# NEW RESEARCH

STOP. RESTORE. END.

## Society Commits $25.3 Million for 60 New MS Research Projects

The National Multiple Sclerosis Society has committed another $25.3 million to support an expected 60 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 effort to expand investments and worldwide collaboration to accelerate research, investing a projected $54 million in 2016 alone to support over 380 new and ongoing studies around the world. The Society pursues all promising paths, while focusing on progressive MS.

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

While we're driving the scientific breakthroughs that will propel the knowledge to end MS, we're identifying everyday solutions that change the lives of people with all forms of MS. The new projects include these, described in more detail in the following pages:

STOP: SUMMIT is an innovative and ambitious research project with the goal of providing a tool that will unravel why and how MS progresses, with the goal of predicting and preventing progression. (see p. 10)

RESTORE: Researchers at Johns Hopkins University are developing versions of a promising compound for possible use in improving cognitive function in MS. (see p. 23)

END: Researchers are tracing the influence of genes on immune cell activity for clues to stopping or preventing MS. (see p. 31)

National Multiple Sclerosis Society

## Inside...

## 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 a role 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—Diagnostic Methods

**Kedar Mahajan, MD, PhD**
Cleveland Clinic
Cleveland, OH
**Award:** NMSS-AAN Clinician Scientist Development Awards
**Term:** 7/1/2016-6/30/2019
**Funding:** $194,394
**Title:** Magnetic resonance fingerprinting and pathology correlations in multiple sclerosis
**Summary:** Cleveland Clinic investigators are using novel imaging and tissue studies to understand how MS impacts an area deep in the brain, called the thalamus, and how its injury contributes to disability.

**Background:** The thalamus is a structure in the brain that relays information entering and leaving the brain. The thalamus plays an important role in cognition, memory, and orientation. Shrinkage of the thalamus occurs early in MS, and injury to the thalamus predicts how well people with MS do over the long term. Little else is known about how the thalamus is affected in people with MS. The thalamus is difficult to image with standard brain magnetic resonance imaging (MRI).

**The Study:** Dr. Mahajan is first looking at the thalamus from autopsied tissues of people who had MS. Lesions in the thalamus are being studied and characterized in these samples. Then, they will then use that information and a new type of MRI called magnetic resonance fingerprinting (MRF) to look for similar lesions in the thalamus of live people with MS (10 with early, relapsing-remitting MS and 10 with late, secondary progressive MS) and 20 controls who do not have MS. They will correlate clinical, cognitive, and conventional imaging data with the MRF data from thalamic lesions. In this way the researchers aim to determine the role that damage to the thalamus plays in disability in MS.

**What's Next:** There is potential to develop thalamic MRF as a method for use in clinical trials to test therapies that help prevent loss of tissue such as the thalamus in MS.

### STOP—Measuring MS Disease Activity

**Erin Beck, MD, PhD**
National Institute of Neurological Disorders and Stroke
Bethesda, MD
**Award:** NMSS-AAN Clinician Scientist Development Awards
**Term:** 7/1/2016-6/30/2019
**Funding:** $194,394
**Title:** Characterization of the pathophysiology, dynamics, and clinical implications of cortical demyelination in MS
**Summary:** Researchers at the National Institute of Neurological Disorders and Stroke are improving magnetic resonance imaging to allow better monitoring of disease progression in people with MS.

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

Consistent with its effort to ensure that people affected by MS have access to comprehensive, high quality health care, the Society has granted two new 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 are the awardees for 2016:

**Lead Mentor: Elliot Frohman, MD**
The University of Texas Southwestern Medical Center, Dallas, TX

**Lead Mentor: Annette Wundes, MD**
University of Washington, Seattle, WA

There are now 11 institutions training MS specialists with this funding. 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.

**Background:** Areas of damage in the brain of people with MS are called "lesions" or "plaques." Most attention has been focused on plaques located in parts of the brain called "white matter," largely because these regions can be visualized fairly easily with imaging techniques such as magnetic resonance imaging (MRI). However, increasing information suggests that plaques located in other parts of the brain called "gray matter" are also important, especially in terms of the cognitive problems that sometimes affect people with MS.

**The Study:** Dr. Beck and her team are optimizing MRI to image gray matter plaques located in the cortex of the brain, employing an animal model of MS. They will then use this optimized MRI to visualize gray matter plaques in people with relapsing-remitting and progressive MS to determine if gray matter plaques are associated with more progressive forms of the disease. They are also investigating if gray matter plaques in humans are associated with cognitive deficits.

**What's Next:** Routine use of these advanced MRI techniques in the future will allow better monitoring of MS disease progression, better prediction of disease course, and better choice of existing therapies and development of new therapies for MS.

**John Chen, MD, PhD**
Massachusetts General Hospital
Boston, MA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $591,388
**Title:** Myeloperoxidase in multiple sclerosis
**Summary:** Researchers at Harvard are using MRI to track a harmful inflammatory molecule called MPO as a possible biomarker of disease activity, and devising ways to block its effects as a potential treatment for MS.

**Background:** Diagnosis and treatment of MS remain challenging, in part because there is no single lab test that can identify whether a person has MS or predict a person's expected disease activity in the future. Researchers have been working to identify "biomarkers," or biological signals, that would serve as indicators or predictors of MS. Cells called macrophages/microglia and neutrophils are present in MS brain and spinal cord lesions (regions of disease activity or damage). These cells make and secrete a protein called "myeloperoxidase" (MPO). MPO is found in large amounts in MS lesions and contributes to tissue damage.

**The Study:** Dr. Chen and his team are using mouse models of MS, called EAE, to investigate whether using magnetic resonance imaging (MRI) to locate MPO in the brain can be used as a biomarker of disease activity. MPO increases inflammation in a variety of ways, and is considered harmful. The team is exploring whether MPO is an informative biomarker for MS disease activity, and building on their previous work showing that blocking one effect of MPO partially improved EAE. Now they are seeking to identify other ways to block MPO functions.

**What's Next:** These results may lead to earlier and better diagnosis, improved monitoring of treatment effects, and optimal targeting of MPO-mediated inflammation, which could ultimately provide better outcomes for people with all forms of MS.

**Elena Herranz Muelas, PhD**
Massachusetts General Hospital
Boston, MA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $111,145
**Title:** In vivo MR-PET imaging of glial activation and its correlates in MS
**Summary:** Researchers at Massachusetts General Hospital and Harvard Medical School are investigating new brain imaging methods for inflammation to increase understanding of MS disease progression and response to treatment.

**Background:** Activated cells called microglia and macrophages produce inflammation and are present in areas of damage to the brain in MS. Current imaging techniques such as magnetic resonance imaging (MRI) can detect some of these activated cells but not all. Detecting all of the activated cells in people with MS will provide better information about the state of their disease and response to treatment.

**The Study:** Dr. Herranz Muelas and colleagues are using novel imaging methods to detect and quantify activated microglia and macrophages in people with MS, including those with relapsing-remitting MS and secondary progressive MS. The first type of imaging is called "MR-PET." This method combines MRI with another type of imaging called positron emission tomography, which can visualize cell processes. The second type of imaging is called ultra-high field 7-Tesla MRI. This

# Five Physicians Receive Training Awards for Specialized MS Care

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

| Awardee | Location | Mentor |
|---|---|---|
| Tamara Bockow Kaplan, MD | Partners MS Center, Brigham & Women's Hospital, Boston | Howard Weiner, MD |
| Marwa Kaisey, MD | David Geffen School of Medicine, University of California, Los Angeles | Barbara Giesser, MD |
| Siamac Esfandi, MD | University of Colorado School of Medicine, Denver | John Corboy, MD |
| Laura Baldassari, MD | University of Utah Health Care, Salt Lake City | John Rose, MD |
| NgocHanh Vu, MD | MS Center, Vanderbilt University Medical Center, Nashville | Subramaniam Sriram, MB, BS |

method allows the team to see with greater detail much smaller areas of the brain than conventional MRI. Participants are undergoing these two types of imaging at the beginning of the study and one year later. Neurological and clinical examinations of these participants are also being performed. Using collected images and clinical information, the team is then asking if the amount of inflammatory cells is related to lesions, damage to the brain, disease progression, and response to treatment.

**What's Next:** Results from this study will allow better characterization of the stages of MS and improved understanding of disease progression and response to treatments. It will also provide better information about links between inflammation and damage, and the role of macrophages and microglia in MS.

