

# NEW RESEARCH



STOP. RESTORE. END.

## Society Commits \$19.4 Million for New MS Research Projects

The National MS Society has just launched 38 new MS research projects, with multiyear commitments totaling \$19.4 million. This commitment is the latest in the Society's relentless research effort to find solutions for everyone affected by MS. Through the collective efforts of each person in the MS movement, the Society invested over 48 million dollars alone in 2013 to fund 380 research projects around the world.

We pursue all promising research paths and collaborate worldwide to drive progress. We are also focused on three priority areas, including progressive MS where no therapies currently exist (p. 2, for example); nervous system repair (see these grants starting on p. 18) — where we're so close to solutions that can restore function that MS has taken away, and wellness and lifestyle, where advancements can change quality of life with MS on a daily basis (see some examples on page 14).

When we make research commitments that span into future years, the money is not yet in hand to meet those needs.

Contributions to the Society's NOW Campaign are vital to fuel these projects as the work progresses in future years. We're driving multi-pronged research across a full spectrum to stop MS in its tracks, restore lost function, and end the disease forever. The new projects include these, described in more detail in the following pages:



### STOP:

- A clinical trial to test whether ibudilast, a repurposed therapy, can protect the nervous system and slow or stop progressive MS. (page 2)



### RESTORE:

- Can dance as a form of exercise improve physical activity, walking, balance and fatigue in people with MS? (page 15)



### END:

- Examining whether an individual benefits from vitamin D therapy depending on that person's genetic make-up. (page 25)

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National  
Multiple Sclerosis  
Society

*Fast Forward*



## STOP

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

### STOP—Therapies

#### **Robert Fox, MD**

The Cleveland Clinic Foundation  
Cleveland, OH

**Title:** Clinical trial of Ibudilast in progressive MS

**Summary:** Clinical trial to test whether ibudilast, a re-purposed therapy, can protect the nervous system and slow or stop progressive MS.

**Background:** There is a significant, unmet need for treatments that can benefit people with progressive forms of MS. Ibudilast inhibits an enzyme called phosphodiesterase, resulting in suppression of inflammation. While considered a “New Molecular Entity” in the United States and Europe, ibudilast is marketed in Japan and Korea to treat cerebrovascular disorders and asthma. It is being also investigated in the U.S. for its potential to treat drug addiction. In a previous study, ibudilast did not reduce relapses or MRI-observed new lesions in a phase II trial of 292 people with relapsing MS. However, some evidence that this agent could protect the nervous system from damage (neuroprotection) was observed.



“There is a significant, unmet need for treatments that can benefit people with progressive forms of MS. This clinical trial of ibudilast will provide important information on a potential way to **stop MS damage.**”

- Timothy Coetzee, PhD  
Chief Research Officer

**The Study:** Robert Fox, MD, MS, FAAN, at the Cleveland Clinic Foundation, is leading a phase II clinical trial of ibudilast (MN-166, MediciNova, Inc.), an oral anti-inflammatory agent, in 250 people with primary-progressive MS or secondary-progressive MS. The study will be conducted at 28 sites and is principally funded by NeuroNEXT Network, a clinical trials initiative of the National Institutes of Health, with additional support by MediciNova, the company that will supply ibudilast. The National MS Society is also providing funding support because it aligns with the Society’s strategic focus on progressive MS, and may answer important questions about the best ways to measure the benefits of therapies aimed at protecting the nervous system from MS. The trial is expected to require approximately three years for enrollment, treatment, and data analyses.



**What's Next?** This clinical trial of ibudilast will provide important information on a potential way to stop MS damage, as well as how to measure treatment benefits, and aligns well with the Society's research agenda for stopping MS progression. This could lead to shorter, more effective trials and the potential for getting new therapies to people with MS faster.

### STOP—Measuring MS Disease Activity

#### Ilya Kister, MD

New York University School of Medicine  
New York, NY

**Title:** Cerebral ultra-high field MR imaging in Neuromyelitis Optica: US-German longitudinal study

**Summary:** Can a cutting-edge imaging technology help to differentiate MS from a similar disorder and explain why MS progresses?

**Background:** Multiple Sclerosis and neuromyelitis optica (NMO) are autoimmune diseases that affect brain, optic nerves and spinal cord. Differentiating between the two diseases is sometimes difficult. Ultra-high-field MR Imaging is a rapidly emerging technology that has potential to help to reliably differentiate between the two disorders.

**The Study:** Drs. Ilya Kister and Yulin Ge of New York University School of Medicine in New York and Drs. Paul and Wuerfel at Charité University Hospital in Berlin, Germany, have independently confirmed that brain lesions of MS and NMO have a different structure when examined with ultra-high-field MRI, a novel research tool for visualizing brain pathology. Now, the two groups are collaborating to collect follow-up ultra-high field MR data on 35 people with NMO and 35

people with MS in order to compare disease progression in the two diseases. An important difference between MS and NMO, is that in MS, relapses are often followed by a progressive phase, which does not appear to be the case in NMO. The investigators hope that their work will help to better understand the reasons for progressive phase in MS.

**What's Next?** This study can help to develop reliable criteria for differentiating NMO from MS based on brain MRI, and yield clues for understanding progression in MS.

#### Mark Lowe, PhD

The Cleveland Clinic Foundation  
Cleveland, OH

**Title:** MRI-DTI and Functional Connectivity as Measures of Disease Progression in MS

**Summary:** Using powerful brain MRI to develop a better way to track MS disease progression.

**Background:** A reliable method to assess disease progression in MS is needed. One method, the Expanded Disability Status Scale (EDSS) focuses primarily on walking ability and may miss other important MS symptoms. The EDSS as well as another test, the MS Functional Composite, are not sensitive enough and may miss changes that occur over the short term (a few years). Magnetic resonance imaging (MRI) has long been used to assess changes in the brain in MS, but improvements in MRI are needed to provide more sensitive assessment of disease progression, therapeutic effectiveness, and to improve the interpretation of clinical trial results.

**The Study:** Mark Lowe, PhD, of The Cleveland Clinic Foundation in Cleveland, Ohio has received a research grant from the National MS Society to develop an improved,



more sensitive MRI method that may overcome current limitations. They are enrolling 22 people with relapsing-remitting or secondary progressive MS and 14 matched individuals who do not have MS. MRI will be performed every 4 months in the first year and every 6 months in the second year. People with MS often have problems with memory, and in the first part of their study, Dr. Lowe's team is studying the relationship between memory and imaging of certain interconnected parts of the brain that are involved in memory. In the second part of the study, they are determining if specific changes that are seen with imaging are linked with changes in motor and memory disability over time. Examining the relationship between imaging changes and disability changes over time will help establish imaging change milestones as biomarkers of disease progression.

**What's Next?** Development of a sensitive imaging biomarker could allow for earlier detection of disease progression, improved care and more rapid development of new therapies.

### STOP—Health Care Delivery/Policy

#### **Robert Buchanan, PhD**

Ohio State University  
Columbus, OH

**Title:** Patient and physician perspectives concerning decision making regarding treatment with MS disease-modifying therapies

**Summary:** Understanding the factors that impact selection of disease-modifying therapy for people with MS.

**Background:** Although there is still no cure for MS, effective strategies are available to modify the disease course. Decisions about

taking a disease-modifying medication are best made by carefully considering and weighing factors including individual lifestyle, disease course, known side effects, and the potential risks and benefits of the different therapies.

**The Study:** Robert Buchanan, PhD, of Ohio State University in Columbus, OH, has received a research grant from the Society to understand the factors involved in selecting a DMT for people with MS, by investigating how physicians and patients approach these decisions, the facilitators and barriers they face, and any unmet decision-making issues. His team is surveying 1,500 people with MS recruited from at least 10 MS centers across the United States, as well as 500 neurologists. From among these groups, they are also conducting more in-depth interviews with 60 people with MS and 60 neurologists. These surveys and interviews are designed to explore demographics, symptoms, disability, quality of life, and caregiver roles. Neurologists are being asked about adherence strategies, their education and training, attitudes about the use of DMTs, the decision-making process, and the role of the patient in the decision-making process.

