NEW RESEARCH

STOP. RESTORE. END.

Society Commits $28 Million for 84 New MS Research Projects

The National Multiple Sclerosis Society has committed another $28 million to support an expected 84 new MS research projects and training awards. These are part of a comprehensive research strategy aimed at stopping MS, restoring function that has been lost, and ending the disease forever – for every single person with MS.

This financial commitment is the latest in the Society's relentless research efforts to move us closer to a world free of MS, investing more than $50.2 million in 2014 alone to support over 380 new and ongoing studies around the world. So that no opportunity is wasted, the Society pursues all promising paths, while focusing on three priority areas: progressive MS (p. 8, for example), nervous system repair (see these grants starting on p. 29), and wellness and lifestyle (see some examples on page 24).

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

National Multiple Sclerosis Society

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

STOP:

- Researchers are investigating the effects of menopause on disease severity in women with MS. (page 7)

RESTORE:

- Researchers are testing thyroid hormone-like drugs to see if they will improve myelin repair. (page 24)

END:

- Researchers are looking for the presence of a virus in newly formed areas of damage on MRI scans. (page 40)

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—Therapies

Ellen Mowry, MD, MCR
Johns Hopkins University
Baltimore, Maryland
Award: Harry Weaver Neuroscience Scholarship
Title: A pilot study of intermittent calorie restriction in multiple sclerosis
Summary: Researchers at Johns Hopkins University in Baltimore are doing a pilot trial testing the safety and tolerability of a diet that intermittently restricts calorie intake as a treatment for disease activity in people with MS.

Background: Many researchers believe that MS is becoming more common, and may reflect, at least in part, recent environmental changes. One such change that may play a role is what people eat. Childhood obesity increases the risk for MS, and lab studies in mouse models of MS suggest that reducing caloric intake can decrease disease severity. Other studies suggest that restricting calories may reduce oxidative stress, inflammation, and dysfunction of the energy factories of cells (mitochondria), which have been implicated as harmful in MS.

The Study: Dr. Mowry and her group are performing a pilot trial to examine the effects of intermittent, dramatic reductions in caloric intake. They are conducting an 8-week randomized trial involving 36 people with MS. These participants are consuming one of three diets to compare potential impacts of a typical diet versus diets in which the amount of calories consumed are intermittently cut or cut a small amount overall. During these first 8 weeks, the food is being provided by the study team. After 8 weeks, all participants will be on calorie-restricted diet regimens for 40 weeks using their own purchased food to check how well people can adhere to the diet. Dr. Mowry and her team are assessing the safety and tolerability of these diets, and how such dietary changes may affect immune function and metabolism.

What's Next? This study will provide preliminary data that will be used to design and implement trials in larger groups of participants to see if dietary restriction will improve disease activity and symptoms in people with MS.

STOP—Psychosocial Aspects of MS

Stefan Gold, PhD
Charité University Medical Center
Berlin, Germany
Award: Research Grant
Title: Molecular mechanisms of T cell dysfunction in multiple sclerosis-associated major depression
Summary: Researchers at Charité University Medical Center in Berlin, Germany are investigating the possible link between immune system dysfunction and depression in MS.

Training Physicians to Provide Exceptional Care to People with MS

Consistent with its mission to move toward a world free of multiple sclerosis, the Society offers the Institutional Clinician Training Award, a five-year award to mentors and institutions to provide training for board-certified/eligible neurologists and physiatrists in MS specialist care. The goal is for fellows to acquire the skills and knowledge necessary to provide the highest quality of care for individuals with MS. Here are the awardees for 2015:

Lead Mentor: Peter Calabresi, MD
Johns Hopkins MS Center, Baltimore, MD

Lead Mentor: Peter Riskind, MD, PhD
University of Massachusetts Medical School, Worcester, MA

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: Depression is a fairly common symptom in MS, and is associated with a lower quality of life and cognitive problems. Why people with MS are at such high risk for depression is not yet known. This team previously showed that depression in MS is linked to damage to brain regions which control emotions, and is associated with elevated levels of the stress hormone, cortisol. In people with MS depression, a type of immune cell called T cells produce more inflammatory messenger proteins, and do not respond normally to cortisol, indicating that they are no longer adequately regulated by this hormone.

The Study: Dr. Gold and his team are exploring a possible link between abnormal immune cell function and depression in MS. They are studying gene activity and alterations in messenger proteins in T cells obtained from women with relapsing-remitting MS who are depressed and who are not depressed, and also women who do not have MS. They aim to identify mechanisms responsible for the impaired regulation of T cells in those with relapsing MS and depression.

What's Next? This study may increase our understanding of the link between the immune system and depression in MS, and may suggest new targets to treat MS depression.

STOP—CNS Repair

Andrés Cruz-Herranz, MD
University of California, San Francisco
San Francisco, California
Award: Postdoctoral Fellowship
Title: Longitudinal Screening of Neuroprotective Therapies in Experimental Autoimmune Encephalomyelitis with Optical Coherence Tomography
Summary: Researchers at the University of California at San Francisco are imaging the back of the eye to visualize signs of myelin repair in mice as a means of identifying agents with potential to stimulate myelin repair in people with MS.

Background: The hallmark of pathology in the brain of people with MS is the loss of myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have been stripped of their myelin do not function properly, producing symptoms in people with the disease. Successful treatments for MS dampen the immune system, but therapies to repair myelin remain to be developed. One barrier to developing such therapies is the inability to quickly and non-invasively test whether new drugs are working.

The Study: During the course of this training fellowship, Dr. Cruz-Herranz and experienced mentors are using an imaging technique called optical coherence tomography (OCT) that can visualize changes in the retina in a non-invasive manner. They are focusing on mice with the MS-like disease experimental autoimmune encephalomyelitis (EAE) and optic neuritis, which is a model of the vision problems that are often seen in MS. They are examining the backs of the eyes (retinas) of these mice over time using OCT and then looking for links between changes seen with OCT and myelin repair. They are also treating mice that have EAE and optic neuritis with candidate drugs that may stimulate myelin repair, using OCT as a way of detecting aspects of myelin repair.

What's Next? Results from this study will help in the development of a way to detect the impact of therapies focusing on protecting the nervous system or repairing myelin in people with MS.

STOP—Infectious Agents

Stanley Perlman, MD, PhD
The University of Iowa
Iowa City, Iowa
Award: Research Grant
Title: Pathogenesis of Demyelination in Mice Infected with a Neurotropic Coronavirus
Summary: University of Iowa researchers are investigating ways to manipulate the immune system in a way that turns off the harmful effects and maintains the helpful effects as a strategy for treating MS.

Background: In MS, the immune system attacks the nervous system, causing a variety of symptoms. Having more specific therapies that can turn off MS immune attacks but keep the rest of the immune system intact to fight infection would be a great leap forward. One type of immune cell that could possibly be manipulated for MS therapy is called "Tregs." These immune cells turn down some of the harmful aspects of the immune system. Thus, controlling Treg activity and the molecules they secrete may be a more specific way of manipulating the immune system in MS.

Eight Physicians Offered Training in Specialized MS Care

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

Awardee	Location	Mentor
Scott Belliston, DO	University of Kansas Medical Center, Kansas City, KS	**Sharon Lynch, MD**
Matthew Carraro, MD	The Ohio State University, Columbus, OH	**Aaron Boster, MD**
Joshua Chalkley, DO	Brigham and Women's Hospital, Boston, MA	**Tanuja Chitnis, MD**
Alison Daigle, DO	Brown University, Providence, RI	**Syed Rizvi, MD**
Janet Elgallab, MD	State University of New York, Stony Brook, NY	**Lauren Krupp, MD**
Fabian Sierra Morales, MD	Beth Israel Deaconess Medical Center, Boston, MA	**Jacob Sloane, MD, PhD**
Sharon Stoll, DO	Yale University, New Haven, CT	**Daniel Pelletier, MD**
Melanie Ward, MD	University of Virginia, Charlottesville, VA	**Myla Goldman, MD**

The Study: Dr. Perlman and his colleagues are using a mouse model in which nervous system tissue damage is induced by a virus. They are examining the characteristics of the Tregs in these mice. His group is also studying another group of molecules, called "prostaglandins," some of which enhance and others of which diminish the immune response. Production of these molecules is decreased when people take ibuprofen and similar compounds. The role of prostaglandins in MS may be important but is not completely understood. This team is also examining the role of prostaglandins in this mouse model.

What's Next? A more specific type of treatment for MS may result if Tregs can be used to control the harmful components of the immune system or if specific prostaglandins are inhibited in MS while leaving the helpful components intact.

STOP—Measuring MS Disease Activity

Lisa Barcellos, PhD
University of California, Berkeley
Berkeley, California
Award: Research Grant
Title: Longitudinal Assessment of Disease Progression and Cognitive Status in MS: A Comprehensive Web-Based Approach for Clinical Research and Translation to Care
Summary: Research collaborators in California and Buffalo are designing a web-based tool to collect data regarding individuals' MS disease progression, mood and cognitive symptoms over time to improve understanding of the disease and clinical care.

Background: Although many people with MS experience disease progression and cognitive problems, there is a need for better ways to track how these problems occur and how they progress over time. One reason for this lack of understanding is that systematic assessment of these problems is not routinely performed by physicians when patients come in for a clinical visit, and these data are not readily available in medical records.

The Study: Dr. Lisa Barcellos and collaborators at the University of California, Berkeley, Kaiser Permanente Division of Research, The State University of New York, Buffalo and University of California, San Francisco are designing and testing a guided web-based interface called "Individual, Internet-Based, Clinical & Longitudinal Information Collection for MS Studies" or "iCLIC-MS." For the first step, the researchers will compare in-person to remote and web-based assessments of MS disease progression and disability, cognitive function and depression screening in individuals to see how well iCLIC-MS performs. After the iCLIC-MS is perfected, it is planned as a web-based survey that can be completed on a tablet, smart phone, or other device.

What's Next? In the future, the system will be tested for its ability to track MS symptoms and progression over time. Ultimately it could lead to better understanding of how MS progresses and will allow for improved research, clinical care and clinical trials.

Ralph Benedict, PhD
The State University of New York at Buffalo
Buffalo, New York
Award: Research Grant
Title: The Role of Cognitive Dysfunction in Defining MS Relapses and Freedom from Disease Activity
Summary: Researchers at the State University of New York at Buffalo are investigating the importance of cognitive problems in MS relapses to more precisely define disease activity during relapses and the absence of disease activity during periods of remission.

Background: MS symptoms may include both physical and cognitive disabilities. Disease-modifying therapies have greatly reduced the incidence and severity of relapses, with some individuals experiencing periods where they are apparently free from symptoms and relapses. But definitions of remission generally involve physical abilities, yet cognitive abilities during relapses and periods of remission are less well understood. This team is tracking cognitive changes over time in people who experience MS relapses to better define and include cognitive changes in definitions of disease activity.