**Hong Jiang, MD, PhD**
University of Miami
Miami, FL
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $540,834
**Title:** The role of retinal microvascular impairment on neurodegeneration in Multiple Sclerosis
**Summary:** Researchers at the University of Miami are studying blood vessels at the back of the eye of people with MS to better understand nerve damage and MS progression.

**Background:** MS involves damaging immune system attacks on the brain and spinal cord. Some individuals with MS show abnormalities in the brain's circulatory system, such as decreased blood flow rate and capillary loss in brain tissue. Inflammation is suggested to be the reason for these blood vessel abnormalities, which in turn may cause or contribute to nerve damage. This potential link is difficult to explore because the location of the brain's microvessels makes them difficult to visualize and assess directly. However, the back of the eye (retina) has a vascular system and since it is an extension of the brain's circulatory system, it may prove an ideal way to study blood circulation in the brain.

**The Study:** The goal of this project is to use advanced imaging devices to study microvessel abnormalities and neural damage in the retinas of 100 people with all types of MS and 100 people without MS. The team will determine whether abnormalities precede or contribute to MS-related neural damage by measuring the retinal microcirculation, microvessel network, and neuronal function and structure. They will follow up with subgroups of the participants for 2 years to observe change during MS progression.

**What's Next:** This research should provide important basic information about how changes in retinal microvessels may associate with MS-related neuronal damage. This project may increase understanding of the progression and underlying neural damage mechanisms of MS, which could set the stage for more effective and beneficial treatments.

**Dzung Pham, PhD**
Henry M. Jackson Foundation
Bethesda, MD
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $576,674
**Title:** Imaging Biomarker Discovery With Advanced Brain Segmentation Algorithms
**Summary:** Researchers at the National Institutes of Health are developing software tools to automatically measure MRI-detected brain lesions in MS to improve diagnosis and clinical trials.

**Background:** Magnetic resonance imaging (MRI) is frequently used and very important for the diagnosis and monitoring of treatment responses in MS. Image processing software has been developed to analyze brain regions visualized with MRI, but these tools are good for analyzing normal brain anatomy and not abnormalities in brain regions such as MS

## Sylvia Lawry Physician Fellowship

As part of the Society's effort to propel knowledge to end MS, the promising young doctors receiving training from a Sylvia Lawry Physician Fellowship learn from top MS experts who mentor their initiation into the complex methods of designing and conducting clinical trials in persons with MS.

| Awardee | Location | Mentor |
|---|---|---|
| Oluwasheyi Ayeni, MD | Icahn School of Medicine at Mount Sinai, New York, NY | Fred Lublin, MD |
| Marisa McGinley, MD | Cleveland Clinic Foundation, OH | Jeffrey Cohen, MD |
| Veronica Penyak Cipriani, MD | University of Chicago Medical Center, Illinois | Anthony Reder, MD |
| Thomas Shoemaker, MD | Johns Hopkins University School of Medicine, Baltimore, MD | Ellen Mowry, MD, and Scott Newsome, MD |

lesions, or areas of tissue damage or disease activity. The manual manipulations required to analyze abnormal anatomy are time consuming, and preclude use of these manipulations in larger populations of patients such as those participating in clinical trials.

**The Study:** Dr. Pham and his team are building the first algorithms (sets of rules for solving mathematical and other problems) and software tools that detect and characterize MS lesions that occur anywhere in the brain. They are then using these tools to develop new imaging biomarkers that can be used to monitor disease progression in MS. They are testing how well the new software tools work using images captured in two different research institutes to see how well they predict disability in MS. They will then make these tools freely available so that all researchers and people with MS can use and benefit from them.

**What's Next:** This software package is expected to improve and accelerate analysis of MRI brain scans in people with MS, and will be especially useful in clinical trials to refine and speed the search for better therapies.

**Alexander Rauscher, MSc, PhD**
University of British Columbia
Vancouver, BC, Canada
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $309,320
**Title:** Imaging markers for tissue damage and repair in MS
**Summary:** Researchers at the University of British Columbia in Vancouver are improving brain MRI to better detect disease activity, severity, and changes over time in people with MS.

**Background:** Magnetic resonance imaging (MRI) is commonly used to diagnose and monitor disease progression in MS. Although MRI can detect the location of damage in the brain, this method cannot be used to measure precisely how severe the damage is. This capability will be very important for understanding how well both approved and experimental therapies work, refining MRI as a -invasive tool for tracking MS is a priority. Ideally, MRI should have high resolution, high sensitivity, and should show specific changes in myelin and other components of the brain and spinal cord damaged in MS.

**The Study:** Dr. Rauscher and his team are working to improve MRI. They are using a technique called "myelin water imaging" and a type of MRI scan that maps the frequency of the MRI signal, both of which are sensitive to the changes in the brain that occur due to tissue damage in MS. They are comparing the scans from these techniques with brain tissue donated from people with MS to investigate the relationship between what the scans show and what the tissue damage looks like under a microscope. They are also using these types of MRI scans to see how MS lesions (areas of damage or disease activity) change over the course of 5 years. The people with MS who are participating in Dr. Rauscher's study are already enrolled in one of several clinical trials and have a range of MS disease types.

**What's Next:** The results should improve how MRI is used to track lesion changes over time in MS, and improve understanding of how well an individual's therapy is working. Having improved MRI would also enable the testing of new therapies faster and cheaper, speeding up research towards a cure for MS.

## STOP—Role of the Immune System

**Clare Baecher-Allan, PhD**
Brigham and Women's Hospital
Boston, MA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $593,987
**Title:** Extracellular Granzyme B mediated regulation of Treg function and immune responses in MS
**Summary:** Researchers at Brigham and Women's Hospital are studying ways to restore regulation of immune system activity as a promising approach to developing better MS therapies.
**Background:** In MS, the immune system, which normally works to protect people from infectious agents such as bacteria or viruses, mistakenly attacks myelin in the brain and spinal cord. Myelin surrounds and protects nerve fibers. The immune system has numerous types of cells, some of which activate and direct immune system activity, while others slow down or turn off activity.

**The Study:** Clare Baecher-Allan, PhD, is studying the influence of an immune cell known as a regulatory T cell (Tregs). These cells ordinarily suppress the activity of other immune system cells that might damage the nervous system. Dr. Baecher-Allan and others have found that Tregs are somehow defective in people with MS, so their ability to control immune attacks is compromised. Her team has recently identified a protein—Extracellular Granzyme B—which is involved in mediating Treg resistance. Now they are examining how this molecule induces Treg resistance, and determining the potential therapeutic value of neutralizing this protein. They are studying how the protein acts on human cells in assays established in laboratory cultures and upon injection in mouse models.

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

**Sophia Bardehle, PhD**
The J. David Gladstone Institutes
San Francisco, CA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $175,431
**Title:** Study of the role of fibrinogen in T-cell recruitment and activation in neuroinflammatory disease.
**Summary:** Investigators at the University of California, San Francisco are examining the role of a protein called fibrinogen in the inappropriate damaging activation of the immune system in MS.

**Background:** MS involves immune-system attacks on the brain and spinal cord. Normally proteins and other substances are kept out of the brain by a structure called the blood-brain barrier (BBB). The BBB does not function properly in MS, and various substances can abnormally enter the brain. A protein called "fibrinogen" is normally found in the blood but not in the brain. Fibrinogen may enter the brain in MS due to a damaged BBB, where it may interact with immune cells, and may be involved in the inappropriate damaging activation of the immune system.

**The Study:** Dr. Bardehle is investigating how fibrinogen interacts with, recruits, and activates immune cells once the protein enters the brain. She and her team are investigating how fibrinogen interacts with three types of immune cells, T cells, microglia, and macrophages, which may be harmful in MS. They are performing live imaging of these immune cells in mice with the MS-like disease EAE in the presence and absence of fibrinogen to observe what happens to the immune cells in these different conditions. They are also growing these immune cells in a dish and observing what types of immune cells are activated by fibrinogen. Finally, they are determining what molecules are activated by fibrinogen.

**What's Next:** Results from this study may suggest novel ways to prevent inflammation in the brain and thus limit MS disease progression.

# SUMMIT: Stopping Progressive MS

Every day people with progressive MS lose some of the ability to move, think, and connect with those they love and the greater world. Despite advances that have produced more than a dozen disease-modifying therapies for relapsing forms of MS, progressive MS remains frustratingly elusive to understand and treat.

Supporting a multi-faceted, global approach to speed the development of therapies that stop MS progression is a high priority for the National MS Society. One critical component of the Society's comprehensive strategy to stop MS progression is the development of an ambitious, large-scale study that tracks and deeply characterizes a group of people with MS over time. The concept is similar to the famous Framingham Heart Study, which identified much of what we now consider common knowledge about heart disease, such as the effects of diet, cholesterol, exercise, and the use of aspirin as a preventive that revolutionized our understanding and treatment of heart disease.

