

NEW RESEARCH



STOP. RESTORE. END.

\$18.4 Million for 52 New MS Research Projects

The National MS Society has just launched up to 52 new MS research and training awards, with multiyear commitments totaling up to \$18.4 million. These new awards are part of a comprehensive research strategy aimed at stopping MS, restoring function, and ending MS forever.

When the National MS Society makes research commitments that span into future years, the money is not yet in hand to meet those needs. Contributions to the Society to help support these projects are essential to ensure that this important research proceeds in future years. All of the Society's research programs and projects are funded through the NOW Campaign.

Here is a sample of these new projects, described in more detail inside.



STOP MS

Why do people with MS stop taking their treatments? Dr. Helen Tremlett, University of British Columbia, is trying to find out if MS progression and other aspects of health are different for people who take their disease-modifying therapies as prescribed compared to those who stop taking their treatments. (Read more on page 13)



RESTORE FUNCTION

Why do people with MS experience pain? Dr. Heather Wishart, Dartmouth

University, is using advanced MRI techniques to determine what parts of the brain are associated with pain in MS. This will help health professionals as they develop strategies to improve pain management and prevention in MS. (Read more on page 23)



What more can we learn from clinical trials? Dr. Robert Naismith, Washington

University, is studying people who participated in a clinical trial comparing Betaseron and Copaxone, mining valuable data to evaluate nerve injury and repair, and to show whether enhanced imaging may be useful for evaluating new therapies. (Read more on page 21)



END MS

Why do we collect genetic material? Dr. Jorge Oksenberg, University of

California, San Francisco, leads a team collecting and storing genetic material from individuals and families with MS to create a vital, shared resource for studies searching for genes that contribute to the risk of getting MS. (Read more on page 25)



National
Multiple Sclerosis
Society

Fast Forward

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Stop MS

Putting a stop to MS requires understanding the role the immune system plays in the cause of MS and ongoing disease activity and finding ways to stop this damaging process. Research in this area includes studies of immune activity in MS; clinical trials of promising therapies; understanding mechanisms that cause tissue injury and drive disease progression; and efforts to ensure we understand health care issues and can gather data to advocate for policies that enable everyone with MS to access quality care and treatment.

Following are descriptions of 32 new research projects focusing on stopping MS.

Elizabeth Blankenhorn, PhD

Drexel University College of Medicine
Philadelphia, PA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$514,789

Title: "Refining the genetic basis of EAE in B6 mice to establish a model for MS-GWAS testing"

Summary: Studies to clarify how specific MS susceptibility genes and gender influence MS.

Women are more likely than men to develop MS. Recent genetic studies (genome-wide association studies, or GWAS) have revealed a number of genes that contribute to how likely someone is to develop MS. However, details of how most of these genes contribute to MS susceptibility are lacking. One way to investigate the role of MS genes is to study how the corresponding genes in mice influence susceptibility to EAE, an animal disease similar to MS.

In this research project Elizabeth Blankenhorn, PhD, is using selective breeding with strains of mice to see how genes on specific chromosomes alter susceptibility to EAE. Her team is also studying how the genes

in cellular structures called mitochondria may influence susceptibility. Mitochondria are energy factories inside cells, and their genes are inherited only from females.

The results of this research will reveal how specific genes may contribute to MS susceptibility, and offer clues to what goes wrong in MS, which may offer promising leads for new treatments.

Wei-Chun Chou, PhD

University of North Carolina at Chapel Hill
Chapel Hill, NC

Award: Postdoctoral Fellowship

Mentor: Jenny Ting, PhD

Term: 7/1/12-6/30/15; Funding: \$169,946

Title: "Role of inflammasome in neuro-inflammation disease"

Summary: Investigating a possible trigger for immune attacks on the brain and spinal cord, for clues to stopping MS activity.

The immune system consists of a number of different types of cells with specialized functions, which interact to protect the body from infectious agents. Some immune cells detect foreign invaders and release signals that activate other cells that can damage or destroy invaders. Others release signals that control or limit immune system activity. In MS, the immune system mistakenly attacks myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. The triggers for the immune attacks in MS are not yet understood.

In this postdoctoral fellowship, Wei-Chun Chou, PhD, is investigating a group of molecules that are known as "inflammasomes" that are found in immune system cells that detect infectious agents and trigger immune reactions. Preliminary work indicates that inflammasomes can influence the severity of EAE, an animal disease similar to MS. Now Dr. Chou and colleagues are looking



at how the signaling molecules released by inflammasomes affect EAE, and why genetically modified mice that lack some inflammasome molecules have less severe EAE.

This research could reveal how the mistaken immune system attack is triggered in MS, and could provide new clues for developing treatments that stop those attacks and prevent nervous system damage.

Anne Cross, MD

Washington University

St. Louis, MO

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$504,349

Title: "Gradient Echo Plural Contrast Imaging to Better Understand MS"

Summary: Evaluating the potential of a new MRI technique as a more sensitive measure of MS disease activity.

Cells of the immune system damage myelin, the substance that surrounds and protects nerve fibers, in the brain and spinal cord. Regions of myelin damage, called lesions, have different amounts of fat and water than the surrounding healthy regions. These differences are visible with magnetic resonance imaging (MRI). Common MRI images are time-consuming and not very sensitive to small changes in MS activity.

Anne Cross, MD, is evaluating a recently developed MRI technique, known as "Gradient Echo Plural Contrast Imaging" (GEPCI). She is collaborating with Professor Dmitriy Yablonskiy, PhD, who invented this technique. GEPCI is fast, with a typical scan time around 10 minutes, and has the potential to yield more detailed information than conventional MRI. Dr. Cross's team is following 30 people with MS and 10 people without MS for three years using GEPCI and clinical measures of

disability, and comparing the information from GEPCI and conventional MRI scans.

This research will show whether GEPCI is a more sensitive measure of the effects of MS and indicate how useful it may be in evaluating the way MS is measured in clinical trials.

Bonnie Dittel, PhD

BloodCenter of Wisconsin

Blood Research Institute

Milwaukee, WI

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$450,431

Title: "Regulation of EAE by CD86 expressed within the CNS"

Summary: Investigating how an immune-system signaling molecule suppresses MS-like disease for clues to new treatments to stop MS disease activity.

In MS, immune system cells that normally protect against infections attack and destroy myelin, the substance that surrounds and protects nerve fibers in the brain and spinal cord. Nerve fibers with damaged myelin fail to transmit signals correctly, leading to the symptoms of MS. The immune system consists of a number of different types of cells that interact using chemical signals. Some of the signaling molecules activate attacks against a target, such as myelin, while other molecules suppress immune attacks.

Bonnie Dittel, PhD, is studying the effects of one of the immune system signaling molecules, CD86, in EAE, an animal disease similar to MS. Previous work showed that mice with low levels of CD86 in the brain and spinal cord have more severe EAE than mice with normal levels. Now Dr. Dittel and colleagues are investigating how CD86 interacts with immune system cells, and how it influences a specific type of immune system cell that suppresses the activity of



cells that damage myelin.

This research will lead to better understanding of how immune system activity in the brain is controlled, and could provide clues for new ways to treat MS.

Shailendra Giri, PhD

TRANSFER PENDING:

Henry Ford Health System
Detroit, MI

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$543,913

Title: "Preclinical evaluation of combination therapy using metformin with conventional MS therapies "

Summary: Investigating, through preclinical testing, whether metformin, an oral treatment for diabetes, has potential for turning off immune attacks in MS.

Damage to myelin and the nerve fibers it surrounds in the brain and spinal cord interferes with the transmission of nerve signals in MS. The immune system, which normally protects against infectious agents, is responsible for the damage to myelin. In order to attack myelin, the cells must cross a structure known as the blood-brain barrier (BBB) that surrounds blood vessels in the brain and normally limits what can get into the brain tissue.