**What's Next?** The results of this study will provide an in-depth understanding of the decision-making factors involved in selecting a DMT including issues involved in adherence, patient and physician attitudes, and caregiver roles.



**Michael Halpern, MD, PhD, MPH**

RTI International  
Washington, DC

**Title:** Secondary analysis of existing data sets: Level of care and cost differences between MS patients receiving care at MS centers versus at neurology outpatient practices

**Summary:** Understanding the care received by people with MS at MS centers vs. private practice to ensure quality care for all people with MS.

**Background:** Most individuals with MS receive medical care from neurologists who are either based at MS centers or are in private practices or neurology clinics. The care received by patients in these two types of settings may be different.

**The Study:** Michael Halpern, MD, PhD, MPH, of RTI International in Washington, DC has received a research grant from the Society to understand differences in the medical care received by people with MS who visit MS centers compared to those who receive care in a private practice or neurology clinic. People who receive care in MS centers may have more advanced disease, have more symptoms, and be more likely to be uninsured or covered by Medicaid. Dr. Halpern and colleagues are analyzing data that were collected from the Sonya Slifka Longitudinal MS Study, sponsored by the National MS Society, which followed more than 2500 people with MS. The Sonya Slifka Longitudinal MS Study used phone interviews to collect information on the symptoms of MS patients and the care they receive. Dr. Halpern is determining if people who receive care at MS centers 1) have more severe disease, 2) are more likely to be uninsured or covered by Medicaid, and 3) require more prescriptions, procedures, and tests compared to those receiving care from

neurologists in private practice or a neurology clinic.

**What's Next?** These results will provide information for planning physician time and medical services needed at MS centers to ensure the highest quality care for all individuals with MS.

**STOP—Neuropathology (Tissue Damage)**

**Oscar Bizzozero, PhD**

University of New Mexico  
Albuquerque, NM

**Title:** Impaired activity of the proteasome activator PA28 in multiple sclerosis

**Summary:** Is impaired removal of damaged proteins a possible contributor to the development of MS?

**Background:** In MS, the immune system attacks the cells in the brain and spinal cord. During this process of damage to cells, proteins within cells become “oxidized,” which is an undesired event that can lead to cell death and nervous system injury. In normal circumstances, oxidized (damaged) proteins are degraded and removed by an enzyme complex called the proteasome. In MS, proteasomes do not appear to function properly. This is possibly because a component that switches the proteasome “on” is present at low levels and also inactive in MS.

**The Study:** Oscar Bizzozero, PhD, of the University of New Mexico in Albuquerque, has received a research grant from the National MS Society to explore and understand a novel possibility in which brain tissue in MS is damaged. He and his colleagues are examining proteasomes in brain samples from people with MS to determine the cause of the reduced activity of proteasomes and if



the failure to switch “on” proteasomes is specific to MS. They are examining postmortem brain samples from a total of 50 people with MS and 50 neurologically healthy controls. They are also comparing the MS samples with samples from patients with Alzheimer’s Disease, Parkinson’s Disease, and non-MS disorders that damage myelin to see if the proteasome component defect is specific to MS.

**What’s Next?** Results from this study will provide novel information on a possible cause or contributor to nervous system damage in MS and may suggest a new therapeutic strategy aimed at restoring the ability of cells to remove abnormal proteins. This could reduce tissue damage and progressive disability in people with MS.

#### **Matilde Inglese, MD**

Mount Sinai School of Medicine  
New York, NY

**Title:** A 7 Tesla MRI post-mortem study of gray matter lesions in MS

**Summary:** Using high-powered brain imaging technology as a window to understanding damage caused by MS.

**Background:** Many people who are diagnosed with MS undergo brain MRI scans so that doctors can track disease activity in the part of the brain known as the white matter, which contains nerve cell fibers that conduct messages. But standard MRI scans are not powerful enough to visualize areas of disease activity in the gray matter, a region of the brain that contains many brain cells and few fibers. Research suggests that gray matter lesions, though difficult to detect, are clinically important in terms of MS symptoms a person may experience, including cognitive problems.

**The Study:** Matilde Inglese, MD, PhD, of Mount Sinai School of Medicine in New York, has received a research grant from the National MS Society to use high-powered MRI to visualize gray matter lesions. They are scanning the brains from 18 people who had secondary-progressive MS in their lifetimes and who donated their tissue to research. This study is in collaboration with Dr. Jeroen Geurts, PhD, from the VU University of Amsterdam in The Netherlands. The team will compare gray matter lesions they see with MRI with what they find by examining the brain tissue under a microscope from the exact areas that were scanned. This will give them a direct understanding of what damage the MRI images are actually detecting. They will also compare what they find in MS to brain samples from people who were neurologically normal in their lifetimes.

**What’s Next?** Results from this study will help researchers identify reliable markers to monitor MS damage to the gray matter of the brain, enhance our understanding of cognitive deficits, and identify new therapeutic targets

#### **STOP—Role of the Immune System**

#### **Murugaiyan Gopal, PhD**

Brigham and Women's Hospital  
Boston, MA

**Title:** Control of inflammatory and regulatory T cells in MS

**Summary:** Understanding the function of the immune system with the aim of reducing MS disease activity.

**Background:** In MS, immune cells attack the brain and spinal cord, causing disruption of nerve signals and an array of symptoms. One type of immune cell, called the T cells, is responsible for much of the aggressive



immune activity in MS. Another type of immune cell, called regulatory T cell, controls the activity of inflammatory T cells. Controlling the activity of inflammatory T cells may be an effective therapeutic strategy in MS.

**The Study:** Murugaiyan Gopal, PhD, of Harvard Medical School and Brigham and Women's Hospital in Boston has received a research grant from the National MS Society to investigate the complex web of interactions that lead to MS immune attacks and the forces capable of turning off those attacks. The particular focus of the team is a type of regulatory cell, called Tr1 cells, which is capable of controlling aggressive T cells. The team is studying the inter-relationships between Tr1 cells and other immune players and comparing their activity in immune cells from people with MS and people without the disease. Using information obtained from this study, the team hopes to find ways to stop or reduce MS disease activity.

**What's Next?** Understanding how to control immune cell function may lead to more effective therapeutic strategies to stop MS.

**Samia Khoury, MD**

Brigham and Women's Hospital  
Boston, MA

**Title:** Transcriptional Regulation of the Resistance of Memory T Cells in EAE

**Summary:** Can the behavior of a type of immune system cell be altered to treat MS?

**Background:** In MS, some cells of the immune system attack and damage myelin, the material that surrounds nerve fibers, in the brain and spinal cord. In addition, the nerve cells themselves are also damaged. The immune system has many types of cells, some of which carry out attacks, while others

suppress activity. And some cells "remember" previous actions of the immune system and contribute to new activity.

**The Study:** Samia Khoury, MD, at Brigham and Women's Hospital in Boston has been awarded a research grant by the National MS Society to investigate whether the behavior of two types of immune cells can be modified in mice with EAE, an animal disease similar to MS. One cell type, known as "memory T cells" seem to perpetuate the attack on myelin. Another type, known as "regulatory T cells" should suppress the activity of the memory cells. However, the memory cells seem to ignore signals from the regulatory cells in MS, so Dr. Khoury is looking for ways to enhance the ability of the regulatory cells to prevent memory cells from launching new attacks on myelin.

**What's Next?** This study could uncover ways to enhance the normal activity of regulatory T cells. This could lead to new techniques to slow or halt the damage to the nervous system in people with MS.

**Vijay Kuchroo, DVM, PhD**

Brigham and Women's Hospital  
Boston, MA

**Title:** Pathogenic and regulatory mechanisms of EAE

**Summary:** Controlling inappropriate immune activities in the brain for clues to stopping MS.

**Background:** In MS, the immune system attacks and destroys certain components of the brain, leading to symptoms and dysfunction. Immune cells called T cells are involved in this process. Several types of T cells exist, and one subset of T cells, called Th17 cells, appears to play a devastating role in MS. Th17 cells produce a factor called



interleukin-17 (IL-17), which induces inflammation and paralysis in a mouse model of MS called EAE. The strategy of blocking Th17 cells and/or the IL-17 they produce is likely to have beneficial effects in MS. Indeed, in a small clinical trial blocking IL-17 in people with MS was shown to reduce MRI-detected disease activity in the brain.

