



NEW RESEARCH

Newly Funded Projects/ Spring 2011

\$17.5 Million for 50 New MS Research Projects

The National MS Society has just launched 50 new MS research projects, with cumulative multiyear commitments of \$17.5 million. These new projects are part of our comprehensive research program aimed at stopping MS, restoring function, and ending MS forever.

The scope of this current launch is made possible by generous support of Society chapters and individual donors. 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.

The new projects include clinical trials testing novel approaches to stopping MS activity and protecting the nervous system

from MS damage; studies of natural molecules that may stimulate repair of the nervous system to restore function; and a study comparing the activity of several viruses that may be involved in triggering immune attacks in people with MS, leading to clues to ending MS through prevention.

Following are brief summaries of the new research projects, grouped according to avenues of MS.

STOPPING MS

Therapy/Management

Searching for better treatments to stop all forms of MS is a high priority for the National MS Society. Well-designed clinical trials are crucial to determining the safety and effectiveness of therapies for MS. The Society's longstanding investment led to better trial designs and to most of the approved therapies for MS.

The National MS Society has current, multi-year commitments of \$11.7 million to support some 22 research projects focusing on improving therapies for people with MS, including Sylvia Lawry Physician Fellowships that provide training in designing and conducting MS clinical trials.

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Raju Kapoor, MD

National Hospital
London, United Kingdom

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$800,515

"A phase II trial of neuroprotection with phenytoin in acute optic neuritis"

A clinical trial to determine whether a therapy for epilepsy can prevent nerve fiber damage in optic neuritis, often an early stage of MS.

Protecting nerve fibers from damage to stop MS progress is a key goal of research. There is evidence that some of the damage to nerve fibers results from their exposure to sodium ions when their protective myelin coating is removed in the course of the immune attack on the brain and spinal cord. The drug phenytoin, which is used to treat epilepsy, blocks entry of sodium ions into nerve fibers.

In this phase II clinical trial, Dr. Kapoor is testing whether phenytoin can reduce or prevent nerve fiber injury significantly more than inactive placebo in 90 people with optic neuritis. Optic neuritis – inflammation of the optic nerve – causes a loss of vision and often is the first symptom in people who go on to develop MS. Damage to optic nerve fibers can be measured relatively easily using a scan known as optical coherence tomography. Dr. Kapoor's team is using this scan to determine the effects of phenytoin on nerve fibers, and they also are measuring visual function to assess the extent to which treatment improves recovery.

Positive results could lead to a full-scale clinical trial to see whether phenytoin can prevent nerve fiber damage to stop the progression of MS.

Ellen Mowry, MD, MCR

(Transferring to Johns Hopkins University, Baltimore)

Area: Maryland Chapter

Award: Research Grant

Term/Amount: 3 years; \$1,312,902

"A randomized controlled trial of vitamin D supplementation in multiple sclerosis"

A clinical trial investigating whether vitamin D supplements can alter disease activity in people with MS who are taking a standard therapy.

A number of genetic and environmental factors influence whether a person will get MS. Research is increasingly pointing to a reduced level of vitamin D in the blood as a risk factor for developing MS. In lab mice, vitamin D can reduce the effects of EAE, an MS-like disease, and growing evidence suggests it is time to test whether vitamin D can provide benefits to people who have MS.

Ellen Mowry, MD, MCR, is conducting a randomized, double-blind clinical trial to determine whether high-dose vitamin D added to standard therapy with glatiramer acetate (Copaxone®, Teva Pharmaceutical Industries) reduces the frequency of MS relapses. In this trial, 172 people who have MS and are receiving standard treatment daily will be randomly assigned to take either 600 IU or 5000 IU of vitamin D. Over two years, information about relapses, disability, MRI scans and other measures of MS activity will be collected. Comparing these measures will show whether high-dose vitamin D affects the course of MS.

This study will provide important evidence to show whether vitamin D supplements are a safe and effective addition to standard MS therapies.

Vijayshree Yadav, MD, MCR

Oregon Health & Science University
Portland, OR

Area: Oregon Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$491,950

"Lipoic acid as a treatment for acute optic neuritis: a pilot trial" A clinical trial to determine whether an oral antioxidant can prevent nerve damage in people with optic neuritis, often the first symptom of MS.

Optic neuritis, which causes blurring and loss of vision, can be one of the first symptom of MS. As with MS, optic neuritis involves damage to myelin, the material that surrounds and protects nerve fibers, and damage to the nerve fibers themselves. Current treatments for optic neuritis, such as corticosteroids, speed recovery from the initial attack, but do not prevent or reverse permanent damage to optic nerve fibers.

Vijayshree Yadav, MD, MCR, and colleagues recently reported that lipoic acid – an antioxidant – reduced inflammation and prevented nerve fiber loss in a mouse model of optic neuritis. They also have shown some immune system changes in an early study in people with MS. Now Dr. Yadav is treating 54 people who have optic neuritis with oral lipoic acid or an inactive placebo to see whether lipoic acid can protect the optic nerve and treat optic neuritis. In this trial, tests of visual acuity and direct measurements of the loss of nerve fibers in the back of the eye (retina) will be compared for the treatment and placebo groups.

This study could lead to a new strategy for preventing nerve fiber damage in optic neuritis, and potentially could be a strategy for neuroprotection in MS.

Clinical Trial Resources

Clinical trials help to determine if a potential therapy is safe and effective. People with MS who are willing to volunteer in these studies make it possible for all of us to look forward to new and better therapies. All of these resources can be found on our Website at nationalMSSociety.org/clinicaltrials:

Find local MS clinical trials recruiting participants: <http://www.nationalmssociety.org/research/clinical-trials/participate-in-clinical-trials/index.aspx>

Download a list of MS clinical trials around the world: <http://www.nationalmssociety.org/research/clinical-trials/participate-in-clinical-trials/download.aspx?id=224>

Download a brochure about things to think about when considering clinical trial participation: <http://www.nationalmssociety.org/research/clinical-trials/download.aspx?id=2583>

Take an online course to help you make the decision about whether to participate: <http://www.nationalmssociety.org/living-with-multiple-sclerosis/getting-the-care-you-need/my-life-my-ms-my-decisions/index.aspx>

Read about what it's like to participate in clinical trials. Download an article from Momentum magazine: <http://www.nationalmssociety.org/research/clinical-trials/download.aspx?id=10222>

Five New Sylvia Lawry Physician Fellows

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

Christina Azevedo, MD

Yale University School of Medicine
New Haven, CT

Area: Connecticut Chapter

Award: Sylvia Lawry Physician Fellowship

Mentor: Daniel Pelletier, MD

Term/Amount: 7/1/11-6/30/13; \$130,000

Christina Azevedo, MD, is completing a two-year fellowship at Yale University under the supervision of Daniel Pelletier, MD, an MS expert and senior researcher whose research focuses on advanced imaging techniques in MS. During the first year, she is obtaining a Master's degree in Public Health at Yale, which will teach her clinical trial methodology. During the second year, she is participating in clinical trials by enrolling patients and managing study protocols, and conducting a research project in which she is establishing a novel MRI technique as a useful marker for future clinical trials.

Alexandra Goodyear, MD

Stanford University

Palo Alto, CA

Area: Northern California Chapter

Award: Sylvia Lawry Physician Fellowship

Mentor: Lawrence Steinman, MD

Term/Amount: 8/1/11-7/31/13; \$130,000

Alexandra L. Goodyear, MD, is completing this fellowship at the Stanford MS Center, under the mentorship of Jeffrey Dunn, MD, Associate Director of Stanford's MS center, and MS expert Larry Steinman, MD. Dr. Goodyear is receiving formal training in the diagnosis and clinical care of people with MS, formal graduate training in biostatistics, epidemiology, and clinical trial design, and active collaboration with leading MS scientists in translational research, including the role of biomarkers in predicting treatment response and monitoring disease course.

Jennifer Graves, MD, PhD

University of California, San Francisco

San Francisco, CA

Area: Northern California Chapter

Award: Sylvia Lawry Physician Fellowship

Mentor: Emmanuelle Waubant, MD, PhD

Term/Amount: 7/1/11-6/30/13; \$130,000

Jennifer Graves MD, PhD, is undertaking her fellowship under the mentorship of Emmanuelle Waubant, MD, PhD, Director of both the MS Center Clinical Research Program and the Regional Pediatric MS Center at the University of California, San Francisco. Dr. Graves is participating in both clinics, developing expertise in the diagnosis and management of all aspects of MS,

Learn to Conduct Clinical Trials in MS

including knowledge pertaining to its natural history, neuro-ophthalmology examination, use of symptomatic therapies, and the effects of approved disease-modifying therapies. Dr. Graves is participating in a trial of riluzole (approved for treating ALS) for neuroprotection in early MS, among other trials. She also is participating in a project studying environmental and genetic susceptibility factors for pediatric MS. Dr. Graves is also completing a Master's degree in clinical research at UCSF.