The Study: Dr. Benedict and his team are using a large sample (1000) of people with relapsing-remitting MS and following them over 4 years. They are identifying relapses ac-

Sylvia Lawry Physician Fellowship

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
Justine Brink, DO	Thomas Jefferson University Philadelphia, Pennsylvania	Thomas Leist, MD, PhD
Carla Francisco, MD	University of California, San Francisco San Francisco, California	Emmanuelle Waubant, MD, PhD
Meredith Frederick, MD	Oregon Health & Science University Portland, Oregon	Dennis Bourdette, MD
Andrew Smith, MD	University of Rochester Rochester, New York	Andrew Goodman, MD
Andrew Smith, MD	Cleveland Clinic Foundation Cleveland, Ohio	Jeffrey Cohen, MD

cording to clinical (i.e., symptomatic) criteria and magnetic resonance imaging. After baseline, assessment tests will be repeated whenever a relapse occurs and then 3 months later after recovery (remission). They are measuring physical decline in the presence or absence of cognitive decline, and assessing the frequency and severity of cognitive symptoms, whether relapses involving only cognitive problems occur, and which test is best for measuring cognitive problems.

What's Next? These results will increase our understanding of the importance of cognitive problems during MS relapses and will more precisely define disease activity to include measures of cognition, giving a fuller picture of MS and its treatment.

Riley Bove, MD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Career Transition Fellowship
Title: Mechanisms underlying the effect of menopause on multiple sclerosis course
Summary: Researchers at Harvard Medical School are investigating the effects of menopause on the brain in women with MS.

Background: Women are far more likely to develop MS than are men, and this and other gender differences have been the subject of research for many years. Women with MS often report that their MS symptoms worsen with menopause. The reasons and implications for this are not clear.

The Study: Dr. Bove and her team are determining how menopause affects MS disease severity and brain lesions. They are looking at 30 women with MS who have had their ovaries removed for the treatment of other conditions, compared to 30 premenopausal women with MS. They are also examining 100 women with MS who have undergone natural menopause. They are using an imaging technique called subtraction magnetic resonance imaging to determine if brain lesions and loss of brain volume increase during menopause. They are also using a related imaging technique called diffusion tensor imaging to look at damage to one particular brain structure called the corpus callosum.

Finally, they are assessing whether hormone replacement therapy protects the brain from any MS-related adverse effects of menopause.

What's Next? These results should shed light on an under-explored aspect of the MS experience, and may suggest ways to overcome negative impacts of menopause on women with MS.

STOP—Biology of Glia

Cheryl Dreyfus, PhD
Rutgers, The State University of New Jersey
Piscataway, New Jersey
Award: Research Grant
Title: The role of glial cell-derived factors in a cuprizone model of MS
Summary: Rutgers University researchers are investigating new molecules that may be capable of protecting cells that make nerve-insulating myelin, with the goal of preventing degeneration of myelin and enhancing its repair in people with MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Without myelin, nerve fibers cannot properly send nerve signals and become vulnerable to damage. The cells in the brain and spinal cord that make myelin are called "oligodendrocytes." One idea to treat people with MS is to protect oligodendrocytes from injury, which may stop disease progression, enhance myelin repair and restore nerve function.

The Study: Dr. Dreyfus and her group are investigating the effects of molecules that have been shown in mouse models of spinal cord injury and neurologic disorders to be able to enhance recovery from these conditions, but they haven't yet been thoroughly explored in MS-relevant models. The molecules are called ACPD and CHPG. In preliminary studies, Dr. Dreyfus and her team used mouse models that mimic some features of MS. In the models, ACPD and CHPG individually improve symptoms and disease pathology, possibly by protecting oligodendrocytes and allowing immature oligodendrocytes to mature and become capable of making myelin. They are now investigating the details of how these molecules work to prevent degeneration and enhance repair in these mouse models to see if they could be developed into therapies for MS.

What's Next? If successful, this research could point to new strategies for protecting the nervous system from damage to stop MS progression.

Alexander Gow, PhD
Wayne State University
Detroit, Michigan
Award: Research Grant
Title: Neurodegeneration associated with metabolic stress in oligodendrocytes
Summary: Wayne State University researchers in Detroit are determining whether processes beyond immune attacks are responsible for nervous system damage in an MS-like disease in mice, for novel ways to stop MS.

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 attack. 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 evidence that metabolic stress in cells is associated with MS.

The Study: Dr. Gow and his team have designed a novel model for MS, known as the OBiden mouse, that does not involve a primary attack on myelin-producing cells by the immune system. The pathology in the brains of these mice can be switched on in older mice so that damage has an adult onset similar to what occurs in most people with MS. They are looking at these mice to see if turning on metabolic stress in myelin-producing cells, which are damaged in MS, produces deficits similar to those seen in MS. In addition, they are testing a drug that reduces metabolic stress to see if disease severity, brain degeneration, and cognitive problems can be stopped or possibly reversed.

What's Next? Decreasing metabolic stress in myelin-making cells may be necessary to achieve a complete treatment effect in MS.

Dimitry Ofengeim, PhD
Harvard Medical School
Boston, Massachusetts
Award: Career Transition Fellowship
Title: RIP1 kinase as a novel target to inhibit neuroinflammatory disease
Summary: Researchers at Harvard Medical School in Boston are examining a possibly harmful molecule called RIP1 kinase and testing whether blocking its actions can protect the nervous system to stop MS progression.

Background: In MS, the immune system attacks the brain and causes loss of myelin, the fatty substance that surrounds and protects nerve fibers. The cells that make myelin are called oligodendrocytes, and many of these cells die in MS. One idea for treating people with MS is to promote myelin repair and prevent the death of oligodendrocytes. Various molecules in the brain control myelin synthesis and cell death and survival.

The Study: Under the mentorship of experienced researchers, Dr. Ofengeim and team are investigating a molecule called RIP1 kinase. This molecule has been suggested to be harmful in MS, and Dr. Ofengeim is further investigating this idea. To do this, they are using mice that have been engineered to be unable to make RIP1 kinase. These mice are being treated with a toxin that causes myelin loss. The myelin and the myelin repair process in these mice that do not have RIP1 kinase activity are being examined. They are also testing the role of RIP1 kinase in cells grown in a dish and in brain tissue from people with MS. In addition, the team is testing whether blocking the action of RIP1 kinase with a specific drug will prevent oligodendrocyte death and/or improve myelin repair.

What's Next? Blocking RIP1 kinase may be a therapeutic strategy in MS that could be developed to stop MS progression.

STOP—Role of the Immune System

Alexander Boyden, PhD
The University of Iowa
Iowa City, Iowa
Award: Postdoctoral Fellowship
Title: The role of CD8+ regulatory T cells in modulating B cell function during EAE
Summary: Researchers at the University of Iowa are investigating the influence of two types of immune cells on each other to better understand and treat MS.

Background: In MS, the immune system functions abnormally. Two types of immune cells called B cells and T cells are thought to play a role in initiating MS attacks on the brain and spinal cord. A type of helpful T cell called "regulatory T cells" controls the function of both T and B cells. Regulatory T cells have been reported to be defective in MS. One therapy for MS called glatiramer acetate works by improving the function of regulatory T cells in people with the disease, but the details of how these immune cells interact with each other are not fully understood.

The Study: Dr. Boyden and his team are investigating how B cells influence regulatory T cells, and how regulatory T cells influence B cells. They are using a mouse model of MS called EAE to perform their experiments. In these mice, they are manipulating one population of immune cells (B cells or regulatory T cells) and then studying the effect that the presence or absence of one population has on the other.

What's Next? The results from these studies will increase our knowledge of how immune cells function in MS, and this may lead to new and improved therapies for people with MS.

Melissa Brown, PhD
Northwestern University
Chicago, Illinois
Award: Research Grant
Title: c-kit differentially regulates EAE susceptibility in male and female SJL mice
Summary: Northwestern University researchers are testing the role of a molecule called c-kit in sex-specific differences in the immune response and protection of neurons in a rodent model of MS called EAE.

Background: Women are three to four times more likely to develop MS than men. Women who develop MS are more likely to show a relapsing-remitting disease course and to be diagnosed at a younger age. Men are more likely to show a primary-progressive disease course, which does not involve periods of relapses and remissions. The reasons for sex-based differences in MS are not completely understood, but sex hormones, sex-specific genetic differences, and a stronger immune response in women may play a role. Dr. Brown's group previously identified a protein called "c-kit" that provides protection from EAE, a rodent model for MS, to male mice but not female mice.

The Study: The c-kit protein is found on at least two types of immune cells called mast cells and innate lymphoid cells. Dr. Brown's group is using mice that are genetically engineered not to have c-kit to determine how c-kit is providing protection in males and not females. They will test: 1) whether male hormones such as testosterone are

required for the protective effect of c-kit; 2) if the action of c-kit in males is to dampen the immune response carried out by the T cells, cells that orchestrate the myelin damage in EAE; and 3) whether c-kit, which is also present in immature and mature nerve cells, is protective to neurons in males. These studies will determine what other molecules are involved in the damaging immune response and why EAE disease activity is different in males and females.

What's Next? FDA-approved drugs that modify the activity of c-kit are already in use for treating other conditions. This project will shed light on whether these drugs may be useful in sex-specific treatments of MS as well.

Claudia Cantoni, PhD
Washington University School of Medicine-M
St. Louis, Missouri
Award: Postdoctoral Fellowship
Title: Role of miR-223 in multiple sclerosis and its animal model
Summary: Researchers at Washington University are examining the role of a molecule that may regulate the immune attacks in MS.

Background: In MS, the immune system leads attacks on tissues in the brain and spinal cord, causing a wide variety of symptoms. Many factors control the function of the immune system. One group of such factors is called "microRNAs", which are small molecules that are involved in turning on or off cell activity. The possible role for microRNAs in MS immune attacks has not been thoroughly explored. One type of microRNA that may be important in MS is called "miR-223". Some research suggests that people with MS have higher levels of miR-223 in their blood than people without the disease. The absence of miR-223 in mice with EAE, a model of MS, reduces disease severity compared to mice with intact miR-223. This molecule is found in a population of immature immune cells that may be involved in disease activity in MS and EAE.

The Study: Dr. Cantoni and her group are further exploring the role of miR-223 in MS and EAE. In the first set of studies, they are investigating mice with EAE that do not have miR-223 and are looking at the number and function of the relevant immune cells in these mice. Then they are using samples of blood and cerebrospinal fluid from people with and without MS and looking at the different types of relevant immune cells in these samples and comparing miR-223 in these immune cells in people with MS in remission and in those experiencing a relapse.

What's Next? This study should shed light on important aspects of the immune attack underlying MS, and may lead to the identification of new therapeutic targets for treating MS.

Maria Ciofani, PhD
Duke University Medical Center
Durham, North Carolina
Award: Research Grant
Title: Network approach to dissecting genetic mediators of Multiple Sclerosis
Summary: Duke University Medical Center researchers are using new technologies to identify genes that are expressed in certain types of cells and that may contribute to causing MS.

