

# NEW RESEARCH



STOP. RESTORE. END.

## Society Commits Over \$25 Million for 51 New MS Research Projects

The National MS Society has just launched up to 51 new MS research projects, with multiyear commitments totaling over \$25 million. These new awards are part of a comprehensive research strategy aimed at stopping MS, restoring function, and ending MS forever.

- This commitment is the latest in the Society's relentless research effort, investing \$44 million in 2012 alone to support over 350 new and ongoing studies to move closer to a world free of MS.
- The Society's longstanding investment in basic and translational research has resulted in new treatments and better diagnosis and disease management for people with MS.
- The Society continues to pursue all promising paths that lead to solutions for everyone affected by MS.
- When we make research commitments that span into future years, the money is not yet in hand to meet those needs. Contributions to the Society's NOW Campaign to support these projects are essential to ensure that this important research continues in future years.

The new projects include these, described in more detail in the following pages:

### STOP MS:

- A clinical trial to determine if green tea added to standard MS therapy can slow nervous system damage (page 2);
- A large, cross-disease consortium to screen therapies that may have potential for protecting the brain from degeneration (page 5).

### RESTORE:

- Cutting-edge efforts to transform normal adult body cells into nervous system stem cells that may be used to stimulate repair of nervous system tissues in MS (page 9);
- Tests of an innovative rehabilitation program to improve balance and movement in people with MS (page 19).

### END MS:

- A novel search for genes that influence who gets MS in the Hispanic/Latino population (page 24).

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Fast Forward

**STOP MS**

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

**STOP -Therapies****Jesus Lovera, MD, MSPH**

Louisiana State Univ. Health Sciences Center  
New Orleans, LA

Award: Research Grant

Term: 10/1/12-9/30/14; Funding: \$359,516

Title: "Safety and neuroprotective effects of polyphenon E in MS"

Summary: Investigating a novel complementary therapy to slow or stop progressive nerve damage in MS.

The initial disabilities of MS result from the damage and destruction of myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord. Nerve fibers that have lost myelin become susceptible to damage, and may die, leading to progressively increasing disability. Current MS treatments reduce immune attacks, but it is not yet clear how much they protect the nerve fibers and nerve cell bodies (neurons) from damage. Much of this damage is thought to be due to chemicals known as "free radicals" that affect mitochondria, the "power houses" of cells.

Jesus Lovera, MD, is investigating whether a strong anti-oxidant found in polyphenon E,

isolated from green tea, can slow the progression of MS. Previous work indicates that a component of polyphenon E reduces the loss of nerve cells in mice with EAE, a disease similar to MS. Now Dr. Lovera and colleagues are using a modified MRI test in a clinical trial to see whether polyphenon E alters the rate of nerve damage in people with MS who are taking one of the standard MS drugs such as interferon beta or glatiramer acetate.

This research could show whether treatment with a well-tolerated anti-oxidant can slow or prevent destruction of nerve cells that leads to long-term progression in MS.

**Gavin Giovannoni, MD, PhD**

Queen Mary and Westfield College  
London, UK

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$779,538

Title: "CSF neurofilaments: a novel phase IIa neuroprotective trial in early SPMS"

Summary: Can a protein in spinal fluid serve as a signal that shows whether a therapy tested for secondary-progressive MS can protect the nervous system?

The initial effects of MS come from damage to myelin, the material that protects nerve fibers, in the brain and spinal cord. Nerve fibers that have lost their myelin coating may also be destroyed, leading to long-term deficits in people with MS.

Following up his studies as a team leader in the National MS Society's Nervous System Repair and Protection Initiative, funded by the Promise: 2010 campaign, in this project Gavin Giovannoni, MD, PhD, is investigating whether the amount of neurofilament protein in the spinal fluid reflects the effects of therapies that may prevent nerve fiber destruction.

Neurofilament (NF) protein is released into the spinal fluid in conditions that cause nerve damage, including MS. Dr. Giovannoni's team



is comparing levels of NF in the spinal fluid of two groups of people with early secondary-progressive MS. One group is treated with oxcarbazepine, an epilepsy therapy that reduces nerve damage in a model of MS. The other group receives inactive placebo. Both groups are continuing current treatment with a standard MS therapy.

The results of this research could provide a new way to measure the ability of therapies to protect the nervous system from MS damage, which would speed the search for ways to stop MS.

### **Jared Bruce, PhD**

University of Missouri - Kansas City  
Kansas City, MO

Award: Health Care Delivery Contract  
Term: 10/1/12-9/30/14; Funding: \$292,470  
(Pending)

Title: "Development of a motivational intervention to improve treatment adherence in MS"

Summary: A strategy to help people with MS re-start their MS medication if they have stopped.

Research shows that many people who have MS do not take their medications as prescribed. Discontinuing medication prescribed by a healthcare provider may cause MS symptoms and disease activity to worsen.

Jared Bruce, PhD, and team are attempting to improve how people adhere to their prescribed medications by developing a "talk therapy." The purpose of the study is to better understand why people stop taking medications and develop a more effective way for healthcare providers to discuss medications with their patients. This five-session talk therapy protocol is done over the phone and is designed to help people weigh the pros and cons of re-starting therapy. Dr. Bruce and team are assessing whether the therapy will

improve medication adherence in MS when compared to people who receive no intervention.

Results from this study could contribute to efforts to improve quality of life for people with MS, as well as reduce MS disease activity and healthcare costs.

### **E. Ann Yeh, MD**

The Hospital for Sick Children  
Toronto, Ontario, CA

Award: Health Care Delivery Contract  
Term: 10/1/12-9/30/15; Funding: \$565,925  
(Pending)

Title: "Treatment adherence in pediatric multiple sclerosis"

Summary: Finding ways to improve the rate at which children and adolescents with MS take their medications as prescribed.

MS occurs in children and adolescents as well as in adults. Although available therapies are thought to be generally safe and effective in pediatric cases, it appears that up to half of children diagnosed with MS don't take their medication as prescribed.

Dr. E. Ann Yeh and collaborators are investigating a strategy to improve the rate of children taking their MS therapies as prescribed. To do this, they will conduct a clinical trial. All children in the study will be given an electronic monitoring device that keeps track of when they receive their medication. Half the children in the study will receive feedback from the device and an individual using motivational interviewing techniques, and half will receive only the device and no information from it. The investigators hope that this feedback will increase the tendency to take medication as directed. Dr. Yeh is also looking for the reasons why children sometimes do not take their medications.

This research will increase our understanding of reasons why children and adolescents



do not always take their medication as prescribed, and may identify ways to increase the rate of adherence to therapy. Doing so is believed to improve function and reduce future complications.

### **STOP - Health Care Delivery**

#### **Sarah Minden, MD**

Brigham and Women's Hospital  
Boston, MA

Award: Health Care Delivery Contract  
Term: 10/1/12-9/30/15; Funding: \$698,337  
(Pending)

Title: "Financial implications of informal (unpaid) caregiving"

Summary: The economic impacts for family members who provide care to people with MS.