**The Study:** Vijay Kuchroo, DVM, PhD, of Brigham and Women's Hospital and Harvard Medical School in Boston, has received a research grant from the National MS Society to figure out why Th17 cells are so harmful and to identify ways to dampen their activity. The team is studying a molecule that turns on the harmful features of Th17 cells and another molecule produced by Th17 cells that is also harmful. They are using mice with EAE to test inhibitors of these two molecules and observing their impact.

**What's Next?** Understanding how Th17 cells are involved in the complex MS immune attack and how these cells are generated and controlled will provide critical information and may provide new strategies to better treat the MS. Molecules that regulate the harmful nature of Th17 and that are produced by harmful Th17 cells are potential new drug target for treating MS.

Visit our Website for more information about research, treatment, programs, and the NOW Campaign to support MS research  
[www.nationalMSSociety.org](http://www.nationalMSSociety.org)

### **Tak Mak, PhD**

The Ontario Cancer Institute  
Toronto, Ontario, Canada

**Title:** Targeting Multiple Sclerosis by inhibiting the Malt1 dependent switch in T cell encephalitogenicity.

**Summary:** Controlling formation of harmful T cells may be a novel therapeutic strategy in MS.

**Background:** MS involves immune attacks to the brain and spinal cord. Immune cells called T cells play a role in this process. One type T cells, called Th17 cells, is particularly harmful. Recent research has shown that a molecule called MALT1 appears to be involved in making these cells harmful. Mice that lack MALT1 do not develop EAE, a disease similar to MS, and the Th17 cells in mice that lack MALT1 are not harmful.

**The Study:** Tak Mak, PhD, of the Ontario Cancer Institute in Toronto, Ontario has received a research grant from the National MS Society to further understand the role of MALT1 in making Th17 cells harmful. They are using mice with differences in various MALT1-related genes to determine how these differences affect the ability of the mice to resist the development of EAE. Results from these studies will be important for understanding ways to possibly prevent and/or treat MS.

**What's Next?** These studies should increase knowledge of the complexities of immune attacks in MS, and may identify a way to block the formation of harmful immune cells, which could lead to the development of a new treatment for MS.



**Nancy Monson, PhD**

The University of Texas Southwestern  
Medical Center  
Dallas, TX

**Title:** Dysregulation of B cells in MS

**Summary:** What alters the behavior of immune cells early in MS and how can they be stopped?.

**Background:** Although the immune system normally protects the body from foreign invaders such as viruses or bacteria, in MS the immune system launches attacks on the brain and spinal cord. A type of immune cell known as a T cell has long been a focus of MS researchers. However, recent evidence suggests a previously unrecognized role of another type of immune system cell known as a B cell.

**The Study:** Nancy Monson, PhD, of the University of Texas Southwestern Medical Center in Dallas, has received a research grant from the National MS Society to investigate how B cells from people with relapsing-remitting MS influence the activity of their own T cells. Preliminary results show that B cells from people with MS who have not started treatment are more active than normal in ways that stimulate T cell activity against brain components. Dr. Monson and colleagues are now trying to determine what alters the behavior of B cells in people with relapsing MS.

**What's Next?** The results of this research project could provide clues for new therapies that specifically target the early stages of relapsing-remitting MS.

**Mohamed Oukka, PhD**

Seattle Children's Research Institute  
Seattle, WA

**Title:** Role of scaffolding proteins in the generation of Th17 cells and in the pathogenesis of EAE

**Summary:** Investigating selective blocking of the entry of only harmful immune cells into the brain as a possible MS treatment for MS.

**Background:** Initiation and progression of MS involve the entry of harmful immune cells into the brain and spinal cord. Some current MS therapies such as natalizumab work by stopping entry of immune cells into the brain. However, because this drug blocks entry of many types of immune cells, even helpful cells, viral infections in the brain sometimes occur as a side effect.

**The Study:** Mohamed Oukka, PhD, of Seattle Children's Research Institute and University of Washington has received a research grant from the National MS Society to explore a new molecule that may affect MS disease progression by impacting development and migration of a harmful type of immune cells called Th17 cells. Dr. Oukka and colleagues have discovered a molecule called Dock8 that is required for the development of Th17 cells and their movement into the brains of mice with the MS-like disease EAE. Mice that do not make Dock8 do not develop EAE. Dr. Oukka and colleagues are currently working to understand in more detail how Dock8 works in specific types of immune cells. Because Dock8 appears to be required for EAE, blocking Dock8 may prevent EAE, and by extension, MS.

**What's Next?** Understanding how Dock8 affects harmful immune cells will help determine if blocking Dock8 will be a



rational strategy for a new MS therapy that more selectively inhibits immune cells from entering the brain.

**Francisco Quintana, PhD**

Brigham and Women's Hospital  
Boston, MA

**Title:** Role of IL-27 signaling in dendritic cells on the development of EAE

**Summary:** Can immune system cells be modified to prevent myelin damage?

**Background:** The immune cells that damage myelin in people who have MS are known as T cells. There are a number of different types of T cells. Some T cells do the actual damage, while others act to decrease the activity of the damaging T cells. In addition, other immune system cells, including a group known as dendritic cells, release chemical signals that modify T cell activity.

**The Study:** Francisco Quintana, PhD, at Harvard's Brigham and Women's Hospital in Boston, has received a research grant from the Society to study the role of dendritic cells in the development and control of the MS-like disease EAE, in mice. If dendritic cells are treated with a signaling molecule known as IL-27, they limit the development of T cells that attack myelin. One of the goals of this work is to find out whether a form of vaccination, which involves injecting dendritic cells treated with IL-27 will suppress the development of the MS-like disease in mice.

**What's Next?** This work could lead to the development of a new treatment for people who have MS by injecting them with their own dendritic cells, modified to prevent T cells from attacking myelin.

**John Russell, PhD**

Washington University School of Medicine  
Saint Louis, MO

**Title:** Regulation of CNS lesion localization by T cell/APC interactions

**Summary:** What determines the location of lesions in MS?

**Background:** People with MS have different types of disabilities, including vision problems, balance problems, and cognitive problems. This clinical variability is due to the fact that lesions – areas of damage or disease activity -- occur in different parts of the brain and spinal cord that control these different functions. Very little is known about how this variability occurs. Recent evidence suggests that different types of immune system cells, which make MS worse, tend to be located in different parts of the brain and spinal cord.

**The Study:** John Russell, PhD, of Washington University School of Medicine in St. Louis, has received a research grant from the National MS Society to investigate the role of different types of immune cells, the chemical messengers they secrete (called cytokines), and their interaction with normal cells in different regions of the brain and spinal cord to induce lesion development in one region or another. The team has found that two types of immune cells are generally found in two different parts of the brain and spinal cord: "Th1" cells are usually found in the spinal cord, and "Th17" cells are usually found in certain parts of the brain. Using a mouse model for MS called EAE, Dr. Russell is asking if the individual cytokines made by these two types of T cells are uniquely responsible for inducing lesions in a particular location.



**What's Next?** Understanding what governs the location of MS lesions will provide better tools for individualized diagnosis and potentially new strategies for developing better treatments for MS.

**Arthur Vandenberg, PhD**

Oregon Health & Science University  
Portland, OR

**Title:** A novel MIF inhibitor as therapy for MS

**Summary:** Pre-clinical testing of a possible new strategy to block entry of harmful immune cells into the brain in MS.

**Background:** In part, MS involves trafficking of harmful immune cells into the brain and spinal cord. Molecules that block such trafficking are potential new MS therapies.

