

NEW RESEARCH



STOP. RESTORE. END.

Society Commits \$18 Million for New MS Research Projects

The National MS Society has just launched up to 65 new MS research projects, with multiyear commitments totaling \$18 million. These awards are part of a comprehensive research strategy aimed at stopping MS, restoring function, and ending MS forever.

- This commitment is the latest in the Society's relentless research effort, investing over \$47 million in 2013 alone to support over 350 new and ongoing studies to move closer to a world free of MS.
- The Society's longstanding investment in basic and translational research has resulted in new treatments and better diagnosis and disease management for people with MS.
- The Society continues to pursue all promising paths that lead to solutions for everyone affected by MS.
- When we make research commitments that span into future years, the money is not yet in hand to meet those needs. Contributions to the Society's NOW Campaign to support these projects are essential to ensure that this important research continues in future years.

The new projects include these, described in more detail in the following pages:



STOP:

- A study asking whether low testosterone levels increase the risk of developing MS for men, to determine whether sex hormones can be manipulated to stop MS in its tracks (page 4).



RESTORE:

- A postdoctoral research project at Oregon Health and Science University seeking to understand changes in the brain that are associated with balance problems, which may help design physical therapy programs to restore balance in people with MS (page 23).



END:

- A multi-center study exploring whether there's a link between microbes in the gut and the risk of developing MS in childhood, for clues to how this link might help to end MS forever (page 25).

Inside...

New Projects - STOP	2
Physicians Training in MS Care	3
New Pilot Awards	12
New Projects - RESTORE	16
Collaborative Center	21
New Projects - END	24
Testing "Medical Food" for MS	26



National
Multiple Sclerosis
Society

Fast Forward



STOP

Stopping MS requires understanding of the factors that contribute to MS disease progression, and finding ways to prevent damage to the nervous system. Stopping MS includes research on potential therapies, measuring disease activity, understanding the role the immune system plays in triggering MS, and gathering data on health care issues to drive advocacy efforts for policies that enable everyone with MS to access quality care and treatment.

STOP—Therapies

Pavan Bhargava, MBBS, MD

Southern Illinois University School of Medicine
Springfield, IL

Award: Sylvia Lawry Physician Fellowship
Mentor: Peter Calabresi, MD

Term: 7/1/2013-6/30/2015; Funding: \$130,000
Title: Multiple sclerosis clinical research fellowship

Summary: Developing the skills involved in the design, implementation, and analysis of clinical trials in MS.

The promising young doctors receiving training from a Sylvia Lawry Physician Fellowship learn from top MS experts who mentor their initiation into the complex methods of designing and conducting clinical trials in persons with MS.

For his training, Pavan Bhargava, MD, has two mentors: Dr. Peter Calabresi, a noted expert in MS clinical care and research and Dr. Ellen Mowry, a previous Sylvia Lawry fellowship recipient and an independent investigator conducting a multi-center trial of vitamin D funded by the National MS Society. Dr. Bhargava is learning the various stages of MS clinical trial management, imaging

techniques and their interpretation, and multidisciplinary management of people with MS including urology, psychiatry, and physical, occupational, and speech therapy.

By the end of their training, Sylvia Lawry fellows emerge fully ready to plan and conduct studies of promising new treatments for multiple sclerosis.

Rebecca Farber, MD

Mount Sinai School of Medicine
New York, NY

Award: Sylvia Lawry Physician Fellowship
Mentor: Fred Lublin, MD

Term: 7/1/2013-6/30/2016; Funding: \$195,000 (Pending)

Title: Multiple sclerosis clinical research fellowship

Summary: Developing the skills involved in the design, implementation, and analysis of clinical trials in MS.

The promising young doctors receiving training from a Sylvia Lawry Physician Fellowship learn from top MS experts who mentor their initiation into the complex methods of designing and conducting clinical trials in persons with MS.

Under the mentorship of experienced MS researcher and neurologist Dr. Fred Lublin, Director of the Corinne Goldsmith Dickinson Center for MS, Dr. Farber is learning patient care during all stages of MS, learning about all aspects of MS clinical trial design, implementation, and analysis of the data from these trials. She is participating in the Masters of Science program in Clinical Research at Mount Sinai, which consists of formal training in clinical investigation and will include courses such as biostatistics and clinical trial design.

By the end of their training, Sylvia Lawry fellows emerge fully ready to plan and conduct studies of promising MS treatments.



Six Physicians Receive Training in Specialized MS Care

The awards provide one year of post-residency training with experienced mentors, to optimize care and quality of life for people with MS.

Awardee	Location	Mentor
Brandon Beaber, MD (pending)	Kaiser Foundation Hospitals Los Angeles, CA	Annette Langer-Gould, MD, PhD
Megan Langille, MD	Children's Hospital of Los Angeles Los Angeles, CA	Lilyana Amezcua, MD
William Meador, MD (pending)	University of Alabama at Birmingham Birmingham, AL	Khurram Bashir, MD, MPH
Sona Narula, MD (pending)	Children's Hospital of Philadelphia Philadelphia, PA	Brenda Banwell, MD
Sara Qureshi, MD (pending)	UT Southwestern Medical Center Dallas, TX	Elliot Frohman, MD, PhD
Nataliya Ternopolska, MD	Weill Cornell Medical College, New York, NY	Timothy Vartanian, MD, PhD

Carrie Hersh, DO

Cleveland Clinic Foundation
Cleveland, OH

Award: Sylvia Lawry Physician Fellowship

Mentor: Jeffrey Cohen, MD

Term: 7/1/2013-6/30/2016; Funding: \$195,000

Title: Multiple sclerosis clinical research fellowship

Summary: Developing the skills involved in the design, implementation, and analysis of clinical trials in MS.

The promising young doctors receiving training from a Sylvia Lawry Physician Fellowship learn from top MS experts who mentor their initiation into the complex methods of designing and conducting clinical trials in persons with MS.

Carrie Hersh, DO, is being mentored by highly experienced MS clinician and researcher Dr. Jeffrey Cohen, Director of the Experimental Therapeutics Program and Professor of Medicine (Neurology) at the Cleveland Clinic Lerner College of Medicine, Mellen Center for MS Treatment and Research. Dr. Hersh is undergoing training in direct patient care, participation in clinical trials, and formal course work in clinical research. Training is provided in the Clinical Research Scholars Program Case Western Reserve University, leading to a Master's Degree. She also is training in MS diagnosis.

By the end of their training, Sylvia Lawry fellows emerge fully ready to plan and conduct studies of promising new treatments for multiple sclerosis.



Erin Longbrake, MD, PhD

Washington University

St. Louis, MO

Award: Sylvia Lawry Physician Fellowship

Mentor: Anne Cross, MD

Term: 7/1/2013-6/30/2016; Funding: \$195,000

Funded by an anonymous donor

Title: Multiple sclerosis clinical research fellowship

Summary: Developing the skills involved in the design, implementation, and analysis of clinical trials in MS.

This project is a three-year fellowship for Erin Longbrake, MD, PhD, to learn to evaluate, diagnose and care for people with MS and to learn to develop, administer, and analyze clinical trials involving MS patients. She will be mentored by Anne Cross, MD, at the John L. Trotter MS Center at Washington University in Saint Louis, with secondary mentoring from the other MS faculty at Washington University.

Dr. Longbrake will develop translational research projects focused on MS and will engage in coursework designed to train clinician investigators via Washington University's Masters of Clinical Investigation postdoctoral program. This program integrates didactic coursework with mentored training to teach junior investigators to develop research projects, use biostatistics and epidemiologic tools, understand ethical and legal issues related to human research, write manuscripts and grants, and compete effectively for research funding.

By the end of their training, Sylvia Lawry fellows emerge fully ready to plan and conduct studies of promising new treatments for multiple sclerosis.