Shailendra Giri, PhD, is looking at whether an oral drug used to treat diabetes, called metformin, can prevent or reduce the effects of EAE, an animal disease similar to MS. Preliminary research shows that metformin may enhance the action of immune system cells that reduce immune attacks, and may increase the ability of the BBB to prevent immune cells from entering brain tissue. Now Dr. Giri and team are looking at how metformin may reduce the severity of EAE, either alone or combined with approved MS drugs glatiramer acetate and interferon beta.

This research represents an important step in preclinical testing of a potential treatment for MS, and it could to clinical trials in people with MS.

Susana Gordo, PhD

Dana Farber Cancer Institute
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Kai Wucherpfennig, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$175,804

Title: "Induction of myelin-specific regulatory T cells with novel biomaterials"

Summary: Developing a method to prevent the specific immune system attack on myelin in MS.

Cells of the immune system normally attack foreign infectious agents, such as viruses or bacteria. In people with MS, the cells mistakenly attack myelin, the substance that surrounds and protects nerve fibers, in the brain and spinal cord. Immune system cells coordinate their actions using a number of signaling molecules. Several of the drugs currently used to treat MS are based on immune system molecules that turn down activity, but they are not specific for the cells that damage myelin.

Susana Gordo, PhD, is experimenting with tiny devices that hold molecules that stimulate specific types of immune system cells and can be placed under the skin. Dr. Gordo and colleagues are searching for the right combination of substances to produce immune system regulatory T cells that specifically suppress the attack on myelin in EAE, an animal disease similar to MS, but leave other immune system activity intact.

The results of this work could lead to new, specific therapies that prevent the immune system from damaging myelin in MS, while keeping it ready to do its normal job of fighting invaders.



Seven 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
Robert Carruthers, MD	Brigham and Women's Hospital, Boston, MA	Howard Weiner, MD
Melissa Cortez, DO	Mayo Clinic in Arizona, MS Center, Scottsdale, AZ	Jonathan Carter, MD
Elizabeth Dragan, MD	Baylor College of Medicine, Houston, TX	George Hutton, MD
Jessica Robb, MD	University of Rochester, NY	Andrew Goodman, MD
Alessandro Serra, MD	Cleveland Clinic Foundation, OH	Jeffrey Cohen, MD
Sana Syed, MD	Beth Israel Deaconess Medical Center, Boston, MA	Revere Kinkel, MD
Wendy Vargas, MD	Weill Cornell Medical Center/NY Presbyterian Hosp, New York, NY	Timothy Vartanian, MD, PhD

Ari Green, MD

University of California San Francisco
San Francisco, CA

Award: Harry Weaver Neuroscience Scholar Award (PENDING)

Term: 7/1/12-6/30/17; Funding: \$771,773

Title: "In vivo neuronal imaging after demyelinating injury to the visual pathway"

Summary: Developing a technique to measure the health and injury of nerve cells, as a potential tool for quickly evaluating the potential of therapies to protect the nervous system in MS.

MS causes the loss of nerve fibers (axons) and nerve cells (neurons) in the brain and spinal cord (CNS). Although measurements of brain volume provide some indication of neuron loss, it is impossible to study the nerve cell loss directly in most of the brain. The only part of the CNS that is directly visible is inside the eye (the retina), but traditional

ophthalmologic instruments cannot provide a window to see individual cells in the retina.

In this research project, Ari Green, MD, will use a special instrument called a confocal scanning laser ophthalmoscope (CSLO) to monitor changes in neurons, axons, and immune system cells in the retinas of mice with EAE, an animal disease similar to MS. Using several different strains of genetically modified mice, Dr. Green and colleagues will be able to see how the nerve cells in the retina are affected by the activity of other types of cells. They will also be able to determine how the changes visible in the retina of people with MS correspond to changes in the retinal cells in the mice.

This research has the potential to reveal important information about how nerve cells are damaged in MS, and could lead to the development of methods for rapid pre-clinical evaluation of treatments intended to prevent nervous system injury.



Judith Grinspan, PhD

Children's Hospital of Philadelphia
Philadelphia, PA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$540,000

Title: "A role for BMP in oxidative stress during demyelination"

Summary: Investigating whether specific proteins that are released during nervous system damage may play a role in limiting natural myelin repair during the course of MS.

In MS, destruction of the myelin sheath that surrounds nerve fibers in the brain and spinal column interferes with nerve signals, leading to the symptoms of MS. Myelin is made by cells called oligodendrocytes. Oligodendrocyte precursor cells (OPCs) can develop into oligodendrocytes with the potential to repair myelin, but appear to be inhibited from maturing either due to a lack of factors that are needed to promote their development, or by local inhibitors increased by the disease. The development of the ability to form new myelin depends on the interaction of a number of protein factors that stimulate or inhibit OPCs.

In this research project, Judith Grinspan, PhD, is studying how bone marrow proteins (BMPs) influence myelin repair. Previous work indicates that BMP is increased during myelin damage. Now Dr. Grinspan's team is investigating how chemically active molecules that contain oxygen and cause a condition known as "oxidative stress" in regions of myelin damage contribute to the increase in BMP. They are using animals that have been genetically modified to produce less BMP, as well as cells grown in the laboratory, to see if lowering BMP levels increases myelin repair.

This research will reveal whether BMP levels play a role in limiting natural myelin repair during the course of MS, and offer

pathways to overcome these limitations to stimulate nervous system repair in MS.

Katarzyna Karwacz, PhD

Brigham and Women's Hospital
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Vijay Kuchroo, DVM, PhD

Term: 7/1/12-6/30/15; Funding: \$163,103

Title: "Molecular mechanisms leading to generation of Tr1 cells and their function in EAE"

Summary: Studying how interferon beta suppresses immune system activity for clues for more effective treatment of MS.

The immune system damages and destroys myelin in the brain and spinal cord of people with MS. Myelin surrounds and insulates nerve fibers, and they fail to conduct signals correctly when myelin is destroyed. The immune system has many types of cell – some initiate immune system attacks, some carry out attacks, and others suppress activity. Interferon-beta, one of the current treatments for MS, helps to suppress immune attacks in MS, but how it does that is not completely known.

In this postdoctoral fellowship, Katarzyna Karwacz, PhD, is studying some of the ways interferon beta reduces immune system activity. Previous research found that interferon beta causes some immune system cells to release a substance known as IL-27, a signaling molecule, which reduces the activity of some of the immune system cells that damage myelin. Now Dr. Karwacz and colleagues have found indications that the IL-27 released in response to interferon beta also enhances the development of "Tr1" immune cells that regulate or turn off immune system attacks. Dr. Karwacz is studying how interferon beta and IL-27 act together to control immune system damage



in mice with EAE, an animal disease similar to MS.

This research will help explain how interferon beta acts and could lead to clues for more effective treatment of MS with substances similar to interferon beta.

Chang Kim, PhD

Purdue University
West Lafayette, IN

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$460,416

Title: "Impact of short chain fatty acids produced by gut commensal bacteria on pathogenesis of CNS inflammation"

Summary: Looking at how molecules produced by bacteria in the intestines may influence immune system activity in the brain for clues to turning off immune attacks in MS.

In MS, the myelin that surrounds and protects nerve fibers in the brain and spinal cord is damaged and destroyed by inflammation produced by immune system cells. Cells that influence the immune system use a number of different molecules to signal each other and coordinate immune system activity.

In this research project, Chang Kim, PhD, is studying molecules known as short chain fatty acids (SCFAs), which are produced by bacteria that live in the gut, mainly in the large intestine. SCFAs react with specific proteins (receptors) on the surface of many types of cells. Previous research with mice deficient with commensal bacteria or their metabolites indicated that they were resistant to EAE, an animal disease similar to MS. Now Dr. Kim and colleagues are determining how SCFAs influence the activity of immune system cells in the brain and spinal cord.