As MS progresses, people with the disease require more care that is often provided informally by caregivers who are often family members. Little is known about the financial aspects of this type of "informal" care.

Dr. Minden and colleagues are conducting a comprehensive analysis of the various types of costs to informal caregivers. They are investigating factors such as lost income, lost promotions, education, and training opportunities, costs incurred if a caregiver develops mental or health problems, and costs incurred if the caregiver becomes ill and the person with MS requires more "formal" (paid) care. They are analyzing new and existing data from various interview-based studies.

The results of this study will help guide policymaking decisions and will ultimately increase the quality of life and quality of care for both people with MS and their caregivers.

#### **Deborah Miller, PhD**

Cleveland Clinic  
Cleveland, OH

Award: Health Care Delivery Contract  
Term: 10/1/12-9/30/14; Funding: \$369,120  
(Pending)

Title: "INFORMS: Improving Neuro-QOL's functionality for outcomes research in MS"

Summary: Developing a way to assess MS symptoms with a standardized patient-reported questionnaire.

The physical, cognitive, and emotional symptoms of MS have a major impact on quality of life. People with MS often report their symptoms during research and doctor visits. These reports provide important information beyond tests such as MRI or neurological exams. However useful this information is, self-reported questionnaires are not standardized nationwide, which would make them more powerful tools to track MS impacts.

Deborah Miller, PhD, and colleagues are working to improve self-reported questionnaires. They are working with an initiative called Neuro-QOL that will help measure these outcomes in people with neurological disorders including MS. Dr. Miller is making Neuro-QOL useful for assessing MS by studying enough people with MS and by standardizing what the scores from Neuro-QOL will mean for people with MS so they can be used across the country and the globe. They are measuring four types of MS symptoms: upper extremity function, mobility, fatigue, and sleep disturbances.

These results will provide a new tool for assessing quality of life and MS symptoms, and would be an important addition to the evaluation of results of clinical trials in people with MS.



## Two New Collaborations to Propel Discoveries for Progressive MS

### MS-STOP Clinical Trial in Secondary-Progressive MS

The National MS Society is providing co-funding for an innovative new clinical trial to test the ability of multiple compounds to slow or stop MS progression in people with secondary-progressive MS, a course of worsening that occurs after relapses and remissions have subsided. This clinical trial addresses an unmet urgent need, with the potential of identifying a therapy to stop MS in its tracks.

- The trial will be conducted by the MS Clinical Trials Network, recently established by the MS Society in the United Kingdom.
- The network has selected four potential therapies that may have nerve-protecting properties and they are now going to be tested at the same time in an advanced adaptive study design that will ultimately determine which of these therapies are most promising.
- The therapies under testing are Ibudilast, Amiloride, Pirfenidone and Riluzole, each of which target different key pathways implicated in MS related neurodegeneration.
- In the first stage, there are 5 groups, each of 70 participants with SPMS, who will receive one of the 4 drugs or placebo. If any of these drugs show a clear effect they will be carried on to stage 2 equivalent to a definitive Phase III trial.
- If Stage 2 proceeds, up to a further 1515 SPMS participants will randomly receive one of the continuing drugs, or placebo, for 3 years, to determine if either drug is clinically effective and shows a change in disability over placebo.

### Collaborative CNS Screening Initiative

The National MS Society is joining forces with the Alzheimer's Drug Discovery Foundation and Beyond Batten Disease Foundation to support a shared resource for discovering drugs active against nerve degeneration.

- With multiple academic drug discovery centers in the US and around the world developing compounds to treat disorders of the brain and spinal cord, there is an opportunity to pull together a "library" of compounds from a wide variety of programs that have activity in the brain.
- This collaborative project involves funding from over a dozen institutions focused on the goal of finding new therapies to protect the nervous system from degeneration.
- The idea is for groups engaged in drug discovery deposit into a central repository compounds that have shown significant brain-relevant activity.
- This relatively small but highly selective library of active and relevant compounds will then be made available to academic drug discovery centers with the intention that they each include the shared library in their ongoing screening.
- This collaborative program includes several steps to simplify the exchange of compounds without the need for lengthy agreements or licensing arrangements.
- This initiative is intended as a low cost and administratively simple way to maximize drug discovery efforts within the neuroscience community.



## STOP - Measuring MS Disease Activity

### Laura Balcer, MD

Transferring to New York University  
New York, NY

Award: Research Grant

Term: 10/1/12-9/30/16; Funding: \$1,100,000  
(Pending)

Title: "Mechanisms of retinal neurodegeneration and visual pathway axonal loss in MS"

Summary: Scanning the eye for clues to understanding nervous system damage and to track repair in MS.

People with MS experience many types of symptoms, including vision problems and vision loss. The eyes in people with MS can be affected by inflammation and also by the loss of nerve cells.

Laura Balcer, MD, and colleagues are using advanced imaging techniques, including optical coherence tomography (OCT) to examine what parts of the eye in people with MS undergo changes that ultimately lead to vision problems. These changes in eye structures appear in most people with MS, even those who do not notice vision problems or inflammation in the eye. Changes that occur in the eye in MS are likely similar to changes that occur in the brain in this disease. If this is correct, the eyes may represent a window for observing disease changes and for tracking the impact of treatments.

These results will help us further understand what happens in the eye and possibly the brain in MS, and may suggest new ideas to promote repair and recovery of function and quality of life in people with MS.

### Yulin Ge, MD

New York University School of Medicine  
New York, NY

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$470,246  
Title: "Brain oxygen metabolism and vascular reactivity in MS: Assessing neurodegeneration using MRI"

Summary: Using recently developed MRI techniques to investigate possible causes of nervous system damage in MS.

In people who have MS, immune system cells attack, damage and destroy myelin, the material that surrounds nerve fibers, in the brain and spinal cord. As MS progresses, nerve fibers that have been stripped of myelin and their nerve cells may die, leading to progressive disability. Not all of the factors that cause the death of nerve cells in people with MS are known.

Yulin Ge, MD, and colleagues are investigating the possibility that nitric oxide (NO) has a role in nerve damage in MS. Previous studies have shown that NO is increased in regions of immune system activity in MS. NO has two potential effects that could damage nerves: it can directly reduce the ability of nerve tissue to use oxygen, and it may disturb the normal blood and oxygen supply to areas where nerves are active. Dr. Ge and colleagues are using recently developed techniques related to MRI scanning to see whether the delivery and use of oxygen are altered in regions where MS damages nerves.

The results of this research could provide new insights into the nervous system damage that occurs in MS and possible ways to prevent it.



**Annette Langer-Gould, MD, PhD**

Kaiser Foundation Hospitals  
Pasadena, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$509,149

Title: "Modifiable risk factors of postpartum MS relapses"

Summary: Exploring factors that may affect the risk of an MS relapse after delivery of a child.