Experts agree that this type of "cohort" study is the best approach for identifying factors that influence and predict disease progression, since cause and effect relationships can only be determined by long-term, prospective studies.

SUMMIT (Serially Unified Multicenter Multiple Sclerosis Investigation) is an innovative and ambitious research project with the goal of providing a tool that will unravel why and how MS progresses, with the goal of predicting and preventing progression. This 5-year study brings together two MS Centers of Excellence: **Harvard's Brigham and Women's Hospital and the University of California, San Francisco**. Each institution has been carefully following MS cohorts for nearly 10 years. SUMMIT will extend and leverage these deep collections of information, clinical data, MRI images, questionnaires and biological specimens involving over 1,000 people with MS. The SUMMIT investigators will recruit and track new and existing participants with annual clinical assessments, bloodwork, MRI and other tests.

SUMMIT will develop an extensive, open database of clinical information with results from cutting edge imaging and biological tests that clinicians and researchers have needed and wanted for years. Given the technological opportunities available today, individuals with MS (and their providers) living anywhere in the world should ultimately be able to access SUMMIT data to contextualize their personal experience relative to others with MS. SUMMIT represents a step toward these longer-term goals.

The National MS Society has committed to finding the funding for the first phase of the project, for **$2,750,000**, and is seeking other funding partners who share our goals of predicting and preventing MS progression.

**Pavan Bhargava, M.B.B.S., MD**
Johns Hopkins University,
Baltimore, MD
**Award:** Career Transition Fellowships
**Term:** 7/1/2016-6/30/2020
**Funding:** $591,630
**Title:** Targeting Leptomeningeal Inflammation for Progressive Multiple Sclerosis
**Summary:** Researchers at Johns Hopkins University are working to establish a better model of progressive MS that will permit research into understanding and treating inflammation of the meninges, the tissue that covers the brain.

**Background:** Although therapies exist for the treatment of relapsing forms of MS, few treatments are available for treating progressive MS. Recent research points to a damaging role of inflammation of the meninges, a covering on the surface of the brain. The inflammatory cells that are present in the meninges may release toxic factors that cause damage more frequently seen in progressive MS compared to relapsing MS. At present, there is no animal model of meningeal inflammation for progressive MS. Developing this type of model for inflammation of the meninges could aid in developing treatments for progressive forms of MS.

**The Study:** Dr. Bhargava and his team have found features of meningeal inflammation in mice with the late stages of the MS-like disease EAE. Dr. Bhargava and his team are using MRI to track the development of meningeal inflammation in mice over time, and are examining the immune cells in these areas to confirm that these mice represent the type of meningeal inflammation seen in people who have MS. They are examining the cells in these inflammatory regions, the molecules secreted by the cells, and the effect of meningeal inflammation on nearby brain regions. Finally, they will use these model mice to screen potential treatments for progressive MS by using MRI to look at changes in meningeal inflammation.

**What's Next:** Establishing a new mouse model will enable the research community to identify potential compounds that target meningeal inflammation, and could lead to testing of those therapies in clinical trials in people with MS, especially progressive MS.

**Murugaiyan Gopal, PhD**
Brigham and Women's Hospital
Boston, MA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $539,320
**Title:** MicroRNA Control of Inflammatory T cells in EAE and MS
**Summary:** Researchers at Harvard Medical School are investigating how a small, naturally occurring molecule regulates the function of harmful types of immune cells in MS.

**Background:** In MS, immune cells called T cells can become harmful and participate in attacking the brain and spinal cord. Two types of harmful T cells called "Th1" and "Th17" cells are of particular importance. Tiny, naturally occurring molecules called "microRNAs" are involved in controlling when genetic instructions are used to synthesize gene products ("gene expression"). One microRNA called "Mir-21" controls genes involved in Th1 and Th17 functions. Research suggests that the absence of Mir-21 blocks their function and makes mice resistant to developing EAE, a model of MS.

**The Study:** Dr. Gopal and his team are investigating in more detail how Mir-21 works to cause the disease-inducing functions of Th1 and Th17 immune cells. They are teasing out how Mir-21 works by continuing studies in mice with EAE that lack certain genes to see which other molecules may play a role. They are also looking at T cells from the blood of people who do not have MS to see how Mir-21 controls the normal development of T cells, and comparing whether there are differences in people with MS. They are also asking if Mir-21 regulation of T cells changes in response to therapy in people with MS.

**What's Next:** Results from this study may indicate whether Mir-21 is a potential therapeutic target for novel treatments for MS.

**Ariele Greenfield, MD**
University of California, San Francisco
San Francisco, CA
**Award:** NMSS-AAN Clinician Scientist Development Awards
**Term:** 7/1/2016-6/30/2019
**Funding:** $198,867
**Title:** Antigen Targets of CNS-Infiltrating B Cells in Early, Untreated Multiple Sclerosis
**Summary:** Researchers at the University of California, San Francisco are determining the targets of harmful immune cells called B cells in MS, which may lead to earlier, more effective treatment of MS or prevention.

**Background:** In MS, immune cells attack components of the brain and spinal cord, leading to various symptoms and disability. No methods exist to prevent MS, because the earliest events that cause these immune cell attacks remain unknown. Certain subtypes of the immune cell group called B cells are found in the spinal fluid (the fluid that bathes the brain and spinal cord) in people with early MS; these are not found in people without MS, people with MS who are in remission, or those with later stages of MS. This timing suggests that these B cells may play a role in triggering MS.

**The Study:** Dr. Greenfield and her team are obtaining blood and spinal fluid samples from people without MS and people with their first attack of MS. They are then isolating the B cells from these samples. Each B cell recognizes a specific set of targets, which can direct the B cell's actions toward a certain tissue. They believe that the B cells are targeting myelin, the fatty substance that surrounds and protects nerve cells. However, the components of myelin targeted by these B cells are not yet known. Dr. Greenfield and her team are determining the individual targets of each B cell to understand what these cells may initially attack.

**What's Next:** Therapies designed to block the interaction between B cells and their specific target may be useful for preventing or stopping MS.

**Mark Johnson, PhD**
University of Washington
Seattle, WA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $175,431
**Title:** Defining T Cell Signatures Associated With Distinct Neuroinflammatory Patterns in Multiple Sclerosis Patients

**Summary:** University of Washington researchers are looking for distinct patterns of proteins in the blood in people with MS which may allow for better disease monitoring, prediction, and use of tailored therapies.

# National MS Society Collaborates Commercially to Develop Treatments for Progressive MS

Getting treatments to people with MS requires bold leadership, tenacity and investment at every stage of the research process. The Society continues to propel promising new therapies by breaking down barriers to commercial development through funding mechanisms like Fast Forward. We drive connections of all the resources necessary to ensure that promising treatments don't languish on a dusty shelf, including this most recent collaboration to develop treatments for people with progressive MS:

**University College London and Queen Mary University (London, UK)**
Researchers at the University College London and Queen Mary University (London, UK) have developed possible neuroprotective therapies for the treatment of neurodegenerative diseases including MS. With previous National MS Society funding through Fast Forward, the team produced a compound (JW47) that was effective in a mouse model of MS. The compound targets mitochondria, the power plants inside cells whose malfunction can lead to nerve cell loss. The collaborators have now received new funding from Fast Forward to refine this and other compounds to optimize their potential use in stopping or slowing progressive MS.

**Funding:** $804,767 to support identification of new neuroprotective compounds to prevent or delay neurodegeneration in progressive MS, and test compounds in mouse models.

**Background:** MS lesions, or damaged areas, can occur in the brain and spinal cord. Spinal cord lesions are associated with a worse clinical diagnosis due to impaired mobility. The reasons why lesions occur in one place rather than another are unknown. One type of immune cell called "T cells" are thought to play a major role in causing MS and both the specificity of, and protein expression by, these T cells may influence the location of lesions.

**The Study:** Dr. Johnson and colleagues are investigating whether differences in T cells may correlate with the localization of lesions to the brain or spinal cord. To do so, they are obtaining blood from people with MS who have lesions localized predominantly in the brain or the spinal cord, as well as from healthy controls. They are then isolating these T cells from the samples and assessing the levels (expression) of a multitude of surface and secreted proteins to distinguish patterns between different MS groups and healthy controls. To help elucidate these patterns, the team is using mathematical modeling to define the unique characteristics of T cells in people with MS whose lesions localize predominantly to the spinal cord or brain.