The results of this research could identify ways to reduce inflammation to treat MS.

Sylvia Klineova, MD

Mt. Sinai School of Medicine
New York, NY

Award: Sylvia Lawry Physician Fellowship

Mentor: Fred Lublin, MD

Term: 7/1/12-6/30/14; Funding: \$130,000

Title: "Sylvia Lawry Physician Fellowship"

Summary: Training in how to design and conduct clinical trials to find better treatments for people with 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.

Sylvia Klineova, MD, is completing her fellowship at Mount Sinai School of Medicine in New York, under the mentorship of MS clinical trial expert Fred Lublin, MD. The Corinne Goldsmith Dickinson Center for MS is a state-of-the-art comprehensive MS care and research center, and is the coordinating center for several nationwide trials. Dr. Klineova is playing an active role in all aspects of the trial design, implementation and analysis of the data, regulatory requirements, clinical scales, and MRI quantification techniques. She also is completing Mount Sinai School of Medicine's Master of Science Program in Clinical Research.

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



Stephen Lalor, PhD

University of Michigan
Ann Arbor, MI

Award: Postdoctoral Fellowship

Mentor: Benjamin Segal, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$169,946

Title: "Investigating the trafficking behavior of encephalitogenic Th17 cells prior to entering the CNS in experimental autoimmune encephalomyelitis and multiple sclerosis"

Summary: Understanding how immune system cells acquire the ability to damage nerve-insulating myelin in MS.

MS involves attacks by immune cells in the brain and spinal cord (central nervous system, or CNS). A recently identified immune cell population called Th17 cells appear to play a crucial role early-on, before the outward appearance of clinical signs. Th17 cells originate outside the CNS, and must migrate from the bloodstream into the brain and spinal cord to attack myelin, the material that surrounds and protects nerve fibers. How Th17 cells become activated and guided into the brain is not well understood.

In this postdoctoral fellowship, Stephen Lalor, PhD, is studying how Th17 cells in mice with EAE, an animal disease similar to MS, acquire the molecules on their surfaces that enable them to move into the brain. Previous research indicates that Th17 cells mature in lymph nodes associated with the gastrointestinal tract (commonly referred to as the gut-associated lymphoid tissue or GALT). Dr. Lalor is using mice with genetic modifications that alter the behavior of Th17 cells as well as tools that specifically block immune cell entry to the GALT to identify the factors that enable Th17 cells to cause EAE.

This research may lead to novel therapies based on manipulating intestinal bacteria to prevent Th17 cells from learning how to get to the CNS and thereby prevent MS relapses.

Sabeen Lulu, MBBS

University of California San Francisco
San Francisco, CA

Award: Sylvia Lawry Physician Fellowship

Mentor: Emmanuelle Waubant, MD, PhD

Term: 7/1/12-6/30/14; Funding: \$130,000

Title: "Sylvia Lawry Physician Fellowship"

Summary: Training in how to design and conduct clinical trials to find better treatments for people with 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.

Sabeen Lulu, MD, is completing her fellowship under the mentorship of MS expert Emmanuelle Waubant, MD, PhD. Dr. Waubant leads the UCSF Regional Pediatric MS Center, so Dr. Lulu is involved with both adult and pediatric clinical trials, learning the intricacies of conducting clinical research in the youngest people with MS. Dr. Lulu is also participating in a unique, nationwide study to determine environmental and genetic risk factors that make children susceptible to developing MS. She is also completing a Master's Degree in Clinical Research in the Department of Epidemiology and Biostatistics at UCSF.

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



Don Mahad, MD, PhD

Cleveland Clinic Foundation
Cleveland, OH

Award: Career Transition Award (PENDING)

Mentor: Bruce Trapp, PhD

Term: 5 years; Funding: \$585,911

Title: "Role of mitochondria in the pathogenesis of multiple sclerosis"

Summary: Looking at how destruction of nerve-insulating myelin in MS may also damage or change small energy factories inside nerve cells, called mitochondria.

In MS, the myelin surrounding nerve fibers is damaged by immune system attacks. The nerve fibers and cells are also often damaged and die, leading to long-term, often progressive, disability. It is not clear what causes the nerves to die, but it is likely to be something in addition to the immune system attack, since the current treatments aimed at the immune system limit damage to myelin, but don't prevent nerve cells from dying.

Don Mahad, MD, PhD, is studying the structures within nerve cells known as mitochondria. Sometimes called the "power houses" of cells, mitochondria are tiny structures that supply the energy a cell needs for its activities. Preliminary work shows that the number and distribution of mitochondria change when myelin is removed from nerve fibers. Dr. Mahad is investigating whether the ability of the mitochondria to provide energy to the nerve fibers is affected and whether their DNA (mitochondria have their own DNA, separate from that in the nucleus of cells) is altered by myelin damage.

This research will determine how myelin destruction affects mitochondria in nerve fibers, and could lead to new ways to prevent the destruction of nerves that occurs in MS.

Gordon Meares, PhD

University of Alabama at Birmingham
Birmingham, AL

Award: Career Transition Award

Mentor: Ety Benveniste, PhD

Term: 7/1/12-6/30/17; Funding: \$581,647

Title: "LKB1 and AMPK Signaling in Neuroinflammation"

Summary: Studying how cells in the brain and spinal cord may influence the immune system in MS, for clues to stopping immune attacks.

Immune system activity in MS involves a number of types of cells, some that enter the brain and spinal cord from the bloodstream, and some that normally reside within the brain and spinal cord. The activity of immune system cells is influenced by a number of chemical signals released by both the immune system and other cells. Astrocytes, the most numerous cells in the brain, release some molecules that influence immune system activity.

In this Career Transition Fellowship, Gordon Meares, PhD, is investigating the role two proteins, LKB1 and AMPK, that act within astrocytes to control their activity. Previous research indicates that these proteins may help astrocytes control inflammation. Dr. Meares is using mice with EAE, an animal disease similar to MS, which have been genetically modified so that LKB1 and AMPK activity in astrocytes can be experimentally controlled to determine how these molecules influence the immune system.

This research will provide a better understanding of the way astrocytes influence immune system activity in the brain and spinal cord, and may reveal new ways to control immune attacks in MS.



Stephen Miller, PhD

Northwestern University
Chicago, IL

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$519,750

Title: "Mechanisms of Th1/Th17 regulation by B7-H4 Ig for the treatment of EAE"

Summary: Understanding how immune system activity is regulated in MS, for clues to developing better treatments that specifically prevent damage to nerve-insulating myelin.

Cells of the immune system which normally attack infectious agents such as viruses or bacteria mistakenly attack myelin, the substance that surrounds and protects nerve fibers, in the brain and spinal cord of people with MS. There are many types of cells in the immune system. Some, such as the ones known as Th1 or Th17, promote attacks on specific substances, such as myelin. Others, known as Treg cells, limit or prevent attacks against specific substances.

In this research project, Stephen Miller, PhD, is investigating the function of a molecule known as "B7-H4 Ig" in mice with EAE, a disease model similar to MS. Previous work has shown that B7-H4 Ig significantly reduces the severity of EAE. Now Dr. Miller and colleagues are studying how B7-H4 Ig alters the development of myelin-damaging Th1/Th17 cells and Treg cells that prevent myelin damage in EAE.

This research should improve our understanding of how immune system activity is regulated, and could provide clues for developing MS treatments that specifically prevent damage to myelin.

Nancy Monson, PhD

University of Texas Southwestern Med. Ctr.
Dallas, TX

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$312,991

Title: "Antibody gene signature in transverse myelitis"

Summary: Looking for patterns of immune gene activity as a way to tell whether an initial attack of transverse myelitis will become MS, which could lead to faster diagnosis and treatment.