STOP—Physiology

Riley Bove, MD

Brigham and Women's Hospital (Harvard)

Boston, MA

Award: NMSS-ABF Clinician Scientist Award

Mentor: Tanuja Chitnis, MD

Term: 7/1/2013-6/30/2015; Funding: \$177,960

Title: Investigation of the role of androgens in multiple sclerosis disease course

Summary: Do blood levels of the male sex hormone testosterone influence MS disease activity in men?

Several lines of evidence suggest an association between low levels of the sex hormone testosterone and MS in males. This study is exploring how blood levels of testosterone may influence whether a person gets MS and influence disease course.

Riley Bove, MD, is comparing hormone levels between males with MS and healthy control subjects, not just in adulthood but also exploring prenatal levels and levels in children. The team is also examining whether testosterone interacts with vitamin D, a hormone that has anti-inflammatory functions and that may be protective in MS. They are also determining whether higher testosterone levels might be protective against disability in MS. For this, they are linking hormone levels with physical and cognitive disability at two time points, two years apart.

These findings could uncover aspects of sex hormones that could be manipulated to treat MS, and, if low testosterone is found to increase the risk of getting MS, this study could lead to strategies to help prevent the disease.



STOP—Neuroprotection

Dimitry Ofengeim, PhD

Harvard Medical School
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Junying Yuan, PhD

Term: 7/1/2013–6/30/2016; Funding: \$175,804

Title: Targeting RIP1 kinase as a therapeutic target in MS to both reduce inflammation and attenuate oligodendrocyte degeneration.

Summary: Early testing of a strategy to reduce inflammation and protect cells that make nerve-insulating myelin as a possible new therapeutic approach to treating MS.

One event in MS that leads to symptoms is the immune system destruction of myelin, the fatty substance that surrounds and protects nerve fibers. Without myelin, the brain and spinal cord do not function properly and nerve fibers are more vulnerable to damage. In the brain and spinal cord, myelin is made by cells called oligodendrocytes.

Dr. Ofengeim is investigating an immune system molecule called tumor necrosis factor-alpha ($TNF\alpha$), which has both good and bad effects in MS. Using mouse models of MS, Dr. Ofengeim is investigating the good and bad roles of $TNF\alpha$ by testing the idea that the beneficial effect of $TNF\alpha$ occurs by killing of harmful immune cells, and that the unwanted effect of $TNF\alpha$ occurs by killing oligodendrocytes. He is looking at a molecule called Necrostatin-1 that appears to selectively block the harmful effects of $TNF\alpha$ and at the same time, retain its beneficial effects.

This study could eventually lead to a new strategy to slow immune attacks and protect against damage to the nervous system in people with MS.

STOP—Measuring MS Disease Activity

Chunlei Liu, PhD

Duke University
Durham, NC

Award: Research Grant

Term: 4/1/2013–3/31/2016; Funding: \$425,765

Title: Improving the Diagnosis of MS with In Vivo MR Imaging of Myelin and Iron

Summary: Developing better imaging to improve early diagnosis and tracking of MS.

Early diagnosis and treatment of MS can lead to effective symptom management and has the potential for reducing future disability. However, diagnosis of MS is not always straightforward, in part because one of the main tools that contribute to diagnosis is brain imaging called magnetic resonance imaging (MRI), which does not always show the subtle damage and disease activity present early in MS in different parts of the nervous system.

Chunlei Liu, PhD, and colleagues are developing a more sensitive and specific MRI technique, called magnetic susceptibility, for early diagnosis of MS. They are developing ways to better view lost myelin, the nerve fiber insulation that is a key target of MS immune attacks, at microscopic levels. In addition, iron is normally present in the brain, but in MS, excess iron may cause additional damage. Another component of Dr. Liu's new MRI technique involves viewing excess levels of iron in the brain of people with MS as a way to visualize the pathology.

This new technique may allow earlier diagnosis of MS resulting in earlier and better treatments. This technique may also lead to better analysis of disease progression, which will be especially important in clinical trials of new therapies aimed at preventing nerve degeneration.



Caterina Mainero, MD, PhD

Massachusetts General Hospital, Harvard
Boston, MA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding:
\$705,149

Title: Cortical Inflammation and
Demyelination in Multiple Sclerosis by
Combined PET and MRI

Summary: Developing better ways to
visualize nervous system damage in people
with secondary-progressive MS.

In people with MS, the fatty substance known as myelin is attacked and destroyed in the brain and spinal cord by the immune system. Because myelin protects and supports nerve fibers, myelin damage leads to loss of nerve signaling and also leaves the nerve vulnerable to injury. Myelin loss is commonly tracked by doctors by detecting lesions using MRI, however, conventional MRI cannot visualize all important types of pathology, and improvements are needed. The purpose of the study is to find out whether people with secondary-progressive MS develop inflammation and lesions in the surface of the brain, and area called the cerebral cortex. The cerebral cortex is largely responsible for sensation, voluntary muscle movement, reasoning, and memory.

Dr. Caterina Mainero and colleagues are improving conventional MRI to look at the importance of myelin loss in the cortex. They are using “ultra-high field MRI” plus another type of imaging called positron emission tomography (PET) to track lesions over time to determine if lesions in the cortex are associated with inflammation and if brain lesions and inflammation progress from the outer surface of the brain inward.

This work will contribute to understanding progressive MS, and who will benefit from earlier therapies.

Vasily Yarnykh, PhD

University of Washington
Seattle, WA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$334,479

Title: Quantitative imaging of white and gray matter demyelination in multiple sclerosis using macromolecular proton fraction mapping

Summary: Investigating a new MRI technique to quantify and predict disease activity and damage in the nervous system in people with progressive or relapsing MS.

The immune system attacks myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord of people who have MS. Loss of myelin prevents nerve fibers from conducting signals correctly, leading to symptoms of MS. In addition, nerve cells also die, leading to long-term deficits. Standard MRI (magnetic resonance imaging) scans show regions of myelin damage in the “white matter” of the brain, where many nerve fibers are found, but MRI scans reveal less information about disease activity in the “gray matter.”

Dr. Vasily Yarnykh and colleagues have developed a new quantitative MRI technique called macromolecular proton fraction (MPF) mapping to obtain information about microscopic myelin changes in white and gray matter which are invisible to standard MRI. The team is using MPF maps to track changes in the myelin content over time in people with relapsing-remitting and secondary-progressive MS and to analyze how myelin damage is related to clinical symptoms, brain atrophy, and the appearance of lesions.

This study may lead to better ways to evaluate and predict disease activity in MS, and evaluating new therapies for MS.



STOP—Neuropathology

Frank Baas, MD, PhD

Academic Medical Center
Amsterdam, The Netherlands

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$617,522

Title: Defining the roles of complement in secondary progressive MS and EAE

Summary: Determining how an immune component, called complement, may worsen secondary-progressive MS.

MS involves immune attacks against the brain and spinal cord. Many people who experience relapses and remissions of MS may eventually develop what is known as secondary-progressive MS, which involves a more steady worsening of disability. One reason for this disease progression may be damage to nerve fibers, which convey the electrical signals that are required for normal brain function. A particular component of the immune system called “complement” has been shown to play a role in other diseases involving neurodegeneration. Dr. Frank Baas and his co-worker Dr. Valeria Ramaglia want to determine whether complement plays a role in nerve damage in MS.

To get at this problem, they will examine whether drugs that can block complement can stop disease progression in a mouse model of secondary-progressive MS. The team will also examine tissue samples from the brains of people with secondary-progressive MS to see whether complement is present on degenerating nerve fibers.

Results from these studies will help us to further understand how MS progresses and may suggest novel strategies to stop MS progression.

