



MS Research Summaries 2004

Record level of research funding

MS Society commits further \$4.5 million to research program; MS Scientific Research Foundation supports two ground-breaking projects for \$7.4 million

In 2004, the Multiple Sclerosis Society of Canada and the related MS Scientific Research Foundation are funding an unprecedented \$11.9 million in MS research projects and scholarships.

The major focuses are: the search for the cause of MS in children and adults, repair of damaged myelin and stopping MS attacks.

In March, the MS Society approved 13 new research projects with terms running up to three years and almost 50 research scholarships for promising young scientists. The total funding commitment is \$4.5 million, which is \$1 million more than was committed in 2003. On an annual basis and through the generous support of donors across Canada, the MS Society research program totals between \$5 and 6 million.

In May, the MS Scientific Research Foundation announced funding of \$7.4 million for two ground-breaking collaborative research studies. The first project is pinpointing the development of MS in children to try to learn more about the cause of MS and to identify the risk of developing MS after an initial attack. The other project is phase four of the Canadian collaborative study of genetic susceptibility to MS, which has, since its beginning in 1993, yielded unprecedented information about who is at risk of developing MS and why.

These investments reflect the strength and depth of Canadian MS research and the generous commitment of Canadian donors who are making an impact on a world-wide basis. This financial commitment is possible because of the support of individual donors, corporate partners and MS Society chapters that raise funds in their local communities.

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Myelin: Repairing 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 protein is wrapped around nerve fibres (axons), 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 forming 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 mechanics of how myelin is wrapped around nerve axons. Many questions still need to be addressed. What genes are involved in myelin growth? What are the interactions between myelin-making cells and nerve cells promoting myelin growth? What cell-cell communications contribute to myelin regrowth? What factors and treatments stimulate myelin regrowth?

Researchers are using a variety of approaches, from cell culture techniques to protein and gene function analyses to animal model studies and clinical trials. As myelin growth and regrowth are mapped out in more detail, researchers will be able to design better 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, an increasing number of central and peripheral nerves are stripped of their myelin sheath. This seriously affects the ability of nerve axons to do their job. Damage to myelin often goes hand in hand with irreversible damage to nerve axons, causing even more severe problems for people with MS.

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

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

Joan Boggs, PhD
Hospital for Sick Children, 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 approaching this problem by studying how proteins in the oligodendrocyte membrane communicate to maintain the health of the myelin sheath.

Dr. Boggs thinks that glycosphingolipids (a fat plus sugar) 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 tested for their ability to transmit 'myelin health' messages.

The question of how oligodendrocyte proteins and glycosphingolipids communicate to convey 'myelin-health' is one that scientists will have to answer before they can effectively rebuild myelin and stop nerve damage in people with 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 seesaw is myelin basic protein (MBP), which makes up a major part of the myelin sheath. In MS, altered forms of MBP disrupt the myelin sheath and are often an indicator of disease severity.

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

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

Timothy Kennedy, PhD
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 adult rats netrin-1 and DCC are made by oligodendrocytes that are actively adding myelin to nerve fibres. 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.

All MS research has a converging aim – to prevent or at least minimize the destruction to myelin in the nervous system.

Mario Moscarello, PhD
Fabrizio Mastronardi, PhD
Hospital for Sick Children, Toronto
\$177,730 (April 1/04 - March 31/06)

Vitamin B12 in combination therapy induces remyelination

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

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

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

MS Research Commitments at a Glance

Total Society-funded research projects	33
Total Foundation-funded large, collaborative projects	4
Total Society-funded MS scholarships	48
Donald Paty Career Development Awards	5
Postdoctoral Fellowships	15
Research Studentships	28
Total Foundation-funded pilot research projects	9

(97% of Society-funded research projects are multi-year grants. 100% of Foundation-funded collaborative projects are multi-year grants.)

Adil Nazarili, PhD
University of Saskatchewan
\$65,506 (April 1/04 - March 31/05)

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

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

Dr. Nazarali has been steadily closing the information gap with research funded by the MS Society over the past two years. He has made considerable progress towards understanding how homeobox (Hox) genes are linked to differentiation in ECs and oligodendrocytes. Hox genes code for proteins that bind to DNA and influence gene activity. He is the first to show that Hoxa2 and Hoxb4 genes are made by ECs and oligodendrocytes. His work also makes a strong case for Hoxa2 being involved in

myelination. With the improved methods he developed for isolating and growing mouse ECs and oligodendrocytes, he is continuing to study the link between Hox genes and EC and oligodendrocyte maturity.