The early stages of MS may be difficult to diagnose. This often means a long period of uncertainty for people who eventually develop MS, and delay in starting therapies that could reduce damage. Inflammation and myelin damage in the optic nerve (optic neuritis, ON) or spinal cord (transverse myelitis, TM) are often the initial signs of MS, but they also can be single clinical events or events related to other diseases.

Nancy Monson, PhD, is attempting to develop a new method that would help identify which cases of TM are likely to develop into MS. Previous work by Dr. Monson identified an antibody gene signature – a specific set of the genes that code for antibodies in immune-system B cells – in the spinal fluid of people with MS who initially had ON or TM. Now Dr. Monson is analyzing spinal fluid of people who have had a single attack of TM to see whether the antibody gene signature of those who develop MS differs from those who do not. Her team is also determining whether the antibody gene signature is present in cells in blood samples.

This research could identify new methods to show which people with ON or TM will develop MS, leading to faster diagnosis and initiation of treatment of MS.



Sze-Ling Ng, PhD

Harvard University
Boston, MA

Award: Postdoctoral Fellowship

Mentor: Jack Strominger, MD

Term: 7/1/12-6/30/15; Funding: \$163,103

Title: "A role for T cell receptors in the cytokine secretion profile of regulatory T cells"

Summary: How the activity of specific cells that prevent immune attacks can be enhanced as a potential therapy to stop MS.

Immune system cells normally protect against infectious agents by identifying their molecular characteristics, attacking them and destroying them. In MS, the immune system mistakenly attacks myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. Immune system cells known as "T cells" are involved in all of the immune system's activities – some T cells help identify what to attack, some are involved in the attack, and some, known as regulatory T cells (Tregs), reduce or prevent attacks.

In this postdoctoral fellowship, Sze-Ling Ng, PhD, is studying ways to enhance the activity of Tregs to control EAE, a model disease similar to MS. Previous research has indicated that a reduction in the number or activity of Tregs may contribute to the damaging activity of the immune system in MS and EAE. Dr. Ng is investigating how information from a structure on the surface of T cells, called the "T cell receptor," influences early T cells to develop into Tregs that are capable of reducing the harmful immune system attack on myelin.

The results of this research could provide clues for new ways to reduce or stop the effects of MS by enhancing Treg activity to prevent immune system cells from attacking the protective myelin.

Michael Racke, MD

The Ohio State University
Columbus, OH

Award: Research Grant

Term: 4/1/12-9/30/13; Funding: \$355,028

Title: "Interferon-beta modulation of microRNA in Multiple Sclerosis"

Summary: Investigating whether interferons alter activity of small segments of RNA, in search of new ways to stop the immune-system attacks and nervous system damage in MS.

Cells of the immune system mistakenly attack and damage myelin, the material that coats nerve fibers, in the brain and spinal cord of people with MS. Interferon beta alters the activity of some immune system cells, and is a common disease-modifying therapy for relapsing forms of MS. Details of how interferon beta works are not fully known, and it is unclear why there are differences in how people respond to it.

In this research project, Michael Racke, MD, is investigating molecules known as microRNAs in immune system cells. MicroRNAs help determine which proteins cells make. Previous work by Dr. Racke and others has shown that microRNAs in immune cells of people with MS differ from those in healthy people. Now they are looking at whether interferon beta alters the types of microRNA in immune cells in ways that reduce myelin attacks.

This research should help clarify how interferon beta works, and could lead to ways to predict a person's response to this therapy, and new ways to control the immune system in people with MS.



Ulf Schulze-Topphoff, PhD

University of California San Francisco
San Francisco, CA

Award: Postdoctoral Fellowship

Scott Zamvil, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$175,804

Title: "Role of B cells in central nervous system autoimmune disease"

Summary: Studying the extent that immune system cells known as B cells influence immune attacks that damage the nervous system in MS, for clues to improving therapy.

Myelin, the material that surrounds and insulates nerve fibers, is destroyed in the brain and spinal cord by activity of the immune system in MS. A number of different types of cell make up the immune system. These cells communicate and coordinate their activities with a number of different signaling molecules. One class of immune system cells, known as T cells, appear to have the most direct effects on myelin. The results of recent studies indicate that another class of immune system cells, B cells, influence the activity of T cells in MS.

Ulf Schulze-Topphoff, PhD, is investigating how B cells influence myelin damage in mice with EAE, a disease with characteristics similar to MS. He and his colleagues are using genetically modified mice to study how B cells, which produce proteins known as antibodies, affect the activity of other immune system cells that damage myelin directly.

The results of this research will improve understanding of how B cells influence immune system activity that damages myelin, and could provide clues for improving treatments for MS.

Nancy Sicotte, MD

Cedars-Sinai Medical Center
Los Angeles, CA

Award: Research Grant

Term: 7/1/12-6/30/14; Funding: \$241,982

Title: "Tracking Hippocampal Subregional Atrophy in Multiple Sclerosis: Effect of Estriol Treatment"

Summary: Using a novel MRI technique to evaluate the potential impacts of estriol treatment on the nervous system during a clinical trial in women with 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 nerve cells in the "gray matter."

Nancy Sicotte, MD, is using advanced MRI analysis techniques to evaluate changes in a region of the gray matter known as the hippocampus, which is involved in memory. Dr. Sicotte's team is applying these techniques to people enrolled in a clinical trial testing a combination of Copaxone and estriol, a form of estrogen. They are comparing a labor-intensive manual analysis of MRI images of the hippocampus with a new rapid automated technique, and correlating changes in MRI images with clinical information.

This study will help define outcomes of the clinical trial, and could lead to new techniques to evaluate changes in brain tissue in people with MS.



William Stohl, MD, PhD

University of Southern California
Los Angeles, CA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$521,806

Title: "The role of the BAFF axis in experimental autoimmune encephalomyelitis"

Summary: Studying the potential for a new treatment approach for MS by altering a molecule that influences immune system cells.

In MS, a person's immune system mistakenly attacks myelin, the material that surrounds and protects nerve fibers, in the brain and spinal cord. Without their myelin sheath, nerve fibers cannot carry signals properly, leading to the symptoms of MS. Although the immune system cells known as T cells have a major role in MS, recent studies suggest that another type of immune cell, called B cells, are also involved in MS.

William Stohl, MD, PhD, is investigating the effects of a molecule known as BAFF (B cell activating factor) on mice with EAE, a disease that is similar to MS. BAFF enhances the survival of B cells, and previous work has shown that it is increased in regions of the brain where myelin is damaged in MS. Now Dr. Stohl and colleagues are looking at whether BAFF can also influence the behavior of other immune system cells including T cells, and whether treatments that reduce BAFF can improve the condition of mice with EAE.

The results of this research could lead to new treatments that suppress the damage caused by the immune system in MS.

Helen Tremlett, PhD

University of British Columbia
Vancouver, CANADA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$286,059

Title: "Adherence to immunomodulators in multiple sclerosis: prevalence and clinical impact (The AIMS Study)"

Summary: Examining how following the recommendations for taking MS drugs affects the course of the disease.

The most commonly prescribed treatments for MS are therapies that modify the activity of the immune system. These include the interferons and glatiramer acetate. While they modify the disease, they are not cures, so they must be taken regularly. In addition, the MS therapies can be costly, which can alter how people take them. It is not currently known how many people with MS using these therapies do not adhere to the recommendations for taking them and how that affects the course of their disease.

Helen Tremlett, PhD, and co-investigator Charity Evans, PhD (University of Saskatchewan), with a group of researchers across Canada, are using databases with information about virtually all people treated for MS in three Canadian provinces between 1996 and 2011. They are looking at how adherence to treatment recommendations affects the course of the disease and the usage of health care services. Among the questions being examined are whether hospitalization rates and progression of the disease are different for those who follow the recommendations for taking the therapies compared to those who do not follow recommendations.