Steven LeVine, PhD

University of Kansas Medical Center
Kansas City, KS

Award: Research Grant

Mentor:

Term: 4/1/2013-3/31/2014; Funding: \$80,703

Title: Pathogenic implications of cerebrovascular changes in a cerebral model of multiple sclerosis

Summary: Investigating how changes in blood vessels may contribute to myelin damage in an MS model.

Myelin, the material that surrounds and protects nerve fibers, is damaged and destroyed in the brain and spinal cord when people have MS. When myelin is damaged, the signals in nerve fibers do not reach their destinations properly, resulting in symptoms of MS such as weakness and visual disturbance. Much of the damage in MS is caused by cells of the immune system that mistakenly attack myelin. However, there is evidence from pathology and MRI studies that abnormalities in the blood vessels of the brain and spinal cord may contribute to some of the damage in MS.

Steven LeVine, PhD, is working with mice with several types of EAE, a model disease similar to MS, that have blood vessel damage similar to that seen in MS. Dr. LeVine and colleagues are trying to determine whether the changes in blood vessels alter the flow of blood in regions where myelin and nerve fibers are damaged, and whether these changes may contribute to the damage.

This research could lead to better understanding of how alterations in blood vessels may contribute to the damage to myelin and nerve fibers in MS, and indicate ways to counteract some of that damage.



Sarah Lutz, PhD

University of California, Irvine
Irvine, CA

Award: Postdoctoral Fellowship

Mentor: Dritan Agalliu, PhD

Term: 7/1/2013-6/30/2016; Funding:
\$175,804

Title: Wnt Signaling in Experimental
Autoimmune Encephalomyelitis

Summary: Exploring ways to reduce the entry
of destructive immune cells into the brain as
a possible approach to stopping MS attacks.

The "blood-brain barrier" is formed by
small blood vessels in the brain and spinal
cord. Blood vessel cells called endothelial
cells which make up the barrier restrict the
molecules and immune cells that are able to
move from the blood into the brain and
cause inflammation. In people with MS,
specialized proteins called "tight junctions"
that fortify the barrier become destroyed.

Previously, this team had identified Wnt
proteins that increase blood-brain barrier
properties during brain development. During
the course of this postdoctoral research
fellowship, Sarah Lutz, PhD, is conducting a
series of studies investigating the potential
of Wnt proteins to restore tight junctions in
mice with MS-like disease.

If successful, this work could provide clues
for restoring barrier function in people with
MS, with the potential of blocking the entry
of immune cells as a possible approach to
stopping MS attacks.

**Visit our Website for more
information about research,
treatment, programs, and the NOW
Campaign to support MS research
www.nationalMSSociety.org**

Brian Popko, PhD

The University of Chicago
Chicago, IL

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$594,000

Title: The DTA oligodendrocyte ablation
model in the study of inflammatory
demyelination

Summary: Using a newly developed model to
uncover clues to factors that trigger myelin
damage in MS.

Cells of the immune system damage and
destroy myelin, the material that surrounds
and protects nerve fibers, in the brain and
spinal cord of people who have MS.
Oligodendrocytes, the cells that make myelin,
are also damaged and destroyed. Without
myelin, nerve fibers do not carry signals
properly and they may also be destroyed. It is
currently not known what causes immune
system cells to attack and damage myelin.

Brian Popko, PhD, in collaboration with co-
investigator Stephen Miller, PhD, of

Northwestern University, is studying mice
that have been genetically modified so that
their oligodendrocytes can be accessed and
destroyed in a controlled way. This produces
extensive destruction of myelin.

Oligodendrocyte stem cells or precursors are
not injured, and they rapidly make new
oligodendrocytes that restore myelin to its
initial condition. However, after a period of
time immune system cells invade the brain
and spinal cord and attack the new myelin.
Since this may echo what occurs in MS, Dr.
Popko and colleagues are trying to find out
how the late immune system attack is
triggered and are testing ways to stop it.

This research could provide new insights
into what triggers MS, and lead to new
targets for therapies that would prevent new
attacks of MS.



Rhonda Voskuhl, MD

University of California, Los Angeles
Los Angeles, CA

Award: Research Grant

Mentor:

Term: 4/1/2013-3/31/2017; Funding: \$505,994

Title: Sex Chromosome Effects in the CNS during EAE

Summary: Looking at how genes on the chromosomes that determine gender may influence the severity of MS.

MS involves immune attacks against the brain and spinal cord. It impacts women and men differently. Women are two to three times more likely to develop MS than men. However, progressive forms of MS lead to disability more rapidly in men than in women. The reasons for these differences between males and females are not yet known.

Rhonda Voskuhl, MD, is investigating how differences in genes on the chromosomes that determine gender, known as sex chromosomes, may influence the development and progression of EAE in lab mice. Females have two X chromosomes, which contain about 2000 genes in humans, while males have one X and the much smaller Y chromosome, which contains about 50 genes. Dr. Voskuhl and colleagues are modifying genes on the X and Y chromosomes of mice and measuring how these changes influence the development of EAE.

This work should increase our understanding of why the progression of MS differs in men and women and could lead to new ideas about how to slow or halt the progression of the disease.

STOP—Role of the Immune System

Dirk Baumjohann, PhD

University of California, San Francisco
San Francisco, CA

Award: Postdoctoral Fellowship

Mentor: K. Mark Ansel, PhD

Term: 7/1/2013-7/31/2016; Funding: \$175,804

Title: MicroRNA regulation of T follicular helper cells in experimental autoimmune encephalomyelitis

Summary: Understanding the function of immune cells in MS-like disease for clues to developing new treatments to stop MS.

A type of immune cell called T follicular helper cell may play a critical role in the inappropriate immune response that occurs in patients with MS. Tiny molecules called microRNAs help control which genes are switched on or off in particular cells. Notably, incorrect patterns of microRNAs have been observed in people with MS.

During his postdoctoral research, Dr. Baumjohann is searching for microRNAs that are especially important in T follicular helper cells to determine whether microRNAs found in these cells regulate the type of disease damage seen in people with MS. Using a mouse model of MS, he is specifically deleting these microRNAs in T cells to understand their importance for disease development and progression.

By manipulating microRNAs or their target genes, scientists may be able to influence how cells act, and eventually control disease activity in MS. These studies may provide new ideas for therapeutic targeting of T follicular helper cells in MS in order to stop destructive immune activity.



Gil Benedek, PhD

Oregon Health & Science University
Portland, OR

Award: Postdoctoral Fellowship

Mentor: Arthur Vandenbark, PhD

Term: 7/1/2013-6/30/2016; Funding:
\$175,804

Title: A Novel CD74-Dependent Mechanism
for Suppressing Experimental Autoimmune
Encephalomyelitis.

Summary: Preventing harmful immune cells
from entering the brain as a possible new
strategy to treat MS.

In MS, the immune system attacks the brain and spinal cord, leading to a variety of symptoms. The immune system is composed of several types of cells, including a type called antigen presenting cells (APCs). Some APCs play a role in MS immune attacks. Thus, controlling entry of these cells into the brain and spinal cord may be an effective approach to treating MS.

Dr. Gil Benedek is studying a molecule called CD74 that is found on the outside surface of antigen presenting cells. CD74 is increased in people with MS and in the animal model of MS. CD74 helps determine whether APCs enter the brain. Dr. Benedek's team has developed a molecule that binds to CD74, called DR-alpha1. Dr. Benedek is testing the ability of DR-alpha1 to block entry of APCs into the brain in a rodent model of MS. He is also testing whether CD74 can be used to measure disease severity and treatment effectiveness in MS.

This work could lead to the development of a new approach for treating MS. Also, if CD74 turns out to be a good indicator or "biomarker" of severity and treatment effectiveness, it could enhance the ability to monitor outcomes and response to therapies.

