NEW RESEARCH

STOP. RESTORE. END.

Society Commits More than $17 Million for 43 New MS Research Projects

The National Multiple Sclerosis Society has committed more than $17 million to support an expected 43 new MS research projects. These are part of a comprehensive approach to accelerate research breakthroughs that will stop MS, restore lost function and end MS forever.

This financial commitment is the latest in the Society's relentless research effort, investing a projected $40 million in 2017 alone to support new and ongoing studies around the world. Research breakthroughs fuel the treatments and solutions people with MS need to overcome the challenges of MS today, with confidence and hope for a world free of MS tomorrow.

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

National Multiple Sclerosis Society

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

STOP: The Society is cofunding a multi-million dollar trial to investigate if statins could become an MS treatment in more than 1,000 people with secondary-progressive MS. (see p. 3)

RESTORE: Researchers at University of Utah are collaborating to understand if stem cells programmed in the laboratory from adult skin cells are beneficial for repair of nervous system damage in models of MS-like disease. (see p. 15)

END: Researchers at Yale are exploring a novel pathway by which genetic variants in people with MS may promote nervous system damage, for clues to stopping and ending MS. (see p.28)

Inside...

STOP

Solutions for progressive MS remain frustratingly elusive. New insights into the pathways contributing to progression have brought promise to the progressive MS treatment pipeline, but much more needs to be done to offer effective solutions for those facing progression. Among the approaches being taken are: determining mechanisms underlying the causes of MS injury, identifying objective indicators of disease activity and progression that measure treatment impact and predict an individual's course and response to therapy, and testing approaches for the prevention and treatment of progression. These approaches will rapidly increase and translate to breakthroughs for everyone affected by MS.

STOP—Human Therapy Trials/Management of MS

Laura Piccio, MD, PhD
Washington University School of Medicine
St. Louis, MO
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $774,853
Title: Randomized controlled trial of intermittent fasting and paleolithic diet in multiple sclerosis
Summary: Investigators at Washington University in St. Louis are conducting a clinical trial comparing intermittent fasting with a normal western diet in people with MS.

Background: This team has been interested in studying the link between diet, body metabolism and the immune attack in MS for many years. They have shown in mice that reduction of calorie intake through calorie restriction or intermittent fasting improves an MS-like disease. They also completed a small proof-of-principle study of intermittent fasting in people with relapsing MS. Preliminary analyses found that fasting was able to modulate the blood levels of "leptin" and "adiponectin," molecules that relate to inflammation.

The Study: Now the team is performing a larger study to compare intermittent fasting (eating about 500 calories/day for two days/week) to a control group eating their normal western-style diet. The diet lasts for 12 weeks and will involve 40 people with relapsing MS. They will undergo several laboratory and clinical assessments before starting the diet, then again at 6 and 12 weeks. The investigators are looking at the effects of diet on leptin and adiponectin levels, immune system activity, and the composition of gut bacteria.

What's Next: This study will examine important questions regarding dietary recommendations for people with MS, which urgently need to be addressed in a more rigorous, controlled manner.

Multi-million Dollar Trial to Investigate if Statins Could Become MS Treatment

Phase 3 trial involving more than 1,000 people with multiple sclerosis will investigate whether inexpensive drug could become a treatment

The British trial will cost almost $7 million and is being funded by a collaboration of the National MS Society (U.S.), the MS Society (U.K.), the National Institute for Health Research (U.K.), the National Health Service (U.K.), and U.K. universities.

The trial will test simvastatin, an inexpensive cholesterol lowering drug, in people with secondary progressive MS (SPMS). There are currently no licensed treatments that target disability progression in people with SPMS.

The research will be led by Dr. Jeremy Chataway, University College London Institute of Neurology, who led the phase 2 trial of simvastatin involving 140 people with SPMS that was published in **The Lancet** in 2014. The research found those taking high doses of the drug had a significant reduction in the rate of brain atrophy (brain shrinkage) over two years, and also had better disability and quality of life scores at the end of the study.

"This drug holds incredible promise for the thousands of people living with secondary progressive MS in the U.K., and around the world, who currently have few options for treatments that have an effect on disability," said Chataway. "This study will establish definitively whether simvastatin is able to slow the rate of disability progression over a three year period, and we are very hopeful it will."