This study will provide important information about the rates of adherence to the recommendations for taking MS therapies, and how following the recommendations affects the outcome of treatment.



Michel Varrin-Doyer, PhD

University of California San Francisco
San Francisco, CA

Award: Postdoctoral Fellowship

Mentor: Scott Zamvil, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$175,804

Title: "AQP4-specific T cells in NMO"

Summary: Investigating how immune system cells are activated in a disease with some features similar to MS.

Neuromyelitis optica (NMO) is a rare disease in which the immune system destroys myelin, the material that surrounds and insulates nerve fibers. In some ways NMO is similar to MS, but it primarily affects the optic nerve and spinal cord and is often aggressive. The majority of people with NMO have antibodies to a molecule known as aquaporin -4 (AQP4), and much research on NMO has focused on the immune system cells that make antibodies (B cells). However, the NMO antibodies are a type that is influenced by the activity of immune T cells, which are involved in immune attacks in MS.

In this postdoctoral fellowship, Michel Varrin-Doyer, PhD, is investigating the role of T cells in NMO. Preliminary work by Dr. Varrin-Doyer and colleagues found T cells that react to AQP4 in both people with NMO and healthy individuals. However, in people with NMO, the proportion of reactive T cells that take part in inflammation was higher while the proportion of T cells that regulate inflammatory responses was lower. Now Dr. Varrin-Doyer is trying to determine the details of how T cells in NMO differ from the T cells in healthy individuals.

This work will contribute to our understanding of how immune system attacks on nerves originate, and could provide new clues for treatments for both NMO and MS.

Wen-Hsuan "Sharon" Way, PhD

University of Chicago
Chicago, IL

Award: Postdoctoral Fellowship

Mentor: Brian Popko, PhD

Term: 7/1/12-6/30/15; Funding: \$163,103

Title: "The protective role of the integrated stress response (ISR) on oligodendrocytes during inflammatory demyelination"

Summary: Studying a natural tissue response to damage and how it might be improved to stimulate repair of nerve-insulating myelin in MS.

Symptoms of MS are caused by the failure of nerve fibers in the brain and spinal cord to carry signals correctly because the myelin that surrounds and insulates them has been destroyed by the immune system. The nerve fibers themselves are also damaged, as are oligodendrocytes, the cells that manufacture and maintain myelin. When cells are damaged, they produce a group of proteins that help to repair the damage, an activity known as the "integrated stress response" (ISR). If the ISR fails to heal the injured oligodendrocytes, they die and cannot repair damaged myelin or maintain undamaged myelin, leading to further myelin loss.

In this postdoctoral fellowship, Wen-Hsuan "Sharon" Way, PhD, is investigating ways of manipulating the ISR in animals with EAE, a disease similar to MS, and in cells grown in the laboratory. Preliminary results indicate that enhancing the ISR results in the death of fewer oligodendrocytes. Now Dr. Way is determining whether drugs that enhance the ISR in oligodendrocytes also enable them to protect myelin from damage in EAE.

The results of this research could lead to clues for how to minimize myelin damage and preserve function in MS.



Restore

Just a few short years ago, there was little belief that nervous system repair was even possible. Through the tireless efforts of the National MS Society and other funding partners and researchers around the world, there is not just belief, but a whole new field that has emerged to pursue strategies to repair the nervous system and restore function to people with MS.

The MS immune attacks on the brain and spinal cord cause damage to nerve fibers and their protective myelin coating. Without their myelin coating, nerve fibers fail to conduct signals properly, leading to symptoms of MS. When nerve fibers and their nerve cells are damaged, long-term disability can result.

Research related to restoring what's been lost in MS focuses on understanding how nerves and myelin work normally, and how repair 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.

There are 17 new research grants and fellowships and 1 new Collaborative MS Research Center Award focusing on restoring function in MS.

Alexander Aruin, PhD, DSc

University of Illinois at Chicago
Chicago, IL

Award: Mentor-Based Rehabilitation Fellowship

Term: 7/1/12-6/30/17; Funding: \$405,991

Title: "Rehabilitation research training to enhance functional performance in MS"

Summary: Training young scientists to conduct research in rehabilitation approaches to help people with MS achieve higher quality of life and maximal function.

The mentor-based postdoctoral fellowship in MS rehabilitation research provides support to recognized experts so that they can provide advanced training to scientists for the conduct of research designed to help people with MS maximize their abilities.

Alexander Aruin, PhD, DSc, and his colleagues have a strong program to train promising young scientists in research on rehabilitation to improve the daily lives of people with MS. In this program, postdoctoral scientists will improve their knowledge and research skills in areas related to improving use of the arms, control of posture and balance, and walking. Facilities available for training include a well-equipped laboratory in which an individual's movements, balance and strength can be measured, and computer programs to analyze the data that is obtained.

Successful completion of this program will provide participants with the knowledge and skills not only to aid individuals with MS with daily activities, but also to conduct research to improve rehabilitation options for people with MS.



Yoko Bekku, PhD

New York University
New York, NY

Award: Postdoctoral Fellowship

Mentor: James Salzer, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$175,804

Title: "Mechanisms of node of Ranvier assembly"

Summary: Looking at how the structure of nerve fibers is affected by myelin, with the goal of finding ways to enhance nerve signaling to restore nerve function in MS.

Myelin, the insulating material surrounding nerve fibers, is damaged in the brain and spinal cord by MS. When myelin is damaged, nerve signals are interrupted, leading to the variety of symptoms possible in MS. Unlike the continuous insulation around an electrical wire, myelin has an alternating series of thin and thick regions, somewhat like a string of sausages. The thinned regions are known as "nodes of Ranvier" or simply nodes. The structure of the nerve fibers is quite different at the nodes than it is in the areas between nodes. Concentrated at the nodes are structures that carry nerve signals, particularly channels in the membrane through which charged particles (ions) move.

In this postdoctoral fellowship, Yoko Bekku, PhD, is studying how ion channels, and a number of other proteins, are anchored in the nerve fiber membrane at the nodes. Dr. Bekku is looking at how the structure of the nerve fiber surface membrane changes as myelin develops, using cells grown in the laboratory.

This research should shed light on how the arrangement of structures that carry signals in nerve fibers change as myelin develops, and could provide clues for how nerve function might be restored after myelin damage in MS.

Matthew Bellizzi, MD, PhD

University of Rochester
Rochester, NY

Award: NMSS-ABF Clinician Scientist Award (PENDING)

Mentor: Harris Gelbard, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$263,622

Title: "Synaptic injury and neuroprotection in multiple sclerosis"

Summary: Identifying processes that contribute to the loss of nerve function in MS, and seeking ways to protect the nervous system from damage.

MS immune attacks lead to destruction of the myelin that surrounds and protects nerve fibers in the brain and spinal cord. Nerve cells and fibers are also damaged in MS and may lead to progressive and long-term disability. The causes of nerve damage are not yet well understood, which has limited progress in developing therapies that prevent damage and preserve nerve function.

In this project, jointly funded by the National MS Society and the American Brain Foundation, Matthew Bellizzi, MD, PhD, is using several approaches to identify processes that contribute to the loss of nerve function and to find ways to protect nerves from damage. Dr. Bellizzi is determining the extent of damage to nerve cell fibers and the connective points between nerve cells (synapses) in brain samples from people who had MS in their lifetimes. In addition, he is looking at the development of nerve damage in mice with EAE, an animal disease similar to MS. He is also developing a system to assess nerve damage that could be useful for pre-clinical testing of drugs with the potential to slow or block that damage.

This research could provide important information and techniques for developing treatments to limit nervous system damage in MS and its resulting progressive disability.