Etty (Tika) Benveniste, PhD

The University of Alabama at Birmingham
Birmingham, AL

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding:
\$478,791

Title: Therapeutic Intervention of the JAK/
STAT Pathway for Neuroinflammation

Summary: Investigating how molecules in
an immune system signaling pathway may
be harnessed to treat MS.

The immune system ordinarily protects the body by destroying foreign invaders, such as viruses or bacteria. In MS, the immune system mistakenly attacks myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. When myelin is damaged, nerve signals are disrupted, leading to the symptoms of MS. A large number of different types of cells take part in the immune system activity in MS, and they coordinate their activity with a number of messengers known as cytokines.

Etty (Tika) Benveniste, PhD, is studying the "JAK/STAT" pathway, one of the most important groups of signaling proteins that regulate immune system activity. The team is taking advantage of MS models to investigate how the activity of the JAK/STAT pathway can be changed. An important goal of this work is to determine whether changes in JAK/STAT signaling activity can reduce or prevent damage to myelin.

The results of this research project will provide new clues about how to control immune attacks against the nervous system in MS, and could lead to new treatment avenues.



Jennifer Blanchfield, PhD

Emory University
Atlanta, GA

Award: Postdoctoral Fellowship

Mentor: Brian Evavold, PhD

Term: 7/1/2013-6/30/2016; Funding: \$169,946

Title: CD4+ T cell affinities to MOG and NFM self antigens determine the course of chronic, demyelinating autoimmune disease

Summary: Understanding how specific immune T cells drive progression of MS symptoms by studying an MS model.

Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and damaged by the immune system in MS. Immune system cells called T cells are involved in these attacks. How strongly T cells respond to myelin and other brain tissues, in addition to the number of nervous system-directed T cells that contribute to MS attacks, are unknown.

Jennifer Blanchfield, PhD, is using a unique and sensitive technology that can test how strongly T cells respond to brain tissues and also identify how many of such T cells are present, both in people with MS and in mice with an MS-like disease. She is looking at the number of T cells that “recognize” particular proteins in the brain, specifically MOG, found in myelin (MOG,) and a second protein found in nerve fibers (NFM). She is also asking if strong or weak interactions between T cells and these myelin or nerve cell components are important in MS disease progression.

Results may help develop new tests that assess or predict disease progression. This could improve the effectiveness of MS therapies, which could be tailored to an individual based on the characteristics of that person’s T cells.

Simon Glatigny, PhD

Benaroya Research Institute
Seattle, WA

Award: Postdoctoral Fellowship

Mentor: Estelle Bettelli, PhD

Term: 7/1/2013-6/30/2015; Funding: \$115,142

Title: Control of regulatory T cell functions by integrin alpha 4

Summary: Understanding how immune cells move into the brain in people with MS, to improve therapies aimed at stopping MS attacks.

MS occurs in part when immune cells enter the brain from the bloodstream and attack brain components. One therapy currently used to treat MS is called Tysabri® (natalizumab, Biogen Idec and Élan). This drug acts by binding to a molecule called alpha4 integrin, which is found on the surface of immune cells. This binding by natalizumab inhibits entry of immune cells into the brain, reducing disease activity, but the drug also has the potential for serious side effects.

Dr. Glatigny is studying alpha4 integrin in greater detail to understand how this molecule gates the entry of cells into the brain. Natalizumab does not appear to uniformly block all types of immune cells from entering the brain. Dr. Glatigny is looking at the role of alpha4 integrin in the movement of various types of immune cells into the brain.

This research could help in developing new therapies that work similarly to natalizumab but with fewer side effects. The development of better therapies to treat MS will improve the quality of life in people with the disease.



12 New Pilot Projects Take Aim at MS

One way the National MS Society propels MS research forward is by funding high-risk, high-potential pilot projects to investigate new, untested ideas and attract new researchers to the field. These unique one-year grants allow researchers to quickly gather data needed to determine if their novel ideas are worth pursuing. The following grants began April 1, 2013.



STOP

Carla Brodley, PhD (Tufts University, Boston, MA) is using novel techniques to mine data from an ongoing study of 1850 people with MS, for clues to understanding disease progression.

Steven LeVine, PhD (University of Kansas Medical Center Research Institute, Kansas City) is investigating whether a common heartburn treatment can lessen disease in mouse models of MS.

Walter Royal, III, MD (University of Maryland, Baltimore, Baltimore) is studying whether MS-like disease in mice can be made worse by exposing the mice to cigarette smoke. (Pending)

Arun Venkatesan, MD, PhD (Johns Hopkins University School of Medicine, Baltimore, MD) is developing new strategies to protect axons from degeneration in MS.

Sheng Xiao, PhD (Brigham and Women's Hospital, Boston, MA) is understanding how one protein regulates the immune attack, for clues to identifying small molecule treatments for MS.

Steven Ziegler, PhD (Benaroya Research Institute, Seattle, WA) is determining the role of a specific population of regulatory cells that may help to suppress the attack in MS.



RESTORE

Alexander Aruin, D.Sc., PhD (University of Illinois at Chicago) is investigating a method for improving balance control in people with MS.

Thorsten Rudroff, PhD (Colorado State University, Fort Collins, CO) is identifying what leg muscles are not functioning well during walking in people with MS.

Nancy Chiaravalloti, PhD (Kessler Foundation Research Center, West Orange, NJ) is investigating a new treatment protocol for learning and memory deficits in people with MS.

Ellen Mowry, MD (Johns Hopkins University, Baltimore, MD) is investigating how often people with MS who present with possible relapses actually have urinary tract infections.

Nadim Srour, MD, MSc (University of Ottawa, Ontario, CANADA) is determining the frequency of lung function and cough abnormalities in people with MS, and testing a possible treatment.

Joanne Wagner, PT, PhD (Saint Louis University, St. Louis, MO) is examining how injury in specific parts of the spinal cord contributes to mobility problems in people with MS. (Pending)



Joan Goverman, PhD

University of Washington
Seattle, WA

Award: Research Grant

Term: 4/1/2013-3/31/2017; Funding: \$595,993
(Pending)

Title: Defining mechanisms by which CD8+ and CD4+ T cells coordinately mediate CNS autoimmune disease

Summary: Studying an MS model to see how cells that cause the disease interact, for clues to new avenues for stopping MS in its tracks.

Cells of the immune system ordinarily defend against infectious invaders such as viruses and bacteria. In MS, however, some immune system cells attack myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. The underlying nerve fibers are also damaged. Nervous system damage disrupts nerve signals, leading to many and variable the symptoms of MS.

Joan Goverman, PhD, is studying how two types of leading immune system cells (CD4+ T cells and CD8+ T cells) interact to damage myelin in mice that have EAE, an experimental disease similar to MS. Dr. Goverman and colleagues altered the genes in the mice so that the two types of T cells react to different portions of myelin in a process that may mimic MS more accurately than some other forms of EAE. Now they are investigating the chemical signals that the two types of T cells use to coordinate their attack against myelin for clues to ways to prevent the attack.

This research could indicate reasons that MS is so variable in different individuals and could lead to new insight for treating the different forms of MS.

Nitin Karandikar, MD, PhD

University of Iowa
Iowa City, IA

Award: Research Grant

Term: 4/1/2013-3/31/2017; Funding: \$712,800

The 2012 Stephen C. Reingold Award for most outstanding research proposal

Title: Role of CNS-specific autoreactive CD8+ T cells in MS

Summary: Looking for ways to treat MS by improving the action of cells that control the immune system attack on myelin.

Cells of the immune system ordinarily protect the body from infectious invaders such as viruses or bacteria. In MS, however, some immune cells mistakenly damage and destroy myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. The immune system has many different types of cells. Some carry out the immune system attacks, while others control the intensity of the attack.

