

# NEW RESEARCH



STOP. RESTORE. END.

## Society Commits \$29 Million for 83 New MS Research Projects

The National Multiple Sclerosis Society has committed another \$29 million to support an expected 83 new MS research projects and training awards. These are part of a comprehensive research strategy aimed at stopping MS, restoring function that has been lost, and ending the disease forever – for every single person with MS.

This financial commitment is the latest in the Society's relentless research efforts to move us closer to a world free of MS, investing more than \$50 million in 2014 alone to support over 380 new and ongoing studies around the world. So that no opportunity is wasted, the Society pursues all promising paths, while focusing on three priority areas: progressive MS (p. 7, for example), nervous system repair (see these grants starting on p. 23), and wellness and lifestyle (see some examples on page 19).

We are confident that with donor response to ongoing research successes, and continued focus on the NOW campaign, the crucial dollars needed to fund these and other research and clinical initiatives will be secured.



National  
Multiple Sclerosis  
Society

While we're driving research to stop MS, restore function and end the disease forever, at the same time we're identifying key interventions and solutions that can help people with MS live their best lives now. The new projects include these, described in more detail in the following pages:



### STOP:

- Researchers are investigating whether damage to the nervous system can be reduced by therapeutically increasing tissue oxygen concentrations. (page 5)



### RESTORE:

- A team of talented rehabilitation experts is seeking to understand the interaction between physical and cognitive functions in MS. (page 21)



### END:

- Scientists ask: Can dietary salt influence the behavior of immune cells in MS? (page 34)

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## 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 how 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 Gross, MD**

Mount Sinai School of Medicine, New York

**Title:** The Sylvia Lawry Physician Fellowship

**Summary:** Training to design and conduct MS clinical trials.

**Background:** 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.

**The Study:** Robert Gross, MD, is being mentored by the expert MS clinician and clinical researcher Fred Lublin, MD, who is the Saunders Family Professor of Neurology and the Director of the Corinne Goldsmith Dickinson Center for MS. Dr. Rossman is completing the MS Fellowship Program at the Center, which comprises a strong emphasis on producing first-rate clinicians capable of directing the care of MS patients from the time of diagnosis onward; involvement in every aspect of clinical trials—design, enrollment, data collection, and analysis; a Master of Science Degree in Clinical Research; and exposure to basic science underlying the development of MS.

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

#### **Bardia Nourbakhsh, MD (Pending)**

University of California, San Francisco

San Francisco, CA

**Title:** The Sylvia Lawry Physician Fellowship

**Summary:** Training to design and conduct MS clinical trials.

**Background:** 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.

**The Study:** Bardia Nourbakhsh, MD, is being mentored by highly experienced MS clinician and researcher Emmanuelle Waubant, MD, PhD, who is Professor of Neurology and Director of the Pediatric MS Center at the UCSF Multiple Sclerosis Center. During the extensive training over three years, Dr. Nourbakhsh will gain formal training in the UCSF Master's program for clinical research, and will participate in multiple clinical trials and studies in different stages of development. The UCSF program offers extensive mentorship in many different aspects of MS research and patient care. Weekly journal clubs and clinical conferences will further supplement his training.

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## Training Physicians to Provide Exceptional Care to People with MS

Consistent with its mission to move toward a world free of multiple sclerosis, the Society now offers the Institutional Clinician Training Award, a five-year award to mentors and institutions to provide training for board-certified/eligible neurologists and physiatrists in MS specialist care. The goal is for fellows to acquire the skills and knowledge necessary to provide the highest quality of care for individuals with MS. Here is a list of the awardees for 2014:

**Jeffrey Cohen, MD**

Cleveland Clinic Foundation  
Cleveland, OH

**Andrew Goodman, MD**

University of Rochester Medical  
Center  
Rochester, NY

**Fred Lublin, MD**

Mount Sinai School of Medicine  
New York, NY

**Brenda Banwell, MD, FRCP, FAAP**

Children's Hospital of Philadelphia  
Philadelphia, PA

**Jeffrey Gelfand, MD**

University of California, San Francisco  
San Francisco, CA

**Anthony Reder, MD**

University of Chicago Medical Center  
Chicago, IL

**Howard Weiner, MD**

Brigham and Women's Hospital  
Boston, MA

This training focuses on all aspects of patient management, including monitoring disease course, utilizing treatments, managing symptoms, multidisciplinary care, as well as exposure to clinical research. The award's unique flexibility allows the mentor and fellow to create a customized training plan tailored to the fellow's background, interests and career goals that may span one to three years. And the Society's five-year award gives mentors the certainty they need to attract and recruit the best candidates.

These awards will produce the next generation of clinical care specialists with a depth and breadth of knowledge required to provide exceptional care to people with MS well into the future.



### Ian Rossman, MD, PhD

The Cleveland Clinic Foundation

**Title:** The Sylvia Lawry Physician Fellowship

**Summary:** Training to design and conduct MS clinical trials.

**Background:** 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.

**The Study:** Ian Rossman, MD, PhD, is being mentored by the expert MS clinician and neuroimmunologist Jeffrey Cohen, MD, who is a Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University; Director of the Mellen Center Experimental Therapeutics Program at Cleveland Clinic; and Director of the Mellen Center Clinical Neuroimmunology Fellowship. Dr. Rossman is completing a Clinical Neuroimmunology Fellowship at Cleveland Clinic, a three-year program designed to provide the skills needed to diagnose and treat people with MS, as well as function as a clinical researcher focusing on clinical trials. This is accomplished through direct patient care, participation in clinical trials, and formal course work in clinical research. This comprehensive program will be tailored to his interest in pediatric MS.

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

### STOP—Neuropathology (Tissue Damage)

### Quasar Padiath, MBBS, PhD

University of Pittsburgh

Pittsburgh, PA

**Title:** The role of the nuclear lamina in myelin regulation and demyelination

**Summary:** Exploring the possible role of a protein that may control genes involved in the repair of nerve-insulating myelin.

**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. Myelin repair in MS is generally incomplete for reasons that are not well understood.

**The Study:** Quasar Padiath, PhD, of the University of Pittsburgh, has received a research grant from the National MS Society to investigate the possible role of a protein called Lamin B1 in controlling activation of genes that are responsible for myelin regulation. Lamin B1 is found in the central nucleus, the part of the cell that contains DNA. Lamin B1 plays a role in regulating gene activation, and increased amounts of Lamin B1 have been found in MS lesions. Dr. Padiath and colleagues have previously shown that a gene mutation that produces increased amounts of the Lamin B1 protein causes another disease that also affects myelin known as a leukodystrophy, which is similar in some aspects to MS. They suggested that increased amounts of Lamin B1 in oligodendrocytes are harmful to these cells due to disruption of proper expression of genes needed to maintain myelin, ultimately resulting in the loss of myelin and insufficient myelin repair. To test the idea, they have created mice that express abnormally high amounts of Lamin B1 in oligodendrocytes.



## Six Physicians Offered Training in Specialized MS Care

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

Awardee	Location	Mentor
Susan Anzalone, MD	University of California, San Francisco San Francisco, CA	Emmanuelle Waubant, MD, PhD
Michelle Bowman, MD	Ohio State University Columbus, OH	Michael Racke, MD
Erik Charlson, MD	Albert Einstein College of Medicine Bronx, NY	Ilya Kister, MD
Neeta Lal, MD	Washington University School of Medicine St. Louis, MO	Barbara Green, MD
Tiffani Stroup, DO	University of Chicago Chicago, IL	Anthony Reder, MD
Adnan Subei, DO	The Cleveland Clinic Foundation Cleveland, OH	Jeffrey Cohen, MD
Danielle Detterman, MD	University of Chicago Chicago, IL	Anthony Reder, MD

These mice show an age-dependent difficulty in movement and muscle wasting. They are examining these mice to understand what genes are incorrectly turned on or off by excess Lamin B1 and how this affects the ability of the oligodendrocytes to make, maintain, and repair myelin.

**What's Next?** Results from this study will increase our understanding of how myelin growth and repair are controlled at the genetic level, and may provide insight into why myelin repair is insufficient in MS and how to fix it. It may also identify a new role for the Lamin B1 protein in MS disease mechanism.

### **Kenneth Smith, PhD**

University College London  
London, Great Britain

**Title:** Towards a greater understanding of multiple sclerosis: recognizing the importance of hypoxia, and new opportunities for therapy.

**Summary:** Can damage to the nervous system be reduced by therapeutically increasing tissue oxygen concentrations?

**Background:** Immune activity in the brain and spinal cord can cause the loss of myelin, the fatty substance that surrounds and protects nerve fibers. The nerve fibers themselves are also damaged. Inflamed MS lesions show evidence of "hypoxia," which



means lower than normal levels of oxygen. This hypoxia may contribute to the damage, slowing recovery.

**The Study:** Kenneth Smith, PhD, of University College London, has received a research grant from the National MS Society to investigate if increasing the oxygen concentration in the brain can help to prevent injury without causing additional damage. His team is also trying to improve ways to measure oxygen and injury in the brain. They are using two laboratory models that show loss of function and loss of myelin, and they plan to use different methods to raise the concentration of oxygen in the CNS. They will then assess whether there is an improvement in function and/or a reduction in lesion severity. They are also exploring whether increasing oxygen delivery can prevent permanent damage to the nervous system. Dr. Smith's group is also exploring how to use MRI to monitor blood flow and oxygen levels in the oxygen-treated tissue. The research is reminiscent of earlier trials involving high pressure (hyperbaric) oxygen therapy in MS, but the new research is founded in a different and new understanding of the mechanisms involved.

**What's Next?** Positive results from this study could lead to clinical trials to test whether administering or increasing oxygen could treat early lesions in MS and prevent permanent damage and symptoms. Dr. Smith cautions, "Don't try this at home" -- until the results on safety are known, there is a risk that damage could be made worse by breathing oxygen.

## STOP—Measuring MS Disease Activity

### **Peter Calabresi, MD**

Johns Hopkins University  
Baltimore, MD

**Title:** Quantitative Spinal Cord MRI as a Predictive Tool for Disease Progression in MS

**Summary:** Can advanced Magnetic Resonance Imaging (MRI) techniques measure the progress of changes in the spinal cord due to MS?

**Background:** The neurological problems that people with MS experience result from damage to regions of the brain and spinal cord. Magnetic Resonance Imaging (MRI) of the brain has been useful in diagnosing and following the course of MS. The spinal cord has very clearly defined regions of nerve cells and nerve fibers, but the much smaller size of the spinal cord compared to the brain and other technical problems has limited the number of informative MRI studies on it.