Background: MS is likely caused by multiple factors, including the activity of specific genes and their interactions with the environment. Over 150 genetic regions have been implicated in MS disease risk, however, identifying

National MS Society Partners with Bionure to Develop Neuroprotective Therapy

The National MS Society has partnered with Bionure, Inc. to accelerate the development of its novel neuroprotective and remyelinating compound, called BN201. Under this agreement, the National MS Society through Fast Forward will provide funding to Bionure for the late-preclinical development of BN201 to enable the company to gather data needed to support a request to the FDA to conduct a Phase 1 clinical study in acute optic neuritis, an eye disorder that is often a first sign of MS. Speeding treatments to people with MS requires bold leadership, tenacity and financial support at every stage of the research process. As an important part of the Society's research infrastructure, investments through Fast Forward focus on closing the gap between promising discoveries and the commercial development necessary to get new treatments to people with MS.

and tracing the functions of the associated risk genes in particular cell types is difficult. In addition, multiple cell types and activities contribute to MS disease initiation and progression, further complicating attempts to identify important genes.

The Study: Dr. Ciofani and her team are using new technologies to trace networks of gene influence in particular types of immune cells. This will allow unprecedented power in prioritizing MS risk-associated genes by mapping them to context-specific disease networks, determining which of these genes plays the most important roles in disease.

What's Next? This study will help identify the most important MS risk genes, provide clues to MS prevention, and lay groundwork for the development of more focused therapies.

Alessandra De Paula Alves Sousa, PhD
National Institute of Neurological Disorders and Stroke
Bethesda, Maryland
Award: Postdoctoral Fellowship
Title: Deep sequencing of T-cell receptor repertoire in patients with neurological immune-mediated disorders
Summary: Researchers are using advanced technology to identify immune cell abnormalities in people with MS.

Background: In MS, the immune system attacks and destroys nervous system tissues The immune system is comprised of many different types of cells, one of which is called the "T cell." T cells normally play multiple roles in fighting off infection. They also play an important and harmful role in MS development and progression. Each T cell expresses a molecule on its surface called the "T cell receptor" (TCR), and each T cell expresses only one type of TCR. Different T cells express different TCRs. The group of TCRs expressed by the group of T cells in a person serves as an immune "fingerprint."

The Study: Under the mentorship of experienced scientists, Dr. De Paula Alves Sousa and team are characterizing the TCR fingerprint in people with MS compared to people without MS and people with a virus-associated neurological disease that resembles MS. To do this, they are using a relatively new technique called "high-throughput sequencing" that allows them to identify the DNA that produces each type of TCR. Using samples from large numbers of people in these three groups, they are looking at T cells in blood and spinal fluid and testing the idea that these three types of people will have different TCR fingerprints.

What's Next? Understanding the repertoire of TCRs in MS compared to other groups of people may help determine in what ways T cells are abnormal in MS and may ultimately allow more personalized approaches to therapy.

Brad E. Hoffman, PhD
University of Florida
Gainesville, Florida
Award: Research Grant
Title: In Vivo Induction of Antigen Specific T-Cell Tolerance to a Neuro-Antigen by AAV Hepatic Gene Therapy
Summary: University of Florida researchers are exploring a way to prevent or treat MS, using the EAE model, by inducing immune tolerance.

Background: Although the cause of MS immune attacks against the brain and spinal cord is not fully understood, one reason may be a failure of the immune system to recognize brain proteins as self, rather than foreign. Such a lack of tolerance by the immune system may allow certain immune cells to become harmful and attack the brain. One idea to control these harmful immune cells is to use a helpful type of regulatory immune cell called "Tregs." However, before they can be useful, Tregs must be "taught" to tolerate relevant self-brain proteins.

The Study: Dr. Hoffman and his colleagues are developing a method that will generate and "teach" Tregs how to tolerate self-brain proteins. They are testing this strategy by treating mice with EAE, a laboratory model of MS. The team is inducing Treg tolerance by displaying an MS-related brain protein in the liver. Dr. Hoffman is then testing if these tolerant Tregs travel to the brain where they can then perform their helpful actions by blocking the harmful activities of other immune cells, and whether blocking these harmful actions improves or prevents EAE.

What's Next? Work will continue to toward developing this therapy into a clinical treatment for early stage MS.

Trevor Kilpatrick, MBBS, PhD
University of Melbourne
Melbourne, Australia
Award: Research Grant
Title: Understanding the Role of MerTK in the etiology and pathogenesis of MS
Summary: Researchers at the University of Melbourne in Australia are investigating the function of an immune cell protein which is abnormal in some people with MS, to understand its potential role in MS.

Background: Both genetic and environmental factors play a role in causing MS, but the details are not clear. Dr. Kilpatrick and his team previously identified a gene called "MERTK" as being associated with a risk for MS. An abnormal form of MERTK is found in about 10% of people with MS. The protein whose manufacture is instructed by the MERTK gene is found on the surface of specif-

ic immune cells and regulates how the cells respond to inflammation. How the abnormal form of the MERTK protein works in MS is not known.

The Study: Dr. Kilpatrick and an international team of collaborators are testing the idea that abnormal MERTK in some people with MS leads to an abnormal response of immune cells to inflammation. Through a series of studies, they are examining the details of the effects of abnormal MERTK proteins on immune cell function, and comparing its presence and activity in people who have different strengths of the MERTK gene. They are also exploring MERTK presence in brain specimens from people who had MS in their lifetimes, armed with information about their clinical course and whether they had this susceptibility gene.

What's Next? This novel study asks the question of how a single gene variation can increase a person's susceptibility to MS. The results could increase our general understanding of immune cell function and dysfunction in MS, and provide a model for ways to figure out the genetics of MS risk.

Nancie MacIver, MD, PhD
Duke University Medical Center
Durham, North Carolina
Award: Research Grant
Title: Identifying molecular mechanisms by which leptin and nutrition target T cell immunity in multiple sclerosis
Summary: Duke University Medical Center researchers are exploring whether a nutrition-regulated hormone called leptin may contribute to immune-system activity in MS.

Background: In MS, the immune system attacks components of the brain, leading to symptoms in people with the disease. Recent clinical studies have identified adolescent obesity as a possible risk factor for developing MS, but how obesity or other factors may increase susceptibility to MS is unclear. We have identified the hormone leptin as a regulator of immune response with a potential role in MS. Leptin levels are regulated by nutrition and are elevated in obese individuals. Some research suggests that leptin levels are higher in people with MS, and that this hormone promotes inflammation and autoimmune disease. Immune cells called T cells are important players in MS attacks, and leptin controls the ratio of helpful T cells to harmful T cells.

The Study: Dr. MacIver and her team are investigating how changes in nutrition and leptin control inflammation and T cell response. To do this, they are using mice that have been genetically engineered to have T cells that are unable to respond to leptin. In these mice, they are inducing a disease called EAE, which is a model for MS. They are looking at how the T cells in these mice show alterations in the way they metabolize fuel for energy and become activated when they are unable to respond to leptin after developing EAE.

What's Next? These studies have potential to provide a link between nutrition and MS disease activity. Understanding how leptin controls T cells and inflammation in MS may lead to whole new approaches to stopping MS with therapies or diet.

Charlotte Madore, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowship
Title: Targeting ApoE pathway to restore unique microglial properties in EAE.
Summary: Researchers at Brigham and Women's Hospital in Boston are exploring the role of immune cells in the brain called microglia and their possible role in nervous system damage in people with MS.

Background: Several types of immune cells play a role in the immune attacks and inflammation characteristic of MS. One sort of immune cell whose role is poorly understood in MS are called "microglia." Microglia may play multiple roles, including causing damage in MS, especially in progressive forms of the disease. In mice with the MS-like disorder EAE, microglia undergo possibly harmful changes in conjunction with changes in a molecule called ApoE.

The Study: Under the mentorship of experienced investigators, Dr. Madore is involved with studies looking at the role of ApoE in inducing inflammatory changes in microglia in mice with EAE. One role of microglia is to clear debris in the brain, including debris left from damaged myelin, which is targeted by MS. They are testing the role of ApoE in microglial clearance of debris by injecting various types of debris into the brain of mice that have ApoE compared to those that do not have active ApoE. In the final set of studies, the team is testing the importance of ApoE presence in microglia themselves compared to its presence in other types of cells.

What's Next? Understanding the biology of brain immune cells and their roles will help development treatments that can protect the brain against injury for people with MS.

Gerd Meyer zu Horste, MD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowship
Title: Fas as a novel regulator of the Th17 / Treg balance in EAE.
Summary: Researchers at Brigham and Women's Hospital in Boston are investigating a molecule that may control the balance between overly aggressive and suppressive immune responses for clues to stopping MS disease activity.

Background: The immune system functions properly when a balance is present between aggression towards foreign invaders such as viruses and bacteria, and suppression of harmful effects such as an attack on the body's own tissues. In MS, the balance appears to be disrupted, and the immune system attacks the brain and spinal cord. Aggressive immune cells include "Th17 cells," and suppressive cells include "T regulatory cells." This balance must be carefully controlled to prevent dangerous immune reactions against one's own body. A molecule called "Fas" may play a role in shifting this balance. Mice that do not have Fas present are protected from developing EAE, an MS-like disease. Thus, Fas may play a harmful role in the immune system balance.

The Study: Under the guidance of experienced researchers, Dr. Meyer zu Horste and colleagues are investigating how Fas works to potentially shift the balance. They are looking at mice with EAE that do not have Fas and are examining the Th17 and T regulatory cells in these mice and apply novel techniques to understand how the molecule works. Although Fas is thought to normally kill aggressive cells, in EAE Fas may actually be detrimental and Fas may work in other ways than the known ways to promote aggressive cells in MS.

What's Next? Several compounds that target Fas are available and may be useful for shifting the immune system to a healthy balance as a way of stopping immune attacks in people with MS.

Frank Schildberg, PhD
Harvard Medical School
Boston, Massachusetts
Award: Postdoctoral Fellowship
Title: "Cell type-specific functions of PD-L1 in controlling EAE"
Summary: Researchers at Harvard are exploring the mechanisms by which a molecule seems to control the initiation and resolution of EAE of MS-like disease.

Background: Multiple sclerosis is a disease in which the brain and spinal cord are attacked by the immune system. This results in the breakdown of myelin, the material that surrounds nerve fibers, and the fibers themselves. This immune attack is driven by T cells, white blood cells which under normal conditions defend against infections. During MS, T cells recognize myelin and try to destroy it, leading to MS symptoms. Investigating the mechanisms that normally control the immune system is essential to identifying new therapies that can stop the immune attack.

The Study: During this fellowship, Dr. Schildberg is working with an experienced team to explore the role of a molecule that seems to be key in regulating the immune system, programmed death 1 (PD-1). PD-1 is found on the surface of T cells and binds to a similar molecule, PD-L1, which is present on a variety of cells. This attachment can work as a brake on the immune response by blocking T cell functions, depending on the type of cell involved. This team has developed mice in which PD-L1 can be eliminated selectively in specific cell types. Using these unique tools to analyze the function of PD-L1 in highly specific cell types, they are determining which cells use PD-L1 to confer protection against damage of the brain and the spinal cord during EAE, an MS-like disease.