Bruce Bebo, Executive Vice President, Research for the National MS Society said, "We are very pleased to be a partner in the public-private funding syndicate that was forged to support a phase 3 clinical trial of a repurposed, generic therapy for people with SPMS, for whom there are few treatment choices."

The simvastatin trial begins in Spring 2017, and will involve 1180 people with SPMS across the U.K. The trial will take six years to complete.

The trial will cost a total of nearly $7 million, with research costs of:

- $1.8M National Institute for Health Research (U.K.)
- $1.4M MS Society (U.K.)
- $1.4M National MS Society (U.S.)

Physicians Receive Training Awards for Specialized MS Care

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

Awardee	Location	Mentor
Mustafa Ansari, MD	University of Southern California	Lilyana Amezcua, MD Dan Pelletier, MD
Lindsay Horton, MD	University of Colorado Denver	John Corboy, MD
Maria del Pilar Guillermo Prieto Eibl, MD	The Ohio State University	Michael Racke, MD
William Kilgo, MD	University of Virginia	John Rinker, MD
David Lapides, MD	University of Alabama at Birmingham	Myla Goldman, MD David Jones, MD
Ahmed Obeidat, MD, PhD	University of Cincinnati	Elizabeth Dragan, MD

STOP—Psychosocial Aspects of MS

Heather Wishart, PhD
Trustees of Dartmouth College
Lebanon, NH
Award: Research Grant
Term: 4/1/2017-3/31/2019
Funding: $366,010
Title: Cognitive evaluation in MS: Expanding clinical research potential through the validation of an online testing battery
Summary: Researchers at the Geisel Medical School at Dartmouth are testing the feasibility of administering cognitive testing online, to improve the process of evaluating cognitive changes in large-scale studies in MS.

Background: Large-scale studies are important for understanding the causes of cognitive changes in MS. Currently, cognitive changes in MS are measured using standardized in-person neuropsychological tests of memory, processing speed, and other abilities. Because of advances in technology, it is now possible to administer cognitive tests online, which makes it more feasible to collect large amounts of data from individuals in widespread geographic regions. However, to date, no online cognitive tests have been de-

veloped that are tailored for MS and validated for use in MS research. The goal of this study is to develop a standardized set of online cognitive tests, tailored for people with MS. These tests will be brief yet sensitive to the difficulties most often experienced by people living with MS.

The Study: People with MS and controls without MS will be recruited to take the new online cognitive tests as well as a set of the standardized in-person tests for comparison. The data will be assessed to determine whether the new online tests are sensitive to MS and measure the cognitive abilities intended in a valid, sensitive, specific, and user-friendly way.

What's Next: The new online tests are not intended to replace standard in-person neuropsychological testing for the clinical care of individual MS patients, though they may be useful in certain cases, such as where geographic or physical barriers prevent access to in-person evaluation. The main purpose of developing the online tests is to foster future large-scale research on the causes and progression of MS cognitive deficits, with the ultimate goal of leading to advances in the treatment and prevention of cognitive problems in MS.

STOP—Epidemiology

Lilyana Amezcua, MD, MS
University of Southern California
Los Angeles, CA
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $685,702
Title: Acculturation, genetic ancestry, and disability in Hispanic Americans with multiple sclerosis

Summary: Researchers at University of Southern California are spearheading a study to understand socio-cultural factors that impact MS in Hispanics and to provide solutions to prevent disease worsening.

Background: Hispanics in the US are diverse in culture and genetic background. Finding socio-cultural or genetic factors that affect MS in this population is important, since some of these factors are modifiable. Dr. Amezcua's team has observed that Hispanics with MS who immigrated to the US at a later age had twice the risk of having walking difficulties compared to those born in the US. Moreover, integration into a new way of life and culture is a stressful life event that has been shown to increase the chances of engaging in unhealthy behaviors, a process known as acculturation, that could make MS worse. Now, this group is attempting to identify such factors.

The Study: The team is evaluating Hispanic people with MS at four centers, using clinical scales to measure whether acculturation is a factor in disease severity. They are then testing if a short film on MS in Hispanics can change disease awareness and perception. The team is also investigating genetic ancestry and examining how much of MS worsening over two years is from social constraints, other conditions besides MS, genetics or a combination of all these factors.