Ilana Katz, MD

Mount Sinai School of Medicine
New York, NY

Area: New York City - Southern NY Chapter

Award: Sylvia Lawry Physician Fellowship

Mentor: Fred D. Lublin, MD

Term/Amount: 7/1/11-6/30/13; \$130,000

Ilana Katz, MD, is undertaking this fellowship at the Corinne Goldsmith Dickinson Center for MS at Mount Sinai Medical School, under the mentorship of MS clinical experts Fred Lublin, MD, and Aaron Miller, MD. She is participating in all aspects of clinical trials, including the planning stages, protocol design, implementation and analysis, and is completing a Masters of Science Program in Clinical Research from the Mount Sinai School of Public Health. The courses will consist of formal training in basic science for the clinical investigator as well as the logistics involved in clinical trial design and implementation. During this second year of the fellowship, she is designing a clinical research proposal.

**The Society supports
training for clinical trials
design and research to
ensure that there are MS
specialists who are ready
to test new therapies**

Jacqueline Nicholas, MD

Ohio State University
Columbus, OH

Area: Ohio Buckeye Chapter

Award: Sylvia Lawry Physician Fellowship

Mentor: Michael K. Racke, MD

Term/Amount: 7/1/11-6/30/14; \$195,000

Jacqueline A. Nicholas, MD, is completing her fellowship at The Ohio State University under the mentorship of MS expert Michael Racke, MD. She is undergoing formal training as a clinical trialist by completing a Masters in Public Health in Clinical Investigations, a program that includes extensive coursework in epidemiology, biostatistics and clinical trial design. She is joining academic MS specialists and trial coordinators in the ongoing management of several investigator-initiated and industry-sponsored trials, including ground-breaking studies using novel MRI technologies coupled with neuropsychometric assessments of people with MS.

RESTORING FUNCTION

Rehabilitation

Rehabilitation regimens that can help people with MS achieve maximal physical, psychological, social and vocational potential have gained increasing acceptance in recent years. But to convince doctors and insurers that rehabilitation really does help, there needs to be scientific evidence that can only come from carefully designed and conducted studies.

The National MS Society has current, multi-year commitments of about \$7 million to support 22 investigations focusing on rehabilitation in MS.

Robert Motl, PhD

University of Illinois at Urbana-Champaign
Urbana, IL

Area: Greater Illinois Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/13; \$286,700

"Project METS in MS: Multimodal exercise training stimulus in multiple sclerosis"

Comparing the effectiveness of a comprehensive exercise regimen on mobility and other functions in people with advanced MS.

Individuals with advanced physical disability from MS have few opportunities for exercise, and yet there is growing evidence that exercise is good for people with MS in terms of mental health, physical health, and even fatigue.

Robert Motl, PhD, is recruiting 40 people with advanced MS for a study comparing the impact of aerobic, resistance, and balance exercise programs versus a control regimen that offers stretching exercises. The primary outcomes will include a comprehensive set

of measures of mobility disability, as well as effects of these programs on lung function, muscle strength, and balance.

This study could provide clinicians and therapists with a stronger basis for integrating comprehensive exercise into regimens for managing the progression of mobility disability people who have MS.

Jacob Sosnoff, PhD

University of Illinois at Urbana-Champaign
Urbana, IL

Area: Greater Illinois Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/13; \$295,673

"Acute exercise, spasticity and functional outcomes in MS: differential effects of duration and intensity"

Evaluating the effectiveness of various cycling regimens for reducing spasticity in people with MS.

Spasticity refers to often sensations of stiffness and a wide range of involuntary muscle spasms, and is one of the more common symptoms of MS. Spasticity may be as mild as the feeling of tightness of muscles or may be so severe as to produce painful, uncontrollable spasms of extremities, usually of the legs.

Jacob J. Sosnoff, PhD, and colleagues have shown that 20 minutes of unloaded leg cycling exercise reduces spasticity in persons with MS for upwards of an hour. Now they are conducting a trial investigating the effects of different durations (10 and 20 minutes) and intensities (light, moderate and hard intensity) of a single bout of leg cycling exercise on spasticity in persons with MS, compared to controls without MS. The study will document exercise-induced alterations in spasticity and changes in postural control and gait.

These findings should contribute to the incorporation of a nonpharmacologic method of reducing spasticity into the treatment regimen of people with MS.

STOPPING MS

Tracking MS

To better understand the course of MS and factors that may influence that course, researchers are using advances in imaging and other techniques. This vital information may eventually be used to diagnose MS earlier, and to help track disease changes, either progression of disease, or improvements due to experimental treatments, before they are apparent clinically.

The National MS Society has current, multi-year commitments of about \$7.6 million to support research projects focusing on ways of tracking disease activity in MS.

Rohit Bakshi, MD

Brigham and Women's Hospital
Brookline, MA

Area: Greater New England Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$389,511

"Magnetic resonance disease severity scale for MS" Developing a scale of novel imaging technologies to more accurately measure damage to the nervous system in MS.

MS causes a number of changes in the structure of the brain and spinal cord. These changes include areas of inflammation, where myelin, the protective covering of nerve fibers, is damaged and lost. Nerve fibers and nerve cells also may be damaged or destroyed, leading to long-term disability.

Traditional magnetic resonance imaging (MRI) provides information mainly about regions of inflammation and myelin damage. Recent advances in the design and power of MRI machines enable them to reveal additional areas of MS damage.

In this research project, Rohit Bakshi, MD, is developing a composite scale that combines information from the latest MRI techniques to give a more complete evaluation of MS damage than has been possible in the past. This scale includes information about changes in the "gray matter" – the regions of the brain and spinal cord that contain nerve cells – to give a better clue about long-term disability. It also includes information about damage to the spinal cord, which has not been demonstrated adequately by more standard MRI techniques.

This magnetic resonance disease severity scale should provide a more comprehensive indication of the clinical significance of MRI results, as well as provide a new way to measure of the effectiveness of treatments in MS.

Advanced imaging techniques
will contribute to efforts to
predict an individual's disease
course and lead to better
ways to detect benefits
of therapies

Salim Chahin, MD

University of Pennsylvania
Philadelphia, PA

Area: Greater Delaware Valley Chapter

Award: NMSS-AAN Clinician Scientist
Development Award

Mentor: Laura J. Balcer, MD

Term/Amount: 7/1/11-6/30/14; \$244,568

"Retinal gray matter in MS: Relation of ganglion cell loss to vision and neurologic impairment" Measuring changes and damage to the optic nerve to develop a method for evaluating neuroprotective treatments in MS.

The immune attacks on the brain and spinal cord damage nerve fibers and their protective myelin coating. It is damage to nerve cells and fibers that leads to long-term disability in MS.

In this project, Salim Chahin, MD, is applying new techniques to measure damage to the optic nerve, which often is the first sign of MS. His mentor, Laura Balcer, MD, is a pioneer in the use of optical coherence tomography, OCT, a quick scan

that can measure thickness of the optic nerve. Dr. Chahin is using cutting-edge variations of OCT technology to measure changes in the thickness of the nerve fiber and ganglion cell layers of the retina at the back of the eye. He is correlating these changes with clinical measurements of disease activity in people with MS.

OCT is emerging as an important tool that could track the effects of therapies designed to prevent MS damage to nervous system tissues. This project will contribute to its continued development.

Julien Cohen-Adad, PhD

Massachusetts General Hospital
Charlestown, MA

Area: Greater New England Chapter

Award: Postdoctoral fellowship

Mentor: Bruce R. Rosen, MD, PhD

Term/Amount: 7/1/11-6/30/14; \$156,515

"In vivo study of white and gray matter pathology in the spinal cord using 7T MRI."

Using high-powered imaging technology to reveal details of spinal cord damage in people with primary-progressive MS.

Magnetic resonance imaging (MRI) has been used to study the damage that occurs in the brain when people have MS. Standard MRI machines are useful for evaluating damage in the "white matter" of the brain, where damage to myelin occurs. They are not powerful enough to reveal much detail in the "gray matter" of the brain or spinal cord, where damage to nerve cells may cause long-term disability. More powerful 7T (versus standard, lower-strength 1.5-3T) MRI systems now available for research yield clearer images of the gray matter in the brain and could provide useful information

about damage in the spinal cord, too.

Julien Cohen-Adad, PhD, and colleagues are improving 7T MRI technology to get highly detailed images of the spinal cord. They are then using this new equipment to study the extent of damage to the gray matter of 20 people who have primary-progressive MS (a type of MS with slowly worsening neurologic function), and correlating findings with clinical aspects of their disease.