Nitin Karandikar, MD, PhD, is investigating the role of a group of immune system cells known as CD8+ T cells in MS and in a similar disease in mice, known as EAE. Dr. Karandikar and colleagues have found that there are several different types of CD8+ T cells. Depending on what specific proteins they recognize and molecules that they make, these cells may have either a weak or a strong effect on limiting the amount of damage other immune cells do to myelin. Dr. Karandikar and colleagues are looking for ways to enhance the activity of the subsets of CD8+ T cells that strongly reduce myelin damage.

The results of this study could lead to new therapies to control damage to myelin in people with MS by enhancing the regulatory activity of some T cells.



Lior Mayo, PhD

Brigham and Women's Hospital (Harvard)
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Howard Weiner, MD

Term: 7/1/2013-6/30/2016; Funding: \$175,804

Title: Interaction between innate and adaptive immunity in CNS inflammation

Summary: How different components of the immune system work together to drive progression of MS, for clues to stopping it.

The symptoms of MS are due in large part to destructive immune system activity against brain and spinal cord tissues. The immune system consists of an innate response that responds quickly to new foreign invaders or stress and an adaptive response that develops over time and that requires previous exposure of the immune system to foreign invaders. Different immune system cell types are involved in these two types of responses, and both are important in MS.

Lior Mayo, PhD, is looking at how the innate and adaptive components of the immune response work together to drive MS progression. Specifically, he is examining how innate cells in the brain and spinal cord (known as microglia and astrocytes) affect the adaptive immunity (represented by immune T cells) and vice-versa. Using cells and organs in a dish and in mouse models of MS, he is examining how the immune cell types in the brain and bloodstream work together to induce and worsen MS.

Understanding how the immune system works in the brain will help identify new targets for new therapies for treating MS, and in particular the unmet need of treatments for progressive MS.

Siobhan Ni Choileain, PhD

Yale University
New Haven, CT

Award: Postdoctoral Fellowship

Mentor: David Hafler, MD

Term: 7/1/2013-6/30/2016; Funding: \$163,103

Title: Gene and protein expression signature of Th1-Tregs and their role in MS

Summary: Looking at the role of immune T cells in MS inflammation and studying ways to modulate it to treat MS.

In MS, the immune system does not function properly and attacks components of the brain, causing disability. One idea for treating MS is to restore proper function of the immune system.

Dr. Ni Choileain is looking at a type of immune cells called T cells. Some T cells normally promote inflammation, and other T cells normally turn off inflammation. In MS, inflammatory T cells are not turned off correctly. Inflammation persists, causing nervous system damage and symptoms. Dr. Ni Choileain is isolating T cells from people with MS and from healthy people and looking at differences in expression of genes that control the cells' activities.

By understanding genes that are abnormally active in immune cells in MS, this study could lead to the development of new therapies to turn off inflammation and hopefully stop MS activity.



Chuan Wu, MD, PhD

Brigham and Women's Hospital (Harvard)
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Vijay Kuchroo, PhD

Term: 7/1/2013-6/30/2016; Funding: \$175,804

Title: Role of SGK1 in differentiation and maintenance of Th17 cells

Summary: Studying immune cells that attack the brain in MS and the potential role of dietary salt intake in their function.

In MS, the immune system attacks components of the brain. Immune cells known as T cells play a major role in these attacks, and a type of T cell called Th17 cells are particularly important.

Dr. Wu is performing studies to understand how Th17 cells are stimulated to attack the brain in people with MS. The team is looking at one particular protein called serum glucocorticoid kinase-1 (SGK1). In studies that remove SGK1 from Th17 cells, symptoms of MS-like disease in mice are reduced. Recent research suggests that SGK1 regulates salt intake, and shows that in mice, a small increase in dietary salt intake makes Th17 cells more harmful and increases disease severity of MS-like disease. Dr. Wu is now asking how dietary salt levels affect the development and function of these cells.

Results from Dr. Wu's studies will help us further understand the immune cells that are involved in attacking the brain in MS and may lead to new ideas for therapies.

Ye Zheng, PhD

The Salk Institute for Biological Studies
San Diego, CA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$483,756

Title: Protective Role of REV-ERBs in EAE

Summary: Investigating how to turn off activity of immune system cells that participate in the attacks involved in MS.

In MS, cells of the immune system attack and destroy parts of the brain and spinal cord. Immune system cells communicate with each other using a number of molecules, some of which initiate or enhance the attack against myelin, while other molecules may limit or halt that attack. Specific immune cells called Th17 cells have been shown to play a major role in MS immune attacks.

Ye Zheng, PhD, is looking at a pair of molecules, known as REV-ERBs, that can inhibit a trigger that stimulates Th17 cell activity. He and colleagues are exploring whether manipulating REV-ERBs could halt immune attacks in mice that have the MS-like disease EAE. REV-ERBs belong to a group of proteins that control whether specific genes are active in cells. The team is attempting to find ways to make REV-ERBs turn off the genes that cause Th17 cells to launch attacks.

This series of investigations could lead to new ways to prevent immune system attacks in people who have MS.



RESTORE

Research related to restoring what's been lost in MS focuses on understanding how nerves and their protective myelin coating work normally, and how repair of these critical tissues and cells can be stimulated. Testing new cell therapies and other therapeutic approaches to rebuild the nervous system is another approach, as well as development of innovative rehabilitation techniques and better ways to reduce MS symptoms.

RESTORE—Rehabilitation

Christoph Heesen, MD

University Medical Center Hamburg-Eppendorf
Hamburg, Germany

Award: Mentor-Based Postdoctoral Fellowship

Term: 7/1/2013-6/30/2018; Funding: \$396,392
Title: Development and validation of behavioral interventions to enhance self-management in MS

Summary: Training in research aimed at developing ways to help people with MS enhance their knowledge and ability for managing their disease.

The goal of the National MS Society's mentor-based postdoctoral fellowship program in multiple sclerosis rehabilitation research is to recruit and train talented clinician-scientists in rehabilitation research specific to MS. The ultimate goal is to get more hands and minds working on the best ways to help people with MS maximize their abilities.

Christoph Heesen, MD, PhD, is the primary mentor for a rehabilitation fellowship program designed to develop education programs that can enhance an individual's

ability to understand evidence and make treatment decisions. The fellows in this program will be trained in evidence-based medicine, and in patient/physician communication, and will be trained to coach patients through this process so that they become experts in self-management strategies.

This fellowship program will provide important training that will help physicians increase the sense of control and therefore the quality of life of people with MS.

Lauren Krupp, MD

State University of New York at Stony Brook
Stony Brook, NY

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$628,313

Title: Plasticity-based, adaptive, computerized cognitive remediation treatment (PACR) for adults with Multiple Sclerosis (MS)

Summary: Evaluating a web-based program to help improve memory and learning in people with MS.

One of the most troubling symptoms commonly experienced by people with MS relates to cognitive changes, such as problems with learning, memory and problem solving.

Lauren Krupp, MD, is evaluating the potential of a program known as "plasticity-based adaptive computerized cognitive remediation" (PACR) to treat some cognitive problems in adults with MS. It consists of a series of cognitive training exercises presented in a gaming format that are continuously adapted at the individual level to maintain user engagement and challenge. The program is web-based so it can be delivered to anyone with a computer and an internet connection. In this project people with MS are randomly assigned to one of two groups: people in one group will play



ordinary computer games while those in the other group will use the PACR program. Both groups will be tested before and after 12 weeks in the program to evaluate any changes in cognitive ability.

The results of this research could provide the basis for improvements in treating cognitive difficulties in people with MS.

Aaron Turner, PhD

University of Washington

Seattle, WA

Award: Mentor-Based Postdoctoral Fellowship

Term: 7/1/2013-6/30/2018; Funding: \$382,459

Title: The Seattle collaborative post-doctoral fellowship in MS rehabilitation research

Summary: A training program to provide fellows research skills that will enable them to conduct studies aimed at improving quality of life for people with MS.