**The Study:** Peter Calabresi, MD, has received a research grant to study how changes revealed by advanced MRI techniques of the spinal cord relate to progression of disability in people who have MS. The MRI techniques the team is using are capable of producing much more detail regarding tissue change in the spinal cord in comparison to previous techniques. Working with collaborator Jiwon Oh, MD, who trained with Dr. Calabresi and is now in her first faculty position at the University of Toronto, the team will obtain follow-up spinal cord MRI scans in a group of people with MS who underwent spinal cord MRI scans 5 years ago, and will compare changes in several types of MRI scans to see how these relate to changes in neurological disability. In addition, the researchers will see whether different forms of MS yield different patterns of MRI changes.



**What's Next?** Long-term follow-up studies using advanced MRI techniques in the spinal cord are needed, and this study will provide information on spinal cord MRI change in MS patients over a follow-up period of 5 years. This research should provide important basic information about how changes in the spinal cord affect the course of MS. This work should also indicate how these advanced MRI techniques could be used to monitor outcomes in clinical trials, in addition to providing improved methods to follow and predict the course of MS in individuals.

**Matilde Inglese, MD**

Mount Sinai School of Medicine  
New York, NY

**Title:** Multimodal longitudinal imaging in progressive MS

**Summary:** Using advanced imaging to track and understand nervous system changes that lead to progression in people with primary-progressive MS.

**Background:** About 15% of people with MS have the primary-progressive form of the disease. In these people, neurological symptoms get steadily worse from the onset of the disease, rather than waxing and waning as in the more common relapsing-remitting forms. The regions of myelin damage seen in traditional MRI studies are less common in primary-progressive MS. Moreover, the therapies used to treat relapsing-remitting MS are generally ineffective for people with primary-progressive MS.

**The Study:** Matilde Inglese, MD, PhD, of the Icahn School of Medicine at Mount Sinai in New York City, received a grant from the National MS Society to study how MRI images of the brain and spinal cord of people with primary-progressive MS change over three

years for clues to the underlying damage leading to disease progression. The team is using techniques that reveal more detail than conventional MRI and looking for subtle changes in the regions of the brain and spinal cord that contain the bodies of nerve cells. The scans from 50 people with primary-progressive MS will be compared those from 30 healthy people without MS (controls).

**What's Next?** The results of this study could provide important clues to the underlying reasons for nervous system damage in primary-progressive MS. In addition, the results could provide new methods for the evaluation of potential treatments for primary-progressive MS.

**Matthew Schindler, MD, PhD (Pending)**

National Institute of Neurological Disorders and Stroke, NIH  
Bethesda, MD

**Title:** Advanced imaging of acute lesion formation and repair in patients with relapse remitting multiple sclerosis

**Summary:** Improving MRI to allow more rapid assessment of disease progression and to improve drug discovery.

**Background:** Assessment of disease progression in MS is time-consuming, inefficient, and not sensitive enough. These problems slow down clinical trials that test new therapies and make the trials more expensive. Thus, finding more sensitive and quicker ways to assess whether a therapy can protect the nervous system or promote repair of nerve-insulating myelin would speed the process of finding new therapies to stop MS and restore function.



**The Study:** Matthew Schindler, MD, PhD, has received a National MS Society/American Brain Foundation Clinician Scientist Award to work on improving magnetic resonance imaging (MRI) to allow more rapid assessment of changes in brain lesions in people with MS. Working under the expert mentorship of Daniel Reich, MD, PhD, of the NIH, Dr. Schindler is performing frequent MRI scanning in people with relapsing-remitting MS using techniques that can look at myelin health and other specific aspects of MS brain lesions. The participants will then be involved in a clinical trial, using these advanced MRI techniques and other measures to see whether a test compound called MRF-008, which has shown promise for protecting myelin forming cells and promoting myelin repair in preliminary lab studies.

**What's Next?** If the test compound proves safe and shows some signs of protecting myelin, it will likely move on to larger clinical trials. Regardless of the drug's outcomes, if the imaging techniques allow for quicker screening of the drug's impact, they are likely to be included in more clinical trials and ultimately could speed the delivery of new therapies to people with MS.

#### **Jie Wen, PhD**

Washington University School of Medicine  
St. Louis, MO

**Title:** Quantification of MS tissue damage in both brain and spinal cord by using tissue-specific quantitative parameters on MRI

**Summary:** Improving MRI to better understand changes in the brain in MS.

**Background:** Magnetic resonance imaging (MRI) is commonly used to track MS disease activity and lesions (areas of activity or damage) in the brains of people with MS.

However, what is seen on MRI scans and the clinical status of the patient can be disconnected.

**The Study:** Jie Wen, PhD, of Washington University School of Medicine in St. Louis, MO has received a research grant from the National MS Society to improve MRI. Dr. Wen is working under the expert mentorship of Anne Cross, MD, to improve MRI by using other settings to detect more lesions, including those in the brain that are difficult to detect with current MRI methods. Spinal cord lesions in MS are largely invisible using current MRI techniques. Thus, Dr. Wen is also using MRI to improve the detection of lesions in the spinal cord, because many people with MS have lesions in this region. Dr. Wen is also comparing this improved method of MRI with other imaging methods currently in use.

**What's Next?** Improving imaging of the brain and spinal cord in people with MS will provide better information about diagnosis and monitoring of disease progression and treatment, and will establish better correlations between MRI data and clinical test results.

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

#### **Dorina Avram, PhD**

Albany Medical College  
Albany, NY

**Title:** A novel ubiquitin ligase with role in EAE severity

**Summary:** Can understanding a regulator of immune cell function translate into the development of a treatment to stop immune attacks in MS?

**Background:** MS is due in part to inappropriate actions of immune cells in the brain. Current MS therapies can reduce



immune attacks but they don't specifically or completely control and stop them. Cellular function is controlled by various proteins, and the stability of proteins in cells is partly controlled by a class of molecules called "ubiquitin ligases." The activity of these ligases can be highly specific. Dr. Dorina Avram's early studies have shown that a single ubiquitin ligase called "Hectd3" may specifically control the function of T cells, a type of immune cell that is important in MS.

**The Study:** Dorina Avram, PhD, of Albany Medical College (Albany, NY) has received a research grant from the National MS Society to further investigate the role of Hectd3 in controlling the function of T cells. Hectd3 may be critically important in the immune response in MS, and to test this she uses a mouse model of MS called EAE. Dr. Avram and her team have shown that the absence of Hectd3 in T cells makes EAE better. They will perform studies to further understand how the presence of Hectd3 makes EAE worse and why its absence makes EAE better.

**What's Next?** These studies will increase our understanding of how the function of immune cells in MS is controlled and will test whether targeting Hectd3 is indeed a good approach for designing a new type of therapy for MS. Such a drug that targets a specific ubiquitin ligase would also be highly specific and would be expected to have fewer side effects than current therapies.

**Michael David, PhD, PharmD**  
University of California San Diego  
San Diego, CA

**Title:** The IRF - type I interferon system in autoimmunity and immune tolerance

**Summary:** Studying the delicate balance of the immune system to understand the causes of MS.

**Background:** The cause of MS is not well understood, however, a misguided immune response clearly plays an important role by launching attacks against the brain and spinal cord. Viruses may be involved in this process by actually triggering the disease. As viral infections can alter the function of the immune system, they may provide some explanation for why the immune system sometimes attacks the body's own tissues.

**The Study:** Michael David, PharmD, PhD, of the University of California at San Diego, has received a research grant from the National MS Society to investigate a possible connection between viral infections and changes in the immune system and how they relate to MS. He is focusing on activities that occur in a gland called the thymus, where harmful immune cells are usually eliminated. Dr. David's group previously showed that mice that lack molecules employed by the virus-fighting protein interferon beta are highly sensitive to developing EAE, a mouse model that resembles MS. A viral infection may alter the levels of interferon-beta, or the response of cells to it, and thus may prevent the elimination of destructive immune cells. Dr. David and his colleagues are exploring the delicate balance that regulates immune cell development, and how this may be upset by viral infections to cause MS attacks.

**What's Next?** Results from this study may lead to a better understanding of the processes that lead to MS, and ultimately may suggest ways to prevent its development.



**Amanda Huber, PhD (Pending)**

University of Michigan

Ann Arbor, MI

**Title:** Type-I Interferon regulation of lymphoid chemokines in MS and EAE.

**Summary:** Developing an approach to predicting a person's response to interferon beta therapy.

**Background:** Interferon beta is a commonly prescribed and often effective medication for treating people with MS. However, a portion of people prescribed the drug either do not initially respond or lose responsiveness to it. Understanding how IFN- $\beta$  works in MS, and predicting who will respond are important goals for developing a "personalized medicine" approach to treating people with MS.

**The Study:** Amanda Huber, PhD, of the University of Michigan in Ann Arbor, has received a postdoctoral fellowship from the National MS Society to understand and predict the response to interferon beta under the mentorship of David Irani, MD. The action of interferon beta is mediated in part by a molecule called interferon regulatory factor 7 (IRF7). IRF7 increases after a person with MS is given interferon beta, but the increase in IRF7 is highly variable from one person to another. Using a mouse model for MS called EAE, the team is investigating how IRF7 levels change in mice with EAE and how these changes in IRF7 are associated with improving or worsening EAE. They are also measuring IRF7 and related factors in blood samples from people with MS before receiving interferon beta treatment and comparing these to levels after treatment to determine whether changes in IRF7 are indicative of a patient's response to interferon-beta therapy.

**What's Next?** The ability to predict a response to interferons will allow selection of patients for this type of therapy and more rapidly identify non-responders who should receive other types of treatment.

**Thomas Forsthuber, MD, PhD**

The University of Texas Health Science

Center at San Antonio

San Antonio, TX

**Title:** M2 proteomics of the EAE model of multiple sclerosis

**Summary:** Working on a blood test that may ultimately be used to monitor disease progression in people with MS.

**Background:** In people with MS, disease progression and response to therapy are monitored clinically and with imaging. A long time may be required to determine whether a person is responding to therapy and whether their disease is worsening. People with MS sometimes undergo several treatments before identifying a successful one. Thus, a test to more rapidly determine disease progression and response to therapy is needed.