What's Next? The results of these studies should provide insights into a new therapeutic avenue for stopping the MS immune attack by targeting the PD-1/PD-L1 binding process.

Bridget Shafit-Zagardo, PhD
Albert Einstein College of Medicine
Bronx, New York
Award: Research Grant
Title: Functional Consequences of Altered AKT3 Signaling
Summary: Researchers at the Albert Einstein College of Medicine are examining the role of a molecule called AKT3, which may be capable of protecting against MS immune attacks.

Background: Regulating the immune system, which is responsible for immune attacks on the brain and spinal cord in MS, is a key concept in designing new therapies. One molecule that appears to play an important role in regulation of the immune system is called "AKT3." AKT3 is found in nerve cells and in a type of immune cell called a T cell. Mice that were genetically engineered to not have functional AKT3 are more susceptible to developing the MS-like disease EAE. This suggests that AKT3 likely plays a beneficial or protective role in EAE, and possibly in MS.

The Study: Dr. Shafit-Zagardo and her team are testing the idea that AKT3 that is found in T cells is protective in EAE by improving the function of beneficial T cells and decreasing the function of harmful T cells. They are examining the molecules that work with AKT3 to modulate this protective effect. They are

New Collaborative MS Research Award Tests a Link Between Gut Bacteria and MS Progression

Lead Investigator: Sergio Baranzini, PhD
University of California at San Francisco

Title: "The MS Microbiome Consortium: An academic multi-disciplinary collaborative effort to elucidate the role of the gut microbiota in MS"

Summary: A comprehensive analysis of gut bacteria in people with MS to determine factors that may drive progression and develop probiotic strategies for stopping progression.

Background:

MS involves immune-system attacks against the brain and spinal cord. The gut, including the small and large intestine, is the largest immune organ in mammals. Each of us has millions of "commensal" bacteria living within our guts. Most of these bacteria are harmless as long as they remain in the inner wall of the intestine. They play a critical role in our normal physiology, and accumulating research suggests that they are critical in the establishment and maintenance of immune balance by the molecules they release.

The Study:

The MS Microbiome Consortium was created in 2013 by the investigators participating in this proposal. Its members have world-class expertise in genomics (Dr. Sergio Baranzini), clinical care and research (Drs. Bruce Cree, UCSF, and Ilana Katz-Sand, Mount Sinai School of Medicine), microbiology (Dr. Sarkis Mazmanian, California Institute of Technology), and neuroscience (Dr. Patrizia Casaccia, Mount Sinai School of Medicine). Dr. Rob Knight (University of California San Diego) new to the field of MS research, pioneered the development of advanced computational methods for identifying microbial species. The consortium is using this award to start a comprehensive microbiome analysis. They are comparing the gut bacteria of people with relapsing MS, people with primary progressive MS, and healthy controls. They believe that significant differences in gut bacteria exist among these groups that may drive MS progression.

What's Next?

These findings will help the Consortium toward its goal of developing biomarkers of MS progression, as well as novel therapeutic approaches based on personalized probiotics.

manipulating the presence of AKT3 in various types of T cells and evaluating the impact on the development of EAE. They expect that mice with enhanced AKT3 will be less susceptible to EAE than mice without AKT3 or genetically normal mice, thus demonstrating a protective effect of AKT3.

What's Next? Results from this study may suggest a new approach to therapies that increase the function of AKT3 to stop MS.

Stephanie Tankou, MD, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowship
Title: Investigation of the role of elevated archaea species in the microbiome of patients with MS.
Summary: Researchers at The Brigham and Women's Hospital are studying the relationship between a specific type of gut microbe and immune function and disease severity in people with MS.

Background: MS involves immune-system attacks against the brain and spinal cord. The gut, including the small and large intestine, is the largest immune organ in mammals. Each of us has millions of "commensal" microbiota (microorganisms, including bacteria) living within our guts. Most are harmless as long as they remain in the inner wall of the intestine. Studies in mouse models of MS are providing preliminary evidence of the possible participation of the gut microbiota in triggering the immune attacks on the nervous system in MS.

The Study: This team compared gut microorganisms from people with MS who were not on any disease-modifying treatment, those on treatment, and healthy controls. Microbes known as archaea were increased in people with MS, whether treated or not. Now Dr. Tankou and colleagues are studying the relationship between archaea abundance and immunological function and disease severity in MS. They are testing the effects of archaea on immune cells isolated from people with MS and healthy controls. They also are determining whether there is any association between archaea activity and MS disease activity on MRI scans or clinical scales.

What's Next? Understanding the potential role of the gut microbiome in MS disease activity may yield insight into the development of MS, and allow for the design of novel approaches for the prevention and/or treatment of MS.

Luc Van Kaer, PhD
Vanderbilt University
Nashville, Tennessee
Award: Research Grant
Title: Promoting regulatory interactions between iNKT cells, MDSCs and Tregs as a therapeutic approach for MS
Summary: Researchers at Vanderbilt University in Nashville are seeking ways to regulate the immune system to retain its helpful functions and turn off its harmful functions to develop a novel way of treating MS.

Background: In MS, the immune system attacks components of the brain and spinal cord, ultimately leading to a variety of neurological symptoms. Current therapies for MS are designed to modulate the immune system. However, some of these therapies may also inhibit helpful components of the immune system, causing side effects such as increased vulnerability to infection. Another idea for treatment of MS is to "retrain" the immune system in a way that removes the harmful aspects of the immune system and leaves the helpful components of the immune system in place.

The Study: Dr. Van Kaer and colleagues are investigating how to retrain a type of immune cell that regulates the function of other immune cells. They are activating these immune cells with a molecule called alpha-galactosylceramide (alpha-GalCer). Cells activated by alpha-GalCer turn down harmful immune effects including autoimmune-like attacks. They are investigating how alpha-GalCer works in a mouse model of MS called EAE. They are also designing and testing novel therapies that could someday be used to treat MS. In the EAE mouse model, they are testing protection against EAE and if other molecules can enhance the beneficial effects of alpha-GalCer.

What's Next? Alpha-GalCer, which can be isolated from marine sponges, may be a novel drug for retraining the immune system in a way that maintains the helpful immune functions and turns off the harmful functions. These studies could lead to novel treatments for MS that are both safe and effective.

Scott Zamvil, MD, PhD
University of California, San Francisco
San Francisco, California
Award: Research Grant
Title: Nrf2-dependent and –independent immune modulation by dimethyl fumarate in CNS autoimmunity
Summary: University of California, San Francisco researchers are investigating how an approved MS therapy called Tecfidera works to dampen the harmful effects of the immune system.

Background: In MS, the immune system attacks and destroys myelin, a fatty substance that surrounds and protects nerve fibers, which convey messages throughout the brain and spinal cord. Another way in which nerve fibers appear to be damaged in MS is through a biological factor called "oxidative stress." The relatively new oral MS therapy called Tecfidera (dimethyl fumarate) reduces relapses and other MS activity, and is thought to act by switching on a molecule called Nrf2, which in turn reduces oxidative stress and protects the nerve fibers in the brain and spinal cord. This therapy may act in two distinct ways that are both beneficial. This study is exploring how dimethyl fumarate works to induce the anti-inflammatory benefits and if they are related to Nrf2 or something else.

The Study: Dr. Zamvil and his colleagues are teasing out the different ways that dimethyl fumarate is beneficial for people with MS. Through a series of tests, the team is exploring the immune cells and activity influenced by this therapy both through Nrf2 and independent of Nrf2 activity. For example, they are examining the effects of dimethyl fumarate in mice that lack Nrf2 and that have EAE, a model of MS. If dimethyl fumarate decreases the inflammatory reaction in these mice without Nrf2, this will show that the therapy works in a second way that does not involve Nrf2. In addition, they are examining what other types of immune cells may be affected by dimethyl fumarate and are looking to see what genes are turned on and off in immune cells in people with MS before and after dimethyl fumarate treatment.

What's Next? Understanding more fully how dimethyl fumarate acts on the body may suggest ways of developing new treatments for relapsing and for progressive MS.

STOP—Biochemistry/Biophysics

Michael Kornberg, MD, PhD
Johns Hopkins University
Baltimore, Maryland
Award: NMSS-ABF Clinician Scientist Award
Title: The role and therapeutic potential of nitric oxide-induced nuclear GAPDH signaling in multiple sclerosis.
Summary: Researchers at Johns Hopkins University are conducting preliminary lab tests to understand whether a therapy called selegiline may be useful for treating MS by blocking the harmful effects of nitric oxide.

Background: Nitric oxide (NO) is a chemical normally produced in the body. However, NO may be harmful in certain circumstances. One way that NO may be harmful is by binding to a protein called GAPDH. When this binding happens, NO-GAPDH molecule moves into the cell nucleus and may turn on genes in a way that is harmful. It is possible that this binding occurs in MS.

The Study: Under the mentorship of Dr. Snyder, Dr. Kornberg and team are testing the role of NO-bound GAPDH in mice with the MS -like disease EAE. They are also exploring its activity in cells grown in a dish. A drug called selegiline prevents NO binding to GAPDH and is used to treat people with Parkinson's disease. This team is testing whether selegiline is beneficial for stopping or reversing symptoms and disease activity in EAE, an important preliminary step before this therapy may be considered to have potential for treating MS.

What's Next? These studies will increase our understanding of the role of NO in MS and whether selegiline has potential use for treating people with MS.

STOP—Neuropathology

Martina Absinta, MD
National Institutes of Health
Bethesda, Maryland
Award: Postdoctoral Fellowship
Title: Chronic Inflammation and Remyelination Failure in MS Lesions: in vivo and Postmortem Investigation of Chronic Lesions with Phase Rims
Summary: Researchers at the National Institutes of Health are using advanced MRI to examine lesions with subtle inflammation in the brains of people with MS to better understand how inflammation affects myelin repair.

Background: In MS, the loss of myelin, the fatty substance that surrounds and protects nerve fibers, is a dominant feature. Nerve fibers that have lost their myelin do not function properly, and they can also be damaged. Areas of myelin loss, called lesions, often show signs of inflammation. Inappropriate inflammation in MS lesions is harmful and may play a role in preventing repair of myelin in these areas with damage. Brain lesions in people with MS are usually visualized and monitored using magnetic resonance imaging (MRI). However, MRI does not readily detect subtle inflammation.

The Study: Dr. Absinta and her colleagues are using an advanced type of MRI called T2*/phase imaging that can provide better details and that may be able to detect inflammation better. T2*/phase imaging can detect features such as iron and free radicals that are found at higher levels in inflamed MS lesions. They would like to know how lesions change over time in individuals. They are exploring whether the size of lesions changes over time and affects surrounding normal tissue. Fifteen people with MS will come for imaging sessions once a year for 3 years. In the second

part of the study, they are looking at the brains of people with MS who have died and donated their tissues to research. They are comparing T2*/phase images of these brains and then looking at the same lesions under a microscope to see if and how subtle inflammation prevents myelin repair.

