



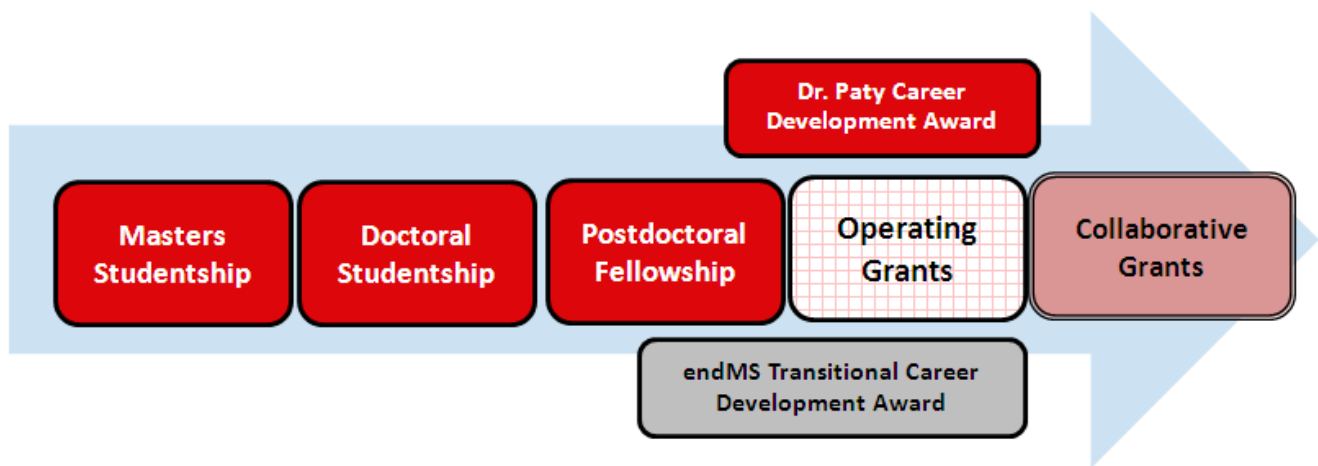
MS Research Summaries 2013

The Multiple Sclerosis Society of Canada is proud to be a leading supporter of groundbreaking MS research around the world. Through generous contributions from individual donors, corporate sponsors, and fundraising events, this year the MS Society committed over \$6 million to fund nearly 70 new projects in areas of top research priority. In addition, the Multiple Sclerosis Scientific Research Foundation (MSSRF) – one of the world’s largest funding bodies dedicated to MS research – continues to support larger, multi-centre collaborative studies so essential to understanding and treating MS. The central goal of the MS Society research program is to stimulate innovative research that will examine important questions about MS, while fostering education and training for the next generation of bright minds.

The MS Society recognizes its responsibility to invest in research of the highest quality. Thus, all grant applications undergo a stringent review process in which researchers, clinicians, and representatives from the community come together and carefully appraise the scientific merit and clinical impact of each research study. Applications are then scored and ranked which determines their status of funding.

The MS Society and MSSRF are determined to support research that will provide the greatest benefit to individuals who are deeply affected by MS. Each year the organization is hopeful that its commitment to research will bring the MS community one step closer to finding a cure for this perplexing and debilitating disease.

MS Society Research Program



- Personnel Awards
- endMS National Personnel Awards
- Operating Grants
- Multiple Sclerosis Scientific Research Foundation

The breadth of the MS Society research program is cultivating a network of exceptional MS researchers. The pictorial above captures the different awards and grants which are administered through the MS Society's Annual Research Grants competition. The arrow signifies progression from academic training to independent research, and the grants and awards which follow the spectrum are tailored to support the needs of researchers at each stage.

Defining our grants and awards:

Studentship Awards: Offered to students/young trainees who are interested in pursuing graduate work in MS. Funding from this program will foster ongoing academic and laboratory training, while broadening the awardee's scientific understanding of MS. There are two types of Studentship Awards:

Doctoral Studentship - for students enrolled in a PhD program

Masters Studentship - for students enrolled in a M.Sc. program

Postdoctoral Fellowship: Intended to retain researchers in the field of MS who hold a doctoral degree. This award will provide fellows with new opportunities for research training, and the necessary funding to conduct work in their area of interest

Operating Grant: Awarded to researchers from Canadian institutions who are interested in looking at the biomedical and clinical aspects of MS. This grant will provide funding for lab operations and critical experiments

Dr. Donald Paty Career Development Award: Named in honor of a pioneering Canadian MS researcher, supports the salary of young faculty members who also conduct research in MS

endMS Transitional Career Development (TCD) Award: Supports trainees who are nearing the completion of their postdoctoral fellowship and are entering their first years as independent researchers

Collaborative Grant: Designed to support high-level projects involving collaboration among multiple institutions and researchers

Progression and Therapies

The advent of oral therapies has dramatically changed the landscape of MS treatment over the last decade. Many Canadian researchers funded by the MS Society contributed to the development of these and other MS therapies and continue to do so as new biological targets are discovered and tested in clinical trials. This year the MS Society approved funding for 21 studies, which will:

- Evaluate current and emerging therapies for MS
- Develop more accurate ways of detecting signs of MS in the central nervous system, arriving at a definitive diagnosis, and tracking progression of MS disease over time
- Test current therapies on new animal and cell models that exhibit characteristics of MS

Recipients – Operating Grants

Dr. Douglas Arnold, M.D., Ph.D.

McGill University

Award: Operating Grant

Funding: \$178,606

Term: April 1, 2013 – March 31, 2015

Imaging inflammation in Multiple Sclerosis

Active multiple sclerosis (MS) lesions have leaky blood vessels that allow inflammatory cells to enter the brain. They also allow agents that are able to identify lesions in the brain on an MRI scan to cross into the brain. The use of stronger MRI machines and special techniques can help identify a greater number of active lesions. However, this increased sensitivity may show that current drugs do not eliminate lesion formation, but only

partially suppress inflammation in lesions that continue to form. We have developed MRI methods to measure this. The results of this project would improve our understanding of how new lesions on MRI are affected by drugs, and allow us to determine how best to use MRI to evaluate the effects of new therapies.

Dr. Denis Gris, Ph.D.

Université de Sherbrooke

Award: Operating Grant

Funding: \$293,061

Term: April 1, 2013 – March 31, 2016

Nlrp12 inhibits inflammation during Multiple Sclerosis (MS)

Canada is known for having one of the highest rates of multiple sclerosis (MS) in the world. Disturbance of the regulation of the immune system is the turning point in development and progression of MS. For this reason, regulating inflammation is a central objective when developing therapeutic strategies to treat MS. A recently discovered protein, called Nlrp12, has shown to inhibit immune responses. Objective of this study is to investigate a role of Nlrp12 in the pathology of MS through use of genetically modified mice, which lack Nlrp12. Our preliminary data shows that these mice are more prone to MS, suggesting that Nlrp12 may be a potential target gene for novel therapies. Conclusions drawn from the work described in this proposal will advance our understanding of progression and development of MS.

Dr. Pere Santamaria, M.D., Ph.D.

University of Calgary

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Peptide-MHC class II-coated nanoparticles for the treatment of central nervous system autoimmunity

Traditionally, vaccines have been used to protect against viruses, bacteria or cancer, or to delete white blood cells capable of causing autoimmune diseases like diabetes, multiple sclerosis (MS) and others. We have developed a 'vaccine' that can blunt autoimmune responses by producing cells called 'autoregulatory' white blood cells. These constitute a new type of 'autoreactive' white blood cells whose function is to put the brakes on the disease-causing autoimmune attack. These cells become activated when they sense an attack on central nervous system. Our vaccine can lead to the production of this population of white blood cells, enhancing their disease-counteracting effects. This vaccine can blunt autoimmune responses without causing generalized suppression of the immune system, a long sought-after goal. Here, we will test the ability of such 'nanovaccines' in pre-clinical models of MS, as an essential step towards human clinical trials.

Dr. Alain Simard, Ph.D.

Université de Moncton

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Cholinergic control of monocyte differentiation, function and recruitment to the CNS

Inflammation is involved in the development of many diseases, including multiple sclerosis (MS). To develop new and more efficient treatments for these disorders, it is important to gain insights into how the body naturally controls inflammation. Acetylcholine is a molecule used by nerve cells to communicate with each other, while Nicotine is a component of tobacco smoke that is known to act in the same way as Acetylcholine. We and others have made the novel and surprising observation that Acetylcholine and Nicotine, but not tobacco smoke, have protective effects in a mice affected with MS-like disease. This project's objective is to determine how inflammatory processes are affected by Acetylcholine and Nicotine. More specifically, we will study the effects of Nicotine on monocyte production and function, which are immune cells that play an important role in MS development, but are also important for recovery from disease. Finally, we will determine if Acetylcholine and Nicotine can modify the recruitment of monocytes to the central nervous system.

** This award is funded in partnership by the MS Society of Canada and the New Brunswick Health Research Foundation (NBHRF).*

Dr. Alan Wilman, Ph.D.

University of Alberta

Award: Operating Grant

Funding: \$288,219

Term: April 1, 2013 – March 31, 2016

MRI measurements of grey matter in progressive Multiple Sclerosis

MRI is often used to diagnose multiple sclerosis (MS) and monitor any changes. In the clinic, MRI is used to track lesions or tissue scarring that can occur in different areas of the brain and at different times. However lesion measurements have been shown to not be effective predictors of patient clinical status. Our goal is to use new MRI methods that we have developed using a triple-strength MRI machine to study important deep brain structures rather than just lesions. We will test the MRI methods in progressive MS and healthy subjects to determine if MRI changes relate to changes in measured clinical symptoms. We will then apply the best methods on a standard clinical MRI as well. Our ultimate goal is to make clinical MRI more useful for individual MS patients by providing measures that are much more specific to disease state than the standard MRI tests.