**The Study:** Thomas Forsthuber, MD, PhD, of the University of Texas at San Antonio, has received a research grant from the National MS Society to identify sensitive and specific laboratory biomarkers of disease progression in MS that can be detected in blood. For this proof-of-concept study, Dr. Forsthuber and his team are using a mouse model of MS called EAE. In these mice, the researchers are able to carefully control disease onset, severity, and recovery. This is enabling them to look for proteins in the brain that change during these different stages, and then look for these proteins in blood. They are testing the idea that disease progression in these



mice can be followed in their blood, and hope to detect specific markers in blood that identify the stage of disease in EAE.

**What's Next?** If specific protein biomarkers can be found in the blood of mice with EAE, the next step will be to look for these markers in the blood of people with MS, and look for the absence of these markers in healthy people. This may ultimately lead to a simple blood test that can rapidly and accurately monitor progression of disease and response to treatment in people with MS.

### **David Hafler, MD**

Yale University  
New Haven, CT

**Title:** Can a High Salt Diet Drive Induction of Pathogenic T Cells in Humans?

**Summary:** Can a high salt diet contribute to the development and severity of MS?

**Background:** Cells of the immune system generally protect people from infectious agents, such as viruses or bacteria. In people with MS, however, some immune system cells attack, damage and destroy the protective myelin coating of nerve fibers in the brain and spinal cord, and the nerve cells can also be damaged. Much progress has been made in understanding the genetic factors that influence immune system activity. In addition to the genetic factors that predispose someone to MS, there seem to be less well understood influences from the environment that contribute to the development of MS.

**The Study:** David Hafler, MD, has received a research grant from the National MS Society to investigate the possibility that high levels of salt in the diet may help trigger or exacerbate MS immune attacks. Previous experiments in mice with EAE, a model



## Studies of the influence of dietary salt on immune cells may lead to dietary recommendations

disease similar to MS, have shown that high salt diets can increase the number of immune system T cells that damage myelin, and also reduce the number of good T cells that can turn off attacks. In this study, Dr. Hafler's team is determining whether aggressive immune T cells from people with MS are similar to those induced in mice by high amounts of salt, and whether the good T cells that limit myelin damage are reduced by high salt concentrations.

**What's Next?** This study could show whether the behavior of both damaging and beneficial immune cells in people with MS can be influenced by high salt intake. This could lead to dietary recommendations to help alleviate some of the problems caused by MS.



**Laurie Harrington, PhD**

University of Alabama at Birmingham  
Birmingham, AL

**Title:** STAT4 regulation of CNS inflammation

**Summary:** How do immune cells become aggressive and attack the brain and spinal cord in MS?

**Background:** MS is due, at least in part, to inappropriate attacks on the brain and spinal cord by immune cells. Immune cells normally learn not to attack “self” molecules and to only attack foreign, “non-self” invaders such as viruses and bacteria. However, sometimes immune cells escape this process of tolerance of self components.

**The Study:** Laurie Harrington, PhD, of the University of Alabama at Birmingham, has received a research grant from the National MS Society to investigate how immune cells learn how to ignore the body’s own proteins. One of the major types of immune cells involved in this process are called CD4 T cells. Normally, CD4 T cells release factors that direct the function of other immune cells. Dr. Harrington is investigating how CD4 T cells become aggressive and acquire the ability to attack the brain and spinal cord, as occurs in MS. Using mice with an MS-like disease called EAE, Dr. Harrington and her team are seeking to understand what molecules are involved in turning CD4 T cells into harmful ones.

**What’s Next?** Understanding how CD4 T cells acquire harmful characteristics will help in designing therapies to stop or prevent this process in people with MS.

**Daniel Hawiger, MD, PhD**

St. Louis University  
St. Louis, MO

**Title:** Hopx-dependent immunoregulation of EAE by dendritic cell-induced regulatory T cells

**Summary:** What role does a protein called Hopx play in determining whether the immune system will attack the brain and spinal cord in MS?

**Background:** In MS, the immune system attacks myelin, the fatty substance that surrounds and protects nerve fibers. Loss of myelin causes symptoms in people with the disease. The immune system normally tolerates and does not attack its own “self” proteins such as those in myelin. Thus, understanding how the immune system learns to ignore, or becomes tolerant to, self proteins and how this process goes wrong will help us design better therapies for MS.

**The Study:** Daniel Hawiger, MD, PhD, received a research grant from the National MS Society to further investigate immune system tolerance. Various types of immune cells interact to train against attacking myelin on nerve fibers. Dr. Hawiger and his team are investigating a particular protein called “Hopx” that is involved in cross-talk among immune cells. Hopx controls the switching on and off of other genes. Dr. Hawiger’s team is using genetically modified mice to understand the role of Hopx in immune-system tolerance to myelin in mice with EAE, a model of MS. Increasing Hopx may induce tolerance and reduce disease activity in EAE.

**What’s Next?** Understanding how immune tolerance works and why it fails will help with the design of better therapies for people with MS that more precisely target the immune system and that will have fewer side effects.



**Igal Ifergan, MSc, PhD (Pending)**

Northwestern University  
Chicago, IL

**Title:** The Wnt Pathway as a Modulator of Tolerogenic APCs in MS

**Summary:** Exploring a molecular “switch” to turn on helpful immune system activity for leads to new treatment approaches to stop MS.

**Background:** In MS, the immune system attacks and destroys components of the brain. Many types of immune cells are found in MS lesions, or damaged areas, in the brain. One group of immune cells called antigen-presenting cells (APCs) is found in lesions. APCs clean up broken down brain components and then can affect other immune cells to make them either helpful or harmful. Thus, controlling the ability of APCs to turn on the helpful effects or turn off the harmful effects of other immune cells could be helpful in people with MS.

**The Study:** Igal Ifergan, PhD, of Northwestern University Medical School in Chicago, IL has received a postdoctoral fellowship from the National MS Society to understand how to control APCs so that they switch on the helpful functions of other immune cells and switch off the harmful functions. Working under the expert mentorship of Stephen Miller, PhD, Dr. Ifergan is looking at a molecule called Wnt. They are testing the idea that Wnt works like a switch and that turning on Wnt in APCs will induce helpful immune responses and make mice with the MS-like disease EAE better.

**What's Next?** If Wnt is shown to be a switch that can turn on the helpful activities of the immune system, Wnt may be explored as a drug target for treating MS.

**Juan Lafaille, PhD**

New York University Medical Center  
New York, NY

**Title:** The role of the innate immune system in Experimental Autoimmune Encephalomyelitis

**Summary:** Do specific immune cells hold the key to stopping MS?

**Background:** Many of the symptoms of MS are due to damage to the brain and spinal cord, led by cells from the immune system. Much of the research on MS immune attacks has focused on immune system cells that enter the central nervous system from the blood. However, there are immune system cells, known as microglia, that spend most or all of their lives in the brain. There is less known about the role that microglia play in MS because there have been few techniques to follow their behavior.

**The Study:** Juan Lafaille, PhD, of New York University School of Medicine in New York City, has received a research grant from the National MS Society to use a newly developed technique to investigate whether microglia contribute to the symptoms of the MS-like disease EAE in lab mice. The team has developed techniques that directly modify some of the genes in microglia without affecting other cells. Now they are looking at how active the microglia are in some forms of EAE, and how microglia interact with immune system cells that enter the brain from the blood stream.

**What's Next?** The results of this work should provide important insight into the role of microglia in EAE and in multiple sclerosis. This could lead to the development of treatments for MS that would target microglia.



**Klaus Lehmann-Horn, MD (Pending)**

University of California, San Francisco  
San Francisco, CA

**Title:** Role of B cells in spontaneous chronic CNS autoimmune disease

**Summary:** Exploring the role of immune “B cells” in MS disease progression.

**Background:** In MS, the immune system attacks components of the brain and spinal cord. Several immune cells and messengers are involved. The role of one type of immune cell called B cells in MS is not completely understood. Results from a clinical trial in which B cells were depleted in relapsing-remitting MS have shown promising results for turning down immune attacks.

**The Study:** Klaus Lehmann-Horn, MD, has received a postdoctoral fellowship from the National MS Society to clarify the role of B cells in relapsing and in progressive phases of MS. Under the mentorship of Scott Zamvil, MD, PhD, the team is exploring B cells in acute (corresponding to relapsing disease) and chronic (corresponding to progressive disease) phases of a model of MS, called EAE, in mice. He is testing if blocking entry of B cells from the bloodstream into the brain and spinal cord can improve acute and chronic EAE. Groups of B cells are found adjacent to the brain and spinal cord of mice with EAE and also in some people with progressive forms of MS, so Dr. Lehmann-Horn is also testing if B cells mature in the brain and spinal cord of these mice and testing whether depleting these B cells using a drug injected into the spinal fluid can improve EAE.

**What’s Next?** These data will provide important insight into the role that B cells play in mice with relapsing and progressive EAE, and whether targeting these cells may be a promising strategy in treating MS.

**Ivan Mascanfroni, PhD (Pending)**

Brigham and Women's Hospital  
Boston, MA

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

**Summary:** Testing ways to control the helpful and harmful immune cells for clues to better treatments for MS.

**Background:** MS involves attacks by the immune system on components of the brain and spinal cord. The immune system is composed of many types of immune cells that control each other’s function. One type of immune cell called T cells are especially important in MS. The function of T cells and their ability to enter the brain are controlled at least in part by another type of immune cell called dendritic cells.

**The Study:** Ivan Mascanfroni, PhD, of Harvard’s Brigham and Women’s Hospital in Boston, has received a postdoctoral research fellowship from the National MS Society to work under the mentorship of Francisco Quintana, PhD, to understand how dendritic cells control T cells. A current therapy for MS called interferon beta triggers the production of a molecule called IL-27. IL-27 acts on dendritic cells to regulate their ability to control T cells. Dr. Mascanfroni and his team are investigating how IL-27 is involved in dendritic cell control of T cell function in the context of mice with the MS-like disease EAE. They are testing the idea that IL-27 is beneficial because it causes dendritic cells to promote production of more helpful T cells and decrease production of harmful T cells.

**What’s Next?** Results from this study may suggest that therapies aimed at increasing IL-27 action on dendritic cells could be beneficial in people with MS.



**Francisco Quintana, PhD (Pending)**

Brigham and Women's Hospital  
Boston, MA

**Title:** Role of astrocytes in multiple sclerosis and experimental autoimmune encephalomyelitis

**Summary:** What role do brain cells called astrocytes play in progressive MS?

**Background:** Some people may be surprised to learn that the most abundant cells in our brains aren't the nerve cells, but the star-shaped cells known as astrocytes. Under normal conditions, astrocytes transport nutrients nerve cells need, and help the brain to function. But in MS, they are also involved in allowing immune cells to enter the brain to attack, and in developing scar tissue, which may inhibit the repair of nerve-insulating myelin. Recent research suggests that astrocytes also control the activity of immune cells that are active during progressive MS.