The results of this study should shed light on how damage to the spinal cord contributes to MS symptoms and could provide new opportunities to evaluate therapies in clinical trials for MS.

Ilya Kister, MD

New York University

New York, NY

Area: New York City - Southern New York Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/12; \$130,121

"Development and application of an MS severity scale using patient-derived metrics of disease progression" Compiling a new way to assess cumulative disability in MS over many functions to provide a tool to improve care and conduct research.

The North American Research Committee on Multiple Sclerosis (NARCOMS) Patient Registry – a project initiated by the Consortium of MS Centers – contains records on disability and symptom severity for over 34,000 patients with MS in North America.

Ilya Kister, MD, is organizing these data into easy-to-use reference tables that would rank each participant's disease activity compared with that of other participants with the same disease duration. These tables

would provide a 'snap-shot' of disability progression in various domains, such as cognition, ambulation, dexterity, visual function, bowel/bladder problems, fatigue and others. The tables would enable clinicians and individuals with MS to determine how much disability an individual accumulated in various areas relative to other participants in the NAROCMS database who had the disease for equal number of years.

This unique study will help clinicians gauge an individual patient's disease severity, and thereby help guide provision of care.

STOPPING MS

Neuropathology – Understanding MS Damage

The immune attack that underlies MS unleashes a cascade of events that damage the wire-like arms of nerve cells (axons) and the insulating tissue (myelin) that wraps around axons, disrupting nerve signal transmission. Understanding these processes is crucial to efforts to stop disease progression and repairing the nervous system. The National MS Society has current, multi-year commitments of about \$5.4 million to support research projects focusing on neuropathology.

National MS Society Research

The National MS Society is committed to freeing the world of MS. Our global support of MS research and treatment focuses on three key areas: STOPPING the progression of the disease, RESTORING function that's been lost, and ultimately ENDING MS forever.

We do this by:

- Funding the most promising avenues
- Engaging the best and brightest minds
- Acting as a vital connector for people, resources and ideas
- Developing more and effective treatments faster
- Identifying and filling gaps in MS research

Research Objectives Outlined in Our Strategic Response 2011-2015

- We better understand the scientific mechanisms that lead to disease progression and we accelerate the development of new therapies.
- We pursue new avenues to discover how nerve cells are damaged and potentially repaired.
- We pursue new rehabilitation techniques and symptomatic treatments to restore neurological function and enhance quality of life.
- We identify risk and triggering factors that cause MS, and understand the biological interactions that lead to its development so that MS can be prevented.
- We expand and strengthen the quantity and quality of MS research worldwide to accelerate new discoveries and treatments for people with MS.

Society Research Spending:

\$37 million in 2010 for 325 projects

Cumulative Investment:

\$721 million (by end FY '10) since first 3 grants in 1947

Major Types of Society Research Support:

Grants: multiyear investigations by university-based scientists for basic and clinical research

High risk/high potential Pilot grants: one-year awards to test innovative, cutting-edge ideas

Industry Partnerships: milestone-driven drug development funding for private companies

Fellowships: to attract and train promising young investigators and doctors to focus on MS

Rehabilitation Research Fellowships: to meet the unmet need for specialists trained to conduct quality rehabilitation research

Health Care Delivery and Policy Contracts: to inform advocacy efforts and enhance quality of life for people with MS

Our Research Fundraising Goal: We will raise \$250 million for MS research by 2015

Learn more about NOW — An MS Research Revolution: nationalmssociety.org

Amit Agarwal, PhD

Johns Hopkins University
Baltimore, MD

Area: Maryland Chapter

Award: Postdoctoral fellowship

Mentor: Dwight E. Bergles, PhD

Term/Amount: 7/1/11-6/30/14; \$156,515

"Glutamatergic signaling between axons and glial progenitors in health and disease." Deciphering biological interactions and signals that may stimulate myelin repair in MS.

Myelin, the fatty material that protects nerve fibers and allows them to carry signals properly, is damaged in the brain and spinal cord in MS. Myelin is made by cells known as oligodendrocytes, which are also lost in MS. Immature oligodendrocyte precursor cells (OPCs) are capable of producing new oligodendrocytes to repair myelin, but they are unable to keep up with the pace of damage in MS.

In this fellowship, Amit Agarwal, PhD, is investigating how nerve fibers pass signals to OPCs that may trigger the formation of new oligodendrocytes. OPCs have structures on their surfaces known as glutamate receptors. These docking sites respond to glutamate, a "neurotransmitter" that is used for communication between many types of nerve cells. Using mice with genetically modified glutamate receptors on their OPCs, Dr. Agarwal is investigating how the OPCs respond to glutamate and similar chemicals, and whether these signals influence the OPCs to develop into oligodendrocytes.

This research could lead to techniques to increase the formation of new oligodendrocytes to repair myelin damage and restore function to people with MS.

Joel Pachter, PhD

University of Connecticut Health Center
Farmington, CT

Area: Connecticut Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$504,497

"Choroid plexus and autoimmune demyelination" Investigating the earliest stages of the immune attack for clues to preventing them in MS.

MS involves immune system attacks on the brain and spinal cord. To get into the nervous system, immune cells must penetrate specialized blood vessels that form the blood-brain barrier (BBB), which typically protects the brain from potentially destructive elements in the bloodstream. Imaging scans clearly show that the BBB breaks down in MS, but it is possible that immune system cells may bypass the BBB initially and enter the brain through a structure known as the choroid plexus - especially early in the disease. The choroid plexus normally produces spinal fluid and controls fluid pressure in the brain.

In this research project Joel Pachter, PhD, is studying the choroid plexus in mice with EAE, an MS-like disease. He wants to identify the signaling molecules that may guide immune cells to the choroid plexus, enabling them to by-pass the normally restrictive BBB and more readily pass into the brain, where they attack the myelin coating on nerve fibers.

The results of this research could lead to a better understanding of the events that initiate the immune system attack in MS and point to novel ways to halt the attack.

Steven Petratos, PhD

Monash University
Melbourne, Australia
Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$510,555

"Targeting the molecular mechanisms of axonal degeneration in multiple sclerosis"

Exploring how alterations in myelin structure affect the behavior of nerve fibers.

In MS, a mistaken attack by the immune system damages and destroys myelin, the material that surrounds, protects, and supports the activity of nerve fibers (axons) in the brain and spinal cord. Without their myelin coating, axons fail to conduct signals properly, leading to symptoms of MS. Moreover, axons and their nerve cells are damaged, leading to long-term disability.

In this research project, Steven Petratos, PhD, is studying the activity of a molecule that inhibits the growth and repair of axons in EAE, a mouse model of MS. This inhibitory substance, known as Nogo-A, appears to be released in regions of myelin damage. Mice that have been genetically modified so that they are unable to produce Nogo-A experience less severe EAE. Dr. Petratos and colleagues are attempting to develop a technique to deliver a substance that attaches to Nogo-A to see whether "mopping it up" will reduce the effects of disease.

The results of this research could lead to new treatment approaches for MS that would help to prevent nerve tissue damage and reduce long-term disability.

Nicole Schaeren-Wiemers, PhD

University of Basel, Klingelbergstrasse
Basel, Switzerland

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$404,238

"The role of innate immunity and glial metabolism in MS grey matter pathology"

Investigating how immune system activity may contribute to long-term disability in MS and its models.

MS involves damage and destruction of myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. Much of the damage occurs in areas known as "white matter," due to the large number of nerve fibers covered by myelin in these regions. Recent research has revealed damage in other areas of the brain and spinal cord, known as "grey matter" (which contain the bodies of nerve cells). Damage to nerve cells contributes to long-term disability in people with MS.

In this research project Nicole Schaeren-Wiemers, PhD, is studying abnormalities in brain cells – known as astrocytes – that surround and help support nerve cells in the grey matter. In previous studies Dr. Schaeren-Wiemers found evidence of low-level immune cell activity and a decrease in some of the functions of astrocytes in brain tissue from people who had MS. Now she is investigating further to see how the inflammation is related to the altered activity of astrocytes, and whether this contributes to nerve cell damage in tissue isolated from people MS and in MS disease models.

Understanding how MS affects cells in the grey matter could lead to new therapies to prevent long-term disability in people who have MS.

STOPPING MS

Why the Immune System Goes Awry

The current therapies for MS emerged from our growing understanding of how the immune system works and how it can be manipulated to suppress or regulate immune attacks. We especially need to know more about the molecules that the immune system uses to attack the nervous system, because each of these serves as a potential therapeutic target for new therapies.