A woman's risk of a relapse of MS is reduced during the third trimester of pregnancy. However, the risk of relapse increases three-fold in the first four months after delivery (postpartum). If she chooses to breastfeed her baby, a woman with MS must delay resumption of the disease-modifying agents. Breastfeeding can also reduce levels of vitamin D, low levels of which have been linked to increased MS activity.

Annette Langer-Gould, MD, PhD, is investigating how breastfeeding affects the risk of MS relapses after delivery. Dr. Langer-Gould and colleagues are enrolling nearly 200 pregnant women with MS to investigate the effects of exclusive, partial, or no breastfeeding, and levels of vitamin D on the risk of MS relapses. In addition, they are reviewing the medical records of an additional 360 women with MS who have given birth previously. Among the factors they are measuring is whether there is a difference in relapse rate between women who breastfeed and women who do not and return to treatment.

The results of this research will provide new information for guiding pregnant women with MS about choices related to breastfeeding and how soon to resume disease-modifying treatments.

**David Pitt, MD**

Transferring to Yale Medical School  
New Haven, CT

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$459,905 (Pending)

Title: "Iron as biomarker for inflammatory activity in MS lesions"

Summary: Investigating the use of an advanced MRI technique to measure immune system activity in MS lesions.

In MS, immune system cells damage tissues in the brain and spinal cord. While standard magnetic resonance imaging (MRI) techniques reveals inflammation associated with blood brain barrier leakage (the lining of cells that protects the brain), they are insensitive to inflammatory activity behind a closed blood-brain barrier. An imaging technique that reveals inflammation more accurately would be very useful for assessing the inflammatory status of patients and for evaluating potential treatments for MS.

In this research project David Pitt, MD, is investigating an advanced MRI technique called gradient-echo phase imaging (GRE), which can detect iron in MS brain lesions (areas of damage). Large amounts of iron are present in some of the immune system cells that cause tissue damage. Dr. Pitt and colleagues are using a number of different approaches including examination of human autopsy material, laboratory models of MS as well as GRE phase imaging of patients in different stages of MS to obtain a clearer picture of the ability of iron-sensitive imaging to visualize MS immune activity.

The results of this research could lead to a new way to rapidly measure the effects of potential treatments against the inflammation that damages myelin, aiding the development of new therapies for MS.



### **Murali Ramanathan, PhD**

The Research Foundation of SUNY  
Buffalo, NY

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$704,784  
(Pending)

Title: "Lipoprotein and lipid metabolism in MS disease progression"

Summary: Understanding the role of cholesterol and related substances to guide diet and lifestyle choices that will improve disease outcomes in people with MS.

Approximately 25% of the body's cholesterol is present in the brain, and most of this cholesterol is present in myelin, the substance that protects the nerve fibers in the brain and that is one of the targets of destruction in MS. Cholesterol and related molecules are also important for immune responses.

Dr. Ramanathan and colleagues are taking advantage of large-scale, ongoing clinical trials to look at cholesterol and related molecules in people with MS. They are looking for a relationship between amounts of cholesterol and various cholesterol-related molecules found in blood and MS disease activity, disability progression, and brain integrity, which they are measuring with MRI scans and other techniques.

These results may allow better management of MS as they could be used to guide therapies, diet, exercise, and other lifestyle choices to reduce MS disease progression.



### **STOP, RESTORE - Neuroprotection**

### **Gabriela Constantin, MD, PhD**

University of Verona  
Verona, Italy

Award: Research Grant

Term: 10/1/12-9/30/14; Funding: \$138,000

Title: "Effect of metabolic intervention with pantethine on experimental autoimmune encephalomyelitis"

Summary: How a substance related to vitamin B5 can treat EAE, a model of MS.

Movement of immune system cells such as T cells from blood vessels into the brain and spinal cord is normally prevented by a structure known as the "blood-brain barrier" (BBB). However, in MS, T cells cross the BBB to attack and destroy nervous system tissues, leading to the symptoms of MS.

Gabriela Constantin, MD, PhD, is investigating how treatment with pentethine, a molecule related to vitamin B5, affects the MS-like disease EAE in lab mice. This work is based on the finding by Dr. Constantin and colleagues suggesting that pentethine reduces the severity of EAE. Now they are working to discover how pentethine affects the movement of T cells into the nervous system, and whether it can prevent tissue damage.

The results of this research project could contribute to the development of a new treatment for MS, since pentethine is already used for treating some other human diseases and appears to have few side effects.



**Gianvito Martino, MD**

San Raffaele Scientific Institute  
Milan, Italy

Award: Research Grant

Term: 10/1/12-9/30/14; Funding: \$311,992

Title: "Induced pluripotent stem cells as a potential source of autologous neural stem cells for multiple sclerosis therapy"

Summary: Transforming normal adult cells into nervous system stem cells that may be used as cells that can help stimulate repair of damaged myelin in MS.

The effects of MS are the result of immune system cells damaging and destroying myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord, and nerve fibers themselves even when the immune system attack is slowed by current treatments. Transplantation of neural stem cells (immature nerve cells) has variably shown to be able to protect from myelin and nerve fiber damage thus representing a promising and alternative therapeutic approach to MS. However, we still need to find a renewable source of these cells to foster bench-to-bedside translation of the pre-clinical work done so far.

Gianvito Martino, MD, and team are investigating the potential of a new type of stem cell, known as "induced pluripotent stem cells" or iPSCs, produced from adult body cells, to develop into neural stem cells that can repair damaged nerve fibers and myelin. This work follows on Dr. Martino's involvement as a team member of the National MS Society's Nervous System Protection and Repair Initiative, funded by the Promise: 2010 campaign. In one part of this project the team is studying mice with EAE, an experimental model of MS, to see how effective neural stem cells derived from iPSCs are at repairing damaged nerve fibers and myelin. They are also comparing characteristics of

iPSC-derived nerve cells and myelin forming cells from people who have MS to iPSCs from people who don't have MS to see whether they differ in their ability to develop into functioning nerve and myelin-forming cells.

The results of this research have great potential for understanding a new technique that may repair nerve fibers and myelin damaged by MS to restore function.

**Adam Kaplin, MD, PhD**

Johns Hopkins University Sch. of Medicine  
Baltimore, MD

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$615,298

Title: "Modulation of glutamate carboxy peptidase II activity to treat cognitive impairment in MS"

Summary: The potential of specific molecules as possible therapies for treating cognitive problems in MS.

When components of the brain and spinal cord are attacked and damaged by the immune system in MS, nerve fibers can fail to conduct signals correctly. In addition to causing mobility and balance problems, this damage can also impact cognitive (thought) processes, such as visual and verbal memory, concentration and processing speed.