**The Study:** Francisco Quintana, PhD, has received a Harry Weaver Neuroscience Scholarship to investigate how the various and sometimes opposing actions of astrocytes influence the course of MS, and to search for potential targets that would change their behavior to benefit people with MS. Dr. Quintana's team is studying the actions of astrocytes using a combination of work with mice that have the MS-like disorder EAE, cells grown in the laboratory, and brain tissue from people who had progressive MS. The researchers are particularly interested in understanding how astrocytes slow the repair of myelin in progressive MS.

**What's Next?** Identifying molecules that regulate the activities of astrocytes at specific stages of MS could lead to the development of therapeutic agents to stop disease progression.

**A.M. Rostami, MD, PhD (Pending)**

Thomas Jefferson University  
Philadelphia, PA

**Title:** IL-9 in the pathogenesis of CNS autoimmune inflammation

**Summary:** Will targeting a specific immune molecule be a promising path for stopping MS immune attacks?

**Background:** The cause of MS is unclear, but inappropriate activities of the immune system likely play a role in the immune attacks against the brain and spinal cord. Immune system cells produce several factors that act on other cells. One such factor, called interleukin-9 (IL-9), seems to make mice with MS-like disease worse.

**The Study:** A.M. Rostami, MD, PhD, is investigating the role of IL-9 in a mouse model of MS, called EAE. IL-9 is mainly produced by a type of immune cell called the T cell. IL-9 acts on a type of T cell that can regulate and reduce harmful immune attacks, and IL-9 also affects specific brain cells. Dr. Rostami's team is studying how IL-9 acts to make EAE worse, and how IL-9 changes the balance from beneficial T cells to harmful T cells. The team is also exploring what happens to specific brain cells when they are treated with IL-9, and how this contributes to making EAE worse.

**What's Next?** The results from this study will help tease out the role of IL-9 in multiple sclerosis, and determine whether IL-9 is a promising target for a new MS therapy.



### **Naresha Saligrama, PhD**

Stanford University  
Stanford, CA

**Title:** Immunophenotypic Analysis, Determination of Clonal Diversity, and Specificity of T cell Repertoire in MS and EAE  
**Summary:** Determining which type of immune cells tend to make MS worse.

**Background:** In MS, the immune system attacks and destroys components of the brain. The immune system is composed of many types of cells, and one type, T cells, are among the most important in MS. Many different sub-types of T cells exist, and their contribution to MS disease pathology has not been thoroughly explored.

**The Study:** Naresha Saligrama, PhD, of Stanford University School of Medicine, has received a postdoctoral fellowship from the National MS Society to explore the role that different types of T cells play in MS and in rodents with the MS-like disorder called EAE. Under the mentorship of Mark M. Davis, PhD, Dr. Saligrama is exploring how subsets of T cells change over time in EAE and how they change during MS relapses and remissions, using blood samples from people. The team is also exploring which molecules the harmful T cells “recognize” and launch attacks against, which is a key question in MS.

**What’s Next?** Having a thorough understanding of the role of different types of T cells in making MS worse will suggest ways to develop more specific therapies to regulate their function and treat MS.

### **Howard Weiner, MD (Pending)**

Brigham and Women's Hospital  
Boston, MA

**Title:** Gut Microbiota in Multiple Sclerosis  
**Summary:** Do microorganisms that live in the intestines influence disease activity in people with MS?

**Background:** In people who have MS, immune system cells that normally protect the body from foreign invaders damage and destroy parts of the brain and spinal cord. The factors that trigger the immune system damage are largely unknown. In recent years, however, we have learned that the flora – bacteria and organisms – in the intestines may influence the behavior of immune cells. Studies suggest that changes in the intestinal flora can affect the course of EAE, a model disease similar to MS.

**The Study:** Howard Weiner, MD, is investigating how gut microorganisms -- especially those belonging to a group known as Archaea – may influence immune system activity in people with MS. With funding from a pilot research award from the National MS Society, Dr. Weiner and colleagues gathered preliminary evidence that the gut microorganisms differ in people who have MS compared to those who do not. To follow up this finding, they are now examining in more detail, and in a greater number of people, how the populations of microorganisms differ, and how the microorganisms are affected by drugs commonly used to treat MS.

**What’s Next?** The results of this study will enable researchers to understand how the numerous microorganisms in the intestines of people with MS influence disease activity, and could lead to new strategies to treat MS.



## New Collaborative MS Research Award Tests Therapies to Stop Immune Attack

### **Jenny Ting, PhD**

University of North Carolina at Chapel Hill  
Chapel Hill, NC

**Title:** Preclinical Therapeutic Development for Multiple Sclerosis

**Summary:** Testing therapies to stop the immune attack and protect the nervous system.

**Background:** MS involves immune system attacks that target the brain and spinal cord, especially the myelin that wraps around nerve fibers. Stopping these attacks and protecting the nervous system from damage are key goals for therapeutic strategies.

**The Study:** Jenny Ting, PhD, has assembled a talented team, with funding from a Collaborative MS Research Center Award, to investigate two promising therapeutic strategies for MS. Her team has found that administering the fat-like molecule “phosphatidylserine” can effectively inhibit immune cells isolated in lab dishes. They have worked with a premiere group to deliver this molecule via nanoparticles (tiny particles) and found that this method of delivery greatly reduced MS-like symptoms in mice. Collaborator Glenn Matsushima, PhD, and his team have identified a small molecule that prevented the death of myelin-making cells in lab dishes, and enhanced myelin repair in an MS model. Now these labs and other UNC experts in nanotechnology and neuropharmacology are joining forces to study these further as single or combined therapies in MS models.

**What's Next?** This study may identify a new class of compounds that can stop MS in its tracks. If they show promise, they would undergo further testing in mouse models and eventually could make it to clinical trials.

### **Lin Wu, PhD (Pending)**

New York University School of Medicine  
New York, NY

**Title:** Characterization of protein dynamics and function in Th17 cell differentiation

**Summary:** Investigating how immune cells control disease for clues to developing new therapies for MS.

**Background:** In MS, the immune system attacks and destroys components of the brain and spinal cord. One type of immune cell, called T cells, are important players in MS attacks. A subset of T cells called Th17 cells is also involved in the disease.



**The Study:** Lin Wu, PhD, of New York University School of Medicine in New York City, has received a postdoctoral fellowship from the National MS Society to gain experience as an MS researcher under the mentorship of Dan Littman, MD, PhD. The focus is to understand how Th17 cells mature. Dr. Wu is using sophisticated genetic techniques to find proteins that are important in inducing the formation of Th17 cells in mice with EAE, a model of MS. His team will then perform experiments to understand how these proteins work to turn on the production of Th17 cells by testing the importance of the identified proteins in EAE.

**What's Next?** This study may provide new targets for drug development for therapies for MS. These therapies will likely be more specific and therefore have fewer side effects than current therapies that have more general effects on the immune system.

### STOP—Epidemiology

#### **Helen Tremlett, BSPHarm, PhD**

University of British Columbia  
Vancouver, British Columbia, Canada

**Title:** Prodromal Multiple Sclerosis: The PrOMS Study

**Summary:** How early before its diagnosis can MS be detected?

**Background:** Early MS can be a challenge to recognize. Most of its early symptoms, such as numbness, weakness, and visual problems are not very specific. The difficulties with determining whether someone with early MS has the disease can be very frustrating. A delay in diagnosing MS may also lead to a delay in starting treatment. Moreover, even when MS is diagnosed soon after symptoms begin, the initial stages of the disease may have existed for an unknown time.

**The Study:** The National MS Society is supporting a research grant with the goal of determining whether examination of medical records and individuals' use of health care facilities can give clues to early symptoms that may be indicators of the eventual development of MS. This study brings together experts from a wide range of fields, and also includes a person with MS to ensure the goals remain highly relevant to the MS community. The team, spanning four provinces across Canada, is led by Helen Tremlett, PhD, of University of British Columbia in Vancouver. Collaborators are at the Universities of: Saskatchewan (Dr. Charity Evans), Manitoba (Dr. Ruth Ann Marrie) and Nova Scotia (Dr. John Fisk). This study is possible because of the extensive health care records in Canada. Dr. Tremlett and colleagues will compare health care records of people who eventually develop MS with those who do not. They hope to identify a distinct pattern of utilization differentiating people destined to develop and be diagnosed with MS from the general population.

**What's Next?** This study may reveal a way to recognize early symptoms of MS. In addition to providing clues about the onset of MS, this could lead to the development of earlier treatment which might slow the development and course of the disease.

### STOP—Biology of Glia

#### **Jennifer Orthmann-Murphy, MD, PhD (Pending)**

Johns Hopkins University  
Baltimore, MD

**Title:** The role of reactive astrocytes in cortical demyelinating lesions

**Summary:** How do brain cells called astrocytes contribute to destruction in MS?



**Background:** In MS, the immune system attacks and destroys myelin, a protective coating that surrounds nerve fibers. When these nerve fibers are left unprotected, they can be damaged and lead to progressive worsening of MS. One type of cell in the brain called astrocytes reacts in a variety of ways to the immune system damage. However, the relationship between these “reactive” astrocytes and nerve fiber damage in MS is not well understood, and it’s possible that these astrocytes may have both beneficial and harmful effects, depending on the activity around them.

**The Study:** Dr. Jennifer Orthmann-Murphy has just finished her residency in neurology at the University of Pennsylvania and is now a National MS Society postdoctoral fellow at Johns Hopkins University (Baltimore). She received her BA in the biological basis of behavior from the University of Pennsylvania (summa cum laude) and her MD and PhD in neuroscience from the Perelman School of Medicine at the University of Pennsylvania. Dr. Orthmann-Murphy received the Dr. William F. Jeffers Prize for meritorious research in the field of neurology (University of Pennsylvania School of Medicine), the American Academy of Neurology Medical Student Prize for Excellence in Neurology, and the Foundation for the Consortium of Multiple Sclerosis Centers annual meeting scholarship award.

**What’s Next?** These studies may provide information on the behavior of astrocytes and potentially identify new targets for therapy to prevent disease progression.