The National MS Society has current, multi-year commitments of about \$36 million to support research projects focusing on stopping the immune system attack in MS.

Clare Baecher-Allan, PhD

Brigham and Women's Hospital
Boston, MA

Area: Greater New England Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$518,466

"Mechanisms of Treg resistance in patients with multiple sclerosis" Looking for ways to restore the normal balance of the immune system to prevent it from attacking the nervous system in MS.

In MS, the immune system, which normally works to protect people from infectious agents such as bacteria or viruses, mistakenly attacks myelin in the brain and spinal cord. Myelin surrounds and protects nerve fibers. The immune system has numerous types of cells, some of which activate and direct immune system activity, while others slow down or turn off activity.

Clare Baecher-Allan, PhD, is studying the influence of an immune cell known as a regulatory T cell (Tregs). These cells ordinarily suppress the activity of other immune

Understanding how and why the immune system misfires to cause damage in the nervous system will lead to better, more targeted therapies for all types of MS, including progressive forms of the disease

system cells that might damage the nervous system. Dr. Baecher-Allan and others have found that Tregs are somehow defective in people with MS, so their ability to control immune attacks is compromised. Now her team is examining immune cells isolated from people with MS to better understand how immune system cells escape from the control of Tregs and what genetic factors may be involved.

This research should help unravel why the normal regulation of the immune system fails in MS, and could lead to new treatments that restore regulation and shut off the attacks in MS.

Jeffrey Bluestone, PhD

University of California, San Francisco
San Francisco, CA

Area: Northern California Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$498,211

"CD4+ FoxP3 lineage cells in CNS autoimmune disease and therapy"

Looking for ways to use the immune system's regulatory mechanisms to stop immune attacks in MS.

In MS, the protective layer of myelin that surrounds nerve fibers in the brain and spinal cord is damaged and destroyed by the immune system. Nerve fibers are damaged as well, contributing to long-term disability. The immune system includes numerous types of cells, some of which activate an attack while others suppress activity.

In this research project, Jeffrey Bluestone, PhD, is studying a group of immune system cells, known as Tregs, that suppress the activity of the cells that attack myelin. Research shows that Tregs may be defective in people with MS, but the basis for these defects is unknown. Dr. Bluestone and his colleagues are using a novel mouse model of MS to study Tregs, and have developed unique tools for tracking these cells during the course of MS-like disease.

The results of this research could lead to a strategy for enhancing the ability of Tregs to prevent the immune attack in MS.

Youhai Chen, MD, PhD

University of Pennsylvania
Philadelphia, PA

Area: Greater Delaware Valley Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$576,675

"Regulation of autoimmune encephalomyelitis" Studying the action of a "master switch" that controls immune system activity in MS.

MS involves immune-system attacks on myelin, the material that coats and protects nerve fibers. Nerve fibers may also die, leading to long-term disability. The attack involves a large number of genes that instruct the movement and activity of immune system cells and signaling proteins.

Youhai Chen, MD, PhD, is studying a gene that appears to be a conductor or a "master switch" that coordinates the action of many inflammatory genes in MS. Dr. Chen is investigating how this gene, known as "c-Rel", controls other genes, and is looking for drugs that could act on c-Rel to slow or block immune activity to prevent nervous system damage in MS. His team is using a combination of genetic, biochemical, and genomic approaches.

This line of research could lead to important new therapies that would slow or stop the destruction of myelin, and help maintain normal nerve function in MS.

Christopher Harp, PhD

Northwestern University
Chicago, IL

Area: Greater Illinois Chapter

Award: Postdoctoral fellowship

Mentor: Stephen D. Miller, PhD

Term/Amount: 7/1/11-6/30/14; \$143,223

"B cell depletion therapy in the treatment of relapsing EAE." Studying a model of MS to improve safety of a potential MS treatment.

The immune system, which normally protects against infectious agents such as viruses and bacteria, mistakenly attacks the brain and spinal cord of people who have MS. In clinical trials, the monoclonal antibody rituximab sharply reduced the number of immune system cells known as "B cells," decreasing MS attacks. However, a few cases of a fatal disease, progressive multifocal leucoencephalopathy (PML), have occurred in people treated with rituximab, possibly because the reduced activity of the immune system allows a virus that causes PML to be activated.

In this fellowship, Christopher Harp, PhD, is studying B cell depletion in mice with EAE, a disease similar to MS. In EAE, as in MS, B cell depletion reduces the symptoms of the disease. Dr. Harp and colleagues are trying to determine the steps in the immune system attack on myelin that are altered by B cell depletion, and are looking for ways to mimic the beneficial effects without decreasing the immune system's protection against infection.

The results of this work could lead to development of therapies that are as effective for treating MS, but without risking re-activation of potentially fatal infections.

Shen-Yi Howng, PhD

University of California, San Francisco
San Francisco, CA

Area: Northern California Chapter

Award: Postdoctoral fellowship

Mentor: Ying-Hui Fu, PhD

Term/Amount: 7/1/11-6/30/14; \$150,800

"Understanding miRNA regulation of astrocyte function in myelination, demyelination, and remyelination."

Studying brain cells that contribute to myelin formation and destruction in MS, for clues to reducing nervous system damage.

In MS, myelin, the protective coating of nerve fibers, is damaged and destroyed by an immune system attack on the brain and spinal cord. Brain cells, known as astrocytes, appear to be involved in this attack. Astrocytes around areas of myelin damage may have contradictory roles, however, as they release molecules that attract cells that repair myelin but also release other molecules that may damage nerve fibers.

Shen-Yi Howng, PhD, is studying substances known as microRNAs (miRNAs) that regulate what proteins cells produce. Dr. Howng and colleagues are attempting to learn how miRNAs control the proteins that astrocytes make during the normal production and maintenance of myelin in mice. They are also using the mice to look at how miRNAs alter the behavior of astrocytes in areas of myelin damage, similar to that which occurs in MS.

This research will help to understand the role of astrocytes in myelin formation and destruction, and may lead to new insights for reducing the myelin damage that occurs in MS.

Dimitry Kremmentsov, PhD

University of Vermont
Burlington, VT

Area: Greater New England Chapter

Award: Postdoctoral fellowship

Mentor: Cory Teuscher, PhD

Term/Amount: 7/1/11-6/30/14; \$150,800

[Funded in part by the Greater New England Chapter in honor of Dr. Hill Panitch](#)

"p38 MAPK as a female-specific druggable target in autoimmune disease of the CNS." Studying the effects of a drug that halts a disease similar to MS in female mice.

MS involves an "autoimmune" response, in which the immune system – which ordinarily protects against infectious agents such as viruses and bacteria – mistakenly attacks myelin, the material that surrounds nerve fibers in the brain and spinal cord. Immune system cells employ a number of molecules to coordinate their activity. Some of these signaling molecules activate immune responses while others limit immune system activity. Most signaling molecules are parts of long pathways in which one molecule causes others to be released.

Dimitry Kremmentsov, PhD, is studying one of the immune system signaling pathways, "p38 MAPK," which is activated in immune cells that attack myelin. His team has found that a drug that blocks the p38 MAPK pathway prevents or halts an MS-like disease in female mice, but has no effect on it in male mice. Now the team is working to determine how the drug works, why it is only effective in female mice and whether similar drugs may treat the disease in both sexes.

This work could lead to new ways to prevent or stop disease activity in MS.

Lori Lebson, PhD

The Johns Hopkins University
Baltimore, MD

Area: Maryland Chapter

Award: Postdoctoral fellowship

Mentor: Peter A. Calabresi, MD

Term/Amount: 7/1/11-6/30/13; \$102,324

"The Role of kruppel-like Factor 4 in the development of EAE." Studying a signaling molecule that may influence resistance to MS therapy.

In MS, a mistaken attack by the immune system damages the brain and spinal cord. There is some evidence that this attack may involve different types of immune system cells in different people, and this may account for some of the variability in responses to treatment.

Lori Lebson, PhD, is studying the role of an immune signaling molecule known as "kruppel-like factor 4" (KLF4) in the MS-like disease EAE. This signaling molecule stimulates a type of immune system cell that damages nerve-insulating myelin but appears to be unresponsive to treatment with interferon beta, an approved class of MS therapy. Dr. Lebson is using genetically modified mice to see how KLF4 activates these immune cells and to look for ways to prevent their activation.

This research could lead to the development of new treatments for people with MS, especially those who do not respond well to the interferons.

Scott Lovitch, MD, PhD

Brigham and Women's Hospital
Boston, MA

Area: Greater New England Chapter

Award: Postdoctoral fellowship

Mentor: Arlene H. Sharpe, MD, PhD

Term/Amount: 7/1/11-6/30/14; \$162,481

"The role of PD-1 in maintenance of peripheral tolerance and control of EAE."