Adam Kaplin, MD, PhD, is investigating the role of an enzyme called GCP II (glutamate carboxylpeptidase II), which is found on the surface of nerve fibers. Dr. Kaplin and colleagues became interested in GCP II when they found that a molecule it breaks down (N-acetylaspartyl glutamate, or NAAG) is found in higher concentrations in the brains of people with MS who do not show signs cognitive problems than in those who do. Now they are investigating this possible lead by studying the effects of molecules that increase the levels of NAAG by blocking the action of GCP II on cognitive behavior of mice with EAE, a



## Society and Critical Path Institute Create the MS Outcome Assessments Consortium

The National MS Society and Critical Path Institute have joined forces to launch the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) — a coalition of industry, academia, patient representatives, regulatory agencies, and the Society to develop new standards for assessing outcomes in clinical trials of MS therapies. Disease progression, or gradual worsening, experienced by people who have MS usually occurs over many years, and it is often difficult to track with the standard clinical measurement scales used by doctors to assess disease activity.

A task force that launched this initiative enlisted the help of the Critical Path Institute to create a cross-sector consortium to collect a database of aggregated clinical data from many MS clinical trials. Over the 4-year, \$3 million project, the MSOAC will enable collection of the data, which will then be standardized and analyzed to arrive at a consensus on the optimal measures for inclusion in a modified tool to track disability as a primary endpoint for future MS trials. This will then be advanced to the U.S. FDA and EMA (European Medicines Agency) for regulatory approval.

This effort should lead to a new way to measure MS progression to speed the development of new treatments for all types of MS, including progressive MS, for which there are few treatment options.

Read more: <http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=7171>

model of MS.

The results of this research could lead to the development of therapies that treat some of the cognitive problems experienced by people with MS.

### **Wensheng Lin, MD, PhD**

University of Minnesota  
Minneapolis, MN

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$572,022

Title: "Endoplasmic reticulum stress in immune-mediated demyelinating diseases"

Summary: Researching strategies to protect the nervous system and increase repair in MS to restore function.

Symptoms of MS occur in part because the immune system attacks and destroys myelin,

the fatty substance that protects nerve fibers. One idea for improving MS symptoms is to increase repair of myelin. The cells that make myelin in the brain that survive immune attacks in MS are only partially able to repair myelin because they experience biological stress during MS disease activity.

Dr. Lin and colleagues are studying strategies to relieve this biological stress. His team has found that activating specific processes inside myelin making cells (called the PERK-eIF2 $\alpha$  pathway) may protect them from MS damage. In this study they are determining whether protecting cells in this way can enhance their ability to regenerate and repair myelin to restore function.

Overall, results from these studies may provide new ideas for therapies to protect brain cells from MS damage and increase myelin repair.



**Fang Liu, MD, PhD**

University of Toronto  
Toronto, Ontario, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$450,000

Title: "Development of novel therapeutics for the treatment of multiple sclerosis"

Summary: Studying whether an experimental therapy can limit damage to nerve cells as a first step to develop a new treatment for MS.

The myelin sheath that surrounds and protects nerve fibers is damaged and destroyed in the brain and spinal cord by MS. Nerve fibers that have lost their myelin coating may also be damaged and destroyed, leading to long-term disability. An important unmet need in MS is finding ways to protect the nervous system from damage caused by MS.

A normal brain chemical called glutamate may play a role in nerve cell death in MS. Fang Liu, MD, PhD, is investigating whether a peptide (small fragment of protein) known as G-Gpеп can limit nerve cell damage by blocking a specific interaction between two proteins (namely, AMPA glutamate receptor and GAPDH) in nerve cells. Dr. Liu and colleagues are looking at the effects of G-Gpеп in mice with EAE, a disease similar to MS. Preliminary results show that G-Gpеп can limit or prevent nerve cell death in EAE and the researchers are now investigating the best doses, and time and route of delivery of the drug.

This research could eventually lead to testing of this potential treatment in people with MS with the idea of preventing nervous system damage.

**Stephen Stohlman, PhD**

Cleveland Clinic  
Cleveland, OH

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$573,177

Title: "IFN-g dependent astrocyte regulation of CNS autoimmunity"

Summary: The role of cells known as astrocytes in regulating immune activity and potential for nervous system repair in chronic progressive MS.

In people with MS, cells from the immune system damage myelin, the material that surrounds and protects nerve fibers in the central nervous system (the brain and spinal cord). In addition to nerve cells and the cells that make myelin, called oligodendrocytes, the brain and spinal cord contain cells known as astrocytes. Astrocytes have a number of roles, and they can produce chemical signals that influence the activity of immune cells, and both enhance and prevent repair.

Stephen Stohlman, PhD, and his team are investigating the roles astrocytes play in mice that have uncontrolled EAE, a disease similar to progressive MS. In previous work, Dr. Stohlman and colleagues found that astrocytes can help regulate immune attacks and the amount of tissue repair that occurs. Now the team is determining how astrocytes influence these vital functions in EAE and in lab dishes, and by implication, in MS.

The results of this research could provide new clues to treatments that target astrocyte functions to limit the damage done to the nervous system and stimulate repair to restore function in MS.



### **Linda Watkins, PhD**

University of Colorado at Boulder  
Boulder, CO

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$555,077

Title: "XT-101 for treatment of MS-related symptoms"

Summary: Investigating a new delivery method for an immune system molecule that could slow or stop MS attacks.

The immune system contains a number of different types of cell that ordinarily protect against foreign invaders, such as viruses or bacteria. Immune cells use many types of chemical molecules to signal each other and coordinate their actions. In MS, some immune system cells mistakenly attack the brain and spinal cord, causing tissue damage and a variety of neurological symptoms.

Linda Watkins, PhD, and team are investigating the potential of XT-101 to treat pain, gait problems and activity of mice with EAE, a model disease similar to MS. XT-101 is a compound made of slow-release microparticles that contain the DNA for an immune messenger chemical known as IL-10. Preliminary studies show that when it is injected early in the disease process, it can reverse some symptoms. They are now extending this work to understand the mechanisms underlying XT-101's effects and exploring its impacts at different stages of the EAE process, including in progressive stages that mimic secondary-progressive MS.

This research has the potential to lead to a new treatment for MS quite rapidly since XT-101 is already in early development for some types of pain.

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

#### **Estelle Bettelli, PhD**

Benaroya Research Institute  
Seattle, WA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$590,517

Title: "Identification of pathogenic T cells in EAE"

Summary: Exploring aspects of how immune cells are controlled by natalizumab for clues to improving therapies for MS.

In MS, immune cells enter the brain and spinal cord and attack brain components including myelin, the substance that protects nerve fibers. These attacks lead to disease activity. Current treatments for MS include natalizumab (Biogen Idec and Élan), believed to work by preventing harmful immune cells from entering the brain and spinal cord, thus dampening disease activity.

Dr. Bettelli and coworkers are trying to understand the effects of natalizumab in more detail. Natalizumab is associated with rare but severe infections because it also prevents normal immune system surveillance of the brain. Dr. Bettelli is exploring the target of natalizumab in more detail to understand how to design therapies that maintain normal immune system function while blocking the harmful effects of the immune system during MS.

Understanding how this current therapy works should enable the development of safer and more specific therapies for MS.



**Melissa Brown, PhD**

Northwestern University  
Chicago, IL

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$560,802

Title: "Meningeal mast cells as orchestrators of inflammation in EAE"

Summary: Identifying new targets for MS therapy that prevent immune cells from gaining access to the central nervous system.