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

Alan Peterson, PhD
McGill University
\$229,020 (April 1/04 - March 31/06)

Regulation of the oligodendrocyte genome

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

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

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

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

Purine receptor-mediated immune regulation in multiple sclerosis

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

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

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

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) are abnormal in these mice.

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

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

Valerie Anne Wallace, PhD
Ottawa Health Research Institute
\$74,746 (April 1/04 – March 31/06)
With additional funding from the Canadian
Institutes of Health Research

The role of neuron-derived morphogens in optic nerve development

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

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

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

V. Wee Yong, PhD
University of Calgary
\$352,500 (April 1/04 - March 31/07)

Beneficial roles of matrix metalloproteinases (MMPs) in myelin formation

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

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

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



Immunology: Halting 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) determining the roles of the different players (T cells, B cells, macrophages, etc.), 2) discovering how cell-cell communications open the tight seal of the blood-brain-barrier (BBB) 3) understanding how and why normally protective immune cells breach the BBB to coordinate the attack on myelin, and 4) identifying how the immune system attack varies from person to person with MS.

Equally important are studies evaluating new and existing immunotherapies, keeping 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 and better therapies bringing the immune system back onside.

Jack Antel, MD
Montreal Neurological Institute
\$306,000 (April 1/04 - March 31/07)

The systemic immune response in multiple sclerosis and effects of therapy

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

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

These studies will get directly at the question of how lymphocytes cross the BBB. In the

future, Dr. Antel's results may help identify particular aspects of lymphocyte-endothelial cell interactions that could serve as new therapeutic targets for people with MS.

Jack Antel, MD and Amit Bar-Or, MD
Montreal Neurological Institute
\$180,000 (April 1/04 - March 31/06)

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

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

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

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

Amit Bar-Or, MD
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.

Samuel David, PhD
McGill University
\$239,921 (April 1/04 - March 31/07)

Pathogenesis and treatment of chronic experimental autoimmune encephalomyelitis

MS is an inflammatory disease of the central nervous system (CNS) that can result in myelin loss, sensory loss and even paralysis. The clinical course of MS varies from person to person and includes relapsing-remitting and chronic (progressive) forms. Although a variety of factors likely trigger MS in susceptible individuals, those that promote inflammation and damage to myelin are good candidates to study. For this reason, Dr. David is focusing on the enzyme PLA₂ whose by-products can dissolve myelin and cause inflammation.

Dr. David's studies have taken place in mice that develop an MS-like disease called experimental autoimmune encephalomyelitis (EAE). He made notable progress during the last period funded by the MS Society. In particular, he showed that PLA₂ is expressed at high levels in spinal cord lesions in the relapsing-remitting form of EAE. He also found that chemical inhibitors of PLA₂ significantly reduce the onset and progression of relapsing-remitting EAE. With new funding from the MS Society he plans to extend his studies to include a mouse model of chronic EAE. The changes in inflammation and nerve damage in the spinal cord at various stages of chronic EAE will be studied, as will the role of PLA₂.

Studying EAE mice will give researchers more clues about how to design treatments, such as PLA₂ inhibitors, that might block inflammation and CNS damage in people with various forms of 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 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.

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.

In 2004, the Multiple Sclerosis Society of Canada and the related MS Scientific Research Foundation are funding an unprecedented \$11.9 million in MS research projects and scholarships.

**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 the changes to 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 to help growing lesions.

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 an 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.

The financial commitment for MS research is possible because of the support of individual donors, corporate partners and MS Society chapters that raise funds in their local communities.

Paul Kubes, PhD
University of Calgary
\$176,352 (April 1/04 - March 31/06)

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

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

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

This innovative research may show that mast cells are the interface for the environmental influences that initiate MS. If this proves to be correct, mast cells and mast cell TLR4 might be two new therapeutic targets for the treatment and prevention of MS.

Michael Mayne, PhD
University of Prince Edward Island
\$170,000 (April 1/03 – 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 triggering and movement into the brain.