**The Study:** Arthur Vandenberg, PhD, of Oregon Health and Science University has received a research grant to understand the effects of a new molecule called DR-alpha 1 that blocks entry of harmful immune cells into the brain in EAE, the animal model of MS. They are examining how DR-alpha 1 interacts with peripheral blood cells from people with clinically isolated syndrome (a first clinical episode with features suggestive of MS), relapsing-remitting MS, primary progressive MS, and secondary progressive MS, compared to healthy people. They are also working to optimize different forms of DR-alpha 1, measure its ability to block migration of harmful immune cells, and examine its ability to block or reverse EAE. Importantly, this molecule is unlikely to provoke an inappropriate immune response in humans, a key factor in its success as a drug.

**What's Next?** Results will provide crucial pre-clinical data that will support testing of DR-alpha 1 in MS clinical trials.

**David Wagner, PhD**

University of Colorado Health Sciences Center  
Aurora, CO

**Title:** The role of Th40 cells in multiple sclerosis: Prediction and Treatment

**Summary:** Improving diagnosis of MS and predicting disease progression.

**Background:** MS involves immune attacks against components of the brain and spinal cord. Currently it can be difficult to diagnose MS, and there is no set way to predict who will develop the disease, or how severe an individual's MS may become. Finding biological indicators, or "biomarkers," to predict these events is an important goal.

**The Study:** David Wagner, PhD, of the University of Colorado at Denver has received a grant to understand if and how the presence of a particular type of immune cell can serve as a predictive biomarker for MS. In particular, a type of immune cell called Th40 cells is highly pathogenic and drives inflammation, and thus, possibly MS. Dr. Wagner and colleagues have observed that Th40 cells are present at very high levels in the blood of people with MS. In this study they are collecting blood samples from people of different ages and MS disease durations, and examining levels of Th40 cells, and asking if the levels can be used to predict the outcome of MS, and whether they reflect disease status. If so, CD40, the unique protein present on Th40 cells, may prove to be a biomarker for MS. The team is also exploring if blocking CD40 in a mouse model of MS called EAE will improve or prevent disease.

**What's Next?** Results could assist in the development of a better way to diagnose MS and help predict an individual's disease course.



## 26 New Pilot Projects Take Aim at MS

One way the National MS Society propels MS research forward is by funding high-risk, high-potential pilot projects to investigate new, untested ideas. These unique one-year grants allow researchers to quickly gather data to determine if ideas are worth pursuing. These grants began June 1 or October 1, 2013.



### STOP

Gerald Ahern, PhD (Georgetown University, Washington, DC) is identifying how sunlight alters immune function.

Sergio Baranzini, PhD (University of California, San Francisco, San Francisco, CA) is investigating a newly identified immune system gene for its ability to predict disease course in MS models.

Alexander Diehl, PhD (University of Buffalo, The State University of New York, Buffalo, NY) is mining data to learn more about optimizing MS treatment for individuals with MS.

Richard Daneman, PhD (University of California, San Francisco, San Francisco, CA) is investigating how to prevent the immune system from entering the brain and spinal cord in MS-like disease.

Alban Gaultier, PhD (University of Virginia, Charlottesville, VA) is investigating a protein that may inhibit myelin repair in MS.

Shin Kang, PhD (Temple University School of Medicine, Philadelphia, PA) is developing a model for studying cells that may be useful in repair strategies for MS.

Robyn Klein, MD, PhD (Washington University School of Medicine, St. Louis, MO) is investigating a molecule that may play a key role in the immune attack in MS.

Unsong Oh, MD (Virginia Commonwealth University, Richmond, VA) is investigating a novel compound for preventing nerve tissue damage in mice with MS-like disease.

Laura Piccio, MD, PhD (Washington University School of Medicine, St. Louis, MO) is studying a type of immune cell that appears only in the spinal fluid of people with MS, for clues to stopping the immune attack.

Andrew Solomon, MD (University of Vermont, Burlington, VT) is gathering data on misdiagnosis of MS for clues to improving diagnosis and treatment.

Yuri Sykulev, PhD (Thomas Jefferson University, Philadelphia, PA) is testing a novel strategy for stopping the immune attack in MS.

Yuhong Yang, PhD (Ohio State University, Columbus, OH) is blocking an immune messenger protein in MS-like disease for clues to stopping the immune attack in MS.



## RESTORE

Dawn Ehde, PhD (University of Washington, Seattle, WA) is investigating a method of reducing pain in people with MS.

Barbara Giesser, MD (University of California, Los Angeles, Los Angeles, CA) is conducting a trial of new cooling device to determine if it can restore function to people with MS.

Margot Mayer-Proschel, PhD (University of Rochester, Rochester, NY) is investigating a possible role for a virus in myelin damage in MS.

David Rintell, EdD (Partners Pediatric Multiple Sclerosis Center, Boston, MA) is understanding the effects on parents of having a child or adolescent diagnosed with MS.

Isobel Scarisbrick, PhD (Mayo Clinic, Rochester, MN) is determining whether inhibiting a molecule can improve repair in MS.

Catherine Siengsukon, PhD (University of Kansas Medical Center, Kansas City, KS) is conducting a trial of aerobic exercise to improve cognitive function and sleep in MS.

Heather Wishart, PhD (Dartmouth College, Lebanon, NH) is evaluating a strategy for improving the detection of cognitive problems in people with MS.

**These 5 pilot projects are being funded by a scratch-off ticket from the Illinois Lottery, which provides seed money to speed research progress on reversing MS damage:**

Richard Kraig, MD, PhD (University of Chicago Medicine) is investigating whether enhancing the antioxidant capacity of the brain can improve myelin repair in an MS model.

Edward McAuley, PhD (University of Illinois at Urbana-Champaign) is testing the ability of a DVD-delivered physical activity intervention to reduce disability in older adults with MS.

Lara A. Pilutti, PhD (University of Illinois at Urbana-Champaign) is testing a home-based exercise program to improve mobility, fatigue and quality of life in people with MS.

Jacob Sosnoff, PhD (University of Illinois at Urbana-Champaign) is determining the effectiveness of treadmill training in persons with MS with severe mobility impairments.

Kenneth Wilund, PhD (University of Illinois at Urbana-Champaign) is evaluating whether Kaatsu (a weightlifting program) improves walking and muscle strength in people with MS.



## END

Patrizia Casaccia, MD, PhD (Mount Sinai School of Medicine, New York, NY) is examining a possible connection between genetics and gut bacteria for clues to factors that trigger MS.

Sreeram Ramagopalan, PhD (Queen Mary University of London, London, UK) is looking at the interaction of genetics and environment for clues to ending MS.



## RESTORE

Research related to restoring what's been lost in MS focuses on understanding how nerves and their protective myelin coating work normally, and how repair of these critical tissues and cells can be facilitated. Research on restoring function also focuses on lifestyle/wellness approaches, including exercise, diet, and rehabilitation strategies.

### RESTORE—Lifestyle/Wellness

#### Charles Bombardier, PhD

University of Washington  
Seattle, WA

**Title:** The effect of aerobic exercise on cognition in multiple sclerosis

**Summary:** Can aerobic exercise improve cognitive impairment in people with MS?

**Background:** People with MS may experience problems with thinking speed and memory, and right now effective therapies to improve cognitive ability are not available. Exercise training has been shown to improve cognitive ability in older normal adults and in those with early Alzheimer's disease, but this has not been fully verified in people with MS.

**The Study:** A team of researchers, Charles Bombardier, PhD, from the University of Washington in Seattle, has teamed up with Rob Motl, PhD, from the University of Illinois Urbana-Champaign and Ralph Benedict, PhD, from the State University of New York at Buffalo, to do a National MS Society-funded, controlled clinical trial to evaluate the effects of two forms of exercise training (aerobic training versus stretching and toning exercise) on cognition in people with MS. In one of the largest studies of its kind, they are studying 125 non-exercising adults with any

type of MS who can walk unassisted and who have evidence of changes in information processing speed. Half of the study participants will undergo aerobic training and the other half will undergo stretching and toning exercises. Each form of exercise will be performed 3 days per week for 6 months. The research team will test the cognitive abilities of these participants before training begins, at the end of the 6-month training program, and 3 months after training is completed to see if aerobic exercise or stretching and toning exercises improve cognitive ability and if any improvement is retained after the exercise period ends.