The immune system is made of cells that circulate in the blood. Upon infection, these immune cells can enter most tissues causing inflammation that destroys the microbe. However in the CNS (central nervous system, brain and spinal cord), such inflammation often does more harm than good because it can also cause irreversible damage to nerves. To prevent this, the CNS has a specialized group of blood vessels called the "blood-brain barrier" (BBB) that normally limit what can leave the blood vessels and enter the brain and spinal cord. In Multiple Sclerosis, the blood-brain barrier does not function properly allowing immune cells to gain entry to the CNS and cause the disease.

Melissa Brown, PhD, is investigating how "mast cells" affect the BBB to allow other immune cells to cross this barrier and enter CNS tissues. Mast cells are a type of immune cell found in many locations of the body and have been studied primarily in allergic disease. In mice with an MS-like disease, Dr. Brown and her team have found that mast cells in the meninges, tissues that surround the CNS, release proteins that attract other immune system cells to the meninges and also open the BBB, allowing inflammatory cells to enter the CNS.

This research is dedicated to identifying targets that can be used new therapies to block the movement of T cells into the CNS and reduce or prevent damage to the nervous system in MS.

**Marina Cella, MD**

Washington University  
St. Louis, MO

Award: Research Grant

Term: 10/1/12-9/30/14; Funding: \$330,000

Title: "The role of plasmacytoid dendritic cells in T-cell mediated autoimmunity in the central nervous system"

Summary: Studying the role of a type of immune cell in MS, for clues to stopping MS in its tracks.

MS involves immune-system attacks against the brain and spinal cord. There are many types of immune cells that play different roles in making MS worse or better. "Plasmacytoid dendritic cells" are one type of immune cell whose role in MS is largely unknown.

Dr. Marina Cella and colleagues are examining the role of these cells and the substances these cells make in mice with EAE, an MS-like disease. They are looking at what happens to the disease course when these cells are missing. Early results suggest that these cells and probably the substances these cells make may be beneficial in MS.

Understanding how these cells work in MS may help design new therapies that will stop MS disease activity.

**Hongbo Chi, PhD**

St. Jude Children's Research Hospital  
Memphis, TN

Award: Research Grant

Term: 11/1/12-9/30/15; Funding: \$660,000 (Pending)

Title: "Innate immune signaling in TH17 differentiation and function and autoimmune neuroinflammation"

Summary: Uncovering messenger molecules that alter the behavior of immune system cells with the aim of stopping damage to the nervous system in MS.



A type of immune system cell known as a TH17 T cell appears to be largely responsible for the destruction of tissues in the brain and spinal cord in people who have MS. These cells also have a major role in disease activity in mice with the MS-like disease known as EAE. The factors that influence T cells to develop into the TH17 variety with the potential to cause damage are poorly understood.

Hongbo Chi, PhD, and team are investigating how another type of immune system cell, dendritic cells, influence the development of TH17 T cells in EAE. Dendritic cells release a number of signaling molecules that affect the behavior of other immune system cells. Some of the signaling molecules increase the activity of TH17 cells, while others turn off their activity. Dr. Chi and colleagues are studying ways to increase the production of the signaling molecules that turn off the activity of TH17 T cells, with an eye toward developing a therapy to turn off MS disease activity.

The results of this research could provide clues for new drug treatments that could reduce or stop the damaging disease activity in people who have MS.

### **Silva Markovic-Plese, MD**

University of North Carolina at Chapel Hill  
Chapel Hill, NC

Award: Research Grant

Term: 10/1/12-9/30/13; Funding: \$100,000  
(Pending)

Title: "The Role of IL-11+CD4+ T-cells in the development of the autoimmune response in MS"

Summary: Identifying immune cells and messenger chemicals that may help launch immune attacks in MS.

Recent studies report that immune cells known as "Th17-cells" play an important role in the development of the immune attacks that damage the brain and spinal cord in peo-

ple with MS. However, it is not clear what conditions lead to the development of this set of cells. Silva Markovic-Plese, MD, has evidence that a messenger chemical called IL-11, which was not previously studied in MS, may drive Th17-cell development.

Now her team is determining which other messenger chemicals, or cytokines, are required to induce IL-11 secretion by immune cells. They are also identifying the molecular makeup of cells that produce IL-11, and exploring the impact of IL-11 on other immune activities.

This series of studies could uncover new targets for potential therapies aimed at turning off immune attacks to stop MS.

### **Stephen Miller, PhD**

Northwestern University  
Chicago, IL

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$577,500

Title: "Immunoregulation and pathology of chronic relapsing EAE"

Summary: Improving MS therapies by more precisely targeting the parts of the immune system that are involved in MS attacks on the nervous system.

In MS, a type of immune cells called T cells attack and destroy myelin, the substance that protects nerve fibers in the brain and spinal cord. These attacks lead to clinical symptoms. In people who don't have MS, T cells do not attack myelin because it is part of their own tissues, and their immune systems are "tolerant" to their own myelin. One goal in MS therapy is restore this normal tolerance to one's own myelin, which would reduce attacks against the brain and likely restore function.

Many current MS therapies globally dampen the immune response, which reduces the ability of people on these therapies to launch



appropriate immune responses to foreign invaders such as bacteria and viruses. Stephen Miller, PhD, and collaborators are looking at an agent in mice with MS-like EAE to determine whether they can restore tolerance to myelin. Ultimately, they hope to translate this approach to people with MS such that normal functions of their immune system are preserved to fight infections.

Results from Dr. Miller's studies could improve MS therapies by making them more precise and more effective, which should reduce side effects such as increased vulnerability to infections.

### **Joel Pachter, PhD**

University of Connecticut Health Center  
Farmington, CT

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$407,637

Title: "Resolving the roles for astrocyte- and endothelial cell-derived CCL2 during evolution of experimental autoimmune encephalomyelitis"

Summary: Understanding the functions of a molecule and its potential as a target for therapy in progressive MS.

The molecule CCL2 plays a critical role in EAE, a model of MS, and is also associated with the human disease where it has been linked to progressive MS. CCL2 is produced at several sites within the body, both in and outside the central nervous system. And while it is generally thought to make the disease worse, it remains possible that CCL2 mediates both good and bad effects during MS.

Joel Pachter, PhD, and colleagues are performing studies to understand how the CCL2 produced at different sites affects development and severity of EAE. It will be important to understand all the different possible actions of CCL2 in the body, so that only actions that worsen disease are targeted for suppres-

sion during drug therapy.

This research will help pave the way for determining whether CCL2 is a good candidate for developing a new therapy to treat MS, possibly including progressive forms of the disease for which there is now little relief.

### **Lawrence Steinman, MD**

Stanford University

Stanford, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$510,975

Title: "Pre-clinical studies on predictive serum biomarker for response to beta-interferon in relapsing-remitting MS"

Summary: Attempting to find a way to predict who will respond to treatment with interferon beta.