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

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

Alexandre Prat, MD, PhD
Montreal University
\$200,000 (April 1/04 - March 31/06)

Role and function of human endothelial cells during CNS inflammation

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

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

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

Luc Vallières, PhD
CHUL Research Centre, Quebec City
\$63,000 (April 1/04 - March 31/06)

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

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

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

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



MRI: A snapshot of MS

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

MRI generates two-dimensional images of the body's internal structures. In MS, MRI is used to contrast white matter (myelin) from grey matter and cerebral spinal fluid. This technique is so sensitive that it can 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 compiles chemical rather than structural information about healthy and diseased tissues.

Because MRI and MRS are non-invasive techniques, they are used to follow individuals with MS on an ongoing basis. Combinations of MRI and MRS monitor how MS lesions respond to different therapies. Scientists are always looking for ways to improve the capabilities of MRI and MRS to get more detailed pictures of what is going

during different stages of MS. The ultimate goal of this research is to develop better imaging tools that can be used for improving diagnosis, managing clinical symptoms and monitoring 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 repairing myelin and controlling nerve damage in MS.

Alex MacKay, MD, David Li, MD, and Donald Paty, MD
University of British Columbia
\$276,810 (April 1/04 - March 31/07)

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

In MS, damage to myelin may cause attacks (relapses) where vision, sensation, coordination and strength are temporarily or permanently lost. With the development of magnetic resonance (MR) techniques researchers are no longer confined to post-mortem observation but can follow physical and chemical changes to myelin in people living with MS.

Drs. MacKay, Li and Paty are using a variety of different MR techniques to pinpoint when myelin loss occurs in MS lesions after the blood-brain-barrier has become leaky, which allows immune cells into the brain and spinal cord. They made some good technical progress during the last period funded by the MS Society. They developed a better MR technique that takes advantage of water trapped in the myelin layers to generate a very high resolution myelin map of a single slice in the brain. They also have a new magnetic resonance spectroscopy (MRS) scanner that gives higher quality 2D images than those obtained in previous years. With their new and improved MR techniques, they will use a number of markers to gauge myelin loss, myelin regrowth, and myelin changes in 'normal appearing' white matter of the brain.

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

Ross Mitchell, PhD and Ursula Tuor, PhD,
University of Calgary
\$259,010 (April 1/03 – 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 outputs to lesion composition, and provide methods for evaluating new therapies and identifying new targets for future preventive therapies.

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

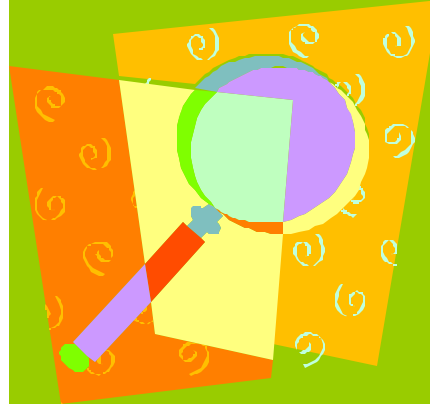
**Wayne Moore, MD, Donald Paty, MD,
Stanley Hashimoto, MD, David Li, MD,
Robert Nugent, MD, Alex MacKay, MD
University of British Columbia
\$249,739 (April 1/02 – March 31/05)**

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: Better management of MS

Multiple sclerosis typically affects young adults in the prime of life, between 15 and 40 years of age. The majority of people with MS start out with a relapsing-remitting form of the disease. However, after a number of years their MS often develops into a more progressive form. 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 tackling the life issues that people with MS are dealing with on an ongoing basis.

The Health Research Review 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 behavioural issues (health education, health promotion sociology and communications). Rather than investigating the cause of MS, health-related research measures the impact of MS on all aspects of health and strives to improve the quality of life for people living with the disease.

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.

Helen Tremlett, PhD, and Joël Oger, MD
University of British Columbia
\$70,360 (April 1/04-March 31/06)

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

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

Because people with MS frequently use multiple medications, they will investigate the risk of liver toxicity from combining different medicines with beta interferon. They will also assess how often people with MS, not taking beta interferon, show abnormal liver test results. A new aspect will be whether the existence of other diseases also increases the likelihood of abnormal liver tests in people with MS. Finally, the researchers plan to monitor how long-term use (over three years) of beta interferon affects disability in people with MS.