The goal of the Society's mentor-based postdoctoral fellowship program in multiple sclerosis rehabilitation research is to recruit and train talented clinician-scientists in rehabilitation research specific to MS. The ultimate goal is to get more hands and minds working on the best ways to help people with MS maximize their abilities.

The VA MS Center of Excellence West and the University of Washington, Department of Rehabilitation Medicine, are jointly running this fellowship program in MS rehabilitation research. Selected candidates will be psychologists and rehabilitation professionals who will be trained in the skills they will need to be independent rehabilitation scientists. Training will consist of developing competencies in core areas of research and rehabilitation science of high relevance to MS including knowledge of factors that limit health status, activities, social participation and health related quality of life, exposure to research methods, grant writing skills, and

the dissemination of scientific findings. Dr. Turner is joined by co-mentors Dr. Dawn Ehde at UW and Dr. Jodie Haselkorn at VA Puget Sound, who are highly experienced MS researchers.

Training at two nationally-recognized hospitals with a broad range of resources available will enrich the fellows' experience.

RESTORE—Myelin/Nervous System Repair

Dritan Agalliu, PhD

University of California, Irvine

Irvine, CA

Award: Research Grant

Term: 7/1/2013-6/30/2016; Funding: \$594,000

Title: Understanding the role of Wnt/beta-catenin signaling pathway in repairing blood-brain barrier breakdown during multiple sclerosis.

Summary: Investigating whether closing the blood-brain barrier can help treat EAE, a disease model similar to MS, and its implications for developing new treatments for MS.

The "blood-brain barrier" is formed by small-caliber blood vessels in the brain and spinal cord. The barrier limits the molecules and immune cells that are able to move from the blood into the brain tissue. In MS and a similar animal model for the disease known as Experimental Autoimmune Encephalomyelitis (EAE), the blood-brain barrier is disrupted. This allows immune cells and substances that damage myelin, the protective material around nerve fibers, to enter the brain and spinal cord and contribute to the effects of EAE or MS.

Dritan Agalliu, PhD, is studying mice with EAE to investigate the role of a complex signaling process, the "Wnt/beta-catenin pathway" that normally contributes to the formation of the blood-brain barrier during



brain development. Although Wnt/beta-catenin activity is normally low in the adult brain, preliminary results show that it increases in early stages of EAE. Dr. Agalliu and colleagues are examining whether increased Wnt/beta-catenin signaling is a response to damage to the blood-brain barrier, and whether barrier repair could be improved by manipulating this signaling pathway.

The results of this research will show whether repairing blood-brain barrier damage can reduce the severity of, or promote the recover from, EAE. Restoring barrier function offers the possibility of preventing disease flare-ups or speeding remission in people with MS.

Linnea Asp, PhD

Mount Sinai School of Medicine
New York, NY

Award: Postdoctoral Fellowship

Mentor: Gareth John, PhD

Term: 7/1/2013-6/30/2016; Funding: \$175,804

Title: Requirement of Krüppel-like factor-6 for myelin formation and repair.

Summary: Understanding a gene that may be a new target to induce myelin repair in people with MS.

In people with MS, the immune system attacks and destroys myelin, the fatty substance that nurtures and protects nerve fibers. The loss of myelin is one reason for the various symptoms experienced by people with MS. In the brain and spinal cord, myelin is made by a type of cell called oligodendrocytes.

Dr. Asp is looking at a gene called Krüppel-like factor-6 (Klf6), which is present in oligodendrocytes and that may be important for normal synthesis of myelin. Using both animal models and cells grown in a dish, Dr. Asp is looking at oligodendrocytes that do

not have Klf6 to understand the importance of this gene. Dr. Asp is also looking at which proteins are affected by Klf6 and their role in myelin synthesis.

One idea for restoring function in people with MS is to repair myelin. By understanding the importance of genes such as Klf6, targets for new therapies to stimulate myelin growth may emerge.

Vittorio Gallo, PhD

The Children's National Medical Center,
Georgetown University

Washington, DC

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$672,838

Title: Role of Sox17 in developmental myelination and remyelination

Summary: Investigating a protein that helps regulate the activity of myelin forming cells and its role in nervous system repair.

MS involves destruction of brain and spinal cord tissues. One casualty is the cell (oligodendrocyte) that manufactures the myelin that wraps around and helps maintain nerve fibers in the brain and spinal cord. Immature versions of oligodendrocytes, called precursor cells, ordinarily replace damaged oligodendrocytes, but they fail to keep up with the damage caused by MS. The factors that stimulate precursor cells to develop into mature oligodendrocytes to repair damaged myelin are not completely understood.

Vittorio Gallo, PhD, is investigating the role of "Sox17," one of the proteins that are involved in the development of oligodendrocytes. Dr. Gallo and colleagues are using mice with genetic modifications that either increase or reduce the amount of Sox17 made by oligodendrocyte precursor cells to see how those changes modify the formation of myelin. They are also studying



how changes in Sox17 influence myelin repair, and measuring Sox17 levels in normal human brain tissue and in MS brain lesions, or damaged areas.

The results of this research will provide new understanding of a potentially key factor related to myelin repair, and could lead to new clues for how to reverse myelin damage in people with MS.

Jacob Hines, PhD

University of Colorado - Denver
Denver, CO

Award: Postdoctoral Fellowship

Mentor: Bruce Appel, PhD

Term: 7/1/2013-6/30/2016; Funding: \$169,946

Title: Activity-dependent regulation of oligodendrocyte gene expression and myelination

Summary: Studying signals that control the growth of nerve-insulating myelin, for clues to finding a way to repair myelin to restore function in MS.

Nerve fibers, which transmit signals in the brain, are normally wrapped and protected by a fatty sheath called myelin. Myelin is one of the brain components attacked and destroyed by the immune system in MS. Myelin is made by cells called oligodendrocytes. One possible way to restore function in people with MS is to stimulate the production of new myelin.

Dr. Hines is looking at how oligodendrocytes are directed to make myelin during development. Specifically, he is using a model organism called the zebrafish, which are transparent during early development, to look at whether and how nerve fibers and immature oligodendrocytes communicate using electrical signals during the myelination process.

Understanding how myelin formation occurs during development may provide new

clues for how to initiate the synthesis of new myelin in adults with MS, and potentially suggest new treatment ideas for MS.

Thomas Lane, PhD

University of California, Irvine
Irvine, CA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$592,266

Title: Human Neural Progenitor Cell-Mediated Therapy in a Viral Model of Demyelination

Summary: Investigating how transplanted adult stem cells may stimulate repair of myelin in a mouse of MS.

In MS, the immune system damages myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord, and the nerve fibers themselves are also damaged, along with the cells that make myelin, called oligodendrocytes. Although some natural repair of myelin can occur, it is insufficient.

Thomas Lane, PhD, is using a mouse model of MS which causes myelin destruction after a viral infection to explore how transplanted human neural stem cells may stimulate myelin repair. The team's preliminary results indicate that, although the transplanted cells disappear within a week, they reduce immune attacks that destroy myelin, and also appear to stimulate myelin repair. The team is investigating how this happens and how these observations may be harnessed in the future as a therapy to reduce MS inflammation and stimulate nervous system repair.

This research could lead to new approaches to repairing the nervous system to restore function in people with MS.



Javier Palazuelos, PhD

State University of New York at Stony Brook
Stony Brook, NY

Award: Postdoctoral Fellowship

Mentor: Adan Aguirre, PhD

Term: 7/1/2013-6/30/2016; Funding:
\$169,946

Title: The role of TGF-beta signaling in
oligodendrocyte development, myelination
and remyelination

Summary: Exploring how a signaling
molecule may influence repair of nerve-
insulating myelin, for clues to MS repair.