What's Next: This study may help us understand factors that impact disease course in Hispanic people with MS and point to solutions to help them live their best lives.

Lisa Barcellos, PhD, MPH
University of California, Berkeley
Berkeley, CA
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $421,569
Title: Cognitive Function and Physical Disability in White, Black and Hispanic MS Patients
Summary: This team is using a novel, web-based tool to study the influence of genetic, environmental and other clinical factors in hundreds of people with MS to help further understand why some develop worse cognitive function and physical disability.

Background: While progress has been made to identify genetic contributions that influence someone's risk to develop MS, much less is known about what causes different disease outcomes. There are likely genetic and environmental influences, but it has been difficult to study because many outcomes are not reliably collected during physician visits or tracked in health records.

The Study: Professor Barcellos's team is using a recently developed web-based tool for regular and remote assessment of comprehensive measures of function in at least 900 individuals with MS. They are integrating these data with data collected from individuals' electronic health records, including pharmacy, clinical and radiology/MRI reports. With these combined sources, they are then studying the influence of genetic, environmental and other clinical factors over time to help further understand why some people develop worse disability or have more difficulties with memory or processing speed. The study will represent the racial and ethnic diversity of the Northern California population.

What's Next: These findings will contribute to understanding MS disease mechanisms, and will lead to more effective approaches to identify, prevent, predict and treat MS.

STOP—Human Genetics

Jennifer Graves, MD, PhD
University of California, San Francisco
San Francisco, CA
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $502,894
Title: The role of biological aging on progression in MS
Summary: Researchers are exploring an association between the biological process of aging and the progression of MS, for clues to stopping MS.

Background: A critical goal is to stop MS progression and the accumulation of neurological disability. There is also a need for reliable biomarkers that can be measured at disease onset to can predict who will experience early progression. Dr. Jennifer Graves and colleagues are investigating the idea that primary and secondary progressive MS are aging-related diseases.

The Study: The team is studying an immune marker of aging, "telomere" length. Telomeres are special caps that protect human chromosomes. They tend to shorten with age, and this shrinking has been linked to aging-related diseases, including heart disease. Dr. Graves' team is measuring telomere length in people in the early stages of progressive MS and determining any connection with increased disability and brain tissue loss. They also are determining if female and male-specific markers of aging – such as declines in ovary function and testosterone levels, are associated with progressive MS.

Sylvia Lawry Physician Fellowship

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

Awardee	Location	Mentor
Ilena George, MD	Icahn School of Medicine at Mount Sinai, New York, NY	Fred Lublin, MD
Laura Baldassari, MD	Cleveland Clinic Foundation, OH	Jeffrey Cohen, MD
William Conte, MD	University of Chicago Medical Center, Illinois	Anthony Reder, MD
Kristen Krysko, MD	University of California, San Francisco	Emmanuelle Waubant, MD, PhD
Elizabeth Silbermann, MD	Oregon Health & Science University	Dennis Bourdette, MD Michelle Cameron, MD
Elias Sotirchos, MD	Johns Hopkins University School of Medicine	Ellen Mowry, MD, Peter Calabresi, MD

What's Next: If they can establish that markers of biological aging are associated with disability and brain and spinal cord tissue loss, it may mean that large, ongoing studies of human aging can help to identify new types of treatments for progressive MS.

STOP—Myelin Biology

Sam Horng, MD, PhD
Icahn School of Medicine at Mount Sinai
New York, NY
Award: Career Transition Fellowship
Term: 7/1/2017-6/30/2020
Funding: TBD
Title: How Does the Astrocyte Barrier Protein, JAM-A, Regulate Immune Cell Entry and Activity in CNS Inflammatory Lesions?
Summary: Researchers at Icahn School of Medicine are exploring a novel strategy that pinpoints the entry of immune cells into the brain, for clues to stopping damage caused by the immune attack in MS.

Background: In the immune attack that occurs in MS, there are two barriers that immune cells must cross to reach the brain and spinal cord. Crossing the first barrier (the blood vessel wall) allows for immune surveillance and defense against infection. Crossing the second barrier (a layer of supporting cells called astrocytes) is how damage and clinical disability occur. If immune cells remain between the first barrier and the second barrier, it may be possible to protect against damage but maintain immune protection against infection. Dr. Horng and colleagues are investigating how immune cells communicate with astrocytes, the cells that make up the second barrier, by studying a protein, JAM-A, that is active on the surface of astrocytes of the second barrier.