What's Next? The ability to better see inflammation in lesions of people with MS will increase our understanding of the role of subtle inflammation in blocking myelin repair, and may suggest new therapeutic targets to overcome this blockage. This imaging technique may also allow better monitoring of treatment effects.

Shing-yan Chiu, PhD
University of Wisconsin-Madison
Madison, Wisconsin
Award: Research Grant
Title: A Novel Specific Treatment for Progressive MS: Elimination of Mitochondrial Anchoring
Summary: Researchers at the University of Wisconsin in Madison are studying mouse models with features similar to progressive MS to investigate possible new approaches to stopping MS progression.

Background: Nerve fibers are long, thin extensions of nerve cells and are responsible for sending and receiving information in the brain, spinal cord, and to and from the rest of the body. At some point during the course of MS, damage to nerve fibers occurs, causing progressive disability. One possible reason for this damage is an abnormal accumulation of tiny energy factories in the cell called mitochondria. This abnormal accumulation of mitochondria may "clog" the nerve fibers, which may contribute to their impaired function. This clogging has been observed in a lab mouse that does not have adequate nerve-insulating myelin around its nerve fibers. When the accumulation of mitochondria is reversed in these mice, the disease severity is reduced.

The Study: Dr. Chiu and colleagues are looking at a molecule called syntaphilin, which acts like a "glue" for mitochondria inside the nerve fibers. They are examining in more detail whether deleting syntaphilin will "unglue" the mitochondria in nerve fibers, reverse the accumulation, and improve disease severity in Shiverer mice. They are also performing studies in a mice with the MS-like disorder EAE. They are testing whether deleting syntaphilin will improve disease severity in later phases of EAE, which shows features similar to the secondary-progressive phase of MS.

What's Next? Results from this study may suggest a new way to stop MS progression.

Ranjan Dutta, PhD
The Cleveland Clinic Foundation
Cleveland, Ohio
Award: Research Grant
Title: Pathogenesis of cortical demyelination underlying progressive disability in MS
Summary: Researchers are examining the brains of people with MS to understand differences between the damage caused by primary-progressive and secondary-progressive MS in search of ways to stop progression.

Background: The initial disease processes of primary-progressive MS (PPMS) and secondary-progressive MS (SPMS) are different, in that PPMS patients show almost no inflammatory activity, whereas SPMS, which by definition starts out as relapsing-remitting MS, is characterized by overt immune activity in earlier stages. Developing therapies to treat progressive MS requires a better understanding of the underlying pathology of MS subtypes.

The Study: The goal of the study is to delineate the cellular and genetic differences leading to brain injury between the two progressive MS subtypes using brain tissues donated by people who had MS. They are investigating how absence of initial immune-related disease activity alters the survival of nerve cells and the capacity for repair of nerve-insulating myelin between PPMS and SPMS. A significant aspect of this study is also to identify biological pathways related to nerves and myelin-making cells that are altered in progressive MS with (SPMS) or without (PPMS) inflammatory relapses.

What's Next? Understanding the differences between the subtypes of progressive MS will help in the design and selection of more personalized therapies and provide new strategies to protect the brain during the progressive disease course.

Shailendra Giri, PhD
Henry Ford Health Sciences Center
Detroit, Michigan
Award: Research Grant
Title: A Metabolomics approach for identifying metabolite signature in MS progression
Summary: Researchers at the Henry Ford Health Science Center in Detroit are analyzing blood samples from people with progressive MS to develop a blood test that may be useful for predicting disease course.

Background: MS has a variety of symptoms, and there is currently no way to predict its course, its future severity, or a person's response to treatments. In addition, there is no single lab test that can determine whether a person has MS, and diagnosing MS can be challenging for non-specialists. When the body breaks down bodily components and drugs, the products of the breakdown process are secreted into the blood and elsewhere in the body. These breakdown products are called "metabolites." The study of large groups of metabolites at once is called "metabolomics." Dr. Giri and his team previously used a metabolomics approach to show that the various metabolites present in the blood are different in healthy mice compared to mice that have EAE, a model of MS.

The Study: Dr. Giri and his team are now investigating the various metabolites in people with MS compared to people who don't have MS. They are working to identify the group of metabolites in blood that distinguish MS from non-MS individuals. This group of metabolites is called a "signature." After determining the MS signature in these blood samples, they will then use additional blood samples from people with other neurological disorders to confirm its ability to distinguish MS.

What's Next? Results from this study may allow development of a diagnostic test for MS that can be performed with a simple blood test. Other applications of such a test may include investigation of a person's response to therapy, increased understanding of disease mechanisms, and identification of new therapeutic targets.

Yang Hu, MD, PhD
Temple University
Philadelphia, Pennsylvania
Award: Research Grant
Title: Targeting Neuronal ER Stress for Neuroprotection in EAE
Summary: Researchers at Temple University in Philadelphia are investigating a way to protect nerve cells from stress in an animal model of visual problems sometimes seen in MS.

Background: In MS, some chronic disabilities, including blindness, muscle weakness, and cognitive problems, are due to damage to nerve cells. Finding a way to protect nerve cells in people with MS may prevent disease progression. One type of damage that nerve cells can experience is called "ER stress," which is stress to a tiny organ in the cell called the endoplasmic reticulum, which is important for synthesizing new proteins. ER stress has been demonstrated in nerve cells in the brains of people with MS, so some researchers believe that blocking events that lead to ER stress in nerve cells may protect these cells from injury.

The Study: Dr. Hu and colleagues are exploring ER stress in mice with MS-like disease called EAE, which can cause vision problems similar to those experienced by people with MS. Using genetic techniques, they are turning on a possibly helpful molecule called "XBP-1" and turning off a possibly harmful molecule called "CHOP." They are then asking three main questions compared to mice without this treatment: Is survival of nerve cells increased? Is degeneration of these cells decreased? Is visual function preserved?

What's Next? Results from this study may indicate that manipulating these two molecules may protect nerve cells from damage in MS.

Christoph Juchem, PhD
Yale University
New Haven, Connecticut
Award: Research Grant
Title: In Vivo Metabolomics of Oxidative Stress with 7 Tesla Magnetic Resonance Spectroscopy
Summary: Researchers at Yale are using two imaging techniques to determine the distribution and importance of the antioxidant glutathione in the brains of people with MS.

Background: In progressive MS, symptoms continually worsen even in the absence of new brains lesions and inflammation which are more prominent in relapsing forms of MS. Therefore, other disease processes must be involved. One idea is that a harmful condition called "oxidative stress" is occurring. Oxidative stress is caused by production of harmful molecules called "free radicals." Free radicals are normally rendered harmless by antioxidants produced by the body, but this antioxidative process may not work correctly in MS. One main antioxidant found in the brain, glutathione, may not work properly in MS.

The Study: Dr. Juchem and colleagues are using two imaging techniques called magnetic resonance spectroscopy and spectroscopic imaging to study glutathione and its associated molecules in the brain of people with MS compared to people without MS, matched for age and gender. They are investigating the presence of glutathione in areas of MS activity or damage (lesions), how glutathione impacts disease progression, and in what regions of the brain glutathione metabolism is altered in MS.

What's Next? This study will help to understand the role of oxidative stress in MS progression, and provide leads for stopping progression.

RESTORE

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

RESTORE—Therapy/Management of MS

Scott Newsome, DO
Johns Hopkins University
Baltimore, Maryland
Award: Research Grant
Title: A Phase 1b, open-label study to evaluate the safety and tolerability of the putative remyelinating agent, liothyronine, in individuals with MS
Summary: Johns Hopkins University researchers are performing a pilot clinical trial of people with MS to test a new therapy called liothyronine for its potential to improve repair of nerve-insulating myelin and protect nerve fibers.

Background: MS involves immune system attacks that injure myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin cannot function properly, and are left vulnerable to damage, leading to symptoms and disability in people with the disease. Repair of myelin, called remyelination, is incomplete in people with MS, and many people with the disease develop progressive, chronic disabilities due to failure of this repair mechanism. One idea for restoring function and preventing progression in people with MS is to improve myelin repair. Enhancing remyelination is likely to protect nerve fibers from harm which in turn could result in halting disability progression in MS.

The Study: Thyroid hormones influence most if not all systems in the body, including the brain and spinal cord. One type of thyroid hormone called T3 may play a role in promoting myelin repair and help prevent disability in MS. A novel synthetic form of T3 called liothyronine has been developed. In a small phase I clinical trial, Dr. Newsome and his team are evaluating the safety and tolerability of liothyronine in people with MS. They are enrolling 20 people with MS who have mild to moderate neurological disability. These participants will receive liothyronine with a dose-escalation schedule for 6 months. Every 6 weeks, participants will be examined for changes in their clinical status. At the beginning and end of the study, levels of T3 in the spinal fluid, and changes in inflammatory cytokines and growth factors in the spinal fluid will be assessed.

What's Next? This study is expected to determine the safe dose of liothyronine in people with MS and provide other data that will help with the design of larger, longer clinical trials of this therapy for its ability to stimulate myelin repair and prevent neurodegeneration.

RESTORE—Lifestyle/Wellness

Tiffany Braley, MD
University of Michigan
Ann Arbor, Michigan
Award: Research Grant
Title: A randomized trial of positive airway pressure therapy to treat cognitive dysfunction in MS patients with obstructive sleep apnea
Summary: University of Michigan researchers will determine whether a commonly used treatment for sleep apnea could improve cognitive performance in people with MS who also have sleep apnea.

Background: In addition to physical symptoms, many people with MS experience cognitive problems, which range from mild to debilitating. Unfortunately, few effective treatments for cognitive problems are available. Research suggests that up to one-half of people with MS may also have obstructive sleep apnea (OSA), a treatable sleep disorder in which the upper airway closes during sleep, decreasing blood oxygen levels. Obstructive sleep apnea may contribute to cognitive problems in people with MS, but the effects of OSA treatment on cognitive function in MS have never been studied.

The Study: Dr. Braley and her team are examining the effects of OSA and a commonly used treatment for OSA called positive airway pressure therapy on cognitive function in people who have both MS and OSA. People with MS who are at high risk for OSA will be recruited and will undergo a cognitive performance test and an overnight sleep study. Participants who are found to have OSA on their sleep study will then be treated with positive airway pressure therapy and have repeat cognitive testing, to see if their cognitive function improves with positive airway pressure therapy.

What's Next? Positive airway pressure therapy may be a new approach for improving cognitive function in some people who have MS and sleep apnea. Dr. Braley's research will also help identify which people with MS are most likely to benefit from sleep evaluations and treatment.

Kevin Patel, MD
Massachusetts General Hospital
Award: Postdoctoral Fellowship
Title: Functional connectivity changes underlying cognitive decline in early multiple sclerosis - evidence of compensatory function or sequelae of structural compromise?
Summary: Researchers are using imaging to understand the relationship between cognitive problems in people with MS and differences in connections between various parts of the brain.