Dr. Robin Yates, Ph.D.

University of Calgary

Award: Operating Grant
Funding: \$293,358
Term: April 1, 2013 – March 31, 2016

Exploring the mechanisms of myelin antigen processing within the endosomal systems of macrophages and dendritic cells

Multiple sclerosis (MS) is a disease in which immune cells mistakenly react to the self-proteins present in the myelin sheath of nerves, resulting in neurologic impairment. While T-cells in particular trigger the inflammation seen in the disease, it is another group of immune cells called antigen presenting cells (APCs) that engulf myelin debris which play a role in initiating T-cell activity in the first place. APCs engulf these proteins and digest them in compartments within the cell called phagosomes and endosomes. Some of the protein fragments resulting from this digestion are then used to activate T-cells, causing them to target and destroy myelin. We have exciting new evidence that the chemical reactions in phagosomes and endosomes can alter protein digestion, and this is critical to determining whether the disease-causing T-cells will become turned on. The research we are proposing will investigate the mechanisms behind this “reprogramming” of protein digestion. By modifying the way APCs digest protein, but not stopping it altogether, it may eventually be possible control MS disease while maintaining beneficial immune responses.

Dr. Shannon Dunn, Ph.D.

University Health Network
Award: Operating Grant
Funding: \$285,000
Term: April 1, 2012 – March 31, 2015

PPARdelta as a regulator of EAE progression

Currently, there are few treatments available to help people with primary or secondary progressive multiple sclerosis (MS). In regards to these forms of MS, what we do know is that for some reason patients are losing neurons in their brain. This neuron loss has been shown to associate with the activity of a group of cells called “microglia” in the brain. Through our research, we have identified a gene, called PPARdelta, which makes microglia less inflammatory and thus less able to damage nerves. We believe that increasing the activity of this gene may be one way of treating progressive MS. In our grant, we explore this possibility by using a number of approaches to increase the activity of this gene and examining the effects of these treatments in a common animal model which mimics MS disease. Another possible reason that we do not have great drugs for progressive MS is that new drugs are often screened in animal models that resemble the relapsing-remitting course of MS. In this proposal, we are also trying to investigate a possible new mouse model that may be more appropriate for screening drugs for progressive MS.

Dr. Stephen Kerfoot, Ph.D.

The University of Western Ontario
Award: Operating Grant

Funding: \$271,950

Term: April 1, 2012 – March 31, 2015

Characterization of the pathogenic mechanisms and potential as therapeutic targets of antigen-experienced B cells in chronic central nervous system autoimmunity

Recent multiple sclerosis clinical trials involving therapies targeting B cells clearly demonstrated the critical role that these cells play in driving disease. The mechanism by which they do this remains unknown. Following activation, B cells have the potential to form into different subsets, each capable of contributing to disease in different ways. Studies in a specific subset of B cells called “memory” B cells are at the cutting edge of B cell biology. However, these studies have not yet revealed the role of B cells in autoimmune diseases. Here, I propose a series of studies to identify how subsets of B cells contribute to MS. We employ different experiments which track B cells involved in autoimmune responses, and determine their specific characteristics. Finally, we will test the effects of different current B cell-targeting therapies.

Dr. Fang Liu, M.D., Ph.D.

Centre for Addiction and Mental Health

Award: Operating Grant

Funding: \$285,000.00

Term: April 1, 2012 – March 31, 2015

Novel therapeutics targeting protein-protein interactions for Multiple Sclerosis

Treatments for multiple sclerosis (MS) need improvement, since current approaches offer incomplete symptom control and do not substantially alter disease outcomes. Most research into MS has focused on the immune system and current treatments are primarily focused on suppressing immunological function to reduce the severity of MS. We wish to investigate a new approach to treating MS, involving an emerging technique that uses a small peptide (protein fragment) that interferes with the binding of two other proteins. One of these proteins is associated with a compound known as glutamate. Glutamate is known to be involved in cell death in many different contexts and diseases. Glutamate toxicity may be killing nerve cells in MS, and our peptide seems to be able to block this in our preliminary experiments with animal models which mimic MS disease. Our preliminary experiments also show that our peptide can prevent the progression of paralysis in conjunction with protecting neurons and other spinal cord cells from damage. We propose to confirm and expand on these promising early results, with the hope of generating enough evidence to eventually test this treatment in the clinic.

Alex Mackay, DPhil.

The University of British Columbia

Award: Operating Grant

Funding: \$277,312.35

Term: April 1, 2012 – March 31, 2015

Anatomical and functional MRI correlates of cognitive dysfunction in Multiple Sclerosis

Cognitive impairment (CI) affects between 45 and 65% of people with multiple sclerosis (MS), and has a significant impact on quality of life in terms of activities of daily living, socialization, and ability to remain in the workplace. Although MS lesions can appear in any part of the brain, the types of CI seen in MS are similar for different people. Therefore, we believe that the integrity of complete brain networks is required for normal brain function. MS lesions occurring anywhere along a network can cause it to become dysfunctional. Neuropsychological assessment of MS subjects is lengthy and often unavailable during routine clinical visits. Using magnetic resonance (MR) imaging, we will apply two new techniques to look at brain networks and compare the results seen on an imaging scan to those from cognitive tests. If this study is successful, these MR techniques will not only identify MS subjects more at risk for developing CI but also enable assessment of the effects of disease-modifying therapies.

Dr. Christopher Power, M.D., FRCPC

University of Alberta

Award: Operating Grant

Funding: \$285,000

Term: April 1, 2012 – March 31, 2015

The inflammasome and its regulation by neurosteroids in Multiple Sclerosis

Inflammation is an important contributor of diseases in brain diseases such as multiple sclerosis (MS). The basic workings of brain inflammation are currently unclear although we have recently reported that certain steroids synthesized within the brain (neurosteroids) protect brain cells by reducing inflammation. Herein, we will investigate the role of the brain's inflammatory components, termed the inflammasome, in MS together with the effects of neurosteroids on brain inflammation. A combined approach will be used in which clinical samples, an animal model which mimics MS disease, and the actions of neurosteroids will be investigated in our laboratories. We expect that different aspects of the brain's inflammation components will be regulated by specific neurosteroids, leading to new preventative and/or treatment options for MS.

Dr. George Robertson, Ph.D.

Dalhousie University

Award: Operating Grant

Funding: \$255,739.05

Term: April 1, 2011 – March 31, 2014

Apoptotic regulation of B cell activity in experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is an animal model that, like in multiple sclerosis (MS), is characterized by paralysis resulting from destruction of the myelin sheath. The myelin sheath surrounds the electrically conductive branch of a nerve cell called the axon. Loss of myelin therefore interferes with communication between nerve cells in the brain resulting in a range of symptoms in EAE and MS. In both cases, damaging to myelin is driven by white blood cells known as T cells. Accumulating evidence indicates that T cells and other immune cells responsible for demyelination are resistant to signals which cause them to die. The purpose of the present proposal is to further investigate this resistance. This work will determine if drugs that control signals that govern death of immune cells may have benefit in the treatment of MS.

Recipients – Personnel Awards

Dr. Hilda De Jong

The University of British Columbia

Supervisor: Dr. Helen Tremlett

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

New indications for old drugs: Do statins, angiotensin converting enzyme inhibitors or proton pump inhibitors impact long-term disease progression in Multiple Sclerosis?

Dr. Jennifer Hahn

University of Calgary

Supervisor: Dr. V. Wee Yong

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Regulation of monocyte-induced neuroinflammation and neuropathology in Multiple Sclerosis by EMMPRIN

Dr. Coral-Ann Lewis

The University of British Columbia

Supervisor: Dr. Fabio Rossi

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Investigation into pathogenic gene expression by blood monocytes during the development of Multiple Sclerosis

Dr. Erin MacMillan

The University of British Columbia

Supervisor: Dr. Anthony Traboulsee

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Detecting MRI-invisible alterations in protein metabolism via magnetic resonance spectroscopy of amide protons

Dr. Mukanthu Nyirenda

Montreal Neurological Institute

Supervisor: Dr. Amit Bar-Or

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Immune responses to novel CNS antigens in pediatric Multiple Sclerosis: defining earliest disease targets

Dr. Chao Wang

Brigham and Women's Hospital

Supervisor: Dr. Vijay Kuchroo

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

The role of PROCR on TH17 cell pathogenicity in autoimmunity

** Recipient of the Asad Wali MS Society of Canada Postdoctoral Fellowship Award*

Dr. Dalia Rotstein

Supervised by Dr. Tanuja Chitnis

Brigham and Women's Hospital

Award: Postdoctoral Fellowship

Funding: \$48,500

Term: July 1, 2013-June 30, 2014

Predictors of treatment response in Multiple Sclerosis patients

Khalil Rawji

University of Calgary

Supervisor: Dr. V. Wee Yong

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Dissecting the beneficial and detrimental roles of macrophages and microglia in remyelination using the lysolecithin demyelination model

** Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Curtis Benson

University of Alberta

Supervisor: Dr. Bradley Kerr

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

The effects of phenelzine and its derivative on motor and non-motor symptoms in experimental autoimmune encephalomyelitis (EAE)

Yu-Hsuan Huang

The University of British Columbia

Supervisor: Dr. Rusung Tan

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

The role of SAP signaling in EAE

**Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Magdalena Lysenko

York University

Supervisor: Dr. Christine Till

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Using functional magnetic resonance imaging to examine greater cerebral activation owing to potential compensatory mechanisms during Go/No-go task in patients with multiple sclerosis

** Recipient of the Brandt Group of Companies MS Society of Canada Doctoral Studentship Award*

Nabeela Nathoo

University of Calgary

Supervisor: Dr. V. Wee Yong

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Characterizing susceptibility weighted imaging in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis

** Recipient of the Sherritt International Corporation MS Society of Canada Doctoral Studentship Award*

Nicolas Guizard

McGill University

Supervisor: Dr. Donald Collins

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Brain atrophy quantification and trajectory in Multiple Sclerosis patients

Jean-François Richard

Université Laval

Supervisor : by Dr. Luc Vallières

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

IL-6-dependent leukocyte recruitment in a model of Multiple Sclerosis

Li-Chun Wang

McGill University

Supervisor: Dr. Guillermina Almazan

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Role of Cdo in p38alpha/beta MAPK regulation of oligodendrocytes differentiation and myelination

Nerve Damage and Repair

Funding from the MS Society will support 19 new studies that will seek information on how myelin is degraded and rebuilt in MS. Myelin is a protective layer that surrounds nerve fibers, termed axons, in the central nervous system. Myelin serves as an insulator, allowing axons to send chemical signals with rapid speed.