Studying how to manipulate a molecule to turn off immune system attacks in MS.

The immune system performs a delicate balancing act: it must recognize proteins belonging to foreign infectious agents, such as viruses or bacteria, and destroy them, but ignore normal body proteins, which often have similar properties. A complex network of control mechanisms and molecules regulates the behavior of the immune system. In MS, and in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, the control of the immune system breaks down, and it attacks myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord.

Scott Lovitch, MD, PhD, is studying the role of PD-1, a molecule that acts as a brake on immune system activity. Mice without PD-1 develop more severe EAE, an MS-like disease, while mice with increased levels of PD-1 are resistant to EAE. Dr. Lovitch is using mice in which the levels of PD-1 can be manipulated to determine how this molecule limits or prevents damage to myelin.

The results of this research could provide clues for developing MS therapeutic strategies that manipulate the function of PD-1.

William Schmalstieg, MD

Mayo Clinic College of Medicine
Rochester, MN

Area: Minnesota Chapter

Award: Postdoctoral fellowship

Mentor: Charles L. Howe, PhD

Term/Amount: 7/1/11-6/30/14; \$175,920

"Role of dysregulated ionic homeostasis in CD8+ T cell mediated axon injury."

Investigating a novel approach to preventing nerve fiber damage in MS.

MS occurs when the immune system attacks and damages myelin, the material that surrounds and protects nerve fibers (axons). Axons are damaged as well, contributing to long-term disability.

William Schmalstieg, MD, is investigating how axons are destroyed in regions of myelin damage and is looking for ways to prevent the loss of axons. The laboratory in which he is working has found that CD8+ T cells – a type of immune cell – damage axons in a mouse model of MS. Nerve cells try to maintain an internal balance of chemicals, a process known as homeostasis. CD8+ T cells release molecules that may cause axons to lose control of their homeostasis, resulting in the death of the fibers. Dr. Schmalstieg is testing drugs that may prevent this damage in cells isolated in the laboratory and in mice with MS-like disease.

This research could provide clues for new treatments that would prevent axon damage and long-term disability in MS.

Patrick Shaw, PhD

New York University
New York, NY

Area: New York City - Southern New York
Chapter

Award: Postdoctoral fellowship

Mentor: Stefan Feske, MD

Term/Amount: 7/1/11-6/30/14; \$156,515

"The role of store-operated Ca²⁺ entry in Th17 cell function and neuroinflammation during EAE." Investigating a novel method with potential for controlling immune attacks in MS.

In MS, the immune system mistakenly damages myelin, a material that surrounds and protects nerve fibers in the brain and spinal cord. Nerve fibers themselves are also damaged. There are many types of immune cells; some activate immune system responses, while others inhibit them. Immune cells use many different types of chemicals to signal each other and coordinate their activity.

Patrick Shaw, PhD, is looking at how a group of immune T cells, known as Th17 cells, utilize chemicals known as "calcium ions" during the course of MS-like disease in mice (called EAE). In both MS and EAE, Th17 cells increase disease activity and damage to myelin. However, in mice with mutations of the genes related to calcium ion function, EAE does not develop. One goal of this research is to see whether disrupting calcium ion activity in Th17 cells can treat or reverse EAE.

This work could lead to a novel strategy for slowing or stopping immune attacks and tissue damage in MS.

Mari Shinohara, PhD

Duke University Medical Center
Durham, NC

Area: Eastern No. Carolina Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$538,553

"Study on innate immune inflammation that enhances EAE" Studying immune inflammation in a model of MS for insights into stopping progression of MS.

Our bodies have two kinds of immune systems: One is called the innate immune system and the other is the adaptive immune system. The innate immune system is the front-line mechanism that protects us against microbial infections. Recent research suggests that inflammation triggered by the innate immune system may also have a significant impact on MS. However, the mechanism by which innate immunity impacts on MS is poorly studied compared to the adaptive immune mechanism.

In this project, Mari Shinohara, PhD, is studying innate immune sensors that trigger inflammation. Her team's research suggests that the MS-like disease in mice, EAE, is worsened when certain sensors are active. The team is examining the activation of sensors during the course of EAE. They also are exploring which inflammatory conditions determine the efficacy of interferon beta (an approved approach for treating MS).

These studies should yield new information about underexplored aspects of the immune attack in MS, and may provide an indicator of people who best respond to interferon therapy.

E. Sally Ward, PhD

UT Southwestern Medical Center at Dallas
Dallas, TX

Area: South Central

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$483,717

"Antigen targeting and tolerance in murine EAE" Looking at ways to stop the immune system attack against myelin in MS-like disease.

The immune system usually detects and destroys infectious agents such as bacteria and viruses. In MS, however, this system mistakenly attacks and damages myelin, the protective coating around nerve fibers. At some point the nerve fibers are also damaged. The balance between "tolerance" – where the immune system ignores myelin – and the attack that occurs in MS is controlled by a number of molecules that immune cells use to signal each other.

In this research project, E. Sally Ward, PhD, is using EAE, a mouse model of MS, to study how tolerance might be induced to turn off the immune system attack. Her team is administering modified versions of one of the myelin proteins that trigger immune attacks in EAE. Some of these modified proteins produce tolerance of immune system cells that cause EAE in mice, and thereby reduce disease activity.

This research could lead to the development of a new treatment strategy that would teach the immune system to ignore myelin, preventing the attacks that cause nerve tissue damage in MS.

**Decades of Society-
supported research have
been laying the
groundwork for finding
ways to restore function in
people with MS**

RESTORING FUNCTION

Nervous System Repair

Decades of research into nerve physiology and the biology of myelin and glial cells that support nerve cells have been laying the groundwork for finding ways to restore normal function in individuals with MS.

The National MS Society has current, multi-year commitments of about \$17.5 million to support research projects focusing on finding ways to repair the nervous system and restore lost function in people with MS. In addition, our \$18.3 million investment toward understanding myelin growth, function and repair (described in the next section) also feed this effort.

Douglas Feinstein, PhD

University of Illinois at Chicago
Chicago, IL

Area: Greater Illinois Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$450,582

"Locus Coeruleus Damage in EAE and MS"

Studying a new approach to treating MS by inhibiting damage to a region in the brain.

MS involves immune-system attacks on the brain and spinal cord, damaging myelin, the protective coating of nerve cells. Nerve cells are damaged as well, and this damage contributes to long-term disability. Nerve cells make noradrenaline, a chemical that transmits signals between nerve cells and also protects nerve cells from some forms of damage. Noradrenaline is distributed widely throughout the brain and spinal cord, and it might help protect other nerve cells from damage in MS.

Douglas Feinstein, PhD, is using several approaches to see how noradrenaline may affect MS. First, he is measuring damage to nerve cells isolated from the brains of people with MS and mice with EAE, a model of MS. He is especially focusing on a specific part of the brain, called the Locus coeruleus, where most of the nerve cells that make noradrenaline are located. He is also looking at whether several drugs that increase noradrenaline – some of which are in clinical trials for other diseases – can enhance the function and survival of these nerve cells and reduce the severity of EAE.

The results of this research could rapidly lead to trials of treatments to protect nerve cells and prevent disability in MS.

Glenn Matsushima, PhD

University of North Carolina at Chapel Hill
Chapel Hill, NC

Area: Eastern No. Carolina Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$527,262

"Enhancing oligodendrocyte survival"

Exploring a therapeutic strategy for improving survival of cells that are needed to repair nerve-insulating myelin in MS.

During MS, the immune assaults on the brain and spinal cord lead to tissue loss and neurological dysfunction. Specifically, the myelin that wraps around nerve fibers is damaged, and so are the cells that make myelin (oligodendrocytes) and the nerve fibers themselves.

Growth factors have been shown to enhance the survival of oligodendrocytes and may reduce activity of MS-like disease in rodent models. However, the therapeutic potential of growth factors face problems because of other factors can hinder or block their function, or prevent transport into the brain. Glenn Matsushima, PhD, is developing a tool to detect other agents that may enhance the survival of oligodendrocytes. His team is screening thousands of compounds to identify drugs or molecules that may provide survival benefits to these critical brain cells. Any candidate drugs that are identified through the screen will be further examined for efficacy and prevention of myelin destruction.

These studies may lead to the discovery of novel usage of drugs that could be developed to enhance the survival of oligodendrocytes and stimulate myelin repair in MS.

David Rowitch, MD, PhD

University of California, San Francisco
San Francisco, CA

Area: Northern California Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$359,868

"APC gene function in oligodendrocyte development and myelin regeneration"

Studying the role of a gene that may be important for myelin repair in MS.