John DeLuca, PhD

Kessler Rehabilitation Institute
West Orange, NJ

Award: Mentor-Based Rehabilitation
Fellowship

Term: 7/1/12-6/30/17; Funding: \$382,865

Title: "MS Fellowship in Neuropsychological
Rehabilitation"

Summary: Training postdoctoral fellows for
success in careers dedicated to research in
cognitive rehabilitation to improve the lives
of people with MS.

The mentor-based postdoctoral
fellowship in MS rehabilitation research
provides support to recognized experts so
that they can provide advanced training to
scientists for the conduct of research
designed to help people with MS maximize
their abilities.

John DeLuca, PhD, and his colleagues
have a proven track record in training young
scientists and clinicians in research on
cognitive rehabilitation. The training program
is customized for each postdoctoral fellow to
build on their individual strengths and
interests. During the program, the fellows
gain skills in research design, scientific
writing, and MS cognitive rehabilitation and
acquire the skills that will enable them to
become independent researchers.

This program is an important training
ground for individuals who are developing
the skills and knowledge to improve
rehabilitation treatments for people who
have MS.

Wenbin Deng, PhD

University of California, Davis
Davis, CA

Award: Research Grant

Term: 7/1/12-6/30/14; Funding: \$295,256

Title: "Application of the Modified-RNA
Technology and iPS Cells for Remyelination"

Summary: Investigating the therapeutic
potential of using cells derived from adult
skin to repair nerve-insulating myelin
damaged during the course of MS.

MS destroys myelin that protects nerve
fibers, and also the cells that make myelin in
the brain and spinal cord, called
oligodendrocytes. The brain has stem cells
called oligodendrocyte precursor cells (OPCs)
that can mature and repair damaged myelin,
but they are unable to keep up with the
damage in MS.

In this research project, Wenbin Deng,
PhD, is exploring the potential of
transplanting cells to provide additional
myelin-making cells in hopes of repairing MS
damage. The cells being used are adult stem
cells derived from other cells in the body, in
this case, skin cells, which are
"reprogrammed" to be other cell types. These
are called induced pluripotent stem cells
(iPCs). Dr. Deng and colleagues are using RNA
molecules that contain the instructions to
make the reprogramming proteins needed to
transform human skin cells into iPCs and
convert them into OPCs. They are testing the
ability of these OPCs to repair damaged
myelin in mice.

The results of this research could lead to
first steps toward repairing myelin damage in
a person with MS using cells derived from
their own skin cells.



New Collaborative MS Research Award Focuses on Nervous System Repair — Follows Up Success of Promise: 2010 Initiative

Peter Calabresi, MD

Johns Hopkins University
Baltimore, MD

Winner of the Stephen C. Reingold Award for most outstanding research proposal

Term: 7/1/12-6/30/17; Funding: \$742,500

Summary: Collaborators from different fields identifying factors that help to increase myelin-making cells, and using this knowledge to develop myelin repair strategies.

A hallmark of multiple sclerosis is the loss of myelin. This fatty substance surrounds nerve cells in the brain and spinal cord. Natural myelin repair does occur, and is mediated by immature myelin-making cells, called oligodendrocyte progenitor cells (OPCs), that live in our brains. In response to myelin damage, OPCs multiply and move to the injured tissue. For reasons that are not yet fully understood, the repair process stalls in MS; OPCs reach the site of damage, but often fail to completely mature into new oligodendrocytes.

This Center aims to identify factors that help to increase myelin-making cells, and use this knowledge to develop myelin repair strategies. Following up on successes achieved by the Society's Nervous System Repair and Protection initiative, Dr. Calabresi has assembled a new team of researchers to tackle this challenge. Team members Dr. Dwight Bergles, new to MS research, is using mouse models to explore why myelin repair does not occur efficiently in response to the immune attack, and to identify compounds that may enhance OPC development into myelin-making oligodendrocytes. Dr. Rothstein, also new to MS, will screen "libraries," or collections, of small molecules for candidates that can promote the maturation of OPCs into mature oligodendrocytes. Team members Dr. Katharine Whartenby, and Dr. Calabresi are determining the ability of drugs identified from the screening to promote generation of new oligodendrocytes isolated in cultures, and in Dr. Bergles's mouse models.

This collaboration brings two talented neuroscientists into the field of MS, and introduces their models and state-of-the-art methodologies to two seasoned MS researchers. Only through regular meetings, shared resources, and regular interactions between graduate students and postdoctoral fellows from the primary investigators' labs can the projects be successfully carried out: Funding from this Center Award allows for this extensive interaction. These studies can provide the necessary preclinical data to move forward with clinical trials of new therapies to promote myelin repair and restore function in people with MS.



Ranjan Dutta, PhD

Cleveland Clinic

Cleveland, OH

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$304,111

Title: "Identification of critical regulators of remyelination in MS brains"

Summary: Looking for ways to stimulate brain cells that have potential to repair nerve-insulating myelin damaged by MS.

Repairing myelin (the material that surrounds and protects nerve fibers) that has been damaged by MS is a high priority. One key to this effort is the population of cells that make myelin, which are called oligodendrocytes. These are also damaged during the course of MS. Immature versions of these cells, called oligodendrocyte precursor cells (OPCs), reside in the brain and can develop into mature oligodendrocytes, which could potentially repair damaged myelin through a process called remyelination. OPCs are found in regions of the brains with myelin damage, but they are not able to repair myelin well enough to keep up with the damage.

Ranjan Dutta, PhD, is looking at the regulators of signaling molecules associated with developing OPCs, which determine how completely they develop into mature oligodendrocytes and whether they begin to produce myelin. The process is controlled by a balance between the activation of genes that either enhance or suppress the maturation of the OPCs. Preliminary work indicates that genes that slow or prevent OPC maturation are found in MS lesions. Dr. Dutta and colleagues are studying the regulators that could be used to turn off the genes that slow development and turn on the genes that may enhance OPC maturation.

This research could improve our understanding of why myelin repair fails in

MS and aid in discovering ways to enhance myelin repair to restore nerve function in MS.

Sharyl Fyffe-Maricich, PhD

Case Western Reserve University

Cleveland, OH

Award: Career Transition Award

Mentor: Robert Miller, PhD

Term: 7/1/12-6/30/17; Funding: \$581,647

Title: "ERK MAP kinase regulation of oligodendrocyte differentiation and remyelination in the CNS"

Summary: Investigating how protein signals influence the repair of nerve-insulating myelin in the brain and spinal cord.

Myelin, produced by cells called oligodendrocytes in the brain and spinal cord, surrounds and insulates nerve fibers. When myelin is damaged by MS, the nerve fibers do not conduct signals correctly, leading to the symptoms of MS. Oligodendrocyte precursor cells (OPCs) can transform into cell with the capacity to repair damaged myelin and restore nerve signaling. In MS, OPCs fail to develop and repair myelin efficiently enough to keep up with the damage, possibly because the signals that tell them to develop are not effective.

Sharyl Fyffe-Maricich, PhD, is studying a chain of proteins that stimulate the activity of cells in response to signals from outside the cells. Preliminary research indicates that these "ERK" proteins are important for OPC development. She is looking at the activity of ERK in biopsy material from people with MS, and is using genetically modified mice and cells grown in the lab to determine whether and how either excess or lack of ERK proteins affects the formation of myelin.

This research will improve our understanding of myelin development, and could provide new clues for ways to repair myelin to restore function in people with MS.



Jeffery Kocsis, PhD

Yale University
New Haven, CT

Award: Research Grant

Term: 7/1/12-6/30/2016; Funding: \$585,327

Title: "Transplantation of OPCs into the demyelinated spinal cord"

Summary: Evaluating the transplantation of myelin-producing cells to repair damaged myelin in an animal model, for clues to the possible safety and benefit in people with MS.