In MS, cells of the immune system mistakenly recognize and attack the body's own myelin. As a result, axons become exposed and vulnerable to damage. Knowing this process in detail is an objective of many researchers whose work is funded by the MS Society. The ultimate goal is to develop therapies that can stop abnormal immune cells in their tracks and lessen or prevent their harmful effects on myelin.

Along with understanding how myelin is affected in MS, it is equally important to explore the potential for myelin repair, which recent evidence suggests is possible in people who have MS. The capacity for myelin repair offers hope that eventually therapies can be created to stimulate the repair process and ultimately restore neurological function in the body.

New and currently funded studies in nerve damage and repair will focus on:

- Protecting myelin and the nerve cells it surrounds
- Preventing further nervous system degeneration
- Promoting remyelination

Recipients – Operating Grants

Dr. Jack Antel, M.D.

McGill University

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013- March 31, 2016

Role of microglia in neuroinflammation

Myeloid cells are cells of the immune system that are found in brain and spinal cord lesions in multiple sclerosis (MS). There are two types of myeloid cells in the brain: 1) microglia which make up the tissue during development and, 2) macrophages which are found around blood vessels under normal conditions, but move to sites of inflammation. Our overall objective is to determine how microglia and macrophages are involved in tissue injury and repair in MS. We hypothesize that small molecules called ‘microRNAs’ can help to determine how myeloid cells behave. We will use human tissue from the central nervous system to identify specific microRNAs associated with each myeloid cell type. We will then establish their functional role and determine whether therapeutic agents used by MS patients target these functions.

Dr. Alyson Fournier, Ph.D.

Montréal Neurological Institute, McGill University

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Immune cell influences on neuronal viability and repair

Multiple sclerosis (MS) is characterized by damage to nerve cells, which disrupts communication within the central nervous system. Sustained neurological disability results from this damage and the failure of nerve cells to repair themselves. The environment in the MS brain is not permissive for nerve cell repair. The aim of this grant is to better understand the signals that limit repair and to use this information to develop molecular therapeutics to promote nerve cell repair. The use of therapeutics to promote nerve cell repair in combination with current therapies targeting immune system dysfunction will lead to improved outcomes for MS patients.

Dr. Mojgan Hodaie, M.D, FRCS(C)

University Health Network

Award: Operating Grant

Funding: \$295,302

Term: April 1, 2013 – March 31, 2016

Neuroimaging correlates of pain in Multiple Sclerosis

A large proportion of multiple sclerosis (MS) patients suffer from pain associated with their disease. *Trigeminal neuralgia* is one of the most severe forms of neuropathic pain and affects MS patients more frequently. Severe neuropathic pain increases disability and worsens patients' quality of life. Detailed anatomical assessment of the trigeminal nerve fibers responsible for facial pain sensation and correlation with the clinical presentation of pain has not been possible primarily due to limitations in imaging technology. We have made important advances in techniques that allow us to identify cues for pain on MRI in MS patients. With this new MRI technology, we are able to image in detail the fibers of the trigeminal nerve extending into the brainstem, and measure the integrity of fiber microstructure. These novel imaging modalities allow us to gain important measures of axon and myelin damage and in turn, help us understand how we can best treat pain and decrease disability in MS.

Dr. Jacqueline Quandt, Ph.D.

The University of British Columbia

Award: Operating Grant

Funding: \$293,559

Term: April 1, 2013 – March 31, 2016

Modulation of neuroprotective pathways in models of Multiple Sclerosis

Therapies which limit the damaging properties of immune cells and also directly protect cells of the nervous system have the greatest promise in treating multiple sclerosis (MS) and preventing disease progression. We have recently identified a family of proteins important for the survival of neurons in the brain. Our studies will use several tools to characterize how these proteins contribute to the disease process in MS. We aim to identify which immune cells or other factors regulate these “neuroprotective” proteins, and explore how bolstering their presence with novel therapies may limit disease progression and disability for those living with MS.

Dr. Wolfram Tetzlaff, Ph.D.

The University of British Columbia, Vancouver

Award: Operating Grant

Funding: \$299,907

Term: April 1, 2013 – March 31, 2016)

Targeting oligodendrocyte maturation for the study of remyelination

Loss of myelin (demyelination) is a hallmark of multiple sclerosis (MS) and understanding the mechanisms of myelin repair (remyelination) is a major focus in MS research. Here we use a genetic approach that allows us to specifically interfere with the maturation of the myelin forming oligodendrocyte precursor cells (OPCs) and measure axon survival in the absence of myelin. This will allow us to address the longstanding question whether

demyelination is a direct mediator of axon death and how long axons can survive without myelin. A variation of this novel model also allows us to visualize directly the generation of new myelin-forming cells (oligodendrocytes) and newly formed myelin sheaths in the injured or normal adult brain. Importantly this will capture new myelin formation in an animal model that exhibits MS-like disease. Thus, we can now address many burning questions in the field, like the normal turnover of myelin in the brain, the morphology of new versus old myelin, functional role of demyelination and the distribution of remyelination in a diseased brain. Last not least it will provide a novel method to conveniently assess therapeutic remyelination strategies in tissue sections as well as in living animals.

Dr. V. Wee Yong, Ph.D.

Award: Operating Grant

University of Calgary

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Chondroitin sulfate proteoglycans (CSPGs) as inhibitors of remyelination in MS

In multiple sclerosis (MS), cells known as oligodendrocytes are formed in lesions in an attempt to promote the repair of myelin (remyelination). However, the process is inadequate in most patients. We have discovered that one cause of remyelination failure is the presence of compounds known as chondroitin sulfate proteoglycans (CSPGs) in MS lesions. We seek now to identify precisely how the CSPGs are preventing oligodendrocyte activity and remyelination, and we have designed and synthesized two new compounds to overcome CSPGs. We will test these compounds in an animal model which resembles MS disease in order to determine if these compounds can block activity of CSPGs leading to myelin repair. We will also run experiments in the animal model to determine if this particular approach can restore deficits that result from the demyelination. Our experiments seek to promote remyelination in MS to improve the prognosis of the disease.

Dr. Yunyan Zhang, M.D., Ph.D

University of Calgary

Award: Operating Grant

Funding: 180,069

Term: April 1, 2013 – March 31, 2015

MRI texture analysis of remyelination in MS: Development of an imaging outcome

Magnetic resonance imaging has become an important tool to evaluate multiple sclerosis (MS), but we still have no way of accurately measuring remyelination, a critical repair process in MS. In this project, I aim to develop a specific indicator of remyelination that can be measured using MRI. Ultimately the goal is to use this measure in clinical trials, based on advanced analysis of MRI images acquired during routine patient care. This research should help accelerate the discovery of repair medicines for MS patients, ultimately to help them regain lost function and slow the progression of disability.

Dr. Guillermina Almazan, PhD.

McGill University

Award: Operating Grant

Funding: \$286,214.80

Term: April 1, 2012 – March 31, 2015)

Trophic signaling in oligodendrocytes: role of insulin-like growth factor 1 in myelination

A major objective in this proposal is to evaluate the roles of the growth hormone Insulin-like growth factor 1 (IGF-1) in the production and activity of myelin-producing oligodendrocyte cells. Our hypothesis is that targeting molecules that associate with IGF-1 may help in the development of therapeutic strategies to prevent oligodendrocyte death and improve remyelination in multiple sclerosis (MS). To start testing this hypothesis, we will pharmacologically target two molecules in particular: PTEN and SHIP2, to assess their role in formation of myelin.

Dr. Jack Antel, M.D.

McGill University

Award: Operating Grant

Funding: \$189,300

Term: April 1, 2012-March 31, 2014

Cellular immune injury of human oligodendrocytes

The neurologic deficits in multiple sclerosis (MS) are a consequence of injury and loss of myelin and its cell of origin in the central nervous system - the oligodendrocyte (OL). Examination of MS lesions indicates that OL injury may result from several different causes. Our work observes OLs isolated from adult human CNS tissue (not from MS patients) to study how these cells may be injured through various mechanisms. One suggested mechanism implicates inflammatory cells (lymphocytes), as are found in MS lesions, are causing injury to OLs. In our 1st aim we will identify the basis whereby such injury occurs. A 2nd postulated mechanism is the OLs within MS lesions are subject to metabolic insults i.e. their environment deprives them of adequate nutrients and energy. In our 2nd aim, we will identify the properties of OLs that make them vulnerable or resistant to such insults and seek means that could potentially be used to protect the cells. In our 3rd aim we will examine whether the cells which produce OLs and are primarily responsible for remyelination, known as progenitor cells, are more or less vulnerable to the same insults as OLs, providing an explanation why repair may be limited in MS.

Dr. Steffany Bennett, Ph.D.