Initially, when myelin – the material that surrounds and protects nerve fibers – is damaged in MS, spontaneous repair occurs. The attempts to repair myelin, however, do not keep up with the damage. Nerve fibers are damaged as well, which contributes to long-term disability.

In a recent study, David Rowitch, MD, PhD, and colleagues demonstrated that the "Wnt signaling pathway" – a complex network of proteins that interact during brain development – may play an important role in the failure of myelin to repair itself in people with MS. Now Dr. Rowitch is studying the role of Wnt signaling further through the APC gene, which regulates this pathway. Dr. Rowitch and colleagues are using cells grown in laboratory dishes and mice with altered APC genes to find out the exact role of the APC gene and to look for drug treatments that may enhance myelin repair.

The results of this research could lead to new treatments to enhance myelin repair in people with MS.

Bridget Shafit-Zagardo, PhD

Albert Einstein College of Medicine
Bronx, NY

Area: New York City - Southern New York Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$587,268

"Strategies to enhance neuroprotection and repair in the inflamed CNS"

Looking for ways to protect against nerve tissue damage in MS.

MS occurs when the immune system attacks and damages myelin, the material that surrounds and protects nerve fibers. Nerve cells and fibers are damaged as well, contributing to long-term disability.

In this research project, Bridget Shafit-Zagardo, PhD, is studying several molecules that affect the survival of nerve cells. Her team is administering the human version of one of these molecules, known as gas6, to mice with several conditions that mimic the myelin damage in MS. Preliminary results indicate that this molecule does improve the survival of nerve cells after myelin damage. Dr. Shafit-Zagardo is also looking at whether gas6 enhances the treatment effect of interferon beta (an approved MS therapy) in these mouse models of MS.

This research should lead to better understanding of how to improve the survival of nerve fibers after myelin has been damaged, and could provide clues for treatments that would be neuroprotective in people with MS.

11 New Pilot Research Projects Launched

These projects were recently funded through the Society's Pilot Research Program, designed to quickly investigate novel or high-risk ideas. They are grouped according to three overarching aims stopping MS, restoring function, and ending MS forever.

STOPPING MS

Robyn Klein, MD, PhD, Washington University, Saint Louis, MO, Gateway Area Chapter

3/1/11-2/29/2012; \$44,000; "Role of lymphoid chemokines in B and T cell interactions during CNS autoimmunity" Mechanisms and immune cell interactions that lead to the misguided MS attacks on the nervous system.

Anat Achiron, MD, PhD, Tel Aviv University, Tel Hashomer, Israel

3/1/11-2/29/2012; \$40,000; "Regulatory networks operating to reduce disease activity in benign MS" How some people with MS to avoid significant disability, for clues to therapies to prevent progression.

Rebecca Spain, MD, MSPH, Oregon Health & Science University, Portland, OR, Oregon Chapter

Funded by MS Hope for a Cure through the New York City-Southern New York Chapter

12/1/10-11/30/11; \$44,000; "Validation of an instrumented gait measure, the immobility, in MS" The sensitivity and quality of an electronic instrument to detect gait abnormalities and to measure changes in mobility over time.

Ralph Suarez, PhD, Harvard Medical School, Boston, MA, Greater New England Chapter

Funded by MS Hope for a Cure through the New York City-Southern New York Chapter

12/1/10-11/30/11; \$44,000; "Functional magnetic resonance imaging of pediatric MS" Measuring the ability of the brain to reorganize in early-stage MS to preserve cognitive function.

Ruchika Prakash, PhD, Ohio State University, Columbus, OH, Ohio Buckeye Chapter

Funded by MS Hope for a Cure through the New York City-Southern New York Chapter

12/1/10-11/30/11; \$44,000; "Functional connectivity of the resting state networks in Multiple Sclerosis" Patterns of brain connections that may be early clues to difficulties with memory or thinking in MS.

RESTORING FUNCTION

Joseph Ciccolo, PhD, The Miriam Hospital, Providence, RI, Rhode Island Chapter

Funded by MS Hope for a Cure through the New York City-Southern New York Chapter

12/1/10-11/30/11; \$43,981; "Resistance training to enhance smoking cessation in MS" Testing whether an exercise program can help people with MS to quit smoking because it has been linked to disease progression.

L. Maureen Dunn, PhD, Hope College, Holland, MI, Michigan Chapter

12/1/10-11/30/11; \$32,487; "Home based balance rehabilitation in multiple sclerosis: Effect of nintendo wii fit" Using an interactive videogaming device to improve balance in people with MS.

Carolyn Schwartz, DSc, Delta Quest Foundation, Concord, MA, Greater New England Chapter

Funded by MS Hope for a Cure through the New York City-Southern New York Chapter

12/1/10-11/30/11; \$44,000; "An investigation of cognitive reserve and appraisal processes in MS" Characteristics of the mind that may contribute to the ability of an individual to preserve function in the face of damage caused by MS attacks.

John Kamholz, MD, PhD, Wayne State University, Detroit, MI, Michigan Chapter

4/1/11-3/31/2012; \$44,000; "Modulation of EAE with infrared light" Does exposure to infrared light have potential to protect the central nervous system from harm caused by MS?

ENDING MS FOREVER

Bryan Cullen, PhD, Duke University, Durham, NC, Eastern No. Carolina Chapter

4/1/11-3/31/2012; \$44,000; "Metagenomic characterization of viral infection in multiple sclerosis" Using cutting-edge technology to search for evidence of viral infection in people with MS.

Raymond Roos, MD, University of Chicago Medical Center, Chicago, IL, Greater Illinois Chapter

3/1/11-2/29/2012; \$44,000; "Saffold virus and demyelination disease" Does a newly identified human virus have the potential for playing a role in the development of MS?

Seema Tiwari-Woodruff, PhD

University of California, Los Angeles
Los Angeles, CA

Area: Southern California & Nevada Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$164,599

"Stimulating endogenous myelination and inhibiting axon damage" Studying how a molecule related to estrogen may be harnessed to limit nervous system damage in MS.

The clinical symptoms of MS subside during pregnancy, a time marked by a dramatic increase in circulating sex hormones such as estrogen. This fact has spurred interest in investigating the therapeutic effect of these hormones in MS patients, and a major clinical trial is underway.

Estrogens and molecules that bind to estrogen docking sites (receptors) ERalpha and ERbeta are promising treatments for MS-induced neurodegeneration. ERalpha is one protein implicated in breast and uterus cancer; so finding a specific drug that only acts on ERbeta would be desirable. Dr. Tiwari-Woodruff and colleagues have shown that such a molecule demonstrates neuroprotective effects in a mouse model of MS, and the team observed significant improvement in the amount of intact myelin and myelin-forming cells in treated mice. Myelin is the substance that insulates nerve fibers and is a major target of the MS attack. Now the team is investigating this potential therapy further to optimize timing of drug delivery and study its effects on gene and protein expression.

This research could lead to exciting new ways to prevent damage in MS.

Jason Weinger, PhD

University of California, Irvine
Irvine, CA

Area: Pacific South Coast Chapter

Award: Postdoctoral fellowship

Mentor: Thomas E. Lane, PhD

Term/Amount: 7/1/11-6/30/14; \$150,800
"Mechanisms of allograft rejection of neural stem cells." Studying a unique method aimed at stimulating myelin repair.

In MS, the immune system attacks and damages myelin, the protective coating of nerve fibers in the brain and spinal cord. Nerve fibers are damaged as well. Laboratory studies suggest that neural stem cells (NSCs, or immature nerve cells) can turn down immune attacks and stimulate myelin repair when injected into mice with MS-like disease. Small clinical trials are underway, or in the planning stages, to start investigating this concept in people with MS and related diseases.

Jason Weinger, PhD, is looking at ways to prevent the immune system from "recognizing" NSCs as foreign and thus worthy of immune attack. Working with mice that have a disease similar to MS, he is investigating the mechanisms involved in rejection of transplanted NSCs to devise a way to trick the immune system into ignoring the foreign NSCs. One potential method being studied is using immune cells from the donor of the NSC cells to induce tolerance of the NSCs in the recipient mouse, which will prevent rejection of the foreign NSCs and allow them to enhance repair of damaged myelin.

This research could ultimately contribute to the development of ways to stimulate repair of damaged myelin and restore function in people who have MS.

RESTORING FUNCTION

Myelin's Growth, Injury and Repair

Myelin insulates the wire-like extensions of nerve cells, speeding nerve conduction and protecting the nerve from harm. Because myelin is thought to be the main target of the immune attack that underlies MS, it's vital that we understand its development, function and repair.

The National MS Society has current, multi-year commitments of about \$18.3 million to support research projects focusing on myelin biology in MS.