Several types of immune system cells are involved in the destructive attack on myelin, the material that surrounds nerve fibers in the brain and spinal cord. The most commonly prescribed treatments for relapsing remitting MS are several forms of interferon beta. However, between 30% and 50% of people with relapsing remitting MS do not respond to interferon beta and continue to have relapses.

Lawrence Steinman, MD, is studying EAE, a disease similar to MS, in mice, to see whether it is possible to determine who will benefit from treatment with interferon beta. The team is investigating how interferon beta, and several other drugs used to treat MS, affect specific types of immune system cells, and how differences in the proportions of the types of immune system cells change the way the mice respond to treatment.

The results of this research could provide clues that clinicians could use to determine which people with MS will respond to interferon beta, and who would benefit from an alternative treatment.



### **H.-Christian von Büdingen, MD**

University of California, San Francisco  
San Francisco, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$485,808

Title: "Characteristics of disease-relevant B cell repertoires in MS"

Summary: Examining the relationship between B cells in the blood and those in the brain to improve MS diagnosis and therapy.

B cells are a type of immune cell that participate in making MS worse. B cells can cause increased immune attacks against myelin, one of the main brain components damaged in MS. B cells are normally found in blood, but are also found in the brain and spinal cord of people with MS.

Hans-Christian von Büdingen, MD, and team are examining the relationship between B cells found in blood and B cells found in the brain and spinal cord. Very recently they found first-ever evidence that some B cells in blood and the central nervous system are related. However, the similarities and differences between those types of cells remains unknown. It is also not known precisely which B cells are involved in the disease course. Identifying them may provide the basis for developing more specific therapies to stop MS activity and damage to the nervous system.

Results from these studies could lead to improvements in MS diagnosis and prognosis and may allow development of new therapies for MS.

### **Yisong Wan, PhD**

University of North Carolina at Chapel Hill  
Chapel Hill, NC

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$557,255 (Pending)

Title: "Therapeutic effect of dihydro-artemisinin on MS through suppressing immune response"

Summary: Determining the potential of an ancient herbal medicine for reducing immune attacks in a model of MS, as a prelude to testing it in people with MS.

MS involves immune attacks against tissues in the brain and spinal cord. There are many cells and messenger chemicals active in turning on immune attacks and also turning them off. Yisong Wan, PhD, and colleagues have shown preliminary evidence that a derivative of an ancient Chinese herbal medicine that has been used to treat fever, malaria and other disorders, called dihydro-artemisinin, can suppress ongoing disease in mice with the MS-like disease EAE.

The team's research has also found that this substance can suppress aggressive immune T cells and promote activity of immune cells, called Tregs, that can turn off immune attacks. Because of these intriguing results, Dr. Wan is now investigating further the therapeutic potential of dihydro-artemisinin by studying its impacts on immune activity.

This study could support the development of this herbal derivative as a potential therapy for MS.



### **James Waschek, PhD**

University of California, Los Angeles  
Los Angeles, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$652,196

Title: "Neuropeptide PACAP/VPAC2 receptor signaling in the regulation of natural Treg expansion in EAE"

Summary: Investigating a messenger molecule that may control damage to the nervous system and may have potential as a target for future therapies aimed at stopping MS.

Several different types of cell form the immune system that ordinarily protects the body from infections by attacking and destroying invaders, such as bacteria or viruses. In MS, however, some immune system cells damage tissues in the brain and spinal cord, leading to a variety of symptoms.

James Waschek, PhD, is investigating the potential of a molecule called PACAP (pituitary adenylyl cyclase-activating peptide) to modify immune system activity in mice with the MS-like disease known as EAE. PACAP acts on a docking site known as VPAC2 that helps to modulate some immune system activity. Dr. Waschek and colleagues have found that EAE is more severe in mice that are missing PACAP or VPAC2. Now they are investigating how PACAP may influence the activity of regulatory T cells, a type of immune system cell that can turn off aggressive immune system activity.

The results of this research project could lead to new ways to limit or stop the activity of immune system cells that damage myelin in people who have MS.

### **Katharine Whartenby, PhD**

Johns Hopkins University  
Baltimore, MD

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$654,729

Title: "The role of KLF4 in transcriptional activation of IL-17 and induction of EAE"

Summary: Determining the molecular switches that convert beneficial immune responses into harmful ones such as those involved in MS.

MS involves immune system attacks on the brain and spinal cord. The myelin that surrounds nerve fibers is a primary target, and nerve fibers are damaged as well. It is not known what causes immune cells, such as T cells, to react against the body's own nervous system.

Katharine Whartenby, PhD, focuses on determining the molecular switches that convert beneficial immune responses into harmful ones. Her team has identified a particular gene, known as the Kruppel-like factor 4 (KLF4), which acts to convert T cell responses from immune-regulating to inflammatory. Mice that did not have this gene were resistant to developing a disease that mimics MS. Now, they are undertaking a series of studies to elucidate the specific role that KLF4 plays in this switch, by studying the immune response in mice in which the gene is deactivated.

This project can determine whether KLF4 may be a potential target for future therapies that stop the immune attack in MS in its tracks.



### **Scott Zamvil, MD, PhD**

University of California, San Francisco  
San Francisco, CA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$614,600

Title: "Aquaporin-4 (AQP4)-specific T cells in CNS autoimmunity"

Summary: Distinguishing immune responses in MS and neuromyelitis optica.

The immune system ordinarily protects the body from foreign invaders, such as viruses and bacteria. In MS and other immune-mediated disorders, parts of the immune system mistakenly attack normal body structures. In MS, the primary target of the immune attack is the myelin sheath around nerve fibers. Until recently, neuromyelitis optica (NMO) was considered a severe variant of MS; the initial symptoms of MS and NMO are sometimes confused. In contrast with MS, the immune attack in NMO is directed to aquaporin-4 (AQP4), a protein that forms a channel for water movement. AQP4 is found on brain cells called astrocytes, which are damaged by antibodies. The formation of AQP4-specific antibodies requires T cells, but their role is not understood.

Scott Zamvil, MD, PhD, is investigating similarities and differences between MS and NMO. Dr. Zamvil's group was the first to identify AQP4-specific T cells in people with NMO and in mice. His team is now comparing how AQP4-specific T cells in people with NMO differ from those in people with MS and healthy controls. They are also investigating whether AQP4-specific T cells can cause manifestations of NMO in mice in the absence or presence of AQP4-specific antibodies.

This work could lead to new ways to distinguish NMO from MS, which should provide information that will improve treatments for both conditions.



### **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 stimulated. Testing new cell therapies and other therapeutic approaches to rebuild the nervous system is another approach, as well as development of innovative rehabilitation techniques and better ways to reduce MS symptoms.

### **RESTORE -Rehabilitation**

#### **Abiodun Akinwuntan, PT, PhD**

Georgia Health Sciences University  
Augusta, GA

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$359,569

Title: "Assessment and rehabilitation of fitness-to-drive in individual with Multiple Sclerosis"

Summary: Evaluating ways to measure and improve the driving ability of people with MS.