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

Daria Trojan, MD
McGill University
\$261,360 (April 1/02 – 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 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 controlling wakefulness) and surrounding areas.

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



Collaboration delivers results

Multiple Sclerosis Scientific Research Foundation Research Grants

The MS Scientific Research Foundation was established in 1973 with an initial investment of \$1,000. Over the years with funding from the MS Society of Canada, the Foundation has become the largest endowment in the world dedicated strictly to MS research. The Foundation supports large cooperative, multi-disciplinary research projects beyond the scope of the MS Society of Canada's regular granting program and to plan for and fund future needs and opportunities. It also funds small pilot research projects which allow investigators to pursue new innovative approaches to MS research where there is insufficient data for them to apply to the regular grants program. Currently, the MS Scientific Research Foundation is funding four flagship collaborative research initiatives.

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.

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

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

Principal Investigators

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

Co-Investigator

Neil Risch, PhD, Stanford University, California

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

Co-Investigator

Neil Risch, PhD, Stanford University, California

Multiple sclerosis is not an inherited disease, but it does tend to occur more often in families where other members are affected. Women are more than twice as likely to develop MS as men. Although symptoms vary greatly, even between identical twins,

more and more research shows that families may share common genes (the particular units of DNA that control an individual's development) making family members more likely to get MS.

Much of the information acquired from genetic studies is obtained by looking at special groups of people, like twins, siblings, half-siblings and adoptees. The knowledge gained from genetic research is absolutely essential for designing new therapies to control susceptibility genes in people with MS.

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 21,000 people with MS registered at 18 MS clinics across Canada.

Phase III of the 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.

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

The Canadian collaborative genetic susceptibility study has confirmed that MS is a complex disease. Several genes are involved in causing MS and often interact with each other. Environmental factors are also important and act at a population level

to strongly influence whether people who are genetically susceptible will develop MS.

The study has provided a number of important insights from Phases I 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.

Phase IV will build on the findings from the first three phases while pursuing increasingly practical applications, specifically:

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

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.

Mission of the Multiple Sclerosis Society of Canada

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

Prospective Study of the Clinical Epidemiology, Pathobiology and Neuroimaging Features of Canadian Children with Clinically Isolated Demyelinating Syndromes

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

Principal Investigators

Dr. Brenda Banwell, MD, Hospital for Sick Children, Toronto

Dr. Douglas Arnold, MD, Montreal Neurological Institute, Montreal

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

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

This ground-breaking Canadian study will examine children who have experienced an initial attack suggestive of MS, also known as clinically isolated syndrome (CIS). It is a five-year, prospective paediatric multiple sclerosis (MS) study with 22 Canadian centres participating in 17 cities, including: Victoria, Vancouver, Edmonton, Calgary, Saskatoon, Winnipeg, London, Hamilton, Windsor, Toronto, Kingston, Ottawa, Sherbrooke, Montreal, Saint John, Halifax and St. John's. Paediatric CIS has never before been examined in detail. This study is now possible through the development of the Paediatric Demyelinating Disease Network, an extensive Canada-wide network of physicians and scientists.

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

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

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

1) Clinical and genetic epidemiology

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

2) Pathobiology

- By defining the earliest immunological events that occur at the time of the first attack (CIS), investigators will strive to identify both the triggers and initial targets of the immune cell response.

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

3) Neuroimaging

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

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



Programs to Attract New Scientific Talent

Dr. Donald Paty Career Development Awards

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

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

Total approved for Awards: \$ 750,000

Dr. Amit Bar-Or
Montreal Neurological Institute
Category: Immunology
Renewal: \$50,000 for each of three years
beginning July 1, 2004

Dr. Paula Foster
Robarts Research Institute, London ON
Category: MRI techniques
New: \$50,000 for each of three years
beginning July 1, 2004

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

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

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

Postdoctoral Fellowships

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

Total approved for Postdoctoral Fellowships:
\$594,500

Andréanne Bédard, PhD
CHUL Research Centre, Quebec City
Supervisor: Dr. Luc Vallières
New: \$39,000