In MS, myelin, the fatty substance that wraps around and protects nerve fibers, is attacked and destroyed by the immune system. Myelin is produced by mature cells called oligodendrocytes, which develop from immature cells. One strategy for restoring function in people with MS is to potentiate the formation of new myelin by the generation of new oligodendrocytes.

Dr. Palazuelos is looking at how immature cells turn into mature oligodendrocytes that can produce myelin. He is looking at a molecule called transforming growth factor beta. This cytokine has multiple roles in MS, for example, it appears to be able to turn down immune attacks in mice with MS-like disease. The team is now investigating a previously unexplored new role for it, which is to cause immature cells to develop into mature oligodendrocytes. Dr. Palazuelos is conducting a series of studies to understand the complex activities that lead to oligodendrocyte development and TGF beta's role.

If TGF beta is important in the development of oligodendrocytes, controlling it may prove key to stimulating myelin repair in MS.

Larry Sherman, PhD

Oregon Health & Science University
Portland, OR

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$439,568

Title: Novel hyaluronidase inhibitors for the
promotion of remyelination

Summary: Investigating a new avenue with
potential to promote repair of myelin in MS.

Myelin, the material that surrounds nerve fibers and increases the speed of nerve impulses, is damaged and destroyed in the brain and spinal cord of people who have MS. When myelin is damaged, nerve signals fail to reach their destinations properly, and the nerve fibers themselves may be damaged. In the brain and spinal cord, myelin is made by cells called oligodendrocytes, which are also be destroyed by MS. Oligodendrocyte stem or precursor cells make new oligodendrocytes, but often cannot keep up with the damage.

Larry Sherman, PhD, is investigating the role of hyaluronan, a molecule that accumulates in areas of nervous system damage in MS, called plaques or lesions. Previous research by Sherman's group found that some of the molecules formed when hyaluronan is broken down by enzymes known as hyaluronidases appear to inhibit oligodendrocyte precursors from developing into functional oligodendrocytes. Dr. Sherman and his team are testing new chemicals that counteract the breakdown of hyaluronan to see whether they can promote the development of new oligodendrocytes and speed the repair of myelin in mice that have myelin damage that is similar to that seen in MS plaques.

The results could lead to new methods to increase repair of myelin and help restore function to people who have MS.



New Collaborative MS Research Award Focuses on Reversing Damage, Restoring Function

Wendy Macklin, PhD

University of Colorado School of Medicine, Denver, CO

Award: Collaborative MS Research Center Award

Term/Funding: 4/1/13-3/30/18; \$740,500

Exploring brain cell interactions to shed new light on how damage occurs in MS and how to reverse the process to restore function to people with MS.

Details: MS involves immune system attacks on the brain and spinal cord. Glial cells are essential cells in the brain and spinal cord, and they interact among themselves and with nerve cells. One glial cell type is the oligodendrocyte, which generates the myelin that supports and insulates nerve fibers, and which can be damaged in MS.

This talented group is tackling an understudied area of MS research – that of glial cell interactions and communication -- that promises to shed new light on why damage occurs and how to restore function to the nervous system. One set of studies focuses on how glial cells communicate with each other in vivo, and also studying this in isolated astrocytes, oligodendrocytes, and other glial cells in tissue culture. These studies involve Dr. Macklin and team member Kenneth Tyler, MD, who is a neurovirologist with extensive experience in developing and using culture systems to study these cells in the laboratory.

Team member Michael Graner, PhD, is investigating the use of “exosomes,” small vesicles that can be released from cells and taken up by other cells. He is treating glial cells with exosomes from other glial cells to assess the impact on cell survival, proliferation and differentiation.

Team member Bruce Appel, PhD, is leading studies using zebrafish to do live imaging of the interactions of glial cells to provide new insight into their impacts. Gregory Owens, PhD, in collaboration with Jeffrey Bennett, MD, PhD, are tracking common or distinct pathways through which disease-specific MS immune antibodies cause injury to myelin and nerve cells. V. Michael Holers, MD, is lending expertise in “complement,” another aspect of immune defenses, to investigate its potential role in glial and nerve cell injury.

The teams are meeting monthly, with members presenting relevant published journal articles or research-in-progress. The team also is bringing in two outside MS researchers each year to present at these seminars and to meet with members of the Center.



Krystyn Van Vliet, PhD

Massachusetts Institute of Technology
Cambridge, MA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$562,773

Title: Do the mechanical properties of MS lesions influence the extent of remyelination?

Summary: Investigating how the stiffness of areas of tissue damage may impede the repair of nerve-insulating myelin repair.

MS damages and destroys myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. Then nerve signals fail to reach their destinations properly, and the nerve fiber themselves may become vulnerable. Myelin is made by cells called oligodendrocytes, the function of which may also be compromised by MS. Stem cells known as oligodendrocyte precursors develop into oligodendrocytes that can repair myelin. However, the repair process is not able to keep up with the damage.

Krystyn Van Vliet, PhD, along with an international group of collaborators, is using an instrument known as an atomic force microscope to measure the stiffness of tiny regions materials and cells. The team has found that the stiffness of the region surrounding oligodendrocyte precursor cells influences whether they can develop into oligodendrocytes. Now they are comparing the stiffness of regions of tissue samples from rodents with normal myelin and regions that have myelin damage. Preliminary data indicate that differences in stiffness between normal and myelin-damaged regions may slow the development of new oligodendrocytes to complete myelin repair.

This research will help us understand why natural myelin repair is insufficient in MS, and could lead to new ways to improve myelin repair to restore function in people with MS.

Lai Man Wu, PhD

UT Southwestern Medical Center
Dallas, TX

Award: Postdoctoral Fellowship

Mentor: Qing Richard Lu, PhD

Term: 7/1/2013-6/30/2016; Funding: \$163,103

Title: Functional study of transcriptional regulator Sip1 in CNS myelination and remyelination

Summary: Exploring the role of a protein for clues to stimulating myelin repair to restore function in MS.

MS symptoms are due in part to immune system destruction of myelin, the fatty substance that surrounds and protects nerve fibers. One strategy to treat MS is to induce repair and synthesis of new myelin. In the brain and spinal cord, myelin is made by cells called oligodendrocytes.

Dr. Wu is conducting studies to understand how myelin is made by oligodendrocytes. Dr. Wu is examining a particular gene called Sip1 (Smad-interacting protein-1). In early development, Sip1 is involved in the growth of the nervous system by telling immature oligodendrocytes to change from immature cells that cannot make myelin to mature cells that can. However, the role of Sip1 in repairing the nervous system in adults is unknown. Using a variety of techniques and models, including screening genes active during myelin repair processes, Dr. Wu is tracing the role of Sip1 as a potential key player in myelin repair.

Undercovering the possible role Sip1 plays in myelin repair may suggest a way to target Sip1 as a new therapy to restore function in people with MS.



RESTORE—Psychosocial Aspects

Victoria Leavitt, PhD

Kessler Foundation Research Center
West Orange, NJ

Award: Research Grant

Term: 4/1/2013-3/31/2018; Funding: \$619,618

Title: Resting State Functional Connectivity as a Predictor of Memory Decline in Multiple Sclerosis

Summary: Looking for a way to predict who will experience memory decline due to MS so that treatments to slow or prevent it can be started early.

MS damages tissue in the brain and spinal cord, interrupting the signals carried by nerve fibers and causing the many symptoms of MS. One of the most troubling aspects of MS for many people is a decline in memory function. Although memory decline is common in people with MS, there is currently no way to predict who will experience it so that treatments to slow or stop memory decline can be started early.

To address this problem, Victoria Leavitt, PhD, is investigating whether functional MRI (fMRI) measurements in people diagnosed with MS can be used to predict whether they will experience memory decline. The scans indicate the level of activity of regions of the brain. Dr. Leavitt and colleagues are measuring how strongly regions associated with memory are connected. The strength of connections inside memory 'networks' of the brain may enable the study team to identify people who are at risk for memory decline in the future.