University of Ottawa

Award: Operating Grant

Funding: \$192,365.50

Term: April 1, 2011 – March 31, 2014

Connexin-mediated control of remyelination

Successful treatment of multiple sclerosis must involve therapy designed not only to limit the extent of brain cell destruction but also to stimulate repopulation of damaged cells. Cell-replacement strategies are key to achieving this goal. The mammalian adult brain, once thought to be composed of cells that no longer divide, is now recognized to contain a certain number of stem cells with bear the capacity to reproduce exact copies of themselves (a process known as self-renewal) as well as the ability to form into functional brain cells. To realize the therapeutic potential of these cells, stem cells must be able to survive in injured tissue, respond to signals that promote growth, and then stop dividing once a normal cell number has been attained. Our research is designed to study functional brain repair in multiple sclerosis. Specifically, by using a unique combination of phytochemical (plant chemistry), genetic (mouse models of human disease), and molecular approaches in cells and animals, we aim to show:

- (a) That changing how stem cells communicate with adjacent cells in adult brain can be used to enhance myelin repair, and
- (b) That compounds found in specific plants can be identified and used to target this type of communication and speed up the replacement of healthy cells in the brain

Dr. Tim Kennedy, Ph.D.

McGill University

Award: Operating Grant

Funding: \$327,812.70

Term: April 1, 2011 – March 31, 2014

Netrin regulation of axonal-oligodendroglial interactions: novel mechanisms and molecular targets

We aim to identify and characterize a new biological pathway that regulates the formation and stability of myelin. We have reported that oligodendrocytes in the healthy adult brain produce proteins called netrins. Netrins are known to be absolutely essential for normal brain development, but why they are made by oligodendrocytes in the mature brain is not clear. Using cell culture studies, we have recently obtained evidence that netrins promote the growth of oligodendrocytes and the stability of the connections made between oligodendrocytes and axons, the nerve fibers which send chemical impulses within the nervous system. Using mouse models we have demonstrated that netrins are essential to maintain normal myelin in the living brain. We will continue to do similar experiments to determine whether this effect is seen for various proteins in the netrin family. Our studies aim to better understand how myelin is generated and maintained, with the ultimate goal of finding ways to promote remyelination by identifying novel therapeutic targets for multiple sclerosis.

Dr. Rashmi Kothary, Ph.D.

Ottawa Health Research Institute

Award: Operating Grant

Amount: \$360,240

Term: April 1, 2011 – March 31, 2014

Cell extrinsic mechanisms in oligodendrocyte biology and CNS myelination – the role of the integrin pathway

Multiple sclerosis (MS) is a disease in which the insulation around the nerves, known as myelin, is damaged by the immune system, resulting in loss of muscle control and partial paralysis. The cell type that produces the myelin sheath (analogous to a jelly roll) around the nerve fibers is called the oligodendrocyte. This cell has to undergo morphological changes prior to being able to wrap around the nerve fibers. Our research is directed towards understanding the molecular mechanisms involved in the steps leading to the morphological changes. We study proteins called integrins which reside at the surface of the oligodendrocytes. These proteins serve as important mediators of communication between oligodendrocytes and their surrounding environment. Such communications will dictate when and how the oligodendrocyte will properly wrap around the nerve fibers. An important compound in the communication cascade is called the integrin linked kinase (ILK). Our goal is to determine the role that ILK plays in myelin formation. This is an important first step towards the development of better treatments for disorders in which this process is aberrant, such as in MS.

Dr. Wayne Moore, M.D., CM, FRCPC, RCPsych.

The University of British Columbia

Award: Operating Grant

Funding: \$283,760.40

Term: April 1, 2012 – March 31, 2015

The pathologic basis of magnetic resonance imaging in Multiple Sclerosis

This project seeks to determine the changes in the brain responsible for the findings seen with magnetic resonance imaging (MRI) of multiple sclerosis (MS), a disorder characterized by loss of the insulating layer (myelin) around the electrical cables (axons) of the brain and spinal cord. On an MRI image one is able to see regions of damage termed plaques, which show complete loss of myelin and some loss of axons. Some regions outside plaques appear normal on routine MRI scans, and are therefore termed normal-appearing white matter (NAWM). Sometimes these areas do show abnormalities with sophisticated non-conventional MRI techniques. Other non-plaque regions show subtle abnormalities on routine MRI imaging, which are referred to as diffusely-abnormal white matter (DAWM). The presence of DAWM may play an important role in MS progression. In this study we intend to characterize DAWM abnormalities and to determine their possible causes. These studies should lead to significant insights into how myelin and axons are lost in MS.

Dr. Catherine Pallen, Ph.D.

The University of British Columbia

Award: Operating Grant

Funding: \$275,998.50

Term: April 1, 2012 – March 31, 2015

Role of PTP alpha in oligodendrocyte maturation and myelination/re-myelination

In multiple sclerosis (MS), attack by the immune system destroys myelin, the protective coating of nerves. The accumulating damage results in the debilitating loss of neurological functions, including movement. A major goal in MS treatment is to find therapies that stimulate myelin repair (remyelination) and reverse or limit myelin destruction. Currently this is hindered by insufficient knowledge not only of remyelination, but also of its similarities and differences with the process of myelination that occurs during normal development. For many years, we have studied a molecule called PTPa that is present in high amounts in brain. We find that mice that do not produce PTPa cannot produce myelin. In the proposed research, we will investigate this in more detail to identify how PTPa may help transmit signals into cells to direct them to mature and make myelin. We will also determine, using experimental models of myelin destruction, if PTPa is required for myelin repair. Our results will improve our knowledge of the molecular control of these intricate processes and may enhance the development of therapies to treat MS.

Dr. Alan Peterson, Ph.D.

McGill University

Award: Operating Grant

Funding: \$158,688.00

Term: April 1, 2012 – March 31, 2014

Cre-expressing transgenes targeted to the oligodendroglial lineage: A resource

The ongoing investigations in my laboratory are designed to determine how oligodendrocytes control myelin synthesis in the central nervous system. Through recent research we have obtained unique insight into the structure of DNA sequences that target expression to oligodendrocytes at specific stages of maturation. In this investigation, we propose to take advantage of that insight and use such characterized sequences to develop new experimental tools. These will provide improved control in experiments that are using gene targeting to probe oligodendrocyte development and myelin re-forming capacity. As we expect these new tools to greatly improve both the efficiency and resolution of ongoing and future investigations across a wide front of investigations focusing on oligodendrocyte biology, we will assure that they are readily available and distributed throughout the research community.

Dr. Stéphane Richard, Ph.D.

McGill University

Funding: \$285,000

Term: April 1, 2012 – March 31, 2015

The role of the quaking proteins in oligodendrocyte physiology and myelination

My laboratory studies the role of quaking proteins in myelination and we have shown that the absence of these proteins causes myelination defects in mice. We have previously shown that quaking proteins can influence the growth and maturation of oligodendrocytes. These studies define a new method by which oligodendrocytes are formed. Our studies are focused on further understanding the ability of quaking proteins in myelin maintenance and myelination. As these proteins are quite influential on oligodendrocyte maturation, these studies may provide a means to repair the myelin sheath by using therapies that enhance quaking protein activity.

Dr. Wolfram Tetzlaff, Ph.D.

The University of British Columbia, Vancouver

Award: Operating Grant

Funding: \$187,241.20

Term: April 1, 2011 – Sept 30, 2013

Oligodendrocyte maturation: a potential target to promote white matter repair

Loss of myelin (insulating material of our nerve fibers) is a hallmark of multiple sclerosis (MS) and reformation of myelin (remyelination) is inefficient due to a hypothesized block in the maturation of oligodendrocyte precursors (OPCs) the cells that give rise to myelin forming cells. This maturation of OPCs is inhibited by myelin debris as it accumulates in a MS lesion. In our preliminary work we found that stimulation of a specific communication pathway between cells can overcome this inhibition. Hence, we propose a series of experiments to understand this pathway in cell experiments and animal models which resemble MS disease. These experiments provide the proof of principle that stimulating the appropriate signaling pathway is beneficial for myelin repair and will open the door to research into novel MS treatments. The second project will address the longstanding question whether demyelination is a direct mediator of axonal death and how long demyelinated axons can survive (the axon is the conducting part of the nerve fibre).

Recipients – Personnel Awards

Dr. Robert Brown

McGill University

Supervisor: Dr. Douglas Arnold

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Longitudinal analysis of demyelination and remyelination in Multiple Sclerosis

Dr. Jeffery Haines

Mount Sinai School of Medicine

Supervisor: Dr. Patrizia Casaccia

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Roles of cofilin, LIM kinase and slingshot phosphatase in oligodendrocyte myelination and remyelination: modulating actin cytoskeletal dynamics as a novel treatment strategy for multiple sclerosis

** Recipient of the Fonds de la recherche en santé du Québec (FRSQ) and Multiple Sclerosis Society of Canada Postdoctoral Fellowship Award*

Dr. SooYuen Leong

McGill University

Supervisor: Dr. Jack Antel

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Characterization and functional analysis of pre-myelinating O4 (+) oligodendrocyte progenitor cells from human brain

Dr. Jason Plemel

University of Calgary

Supervisor: by Dr. V. Wee Yong

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Protection against neurodegeneration by inducing remyelination

** Recipient of the Donna Joan Oxford MS Society of Canada Postdoctoral Fellowship Award*

Dr. Simon Zhornitsky

University of Calgary

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Quetiapine as a remyelinating agent in Multiple Sclerosis: A pilot, safety and tolerability study

Jenea Maria Bin

McGill University

Supervisor: Dr. Timothy Kennedy

Award: Doctoral Studentship

Funding: \$20,000

Term: Sept 1, 2013-Aug 31, 2014

Determining the role of netrin-1 in myelin maintenance and remyelination

** Recipient of the William J. McIlroy MS Society of Canada Doctoral Studentship Award*

Vahid Hoghooghi

University of Calgary

Supervisor: Dr. Shalina Ousman

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Cystatin C: friend or foe in Multiple Sclerosis?

**Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Michael Keough

University of Calgary

Supervised by Dr. V. Wee Yong

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Altering the inhibitory microenvironment to promote oligodendrocyte maturation and remyelination

**Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Alexandre Paré

Université Laval

Supervisor: Dr. Steve Lacroix

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Early impacts of IL-1 β on cell migration and development of EAE

Megan Rae Whaley

University of Calgary

Supervisor: Dr. V. Wee Yong

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

T cell-microglia interactions and impact on central nervous system pathology

** Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Camille Juzwik

McGill University

Supervisor: Dr. Alyson Fournier

Award: Masters Studentship

Funding: \$18,000

Term: July 1, 2013- June 30, 2014

Immune cell influences on neuronal viability, repair and morphology in Multiple Sclerosis

Cause and Risk Factors

Despite decades of research, the cause of MS is still a mystery. Several lines of evidence propose that lifestyle, environmental, genetic and biological factors all contribute to the development of MS, but how and to what degree they do is still being investigated.

Knowing what triggers MS is a critical step towards understanding and developing a cure for this perplexing and often unpredictable disease. Understanding triggers also holds potential for solving the mystery of autoimmune diseases in general as they all exhibit similar patterns of overactive immune systems that recognize and attack tissues in the body.

This year the MS Society approved funding for 18 new studies focused on uncovering answers to questions such as:

- What events precede the first signs of MS?
- How do lifestyle factors and environmental components contribute to MS disease?
- What role does genetics play in MS?
- What makes someone more or less susceptible to MS?

Recipients – Operating Grants

Dr. Nathalie Arbour, Ph.D.

Centre de recherche du Centre hospitalier de l'Université de Montréal

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Role of NKG2D in Multiple Sclerosis

Multiple sclerosis (MS) is the most common disease of the brain in young adults: more than 2 million people are affected worldwide. Despite many years of research, the cause of this illness is still unknown. The immune system usually provides protection against microbes. However, the immune system in multiple sclerosis patients shows abnormalities and it attacks components of the brain as if they were foreign microbes. The purpose of our study is to identify molecules present in the brain of multiple sclerosis patients that are used by the immune system to attack it. Particular types of white blood cells bear the capacity to kill other cells and these cells were observed in the brain of MS patients at the site of tissue destruction. The goal is to analyze these killing cells and determine what potentiate their capacity to be toxic in the brain of multiple sclerosis patients. We hope to identify new molecules and cells that could eventually be targeted by future treatments.

Dr. Jennifer Gommerman, Ph.D.

University of Toronto

Award: Operating Grant

Funding: \$300,000

Term: April 1, 2013 – March 31, 2016

Microenvironments that foster B cell activation in Multiple Sclerosis: Function follows form

While we do not know the precise trigger that initiates multiple sclerosis (MS), immune cells play an important role in the disease process. Most of our efforts have been directed towards the understanding of how a group of immune cells known as T-lymphocytes, or T-cells, cause neurological damage during MS. However, another group of immune cells known as B cells, which have been largely overlooked in MS research, have now come to the forefront as important participants in MS disease. This is because removal of B cells has been shown to produce a beneficial effect on relapsing-remitting MS (RRMS). In spite of their importance in the MS disease process, we don't know how B cells are contributing to neurological disease. Our lab will do a series of novel experiments to get to the bottom of how B cells participate in the MS disease process. These experiments will also allow us to model some of the disease attributes of progressive MS, namely the appearance of bunches of B cells in the parts of the brain. Together, the aims of our proposal provide hope that we can generate better therapies for the treatment of relapsing and progressive MS.

Dr. Fiona Costello

University of Calgary

Award: Operating grant

Funding: \$199,994.18

Term: March 3, 2010 – July 31, 2013

Determining the relationship between chronic cerebrospinal venous insufficiency (CCSVI) and Multiple Sclerosis: A cross-sectional, case control study comparing ultrasonography and magnetic resonance venography measures of venous patency to structural and functional outcomes in Multiple Sclerosis

Traditionally, multiple sclerosis has been considered a disorder controlled by cells of the immune system, which are prompted by an unknown trigger to attack the brain and spinal cord. Recently, a newly proposed mechanism, coined “chronic cerebrospinal venous insufficiency” (CCSVI), has challenged conventional thinking regarding mechanisms of injury in MS. According to the CCSVI theory, venous pathways that drain blood from the brain are blocked, causing these vessels to distend and leak. This leakage of blood products, in turn, has been proposed to provoke an inflammatory response in the central nervous system (CNS), which accounts for the signs and symptoms of MS. In this study, our goal is to carefully compare the pathways of venous drainage between MS patients and healthy control subjects with state-of-the-art ultrasonography and magnetic resonance imaging (MRI) techniques. In this way, we will determine whether MS patients have abnormalities in venous outflow that may contribute to their disease. In MS patients with abnormalities of

venous drainage, we will also explore whether the sites and severity of venous lesions correlate with other markers of disease activity.

Dr. Samuel David, Ph.D.

McGill University

Award: Operating Grant

Funding: \$279,059.65

Term: April 1, 2011 – March 31, 2014

Dysregulation of iron homeostasis in the CNS in EAE and Multiple Sclerosis and its role in pathogenesis

Recently, there has been much interest in the presence of iron in lesions in multiple sclerosis, and how that contributes to severity of disease. Although there is MRI evidence suggesting accumulation of iron in MS brain lesions, there is very little information from tissue studies. In other words, we still do not have definite information on which cells accumulate iron and the reasons why it accumulates. The proposed work is designed to study these questions in samples of MS brain tissue and in the mouse model which mimics MS disease, known as experimental autoimmune encephalomyelitis (EAE). In addition, we propose to test the effects of an iron chelator (an agent which attaches to and removes iron) on disease progression in the EAE model. This work will provide much needed information on the role of iron in MS disease.

Dr. Eleanor Fish, Ph.D.

Toronto General Research Institute

Award: Operating Grant

Funding: \$338,295

Term: April 1, 2011 – March 31, 2014

The Role of IFN- β in the pathogenesis of Multiple Sclerosis

Interferon beta (IFN- β) therapy is effective in the treatment of multiple sclerosis (MS), yet its mechanism of action is not understood. We are using mice lacking the gene which encodes the IFN- β molecule in an animal model of MS to better understand its role. Mice lacking IFN- β are more susceptible to MS and have higher levels of immune cells in their brains. These cells are implicated in driving MS disease. Our studies are directed at understanding how IFN- β treatment regulates the production of these inflammatory immune cells. In studies funded by the MS Society we have accumulated preliminary data that reveal how IFN- β may regulate these cells, thereby stopping MS disease onset and development. We also have evidence that IFN- β levels may contribute to the sex differences in incidence of MS: we show that female mice lacking IFN- β are at higher risk of developing MS than male mice lacking IFN- β . Our ongoing studies continue to examine how IFN- β protects against MS. In addition, we are focusing on defining the sex-specific events that also controlled by IFN- β . By identifying specific targets of IFN- β , it will be possible to develop additional therapeutic interventions for MS.

Dr. Marc Horwitz, Ph.D.

The University of British Columbia

Award: Operating Grant

Funding: \$341,799.55

Term: April 1, 2011 – March 31, 2014

A novel mechanism revealing Epstein-Barr Virus-induced neuropathology

Viruses have been implicated in the development of multiple Sclerosis (MS). Several lines of evidence have identified infection with Epstein –Barr virus (EBV) as a potential trigger of MS. Studies which look at disease patterns in human populations indicate that the risk of developing MS is tenfold greater in individuals who were infected by EBV during childhood and twenty fold greater in those developing mononucleosis - “Mono”. Additionally, EBV infected cells have been found in the brain of MS patients. The blood brain barrier (BBB) is comprised of a group of cells that protect the brain by blocking the passage of molecules and immune cells. If the BBB is damaged, it can become more permeable and allow the passage of inflammatory cells that can start to react and destroy myelin. An increase in permeability of the BBB is one of the primary stages in the development of MS. This project’s aim is to study whether EBV is able to infect BBB cells. As a consequence of the viral infection the cells become inflamed and this inflammation damages the BBB and allows the passage of immune cells that destroy myelin.

Dr. Steve Lacroix, Ph.D.

Université Laval

Award: Operating Grant

Funding: \$285,000

Term: April 1, 2012 – March 31, 2015

Dichotomous actions of the IL-1 system in Multiple Sclerosis

Most researchers agree that multiple sclerosis (MS) results in the breakdown of the blood-brain barrier and the attack of brain and spinal cord cells by aggressive immune cells that invade the central nervous system (CNS); causing damage to myelin (demyelination), resulting in the loss of motor, sensory, and autonomic functions. Recent evidence obtained in our laboratory has demonstrated that a key player in this process is the interleukin (IL) - 1 β , which is a small molecule that promotes inflammation. In a mouse model that mimics MS disease, blocking the activity of IL-1 β prevents mice from developing MS-like symptoms. However, IL-1 β could exert other effects during MS, a theory supported by earlier conflicting reports on the role of IL-1 β in remyelination. The main objectives of this research proposal are therefore: 1) to clarify whether the IL-1 system may exert both detrimental and beneficial actions during MS, 2) to understand how these effects are mediated, and 3) to verify whether we can stop the negative effects of IL-1 β without suppressing its beneficial actions.

Dr. Alexandre Prat, M.D., Ph.D.

Université de Montréal

Award: Operating Grant

Funding: \$280,787.13

Term: April 1, 2012 – March 31, 2015

Ninjurin-1 in CNS inflammation

The blood-brain barrier (BBB) restricts the passage of cells and molecules from the peripheral blood to the brain. In the disease multiple sclerosis (MS), the BBB fails to prevent the entry of aggressive immune cells into the brain. These cells are thought to be responsible for damage to tissue. Our work focuses on both the intact and damaged BBB and its role in the development of aggressive immune cells which attack myelin and axons. We intend to understand the biological pathways which govern the migration of dendritic cells across the BBB and to study the molecules which affect the survival and the maturation of these aggressive immune cells within the human brain.