**What's Next:** These studies may identify biomarkers that could be detected in blood which may be useful for predicting an individual's disease course and for monitoring responses to therapies.

**Alexandra Kitz, PhD**
Yale University School of Medicine
New Haven, CT
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $175,431
**Title:** Role of Akt kinases in regulating high-salt induced Treg dysfunction
**Summary:** Researchers at Yale School of Medicine are using immune cells from the blood of healthy people and people with newly diagnosed MS to investigate how high salt may switch a helpful type of immune cell called Tregs to a harmful type called Th1 Tregs and if the helpful function can be restored.

**Background:** In MS, various types of immune cells are involved in the attack on the brain and spinal cord. Specifically, decreased function of a helpful type of immune cell called "Tregs" has been observed. Recent work has shown that high levels of dietary salt can turn off the function of these helpful type of Tregs. Another study showed the presence of high levels of a harmful type of immune cell called "Th1 Tregs" in the blood of people with MS. These are considered to be improperly functioning Tregs.

**The Study:** Dr. Kitz and colleagues are examining whether high dietary salt is involved in switching Tregs from a helpful function to a harmful one. They are testing whether blocking the molecules involved in the high salt-mediated harmful function of Tregs can switch them back to a more helpful function. These studies are being performed with immune cells isolated from the blood of people with untreated, newly diagnosed MS and people who do not have MS.

**What's Next:** Results from this study may suggest ways to therapeutically switch harmful Tregs to a more beneficial type of Tregs, which would be a novel strategy for treating people with MS.

**Robyn Klein, MD, PhD**
Washington University School of Medicine
St. Louis, MO
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $662,811
**Title:** Targeting S1PR2 to prevent disease progression in females with CNS autoimmunity
**Summary:** Investigators at Washington University School of Medicine are investigating a molecule that appears to be involved in sex differences and possibly disease progression, in a model of MS and in people with MS.

**Background:** Women are three to four times more likely than men to develop MS. Approximately 65% of people with relapsing-remitting MS, the most common form of the disease in women, develop a progressive form of the disease called secondary progressive MS. The mechanisms underlying sex differences in MS and how sex differences may drive disease progression are not well understood. Entry of harmful immune cells into the brain in MS is partially mediated by a molecule called S1PR2, which is expressed at high levels in females with MS. Blocking S1PR2 in a mouse model of MS called EAE improves disease severity in female, but not male, mice.

**The Study:** Prof. Klein and her team are investigating whether increased levels of S1PR2 in mice with the relapsing-remitting form of EAE promote accumulation of harmful immune cells that in turn promote disease progres-

sion. They are also developing ways to image S1PR2 in mice. Finally, they are looking at where S1PR2 is found in the brains of people with MS and if expression is different in women compared to men with MS. Results will reveal if S1PR2 activity in the brain is different in men and women who have MS, and whether targeting S1PR2 would be likely to prevent disease progression.

**What's Next:** This project could uncover new approaches to treating MS and imaging disease activity.

**Jianrong Li, PhD**
Texas A&M AgriLife Research
College Station, TX
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $554,288
**Title:** Stat3 in myeloid cells: a regulator of autoimmune demyelination
**Summary:** Texas A&M University researchers are targeting a molecule whose signals may be crucial to stopping the immune attack on the brain and spinal cord in MS.

**Background:** In MS, immune cells attack myelin—the substance that surrounds and protects nerve fibers—and oligodendrocytes, the cells that make myelin. A variety of immune processes are involved in this attack. Jianrong Li, PhD, and colleagues propose that abnormal regulation of cells, known as macrophages, occurs early and contributes to the development of MS. This team recently found that a major signaling molecule called Stat3 is activated in macrophages and plays a critical role in triggering immune cell invasion into the brain and spinal cord and causing damage in a mouse model of MS. Mice that lack this molecule in their macrophages are protected from MS-like disease.

**The Study:** Now the team is studying how Stat3 activation causes myelin damage in hopes of identifying key components in the pathway that can be targeted therapeutically to prevent this damage. Dr. Li and colleagues are using genetic tools to selectively target Stat3 signaling in macrophages in mice. By observing disease processes in these mice, they hope to determine how Stat3 regulates cell function, whether it affects immune reactions differently at different disease stages, and the impact on disease severity.

**What's Next:** Identifying the key signals responsible for immune cell invasion will be key to targeting these cells for therapeutic intervention to prevent further myelin damage. Treatments that target Stat3 are under development for other diseases, so insights obtained from this project have many implications in therapeutic strategy development for MS.

**Lior Mayo, PhD**
Brigham and Women's Hospital
Boston, MA
**Award:** Career Transition Fellowships
**Term:** 7/1/2016-6/30/2020
**Funding:** $589,849
**Title:** Role of CD38 in the control of the innate and adaptive immune responses during CNS inflammation
**Summary:** Researchers at Brigham and Women's Hospital are investigating an immune-system protein for its role in driving MS progression, for clues to stopping progression in its tracks.

**Background:** Despite advances in other forms of MS, progressive MS remains frustratingly elusive to understand and treat. This proposal is designed to study mechanisms that contribute to disease progression, and to explore the therapeutic potential of these

mechanisms for MS. Lior Mayo, PhD, and colleagues discovered that a protein called CD38 promotes the development of clinical symptoms and signs of nerve degeneration in a mouse model of MS, and that it regulates the activation of immune T-cells and brain cells.

**The Study:** The team is exploring what mechanisms mediated these observations in the hopes of learning what underlies MS progression. They are conducting a serious of studies both on isolated cells and in mouse models that mimic both relapsing-remitting and secondary progressive forms of MS. In cells grown in lab dishes, they are investigating mechanisms regulated by CD38, and in mouse models, they are determining the importance of these mechanisms to disease progression and exploring the therapeutic potential of targeting CD38.

**What's Next:** A CD38-targeting antibody was recently approved by the U.S. Food and Drug Administration to treat cancer, so the studies outlined in this research proposal may lead to the use of anti-CD38 therapies for MS in an expedited manner.

**Joseph Sabatino, MD, PhD**
University of California, San Francisco
San Francisco, CA
**Award:** NMSS-AAN Clinician Scientist Development Awards
**Term:** 7/1/2016-6/30/2019
**Funding:** AMOUNT PENDING
**Title:** Myelin-specific CD8+ T cell pathogenicity in multiple sclerosis
**Summary:** Investigators at the University of California, San Francisco are examining the possible role of a type of immune cell in causing and/or worsening MS to determine if blocking these cells could lead to a more specific therapy for MS.

**Background:** In MS, the immune system attacks and destroys components of the brain and spinal cord, leading to disability in people with the disease. The immune system consists of different types of cells. Although the role of many types of immune cells has been investigated in MS, the role of one type of immune cell called "CD8+ T cells" is still unclear.

One component of the brain that is attacked by immune cells is myelin, which is the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function properly, producing symptoms in people with the disease. CD8+ T cells that recognize myelin are present in both people with and without MS, but how these cells may be different in these two groups is not known.

**The Study:** Dr. Sabatino and his team are investigating differences in these cells in people who have MS and people who do not. They are isolating CD8+ T cells that recognize myelin from both groups and are asking if the number of cells is different, and whether CD8+ T cells from people with MS have more inflammatory properties. Finally, they are asking if CD8+ T cells from people with MS bind myelin more tightly than cells from people without MS.

**What's Next:** These studies will provide information as to whether and how CD8+ T cells play a role in causing and/or worsening MS, and could lead to new therapies that more specifically eliminate damaging immune cells.

**David W. Scott, PhD**
Henry M. Jackson Foundation
Bethesda, MD
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2017
**Funding:** $163,909
**Title:** Generation and function of engineered CNS-specific human and murine T regulatory cells
**Summary:** Investigators at Uniformed Services University of Health Sciences in Bethesda are engineering novel cells and molecules aimed at stopping MS immune attacks and progression.

**Background:** MS occurs when the immune system attacks the brain and spinal cord. Immune cells known as "T cells" from people with MS have been shown to respond to a variety of molecules, and dousing this responsiveness is important for therapeutic intervention in MS. Professor David Scott and colleagues have created engineered human regulatory T cells (Tregs) to "turn off" the disease-causing immune responses in MS. These Tregs are specific for the molecules that are recognized by the immune system of people with MS and act to specifically control the specific responses to these molecules, as opposed to general immune-suppressing activity.