MS can damage many parts of the brain and spinal cord that are important for daily activities such as driving. Many of the problems that people with MS experience, such as muscle weakness, changes in coordination, fatigue, blurred or double vision, and slowed reaction times affect the ability to drive safely. Studies suggest that people with MS have a higher motor vehicle accident rate than individuals of the same age who do not have MS.

Abiodun Akinwuntan, PhD, MPH is studying driving ability in people with MS. This study, involving 180 people with moderate MS, has one main goal, which is to determine whether a set of easy to administer tests can be used to assess ability to drive of people



with MS. The driving ability of participants in the study will be assessed on a standardized road test.

The results of this research program may suggest shorter strategies to help assess the ability to drive of people with MS.

**Bo Fernhall, PhD**

University of Illinois  
Chicago, IL

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$685,183

Title: "Exercise, subclinical atherosclerosis and walking mobility in multiple sclerosis"

Summary: Evaluating a home-based exercise program with the potential to improve mobility and cardiovascular health in people with MS.

People with MS generally have decreased mobility as the disease progresses. Reduced activity may contribute to the development of atherosclerosis – a build-up of fatty material in the arteries that can be life-threatening and is the main reason people have a heart attack or stroke. A number of studies indicate that exercise can reduce early atherosclerosis in otherwise healthy individuals, but there are few studies of the effects of exercise on atherosclerosis in people who have MS.

Professor Bo Fernhall is investigating whether a home-based exercise program can improve mobility and have a beneficial effect on cardiovascular health in people who have MS. The study is comparing measures of both mobility and of atherosclerosis in two groups of people with MS. One group will exercise three times a week on bicycles that measure the amount of exercise, and the other group will do a series of stretching exercises three times a week.

The results of this study should establish whether the more rigorous exercise program

improves mobility and measures of cardiovascular health, and may provide the basis for future home-based programs to improve mobility and reduce the development of atherosclerosis in people who have MS.

**Jeffrey Hebert, PT, PhD**

University of Colorado Denver - Anschutz  
Medical Campus  
Denver, CO

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$536,295

Title: "Vestibular rehabilitation for persons with multiple sclerosis: who benefits the most?"

Summary: The potential of balance and eye movement training for improving mobility in people with MS.

In people with MS the immune system damages parts of the brain and spinal cord. The specific effects of this damage depend on what parts of the nervous system are affected. Portions of the brain known as the cerebellum and brainstem process signals from various systems of the body including sensory, visual and inner ear (vestibular system) that attempt to control balance and coordinated movements. Damage to these areas can cause problems with balance, which may be severe enough to cause falls.

Following up on positive results from a National MS Society pilot research project, Jeffrey Hebert, PT, PhD, MSCS is investigating whether vestibular rehabilitation improves balance more in people with MS who have cerebellar or brainstem damage. The rehabilitation program involves balance and eye movement training, and his team is comparing results in those with cerebellar or brainstem damage to results in people with MS who do not have any signs of that type of damage. In addition, Dr. Herbert and colleagues are determining whether improve-



## 8 New Pilot Projects Aim at Restoring Function in MS



### — Program supported by Illinois Lottery Funds

Nearly \$1 million in new MS research projects were launched by the National MS Society thanks to funds from a scratch-off ticket from the Illinois Lottery. The 8 one-year projects at universities across Illinois are focusing on reversing MS damage through novel rehabilitation techniques and approaches to stimulating nervous system repair. The new projects spring from a special initiative that focuses on small-scale pilot projects that provide seed money to test new ideas and speed research progress.

Their success has the potential to improve quality of life for people with MS not only in Illinois, but throughout the world by changing rehabilitation strategies and by contributing to knowledge needed to develop therapeutic strategies that will repair damage to the nervous system and restore function.

The new projects include:

#### Studies to Drive Nervous System Repair

- Deyu Fang, PhD (Northwestern University), studying a new target to reduce disease development and allow natural repair systems to work in MS.
- Douglas Feinstein, PhD (University of Illinois), investigating a possible new therapy to slow nerve damage and enhance nerve growth and myelin repair, to help restore function in people with MS.
- Brian Popko, PhD (University of Chicago), aiming to develop new drugs to improve walking in people with MS and for use in imaging studies.
- Sara Szuchet, PhD (University of Chicago), studying how myelin, which is attacked by the immune system in MS, is normally made, for clues to new ways to repair it to restore function in people with MS.

#### Innovative Rehabilitation Approaches

- Robert Motl, PhD (University of Illinois at Urbana-Champaign), expanding a clinical trial testing the ability of exercise to improve function in people with advanced MS; and developing ways to evaluate fitness in people with advanced disability from MS.
- Ian Rice, PhD (University of Illinois at Urbana-Champaign), focusing on promoting physical activity in people with MS who use powered wheelchairs by adding the use of manual wheelchairs.
- Jacob Sosnoff, PhD (University of Illinois at Urbana-Champaign), testing strategies to reduce falling in people with MS.



ment in balance control can reduce the fatigue that many people with MS experience.

The results may confirm that balance and fatigue can be improved by a specific exercise program, and determine which persons with MS would benefit most.

### **RESTORE - Myelin/Nervous System Repair**

#### **Regina Armstrong, PhD**

Henry M. Jackson Foundation  
Uniformed Serv. Univ. of the Health Sciences  
Bethesda, MD

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$577,597

Title: "Enhancing neural stem cell activation to improve remyelination capacity and axon integrity following chronic demyelination"

Summary: Testing a strategy to repair damage that occurs in the nervous system of people with MS to possibly restore function.

In MS, myelin, the substance that surrounds and protects nerve fibers in the brain, is damaged, and so are the underlying nerve fibers. This damage prevents the brain from properly sending signals, which leads to MS symptoms. One possible way to repair this damage is to stimulate natural myelin repair processes.

Regina Armstrong, PhD, and team are using a mouse model of chronic myelin damage and searching for a way to induce myelin repair by increasing the number of cells that make myelin. One way to do this is to stimulate production of new myelin-synthesizing cells from a naturally occurring population of immature cells present in the brain. Dr. Armstrong is studying a molecule called "Sonic hedgehog," which is known to increase cell division of this type of cell, increasing the number of cells available to make new myelin.

If this research is successful, it could lead to new insights into stimulating myelin repair in people with MS. This has the potential of improving symptoms and restoring function.

#### **Ben Barres, MD, PhD**

Stanford University

Stanford, CA

Award: Research Grant

Term: 1/1/13-12/31/15; Funding: \$505,936

Title: "How does the actin cytoskeleton control CNS myelination?"

Summary: Basic exploration of how myelin is made, with the goal of finding ways to repair damaged myelin in people with MS.

Myelin, the material that surrounds and protects nerve fibers, is damaged and destroyed in the brain and spinal cord by MS. Nerve fibers that have lost myelin may also be damaged, leading to progressive disability. Myelin is made by cells called oligodendrocytes, which extend thin sheets that wrap many times around nerve fibers, and then "collapse" to form the dense insulating myelin. The details of how they do this are not well known.