Dr. Alexandre Prat, M.D., Ph.D.

Research Centre of the University of Montréal Hospital Centre (CR-CHUM)

Award: Operating Grant

Funding: \$431,775

Term: April 1, 2012 – March 31, 2015

ALCAM expression in brain vasculature and its role in neuroinflammation

White blood cells travel from the blood to sites of inflammation where they fight against infections. Normally, cells of the immune system cannot enter the brain due to the presence of the blood- brain barrier (BBB). However, in brain disease such as multiple sclerosis (MS), an abnormally large number of white blood cells readily cross the BBB, infiltrate the brain which eventually lead to the formation of MS lesions. The movement of immune cells from the blood to the CNS is orchestrated by many factors, including special molecules (CAMs) that enable immune cells to attach to and cross over the BBB. We have identified ALCAM as a one type of CAM that plays a critical role in the migration of immune cells into the CNS. For that reason, ALCAM is an attractive target for MS therapies. Our research will focus on this newly discovered route used by immune cells to enter the brain and its role in the development of MS lesions.

Dr. Fabio Rossi, Ph.D.

The University of British Columbia

Award: Operating Grant

Funding: \$284,489.85

Term: April 1, 2011 – March 31, 2014

Role of circulating monocytes in EAE progression

In multiple sclerosis (MS), entry of circulating white blood cells – called monocytes - in the central nervous system (CNS) is associated with the presence of lesions or tissue damage. Whether the incoming cells play an active role in causing the damage or are just attracted to clean the debris created by the damage is controversial. Here we will use a novel experimental strategy based on surgically joining two mice in a way that leads to their blood to be shared, to address this question. As this approach also allow us to completely replace white blood cells in a mouse without affecting the cells that are already present in the CNS, it will also allow us to easily distinguish the "incoming" from the resident cells and therefore identify specific roles for each of these. In addition, we will study whether the increase in vessel leakiness observed prior to clear symptoms in MS has a role in determining where and when circulating cells can enter the CNS.

Dr. Carlos Torres

Ottawa Hospital Research Institute

Award: Operating Grant

Funding: \$102,866.00

Term: July 1, 2010 – February 28, 2013

Chronic Cerebrospinal Venous Insufficiency in relation to Multiple Sclerosis

Chronic cerebrospinal venous insufficiency is theorized to give rise to MS via chronic iron deposition in the central nervous system due abnormal narrowing of veins. Using powerful imaging technology, we aim to determine if there is truly a difference in vein anatomy and iron deposition in the brains of MS patients versus healthy controls. We also seek to determine if there is a relationship between vein narrowing and levels of iron in the brain.

Dr. Anthony Trabousee

The University of British Columbia

Award: Operating Grant

Funding: \$200,000

Term: July 1, 2010 – December 30, 2013

Investigation into Venous Insufficiency in Multiple Sclerosis

We will objectively determine if chronic cerebrospinal venous insufficiency (CCSVI) is seen significantly more often in people with multiple sclerosis (MS) compared to healthy controls and family member controls known to have a higher genetic risk for MS (e.g. female identical twin of an MS patient). The unique inclusion of a family member controls should allow us to gain further insight into the possible role of CCSVI in the onset of MS disease. We will use catheter venography as the gold standard for assessing abnormalities in vein structure, and compare the findings to MR venography and ultrasound as potential screening tests.

Dr. Luc Vallières, Ph.D.

Université Laval

Award: Operating Grant

Funding: \$285,000

Term: April 1, 2012 – March 31, 2015

Mechanism of leukocyte recruitment at the blood-brain interface

Multiple sclerosis (MS) disease can be influenced by environmental factors, such as the presence of microbes and their toxins. Our goal is to understand how microbial agents affect traffic of white blood cells within the nervous system. For this project we will study the mechanism of action of pertussis toxin (PTX), which is commonly used to induce MS-like symptoms in mouse models. We will test the hypothesis that PTX would induce inflammation. This study should help to understand how microbial agents influence the course of MS and to identify potential therapeutic target.

Dr. Christina Wolfson, Ph.D.

McGill University, Montréal

Award: Operating Grant

Funding: \$188,891.35

Term: April 1, 2011 – March 31, 2014

A population study of risk factors for Multiple Sclerosis: the Canadian contribution to an international study

The cause of multiple sclerosis (MS) remains unknown despite more than 100 years of research. There are, however, a few promising individual risk factors including infectious agents, smoking and vitamin D exposure through diet and sunlight. However there have been no studies large enough to examine how these possible risk factors act together. A team of MS researchers from Europe and Canada are conducting a study including participants from 5 countries with differing MS risk that is large enough to examine how the factors work together. The International case-control study on Environmental factors In Multiple Sclerosis (EnvIMS) has been launched in Norway, Italy, Sweden and Serbia and the focus of the current proposal is the Canadian component of this 5 country study. An important feature is that a common methodology is being applied and a common questionnaire is being used to collect information on early life infections, smoking, and vitamin D exposure through diet and sunlight. The questionnaire has been adapted to ensure that sources of vitamin D exposure through diet are appropriate for each country and that other questions take into account cultural variability. Once completed this case control will be the largest MS risk factor study ever conducted.

Recipients – Personnel Awards

Dr. Stefanie Black

University of Calgary

Supervisor: Dr. Gerald Zamponi

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

The role of N-methyl-d-aspartate receptors in the cuprizone model of demyelination

Dr. Olga Rojas

University of Toronto

Supervisor: Dr. Jennifer Gommerman

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Evaluating novel B cell effector functions in experimental autoimmune encephalomyelitis (EAE)/Multiple Sclerosis (MS)

Dr. Kenrick Vassall

University of Guelph

Supervisor: Dr. George Harauz

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

Analysis of the conformational transitions of myelin basic protein

Elodie Brison

INRS-Institut Armand-Frappier

Supervisor: Dr. Pierre Talbot

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

From respiratory disease to Multiple Sclerosis-like disability: importance of the spike protein of human respiratory coronavirus OC43

Brian Lut Ming Cheng

University of Chicago

Supervisor: Dr. Raymond Roos

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

The pathogenesis of Theiler's virus-induced demyelinating disease

Miguel De Avila

University of Guelph

Supervisor: Dr. George Harauz

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Myelin basic protein interactions with SH3 domains

Omar de Faria

McGill University

Supervisor: Dr. Timothy Kennedy

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Investigating the role of netrin-1 in myelin maintenance and resistance to CNS inflammation

**Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Mohammad Karim

The University of British Columbia

Supervisor: Dr. Paul Gustafson

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Causal inference with observational Multiple Sclerosis data

** Recipient of the National Bank Financial Group MS Society of Canada Doctoral Studentship Award*

Joshua Lee

University of British Columbia

Supervisor: Dr. Dessa Sadovnick

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Multiple Sclerosis in Asians: The genetic and environmental determinants of variable susceptibility and clinical profile

Lindsay Madeleine Petley-Ragan

The University of British Columbia

Supervisor: Dr. Vanessa Auld

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Role of basigin in maintaining glial wrapping and survival

Natalia Pikor

University of Toronto

Supervisor: Dr. Jennifer Gommerman

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Dissecting immune function and gene alterations in chronic versus relapsing EAE

** Recipient of the Brandt Group of Companies MS Society of Canada Doctoral Studentship Award*

Neda RazazRahmati

The University of British Columbia

Supervisor: Dr. Helen Tremlett

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Children of Multiple Sclerosis: impact of chronic disease in parents on early development

Hanane Touil

Montréal Neurological Institute

Supervisor: Dr. Amit Bar-Or

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Impact of human glial cells on B cells and consequences to the compartmentalized CNS inflammation of Multiple Sclerosis

Monan Angela Zhang

University of Toronto

Supervisor: Dr. Shannon Dunn

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Understanding sex differences in multiple sclerosis (MS): sexually dimorphic role for peroxisome proliferator-activated receptor alpha (PPARA) in dampening pathogenic t helper 1 (th1) responses in humans and mice

Fei Zhao

University of Toronto

Supervisor: Dr. Shannon Dunn

Award: Doctoral Studentship

Funding: \$20,000

The role of PPARdelta in limiting pathogenic t helper cells in EAE

** Recipient of the Co-operators MS Society of Canada Doctoral Studentship Award*

Paulina Drohomyrecky

University of Toronto

Supervisor: Dr. Shannon Dunn

Award: Masters Studentship

Funding: \$18,000

Symptom Management and Quality of Life

Living with MS presents many challenges to an individual and their family members and friends. MS often leads to symptoms such as impaired mobility, vision loss, cognitive deficiencies, fatigue, depression, and learning impediments any of which may be mild or dauntingly severe. Pioneering methods to manage such symptoms has been at the forefront of MS research over the years. Researchers and clinicians continue to collaborate to improve MS symptom management, a key to enhancing the quality of life for everyone living with this disease.

This year the MS Society received a record number of grant applications focused on non-basic science areas such as symptom management, quality of life, disease patterns in the population, and how lifestyle factors impact the clinical aspects of MS.

Recipients – Operating Grants

Dr. Marcia Finlayson

Queen's University

Award: Operating Grant

Funding: \$284,832.00

Term: April 1, 2013 – March 31, 2016

A longitudinal, multi-method investigation of transitions into nursing homes among people with multiple sclerosis

Multiple sclerosis (MS) is a chronic, progressive neurological disease that often leads to significant limitations in a person's ability to meet the demands of daily life. When family members are unable to compensate for these limitations, sometimes a nursing home (NH) must be considered. Since people with MS do not want to live in NHs, we must determine the factors which may lead to entry into a NH and how they evolve over time. This knowledge would inform programs and policies to prevent or delay NH admission. Age, sex, socioeconomic status, use of health care services, and the health of family members are potential factors that need to be examined. In our study, we will examine these and others factors using three sources: (1) a unique population-based health care utilization data repository, (2) interviews with NH experts, and (3) focus groups with people with MS and their families. Together, this information will provide insight for both regulatory and personal applications.