**The Study:** Now, this team is using molecular biology to engineer specific docking sites for these Tregs in human and mouse T cells, and will test them in cell samples isolated in the laboratory. Then, they will test if these Tregs can suppress EAE, a model of MS, in mice.

**What's Next:** If these specified Tregs can reduce the activity of disease-causing T cells, this project can be translated into the development of a potential therapy for multiple sclerosis.

**Howard Weiner, MD**
Brigham and Women's Hospital
Boston, MA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $528,623
**Title:** Investigation of Pathogenic Gene Signature of Human TH17 cells in MS
**Summary:** Researchers at Harvard Medical School are looking at genetic differences in a specific type of immune cell ("Th17") which can be both harmful and beneficial in people with MS, to provide a strategy for more specific therapies.

**Background:** In MS, the immune system attacks and damages components of the brain and spinal cord, producing a variety of symptoms. The immune system is composed of many different types of cells, some of which are helpful and some of which are harmful. One type of immune cell, called "Th17 cells," can be divided into two sets: harmful Th17 cells and protective Th17 cells. Previous studies have established a "signature" of genes that differentiates harmful and protective Th17 cells. However, the role of these two cell types in MS is unknown.

**The Study:** Dr. Weiner and his group are isolating Th17 cells from the blood of 25 untreated people with relapsing-remitting MS and 25 people without MS. Using the genetic signature, they are investigating whether most cells in people with MS are of the harmful type and if the proportion of harmful cells is different in people who don't have MS. Next, they are looking for new signature genes and if the gene signature changes in response to therapy. To determine if treatment affects the Th17 genetic signature, they are examining Th17 cells from people with MS who are taking interferon beta, glatiramer acetate, fingolimod, or dimethyl fumarate.

# New Collaborative MS Research Award Takes Novel Approach to Stopping MS Progression

**Title:** "Metabolic Dysfunction in MS Pathogenesis and Disease Progression"
**Term:** 4/1/16-3/31/21
**Grant Amount:** $825,000
**Lead Investigators:** Claudia Lucchinetti, MD and Charles Howe, PhD
Mayo Clinic and Foundation, Rochester, MN

**Background:** MS can involve damage to several parts of the brain and spinal cord, and that damage appears to go beyond what might be ascribed to the immune attacks that occur. Another possible type of pathology that could lead to nervous system damage is called metabolic stress. Metabolic stress in cells encompasses a variety of problems including energy deficits and failure to recycle and break down unneeded proteins. There is growing evidence that metabolic stress in cells is associated with MS progression. Drs. Claudia Lucchinetti and Charles Howe have assembled a talented team that aims to conduct "metabolic profiling" of people with MS in hopes of revealing novel markers of progression that can be used to inform clinical care and the development of new therapeutic strategies.

**The Study:** Drs. Lucchinetti and Orhun Kantarci will recruit people with MS to this effort, including a large cohort of people with progressive MS, and Dr. Lucchinetti will direct the use of tissue specimens amassed by the MS Lesion Project (an international effort established with funding from the Society). Metabalomics expert Dr. Sreekumaran Nair will provide access to state-of-the-art facilities for high-throughput screening of metabolites and Dr. Tumpa Dutta will lend her expertise in the analysis of large metabolomics datasets. An intriguing aspect of this project is that the team will create stem cells by reprogramming skin cells from people with MS. The idea is to grow the stem cells in lab dishes and then see if they display abnormal energy processes. This would create "MS in a dish" and give the team an opportunity not only to study the abnormalities up close, but also to easily test therapies to see whether any of them might fix the problem. Drs. Eugenia Trushina and Grazia Isaya will bring expertise in the study of metabolism and Dr. Timothy Nelson will provide expertise in stem cell biology. Dr. Howe will bring expertise in the basic biology of stem cell-derived neurons and neuronal metabolism.

**What's Next?** By combining the novel skills of non-MS investigators with the disease insights of the core MS research group, this team intends to forge a multidisciplinary approach to MS metabolomics and metabolic profiling with an eye toward stopping MS progression in its tracks.

**What's Next:** Results from this study may guide future development of novel MS therapies that inhibit harmful immune activity while sparing important, protective qualities of the immune system.

## STOP—Neuropathology

**Tsen-Hsuan (Abby) Lin, PhD**
Washington University School of Medicine
St. Louis, MO
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2018
**Funding:** $114,963
**Title:** Imaging optic nerve function and pathologies in MS
**Summary:** Researchers at Washington University School of Medicine are developing imaging methods to visualize damage in the eye and relate this damage to visual function in people with MS.

**Background:** MS progresses in a variable and unpredictable way. A person's function as assessed in the clinic is not specifically related to tissue damage in the brain and spinal cord as seen on MRI scans. Having a better way to measure tissue damage and dysfunction it causes would provide a means to monitor MS progression and the treatment response.

**The Study:** Research suggests that function and damage of the optic nerve, which runs between the eye and the brain, likely represents more global damage in other parts of the central nervous system. Dr. Lin and colleagues are using a type of imaging that is related to MRI, called diffusion basis spectrum imaging (DBSI), to view optic nerve damage and establish a specific relationship between injury and visual function. DBSI has been established in mice and is now being optimized for use in people, in combination with MRI. The team is imaging the optic nerve of people with and without MS.

**What's Next:** The ability to better image optic nerve damage will increase understanding of the relationship between MS damage and visual function and lead to improved selection of treatments for people with MS.

## STOP—Neurophysiology

**Amy Lovett-Racke, PhD**
Ohio State University
Columbus, OH
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $575,622
**Title:** Neuroprotective Role of Vitamin D During Childhood
**Summary:** Researchers at The Ohio State University are seeking to determine if low vitamin D in early life increases the risk of developing MS.

**Background:** The cause of MS is unknown, but vitamin D deficiency is emerging as an important risk factor for MS. Studies of migration and sun exposure indicate that susceptibility to developing MS is determined in childhood, although disease onset occurs later in life. The goal of this study is to explore mechanisms related to vitamin D and deficient vitamin D in mice, for clues to how low vitamin D levels in early life may increase the risk of developing MS.

**The Study:** Dr. Amy Lovett-Racke and colleagues are utilizing a mouse model in which vitamin D signaling is only compromised in neurons (nerve cells). They are comparing reduced vitamin D signaling in early life compared to adulthood. First, they are determining if vitamin D induces neurons to produce molecules that dampen inflammation in the brain and spinal cord. Second, they are determining if low vitamin D affects how brain cells respond to inflammation and infection, since this may be a mechanism that initiates MS. Third, they are determining if reduced vitamin D signaling in neurons in early life increases the risk of developing an immune response against the central nervous system.

**What's Next:** If evidence from this and other studies suggests that early life vitamin D influences susceptibility to MS, it may be possible to reduce the incidence of MS by increasing vitamin D in the diets of children.

## 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

**Helen Genova, PhD**
Kessler Foundation Research Center
West Orange, NJ
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $479,783
**Title:** Remediation of Emotional Processing Deficits in MS: A Randomized Clinical Trial

**Summary:** Researchers at the Kessler Foundation are testing a strategy aimed at improving emotional processing abilities in individuals with MS.

**Background:** Recent research suggests that some individuals with MS have difficulty in emotional processing—specifically, impairments in recognizing the emotions from an individual's face. This can lead to issues in social functioning, and difficulty in interpersonal relationships. For this reason, finding ways to improve emotional processing in MS may lead to better social functioning and improved quality of life.

**The Study:** Dr. Helen Genova and her team are examining the effects of an intervention aimed at improving emotional processing abilities in individuals with MS. The intervention consists of a computerized program aimed at improving facial affect recognition, and an interactive training that uses examples of the individual's own emotional experiences. This method has been shown to be useful in the team's previous small pilot study in people with MS, and it has also been shown to help people with other disorders. Now they are enrolling 50 subjects with relapsing-remitting MS who will be randomly assigned to either a treatment group that will undergo emotional processing for 12 sessions, or a control group that will undergo inactive sessions.

**What's Next:** This study may provide important evidence to show that this strategy can be a solution for improving social functioning and quality of life for people with MS.

**Stefan Gold, PhD**
Charité - Universitätsmedizin Berlin
Berlin, Germany
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2020
**Funding:** $1,533,981
**Title:** Online program to reduce depression in MS – a phase III international multicenter randomized controlled trial
**Summary:** Researchers at Berlin, Germany's Charité University Medical Center are testing the effectiveness of a computer program for overcoming MS-related depression.