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

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

Julie Fotheringham, PhD
National Institutes of Health (Bethesda, Md., USA)
Supervisor: Dr. Stephen Jacobson
New: \$39,000

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

Isaias Glezer, PhD
CHUL Research Centre, Quebec City
Supervisor: Dr. Serge Rivest
New: \$39,000

Yanping Gong, PhD
Hospital for Sick Children, Toronto
Supervisor: Dr. Joan Boggs
Renewal: \$39,000

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

Daniel Larocque, PhD
University of California at Los Angeles
Supervisor: Dr. Pedro Lowenstein
New: \$39,000

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

Tiona Todoruk, PhD
University of Calgary
Supervisor: Dr. Wee Yong
New: \$39,000

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

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

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

Rana Zabad, MD
University of Calgary
Supervisors: Dr. Luanne Metz and Dr. Wee Yong
Renewal: \$48,500

Research Studentships

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

Total approved for Studentships: \$534,666

Joseph Antony
Location: University of Calgary
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Renewal: \$20,000

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Renewal: \$20,000

Jennifer Berard
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Supervisor: Dr. Samuel David
New: \$18,000

Thor Bjarnason
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Renewal: \$18,000

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Renewal: \$20,000

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New: \$20,000

Carol Anne Chénard
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Renewal: \$18,000

Qiaoling Cui
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Supervisor: Dr. Guillermina Almazan
Renewal: \$20,000

Angelika Goncalvez DaSilva
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New: \$20,000

Gabriel DeLuca
University of Oxford
Supervisor: Dr. George Ebers
Renewal: \$6,666

Nancy Dionne
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Renewal: \$20,000

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Supervisor: Dr. David Haegart
Renewal: \$18,000

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

Igal Ifergan
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Renewal: \$20,000

Carolyn Jack
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Andrew Jarjour
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Peter Larsen
University of Calgary
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Renewal: \$20,000

Matthew Lincoln
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Kenneth Liu
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Renewal: \$20,000

Gregory Mayer
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Renewal: \$20,000

Jason Millward
Montreal Neurological Institute
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Renewal: \$20,000

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

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

Leah Remington
McGill University
Supervisor: Dr. Trevor Owens
New: \$18,000

Henrik Toft-Hansen
Montreal Neurological Institute
Supervisor: Dr. Trevor Owens
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.

- **Lenora Brown, PhD and Luanne Metz, MD**, University of Calgary
Health Research – A preliminary investigation of an outcome measurement in MS
\$22,582 – June 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 – March 2003
- **Anne Cranney, MD**, Queen's University
Health Research – The effect of MS on bone mass
\$34,976 – January 2003
- **Jean-Françoise Gauchat, PhD**, University of Montreal
Biomedical Research – Cardiotrophin-like cytokine in experimental autoimmune encephalitis
\$34,998 – February 2003
- **Bradley Goodyear, PhD**, University of Calgary
Biomedical Research – MRI techniques to assess cognition in MS
\$34,987 – September 2003
- **Paul O'Connor, MD and Farzin Forooghian, MD**, St. Michael's Hospital and University of Toronto
Biomedical Research – Autoimmune retinopathy in MS – a pilot study
\$33,600 – September 2003
- **Paul O'Connor, MD and Melanie Ursell**, St. Michael's Hospital, Toronto
Biomedical Research – A phase 1 dose escalation study of Vitamin D3 with calcium supplementation in patients with MS
\$35,000 – Start date: May 2004
- **George Robertson, PhD**, Dalhousie University
Biomedical Research – Therapeutic assessment of a non-emetic PDE4 inhibitor in an EAE model
\$34,630 – June 2003
- **Dessa Sadovnick, PhD, and George Ebers, MD**, University of British Columbia and University of Oxford
Health Research – Vitamin D status in MS patients and their families
\$30,000 – June 2003

Glossary 2004

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

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

Angiogenesis - The formation of new blood vessels.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Magnetic resonance imaging (MRI) - A technological tool that detects energy released from hydrogen atoms to create anatomical images. MR images of soft tissues of the body including the brain and

spinal cord clearly show MS lesions and may be used to track disease progress.

Magnetic resonance spectroscopy (MRS)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Our Mission

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

MS Research Summaries 2004

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in the MS Research section
under Current Research Projects.

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