliminary results suggest that the disease process can be stopped in some people with MS. ■

# Into the Future

**The mission of the MS Society of Canada is to find a cure — to end MS in our lifetime. Such an achievement will require innovative ideas from our best and brightest researchers and clinicians. As this publication outlines, Canadian researchers are making great strides toward a better understanding of why MS develops, how it progresses, and how neurological disabilities might be prevented.**

Throughout the history of MS research, Canada has made vital contributions to our understanding of MS: how it develops, how it evolves, and how to treat it. This legacy of research excellence continues to this day with world-class research centres across Canada and hundreds of doctors and scientists searching for a cure.

Since its inception in 1948, the MS Society of Canada has played a vital role in coordinating and funding MS research. Every year, Canadian researchers submit their most innovative ideas to the MS Society's grants review committees and Medical Advisory Committee (MAC). Applicants must meet two criteria: the project must focus on MS, and it must meet the standard of scientific excellence. The MAC forwards its recommendations for funding to the Board of Directors of the MS Society, and the MS Scientific Research Foundation, which then award grants according to the available resources.

The MS Scientific Research Foundation provides pilot grants for promising new ideas, and funds large, collaborative projects that would not be possible otherwise. In recent years, the Foundation has funded four landmark studies:

- The Canadian Collaborative Project on Genetic Susceptibility to MS, which has provided us with many of the insights we now have about the genetics of MS

- A prospective study of clinically isolated syndrome (CIS) in children, the first study of its kind in the world
- A study on the potential benefits of autologous stem cell transplant in people with rapidly progressing MS
- A phase III trial of minocycline in CIS by **Dr. Luanne Metz, University of Calgary**, and colleagues. This important trial will investigate the effectiveness of a low-cost oral antibiotic therapy in preventing or delaying the onset of MS in people at risk. The researchers plan to enrol about 200 people at MS centres across Canada. The preliminary work on minocycline was conducted by researchers at the University of Calgary with a grant from the MS Society.

To achieve the goal of ending MS, the MS Society commits over \$10 million per year to MS research. Over the next three years, the MS Scientific Research Foundation will invest another \$12 million. All of these grants have been made possible because of the thousands of individual and corporate donations from across Canada. This generosity has already paid dividends — as seen by the countless number of clinical trials of new medications for MS. Across the country, thousands of people with MS have committed themselves to participating in trials, many of which have been funded by the MS Society of Canada. Their dedication and participation have helped enormously in contributing to our store of knowledge about MS, and it is hoped that through their efforts we will find a cure.

The current boom in MS research has already provided important insights as to why MS strikes some people, how the disease develops, and how people can be better managed to improve the quality of their lives. Effective medications are now available, and many more are now in development. Over the next few years, we may witness a whole new era in MS care — with medications that protect the nervous system from damage, and reverse some of the disability seen in this devastating disease. With the combined efforts of researchers, industry and the Canadian public, we can bring about the end of MS in our lifetime. ■





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