Ben Barres, MD, PhD, is looking at how a protein called actin helps to extend the thin sheets from the oligodendrocytes and wrap them around nerve fibers. Once the myelin sheets wrap and begin to collapse, actin is lost from the structure. Dr. Barres and colleagues have identified two genes that make proteins that help remove actin, and they are looking for others that are involved in the process of forming myelin.

The results of this research project may lead to ways to enhance the formation of myelin to repair damage from MS and restore function to people who have MS.



### **Benjamin Deneen, PhD**

Baylor College of Medicine  
Houston, TX

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$504,636

Title: "The role of NFIA in developmental and regenerative oligodendrocyte differentiation"

Summary: Looking for a way to enhance the development of cells that could repair damaged myelin in MS.

Myelin, the material that surrounds and insulates nerve fibers, is made by cells called oligodendrocytes in the brain and spinal cord. Immature precursors of oligodendrocytes eventually mature into myelin making cells. In MS, the immune system damages and destroys myelin. Without their myelin covering, nerve fibers fail to conduct signals correctly, and this failure leads to the numerous symptoms of MS. Precursor cells are found in areas of myelin damage in MS, but not enough of them develop into mature myelin making cells to repair the myelin damage.

Benjamin Deneen, PhD, is looking at the role of a molecule known as NFIA (Nuclear Factor-IA) that attaches to specific sites on DNA and helps to determine whether the information in genes at those sites can be used to make proteins. Dr. Deneen and colleagues have found that NFIA apparently prevents oligodendrocyte precursors from using the information in several genes that would enable them to mature into myelin forming cells. The team is now investigating how NFIA interacts with these genes, and looking for methods that would overcome the NFIA interference so that myelin repair can occur more efficiently in MS.

The results of this research could provide clues for ways to enhance myelin repair in MS to restore function.

### **Pablo Paez, MD, PhD**

University of California, Los Angeles  
Los Angeles, CA

Award: Research Grant

Term: 10/1/12-9/30/14; Funding: \$352,749

Title: "Modulation of oligodendrocyte development by voltage-operated calcium channels"

Summary: Studying how calcium influences the repair of myelin for clues to restoring function in MS.

Myelin, the material that surrounds and protects nerve fibers in the brain and spinal cord, is damaged and destroyed by MS. The cells that manufacture myelin, oligodendrocytes, and the immature cells that mature to become oligodendrocytes, known as oligodendrocyte precursor cells (OPCs), repair some myelin damage, but cannot keep up with the destruction caused by MS.

Based on positive data gathered with the help of a National MS Society pilot research award, Pablo Paez, MD, PhD, is now investigating structures known as voltage-operated calcium channels (VOCCs) on the surface of OPCs and oligodendrocytes. These structures form pores or passages through the membrane that allow calcium molecules to enter the cells. VOCCs influence the maturation of OPCs and the ability of oligodendrocytes to form myelin. Dr. Paez and team are looking at whether the calcium regulates the activity of genes that are important for the maturation of OPCs and for the production of myelin. They are using cells grown in the laboratory in addition to several strains of genetically modified mice to determine how calcium affects myelin formation.

The results this research could provide new clues for ways to stimulate the repair of damaged myelin in MS.



**Matthew Rasband, PhD**

Baylor College of Medicine  
Houston, TX

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$659,781

Title: "Spectrins as regulators of CNS myelination and axon integrity"

Summary: Examining a molecule that may need to be protected from damage in MS.

In MS, damage occurs to myelin (the substance that protects nerve fibers), to the cells that make myelin, and to the nerve fibers themselves. In addition to available therapies that dampen immune attacks in MS, new strategies are being developed to treat MS by repairing myelin and preventing damage to the nerve fibers and cells that make myelin (neuroprotection).

Matthew Rasband, PhD, and colleagues are looking at a molecule called "spectrin," which helps both myelin-making cells and nerve fibers maintain their shape. Maintaining cell shape is important for normal function. Spectrins are damaged in MS, which likely affects the function of both the nerve fibers and the myelin-making cells. Dr. Rasband's group is examining the importance of spectrins in normal synthesis of myelin, myelin-producing cells, and nerve fibers.

If spectrins are indeed important for normal function, preventing spectrin destruction in MS may be a strategy to preserve myelin and nerve fibers and to promote myelin repair.

**Patricia Wight, PhD**

University of Arkansas for Medical Sciences  
Little Rock, AK

Award: Research Grant

Term: 10/1/12-9/30/13; Funding: \$207,060

Title: "Control of human myelin proteolipid protein gene expression during development and remyelination"

Summary: Understanding how amounts of a protein present in myelin are regulated, for clues to stimulating myelin repair in MS.

Myelin is the material that surrounds nerve fibers and helps the fibers send the electrical messages required for normal brain function. Myelin is one of the main components in the brain and spinal cord that is attacked and damaged in MS. Myelin is composed of both lipids and proteins. One of the proteins present in the highest amounts in myelin is called proteolipid protein or PLP.

Dr. Wight and colleagues are studying how the gene which encodes PLP is regulated so that just the right amount of the protein is made. Too much or too little of PLP can have detrimental effects. Dr. Wight's group is using mice that have been manipulated such that they carry an extra gene called a transgene. The transgene contains portions of the human PLP gene, which will be used to determine the parts of the gene that are important in controlling that just the right amount of PLP be made.

Because myelin repair in people with MS is inadequate and incomplete, understanding how the PLP gene works may provide future strategies for restoring lost myelin in people with MS.



STOP. RESTORE. END.



## END MS FOREVER

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

### END MS—Genetics

#### Jacob McCauley, PhD

John P. Hussman Inst. for Human Genomics  
University of Miami  
Miami, FL

Award: Research Grant

Term: 10/1/12-9/30/15; Funding: \$641,141

Title: "Exploring MS genetics in Hispanics"

Summary: Looking for genes that make people susceptible to developing MS in individuals of the U.S. Hispanic/Latino population.

Both environmental and genetic factors combine to make people susceptible to developing MS. Many genes have been identified as being involved in MS susceptibility, but the current list of identified genes is incomplete and explains only a small part of the genetic causes of the disease. Thus, new MS-related genes remain to be discovered.

Most gene studies in MS have examined genes in Caucasians of Northern European descent. Although the prevalence of MS in people of Hispanic/Latino descent is relatively high, the MS-related genetics of this population has not been extensively studied. Using DNA from Hispanic individuals with and without MS, Dr. McCauley and colleagues are examining known genes that influence MS and

looking for new genes that may be involved in MS specifically in the Hispanic/Latino population.

The results from these studies will help pinpoint additional genetic risk factors for MS, and may help inform efforts to develop new therapies, as well as finding ways to prevent the disease.

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for more information about research, treatment, programs, and the NOW Campaign to support MS research

[www.nationalMSSociety.org](http://www.nationalMSSociety.org)

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Fast Forward