**Background:** Depression is a common symptom experienced by people living with multiple sclerosis. At the same time, MS symptoms such as walking difficulties, cognitive problems, and fatigue can make it difficult to attend sessions with a therapist. Dr. Stefan Gold's team has recently conducted a small trial using a fully-automated, computer-based program to reduce depression in patients with MS. The program can be accessed over the internet and completed from an individual's home, eliminating the need to travel. The team's preliminary results suggested that this program, called "Deprexis," may reduce depression in MS.

**The Study:** Dr. Gold and colleagues are now conducting a large-scale, phase III trial at five MS centers in Germany and the U.S. to test the effectiveness of the Deprexis computer program in 400 people with MS. Participants in the trial will be randomly assigned to either receive the program immediately and work with it for three months, or to wait for half a year and then work with the program. Every participant will come to a specialized MS center at the beginning and after three months for psychological and neurological evaluations, as well as questionnaires to measure the severity of depressive symptoms. Participants also will be evaluated again after 6 and 12 months to see if any improvements in depression are maintained over an extended period of time.

**What's Next:** If the trial is positive, given that the Deprexis program is computer-based and commercially available in English and German, this study could have powerful impact on the lives of people living with MS and depression.

**Jeffrey Hausdorff, PhD**
Tel Aviv Sourasky Medical Center
Tel Aviv, Israel
**Award:** Research Grants
**Term:** 4/1/2016-4/31/2020
**Funding:** $1,031,478
**Title:** Virtual Reality-treadmill combined intervention for enhancing mobility and cognitive function in patients with Relapsing-Remitting Multiple Sclerosis
**Summary:** Researchers at the Tel Aviv Sourasky Medical Center, Israel and the University of Illinois at Urbana-Champaign are conducting a trial to test a rehabilitation strategy that addresses walking and thinking issues in a single, integrated approach.

**Background:** Problems with walking become exaggerated when people with MS try to walk while doing something else (such as talking to a friend). Traditional rehabilitation methods treat walking and thinking as independent symptoms. Exciting preliminary work by Dr. Hausdorff's group suggests that a rehabilitation strategy that simultaneously addresses walking and thinking in a single, integrated approach has the potential to improve both symptoms and enhance the quality of life for people with MS. This novel approach combines treadmill training with virtual reality simulations to implicitly teach patients to walk safely, think, and multi-task.

**The Study:** The goal of this project is to confirm pilot findings on a larger group of people in a well-controlled study, to compare treadmill training in the virtual environment against conventional treadmill training, and to evaluate whether benefits last at least 3 months. This study will be conducted in Illinois and Tel Aviv. About 144 individuals with MS will participate. The active control group will complete 18 sessions of progressive (i.e., increasing difficulty) treadmill training over 6 weeks. The experimental group will complete 18 sessions of progressive treadmill along with virtual reality training over 6 weeks. Walking, thinking, and quality of life will be tested before and after the intervention.

**What's Next:** This trial could change approaches to MS rehabilitation, leading to better care and quality of life, and lower costs.

**Lauren Krupp, MD**
New York University
New York, NY
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2020
**Funding:** $1,046,675
**Title:** The neurodevelopmental influence of pediatric versus adult onset MS on cognition
**Summary:** Researchers are studying how MS affects cognitive abilities in children and adolescents, to help guide interventions.

**Background:** MS can cause problems with attention, concentration and learning. For younger children, the potential risk for cognitive impairment is particularly important as they are still in the process of development and completing their education. This project addresses the concern of cognitive problems in these younger children with MS by identifying who is at risk, to help guide interventions.

**The Study:** The study will involve the Network of U.S. Pediatric MS Centers, and will enroll 150 individuals with pediatric-onset MS, a group of 100 similarly aged controls without MS, and a group of 100 individuals with adult-onset MS. All study participants will undergo a cognitive assessment at the beginning, and then again after 2 years. The investigators will determine whether there are differences between those with pediatric onset MS and those of a similar age who don't have MS, and whether there are changes in cognitive function two years later. These results will be compared to see how changes differ between those with pediatric versus adult onset MS, and the investigators will identify factors that can help predict who among those with pediatric onset MS are at risk for cognitive decline.

**What's Next:** These results will also provide key groundwork for developing future rehabilitative strategies, as have been established for other pediatric conditions. The data gathered will explain how MS affects cognitive development, and can guide families, educators, and health care providers in optimizing these children's care.

## RESTORE—Preclinical Drug Development

**Barbara Slusher, PhD**
Johns Hopkins University
Baltimore, MD
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $654,165
**Title:** Development of 2-PMPA prodrugs for the treatment of cognitive impairment in multiple sclerosis
**Summary:** Researchers at Johns Hopkins University are developing versions of a promising compound for possible use in improving cognitive function in MS.

**Background:** People with MS and cognitive impairment are at greater risk for difficulties and conflicts affecting employment, social relationships and activities of daily living. No treatments are approved yet to prevent or treat MS-related cognitive impairment. Prof. Barbara Slusher's team has shown that inhibiting a molecule called "GCPII" dramatically improved cognitive performance in a mouse model of MS. However, it required very high doses administered by injection into the abdomen.

**The Study:** Now this team is attempting to create an oral version of the GCPII inhibitor that could be used by people with MS, if shown to be safe and effective. They have assembled an experienced drug discovery team with deep expertise in GCPII pharmacology, synthetic chemistry, drug metabolism and pharmacokinetics, and animal models of MS and cognition. The team will synthesize 20 to 30 new compounds and evaluate their drug metabolism and pharmacokinetics profile in mice using a systematic screening strategy. Promising candidates will then be tested in a mouse model of MS cognition.

**What's Next:** Successful completion of this project could lead to clinical trials aimed at proving safety and benefits of a novel therapy to treat cognitive deficits.

## RESTORE—Nervous System Repair

**Fu-Dong Shi, MD, PhD**
St. Joseph's Hospital and Medical Center
Phoenix, AZ
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $438,900
**Title:** Neurorepair following brain inflammation

**Summary:** Researchers are investigating a type of cell that may play a role in inhibiting nervous system repair in MS, for clues to restoring function in people with MS.

**Background:** The central nervous system (brain and spinal cord) has a unique environment that allows intimate interactions between brain cells and immune cells. During an immune attack such as occurs in MS, these interactions can determine the magnitude of damage to nervous system tissue, and perhaps play critical roles in shaping subsequent repair mechanisms. Dr. Fu-Dong Shi and colleagues are seeking to understand how Natural Killer (NK) cells, a type of immune cell, participate in these interactions. They have developed unique tools that allow them to track NK cells following their recruitment into the brain and study their interaction with brain cells during MS-like disease in mice, and MS itself. Using these tools, they have found that NK cells remain in the brain of people with MS and in mice with MS-like disease during the recovery phase of the disease. Eliminating NK cells in mice was found to significantly improve their recovery.

**The Study:** Based on these findings, the team is studying whether the NK cells that are retained in the brain inhibit brain repair mechanisms. To test this idea, they are investigating the mechanisms by which NK cells are retained in the brain during recovery from MS-like disease in mice. They are also examining the mechanisms by which NK cells may interfere with repair, and determining if manipulating or inhibiting NK cells can turn on natural repair processes.

**What's Next:** Unveiling new mechanisms that control repair after brain inflammation may translate into novel approaches to promote natural nervous system repair in MS.

## RESTORE— Myelin Biology

**Kae-Jiun Chang, PhD**
University of California, San Francisco
San Francisco, CA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $175,431
**Title:** Manipulation of membrane remodeling to maximize CNS remyelination
**Summary:** Investigators at the University of California, San Francisco are examining membrane-curving proteins that may play a role in making nerve-insulating myelin, and that may be targets for improving myelin repair in people with MS.

**Background:** In MS, myelin in the brain and spinal cord is attacked and damaged. Myelin is the fatty substance that surrounds and protects nerve fibers, and nerve fibers that have lost their myelin do not function properly and are more vulnerable to damage. Improving myelin repair and preventing further damage are important strategies for treating MS. Our knowledge is limited about factors in the brain that may induce or inhibit myelin repair.

**The Study:** Dr. Chang is working to understand aspects of how myelin synthesis occurs normally and to identify possible therapeutic targets to increase myelin repair in diseases such as MS. The cells in the brain that make myelin are called "oligodendrocytes." Dr. Chang and his team are examining the ability of oligodendrocytes to make myelin when potentially important factors are removed from the cells, or present at higher than normal levels. Initial studies are being done with oligodendrocytes grown in lab dishes, and later studies will focus on myelin growth in mice.