Demyelination, or the destruction of myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord, leads to the disruption of nerve signals in MS. Oligodendrocytes, the cells that manufacture and maintain myelin, are also destroyed. The brain possesses potential replacement cells, called oligodendrocyte precursor cells (OPCs), which to some degree can repair damaged myelin, but they generally don't do a good job keeping up with MS damage.

Jeffery Kocsis, PhD, is assessing the ability of OPCs derived from stem cells implanted into the spinal cords of animal models to repair myelin damage. The OPCs Dr. Kocsis is using have been approved by the FDA for clinical trials in human spinal cord damage. Dr. Kocsis is evaluating the amount of myelin repair with both microscopic studies of the spinal cord and with clinical studies to see whether myelin repair restores functional ability. Dr. Kocsis and colleagues will also evaluate the safety of the implants.

This research will show whether implanted OPCs have the potential to repair myelin damage, detect any obvious safety issues, and could ultimately lead to clinical trials for repair of myelin damage in MS.

Qing Richard Lu, PhD

UT Southwestern Medical Center
Dallas, TX

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$516,614

Title: "microRNA Control of Myelination and Remyelination in the Central Nervous System"

Summary: Investigating ways to encourage brain cells to mature and initiate the repair of nerve-insulating myelin to restore function in people with MS.

MS destroys myelin, the material that surrounds and insulates nerve fibers in the brain and spinal cord (central nervous system). The cells that make and maintain myelin, called oligodendrocytes, are also destroyed. The brain has spare parts in the form of stem cells to help repair tissues after injury, including oligodendrocyte precursor cells (OPCs) that are capable of developing into mature myelin repair cells. For some reason in MS, the OPCs do not do a good job or can't keep up with the damage.

Qing Richard Lu, PhD, is investigating small molecules, known as micro-RNAs, that regulate the production of proteins. In particular, his team is studying a micro-RNA called miR-219 that regulates the development of oligodendrocytes. Previous research has shown that reducing miR-219 prevents OPC maturation, while increased amounts of miR-219 speed up maturation. Now Dr. Lu is using genetically modified mice to see how changes in micro-RNA affect the repair of myelin in EAE, an animal disease similar to MS.

The results of this research will increase understanding of how OPCs mature to produce myelin, and could provide important clues for ways to enhance myelin repair and restore function in people with MS.



Wendy Macklin, PhD

University of Colorado Denver
Denver, CO

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$587,653

Title: "Role of integrin linked kinase in CNS myelination"

Summary: Investigating a protein that may help steer myelin repair cells to areas of damage, which may have important implications for efforts to repair the nervous system in MS.

After myelin, the protective material that surrounds nerve fibers, is destroyed in the brain and spinal cord by MS, some myelin repair naturally occurs. This is carried out by progenitor cells that are resident in the brain, called oligodendrocyte precursor cells (OPCs). They can migrate to regions of myelin damage, mature into myelin-making oligodendrocytes, and repair myelin, but they fail to keep up with the damage in MS.

Wendy Macklin, PhD, is studying the role of a protein, "integrin linked kinase" (ILK), which previous work has indicated may help OPCs migrate to regions where they are needed. Dr. Macklin and colleagues are using genetically modified rodent and zebrafish models to determine how ILK enhances the migration of OPCs, and whether ILK is involved in the production of myelin by oligodendrocytes.

The results of this work will provide a better understanding of how OPCs move to regions where myelin repair is needed and could provide new clues for stimulating nervous system repair in people with MS.

Robert Naismith, MD

Washington University
St. Louis, MO

Award: Research Grant

Term: 4/1/12-3/31/14; Funding: \$416,565

Title: "Quantitative imaging of tissue recovery, repair and clinical outcomes in multiple sclerosis"

Summary: Applying advanced imaging techniques to evaluate nerve tissue injury and repair for measure the ability of new therapies to restore function in MS.

MS damages myelin, the material that surrounds and protects nerve fibers, in the brain and spinal column. Nerve fibers stripped of their myelin coating fail to carry signals correctly, leading to the symptoms of MS. Eventually the nerve fibers themselves may be destroyed, causing long-term disability. Conventional magnetic resonance imaging (MRI) reveals the initial damage to regions of myelin, but does not provide much information about the condition of the nerve fibers.

In this research project Robert Naismith, MD, is taking advantage of data amassed during the course of a clinical trial to evaluate the potential of two advanced techniques, based on MRI, to provide information about changes to nerve fibers in MS. The two techniques, known as "diffusion tensor imaging" (DTI) and "magnetization transfer imaging" (MTI), reveal information about the arrangement of nerve fibers that is not visible in conventional MRI images. Dr. Naismith and colleagues are correlating the information from monthly scans using these techniques with clinical information about disability.

The results of this research will lead to better ways to evaluate the condition of nerve fibers in MS, and show whether these enhanced imaging techniques may be useful in evaluating new therapies for MS.



James Salzer, MD, PhD

New York University School of Medicine
New York, NY

Award: Research Grant (PENDING)

Term: 7/1/12-6/30/15; Funding: \$465,741

Title: "Assembly of CNS Nodes of Ranvier"

Summary: Determining how the specialized nerve fiber regions that carry nerve signals develop, with the goal of preserving or restoring proper nerve signaling and function in MS.

Proper nerve signaling depends on multiple structures and activities. Unlike the continuous insulation around an electrical wire, myelin, the material that surrounds and insulates nerve fibers, looks more like a string of sausages, with alternating thick and very thin regions. At the thin regions, known as nodes of Ranvier, the surface of the nerve fiber is almost bare. The structure of the nerve fiber surface at nodes of Ranvier is specialized for signal conduction, with a large number of protein "channels" through which charged sodium ions move to generate the nerve signal.

James Salzer, MD, PhD, is studying the processes that produce the specialized structure of nerve fiber surface at nodes of Ranvier. Dr. Salzer is using genetically modified mice, and cells grown in the laboratory, to determine how proteins in the nerve fiber membranes, such as the ion channels for sodium, group together at the nodes as myelin develops around nerve fibers.

This research will determine how the molecules that carry nerve signals are grouped at nodes of Ranvier, and could provide important clues for how to preserve and restore nerve function in people with MS.

Leslie Summers deLuca, PhD

New York University
New York, NY

Award: Postdoctoral Fellowship

Mentor: Susan Schwab, PhD

Term: 7/1/12-6/30/15; Funding: \$163,103

Title: "Regulation of central nervous system S1P production and the role of S1P signaling on Bergmann glia in an animal model of multiple sclerosis."

Summary: Studying how an important signaling molecule contributes to immune system activity in MS, for clues to refining its therapeutic activity to better treat MS.

In MS, immune cells move from blood into the tissue of the brain and spinal cord. Once there, the cells damage myelin, the coating on nerve fibers, and the nerve cells themselves are damaged. Fingolimod (Gilenya), an oral therapy approved for treating relapsing MS, targets a set of receptors, or docking sites, called sphingosine-1-phosphate (S1P) receptors, which are found on several types of cells. It is not yet clear how fingolimod helps control immune attacks in people with MS, however S1P, a molecule that activates the S1P receptors, is elevated in the brain during MS, and recent work suggests that fingolimod's therapeutic effects may be through blocking S1P receptors on brain cells called astrocytes.

Leslie Summers deLuca, PhD, is investigating how S1P actually influences MS by studying mice that have EAE, a disease similar to MS. She is exploring how S1P levels are regulated in the brain, how S1P receptors affect astrocyte function, and the possibility that S1P signaling allows astrocytes to guide immune cells deeper into the brain.

This research will increase understanding of how an approved therapy works, and could lead to clues for developing more targeted treatments that block S1P's



destructive effects but leave its normal functions unaltered.

William Talbot, PhD

Stanford University
Stanford, CA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$446,243

Title: "Genetic mechanisms of CNS myelination"

Summary: Identifying genes involved in the production of myelin to find new ways to repair damaged myelin in MS.