Dr. Michelle Driedger, Ph.D.

University of Manitoba

Award: Operating Grant

Funding: \$279,700.55

Term: April 1, 2012 – March 31, 2015

Improving health policy decision making in the face of uncertainty: A case study of endovascular treatment for Multiple Sclerosis

Health policy makers must often make decisions in an environment of uncertainty. The controversial CCSVI hypothesis and "Liberation Therapy" treatment for multiple sclerosis (MS) offer a timely opportunity to study health policy making under these conditions. Scientific evidence about the CCSVI hypothesis and the effectiveness and safety of the treatment remains unclear, but policy makers face pressure from intense patient demand fueled by media coverage and the advanced networking opportunities provided by social media tools like Facebook and Twitter. The study's objectives are to (1) identify types and sources of uncertainty health policy decision-makers face, (2) identify the impacts that uncertainty has on decision-making, (3) identify strategies to help decision-makers manage and mitigate uncertainty, and (4) develop an instrument to measure uncertainty. These objectives will be addressed with a mixed-method strategy consisting of (1) a media analysis of newspaper coverage and social media discourses, (2) interviews with policy makers and clinicians, (3) focus groups with MS patients, and (4) test construction. Our research will address an important gap in the MS community, create new knowledge to advance the scientific understanding of uncertainty, and develop practical tools to help policy makers make better decisions about MS.

** Recipient of the Manitoba Health Research Council and MS Society of Canada Partnership*

Dr. Anthony Feinstein, MPhil, PhD., MRPsych, FRCPC

Sunnybrook Health Sciences Centre

Award: Operating Grant

Funding: \$134,929.50

Term: April 1, 2010 – October 30, 2013

Detecting cognitive dysfunction in patients with Multiple Sclerosis: assessing the validity of a computerized battery

Cognitive dysfunction will affect more than half of all multiple sclerosis (MS) patients. To assess cognition, MS patients should have access to a neuropsychology service. However, there are few neuropsychologists working with MS patients which mean that many patients cannot be assessed. The present proposal aims to address this by developing a computerized battery of cognitive tests. These tests are easy to administer and can be given to MS patients by a clinic nurse or occupational therapist or research assistant. The study aims to show that such an approach is comparable to the testing carried out by a neuropsychologist. If successful, the study has the ability to make cognitive testing more widely available to the MS community thereby improving quality of care for patients.

Dr. Anthony Feinstein, MPhil, PhD., MRPsych, FRCPC

Sunnybrook Health Sciences Centre

Award: Operating Grant

Funding: \$126,210.83

Term: April 1, 2011 – March 31, 2014

The effects of cannabis on information processing speed in MS: a fMRI study

Cognitive dysfunction affects 40-60% of multiple sclerosis (MS) patients. Patients experiencing cognitive impairment tend to have greater difficulties at work, in recreational pursuits and maintaining relationships. Studies using Magnetic Resonance Imaging (MRI) have linked cognitive impairments to structural brain abnormalities in MS patients. Of note is that functional MRI (fMRI) studies have demonstrated that in MS patients, additional brain regions are activated during performance of cognitive tasks, presumably to compensate for the structural abnormalities of the brain. MS patients use cannabis for many reasons, most commonly in response to pain and spasticity. Previous work from our group has shown that MS patients who smoke cannabis may have additional cognitive deficits in information processing speed as measured by the Symbol-Digit-Modality Test (SDMT). The proposed study will investigate how inhaled cannabis may affect cognitive function and fMRI activation patterns while patients undergo the SDMT. This study will determine whether and to what degree inhaled cannabis alters compensatory brain activation in MS patients and determine the relationship between the putative negative effects of cannabis and brain function. Knowledge of the full range of effects of cannabis would be of considerable benefit to patients and healthcare professionals in making decisions regarding the management of MS symptoms.

Dr. Bradley Kerr, Ph.D.

University of Alberta

Award: Operating Grant

Funding: \$236,092.10

Term: April 1, 2011 – March 31, 2014

Examining the underlying mechanisms of neuropathic pain in Multiple Sclerosis

Chronic pain has a major effect on the quality of life of patients with multiple sclerosis (MS). "Neuropathic" pain occurs when there is an injury or disease in the nervous system and is the most prevalent and difficult to treat pain syndrome seen in MS patients. Unfortunately, there are few effective treatments to relieve this pain because very little is known about its underlying causes. Proteins called glutamate transporters are important for controlling pain signals in the nervous system. My research will test the hypothesis that in MS, glutamate transporter function is impaired leading to neuropathic pain. Using a mouse model of MS, we will identify the areas of the brain and spinal cord where glutamate transporters are affected.

We will examine how cells in these areas respond to painful and non-painful stimuli to better understand how the disease affects the responses of cells to sensory stimulation. We will then test whether a specific drug that restores glutamate transporter function can prevent neuropathic pain. Finally, we will examine how a clinical treatment that reduces inflammation affects neuropathic pain and determine if it has any effects on glutamate transporters in animal models which exhibit MS-like disease.

Dr. Ruth Ann Marrie, M.D., Ph.D.

University of Manitoba

Award: Operating Grant

Funding: \$155,593.55

Term: April 1, 2012 – March 31, 2015

The impact of comorbidity and secular time on hospitalizations and mortality in Multiple Sclerosis

Multiple sclerosis (MS) affects 70,000 Canadians, many of whom also face co-existing (comorbid) health conditions, and the prospect of reduced survival. We do not know much about the relationships between multiple sclerosis and comorbid conditions. The long-term goal of our research program is to shed light on the interactions between MS and comorbid conditions in order to reduce illness and death due to the combined presence of MS and comorbidity. We will compare hospitalizations and survival in the MS and general populations. We will describe the frequency of hospitalizations, reasons for hospitalization, and causes of death in MS. Also, we will look at how hospitalizations and survival are changing over time, and how they are affected by comorbid conditions. We will do this by using health claims data. Findings from our study will help clinicians to give accurate prognostic information to persons with MS. Our study will also provide information that policymakers need to make decisions about health services. Finally, this study will take an important step toward identifying the comorbid conditions which have the biggest impact on hospitalizations and survival in MS; so that we can develop interventions to reduce their impact.

Dr. Neil Rector, Ph.D, C. Psych.

Sunnybrook Research Institute

Award: Operating Grant

Funding: \$263,305.30

Term: April 1, 2012 – March 31, 2015

A randomized controlled trial testing the additive benefits of CBT and exercise for depression and cognitive dysfunction in Multiple Sclerosis

Multiple sclerosis (MS) is a disease that affects not only physical functioning. Depression and cognitive deficits affect at least half or more of all patients over the course of their lives with MS. While cognitive deficits can occur in the absence of depression there is evidence that depression may worsen the cognitive burden. What is not yet known is whether treating the depression can in turn lead to cognitive improvement. This question forms the

gist of our study. Studies have already shown that a particular form of therapy, namely Cognitive Behavior Therapy (CBT), is effective in successfully treating depression. CBT is just as effective as antidepressant medication and does not have side effects. Studies have also shown that exercise is beneficial to mood and cognitive function. We therefore propose undertaking a study investigating the effects of CBT, exercise, and CBT plus exercise compared to waitlist controls on depression and neuropsychological functioning. While we hypothesize that all active treatments will produce significant improvements, we further hypothesize that the combined CBT and exercise package will be more effective than either treatment alone.

Dr. Daria Trojan, M.D., MSc, B.A.

McGill University

Award: Operating Grant

Funding: \$284,712.15

Term: April 1, 2012 – March 31, 2015

A randomized, controlled, clinical trial of continuous positive airway pressure treatment of obstructive sleep apnea-hypopnea in Multiple Sclerosis

We found in a recent study funded by the MS Society of Canada that obstructive sleep apnea-hypopnea (OSAH) is the most common sleep abnormality in multiple sclerosis (MS) patients. We also found a relationship between OSAH and higher fatigue scores in our MS patients. Our preliminary work from this group of subjects shows that treatment of sleep disorders (mostly OSAH) can markedly improve fatigue and other symptoms in some MS patients. However, we now need to test the effect of OSAH treatment in a scientifically rigorous study to be sure that it really does improve fatigue and other symptoms. The best treatment for OSAH in the general population is continuous positive airway pressure (CPAP). This treatment has been well tolerated by most of our MS patients who have used the device. This project will be a randomized, controlled, clinical trial of CPAP in MS patients with OSAH. The effects of six months of CPAP treatment on fatigue as well as sleep quality, somnolence, pain, disability, and quality of life will be studied.