**What's Next?** Results from this study could add important evidence for a non-pharmaceutical approach to improving cognitive abilities in people with MS.

#### Albert Lo, MD, PhD

Saint Francis Care Mandell MS Center  
Hartford, CT

**Title:** Characterizing Upper Extremity Function in Individuals with Multiple Sclerosis

**Summary:** Understanding upper extremity dysfunction in people with MS.

**Background:** Difficulty with lower extremity functions such as walking is commonly reported in people with MS and has been extensively studied. However, although upper extremity (i.e., shoulders, arms, hands) dysfunction is also reported, it has not been thoroughly examined. Upper extremity dysfunction can have profound impact on daily function and the quality of life in people with MS, and studies are needed to understand this type of problem in more detail.



**The Study:** Albert Lo, MD, PhD, and Elizabeth Triche, PhD, of the Mandell Center for MS, Mount Sinai Rehabilitation Hospital in Hartford, CT, have received a research grant from the National MS Society to characterize in greater detail the upper extremity functional problems experienced by people with MS. To understand the frequency, extent, and severity of upper extremity impairment in MS, Dr. Lo's team is studying 300 people with all types of MS (relapsing-remitting MS and primary-progressive MS, different disease durations, and with different levels of severity involving the upper extremity). They are investigating if the range of impairments in upper extremity function (e.g., motor, sensory, tone) varies based on the type of MS a person has, duration of disease as well as personal characteristics. The team is measuring the capacity as well as performance of the arm and hand through joint mobility, muscle function, coordination, tremor, and sensation, as well as simulated self-care and domestic activities. They are also analyzing the impact factors such as fatigue and pain on upper extremity dysfunction.

**What's Next?** This study will provide critical information that will assist in the future development of rehabilitative strategies to restore and maintain productivity and independence, and improve comfort and quality of life for people with MS.

**Albert Lo, MD, PhD**

Brown University  
Providence, RI

**Title:** Progressive structured dance intervention to enhance physical activity in MS

**Summary:** Dance as a form of exercise to improve physical activity, walking, balance and fatigue in people with MS.

**Background:** People with MS experience problems with physical activity, walking, balance, and fatigue. Exercise and physical therapy are known to improve these problems. Dance as a form of exercise has been shown to have a high rate of continued participation and enjoyment. Other populations have experienced benefits from dance has not been studied systematically in the MS population. This study will explore the benefits of dance in people with MS, particularly in the areas of increased physical activity, and as a means to improve balance and gait function.

**The Study:** Albert Lo, MD, PhD, of Brown University in Providence, Rhode Island and the Providence VA Medical Center has received a research grant from the Society to study whether dance as a form of exercise can improve physical activity, walking, balance and fatigue in people with MS. People with MS experience a variety of mobility problems including problems with gait, walking, balance, and fatigue. People with MS often participate in less physical activity than healthy people, and the effects of lack of exercise can be serious. Other populations have experienced benefits from dance as a form of exercise including increased participation due to enjoyment and the social aspects of dance. Dr. Lo and colleagues are testing dance as a form of exercise in people with MS. They are enrolling 60 to 70 individuals with MS. For 12 weeks, half of the participants will participate in two 1-hour dance classes with 30 minutes of at-home practice per week. The other half will have a delayed start in this program. Dr. Lo and his team are comparing the two groups in terms of improvements in physical activity, walking, balance, gait, and self-motivation. They are also determining how long the effects last after stopping the dance



classes, and they are examining safety considerations. Dr. Lo and his team hope that the social enjoyment that often accompanies dance classes will lead to increased participation in their study group, leading to increased physical abilities.

**What's Next?** Dance as a form of physical therapy may improve the personal goals and the health needs of individuals with walking and balance problems due to MS and may lead to a more widespread use of dance as a form of physical therapy for people with MS.

**Phillip Rumrill, CRC, PhD**

Kent State University  
Kent, OH

**Title:** An examination of the impact of the Americans with Disabilities Act on the employment concerns and outcomes of Americans with MS

**Summary:** How has the Americans with Disabilities Act impacted the quality of work life in people with MS over the last 10 years?

**Background:** The Americans with Disabilities Act (ADA) exists in part to reduce discrimination against people with disabilities and to promote retention of people with disabilities in the workforce. This study will investigate the effectiveness of the ADA over the last 10 years in preventing employer discrimination and retaining workers with MS.

**The Study:** Phillip Rumrill, PhD, of Kent State University in Kent, Ohio has received a research grant from the Society to obtain current data to compare with a prior study investigating the effectiveness of the ADA in retaining workers with MS. In 2002, soon after the ADA was implemented, Dr. Rumrill and his team performed a survey in which they investigated the experience and employment

concerns of people with MS in the workforce. The current study is investigating similar parameters, which will be compared with the 2002 data, to determine how the employment concerns of adults with MS have changed since 2002. They are asking how the previously identified employment concerns have changed in the last 10 years. They are surveying a nationwide sample of 8,000 adults with MS to replicate their study of the employment incentives and disincentives affecting job acquisition and retention. In addition, they are also determining employment discrimination events and outcomes that influence the quality of the work lives of people with MS (using data from the Equal Employment Opportunities Commission database). This research is needed to gain a clearer sense of how workplace discrimination occurs and is resolved in employees with MS.

**What's Next?** Results from this study will contribute to the development of interventions to help employees with MS take advantage of resources for sustaining employment, minimize the impact of employment disincentives, and respond to discrimination in the workplace.



## RESTORE—Psychosocial Aspects

### Heather Wishart, PhD

Dartmouth College

Lebanon, NH

**Title:** Differential patterns of brain activation during pain processing in patients with MS and healthy controls

**Summary:** Understanding how the brains of people with MS process pain to work toward better treatments.

**Background:** Many people who have multiple sclerosis experience pain, causing debilitating effects and reducing quality of life. Overall, pain is under-recognized and under-treated in people with MS. When pain is not effectively treated, the way the brain processes pain changes and can make the pain even worse.

**The Study:** Heather Wishart, PhD, of Dartmouth College in Lebanon, New Hampshire, has received a research grant from the National MS Society to understand how pain is processed in the brains of people with MS. She and her team are using a type of brain imaging called functional magnetic resonance imaging (fMRI), which shows real-time brain activity that occurs in response to stimulation. They are studying 40 people who have mild to moderate relapsing-remitting or secondary progressive MS and 20 people who do not have MS as controls. They are looking to see if the brains of people with MS show different patterns of activity in response to a mild pain stimulus (mechanical pressure on the thumbnail bed), compared to healthy controls.



When pain is not effectively treated, the way the brain processes pain changes and can make the pain even worse... This study may provide an opportunity for **earlier pain intervention** in people with MS before sensitization and chronic pain set in.

**What's Next?** This study will help scientists better understand pain in MS and determine if early fMRI can predict early pain sensitization and increased pain sensation. This may provide an opportunity for earlier pain intervention in people with MS before sensitization and chronic pain set in. Dr. Wishart's study may also suggest ways to individualize pain treatment in people with MS to improve quality of life.



## RESTORE—Nervous System Repair

### Charles Abrams, MD

SUNY Downstate  
Brooklyn, NY

**Title:** Roles of Cx32 and Cx47 in oligodendrocytes

**Summary:** Does the loss of connexins, molecules that mediate communication between brain cells, make the animal model of MS worse?

**Background:** Factors that cause and worsen MS have been incompletely explored. The role of one possible factor, a group of proteins called connexins, may be important.

**The Study:** Charles Abrams, MD, PhD, of the State University of New York-Downstate Medical Center in Brooklyn, NY has received a research grant from the Society to examine the role of proteins called connexins in the animal model for MS called EAE. Connexins are proteins that form channels between cells, including brain cells involved in MS and EAE. Functional connexins allow various molecules to pass from one cell to another, permitting communication between cells. Dr. Abrams and his team are asking if the loss of one of two connexins, called Cx32 and Cx47, makes mice more susceptible to EAE, and if so, how this happens. In the absence of Cx32 or Cx47, they are asking if more harmful immune cells enter the brain, if oligodendrocytes (the cells in the brain that make myelin, which is attacked in MS) are harmed or killed, and if mitochondria (the parts of cells that supply energy) are harmed.