## 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

#### **Kevin Alschuler, PhD**

University of Washington  
Seattle, WA

**Title:** Life after MS diagnosis: a biopsychosocial assessment of symptom trajectory

**Summary:** How does quality of life change for individuals over the first year after diagnosis with MS?

**Background:** Being diagnosed with MS potentially brings challenges and changes in health, happiness, employment abilities, and satisfaction as MS symptoms such as fatigue, depression, cognitive problems, and mobility problems come and go. Thoroughly understanding these changes may identify key ways to help people with MS live their best lives.

**The Study:** Kevin Alschuler, PhD, of the University of Washington in Seattle, has received a research grant from the National MS Society to assess how individuals’ quality of life changes during their first year after receiving an MS diagnosis. The team is involving 250 people who were recently diagnosed with MS. They are asking questions about quality of life, MS symptoms, and other aspects of life with MS six times during this



first year. Quality of life can increase, decrease, remain poor, or remain good, and this study is designed to identify different patterns in people over time. This will allow precise assessment of how quality of life can change during the first year following diagnosis and how MS symptoms or other aspects of life with MS influence those patterns.

**What's Next?** This study will identify key areas for intervention, with the goal of helping people improve in the areas that increase quality of life and protect against factors that reduce quality of life.

**Nancy Chiaravalloti, PhD**

Kessler Foundation Research Center  
West Orange, NJ

**Title:** Speed of Processing Training to Improve Cognition in MS: A Randomized Clinical Trial

**Summary:** Can a training program to improve the speed of processing information help people with MS?

**Background:** People with MS may experience cognitive problems, including processing information more slowly than normal. Reduced processing speed underlies many of the problems people with MS have with work and social activities. Although the cause of this problem is not clear, one treatment may help people with MS increase their information processing speed and alleviate some of the problems they have with activities of daily living.

**The Study:** Nancy Chiaravalloti, PhD, of the Kessler Foundation in West Orange, NJ, has received a research grant from the National MS Society to test whether a treatment program known as Speed of Processing Training (SPT) can improve test scores and

everyday functions of people with MS. SPT has been shown to improve processing speed in older adults. In this study, Dr. Chiaravalloti and colleagues will conduct a randomized, double-blind trial of SPT. In the study, 100 people with definite MS and reduced processing speed will be randomly assigned to treatment or control groups. Tests will examine changes in processing time for people in the treatment and control groups.

**What's Next?** If this study shows that the treatment program improves the speed with which people with MS process information, it will provide the basis for improved treatment of these kinds of cognitive problems.

**Geetanjali Dutta, PT, PhD**

Oregon Health & Science University  
Portland, OR

**Title:** Effect of balance training on postural responses in people with multiple sclerosis

**Summary:** What type of balance training can improve stability in people with MS?

**Background:** Many people with MS experience balance or mobility problems at some point during the course of their disease, which may reduce their participation in work and social activities and possibly decrease quality of life. Understanding the underlying mechanisms behind balance problems and identifying the best methods of training to improve balance and stability is expected to increase quality of life and reduce falls.

**The Study:** Geetanjali Gera Dutta, PT, PhD, has received a postdoctoral fellowship from the National MS Society to investigate the underlying deficits in postural control and benefits of balance training on the ability to recover stability in response to circumstances such as trips, slips or jolts, to avoid falls. Under the mentorship of Fay



## New Collaborative MS Research Award Addresses Cognition

**John DeLuca, PhD**

Kessler Foundation Research Center

West Orange, NJ

**Title:** MS Collaborative Network of New Jersey

**Summary:** What is the connection between cognitive and motor functions in MS?

**Background:** Cognitive changes are common in people with MS. MS also affects mobility. Rehabilitation professionals tend to specialize in cognitive functioning or physical functioning; however, the brain maintains control over both motor and cognitive functions so that they may interact. Understanding this interaction may help improve both functions.

**The Study:** Scientists in Neuropsychology & Neuroscience Research at Kessler Foundation strive to discover ways to improve cognition, prevent its decline, and understand the neural underpinnings. In Human Performance & Engineering Research, researchers seek to improve mobility, independence and quality of life for people with sensory and motor deficits caused by neurological conditions such as MS. Now John DeLuca, PhD, is merging efforts of these two areas of research and the eleven research scientists working in them to address the problem of cognitive-motor integration in MS, with funding from a Collaborative MS Research Center Award. Funding will allow the group the flexibility to ask new questions and conduct pilot projects that will complement and drive their other rehabilitation and research activities.

**What's Next?** Facilitating this collaboration has the potential to maximize resources and talent, increase understanding of the interaction between physical and cognitive functions in MS, and greatly improve the understanding and ability to effectively treat people with MS.

Horak, PT, PhD, balance training will be performed by exposing people with MS to multiple sessions of variable magnitudes of continuous forward and backward surface translations. Data gathered from people with MS will be compared to healthy subjects.

**What's Next?** These results will help develop balance rehabilitation strategies that specifically target instability and postural response problems in people with MS to improve mobility and prevent falls.



**Marcia Finlayson, PhD**

Queen's University  
Kingston, Ontario, Canada

**Title:** Building capacity for MS self-management research and knowledge translation

**Summary:** Mentor-Based Postdoctoral Fellowship in MS Rehabilitation Research to provide training in research into self-management programs for people with MS.

**Background:** People with MS face many challenges. Managing these challenges often requires skills and knowledge to self-manage the disease and its consequences. Supporting people with MS to develop self-management skills and knowledge is an important part of MS rehabilitation. Despite this, few MS rehabilitation researchers have the training needed to ensure that self-management programs and practices are evidence-based. One way to change this situation is to provide postdoctoral training in MS self-management research. This training program seeks to develop two MS rehabilitation researchers with the skills necessary to conduct excellent MS self-management research and translate findings into use in clinical settings.

**The Study:** With funding from the National MS Society, Marcia Finlayson, PhD, an MS rehabilitation researcher with many years of experience, will direct a training program at the School of Rehabilitation Therapy at Queen's University in Kingston, Ontario, Canada. Dr. Simon French and Dr. Nandini Deshpande will be secondary mentors. To begin, selected trainees will immerse into the everyday operations of the International MS Falls Prevention Research Network. By working with this Network, trainees will learn to write grants; work on teams; plan and implement studies; and manage data across many research sites. These experiences will

prepare the trainees to address a full range of issues associated with planning and conducting MS self-management research and translating it into clinical practice.

**What's Next?** The ultimate goal of this training program is to produce MS rehabilitation researchers who can make ongoing and meaningful contributions to the everyday lives of people with MS by conducting and translating rigorous and relevant research that positively influences rehabilitation practice.

**Fay Horak, PT, PhD**

Oregon Health & Science University  
Portland, OR

**Title:** Rehabilitation Research Training in Postural Control of Multiple Sclerosis

**Summary:** Mentor-Based Postdoctoral Fellowship in MS Rehabilitation Research to enhance research into ways to use rehabilitation to improve balance and gait in people with MS..

**Background:** Many people with MS have balance problems and these balance problems lead to falls, injuries, immobility and decreased quality of life. MS can affect many parts of the nervous system important for balance control but the relationship between the affected parts of the nervous system and poor balance is unknown. Successful rehabilitation of balance disorders in people with MS requires a better understanding of the postural systems affected in each person so that specific therapies can be targeted for each individual.

**The Study:** Fay Horak, PT, PhD, is renowned for her research on balance and gait disorders and their rehabilitation. Fellows who are recruited through this program will be mentored by Dr. Horak, together with Dennis



Bourdette, MD, who is well known for his research on MS. Fellows with either a scientific, engineering, or medical background will have a customized training experience in the rehabilitation of balance and gait disorders in MS. They will learn how to quantify balance and gait disorders and their pathology using state-of-the-art technology, and they will work with experts in neuroscience, engineering, rehabilitation and neurology to better understand how MS impacts control of balance and gait in order to design improved rehabilitation programs to prevent mobility disability.

**What's Next?** This program will recruit and train talented clinician-scientists in rehabilitation research specific to MS. This will get more hands and minds working on the best ways to help people with MS maximize their abilities.

#### **Rob Motl, PhD**

University of Illinois at Urbana-Champaign

**Title:** Training in Physical Activity Promotion for Multiple Sclerosis

**Summary:** Mentor-Based Postdoctoral Fellowship in MS Rehabilitation Research to provide training in physical activity promotion for MS.

**Background:** There is increasing evidence for the benefits of engaging in physical activity among persons living with MS, yet on average they engage in less physical activity than those in the general population in the U.S. This fact underscores the need for research to find the best ways to promote consistent physical activity in people with MS.

**The Study:** The National MS Society has awarded a training grant that will allow two postdoctoral fellows to work with Dr. Robert Motl, who is a recognized leader in physical

activity and its measurement, determinants, consequences, and promotion in MS. Trainees will also work with Dr. Edward McAuley, who is an international leader with similar scholarly interests in older adults, over a five-year period. The mentors will provide tailored training in the measurement, determinants, and consequences of physical activity combined with the design of behavioral interventions for promotion and maintenance of physical activity. The post-doctoral fellows will learn methods of quantifying physical activity and its outcomes and the design and evaluation of behavioral interventions that can be delivered face-to-face or through various channels, including the Internet, phone, or newsletters.

**What's Next?** The postdoctoral fellows will develop expertise necessary for improving the lives of persons with MS through the promotion of physical activity.

#### **Jessie Huisinga, PhD**

University of Kansas Medical Center - Kansas City

Kansas City, KS

**Title:** Identification of gait and balance deficits in patients with multiple sclerosis using wireless sensors

**Summary:** Testing new methods to rapidly assess walking and balance problems in people with MS.

**Background:** Walking and balance problems are common in people with MS, but methods to assess these problems are not specific to MS, are not very sensitive or quantitative, or require a long time to obtain. Better methods are needed to assess outcomes of therapy in the clinic, and in people with MS enrolled in clinical trials.



**The Study:** Jessie Huisinga, PhD, of the University of Kansas Medical Center, has received a research grant from the National MS Society to develop better methods for assessing walking and balance problems in people with MS. Dr. Huisinga's team uses motion capture movement analysis techniques that are currently used in research laboratories and that provide specific but not rapid data regarding gait and balance changes in persons with MS. The team is adapting these movement analysis techniques by using wireless sensors which are clinically useful for assessing gait and balance since they are rapid, specific, quantitative, and sensitive to changes during the disease course of MS.

**What's Next?** Further development of these methods should enable researchers to more rapidly test that ability of interventions to improve gait and balance in people with MS.