**What's Next:** Increased understanding of how various factors affect the myelin-making process will suggest ways to manipulate these factors to improve myelin repair and function in people with MS.

**Judith Grinspan, PhD**
Children's Hospital of Philadelphia
Philadelphia, PA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $583,760
**Title:** A key role for sterol regulatory element binding proteins in myelination
**Summary:** Researchers at Children's Hospital of Philadelphia are investigating the role of a specific protein in myelin regeneration for clues to restoring function in people with MS.

**Background:** In the course of multiple sclerosis, the myelin sheath that surrounds and protects nerves and is necessary for the transmission of nerve impulses is destroyed in areas of the brain and spinal cord. Myelin is made by cells called "oligodendrocytes," and these cells may also be harmed during MS. The brain contains immature cells and stem cells that are able to become oligodendrocytes and make new myelin, but natural repair falls short in MS. Research suggests that conditions in the brain around the destroyed myelin must be right to make new myelin. Dr. Judith Grinspan and colleagues are trying to figure out what these conditions are and how to encourage myelin to regenerate.

**The Study:** Dr. Grinspan's team is studying a protein called "sterol regulatory element binding protein (SREBP)," which controls the synthesis of cholesterol and other lipids all over the body. Preliminary experiments show that this protein can be detected in oligodendrocytes and if it's inhibited, the oligodendrocytes do not form new myelin. Now they are

# 11 New Pilot Projects Take Aim at MS

One way the Society propels the knowledge to end MS 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, 2016.

## STOP

**Judith Greer, PhD** (The University of Queensland, Brisbane, Australia) is investigating a novel target for stopping the immune attack in MS.

**Jae Lee, PhD** (University of Miami, Miami, FL) is investigating a novel strategy in mice that may yield a solution for primary progressive MS.

**Stefano Morara, PhD** (Consiglio Nazionale delle Ricerche, Rome, Italy) is studying a strategy for stopping progression in a mouse model of progressive MS.

**Ashlee Moses, PhD** (Oregon Health & Science University, Portland, OR) is testing a novel strategy for stopping infection from triggering an immune attack in a model of MS.

**Kevin O'Connor, PhD** (Yale University School of Medicine, New Haven, CT) is exploring components of the immune system that may age prematurely in people with MS, for clues to stopping the immune attack in this disease.

**David Sabatini, MD, PhD** (Whitehead Institute for Biomedical Research, Cambridge, MA) is exploring the mechanism of action of one therapy approved to treat people with MS.

**Mari Shinohara, PhD** (Duke University Medical Center, Durham, NC) is exploring an immune system molecule that protects mice from developing MS-like disease.

## RESTORE

**Alexander Aruin, PhD (**University of Illinois at Chicago, Chicago, IL) is investigating a method of improving balance in people with MS.

**Valentina Fossati, PhD** (The New York Stem Cell Foundation) is using novel technology to generate human myelin-making cells in the laboratory, for clues to stimulating MS repair.

**Lana Harder, PhD** (The University of Texas Southwestern Medical Center, Dallas, TX) is using an online system to ensure neuropsychological care of children and teens with MS.

**Ivan Molton, PhD** (University of Washington, Seattle, WA) is exploring whether a specific type of counseling can help people newly diagnosed with MS to cope with the unpredictable nature of the disease.

studying this protein further in oligodendrocyte precursors in lab dishes and in a mouse model in which the SREBP protein is inactivated in oligodendrocytes. This research may reveal novel ways of bypassing inhibitors that could turn on myelin repair.

**What's Next:** These studies can reveal novel strategies for facilitating myelin repair and restoring function to people with MS.

**Qing Lu, PhD**
Children's Hospital Medical Center
Cincinnati, OH
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $698,639
**Title:** Long non-coding RNA control of CNS myelination and remyelination
**Summary:** Researchers are investigating the possible role of a type of molecule called long noncoding RNA that may regulate repair of myelin, which is destroyed in MS.

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers, leading to disabilities in people with the disease. Encouraging myelin repair is thought be an important strategy for retaining and restoring function. Myelin is synthesized by cells called oligodendrocytes. Myelin repair is incomplete in MS, at least in part because not enough oligodendrocytes are produced from the pool of immature cells. Thus, identifying factors that promote maturation of oligodendrocytes is important for myelin repair.

**The Study:** Dr. Lu and his team are studying a type of RNA molecule called "long noncoding RNAs." Rather than encoding information to make a protein, long noncoding RNAs may regulate cellular functions. Dr. Lu and his group have identified several long noncoding RNAs that are specifically expressed in oligodendrocytes. They are now investigating the function of these RNAs during normal development and in a model of myelin injury. They are able to over-produce or delete specific long noncoding RNAs in mice in different cell types and different stages of development and then are studying what happens to oligodendrocytes during growth and under conditions of myelin injury.

**What's Next:** This work may identify long noncoding RNAs as factors that regulate oligodendrocyte maturation and thus, myelin repair, and may show that long noncoding RNAs are a target for new therapies in MS.

**Kelly Monk, PhD**
Washington University School of Medicine
St. Louis, MO
**Award:** Harry Weaver Neuroscience Scholarship
**Term:** 7/1/2016-6/30/2020
**Funding:** $521,022
**Title:** Molecular mechanisms that govern oligodendrocyte biology
**Summary:** Researchers are investigating how certain genes control the formation of nerve-insulating myelin, for clues to developing myelin repair strategies.

**Background:** In MS, myelin in the brain and spinal cord is a target of the immune attack. Despite the importance of myelin for proper nervous system function, we do not fully understand how it is formed in normal development, or how to promote its regeneration in diseases like MS. Dr. Kelly Monk and col-

leagues have discovered two genes that control myelin development, though it is unclear exactly how these genes function. These two genes may represent excellent therapeutic targets for future approaches in myelin repair. To lay the foundation needed to target these genes, the team is attempting to understand their normal function in development and remyelination, and to find compounds that target at least one of the genes to stimulate myelin repair.

**The Study:** This project focuses on two models for studying myelin—zebrafish and mice. Both have myelin similar to human myelin, and each model has specific strengths that will allow the team to complete their goals. The developing zebrafish are transparent, allowing researchers to see with incredible resolution the development of the cells that make myelin as well as myelin itself. Dr. Monk and colleague are examining the nervous system in normal and mutant zebrafish to elucidate how the two novel genes function. Since zebrafish live in water, the investigators can deliver compounds directly to their water to find ones that can drive remyelination. In mice, the team is able to remove the genes specifically from one type of cell (instead of every cell in the animal) to fully understand how these genes function. They also are using mice to test the promising compounds they discover in zebrafish.

**What's Next:** This work may uncover fundamental mechanisms that regulate myelin formation and repair, highlighting novel targets that could lead to the development of strategies to repair myelin and restore function to people with MS.

**Sarah Moyon, PhD**
Icahn School of Medicine at Mount Sinai
New York, NY
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $175,431
**Title:** Investigating the role of DNA methylation and hydroxymethylation in adult oligodendrocyte progenitor cells during remyelination

**Summary:** Researchers at the Icahn School of Medicine at Mount Sinai in New York are investigating age-related changes to genes that may affect the maturation of cells needed to repair myelin, which is damaged in MS.

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function properly, leading to symptoms in people with the disease. Treatments to improve myelin repair will be needed to restore function. The cells that make myelin in the brain and spinal cord are called oligodendrocytes. These cells are derived from a pool of immature cells called "oligodendrocyte precursor cells" or OPCs.

Gene sequences can be modified by the addition of natural chemicals called methyl groups and hydroxymethyl groups. These modifications often determine whether the gene can be switched on or off. Methylation and hydroxymethylation change with age, especially in brain tissues, where the myelin repair capacity also declines with age.

**The Study:** Dr. Moyon and her colleagues are asking whether changes in methylation and hydroxymethylation affect the myelin repair capacity in relation to age. First, they are looking at how methylation and hydroxymethylation are regulated during myelin repair in OPCs from old and young mice with myelin damage. They are also looking at the enzymes involved in adding methyl and hydroxymethyl groups to determine their role as OPCs evolve into mature oligodendrocytes.

**What's Next:** Results from these experiments may suggest ways to improve myelin repair in people with MS.

**Julia Patzig, PhD**
Icahn School of Medicine at Mount Sinai
New York, NY
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $182,327
**Title:** The impact of nuclear structure on oligodendrocyte development and pathology.
**Summary:** Researchers are asking whether a molecule called LmnA, which is present in the nucleus of many cells including those that make myelin, is involved in normal myelin synthesis and in the loss of myelin in people with MS.