Background: Cognitive impairment may occur early in multiple sclerosis, manifesting as problems with household tasks, driving, and social function. An MRI technique called "resting state functional connectivity" allows neuroscientists to observe and understand the patterns in which the parts of the brain are activated and interact with one another. Individuals with cognitive impairment have altered patterns of brain activity, and researchers can't explain the role these patterns play in cognitive impairment.

The Study: To better understand the part connectivity patterns play in MS, this team is using state of the art technology developed for the Human Connectome Project, a multicenter endeavor to map the connections in the human brain. An exceptionally powerful MRI scanner will collect functional connectivity data from 30 people with early MS and healthy controls. Findings will be correlated with the results of an extensive battery of neurocognitive tests.

What's Next? Providing accurate characterization of cognitive impairment and its associated changes seen with imaging may identify markers that will improve diagnosis, allow early detection of disease, and provide insight into prognosis.

Maria Schultheis, PhD
Drexel University
Philadelphia, Pennsylvania
Award: Research Grant
Title: Multitasking and MS: A cognitively-based approach to vocational rehabilitation
Summary: Drexel University researchers are studying multitasking in people with MS to find solutions for cognitive problems that affect employment.

Background: Cognitive changes are common in people with MS -- about half of all people with MS may develop problems with cognition. Cognition refers to a range of high-level brain functions, including the ability to learn and remember information; organize, plan and problem-solve; focus, maintain and shift attention as necessary; understand and use language; accurately perceive the environment; and perform calculations. Early recognition, assessment and treatment are important because cognitive changes -- along with fatigue -- can significantly affect a person's quality of life and are the primary cause of early departure from the workforce.

The Study: Initial evidence from this team has shown that multitasking -- the ability to do more than one activity at the same time -- was a better predictor of how people with MS function at work than traditional neuropsychological testing. The current study will build on this initial finding in two important ways. First, the study will employ a novel performance measure of multitasking ability that incorporates "real-world" tasks relevant to the workplace. The study will recruit individuals with and without MS to compare performance on this novel measure of multitasking ability, and will examine specific factors related to multitasking ability, such as fatigue. The investigators will also examine the effectiveness of specific rehabilitation interventions designed to address multitasking problems.

What's Next? These findings can enhance our understanding of factors that lead to unemployment in people with MS and inform rehabilitation efforts to improve quality of life and to help people stay in the workforce.

E. Yeh, MD
The Hospital for Sick Children
Toronto, Canada
Award: Mentor-Based Postdoctoral Fellowship Program
Title: Pediatric MS: Shaping the future of outcomes and disability
Summary: This training program at the University of Toronto Hospital for Sick Children will equip researchers with experience and knowledge to design and conduct research aimed at improving wellness in children with MS.

Background: Research on children with MS suggests that how well they do is linked to lifestyle factors, such as diet and physical activity, and also how well they stick to taking their medications. The research program led by Dr. Yeh is oriented towards understanding relationships between common symptoms and MS disease activity, risk factors for the development of these problems, and potential interventions for these problems. The program also focuses on understanding barriers to following medical recommendations and ways to encourage adherence with recommendations that will enhance the children's wellness.

The Study: The specific focus of the postdoctoral research training program is on rehabilitation strategies for children with MS, specifically (1) motor, cognitive and psychosocial

New Collaborative MS Research Award Testing Wellness Strategies

Lead Investigator: Dennis Bourdette, MD

Oregon Health & Science University, Portland

Title: "Developing patient-centered, evidence-based wellness programs for MS"

Summary: collaborating to develop patient-centered and evidenced-based wellness programs to improve the daily life of people with MS.

Background:

There is growing evidence that wellness/lifestyle factors are important to the long term health and quality of life of people with MS. This evidence comes from a variety of sources which indicate that factors such as low vitamin D, stress, or smoking may increase disease activity. People with MS are generally very interested in things they can do for themselves that will improve their health. However, they generally receive little guidance from their neurologists and other traditional health care providers because of the lack of sound evidence-based recommendations. This award aims to fill the knowledge void and provide people with wellness approaches based on rigorous research and that are affordable and achievable.

The Study:

Dr. Bourdette has gathered together a group of investigators with experience in conducting clinical investigations and trials in MS (himself, along with Drs. Vijayshree Yadav and Rebecca Spain), mindfulness meditation (Drs. Lynne Shinto and Angela Senders), and advanced magnetic resonance imaging techniques (Dr. Bill Rooney). Drs. Diane Stadler and Kerry Kuehl are new to the field of MS research, and were invited to join the Collaborative Center for their expertise in designing effective long-term dietary and exercise programs for health promotion in people with chronic disease. The initial three studies launched during the term of this Award will be a diet intervention, an aerobic exercise intervention, and an evaluation of existing wellness strategies among the local MS population. Each study will measure effectiveness, feasibility, and cost-effectiveness, to provide information for larger studies.

What's Next?

Upon completion of the pilot studies, the team is applying for national funding for larger, long-term studies and will set up an interactive website as a resource for people with MS.

with emphasis on modifiable lifestyle factors, including physical activity and diet; and (3) interventions to address these risk factors. This post-doctoral research fellowship is intended to provide exposure to and training in clinical aspects of pediatric MS and related disorders while at the same time providing research training in clinical research methods, and the opportunity to develop and complete independent research projects supported by a variety of scientists at the institution. The fellow will be offered 1, 2, or 3 year postdoctoral fellowship, depending on the nature and complexity of the research plan.

What's Next? Fellows who complete the training will be uniquely equipped to conduct rehabilitation-oriented research focusing on improving quality of life and outcomes for children who have MS.

Kathleen Zackowski, PhD
Kennedy Krieger Research Institute
Baltimore, Maryland
Award: Mentor-Based Postdoctoral Fellowship Program
Title: Advancing multiple sclerosis research through neuroscience
Summary: This training program will equip two fellows with crucial clinical and research skills necessary to conduct rehabilitation research aimed at improving wellness for people with MS.

Background: Rehabilitation in MS is still an underdeveloped area of MS research with the potential to greatly advance the field as a whole. Traditional rehabilitation uses techniques to improve activities such as walking and balance, without taking into account neural mechanisms responsible for walking or balance abnormalities. Linking the neuropathology of MS with symptoms and movement limitations provides a rational basis for choosing rehabilitative interventions. This is a major focus of the MS research at Kennedy Krieger Institute/Johns Hopkins University School of Medicine.

The Study: In this 3-year program trainees will have one-on-one instruction by an expert mentor in MS Rehabilitation. A senior MS specialist in Neurology and an expert in motor control/rehabilitation research will provide supportive guidance, and trainees will work side-by-side with other MS specialists, expert in a range of fields, including physical therapy, medicine, radiology, biomedical engineering, neuroscience, and social work. Initially the trainees will learn basic rehabilitation techniques important for evaluating and treating people with MS. The trainees will also have formal teaching in the classroom setting, on topics such as data analysis, clinical trial design, scientific writing, and research ethics, all of which are necessary for a successful career in research. Initially, the fellows will work with their mentor on MS research projects already underway. Later, as the fellows gathers experience, they will develop an independent research project with guidance from the mentor and a Senior Advisory Committee.

What's Next? This training program offers a unique opportunity for two fellows to train at a center on the forefront of MS research. The fellows will learn crucial clinical and research skills necessary to build a career in MS rehabilitation research. By the end of the program the trainee will have gained skills necessary to begin their own independent research program in MS.

RESTORE—Nervous System Repair

Dennis Bourdette, MD
Oregon Health & Science University
Portland, Oregon
Award: Research Grant
Title: Promoting remyelination in models of MS with a selective thyromimetic drug
Summary: Researchers at Oregon Health and Science University in Portland are testing a drug called sobetirome that may promote myelin repair in animal models of myelin loss.

Background: In MS, myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed. Nerve fibers that have lost their myelin do not function properly, and the may also be destroyed through the disease process. We don't yet have therapies focusing on promoting myelin repair. The cells in the brain and spinal cord that make myelin are called oligodendrocytes. Mature, myelin-making oligodendrocytes are derived from immature oligodendrocyte precursor cells.

A thyroid hormone called "T3" promotes the maturation of immature oligodendrocytes into mature, myelin-making cells and promotes myelin repair in some mouse models with myelin damage. However, T3 cannot be given to people because it is toxic. A drug similar to T3 called "sobetirome" has been used in an FDA-approved phase I clinical trial to lower cholesterol. Sobetirome is more specific than T3 and does not produce the side effects associated with T3 toxicity. Sobetirome may be useful for promoting myelin repair in MS, but its effects on oligodendrocytes have not been tested.

The Study: Dr. Bourdette and his team are growing immature oligodendrocytes in a dish and asking if sobetirome promotes their maturation. Then they are testing whether sobetirome improves myelin repair in mice with myelin damage caused by a toxin, and finally, they are testing whether sobetirome promotes myelin repair in a mouse model of MS called EAE.

What's Next? If these preliminary tests of sobetirome are successful, clinical trials testing sobetirome in people with MS may be the next logical step for determining whether this agent has potential as a repair strategy.

Laura Dickey, PhD
University of Utah
Salt Lake City, Utah
Award: Postdoctoral Fellowship
Title: Human neural precursor cell-mediated remyelination in a viral model of MS
Summary: Researchers at the University of Utah are testing the idea that molecules secreted by stem cells improve potential for repairing nerve-insulating myelin.

Background: In MS, the fatty substance called myelin, which protects nerve fibers, is attacked and destroyed. This leads to symptoms in people with the disease and leaves nerve fibers vulnerable to injury. One idea to improve symptoms in people with MS is to design therapies that increase the myelin repair process. The cells in the brain that make and repair myelin are called oligodendrocytes. These cells are derived from immature oligodendrocytes. Previous studies showed that myelin repair is improved in mice when they receive injections of neural stem cells. The mouse's immune system quickly removes the foreign neural stem cells, but the positive effects remain much longer after the stem cells are gone. This suggests that the neural stem cells leave behind helpful factors that improve myelin repair.

The Study: During this fellowship, Dr. Dickey is working with an experienced team to determine if these neural stem cell factors are sufficient to improve myelin repair by promoting maturation of immature cells into myelinating oligodendrocytes. First they are growing neural stem cells in a dish and injecting only the liquid the cells grow in, and not the cells themselves, into mice that have myelin damage. If myelin repair is improved, this will indicate that the stem cells make one or more factors that are secreted into the dish that improve myelination. Next they are testing the possibility that a molecule called "transforming growth factor beta" or "TGF-beta" is one of the factors made by the neural stem cells. They are observing the impacts of introducing TGF-beta into the brains of these mice and also observing mice that cannot make TGF-beta to test the importance of this molecule in myelin repair.

What's Next? Results should improve our understanding of stem cell-mediated myelin repair and may lay groundwork for the development of a therapy using stem cell-secreted factors, bypassing the need to transplant stem cells.