**What's Next?** If loss of connexins worsens EAE, connexins and the processes they affect may be new therapeutic targets in MS.

### Rashmi Bansal, PhD

University of Connecticut Health Center  
Farmington, CT

**Title:** Role of ERK1/2 in Myelin Assembly, Maintenance and Remyelination

**Summary:** Searching for ways to encourage repair of nerve-protecting myelin in people with MS.

**Background:** Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS, disrupting nerve signals and eventually resulting in disability. The body has the natural ability to repair myelin but it is inefficient in the face of ongoing MS. Therefore, identifying ways to promote repair of myelin in people with MS is of great importance and has the potential to protect against further damage and restore function. Increasing our understanding of ways to promote myelin repair will lead to new therapeutic strategies to improve function in people with MS.

**The Study:** Rashmi Bansal, PhD, of the University of Connecticut Medical School in Farmington has received a research grant from the National MS Society to perform studies to understand the basic processes of how myelin synthesis and repair occur. In particular, she and her team are studying a molecule called ERK1-2/MAPK, which may have a positive effect on myelin repair. The cells in the brain that make myelin are called oligodendrocytes. Dr. Bansal's team is investigating the role of ERK1/2-MAPK in oligodendrocytes in mice in part by turning on and off ERK1/2-MAPK activity in oligodendrocytes and observing the impacts. Importantly, they are also examining whether increasing ERK1/2-MAPK can enhance the repair of myelin.



**What's Next?** Dr. Bansal's work will increase our understanding of how myelin synthesis and repair are controlled, and could pave the way for new therapeutic strategies to increase myelin repair in people with MS, which will ultimately improve function and decrease disability.

**Stephen Crocker, PhD**

University of Connecticut Health Center  
Farmington, CT

**Title:** TIMP-1 Regulation of Oligodendrocyte Differentiation for CNS Remyelination

**Summary:** Understanding how myelin repair may be improved with a molecule called TIMP-1.

**Background:** In MS, the immune system attacks myelin, the fatty substance that surrounds and protects nerve fibers. Loss of myelin impairs nerve signaling, leading to disability in people with MS. In the brain, myelin is made by a type of cell called the oligodendrocyte. The ability of oligodendrocytes to make myelin is enhanced by a molecule called TIMP-1, which is made by another type of cell in the brain called the astrocyte. One idea about what goes wrong in MS is that astrocytes stop making TIMP-1, and therefore, they lose the ability to help oligodendrocytes make new myelin.

**The Study:** Stephen Crocker, PhD, of the University of Connecticut Health Center in Farmington has received a research grant from the National MS Society to investigate a molecule called TIMP-1 that may be important for repairing myelin that has been damaged by MS. This team is working to understand how TIMP-1 stimulates immature oligodendrocytes to mature and become capable of making new myelin. They are also investigating how TIMP-1 works on oligodendrocytes. Finally, they are using mice that cannot make TIMP-1 in their brains to ask whether its absence worsens EAE, a model that resembles some aspects of MS.

**What's Next?** The results from this study are expected to suggest new ways to increase myelin synthesis and repair in the nervous systems of people with MS, with the hope of improving function.

**James Goldman, MD, PhD**

Columbia University  
New York, NY

**Title:** HGF : c-met signaling in oligodendrocyte development and its inhibition by CD82

**Summary:** Does a molecule called CD82 hold a key to promoting myelin repair in MS?

**Background:** Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS. The cells in the brain that make myelin are called oligodendrocytes. The brain contains a population of "spare" immature oligodendrocytes that need to mature in order to produce and replace myelin. Finding ways to encourage this maturation process is likely to be important for stimulating myelin repair in the brains of people with MS.



**The Study:** James Goldman, MD, PhD, of Columbia University in New York has received a research grant from the National MS Society to better understand what drives and controls the maturation of the immature oligodendrocytes. Dr. Goldman's team is studying a molecule called CD82, which promotes this maturation process. Using cells grown in lab dishes and rodent models, the team is uncovering how CD82 works. They are turning CD82 on and off and examining the results to get a better idea of how the molecule is involved in the maturation of oligodendrocytes, and also examining its role in the myelin repair process in mice fed a toxin that induces myelin destruction.

**What's Next?** Understanding how to promote oligodendrocyte maturation may suggest new therapeutic avenues to promoting myelin repair in people with MS.

**William Talbot, PhD**

Stanford University  
Stanford, CA

**Title:** Mechanism and function of myelin basic protein mRNA localization in oligodendrocytes

**Summary:** How do the instructions to make nerve-insulating myelin move from inside the cell out to where its construction occurs?

**Background:** Myelin, the material that is initially damaged in MS, is a thin sheet of fats and proteins produced by cells called oligodendrocytes, which wraps around and protects nerve fibers. Genes can be thought of as the blueprint for the myelin proteins, and messenger RNA translates the genetic blueprint with the information needed to construct myelin proteins. The messenger RNA is not found in the main portion of the oligodendrocyte, but is found near the myelin. No one knows how the messenger

RNA moves from the cell nucleus, where it is copied from the DNA in the oligodendrocyte's genes, into the myelin. Answering this question could further efforts to find ways to repair myelin after it has been damaged by MS.

**The Study:** William Talbot, PhD, of Stanford University in California, has received a research grant from the National MS Society to discover how the messenger RNA for myelin basic protein, the major protein in myelin, is transported from inside the cell out to myelin. His team is using zebrafish, which are easy to watch and manipulate, as efficient models for studying myelin. The team is using state-of-the-art techniques to mutate specific regions of the myelin basic protein messenger RNA to see which portions of it cooperate with the proteins that move it from the cell nucleus into myelin sheets.

**What's Next?** Understanding how the instructions to make myelin proteins move into myelin could be an important step toward the development of new therapies that repair damaged myelin and restore function in people who have MS.

**Carla Taveggia, PhD**

San Raffaele  
Scientific Institute  
Milan, Italy

**Title:** Role of ADAM 17 in CNS myelination and remyelination

**Summary:** Understanding how nerve-insulating myelin is controlled to promote repair in the brains of people with MS.



**Background:** Myelin, the fatty substance that ensheaths and protects nerve fibers, is attacked and destroyed in MS, leading to various symptoms. In the brain and spinal cord, the cells that make and repair myelin are called oligodendrocytes.

**The Study:** Carla Taveggia, PhD, of the San Raffaele Scientific Institute in Milan, Italy has received a research grant from the National MS Society to explore how myelin growth is controlled in the brain and spinal cord. The team is investigating signals given off by nerve fibers that help dictate myelin growth and possibly its repair after damage. In particular, they are researching a molecule called ADAM 17 that appears to help regulate myelin synthesis by oligodendrocytes, and whose function appears to be altered in the brains of people with MS. They are using a variety of techniques to understand how ADAM 17 controls myelin synthesis and whether ADAM 17 is important in myelin repair.

**What's Next?** If we can understand the details of how myelin synthesis is controlled, we may be able to design new therapies that will promote repair of damaged myelin in people with MS.

**Glenn Matsushima, PhD**

University of North Carolina at Chapel Hill

**Title:** Targeting Repair of Demyelinating Lesions

**Summary:** Searching for therapies to prevent progressive disability in MS.

**Background:** Myelin, the material that surrounds nerve fibers and facilitates the rapid movement of nerve signals, is damaged and destroyed by immune system cells in the brain and spinal cord of people who have MS. Although the body repairs some myelin damage, the cells that make myelin (oligodendrocytes) and nerve cells are also destroyed in many people who have MS, resulting in progressive disability. Most of the treatments currently available for MS slow the initial destruction of myelin but are generally not effective in the progressive stages of the disease.