### RESTORE—Nervous System Repair

#### **Katerina Akassoglou, PhD**

The J. David Gladstone Institutes  
San Francisco, CA

**Title:** Role of fibrinogen in the inhibition of oligodendrocyte differentiation

**Summary:** Can a blood protein that may inhibit myelin repair in MS be overridden to spur repair?

**Background:** In MS, myelin, the fatty substance that surrounds and supports nerve fibers, is attacked and destroyed. Repairing myelin is expected to help restore function and protect the underlying nerve fibers. Myelin repair in MS is limited, possibly because certain factors present in MS lesions inhibit the function of the cells that make myelin, called oligodendrocytes. Dr.

Akassoglou is investigating a possible inhibitory factor present in MS plaques to develop strategies to override it to improve repair.

**The Study:** Katerina Akassoglou, PhD, of the Gladstone Institute of Neurological Disease at the University of California at San Francisco, has received a grant from the National MS Society to investigate the possible role of a blood protein called fibrinogen in inhibiting myelin repair in MS. Fibrinogen is normally present only in the bloodstream and has no direct access to the brain. However, in MS lesions, blood vessels leak, and fibrinogen is found in MS lesions. In a laboratory dish, Dr. Akassoglou's team has shown that fibrinogen directly inhibits the ability of immature oligodendrocytes to mature and acquire the ability to make myelin. They are now investigating how this inhibition occurs by determining exactly how fibrinogen interacts with and affects immature oligodendrocytes to inhibit their function.

**What's Next?** The results from this study may suggest a new therapeutic strategy for blocking the effects of fibrinogen, which may then allow repair of myelin and subsequent restoration of function in people with MS.

#### **Anne Simone Baron-Van Evercooren, PhD**

Institut National de la Santé et de la  
Recherche Médicale- INSERM U975  
Paris, France

**Title:** Molecular and cellular analysis of the PNS/CNS boundary

**Summary:** Using myelin-making cells from outside the brain and spinal cord to repair MS lesions.

**Background:** In MS, myelin, the fatty substance that surrounds and protects nerve fibers of the brain and spinal cord, is attacked



and destroyed. Loss of myelin leads to symptoms and dysfunction in people with the disease. One of several ideas being pursued by investigators to restore function is to induce myelin repair by transplanting cells that make myelin into damaged areas of the brain or by activating the spare pool of cells residing in the brain which are spared. Dr. Baron-Van Evercooren is exploring one strategy for enhancing myelin repair in MS.

**The Study:** Anne Simone Baron-Van Evercooren, PhD, has received a research grant from the National MS Society to investigate strategies for myelin repair in the brain. In the brain and spinal cord, the cells that make myelin are called oligodendrocytes. In all other parts of the body, the cells that make myelin around the nerves are different and are called Schwann cells. Schwann cells may be able to function in the brain and spinal cord to make new myelin, but their ability to repair myelin is inhibited by oligodendrocytes and other glial cells present in the brain. Dr. Baron-Van Evercooren's team is performing preliminary studies to understand how Schwann cells interact with cells in the brain and spinal cord, regions of the body where they are normally not present. These studies are being performed to understand how to bypass these inhibitory interactions and allow Schwann cells to repair myelin. They are performing studies both in culture dishes and in mice.

**What's Next?** Results from this study will provide important information about the potential of using peripheral myelin-making cells as "spare parts" to repair myelin in the brain, and suggest strategies to possibly repair myelin in the brain of people with MS in the future.

**Jeff Bulte, PhD**

Johns Hopkins University  
Baltimore, MD

**Title:** Immunomodulation and Remyelination by Transplanted Stem Cells and Progenitors: A Two-Prong Approach

**Summary:** Can cell therapy reduce immune attacks and at the same time also stimulate the repair of nerve-insulating myelin in an MS model?

**Background:** MS involves immune attacks in the brain and spinal cord that cause damage to nerve-encasing myelin and the cells that make myelin. One strategy for repairing nervous system damage and restoring function in people with MS is implanting cells that will change the response of the immune system and stimulate nervous system repair. Several clinical trials underway are exploring transplanting a person's own adult stem cells, and thus far it appears that their main impact is to dampen immune attacks, rather than directly growing new myelin themselves.

**The Study:** Jeff Bulte, PhD, is studying the ability of different types of transplanted cells to modulate the immune system and promote repair. The team recently transplanted a type of cell that was expected to enter the brain of mice with EAE, a model of MS, and promote repair. These transplanted cells did not enter the brain or induce repair and did not survive long, but they had promising effects on immune attacks. Dr. Bulte's team is now able to image the cells they transplant so that they can follow their fate at different times in a single mouse. They are exploring what characteristics of transplanted cells are responsible for the beneficial effects, what cell types work best, and if multiple cell types can work together to improve repair.



**What's Next?** In the future, cell transplantation may be an important strategy for restoring function to people with MS. This study will provide important information to move this strategy along.

**Ludovic D'auria, PhD (Pending)**

University of Illinois at Chicago  
Chicago, IL

**Title:** The organization and the role of lipid domains during myelin modeling

**Summary:** The role of lipids in synthesis of myelin, the fatty substance that is attacked in the brain of people with MS.

**Background:** In MS, myelin, the substance that surrounds and protects nerve fibers, is attacked and destroyed. Myelin is made by cells called oligodendrocytes. Understanding how to repair myelin in the brains of people with MS requires an understanding of the basic processes involved in how oligodendrocytes make myelin. Myelin is composed of multiple components, one of which is lipids, which are fat-like substances.

**The Study:** Ludovic D'auria, PhD, has received a postdoctoral fellowship to investigate the role of lipids in myelin synthesis, under the mentorship of Ernesto R. Bongarzone, PhD. Myelin is composed of a large amount of lipids, but studying lipids has been difficult due to a lack of appropriate laboratory techniques and tools. Using newly developed tools, Dr. D'auria is determining how lipids work to allow myelin to wrap around nerve fibers. He is also looking at how lipids become organized during the myelin synthesis process, and how lipids interact with proteins, another important component of myelin.

**What's Next?** Results will aid our understanding of the role of lipids in myelin

growth, maintenance and regeneration, which may contribute to the development of ways to protect myelin from MS attacks and promote myelin repair.

**Hyun Kyoung Lee, PhD**

Baylor College of Medicine  
Houston, TX

**Title:** The Role of Daam2 in Oligodendrocyte Development and Multiple Sclerosis

**Summary:** Focusing on molecules that control the maturation process of cells that can repair lost myelin in MS.

**Background:** In MS, the immune system attacks and destroys myelin, the substance that surrounds and protects nerve fibers. Loss of myelin, and damage to the underlying nerve fibers, causes MS symptoms. Although some myelin repair does occur, it is often not adequate to keep up with the damage. The cells that make myelin in the brain are called oligodendrocytes, which are derived from a pool of immature "precursors."

**The Study:** Hyun Kyoung Lee, PhD, has received a Career Transition Fellowship to investigate some of the molecular signals involved in getting oligodendrocyte precursors to mature into myelin-making oligodendrocytes. Under the mentorship of Benjamin Deneen, PhD, Dr. Lee is investigating molecules that may be involved in this maturation process, including "Daam2." The team aims to discover how molecules like Daam2 interact to inhibit the maturation process by examining immature oligodendrocytes both during development and after myelin damage. The team will also examine Daam2 activity in samples of MS brain lesions, and test whether a compound that blocks the Daam2 pathway can promote myelin repair.



**What's Next?** Further understanding of the complex signaling involved in the growth of myelin-making cells could lead to new strategies to block negative activity to promote myelin repair in MS.

**Netta Levin, MD, PhD**

Hadassah Hebrew University Hospital  
Jerusalem, Israel

**Title:** Temporal reorganization to overcome monocular demyelination – unique plasticity mechanism in MS

**Summary:** Understanding how the brain compensates for damage to restore visual function in people with MS.

**Background:** Following an MS attack that includes loss of myelin (the fatty substance that surrounds and protects nerve fibers), functional recovery from symptoms involves both repair of the damage and adaptation by the brain to restore the lost function. The visual system is often attacked in MS, causing optic neuritis, which involves inflammation and often temporary vision loss.

**The Study:** Netta Levin, MD, PhD, is exploring how the brain compensates for MS damage over time. Delays in recovery following an MS attack may be due to the time required not only for repair of damage but also for the brain to develop a way to compensate for a lost function. They are focusing on the visual system, examining people with MS with and without optic neuritis, as well as healthy people. They are testing if delays in the electrical signal that occur when myelin is damaged can be compensated for by other areas of the brain. The team is also performing behavioral analysis and imaging and looking to see if the length of time required for functional recovery depends on the severity of the attack, and if adaptation is limited in patients with severe tissue damage.

**What's Next?** The results from this study will help design rehabilitation strategies to encourage recovery of function after MS attacks not just to the visual system, but other parts of the brain and spinal cord.

**Laura Magri, PhD**

Mount Sinai School of Medicine  
New York, NY

**Title:** The role of NDRG1 in oligodendrocyte survival and its implications for MS

**Summary:** Does a gene's response to stress reduce myelin repair in MS?

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Myelin is made in the brain by specialized cells called oligodendrocytes. Myelin synthesis and repair is in part genetically controlled. A recent discovery suggests that a gene called NDRG1 is present in oligodendrocytes and is needed for myelin maintenance. Interestingly, this gene is downregulated in some people with MS, due to the addition of chemical groups, called methyl groups, in the gene coding for NDRG1. The presence of these methyl groups reduces the presence, or "expression," of NDRG1, rendering oligodendrocytes more susceptible to loss.

**The Study:** Laura Magri, PhD, of Mount Sinai School of Medicine in New York, has received a postdoctoral research fellowship from the National MS Society to investigate the details of how changes in NDG1 levels affect myelin maintenance, and whether the environment, such as stress, can modify the levels of expression of NDRG1. Under the mentorship of Patrizia Casaccia, MD, PhD, the team is turning NDRG1 on and off in oligodendrocytes cultured in the lab to examine how the survival of



oligodendrocytes changes in accordance with changes in NDRG1 expression. Then they will ask if various types of stress on oligodendrocytes can change the levels of methyl groups on the regulatory regions of the gene encoding for NDRG1, which may decrease the amount of NDRG1 produced by the cells and induce the oligodendrocytes to die. They are examining oligodendrocytes from people with MS and from mice with EAE, an animal model of MS.