Holly Colognato, PhD

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

Area: Long Island Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$565,739

"Adhesion-regulated signaling mechanisms during myelination and remyelination" Studying how immature cells are stimulated to form cells capable of repairing nerve-insulating myelin in MS.

In MS, myelin, the material that surrounds and protects nerve fibers, is damaged and destroyed in the brain and spinal cord.

Myelin is made by cells called oligodendrocytes, which are also damaged in MS. Immature oligodendrocyte precursor cells (OPCs) can develop into oligodendrocytes, and replace damaged myelin. However, this repair does not keep up with the damage in MS. The signals that cause OPCs to make new oligodendrocytes are not understood.

In this research project, Holly Colognato, PhD, is studying one of the signaling pathways that enable OPCs to develop into

oligodendrocytes capable of making new myelin. Dr. Colognato is using mice with genetic modifications that alter the molecules involved in transforming OPCs into oligodendrocytes, as well as in regulating their capacity for myelin production. Her study involves tracking repair of damaged myelin to see how these signaling alterations change the ability of the cells to make new myelin.

This research will increase understanding of how oligodendrocytes develop and produce myelin, and could lead to new avenues to improve repair of damaged myelin in MS.

Tara DeSilva, PhD

University of Alabama at Birmingham
Birmingham, AL

Area: Alabama - Mississippi Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$559,954

"Glutamatergic signaling in demyelination and remyelination in multiple sclerosis" Exploring how MS immune activity alters a brain chemical active during myelin damage and repair, for clues to stopping MS progression.

MS involves immune-cell infiltration into the brain and spinal cord that excites other immune processes including inflammation, causing damage to nerve-insulating myelin, the cells that make myelin (called oligodendrocytes), and the nerve fibers themselves. Glutamate, a neurotransmitter (a substance released from nerve cells to transmit nerve impulses to another cell) may play a role in the death of oligodendrocytes by overly exciting the central nervous system.

Because myelin is thought
to be a main target of the
immune attack in MS,
understanding its
development, function and
repair is vital to reversing
the damage to restore
function

Tara DeSilva, PhD, is studying how immune system activity affects glutamate's actions in oligodendrocytes isolated in the laboratory. Her team also is testing a strategy for blocking glutamate activity in mice with an MS-like disease. Finally they are examining what signals glutamate might be emitting during spontaneous myelin repair.

This project should provide important clues to new avenues to prevent MS nervous system injury and stimulate its repair.

Vittorio Gallo, PhD

The Children's National Medical Center
Washington, DC

Area: National Capital Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$537,577

"Role of Endothelin-1 in reactive gliosis and remyelination" Exploring a signaling molecule that may be key to improving myelin repair in MS.

In MS, myelin, the material that surrounds and protects nerve fibers, is damaged in the brain and spinal cord. In regions of myelin damage, cells known as astrocytes are activated. Other cells, including the oligodendrocytes that could repair myelin, and the immature oligodendrocyte precursor cells (OPCs) that form oligodendrocytes, move into regions of myelin damage. Although some myelin repair occurs, this repair does not keep pace with damage.

Various cells in regions of myelin damage communicate with each other by releasing molecules that stimulate or inhibit the activity of other cells. Vittorio Gallo, PhD, is studying one of these molecules known as endothelin-1 (ET-1). Preliminary results indicate that ET-1 is released by astrocytes in regions of myelin damage, and prevents OPCs that have migrated to the region from developing into oligodendrocytes that could repair the damage. Now Dr. Gallo is investigating ways to prevent ET-1 from acting on OPCs so that they can form new oligodendrocytes and repair damaged myelin.

This work could lead to new ways to repair myelin damage to restore function in people who have MS.

Danielle Harlow, PhD

University of Colorado
Aurora, CO

Area: Colorado - Wyoming Chapter

Award: Postdoctoral fellowship

Mentor: Wendy B. Macklin, PhD

Term/Amount: 7/1/11-6/30/14; \$150,800

"Chemotropic molecules in oligodendrocyte precursor migration."

Looking for clues to enhancing myelin regeneration in MS by naturally occurring repair cells in the brain.

Myelin, the fatty material that surrounds and protects nerve fibers, is destroyed in the brain and spinal cord in MS. The cells that manufacture and maintain myelin, oligodendrocytes, are also damaged. During development, immature cells known as oligodendrocyte precursor cells (OPCs) transform into oligodendrocytes. Some OPCs persist in adults, and they do make new oligodendrocytes that initially attempt to repair damaged myelin. However, OPCs and oligodendrocytes fail to move into areas of prolonged myelin destruction in people with MS.

Danielle Harlow, PhD, is studying "chemotropic" molecules that induce OPCs to move and provide them with clues about where to go. Using a combination of work with mice and with cells grown in the laboratory, Dr. Harlow is aiming to identify the clues that guide OPCs to sites of myelin production during development, and determine whether these clues are weakened or absent in regions of myelin damage. Deciphering these clues may provide new strategies for enhancing myelin repair in people with MS.

Trevor Kilpatrick, MBBS, PhD

University of Melbourne
Melbourne, Australia

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$507,874

"BDNF signalling and its impact upon oligodendrocyte myelination in vivo"

Investigating a molecule that may stimulate the repair of myelin in MS.

Oligodendrocytes are the cells of the brain and spinal cord that make and maintain myelin. Myelin surrounds and protects nerve fibers, enabling them to carry signals correctly. In MS, both myelin and oligodendrocytes are damaged and destroyed, disrupting nerve impulse transmission and causing the symptoms that people with MS experience. Nerve fibers are damaged as well, contributing to long-term disability. Although oligodendrocytes do repair some of the damage to myelin, they fail to repair it fast enough to keep up with the damage caused by MS.

Dr. Trevor Kilpatrick and his colleagues, Simon Murray and Junhua Xiao, are investigating a naturally occurring molecule known as brain derived neurotrophic factor (BDNF). Their research group has shown that, in cells grown in the laboratory, BDNF stimulates oligodendrocytes to form myelin. Now they are studying the details of how BDNF activates myelin formation in rodent models for insight into how myelin repair might be stimulated.

This research could lead to new strategies for repairing myelin damage and restoring function in people with MS.

Qing Lu, PhD

UT Southwestern Medical Center at Dallas
Dallas, TX

Area: South Central

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$486,968

"Chromatin remodeling in oligodendrocyte myelination and remyelination" Investigating a novel strategy for enhancing myelin repair in MS.

In MS, the immune system mistakenly attacks and destroys myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. Oligodendrocytes, the cells that manufacture and maintain myelin, are lost as well. Oligodendrocyte precursor cells (OPCs), which have the potential to form new oligodendrocytes that could repair myelin, exist in regions of myelin damage, but do not form new oligodendrocytes rapidly enough to keep up with the damage in MS.

In this research project, Qing Richard Lu, PhD, is studying the role of an enzyme that modifies chromatin, the material in which genes are packaged in cells. The structure of chromatin controls what genes a cell can "read" to make proteins. Dr. Lu is looking for ways to alter the structure of chromatin in OPCs so that they make proteins that enhance their ability to form new oligodendrocytes and repair myelin more rapidly.

This research has great potential to identify a novel way of enhancing myelin repair in MS.

Jack Rosenbluth, MD

New York University Medical Center
New York, NY

Area: New York City - Southern New York Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$490,628

"Role of the paranodal junction in myelinated nerve fibers." Looking at how alterations in myelin structure affect the behavior of nerve fibers.

The myelin sheath that insulates nerve fibers is not continuous; rather, it is separated by bare areas called nodes. Tiny channels clustered around the nodes regulate the flow of sodium and potassium ions that generate the nerve impulse. Flanking each node is a region called the paranodal junction, where the axon makes contact with oligodendrocytes, the cells that produce myelin. Recent studies indicate that defects in the paranodal junction may compromise nerve conduction and contribute to the signs and symptoms of multiple sclerosis.

Jack Rosenbluth, MD, is studying how the structure of the paranodal region changes under different experimental conditions and how the changes affect the ability of the nerves to carry signals. In addition to normal mice, Dr. Rosenbluth is using mice with mutations that alter the structure of the nodal and paranodal regions of their myelin.

This research will lead to better understanding of how changes in the structure of myelin alter the ability of nerve fibers to carry signals, and may contribute to efforts to restore function after damage has occurred.

Jae Kyu Ryu, PhD

University of California, San Francisco
San Francisco, CA

Area: Northern California Chapter

Award: Postdoctoral fellowship

Mentor: Katerina Akassoglou, PhD

Term/Amount: 7/1/11-6/30/14; \$156,516

"Study of spontaneous autoimmune demyelination induced by the blood protein fibrinogen." Studying a molecule that may trigger immune attacks that cause nerve tissue damage in MS.