**The Study:** Glenn Matsushima, PhD, at the University of North Carolina's School of Medicine in Chapel Hill, has received a grant from the Society to look for medicines that may reduce or halt damage to oligodendrocytes and nerve cells. In the first part of this study, Dr. Matsushima and his team are screening a number of compounds to see whether they prevent damage to oligodendrocytes grown in laboratory glassware. In the next part of the study they will test whether compounds that appear to have promise from the screen can halt the effects of the MS-like disease in mice.

**What's Next?** The compounds that Dr. Matsushima's group is testing are related to medicines that have already been approved by the FDA for other uses. Therefore, any that show promise could be moved rapidly into clinical trials.



**James Salzer, MD, PhD**

NYU School of Medicine  
New York, NY

**Title:** Mobilizing adult neural stem cells for remyelination

**Summary:** Searching for ways to increase the production of brain cells that can repair myelin damaged by MS.

**Background:** Myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord, is made by cells known as oligodendrocytes. In MS, damage occurs to myelin, oligodendrocytes and eventually the nerve fibers previously protected by myelin. Immature oligodendrocytes and stem cells residing in the brain can develop into new oligodendrocytes that replace damaged myelin. However, production of new oligodendrocytes does not keep up with the damage. Finding ways to increase natural myelin repair is an important goal of nervous system repair research.

**The Study:** James Salzer, MD, PhD, of New York University School of Medicine in New York, has received a research grant from the National MS Society to study neural stem cells, a type of cell found in regions of the brain that can form new oligodendrocytes. Working with mice with EAE, a disease similar to MS, and other mouse models of myelin damage, Dr. Salzer and colleagues are investigating whether neural stem cells can be stimulated to produce greater numbers of new oligodendrocytes that will increase the rate of repair of myelin.

**What's Next?** If this study identifies the natural chemical signals that encourage neural stem cells to make myelin-forming oligodendrocytes, it could lead to the development of new treatments to repair

myelin damage to restore function in people who have MS.

**Fraser Sim, PhD**

University at Buffalo

**Title:** Muscarinic receptor regulation of oligodendrocyte differentiation

**Summary:** Can an FDA-approved therapy promote the repair of nerve-insulating myelin?

**Background:** Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS. No current therapies exist to stimulate repair and synthesis of new myelin. Myelin is made by cells known as oligodendrocytes. Much of the data about oligodendrocytes and their ability to make myelin have been done in rodents (rats and mice). Dr. Sim previously identified a gene called the acetylcholine muscarinic receptor type 3 (M3 receptor) gene, which when activated blocks the ability of immature oligodendrocytes to turn into mature oligodendrocytes than can make myelin.

**The Study:** Fraser Sim, PhD, of the State University of New York (SUNY) in Buffalo, New York has received a research grant from the National MS Society to further investigate the importance of the M3 receptor in myelin repair. They are determining what if blocking the M3 receptor will promote myelin repair. They are treating mice with reduced myelin with a drug called solifenacin, which is an FDA-approved therapy for overactive bladder that blocks the M3 receptor. They are asking if solifenacin can increase myelin synthesis when mice are treated with the drug. They are also treating rats with myelin loss with an M3 receptor activator to see if myelin repair is blocked.



**What's Next?** These studies should determine whether targeting the M3 receptor is a viable strategy to regulate myelin growth and stimulate myelin repair in MS. Since he is testing a drug already approved for human use, if it turns out to stimulate myelin repair, several steps in the drug development and approval process could be skipped.

**Seema Tiwari-Woodruff, PhD**

University of California, Los Angeles

**Title:** Preservation of axons by Estrogen Receptor Beta signaling induced axon remyelination in a chronic mouse model of multiple sclerosis

**Summary:** Can estrogen-like compounds protect the brain from MS damage?

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects the nerve fibers, and the nerve fibers can also be damaged. Current therapies are mostly aimed at dampening the immune system. However, a therapy that directly protects the myelin and nerve fibers is also necessary. The sex hormone estrogen has been shown in rodent studies to protect the brain, but estrogens impact the reproductive system and have been linked to cancers. An estrogen-like therapy that specifically protects the brain without affecting the female reproductive system is desired, and could even be used in both men and women.

**The Study:** Seema Tiwari-Woodruff, PhD, of the University of California at Los Angeles, has received a research grant from the National MS Society to test estrogen-like compounds that act on estrogen docking sites in the brain and may provide nervous system protection, without impacting the reproductive system. They are testing various forms in a mouse model of MS called EAE, and determining if versions of these compounds can protect the brain, and even stimulate myelin repair. She and her team are also seeking to learn how these compounds work.

**What's Next?** If any of these compounds prove promising, they would be put to further preclinical tests required to demonstrate their promise and safety and to continue their progress along the pipeline toward drug development. Finding a way to protect the brain from MS destruction and stimulate repair of damaged myelin would be a major step forward in efforts to stop MS progression and restore function.



## RESTORE—Neurophysiology

### Alexandr Klistorner, PhD

University of Sydney  
Sydney, Australia

**Title:** Investigating mechanisms of axonal degeneration in multiple sclerosis

**Summary:** What mechanisms drive progressive nervous system damage in MS?

**Background:** In MS, nerve fibers, which are responsible for sending electrical signals in the brain, can degenerate, and so can the nerve cell bodies, or neurons. Nerve damage leads to progressive disability. There is an open question about what drives nerve fiber destruction and its timing, how it relates to the destruction of the myelin that encases nerve fibers, and whether it occurs only in the presence of immune attacks and inflammation. The visual system, which is often affected in MS, is an ideal window for answering some of these important questions.

**The Study:** Alexander Klistorner, PhD, of the University of Sydney (Australia) has received a research grant from the National MS Society to use various imaging techniques to study mechanisms and timing of progressive degeneration of the nerve fibers in the visual system occurs in people with MS. Specifically, Dr. Klistorner's team is investigating fiber loss in the visual pathways of people with MS who show no inflammation in the visual system and contrasting this with findings from people MS who do have a history of inflammation in the visual system.

**What's Next?** The results of the study will increase our understanding of factors that trigger and drive MS progression and will aid in the development of therapies aimed at preventing nerve degeneration.

### Maarten Kole, MSc, PhD

Netherlands Institute for Neuroscience  
Amsterdam, Netherlands

**Title:** Spike generation in demyelinated axons; a molecular and functional analysis of the axon initial segment

**Summary:** Understanding electrical impulse dysfunction in MS that occurs following the destruction of myelin.

**Background:** In MS, the myelin sheath, which surrounds and protects nerve fibers, is attacked and destroyed. Without the myelin sheath, nerve fibers can no longer properly send electrical signals throughout the brain. This dysfunction in nerve fibers causes the symptoms and disability in people with MS.

**The Study:** Maarten Kole, PhD, of the Netherlands Institute for Neuroscience in Amsterdam has received a research grant from the Society to understand the details of how nerve fibers without myelin fail to function properly. They are exposing mice to a toxin called cuprizone that causes loss of myelin and then will look for harmful changes in the nerve fibers that may lead to loss of normal function. Using novel techniques to measure electrical activity they will determine how electrical impulses are both started and are traveling along nerve fibers with and without myelin, to look for harmful changes in nerve fiber function. They are also examining the changes in electrical signals that occur in the short term compared to changes in the long term that may be permanent.

**What's Next?** These changes in nerve fiber function will help to explain symptoms in MS and may lead to new therapeutic strategies to treat or prevent damage in nerve fiber activities, which will improve the quality of life in people with MS.

**END**

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

**END—Risk Factors****Alberto Ascherio, MD, MPH**

Harvard School of Public Health  
Boston, MA

**Title:** Exploring the interaction between serum 25(OH)D, vitamin D metabolism gene variants, RNA expression and MS progression

**Summary:** Searching for a genetic link between the positive effects of vitamin D and MS.

**Background:** Research hints that high levels of vitamin D may protect against the development of MS, and tests are underway to determine whether it has a favorable effect on disease activity in people with the disease. It is possible that whether an individual benefits from vitamin D therapy may depend on that person's genetic make-up.