Myelin, the material that surrounds and protects nerve fibers, is made by cells known as oligodendrocytes in the brain and spinal cord (CNS). Myelin and oligodendrocytes are damaged in MS. In addition, nerve fibers may also die, leading to long-term deficits and disability. Myelin is a complex substance, and many of the details of how oligodendrocytes make it are not well known.

William Talbot, PhD, is using animals that have gene mutations that alter their ability to produce myelin in the CNS. By using a combination of molecular genetic techniques, Dr. Talbot is attempting to identify which genes have the mutations that cause the myelin defects, and determine the roles of those genes normally have in producing myelin.

The results of this research could provide clues that would lead to new ways to enhance myelin repair and restore nerve function in MS.

Heather Wishart, PhD

Dartmouth College

Lebanon, NH

Award: Research Grant

Term: 7/1/12-6/30/14; Funding: \$300,236

Title: "Imaging the neural basis of pain in patients with MS"

Summary: Using advanced MRI analysis to determine how the brain regions associated with pain are affected by MS.

Nervous system damage caused by multiple sclerosis can cause a variety of symptoms. One problem often experienced by people with MS is pain that can sometimes be severe enough to interfere with daily activities. The experience of pain is complex, with contributions from pain receptors throughout the body and processes that occur in various regions of the brain.

In this research project, Heather Wishart, PhD, is investigating the role of nerve cell damage in the part of the brain known as the thalamus, in pain experienced by people with MS. Previous research shows changes in the size of the thalamus in people with MS that indicate that nerve cell loss. Now Dr. Wishart and colleagues are correlating advanced MRI analysis techniques that measure loss of material from the thalamus with an array of clinical measures of the level of pain people with MS experience.

This work will help establish how damage to the brain circuits that process pain information contributes to the pain some people with MS experience, and could lead to clues for improved pain management.



Tracy Yuen, PhD

University of California San Francisco
San Francisco, CA

Award: Postdoctoral Fellowship

Mentor: David Rowitch, MD, PhD

Term: 7/1/12-6/30/15; Funding: \$163,103

Title: "The regulation of oligodendrocyte precursor remyelination by glucocorticoids and the Wnt pathway"

Summary: Studying how glucocorticoids, steroid-like drugs often used to treat acute MS attacks, may influence the repair of myelin.

Myelin, the material that surrounds and insulates nerve fibers, is damaged and destroyed in the brain and spinal cord by MS. The cells that make and maintain myelin, oligodendrocytes, are also damaged and destroyed. Oligodendrocyte precursor cells (OPCs) can develop into oligodendrocytes and are found in regions of myelin damage. However, these OPCs often fail to mature into oligodendrocytes and repair myelin rapidly enough to keep up with the damage in MS. Drugs known as glucocorticoids are commonly used to treat MS relapses, but it is not known whether these drugs affect myelin repair by oligodendrocytes.

Tracy Yuen, PhD, is investigating how glucocorticoids affect OPCs and myelin repair. Dr. Yuen is looking at how one such glucocorticoid, called dexamethasone, affects the development and repair of myelin in slices of brain tissue. In addition, she is looking at whether dexamethasone alters the rate at which OPCs develop and transform into myelin-producing oligodendrocytes in development and repair in mice.

The results of this research will clarify whether and how corticosteroid drugs affect myelin repair, and could provide clues for improving the use of corticosteroids and related drugs to treat MS.



End MS Forever

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.

Three new projects focus on ending MS forever. Their work also applies to efforts to STOP MS.



Lloyd Kasper, MD

Dartmouth College



Lebanon, NH

Award: Research Grant (PENDING)

Term: 7/1/12-6/30/2016;

Funding: \$685,573

Title: "Regulation of immunity by gut commensal bacteria in MS"

Summary: Looking at whether a molecule produced by common bacteria in the intestines may hold promise for treating MS or provide clues to how MS is triggered.

Funded in full by a Conrad N. Hilton Foundation grant to the National MS Society Southern California & Nevada Chapter

MS involves immune-system attacks against the brain and spinal cord. Although genes have a major role in determining who is susceptible to MS, factors from the environment also influence the activity of the immune system. The gut including the small and large intestine is the largest immune organ in the mammalian body. Each of us has millions of commensal bacteria living in our guts. Most of these bacteria are harmless as long as they remain with the inner wall of the



intestine. They play a critical role in our normal physiology, and are critical in the establishment and maintenance of immune balance by the molecules they release. These molecules are absorbed by the complex structure of immune cells that are contained in the immune tissue associated with the gut.

Lloyd Kasper, MD, is examining the effects of a molecule called polysaccharide A (PSA) that is released by specific species of gut bacteria (*Bacteroides*) that colonize almost 95% of people worldwide. Previous work showed that PSA can reduce the effects of EAE, an animal disease similar to MS, by stimulating the production of immune system cells that regulate inflammation. Now Dr. Kasper is investigating how bacterial PSA affects immune system cells from healthy individuals and people with MS when the cells are cultured in the laboratory.

The results of this research could open new pathways for stopping immune attacks in people with MS.

Jorge Oksenberg, PhD

University of California San Francisco
San Francisco, CA

Award: Research Grant (PENDING)

Term: 4/1/12-3/31/17; Funding: \$1,560,377

Title: "MS DNA Bank as a resource for genetics studies"

Summary: Banking genetic material from individuals and families with MS as a shared resource for studies searching for genes that confer susceptibility to MS.

MS is not inherited in the classic sense, but there is a wealth of evidence that genetic factors confer susceptibility to MS. With funding from the National MS Society, the UCSF group established a DNA bank that spearheaded multiple successful collaborations to identify variants in the genome that influence the individual's risk to

develop multiple MS. Dr. Jorge Oksenberg is now taking over leadership of this strategic resource. The group's goal is to maintain and further develop this unique MS bio-repository to allow researcher within and outside this group to test and confirm novel ideas.

The DNA Bank is maintaining and expanding its core DNA repository of MS patients, family members and unrelated controls, linking it to a sophisticated relational database system for the storage and pairing of detailed sample inventory, clinical, demographic, and laboratory data. Blood samples will be drawn for storage of serum, cells, DNA and RNA. Urine and stool specimens will be collected in a subset of individuals.

They will also assemble data using questionnaires and interviews to assess historical as well as contemporary exposures to potential risk factors and to document comorbidities, education, and lifestyle. This Bank provides an outstanding opportunity to identify and characterize MS-related genes. This information may translate into clinically useful genetic biomarkers and reveal novel targets for new therapies.

Stanley Perlman, MD, PhD

University of Iowa

Iowa City, IA

Award: Research Grant

Term: 7/1/12-6/30/15; Funding: \$103,125

Title: "Pathogenesis of Demyelination in Mice Infected with a Neurotropic Coronavirus"

Summary: Looking for a way to specifically control immune system attacks against myelin in a viral disease similar to MS, for clues to stopping MS and ending it forever.

MS involves immune-system attacks against nerve-insulating myelin in the brain and spinal cord. There are many types of immune system cell; some carry out the



STOP. RESTORE. END.

attacks against targets, while others suppress or prevent attacks.

Stanley Perlman, MD, PhD, is studying immune system responses to a specific virus in mice. Some of the immune system cells that respond to a specific portion of a protein from the virus also recognize and attack myelin in the brain and spinal cord of the mice. Other cells, known as regulatory T cells or Tregs, develop during an infection and prevent further attacks on myelin. Dr. Perlman is attempting to determine the factors that influence the balance between attacking immune cells and the Tregs that limit attacks.

The results could provide groundwork for developing therapies that would specifically control the immune cells that attack myelin in MS while not suppressing the beneficial actions of immune system. By exploring a model disease that is triggered by a virus, this study may also offer clues to how MS is triggered, and how it might be prevented.

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