**Background:** In MS, the fatty substance that surrounds and protects nerve fibers, called myelin, is attacked and destroyed. In addition, myelin-producing cells do not function properly. Myelin repair is inefficient in MS and insufficient to restore function. Therefore, although current therapies for MS stop the attack on myelin, they do not promote myelin repair and function of myelin-producing cells. Such therapies are needed to improve function in people with MS.

The DNA present in the nucleus (control center) of cells is organized by a network of proteins. The interactions between the DNA and proteins affects whether genes are turned on or off. Previous studies have shown that in people with MS, the DNA-protein network is altered. These alterations may ultimately affect the myelin repair and maintenance process.

**The Study:** Dr. Patzig and colleagues are investigating a protein called "LmnA", which is part of the DNA-protein network. They are testing whether myelin maintenance is impaired in mice that lack LmnA in cells that make myelin and support the function of nerve fibers. They are also determining what regions of DNA interact with LmnA, and exploring whether the abnormal changes in mice that lack LmnA are also present in tissue samples from the brains of people with MS.

**What's Next:** LmnA or the genes affected by alterations in LmnA function may be targets for future therapies aimed at improving myelin maintenance and repair in people with MS.

## RESTORE— Neurophysiology

**Bart Rypma, PhD**
The University of Texas at Dallas, TX
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2019
**Funding:** $492,792
**Title:** The Effect of Neural-Vascular Coupling Changes on Cognitive Performance in Multiple Sclerosis
**Summary:** University of Texas, Dallas researchers are seeking to understand biological mechanisms that underlie MS "brain fog" as a path toward finding solutions to cognitive problems in MS.

**Background:** People with MS can experience an overall slowing of thought, or "brain fog," also known as cognitive slowing. Little is known about the biological basis of cognitive slowing in MS. The damage that occurs to the brain and spinal cord in MS can be associated with changes in blood flow. Bart Rypma, PhD, and his team are investigating whether these changes limit the availability of oxygen to brain cells, resulting in cognitive slowing.

**The Study:** Dr. Rypma and colleagues are comparing people with MS and people without MS using advanced MRI techniques and psychological testing. They are measuring blood oxygen levels, cerebral blood flow, and other factors and assessing the possible relative contributions of each system to MS-related cognitive slowing.

**What's Next:** This project will yield new discoveries regarding the mechanisms that may be responsible for cognitive slowing in MS and guide the search for solutions to cognitive problems.

## 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

**Kathryn Fitzgerald, ScD**
Johns Hopkins University
Baltimore, MD
**Award:** Postdoctoral Fellowships
**Term:** 7/1/2016-6/30/2019
**Funding:** $187,527
**Title:** Integrative Analysis of Multiple Sclerosis Risk and Progression
**Summary:** Researchers at Johns Hopkins are conducting studies characterizing how vitamin D protects individuals from getting MS and looking at genetic predictors of changes and progression in MS using measures of the eye.

**Background:** Both genetic and environmental factors affect whether a person will develop MS and how the disease progresses. Vitamin D can regulate hundreds of genes and may protect against MS. In addition, genetic factors may predict disease progression. Few studies have explored genetic factors that predict progression in MS.

# New Funding for Network of Pediatric MS Centers

**Title:** The Network of Pediatric MS Centers
**Term:** 7/1/16 - 6/30/19
**Grant Amount:** $3,000,000 of additional funding
**Lead Investigator:** Theron Casper, PhD, University of Utah

The Network of Pediatric MS Centers (NPMSC) was launched with Society funding in 2006 to set the standard for pediatric MS care, educate the medical community about this underserved population, and create the framework to conduct critical research—both to understand childhood MS and to unlock the mysteries of MS in adults. This initiative, funded through the Society's Promise: 2010 campaign, laid the groundwork for current studies by the NPMSC to measure clinical and cognitive manifestations of early-onset MS, and track environmental and genetic triggering. In contrast to adult MS, pediatric MS appears to have a narrower window of onset with more rapid and pervasive cognitive symptoms, which need to be better understood if effective treatments are to be provided.

The Society's renewed investment supports research activities of individual centers and the University of Utah Data Coordinating and Analysis Center, which is responsible for patient registry and center collaboration. Funding for the network provides essential infrastructure to facilitate research, including searching for the cause of MS by studying risk factors for the disease in children, close to the time of exposure. It also gives NPMSC members the chance to leverage additional funding sources for specific research questions.

The Network of Pediatric MS Centers currently includes **Children's Hospital Boston, Cleveland Clinic, Loma Linda University, Massachusetts General Hospital, The Lourie Center for Pediatric MS at Stony Brook University, Mayo Clinic College of Medicine, State University of New York at Buffalo, New York University Langone Medical Center, Texas Children's Hospital, University of Alabama at Birmingham, University of California San Francisco, the University of Colorado,** and **Washington University in St. Louis.**

This strategic investment provides the infrastructure and research support needed to keep this unique network—with the largest group of well-characterized pediatric MS cases in the world—moving forward. The network will continue to systematically expand to other centers to enhance research efforts.

**The Study:** Dr. Fitzgerald and her team are asking if vitamin D differently affects levels of groups of blood-based metabolites, which are molecules that are produced or are needed for various reactions in the body in people with MS who take vitamin D supplements and people who take supplements and do not have MS. These metabolites can be affected by supplements but also are influenced by genetic and other environmental factors. The team is exploring the relationship among vitamin D, metabolites, and genetic factors for clues to changes that may be protective against MS. The team is also looking at changes in the eyes of people with MS whose genetic makeup has been characterized. The participants will undergo a test called optical coherence tomography to see how damage to the nerves in the back of the eye changes over time and how these changes might be related to genetic differences.

**What's Next:** Results from the vitamin D study may suggest ways to treat or prevent MS, and results from the visual monitoring study may help explain why MS progression varies among individuals.

**William Housley, PhD**
Yale University
New Haven, CT
**Award:** Career Transition Fellowships
**Term:** 7/1/2016-6/30/2020
**Funding:** $589,849
**Title:** Human genetic variation in NFkB signaling in multiple sclerosis risk and progression
**Summary:** Researchers are tracing the influence of genes on immune cell activity for clues to stopping or preventing MS.

**Background:** Research suggests that no single change in a gene or a single environmental factor leads to MS, but rather a combination of genetic and environmental factors contribute to risk. If we can identify how genetic and environmental changes lead to changes in immune responses and ultimately to MS, we may be able to identify novel targets to block disease development.

**The Study:** William Housley, PhD, and colleagues have developed a new approach to understand how subtle changes in genes may lead to the risk of developing MS. Using this approach, they previously confirmed a primary role for the protein "nuclear factor kappa-B," which controls the "transcription" of DNA (a process that results in a change of cell function). They are now studying how nuclear factor kappa-B signaling changes the responses of immune cells that are known to be involved in disease progression, including CD4 T cells, regulatory T cells, and monocytes. These studies are being performed with cell samples from people MS and people who do not have MS.

**What's Next:** The strategy used by these investigators offers a roadmap for tracing the influence of genes on cell activity, and promises new insights for interrupting the MS disease process and ultimately preventing MS.

**Jorge Oksenberg, PhD**
University of California, San Francisco
San Francisco, CA
**Award:** Research Grants
**Term:** 4/1/2016-3/31/2017
**Funding:** $165,000
**Title:** Cell-specific microRNA profiling and function in experimental autoimmune encephalomyelitis
**Summary:** University of California, San Francisco investigators are using new methods to study a group of molecules called miRNAs specifically in myelin-making cells to understand if they may be useful targets for gene therapy to treat MS.

**Background:** In MS, myelin, the fatty substance that surrounds and protects nerve fibers, is damaged. The cells in the brain and spinal cord that make and repair myelin are called "oligodendrocytes." Molecules called "micro RNAs" or "miRNAs" play a role in controlling gene activity, and as such play an important regulatory role in oligodendrocyte function. The study of abnormal changes in miRNAs in oligodendrocytes may provide new information about what goes wrong in MS and suggest ways to correct those problems.

**The Study:** In the first part of the study, Prof. Oksenberg and his team are using a new method called "miRAP" to isolate and study miRNAs exclusively from oligodendrocytes in mice with the MS-like disease EAE, at different stages of the disease. In the second part of the study, they are using these isolated miRNAs to assess whether they can be used as targets to improve EAE in mice.

**What's Next:** Results from this novel study could be used to design gene therapy treatments to improve MS.

**"New Research" is published by the National MS Society, 733 Third Avenue, New York, NY 10017.**