**The Study:** Alberto Ascherio, MD, MPH, of the Harvard School of Public Health in Boston has received a research grant from the National MS Society to study whether an individual's vitamin D-related genes impact the effect of vitamin D supplementation in MS. The team is using serum samples from participants in

two large, previously completed phase III clinical trials of interferon beta that were conducted in people with relapsing-remitting MS and in people with clinically isolated syndrome, which sometimes progresses to MS. They are also examining if the activation characteristics of certain immunologically important genes that play a role in MS vary based on a person's vitamin D levels.

**What's Next?** These results may allow for more personalized treatment approaches by identifying individuals who will benefit the most from vitamin D supplementation. In addition, by examining changes in gene expression, this study may provide better understanding of the beneficial effect of vitamin D in preventing or delaying MS progression, which could be important for the design of future therapeutic and preventative strategies.

**Philip De Jager, MD, PhD**

Brigham and Women's Hospital  
Boston, MA

**Title:** Integrating risk factors and biomarkers for prediction in presymptomatic MS

**Summary:** Identifying individuals without symptoms who are at high risk for MS.

**Background:** The risk for MS is difficult to determine. Family members of people with MS are often at higher risk for developing the disease, but finding a way to predict who may actually develop the disease is not possible. MS lesions, or spots of potential disease activity, can be detected with brain imaging in individuals years before any actual MS symptoms occur. Determining high-risk individuals could enable early screening, leading to early therapeutic intervention and reduced disability in the long term.



**The Study:** Philip L. De Jager, MD, PhD, of Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts has received a research grant from the Society to develop a method of determining a person's risk for developing MS. This team is looking at over 2000 first-degree relatives of people with MS (sibling, parent, child) who have not experienced any symptoms, with the aim of developing an individualized risk prediction tool that incorporates the latest knowledge in MS genetics, environmental exposure, and blood biomarkers. First, they are determining whether individuals with high genetic and environmental risk for MS show the presence of MS-like biomarkers in their blood. Next, they will test their risk assessment tool using pre-symptomatic blood samples from people who went on to develop MS to see if their tool was able to predict development of the disease. Finally, they will test the effectiveness of their tool in predicting the presence of MS-like brain lesions in people who are without symptoms but who are at high risk for MS according to the tool.

**What's Next?** Developing a test that reliably predicts the risk of MS in individuals would allow early detection and timely intervention, and which has the potential for reducing long-term disability and the overall cost to the health care system. Results from this study can also be used to test strategies aimed at preventing the onset of MS.

**John Kriesel, MD**

University of Utah  
Salt Lake City, UT

**Title:** Deep Sequencing for the Detection of Microbes

in the Brains of Patients with Acute Demyelinating Disease

**Summary:** Searching for hints of a possible virus in the brain that may trigger MS.

**Background:** The cause of MS is unclear, but one possibility is that a viral infection may trigger the destruction of the myelin coating on nerve fibers in the brain and spinal cord. This "demyelination" is one of the pathological events that occurs in people with MS and it leads to symptoms and disability. Technology has vastly improved scientists' ability to search for viruses, and a technique called "deep sequencing" can be used to detect viral genetic material in different types of samples.

**The Study:** John Kriesel, MD, of the University of Utah School of Medicine in Salt Lake City, has received a research grant from the National MS Society to search for genetic material from viruses in the brain, blood, and cerebrospinal fluid from 16 people with acute demyelination (myelin destruction that shows up as an attack of neurological symptoms) compared to samples from healthy individuals. Individuals with acute demyelination often have or will go on to develop MS. Studying tissue samples from these individuals maximizes the chance of identifying a virus because their disease is recent or active.

**What's Next?** Results from this project offer the hope of identifying a virus that may trigger or contribute to triggering MS. This could spur new diagnostic strategies, new treatments, and even preventative measures for MS.



### **Helen Tremlett, PhD**

University of British Columbia  
Vancouver, British Columbia, Canada

**Title:** Do the beta interferons prolong life in people with multiple sclerosis?

**Summary:** Investigating if beta interferons can extend the survival of people with MS.

**Background:** While most people with MS have a normal or near-normal life expectancy, severe MS can shorten life. The most commonly used drugs to treat MS symptoms are called the beta interferons. The beta interferons reduce the relapse rate, but their possible role in impacting survival in people with MS is unknown. Because many people with MS are prescribed a beta interferon, often for many years, determining the potential impact of this drug on survival in people with MS is important.

**The Study:** Helen Tremlett, PhD, and Elaine Kingwell, PhD, of the University of British Columbia (UBC) in Vancouver, British Columbia, Canada have received a research grant from the Society to determine whether the beta interferons impact the survival of people with MS. To do this, Drs. Tremlett and Kingwell, together with Drs Joel Oger and John Petkau (UBC) and Drs Emmanuelle Leray and Gilles Edan (the French School of Public Health and University of Rennes, France) are collecting data regarding drug treatment, length of survival, and cause of death from up to 10,000 people with relapsing-remitting or secondary-progressive MS from British Columbia, Canada and Rennes, France who have been followed up for up to 25 years. They are also examining the cause of death in beta interferon-treated people with MS compared to people with MS who were not treated with beta interferons. In addition, they are investigating the impact of glatiramer acetate, another drug used to treat people with MS, on survival.



Technology has vastly improved scientists' ability to search for viruses, and a technique called "deep sequencing" can be used to detect viral genetic material... This study could spur new diagnostic strategies, new treatments, and even **preventative measures** for MS.

**What's Next?** Increased understanding of any survival benefits of the beta interferons, the most frequently prescribed first-line therapy for MS, will provide a more balanced risk assessment so that patients and doctors can make informed treatment decisions.

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



## National MS Society Funds Unique Imaging Study and New Research to Speed Nervous System Repair

The National Multiple Sclerosis Society recently announced several new commercial development projects funded through Fast Forward:

- The Society entered into a research collaboration agreement with GE Healthcare to co-fund a clinical study with the GE investigational PET tracer, GE180, in patients with multiple sclerosis. The clinical study, which will be enrolling patients in the United Kingdom, is aimed to aid in physicians' understanding whether imaging neuroinflammation in MS patients before and after treatment with natalizumab (Tysabri®) can help identify which patients may respond to treatment.

Finding ways to restore and protect the damaged nervous system is a key priority of National MS Society's No Opportunity Wasted (NOW) Campaign research to stop the disease in its tracks, to restore function, and ultimately end MS forever. The Society's new commercial investments in drug development through Fast Forward include:

- CuroNZ, an Auckland biotechnology company, was awarded \$ 540,000 to support preclinical studies to develop CuroNZ's NRP2945 candidate as a potential therapy to protect the nervous system from MS damage. The funding will enable CuroNZ to undertake pre-clinical proof of concept, pharmacokinetic and toxicity studies to bring the drug candidate lead NRP2945 closer to an investigational new drug (IND) application. CuroNZ will collaborate with leading research organizations including the University of Auckland and Monash University in Melbourne.
- ENDECE Neural, a private biotechnology company, has received \$225,000 in funding to advance the preclinical development of the company's lead compound, NDC-1308, focusing on repairing the protective myelin covering surrounding axons (nerve fibers) in the brain and spinal cord. Previous studies in NDC-1308 demonstrated the ability to significantly remyelinate the myelin sheath in mice.
- Karo Bio AB, an emerging pharmaceutical company, has been awarded \$499,631 for preclinical development of a novel treatment, ERbeta agonists, which have potential to slow disease progression in MS based on preclinical models showing that it protects neurons and restores myelin. This envisaged profile differs dramatically from currently approved MS therapies.
- Karyopharm Therapeutics Inc., a clinical-stage pharmaceutical company, has been awarded \$500,000 to conduct tests on Selective Inhibitors of Nuclear Export (SINE) compounds for development as a treatment aimed at protecting the nervous system and stopping MS progression. These compounds inhibit release of inflammatory proteins and increase concentrations of neuroprotective factors. The company is determining the mechanism of action and possible toxic effects, and gathering data to select a leading SINE candidate.