Meredith Hartley, PhD
Oregon Health & Science University
Portland, Oregon
Award: Postdoctoral Fellowship
Title: A thyroid hormone-based strategy for promoting remyelination
Summary: Researchers at Oregon Health & Science University are testing thyroid hormone-like drugs to see if they will improve myelin repair and to determine their potential for development as a treatment for MS.

Background: The current therapies for MS all work by dampening the immune system, which does not function properly in people with the disease. However, MS also involves damage to the myelin sheath, the fatty substance that surrounds and protects nerve fibers. A promising therapeutic strategy is to promote repair of myelin, which is likely to complement available therapies. Thyroid hormone initiates normal myelin production in infants and improves myelin repair in disease models of MS. Unfortunately, elevated levels of thyroid hormone are unsafe in humans. An alternate, related type of molecule called a "thyromimetic" may provide the desired effect while avoiding toxicity.

The Study: Under the mentorship of experienced researchers, Dr. Hartley and team are testing the role of thyroid hormone and the effects of a thyromimetic in mice that have myelin damage. First they are confirming that myelin repair depends on the levels of thyroid hormone. Next they are testing a thyromimetic called sobetirome and improved versions of sobetirome that have greater access to the brain to determine if these will improve myelin repair in these mice.

What's Next? Promoting myelin repair is expected to complement therapies that modulate the immune system. Results from these studies will determine whether thyroid hormone-like therapies restore myelin in MS.

Abraham Langseth, PhD
Johns Hopkins University
Baltimore, Maryland
Award: Postdoctoral Fellowship
Title: The role of Megf11 in oligodendrocyte precursor cell engulfment and remyelination
Summary: Researchers at Johns Hopkins University in Baltimore are examining the role of a protein called Megf11 in oligodendrocyte maturation and the clean-up of myelin debris, which are both required for myelin repair.

Background: In MS, nerve-insulating myelin and nerve cells are damaged. One idea for restoring function for people with MS is to improve the myelin repair process, which is generally inefficient and incomplete. The cells in the brain and spinal cord that make myelin are called oligodendrocytes. New oligodendrocytes that can make new myelin are derived from immature oligodendrocytes (oligodendrocyte precursor cells or OPCs) that are found throughout the brain and can move to areas of damage when needed. When myelin is destroyed, myelin debris is left behind. Some research suggests that myelin debris inhibits the maturation process of oligodendrocytes, suggesting that cleaning up the old myelin debris may be a necessary step in the myelin repair process. Some evidence generated by this team suggests that OPCs help to clean up myelin debris, and they may perform this function using a molecule called "Megf11". If debris cleanup slows the myelin repair process, then understanding this process may lead to important discoveries for speeding myelin repair in MS.

The Study: Dr. Langseth and team are investigating the role of Megf11 in myelin debris clean-up, oligodendrocyte maturation, and the myelin repair process. They are growing OPCs in a dish and are investigating the importance of Megf11 in clean-up of myelin debris and in their differentiation to mature oligodendrocytes. Then they are investigating Megf11 in myelin clean-up and in oligodendrocyte maturation in mice that have myelin damage. Finally, they are evaluating the presence of Megf11 in immature oligodendrocytes in brain lesions from people with MS.

What's Next? The results from this study may identify new therapeutic targets for improving myelin repair in MS.

Wendy Macklin, PhD
University of Colorado
Denver, Colorado
Award: Research Grant
Title: Developing zebrafish as a drug screen model
Summary: University of Colorado researchers are investigating the usefulness of a type of fish called zebrafish to rapidly screen drugs that may someday be useful for stimulating repair of nerve-insulating myelin in MS.

Background: In MS, the immune system attacks and destroys myelin, the substance that surrounds and protects nerve fibers. One strategy for restoring function is to stimulate myelin repair. Screening large numbers of possible new drugs requires an inexpensive and convenient model that will allow researchers to identify ones with repair potential for repairing myelin.

The Study: Dr. Macklin and her colleagues are using a type of fish called zebrafish as a model for screening these compounds. Zebrafish may respond to drugs in a way that is similar to humans and represent a model for screening drugs for both toxicity and myelin repair. The team is using zebrafish that have been genetically engineered with a green fluorescent protein on myelin-making cells called "oligodendrocytes." The green label provides a rapid readout of changes in myelin in these fish following drug treatment. They are using these fish to determine how different drugs work to increase myelination. Another approach they are using is to damage oligodendrocytes in the fish and examining how drugs work to restore the lost cells and increase myelination.

What's Next? The ability to rapidly screen drugs with potential for repairing myelin is likely to speed development of MS therapies.

Isobel Scarisbrick, PhD
Mayo Clinic Rochester
Rochester, Minnesota
Award: Research Grant
Title: Targeting Protease Activated Receptor 1 to Promote Myelin Repair
Summary: Researchers at the Mayo Clinic are investigating the importance of a molecule called PAR1 in myelin protection and repair to determine if currently approved drugs that target PAR1 for treatment of other diseases could be used to treat people with MS.

Background: In MS, the immune system attacks and destroys myelin, which is the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin cannot send their signals properly, leading to symptoms in people with the disease. Understanding how myelin destruction and repair is controlled is important.

The Study: A molecule called PAR1 (also known as the thrombin receptor) is expressed on the surface of cells. The FDA has approved medications that target PAR1, and these drugs are being tested in clinical trials to treat people with other diseases. Dr. Scarisbrick and her team are investigating the importance of PAR1 and associated molecules in myelin destruction and repair. They are using mice that do not express PAR1 to analyze how myelin is formed and how myelin is repaired after myelin destruction.

What's Next? If PAR1 is important for protection and repair of myelin, there are clinical trials already underway in other diseases and these agents could potentially be quickly repurposed to test benefits in people with MS.

Haley Titus-Mitchell, M.S.
Northwestern University
Chicago, Illinois
Award: Postdoctoral Fellowship
Title: Immunoregulatory and myelin repair therapies in T cell-mediated mouse models of Multiple Sclerosis.
Summary: Researchers at Northwestern University are trying to develop a two-step approach to therapy for MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers, and the nerve fibers are also injured. Current therapies for MS dampen the immune system, but they also affect a person's ability to fight off infections. There is also a need for therapies that can promote myelin repair to restore function in people with MS.

The Study: Haley Titus-Mitchell, PhD, and colleagues are testing a two-step approach to treating MS. In the first step, they are using a therapy to "teach" the immune system to view myelin components as "self" rather than "foreign," while leaving it intact to fight off infections. In the second step, they are testing therapies that they believe will improve myelin repair. Their idea is that repair-promoting therapies will work better if the immune system is no longer attacking the myelin. First, they are determining the effect of myelin-repair molecules in mice that have myelin destruction independent of the immune system. Next, they are using a model of MS called EAE and trying to "teach" the immune system to tolerate, rather than attack, myelin components. They will optimize this approach to see if myelin repair improves in the setting of less immune destruction.

What's Next? Results from this study may suggest combination therapies that will optimize MS treatment.

19 New Pilot Projects Take Aim at MS

One way the Society propels MS research forward is by funding high-risk, high-potential pilot projects to investigate untested ideas. These one-year grants allow researchers to quickly gather data to determine if ideas are worth pursuing. Grants began April 1, 2015.

STOP

Myriam Chaumeil, PhD (University of California, San Francisco) is using novel imaging to differentiate between helpful and harmful immune cells.

Jennifer Graves, MD, PhD (UCSF) is exploring hormonal aging and MS progression.

Javier Ochoa-Reparaz, PhD (Geisel School of Medicine at Dartmouth, Lebanon, NH) is determining whether gut bacteria contribute to MS progression.

David Pitt, MD (Yale University, New Haven, CT) is exploring the reason for MS variability.

Andrew Steelman, PhD (University of Illinois at Urbana-Champaign, Urbana, IL) is exploring how infections may trigger MS relapses, for clues to relapse prevention.

Alastair Wilkins, FRCP, PhD (University of Bristol, Bristol, UK) is testing a mechanism that may underlie MS progression, for clues to stopping progression in its tracks.

Xiaoming Zhou, PhD (Uniformed Services University of the Health Sciences, Bethesda, MD) is testing a method of stopping the immune attack in MS-like disease.

RESTORE

Deborah Backus, PhD (Sheperd Center, Atlanta, GA) is testing whether FES cycling improves fatigue in people with fatigue who depend on wheelchairs for mobility.

Shuo-Hsiu Chang, PhD (The University of Texas Health Science Center, San Antonio) is studying the effectiveness of a wearable exoskeleton to improve walking in people with MS.

Pierfilippo De Sanctis, PhD (Albert Einstein College of Medicine, Bronx, NY) is using novel imaging to test the ability of people with MS to perform cognitive tasks while walking.

Nandini Deshpande, PhD (Queen's University, Kingston, Ontario, Canada) is testing mobility in real-life situations in people with MS.

Paula Dore-Duffy, PhD (Wayne State University, Detroit, MI) is determining whether a novel type of adult stem cell can promote repair in MS models.

Babette Fuss, PhD (Virginia Commonwealth University, Richmond, VA) is testing a molecule that may help brain cells to promote myelin repair and neuroprotection.

Bonnie Glanz, PhD (Brigham and Women's Hospital, Boston, MA) is testing a method of computerized cognitive rehabilitation in MS.

Jane Kent, PhD (University of Massachusetts Amherst, Amherst, MA) is evaluating the usefulness of foot tap speed as a way of predicting changes in mobility in people with MS.

Citlali Lopez-Ortiz, PhD (University of Illinois at Urbana-Champaign, Urbana, IL) is testing a dance program for improving MS symptoms.

Paul Rosenberg, MD, PhD (Boston Children's Hospital, Boston, MA) is investigating a protein that may put the brakes on myelin formation in MS.

Wendy Vargas, MD (Columbia University, New York, NY) is studying academic performance in children with MS for clues to early intervention to address cognitive problems.

END

Luwen Zhang, PhD (University of Nebraska, Lincoln) is studying a virus in MS.

RESTORE— Biology of Glia

Patrizia Casaccia, MD, PhD
Icahn School of Medicine at Mount Sinai
New York, New York
Award: Research Grant
Title: Understanding the role of gene/environment interaction in oligodendrocytes
Summary: Mount Sinai School of Medicine researchers are exploring how environmental factors can be harmful or protective to the cells that maintain myelin and are damaged in the course of MS.

Background: Progress has been made in identifying genes that make people susceptible to developing MS, but there are many gaps in our knowledge, such as what factors drive disease progression and how do environmental factors interact with MS genes to possibly influence disease course. In the brain and spinal cord, cells called oligodendrocytes make myelin, the fatty substance that surrounds and protects nerve fibers. In MS, myelin is attacked and destroyed, leading to symptoms. Environmental factors may affect the activity, or "expression" of genes that protect oligodendrocytes, and these factors may have harmful or beneficial effects. One way that the environment can modify gene expression is by a chemical modification of the DNA, which is called "methylation." A recent study from Dr. Casaccia's lab showed differences in DNA methylation in brain tissue between people without MS and those with MS in areas without lesions. DNA methylation, and thus gene expression, may be abnormal in people with MS, even in areas of the brain that otherwise look normal.