This research could provide a way to determine which people newly diagnosed with MS are likely to experience memory decline so that early interventions could slow and compensate for that decline.

RESTORE—Neurophysiology

Brett Fling, PhD

Oregon Health and Science University
Portland, OR

Award: Postdoctoral Fellowship

Mentor: Fay Horak, PhD

Term: 7/1/2013-6/30/2016; Funding: \$170,196

Title: The neural characteristics of proprioceptive-related balance deficits in Multiple Sclerosis

Summary: Understanding factors that influence balance control in people with MS for clues to improving function.

Balance problems are common in people with MS and lead to falls and injury. One possible reason for balance problems is that nervous system messages traveling from the foot/ankle to the brain may be slower in people with MS.

Dr. Fling is testing whether messages traveling from the foot/ankle to the brain are indeed slower in people with MS and if the resulting adjustments to changes in posture are too late, incorrect, or absent. Dr. Fling is also using a type of brain imaging called functional magnetic resonance imaging to observe the possible relationship between differences in brain function and balance problems in people with MS.

Results from Dr. Fling's studies will help us understand changes in the brain that are associated with balance problems and may help us design physical therapy programs that will prevent or delay balance problems, or improve balance in people with MS.



RESTORE—Physiology

Scott Davis, PhD

Southern Methodist University
Dallas, TX

Award: Research Grant
Term/Funding: Pending

Title: Pending

Summary: Studying how MS affects the regulation of blood pressure in response to exercise for clues to potential strategies to improve function.

MS damages and destroys myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. The destruction of myelin interferes with the signals nerve fibers carry. In addition to nerves that control movement and sensation, such as vision, nerves that are involved in functions such as the regulation of blood pressure and balance can be affected by MS. Problems with balance and dizziness that result from lowered blood pressure, coupled with muscle weakness, can contribute to potentially dangerous falls or fainting in people who have MS.

Scott Davis, PhD, is investigating how MS affects the regulation of blood pressure. Dr. Davis and colleagues are comparing how blood pressure changes in response to various amounts of exercise and changes in temperature in people who have MS and in healthy "control" individuals.

The results of this research will improve understanding of how MS affects the control of blood pressure and may lead to the development of ways to help people with MS cope with stress due to activity and elevated temperatures.



END

Ending MS forever means finding the cause of MS, what triggers it, and what may protect against it so that we can prevent MS for future generations. Research into ending MS includes studies to identify MS-related genes, because genes make people susceptible to MS. Another research area is to better understand factors in the environment that influence whether a person gets MS, and identifying possible infectious triggers for MS.

END—Epidemiology

Harvey Checkoway, MPH, PhD

University of Washington
Seattle, WA

Award: Research Grant

Term: 4/1/2013-3/31/2015; Funding: \$360,907 (Pending)

Title: Lifetime UVB Exposure, Vitamin D, and Multiple Sclerosis in a Cohort of U.S.

Radiologic Technologists

Summary: Using a questionnaire to explore the role of exposure to sunlight with the risk of developing MS.

MS is more common in populations distant from the equator, where sunlight is weaker. A component of sunlight, ultraviolet B (UVB), facilitates the production of vitamin D in the skin. There is some evidence that vitamin D has a protective effect that lowers the chance of developing MS, and studies are exploring whether vitamin D supplements can reduce MS severity.

Harvey Checkoway, PhD, in collaboration with colleagues from the University of Minnesota and the National Cancer Institute, is gathering information from responses to questionnaires provided by a group of over 60,000 radiologic technologists. The study is comparing UVB exposures and throughout



life between an estimated 350 MS cases and approximately 700 participants without MS identified from the population of radiologic technologists. Dr. Checkoway and colleagues are correlating the history of residential locations at various ages with measurements of ultraviolet light measured by NASA's Total Ozone Mapping Spectrometer satellites. They will then compare UVB exposures of the MS cases and those without MS.

The results of this research could add to evidence needed to find a way to prevent MS.

Emmanuelle Waubant, MD, PhD

University of California, San Francisco
San Francisco, CA

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$542,554

Title: Microbiomes in pediatric MS

Summary: Understanding the association between microbes in the digestive tract and the risk of developing MS in childhood.

Recent research suggests that bacteria that live in the body, called commensal bacteria, may play a role in shaping later immune responses, such as those that set off the immune attack against the nervous system in MS. Pediatric MS, although less common than adult MS, provides a unique window of opportunity to study risk factors closer to the time of exposure.

This study, involving a network of Pediatric MS Centers established by the Society through the Promise: 2010 initiative including a data coordinating and analysis center, leverages an ongoing multicenter NIH-sponsored project headed by Emmanuelle Waubant, MD, PhD, which is examining environmental and genetic risk factors for pediatric MS, and their interactions. With this award from the Society, the Pediatric MS Network is looking at a subgroup of 100 children with MS and matched controls for

whom comprehensive environmental data has been obtained. They are evaluating the association of commensal bacteria in the digestive tract with MS risk and disease course and other factors.

Data from this study will help increase understanding of the association between commensal bacteria and MS.

Christina Wolfson, PhD

McGill University
Montreal, Quebec, Canada

Award: Research Grant

Term: 4/1/2013-3/31/2016; Funding: \$131,144

Title: Developing a Tool-Kit of epidemiological resources for etiological research in pediatric MS

Summary: Identifying high-quality resources to allow researchers to search for factors that trigger MS in children and adults.

MS is rare in children, but children with MS are thought to share similar risk factors to adults with MS. Because they are younger, they were likely exposed to the MS triggering factor or factors at a time closer to disease onset than adults, and thus offer a possibility for discovering what factors trigger MS.

Christina Wolfson, PhD, along with her PhD Candidate, Sandra Magalhaes, is developing resources aimed at helping researchers search for risk factors in children who get MS. In collaboration with MS experts, they will identify high-quality questionnaires that researchers can use to collect information from their study participants, or parents, about their past exposures and experiences. The team is also developing the methodology that is needed to pool information collected in more than one study.

This study will provide important resources with which to study and perhaps identify factors that drive the development of MS.



National MS Society Partners with University of Miami and Accera, Inc. to Test “Medical Food” for MS Cognitive Impairment

The National MS Society’s Fast Forward drug development subsidiary is partnering with Accera, Inc., and the University of Miami’s Miller School of Medicine in a clinical trial to determine potential benefits of Accera’s medical food, Axona[®] (caprylic triglyceride), on cognitive impairment in people with MS. Funding to test this novel dietary approach to a troubling MS symptom provides University of Miami with funding over a 36-month period, and like other Fast Forward research partnerships, payments will be contingent upon the completion of specific milestones achieved during the trial.

Axona is an FDA-regulated “medical food.” Axona has been approved by the FDA for management of biological processes associated with mild to moderate Alzheimer’s disease. As a medical food, Axona is intended to be used under physician supervision. It has not been approved by the FDA for use in MS.

Cognitive problems are a common symptom in individuals with MS and may have a negative impact on relationships, work, and quality of life. Treatment options are limited. Glucose (a type of sugar) is used to fuel brain cells. For people with neurological conditions such as MS, glucose may not be converted into energy as efficiently as it would be in a healthy brain, which can lead to a decrease in cognitive function. Axona may work to bypass this problem by providing an alternative energy source that is processed in the liver and used by the brain. This placebo-controlled study will be conducted by researchers at the University of Miami MS Center and will enroll 158 people with MS to determine whether Axona can help restore cognitive function to people with MS.

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The National MS Society is proud to be a source of information about multiple sclerosis. Our comments are based on professional advice, published experience and expert opinion, but do not represent therapeutic recommendation or prescription. For specific information and advice, consult your personal physician.



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