Recipients – Personnel Awards

Dr. Sura Alwan

University of British Columbia

Supervisor: Dr. Dessa Sadovnick

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

A North American Multiple Sclerosis pregnancy registry

Dr. Lindsay Berrigan

Dalhousie University

Supervisor: Dr. John Fisk

Award: Postdoctoral Fellowship

Funding: \$39,000

Term: July 1, 2013-June 30, 2014

An Investigation of the impact of mental health comorbidity on cognitive functioning and health outcomes in Multiple Sclerosis

** Recipient of the Jordan James Pickell MS Society of Canada Postdoctoral Fellowship Award*

Nadine Akbar

University of Toronto

Supervisor: Dr. Brenda Banwell

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Functional magnetic resonance imaging correlates of cognitive dysfunction in pediatric Multiple Sclerosis

Karissa Canning

McMaster University

Supervisor: Dr. Audrey Hicks

Award: Doctoral Studentship

Funding: \$20,000

Term: Sept 1, 2013- Aug 31, 2014

Efficacy and effectiveness of evidence-based consensus physical activity guidelines for adults with Multiple Sclerosis

** Recipient of the Brandt Group of Companies MS Society of Canada Doctoral Studentship Award*

Liam Potter

University of Alberta

Supervisor: Dr. Bradley Kerr

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Pain and cellular activation in experimental autoimmune encephalomyelitis

** Recipient of the Waugh Family MS Society of Canada Doctoral Studentship Award*

Bravina Kuni

York University

Supervisor: Dr. Christine Till

Award: Doctoral Studentship

Funding: \$20,000

Term: July 1, 2013-June 30, 2014

Working memory training for patients with pediatric-onset Multiple Sclerosis: Effects across multiple domains of cognitive functioning

Kyla Anne McKay

The University of British Columbia

Supervisor: Dr. Helen Tremlett

Award: Masters Studentship

Funding: \$18,000

Term: July 1, 2013- June 30, 2014

Aging with Multiple Sclerosis - A focus on mood disorder comorbidity and associations with disease modifying therapies

** Recipient of the Alistair Fraser MS Society of Canada Master Studentship Award*

Dr. Donald Paty Career Development Award

In addition to funding innovative research in MS, The MS Society lends support to young faculty in the form of a salary award. The Dr. Donald Paty Career Development Award serves to support researchers who hold a Canadian university faculty appointment and an operating grant from either the MS Society of Canada or another funding agency. This is the final year that the Dr. Donald Paty Career Development Award will be issued.

Recipients:

Dr. Shannon Dunn

University Health Network

Funding: \$150,000

Term: July 1, 2011 – June 30, 2014

Dr. Bradley Kerr

University of Alberta

Funding: \$150,000

Term: July 1, 2012 – June 30, 2015

Dr. Ruth Ann Marrie

University of Manitoba

Funding: \$150,000

Term: July 1, 2013 – June 30, 2016

Dr. Shalina Ousman

University of Calgary

Funding: \$150,000

Term: July 1, 2012 – June 30, 2015

Dr. Jacqueline Quandt

University of British Columbia

Funding: \$150,000

Term: July 1, 2013 – June 30, 2016

Dr. Helen Tremlett

University of British Columbia

Funding: \$150,000

Term: July 1, 2010 – June 30, 2013

MS Scientific Research Foundation Collaborative Awards

The complexity of MS raises the need for collaboration across a broad range of disciplines, areas of scientific expertise, and, obviously, geographical locations. In order to meet this need, the Multiple Sclerosis Scientific Research Foundation (MSSRF) funds large, multi-centre collaborative studies designed to lead to major advancements in the field of MS.

Recipients:

Dr. Brenda Banwell, M.D., Hospital for Sick Children,

Dr. Amit Bar-Or, M.D., Montreal Neurological Institute,

Dr. Dessa Sadovnick, Ph.D., University of British Columbia

Dr. Douglas Arnold, M.D., Montreal Neurological Institute

Dr. Ruth Ann Marrie, M.D., Ph.D., University of Manitoba

Funding: \$4,300,000

Prospective study of the clinical epidemiology, pathobiology, & neuroimaging features of Canadian children with acquired demyelinating syndromes

Demyelinating disease of the nervous system represents a serious illness that is increasingly diagnosed in children and adolescents. Symptoms resulting from demyelination (damage to myelin) include loss of vision, inability to walk, numbness, impaired sense of balance, and even coma. Some children will completely recover from an attack of demyelination, while others will experience further attacks that are characteristic of multiple sclerosis (MS).

Our work is designed to better understand the symptoms of demyelination in children, to visualize the appearance of demyelination in brain using magnetic resonance imaging (MRI), to explore whether genes (the instructions inside every cell) influence risk, and to investigate why the immune cells (cells that normally fight infection) attack the brain and spine.

Twenty-three centers across Canada participate in this study, with a goal of offering inclusion to every child with demyelination in Canada. All children are followed carefully for up to 8 years in order to recognize those children who develop new attacks, which

would confirm a diagnosis of MS, and to evaluate those children who recover. All children and their families will be asked to tell us how demyelination has impacted their quality of life, so that we might better appreciate the consequences of this illness on child and youth health. Finally, given that demyelination in children occurs in the still developing brain and during the period of core academic study, we will also evaluate the impact of demyelination on learning.

By comparing the features of children diagnosed with MS to the features of children who experience a full recovery, we hope to learn important information about the causes of MS. The ability to predict MS in patients at risk will also allow earlier treatment to reduce attack, and may identify opportunities to reduce risk.

Dr. Mark Freedman, M.D., Ottawa Hospital Research Institute

Dr. Harold Atkins, M.D., Ottawa Hospital Research Institute

Funding: \$2,419,701

Long term outcomes following immunoablative therapy and autologous stem cell transplant for poor prognosis MS

In 2000, the Multiple Sclerosis Scientific Research Foundation funded a multi-centre project, entitled 'Targeting Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoablative Therapy and Immunological Reconstitution to determine definitively whether transplanting bone marrow stem cells in people with MS can stop the disease'. The study involved 25 people with rapidly progressing multiple sclerosis who were likely to become severely disabled. Twenty-four of the participants received bone marrow transplantation (BMT) while two participants with the same kind of MS but who did not wish to have the procedure were enrolled in the control group. Recruitment began in October 2000 and the first transplant was completed in October 2001. Follow-up of the patients now ranges from 1 month to 8 years.

To date, all patients post BMT remain relapse and MRI- free of new disease activity. Several patients showed unexpected recovery of function and all remain off of disease modifying drugs.

In order to establish whether this treatment will induce a long lasting MS-free state, long term follow-up is essential. Furthermore, to better understand the recovery observed in the primary study, researchers added a number of new investigations including new MRI studies and assessments of vision and cognition. Any patient with MS who had a bone marrow transplant is eligible to enroll in the study. Comprehensive clinical, MRI and immunological studies will be performed on study participants from 2007 through 2012.

Dr. Luanne Metz, M.D.,
University of Calgary
Funding: \$4,047,255

Phase III double-blind, randomized, placebo-controlled trial of minocycline in clinically isolated syndromes (CIS)

Minocycline continues to show promise as a potential therapy for MS. A recently completed Canadian study of minocycline taken with Copaxone suggests that this combination of therapies may be beneficial and that further examination is warranted. This randomized, double-blind placebo-controlled clinical trial aims to determine if minocycline at a dose of 100 mg taken orally twice a day reduces the proportion of participants with a clinically isolated syndrome (CIS) who go on to develop MS.

Sometimes, despite the occurrence of a typical neurological event that suggests MS, there is not enough evidence to confirm a diagnosis of MS. However, the neurologist can find no other reason for the symptoms. If this is the case, a person may be told that they have suspected or probable MS. The term sometimes used to describe this early situation is Clinically Isolated Syndrome (CIS). This is because there has been an isolated (single) event rather than multiple events like what is observed in MS.

This phase III clinical trial will determine if minocycline can prevent or delay further disease activity in people with suspected multiple sclerosis (MS) compared to placebo or treatment with a mock medication. Study sites include MS Clinics in Vancouver, Burnaby, Edmonton, Toronto-Sunnybrook, London, Kingston, Ottawa, Montreal, Quebec, Greenfield Park, and Halifax.

Dr. Peter Stys, M.D., University of Calgary
Dr. Jeroen Geurts, Ph.D., VU University Medical Center
Dr. Jan Van Minnen, Ph.D., University of Calgary
Dr. Serge Rivest, Ph.D., Université Laval
Dr. Wayne Moore, M.D., CM, FRCPC, RCPATH., UBC
Dr. V. Wee Yong, Ph.D., University of Calgary
Funding: \$3,800,000

Pathobiology of MS: complex interplay between degeneration and inflammation

MS is a relentless disease that has features of both brain inflammation and degeneration. While we do not yet know what the root cause is, it is apparent that a vicious cycle of degeneration and attack by inflammatory cells drives tissue damage and patient disability, despite our best drug treatments. Through pathological examination, we've known for over a century that nerve fibers die in MS, but to this day we do not know why.

This team project will study the molecular mechanisms of how nerve fibers are permanently injured in the brain and spinal cord of MS patients. We will also research

which immune cells are most responsible for further propagating this relentless cellular injury. Finally, sophisticated magnetic resonance imaging studies on patients with MS will endeavor to better understand what happens in the earliest phases of this disease, and how better to predict the evolution of brain lesions and eventual permanent disability.

endMS Transitional Career Development Awards

Promising research trainees have a critical transition to make at the end of their post-doctoral studies: If they are to become independent investigators, they need to conduct their own projects using what they have learned under their mentors. This important program provides outstanding future MS researchers \$500,000 over a term of five years, covering their last two years of directed postdoctoral studies and their first three years as independent investigators within an MS-related faculty position at a Canadian institution.

Recipients:

Dr. Steven Kerfoot

Western University

Award: 2009 Garrett Herman endMS TCD Award

Identification of Cellular Interactions through Which B Cells Drive Central Nervous System Autoimmune Disease in vivo.

Dr. Cornelia Laule

The University of British Columbia

Award: 2009 WAMS endMS TCD Award

Unraveling Recovery in MS: Insights from Immunology, Molecular Biology and Imaging

Dr. Manu Rangachari

Brigham & Women's Hospital

Award: 2010 EMD Serono endMS TCD Award

Role of the Tim-3 signaling pathway in modulating CNS autoimmunity

Dr. Jorge Alvarez

University of Montréal Hospital Research Centre (CRCHUM)

Award: 2011 David L. Torrey endMS TCD Award

Role of non-conventional CNS barriers during homeostasis and neuroinflammation

Dr. Jiwon Oh

Johns Hopkins University

Award: 2012 Decker Family endMS TCD Award

Multiparametric MRI Correlates of Sensorimotor Dysfunction in the Spinal Cord in Multiple Sclerosis

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The Multiple Sclerosis Society of Canada thanks the thousands of individual donors, corporations and companies, and MS Society chapters and units for their dedicated support of MS research. Together, we are making a difference.

Our Mission

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