The Study: Dr. Casaccia and colleagues are testing this idea of environment-driven changes in gene expression in oligodendrocytes. They are looking at a gene called NDRG1 that is present at very high levels in myelin of healthy subjects and decreased in myelin of MS patients. In normal-appearing brain tissue from people with MS, NDRG1 is excessively methylated, and the expression of the NDRG1 gene is decreased, but the function of this molecule remains unknown. In this study, they will test the idea that low levels of NDRG1 are harmful and high levels of NDRG1 are protective in a mouse model of MS called EAE. They are also asking whether the reason for the low levels of NDRG1 in MS brains is the presence of excessive DNA methylation in oligodendrocytes. They are also using mice to understand whether environmental conditions, such as a high fat and high salt diet (reported as a possible risk factor for MS), induce changes in DNA methylation of NDRG1.

What's Next? Results from this study may reveal a new way to protect myelin-making cells from injury, and may offer new clues to dietary factors that may affect disease course.

Meng-meng Fu, PhD
Stanford University
Stanford, California
Award: Postdoctoral Fellowship
Title: Regulation of MBP mRNA Transport in Oligodendrocytes
Summary: Researchers at Stanford University are investigating how a protein critical to the formation of nerve-insulating myelin is made and how its message is transported, to gather information that may be critical to finding a way to repair myelin in MS.

Background: Healthy nerve fibers are protected and insulated by a fatty substance called myelin. In MS, myelin is destroyed, resulting in disruption of nerve fiber function and symptoms in people with MS. Though some amount of myelin repair is possible in early stages of MS, it becomes less and less

efficient in later stages. One idea to improve symptoms in MS is to improve myelin repair. The cells that make myelin are called oligodendrocytes. These cells make many different kinds of proteins using information in messenger RNA (mRNA) that comes from DNA in the cell's nucleus. Most proteins are made in areas very close to the nucleus. However, the most abundant mRNA in oligodendrocytes, which encodes MBP (myelin basic protein) is different; its mRNA is shipped to regions far from the nucleus, and the protein is made in these remote regions. This process is important, because in mice with gene abnormalities that cause improper myelin growth, this distant localization of MBP mRNA is disrupted.

The Study: As part of her fellowship training, Dr. Fu is working with an experienced team to perform studies to further understand how and why MBP mRNA is transported far from the nucleus for the protein to be made. First, they are using cells grown in a dish to examine this mRNA transport process in detail. Next they are working to identify proteins that are involved in transport of MBP mRNA to distant locations. Then they will try to understand why this transport is necessary by making a version of the MBP mRNA that cannot be transported to distant sites in the cell. This non-transportable MBP mRNA will be introduced into mice to see if myelin synthesis is perhaps abnormal.

What's Next? Results from this study will increase our understanding of the basic process of myelin manufacturing and may identify novel targets for new treatments to increase myelin repair in people with MS.

Stefanie Giera, PhD
Boston Children's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowship
Title: Characterization of a novel G protein-coupled receptor in oligodendrocyte development
Summary: Researchers at Boston Children's Hospital are investigating the importance of a specific molecule in the ability of myelin-making cells to mature and make nerve-insulating myelin, for clues to promoting myelin repair in MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers are also injured. Myelin is made by cells called oligodendrocytes. There are spare, immature oligodendrocytes residing in parts of the brain, and one idea for restoring function in MS is to find ways to increase oligodendrocyte maturation to produce more cells that can repair myelin. A group of proteins called "G-protein coupled receptors" or "GPCRs" are found in many parts of the body. About one-third of the current drugs available for treating many types of illnesses target GPCRs. One GPCR called GPR56 is required for cell division of immature oligodendrocytes and may play a role in maturation of these cells.

The Study: As part of her postdoctoral research training, Dr. Giera is working on a team that is conducting studies to establish the importance of GPR56 in oligodendrocyte development and myelin formation. To do this, they are developed mice that do not make GPR56, and examining the myelin and oligodendrocytes in these mice. They are also determining what molecules binds to GPR56 to make it work, as well as other molecules that work with GPR56.

What's Next? If GPR56 is important for oligodendrocyte maturation, this molecule may represent an important future target for developing therapies to stimulate myelin repair in people with MS.

Qing Lu, PhD
Children's Hospital Medical Center
Cincinnati, Ohio
Award: Research Grant
Title: Histone deacetylase control of CNS myelination and remyelination
Summary: Cincinnati Children's Hospital Medical Center researchers are focusing on how an enzyme controls myelin growth and repair, with a future possibility of stimulating this enzyme to repair myelin 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 been stripped of their myelin do not function properly, and are vulnerable to damage. The cells in the brain and spinal cord that make myelin are called "oligodendrocytes." Mature oligodendrocytes that can make myelin are derived from immature precursor cells that reside in the brain. One idea to treat MS is to increase the number of mature oligodendrocytes by coaxing immature cells to mature. This process is controlled by genes, through enzymes called histone deacetylases, which are important for oligodendrocyte maturation.

The Study: Dr. Lu and his colleagues are examining one type of histone deacetylase called "Hdac3," which is important in this process of oligodendrocyte maturation. They are looking at what steps in the maturation process are controlled by Hdac3 and what genes are turned on or off by the activity of Hdac3. To do this, they are using mice with mutations in Hdac3 in oligodendrocytes at different stages of maturation. They are also using various genetic techniques to identify the specific genes that are regulated by Hdac3.

What's Next? Results from this study may suggest that Hdac3 is a target for future development of drugs that can be used to improve oligodendrocyte maturation, which is expected to improve myelin repair in MS.

Teresa Wood, PhD
Rutgers, The State University of New Jersey
Piscataway, New Jersey
Award: Research Grant
Title: mTOR Signaling Targets and Pathway Intersections in Oligodendrocyte Differentiation and Myelination
Summary: Researchers at Rutgers, the State University of New Jersey, are investigating the role of a molecule called mTOR and associated molecules in enhancing myelin repair.

Background: In MS, myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed, and the nerve fibers are also damaged. Natural myelin repair and synthesis in the brain and spinal cord are performed by cells called "oligodendrocytes." Myelin repair in MS is incomplete and fails over time, but the potential for repair exists in both early and late stages of MS. One strategy for providing better treatment for MS is to protect oligodendrocytes and increase their ability to synthesize new myelin and protect the nerve fibers.

The Study: Dr. Wood and her team are investigating a molecule called "mammalian target of rapamycin" or "mTOR." This molecule controls the maturation of oligodendrocytes, and also myelin growth and repair. Using cells grown in a dish and mice in which the expression of mTOR and other related molecules can be controlled genetically, Dr. Wood is investigating how other molecules work with mTOR to control these processes.

What's Next? If this research successfully identifies mTOR and related molecules that work together to promote myelin repair, it will uncover new strategies for therapies designed to repair damage in the MS brain and restore function.

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New Collaborative MS Research Award Takes the Next Step in MS Genetics

Lead Investigator: David Hafler, MD
Yale University, New Haven, CT

Title: "Systematic Genome Editing of the Risk Variants in Multiple Sclerosis"

Summary: Researchers at Yale, Harvard, and two University of California institutions have teamed up to apply highly advanced technology to manipulate MS risk genes to tease out the exact pathways by which MS develops.

Background:

The next generation of MS genetics began when the International MS Genetics Consortium was launched with early seed funding from a National MS Society Collaborative MS Research Center Award. The consortium has identified more than 159 genetic variations related to MS, and has begun to identify the specific immune cells and proteins involved. Interpreting the genetic variations identified by such large-scale studies remains a challenge. Researchers are now taking the next steps toward understanding how genes contribute to the development of the immune attack in MS and how to use this knowledge to stop the immune attack in its tracks.

The Study:

This Collaborative Center connects major laboratories nationwide. It brings together MS immunology experts –Dr. Hafler and Dr. Vijay Kuchroo (Harvard University); genetics experts – Dr. Hafler and Dr. Alexander Marson (University of California, San Francisco); and Dr. Jennifer Doudna (University of California, Berkeley), who pioneered a new technology to precisely "edit" genetic material to tease out what role each gene plays. Dr. Doudna will employ cutting-edge techniques to perform this 'molecular surgery' on specific genes that have been identified to carry risk of MS. In parallel, Dr. Hafler and Dr. Marson will examine sets of genetic material ("genomes") of a large group of people with MS and people without MS to assess how these genes interact with one another to disrupt immune system activity. Dr. Kuchroo will use models to tease out how these genes affect the development of MS-like disease in mice.

What's Next?

These efforts not only promise to discover the pathways by which MS develops, but also provide a basis for using this knowledge to explore novel strategies for treatment and prevention.

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

Cory Teuscher, PhD
University of Vermont
Burlington, Vermont
Award: Research Grant
Title: Identification of gene-by-environment interactions contributing to CNS autoimmune disease
Summary: University of Vermont researchers are using mice with MS-like disease to look at interactions between genes and the environmental factors Vitamin D and exposure to UV/sunlight for clues to preventing or treating MS.

Background: Both genetic and environmental factors contribute to a person's risk of developing MS. Studies involving twins have shown that about 30% of risk is due to genetics, and the remaining 70% is due to the environment or interactions between genes and the environment. Understanding how genes and the environment interact in people is difficult. A mouse model of MS called EAE reproduces many of the susceptibility factors for MS.

The Study: Dr. Teuscher and colleagues are using mice with EAE to study the effects of the environmental factors Vitamin D and ultraviolet (UV)/sunlight exposure, which are thought to be protective in MS, on the disease process. Vitamin D is made by the body through the skin's exposure to sunlight. They are looking at segments of genetic material that may harbor genes that interact with Vitamin D and/or UV/sunlight exposure to influence susceptibility to EAE. The team is conducting a series of studies designed to independently test the role of Vitamin D and UV/sunlight exposure to determine if one or the other is a better protective factor.

What's Next? Determining environmental factors that may be protective, and identifying the genes that modulate these protective effects, may help determine how to prevent MS and develop optimal therapies for people who have MS.

Howard Lipton, MD
University of Illinois at Chicago
Chicago, Illinois
Award: Research Grant
Title: Generic approaches for detecting a virus in MS in acute demyelinating lesions
Summary: University of Illinois at Chicago researchers are devising a method to detect the presence of viruses in newly forming MS lesions, in hopes of identifying the cause of MS and preventing its development.

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

The Study: Howard Lipton, MD, of the University of Illinois at Chicago, has received a research grant from the National MS Society to devise a method to detect the presence of viruses in newly forming MS brain lesions, regardless of the type of virus that is present. Dr. Lipton and colleagues are devising a method to uncover generic viruses by detecting a molecule called long dsRNA, which is present in nearly all virus infections but not present in normal or stressed cells or in most other types of microbes (such as bacteria). Thus, the presence of long dsRNA in MS lesions might suggest the presence of a virus that may cause the disease.

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

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