**What's Next?** These studies may identify NDRG1 as a potential target for the development of therapies to protect and repair the nervous system in people MS.

**Mary (Marnie) Preston, PhD (Pending)**  
University of Colorado Health Sciences Center  
Aurora, CO

**Title:** Integration of Nuclear Receptor signaling cascades during myelination in zebrafish.

**Summary:** Searching for clues to promoting myelin repair by exploring details of the myelin-making process.

**Background:** In MS, the fatty substance that surrounds and protects nerve fibers, called myelin, is attacked and destroyed. Loss of myelin impairs the function of nerve fibers and leads to symptoms in people with the disease. Myelin repair is important for restoring function in people with MS, but myelin repair is incomplete for reasons that are not well understood.

**The Study:** Mary "Marnie" Preston, PhD, of the University of Colorado Health Sciences Center in Denver, has received a postdoctoral fellowship from the National MS Society to increase our understanding of the process of myelination under the mentorship of Wendy Macklin, PhD. The cells that make myelin are called oligodendrocytes, and their function

depends on various genes and molecules. One such set of molecules that may control the process of myelination are called retinoid X receptors (RXRs). RXRs and related molecules may control oligodendrocyte maturation and myelin synthesis. The team is using a type of fish called zebrafish, which allows careful monitoring of myelin growth. Many zebrafish at a time can be manipulated with drugs, a set-up that cannot be performed using rodents. They are manipulating the levels of RXRs and related molecules in zebrafish and asking if this manipulation affects myelin synthesis.

**What's Next?** Results from this study may identify RXRs and related molecules as therapeutic targets for new therapies that would stimulate myelin repair to restore function in people with MS.

**David Rowitch, MD, PhD (Pending)**  
University of California, San Francisco  
San Francisco, CA

**Title:** Oligodendrocyte-mediated vascular remodeling of white matter in development and remyelination

**Summary:** How do cells that form myelin obtain the oxygen supply they need to ramp up myelin repair?

**Background:** Myelin, the material that surrounds and supports nerve fibers in the brain and spinal cord, is manufactured by cells called oligodendrocytes. In people with MS, myelin is damaged and destroyed, and the resulting interruption of nerve signals leads to the symptoms of MS. Although oligodendrocytes do repair some myelin, they are unable to keep up with the damage. One reason for this failure may be that the blood vessels of the brain are unable to supply enough oxygen and nutrients for intensive myelin repair.



**The Study:** David Rowitch, MD, PhD, is testing a novel idea for how oligodendrocytes may obtain the increased amounts of oxygen and nutrients they need as they form new myelin. Dr. Rowitch and colleagues are using genetically designed (“transgenic”) mice and cells grown in laboratory glassware to investigate how oligodendrocytes modify the growth of blood vessels into damaged areas of the brain to obtain the material they need to form new myelin. The research could show that even transplanted oligodendrocytes might draw in blood vessels to aide myelin repair.

**What’s Next?** The results of this research could provide important new information that could lead to treatments that will improve the repair of myelin damaged by MS.

**Jessica Williams, PhD (Pending)**

Washington University School of Medicine  
St. Louis, MO

**Title:** Mechanisms of CXCL12-mediated remyelination

**Summary:** The role of a family of molecules called chemokines in brain repair.

**Background:** Currently, the disease-modifying therapies that are available to treat MS focus on reducing immune attacks against nerve-insulating myelin in the brain and spinal cord. As yet, there are no therapies that can repair the damage to myelin. Since the brain has a natural capacity to facilitate myelin repair, one research strategy is to discover the mechanisms underlying natural repair so that it may be stimulated during MS. The possibility that certain proteins called chemokines have potential to promote repair is being explored in part because they increase the maturation of myelin-making cells called oligodendrocytes.

**The Study:** Jessica Williams, PhD, of Washington University School of Medicine in St. Louis, has received a postdoctoral fellowship from the National MS Society to work under the mentorship of Robyn Klein, MD, PhD, investigating the role of chemokines in mediating myelin repair. Dr. Williams is using mice that have damage to the nervous system similar to that seen in MS, and looking at the role of different types of chemokines in inducing maturation of oligodendrocytes and repair of myelin. The team is also examining immature oligodendrocytes grown in the lab and asking how these chemokines interact with other molecules present during inflammation to affect the function and maturation of oligodendrocytes.

**What’s Next?** This study may identify particular chemokines as targets for new therapies aimed at improving repair in the brain of people with MS. In addition, this fellowship will provide valuable training to Dr. Williams for a future career in MS research.

**Teresa Wood, PhD (Pending)**

Rutgers University, New Jersey Medical School  
Newark, NJ

**Title:** Activation of mTOR Signaling in Remyelination in Human MS Lesions and EAE

**Summary:** Investigating the role a group of molecules play in repairing myelin, which is attacked in MS.

**Background:** One of the causes of the symptoms of MS is damage to myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. Extensive research is underway to find ways to enhance the repair of damaged myelin, including early-stage clinical trials.



**The Study:** Teresa Wood, PhD, of Rutgers University, New Jersey Medical School in Newark, NJ, has received a Daniel Haughton Senior Faculty Award from the National MS Society to investigate whether a mechanism that promotes new myelin formation. Dr. Wood is visiting the lab of Brahim Nait Oumesmar, PhD, at the University of Pierre and Marie Curie, INSERM, in Paris, to collaborate with his group to see whether the molecules that promote new myelin formation in rodents is active in regions where myelin repair occurs in human MS lesions, or areas of damage. In addition, Dr. Wood and colleagues will use rodent cells grown in the laboratory and mouse models of MS to investigate whether some drug treatments can alter or improve the repair of myelin.

**What's Next?** The primary purpose of this project is to provide Dr. Wood with the opportunity to work with human MS tissues and to collaborate with the outstanding investigators in the Paris laboratory of Dr Nait-Oumesmar. At the same time, with the information it provides, this research could ultimately lead to ways to enhance the repair of myelin that has been damaged by MS.

**J. Bradley Zuchero, PhD (Pending)**

Stanford University  
Palo Alto, CA

**Title:** What is the cellular mechanism of CNS myelin wrapping?

**Summary:** Can understanding the role of cellular "scaffolding" in the formation of nerve-insulating myelin provide new targets to promote myelin repair in MS?

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Loss of myelin causes symptoms in

people with MS. Therapies aimed at promoting myelin repair in MS are needed. The cells that make myelin in the brain are called oligodendrocytes. Myelin is a multi-layered, compact structure that is wrapped around nerve fibers. How myelin forms and becomes compacted is not completely understood, but may hold the key to promoting myelin repair in MS.

**The Study:** J. Bradley Zuchero, PhD, of Stanford University, has received a Career Transition Fellowship Award from the National MS Society to investigate how myelin wraps around nerve fibers and becomes compacted, under the mentorship of neurobiologist Ben Barres, MD, PhD. Movements by cells are mediated by scaffold-like structures inside cells. Dr. Zuchero and his team are investigating the role of this scaffolding, called the cytoskeleton, which is present inside oligodendrocytes in the formation and compaction of myelin. The scaffolding changes as myelin is first wrapped around nerve fibers and as layers of compact myelin are formed. Dr. Zuchero is investigating how these changes are controlled by specific genes.

**What's Next?** Understanding elements key to myelin formation may be crucial information for the development of therapies, possibly targeting these elements, to promote myelin repair and restore function in people with MS. In addition, this Career Transition Fellowship Award will help Dr. Zuchero move into a faculty position and cement his dedication to MS research.



## RESTORE— Measuring Disease Activity

### **Yanming Wang, PhD**

Case Western Reserve University  
Cleveland, OH

**Title:** Myelin Imaging in Multiple Sclerosis

**Summary:** Developing a technique to measure the success of treatments to restore myelin.

**Background:** In people who have MS, the myelin sheaths that wrap around nerve fibers (axons) in the brain and spinal cord is damaged and destroyed. Without their myelin coating, axons become vulnerable to damage and fail to carry signals effectively, leading to many of the symptoms of MS. Conventional MRI scans can pinpoint MS immune activity in the brain in people with MS, but they aren't specific enough at helping doctors track the integrity of myelin, or its damage and repair.

**The Study:** Yanming Wang, PhD, has received a research grant from the National MS Society to evaluate the potential of a clinical imaging technique known as positron emission tomography (PET) to measure myelin repair in MS. Dr. Wang and colleagues are examining several radiotracers, or markers, as to how they readily enter the brain and spinal cord and illuminate myelin damage and its repair in rodent models.

**What's Next?** The results of this study should show how useful these markers are for monitoring myelin repair with PET scans in a clinical setting. They would then need to undergo testing in people. Ultimately, having a rapid way to quantitatively detect myelin integrity and repair would greatly improve the ability to evaluate the efficacy in clinical trials of promising myelin repair strategies.

### **Leorah Freeman, MD (Pending)**

The University of Texas Health Science Center at Houston  
Houston, TX

**Title:** Cerebral white matter hypoperfusion and its relationship to lesion formation and repair in MS: a longitudinal multimodal MRI study.

**Summary:** Imaging blood flow in MS lesions in the brain to understand damage to nerve fibers.

**Background:** Nerve fibers transmit messages throughout the brain, spinal cord, and body. In MS, the immune system attacks various components in the brain, including the protective coating around nerve fibers. The loss of this protective coating leads to nerve fiber damage, which is generally permanent. Thus, preventing damage to nerve fibers in MS is important.

**The Study:** Leorah Freeman, MD, has received a postdoctoral fellowship to investigate and monitor damage to nerve fibers in people with MS under the mentorship of Ponnada Narayana, PhD and Jerry Wolinsky, MD. Some research suggests that blood flow and oxygen levels can be reduced in parts of the brain in MS, and the team is testing the idea that reduced oxygen and blood flow play a role in damaging nerve fibers in MS lesions. To monitor blood flow, they are using MRI scans to look at MS brain lesions and are investigating the idea that adequate blood flow is required for nervous system repair, and that reduced blood flow leads to more nerve fiber damage.

**What's Next?** Results from this study will help us understand the causes of damage to nerve fibers in MS and may suggest ways to prevent this damage, thus slowing down progression of disability.



## RESTORE—Neurophysiology

### **John Hart, MD**

University of Texas at Dallas  
Dallas, TX

**Title:** Identifying and Characterizing Auditory Processing Disruptions in Multiple Sclerosis

**Summary:** Developing a better way to track the problem of understanding spoken language in people with MS.

**Background:** One of the many cognitive problems reported by people with MS is difficulty understanding spoken language, such as difficulty in following the conversations of others. These can have an important impact on the ability of the person with MS to interact socially/professionally.