The blood-brain barrier (BBB) is a protective membrane that normally controls the passage of substances from the blood into the brain. In MS, regions of the BBB break down, allowing cells from the immune system and other material to enter the brain and damage tissues in the brain and spinal cord.

Jae Kyu Ryu, PhD, is studying the effects of one of the substances that enters the brain through defects in the BBB. This substance, fibrinogen, is a blood protein that is ordinarily involved in blood clotting. However, Dr. Ryu and colleagues, working with mice, have found that when fibrinogen is injected into brain tissue, it appears to trigger one arm of the immune system, known as the innate immune system, to damage nerve-insulating myelin. Now the scientists are attempting to determine the cellular and molecular mechanisms that link BBB disruption with autoimmunity in the onset and progression of inflammatory demyelination.

This research could lead to new ways to block some of the initial events leading to myelin damage in early stages of MS.

Steven Scherer, MD, PhD

University of Pennsylvania
Philadelphia, PA

Area: Greater Delaware Valley Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$531,792

"Essential roles of gap junction proteins in oligodendrocytes" Studying cell components that may be important for maintaining myelin in MS-like disease.

Oligodendrocytes are the cells in the brain and spinal cord that make myelin, a material that surrounds and protects nerve fibers. In MS, myelin and oligodendrocytes are damaged and destroyed. Nerve fibers are also damaged. Healthy oligodendrocytes make contacts known as "gap junctions" with brain cells called astrocytes. Molecules that may be important to maintain healthy oligodendrocytes can be transferred through these gap junctions.

Steven Scherer, MD, PhD, is studying the function of gap junctions in oligodendrocytes. Using cells grown in the laboratory, Dr. Scherer is seeing how manipulating the genes that control gap junction proteins affects the transfer of molecules between oligodendrocytes and astrocytes. His team is inducing similar genetic alterations in mice with an MS-like disease to determine whether changes in gap junctions alter the course of the disease.

This research could lead to clues for improving the survival of myelin-making oligodendrocytes in MS, which could reduce the damage that results from myelin loss.

Andrew Steelman, PhD

Texas A&M University

College Station, TX

Area: South Central

Award: Postdoctoral fellowship

Mentor: Jianrong Li, PhD

Term/Amount: 7/1/11-6/30/14; \$156,515

"The role of the Tim-3/galectin-9 pathway in microglia activation and demyelination." Studying immune system signals for strategies to limit immune attacks and damage in MS.

In MS, the immune system damages and destroys myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. Cells of the immune system use many molecules to coordinate their activity to turn on and turn off immune attacks.

Andrew Steelman, PhD, is using a mouse model of MS to study how a molecular signal known as the Tim3/galectin-9 pathway contributes to myelin damage. Dr. Steelman and colleagues are looking at how both members of the pathway influence immune cells grown in the laboratory. In addition, they are examining whether myelin damage is altered in mice that have been genetically modified to lack the other member of the signaling pathway, galectin-9.

This research will provide new information about how immune system cells act to damage myelin, and could provide new ways to stop the immune attack in MS.

Nada Zecevic, MD, PhD

University of Connecticut Health Center

Farmington, CT

Area: Connecticut Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$335,723

"Development of oligodendrocytes in the human brain: relevance for MS" Studying the growth processes of cells that make nerve-insulating myelin for clues to what goes wrong in MS.

Myelin, the material that surrounds and protects nerve fibers, is destroyed during immune attacks on the brain and spinal cord in MS. Myelin is manufactured and maintained by cells known as oligodendrocytes, which are also lost during the course of MS. The details of how oligodendrocytes develop from immature precursor cells and acquire the ability to make myelin are not well known.

In this research project, Nada Zecevic, MD, PhD, is studying how the development of human oligodendrocytes from earlier cells known as radial glial cells is regulated. By comparing the development of these cells in humans with the more completely understood development of oligodendrocytes in mice, Dr. Zecevic is seeking clues that may reveal why MS is triggered in people.

The results of this research should lead to a better understanding of how oligodendrocytes and myelin normally develop, and could provide new clues for what goes wrong in MS.

ENDING MS FOREVER

Seeking Risk Factors

Because MS is thought to occur in people whose genes make them susceptible, researchers have been exploring the possibility that viruses or bacteria could act as disease triggers for MS. Other factors, such as exposure to sunlight or something else in the environment, could also play a role. The Society has multi-year investments totaling \$14 million in research projects focusing on these questions. This includes \$2 million in epidemiology studies, \$8.6 million in studies focusing on identifying MS genes, and \$3.3 million on projects focusing on identifying possible infectious triggers.

Many immunology projects are closely related to this effort as well.

Igor Koralnik, MD

Beth Israel Deaconess Medical Center
Boston, MA

Area: Greater New England Chapter

Award: Research Grant

Term/Amount: 4/1/11-3/31/13; \$182,567

"Mechanisms of JC virus reactivation and pathogenesis in multiple sclerosis"

Studying how to prevent a PML, potentially fatal brain infection, in people taking an approved MS therapy.

Natalizumab is a laboratory-produced monoclonal antibody. It is designed to hamper movement of potentially damaging immune cells from the bloodstream, across the "blood-brain barrier" into the brain and spinal cord. It can be highly effective in reducing MS disease activity, but approximately 1 out of 1,000 people who take natalizumab have developed PML (progressive multifocal

**One strategic goal for
Society research is to
identify risk and triggering
factors that cause MS so
that it can be prevented**

leukoencephalopathy), a rare and potentially fatal brain infection. PML has also occurred in people taking powerful immune-suppressing drugs for other indications, so learning more about how it occurs and how to prevent it is an important goal.

PML is caused by the JC virus, which many people harbor in a de-activated state within their bodies. In this research grant, Igor Koralnik, MD, is studying JC virus in people with MS who have been treated with natalizumab versus those treated with other MS drugs and untreated controls. To determine how the virus becomes activated, Dr. Koralnik is measuring the levels of JC virus in blood and other bodily fluids, looking at how immune system cells react to JC virus, and how the virus is spread through the body. In addition, he is studying brain tissue derived via autopsy from someone who died of PML to see how the infection interacts with regions of myelin damage due to MS.

This research could lead to clues to how the JC virus might be blocked to prevent PML.

J. William Lindsey, MD

Univ of Texas Health Science Center, Houston
Houston, TX

Area: South Central

Award: Research Grant

Term/Amount: 4/1/11-3/31/14; \$457,938

"Epstein-Barr virus and multiple sclerosis: correlation of activity" Comparing the activity of several viruses in people with MS that may be involved in triggering immune attacks.

It is not known what triggers the immune system attack on the brain and spinal cord in MS. Several infectious agents have been linked to MS, leading some researchers to suggest that the way the immune system responds to infections, rather than any infectious agent itself, may lead to the onset of MS.

William Lindsey, MD, is testing the idea that Epstein-Barr virus may start MS and also be responsible for the repeated attacks on the brain and spinal cord launched by the immune system during the course of the disease. He is studying Epstein-Barr virus, human herpes virus 6, and varicella zoster virus in 20 people with MS. All three viruses cause long-term, low level infections, and all have been suggested as possible triggers of MS. This study is measuring the activity of the viruses, the level of immune system responses to the viruses, and MS disease activity revealed by MRI. This should show whether immune system activation in response to one of the viruses is followed by increased disease activity.

This research could provide evidence that one of these viruses may trigger MS attacks, and could provide insights into new ways to prevent them to stop MS.

Nikolaos Patsopoulos, MD, PhD

Brigham and Women's Hospital
Boston, MA

Area: Greater New England Chapter

Award: Postdoctoral fellowship

Mentor: Philip L. De Jager, MD, PhD

Term/Amount: 7/1/11-6/30/13; \$102,324

"The role of common, low-frequency and rare variation in the etiology of MS."

Identifying variations in genes that may be important in the risk of developing MS.

Whether someone is susceptible to MS depends on both environmental and genetic factors. A few MS susceptibility genes have been identified, but it is clear that a large number of genes influence how likely it is that a person will develop MS. A technique known as "genome-wide association study" makes it possible to look for millions of small variations in the human genome, the collection of all human genes.

In this postdoctoral fellowship, Nikolaos Patsopoulos, MD, PhD, is analyzing combined data from eight different studies looking for MS susceptibility genes. This "meta-analysis" will compare genetic information from more than 17,000 people with MS and 30,000 people who do not have the disease. Areas of the genome identified as contributing to MS will then be verified in a further group of 10,000 people with MS and 10,000 people who do not have it.

The amount of genetic data available for this project makes it likely to identify new variations in genes that make small but important contributions to MS susceptibility. In addition, this new information could lead to better understanding of the pathogenesis of MS.

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