**The Study:** John Hart, MD, is obtaining objective measures of how the brain processes speech in people with MS and healthy controls. The brain utilizes multiple brain regions and stages to process speech, including perceiving sounds as language, remembering the context of a word within a sentence or story, applying the rules of word order and grammar, and unifying the words into sentence-level meaning. Dr. Hart and his team are examining people with relapsing-remitting MS, both those who report problems with understanding speech and those who do not, as well as healthy controls. They are using neuropsychological assessment and electroencephalography (EEG) of the brain to measure the speed and integrity of speech processing during these stages. They are looking for associations between abnormal EEG and areas of the brain affected by MS that mediate these processes.

**What's Next?** Results from this study will allow better ways to monitor speech processing problems 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

### **Howard Lipton, MD**

University of Illinois at Chicago  
Chicago, IL

**Title:** Generic approaches for detecting a virus in MS in acute demyelinating lesions

**Summary:** Can a new laboratory technique help determine whether a virus triggers MS?

**Background:** MS involves immune system attacks on the nervous system. The idea that the immune system attacks “self” molecules in the brain has received much attention, but definitive proof that MS is an autoimmune disease remains elusive. Another possibility is that a virus is present in the brain and that MS is due to the immune system trying to get rid of the virus. However, to date, researchers have not been able to prove a single virus or other infectious trigger for MS.

**The Study:** Howard Lipton, MD, of the University of Illinois at Chicago, has received a research grant from the National MS Society to devise a method to detect the presence of viruses in newly forming MS brain lesions, regardless of the type of virus that is present. Dr. Lipton and colleagues are devising a method to uncover generic viruses by



detecting a molecule called long dsRNA, which is present in nearly all virus infections but not present in normal or stressed cells or in most other types of microbes (such as bacteria). Thus, the presence of long dsRNA in MS lesions might suggest the presence of a virus that may cause the disease.

**What's Next?** Results from this study will prompt further work to confirm findings, to identify specific viruses, and to show that they are causative. Such studies may ultimately lead to prevention of MS with vaccination or treatment for MS with antiviral medications.

### **Kassandra Munger, DSc**

Harvard School of Public Health  
Boston, MA

**Title:** Sodium intake and multiple sclerosis risk and progression

**Summary:** Does a high-salt diet contribute to causing MS or making it worse?

**Background:** The cause of MS is unknown. Previous studies have suggested that high dietary salt increases the harmful nature of immune cells that are important in MS and that a high-salt diet makes mice with an MS-like disease worse. So an important question is whether high dietary salt intake increases the risk for developing MS and/or makes MS worse in those who already have it.

**The Study:** Kassandra Munger, DSc, an epidemiologist at the Harvard School of Public Health in Boston, has received a research grant from the National MS Society to leverage existing study data to investigate the question of dietary salt and MS. She is conducting two studies. In the first, she is investigating women enrolled in the Nurses' Health Study and Nurses' Health Study II, which together include over 200,000 women



Identifying specific viruses, and

showing they are triggers, may ultimately lead to prevention of MS with a vaccine or treatment of MS with antiviral medications

and over 600 cases of MS. Her team is asking whether high dietary salt – based on food intake questionnaires -- is associated with an increased likelihood of developing MS. In the second study, they are analyzing data from 468 participants enrolled in a clinical trial called Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT). This study examined the effectiveness of interferon-1b in blocking conversion from the first MS-like attack (called clinically isolated syndrome or CIS) to confirmed MS. Participants in this study provided urine samples, and Dr. Munger's team is investigating whether a high sodium concentration in urine is associated with conversion from CIS to MS, worsening of MS symptoms, higher relapse rates, or more lesions in the brain.

**What's Next?** Data from will provide information about whether a high-salt diet is a risk factor for MS or disease progression and may prompt clinical studies to examine the relationship between dietary salt and MS.



**Nikolaos Patsopoulos, MD, PhD (Pending)**

Brigham and Women's Hospital  
Boston, MA

**Title:** Identification of the MS specific and the shared with other autoimmune diseases genetic component and their functional impact

**Summary:** What can we learn by comparing genetic risk factors between MS and other immune-mediated diseases?

**Background:** In MS, the immune system damages and destroys portions of tissue in the brain and spinal cord. There are other disorders, called "autoimmune" disorders, where the immune system attacks different tissues in the body. So far scientists have identified variations in about 100 genetic regions are associated with the tendency to develop MS. Many of these regions are not in genes, but in DNA that influences how genes work. Some of these variations contribute to other immune-mediated diseases, while others may be unique to MS.

**The Study:** Nikolaos Patsopoulos, MD, PhD, of Harvard's Brigham and Women's Hospital in Boston, has received a Career Transition Fellowship from the National MS Society to identify genetic variations that are shared between MS and other autoimmune diseases, and those that are unique to MS. Under the skilled mentorship of Philip De Jager, MD, PhD, Dr. Patsopoulos is using sophisticated statistical analysis of data from a number of scientific studies and from large databases to determine the relative contributions to MS of genetic variations that are specific to the disease, and variations that are shared with other immune-mediated diseases.

**What's Next?** This study will clearly identify genetic variations that make unique contributions to MS. Ultimately these results should aid in the development of new

therapeutic agents and clues to preventing MS. In addition, this Career Transition Fellowship Award will help Dr. Patsopoulos move into a faculty position and cement his dedication to MS research.

**Timothy Vartanian, MD, PhD (Pending)**

Cornell University Medical College  
New York, NY

**Title:** Identification of an environmental trigger for MS

**Summary:** Is a toxin produced by bacteria a trigger for MS?

**Background:** The cause of MS is still unknown. However, several factors suggest that an infectious agent or agents may be involved in triggering MS in susceptible individuals. To date, researchers have not been able to identify a single infectious trigger for MS. Some research has suggested that very early MS lesions in the brain show damage to cells that make nerve-supporting myelin and not large numbers of immune cells. These observations open up the possibility that the immune response in MS may come later, after a toxic insult to myelin-making cells (oligodendrocytes).

**The Study:** Timothy Vartanian, MD, PhD, of Cornell Medical College in New York, received a research grant from the National MS Society to explore the possibility that a substance that is toxic to oligodendrocytes is responsible for the onset of MS and may therefore be found in tissue samples from people with the disease. Specifically, they are looking for bacteria (*Clostridium Perfringens*) that produce Epsilon toxin. They are analyzing body tissue samples from 100 people with MS and 100 healthy controls to look for the presence of bacteria and antibodies against the toxin, which would suggest prior exposure.



## 13 New Pilot Projects Take Aim at MS

One way the Society propels MS research forward is by funding high-risk, high-potential pilot projects to investigate untested ideas. These one-year grants allow researchers to quickly gather data to determine if ideas are worth pursuing. Grants began April 1, 2014.



### STOP

Eitan Akirav, PhD (Winthrop University, Mineola, NY) is testing an affordable and minimally invasive tool for evaluating MS progression and testing MS therapies.

Suhayl Dhib-Jalbut, MD (Rutgers University, New Brunswick, NJ) is examining a protein that may help to protect nerve cells from damage in MS models.

Brad Hoffman, PhD (University of Florida, Gainesville, FL) is investigating a novel method of gene therapy for use in stopping the immune attack in MS models.

Shelley Hooks, PhD (University of Georgia, Athens, GA) is investigating a protein that may affect the immune attack in MS, and one treatment currently used to stop that attack.

Hong Jiang, MD, PhD (University of Miami, Miami, FL) is investigating a novel mechanism for damage to nerve fibers in the eye, for clues to understanding MS-related damage.

Linda Wooldridge, PhD (University of Bristol, Bristol, UK) is exploring a strategy for stopping the immune attack in MS models without blocking protection against infection.



### RESTORE

Jaime Grutzendler, MD (Yale University, New Haven, CT) is imaging myelin repair as it happens in mice for clues to MS repair strategies.

Jeffrey Huang, PhD (Georgetown University, Washington, DC) is investigating a gene associated with the immune system that may play a role in myelin formation and repair.

Albert Lo, MD, PhD (Brown University, Providence, RI) is testing whether backward walking can improve gait problems and the detection of these problems in people with MS.

Sam Pleasure, MD, PhD (University of California, San Francisco, San Francisco, CA) is using a novel technique to determine why myelin-making cells fail to repair damage.

Ruchika Prakash, PhD (Ohio State University, Columbus, OH) is testing meditation for improving emotional function in people with MS.

Laura Rice, PhD (University of Illinois at Urbana-Champaign, Urbana, IL) is testing a method of reducing falls in homebound people with MS.

Lynne Shinto, ND (Oregon Health & Science University, Portland, OR) is conducting a clinical trial testing lipoic acid combined with fatty acid for cognitive impairment in MS.



**What's Next?** The presence of such toxin-producing bacteria in people with MS but not healthy controls will prompt further studies to determine if the toxin indeed can trigger MS.

### **Chuan Wu, MD, PhD**

Brigham and Women's Hospital  
Boston, MA

**Title:** High salt diet influences the development of autoimmunity via inducible salt sensing kinase SGK1

**Summary:** How might dietary salt influence the behavior of immune cells in MS?

**Background:** The cause of MS is unknown, but multiple factors are likely to play a role. In addition to genetic factors, one environmental factor that has been explored recently by researchers at Harvard and Yale is a high-salt diet. An enzyme called serum glucocorticoid kinase-1 (SGK1) may play a role in controlling both salt intake into cells and the balance between harmful and helpful immune cells in MS.

**The Study:** Chuan Wu, MD, PhD, has received a Career Transition Fellowship to investigate these mechanisms under the mentorship of immunologist Vijay Kuchroo, DVM, PhD, who was part of the original team that reported on the potential influence of salt on MS. Previous studies have shown that SGK1 controls entry of salt into cells, decreases the numbers of helpful immune cells, and increases the numbers of harmful immune cells. Dr. Wu and colleagues are investigating the details of how SGK1 makes mice worse when they have the MS-like disorder EAE. They are researching how SGK1 increases salt intake into cells and how SGK1 affects the various immune cells and immune molecules that play roles not just in EAE but also possibly in MS.

**What's Next?** This study may identify SGK1 as a target for a new type of therapy for people with MS. In addition, this Career Transition Fellowship will help Dr. Wu move into a faculty position and cement his dedication to MS research.

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