The Study: The team is testing how JAM-A controls immune cell migration in a mouse model in which JAM-A has been selectively deleted only in astrocytes exposed to inflammation. Next, they are testing what cell functions JAM-A signaling controls in cells isolated in the laboratory in the presence and absence of JAM-A. They also are testing how JAM-A affects immune cell migration past the second astrocyte barrier in a mouse model of MS-like disease. In addition, the team will explore therapeutic strategies aimed at blocking immune cell migration past the astrocyte barrier.

What's Next: This study may yield novel information on how damaging immune cells breach the brain in MS, for clues to stopping the damage that occurs in people with MS.

Lucas Schirmer, MD
University of California, San Francisco
San Francisco, CA
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $178,467
Title: Understanding and modulating astrocyte diversity in MS and experimental demyelination
Summary: Researchers at the University of California at San Francisco are investigating characteristics of the various types of astrocytes, a cell type that forms scars and blocks repair in lesions found in the brain in MS.

Background: Cells in the brain called astrocytes form a scar in chronic areas of damage (lesions) in the brains of people with MS. This astrocyte scar can inhibit natural repair processes. Astrocytes, which perform various functions in the healthy brain, become reactive in MS and secrete molecules that are either harmful or beneficial to nerve cells and other cell types. The diversity of astrocytes and the molecules they secrete are not clearly understood.

The Study: Dr. Schirmer and his colleagues are studying the variety of astrocytes present in lesions in mice with MS-like disease at different times during the disease process. These different times reflect the different lesion stages in MS. They are also examining how astrocytes are different in young compared to older animals. These observations are being compared to brain lesions in tissue from people with MS.

What's Next: This research will contribute important knowledge to an underexplored area of MS research. It is possible that compounds that decrease astrocyte scarring could be developed to minimize damage and increase nervous system repair in MS.

STOP—Role of the Immune System

Hongbo Chi, PhD
St. Jude Children's Research Hospital
Memphis, TN
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $660,000
Title: Metabolic control of TH17 cell plasticity and pathogenicity in neuroinflammation
Summary: Researchers are studying a novel immune pathway that may help to protect mice from developing MS-like disease, for clues to stopping the attack in MS.

Background: MS involves an immune system attack on the brain and spinal cord, featuring a population of white blood cells specialized in tissue inflammation known as TH17 cells. However, how TH17 cells cause inflammation in MS remains unclear. Identifying genes and pathways involved in the development of TH17 cells will help us understand mechanisms of MS inflammation, and may lead to new therapeutic strategies to stop inflammation in its tracks. Dr. Chi's team has identified the critical role of a molecular pathway known as "mTOR" in this process. When this pathway is inhibited, mice become protected from developing MS-like disease. The team has shown that mTOR's mechanism of action is to mobilize energy production inside TH17 cells. The goal of this project is to investigate how mTOR may induce TH17 cells to attack in people with MS.

The Study: Dr. Chi's team is developing mice in which mTOR is removed, to determine its effect on the development of MS-like disease. They are studying the interaction between mTOR and energy production and investigating how mTOR regulates inflammatory factors in TH17 cells. They are also inhibiting enzymes involved in energy production to examine how that impacts the development of MS-like disease.

What's Next: Since existing and new therapies are available to modulate some of the cellular processes under exploration, these studies hold the promise of translating into the development of innovative therapies against MS.

Ulrike Kaufmann, PhD
New York University School of Medicine
New York, NY
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $184,654
Title: Calcium and other ion channels as new therapeutic targets for MS
Summary: Researchers at New York University are testing a type of therapy called a calcium channel inhibitor to see if it blocks harmful immune attacks and enhances myelin repair in a lab model of MS.

Background: T cells are a type of immune cell found in the blood. Some T cells that recognize components of the brain can enter the brain from the bloodstream and are involved in many aspects of MS pathology. T cells become activated via the T cell receptor, a docking site on the surface of T cells. Activating T cell receptors causes the opening of calcium channels, which are tiny pores in the cell's outer membrane that allow calcium ions to enter the T cells. This leads to T cell activation and subsequent harmful effects in MS. Dr. Kaufmann's group previously showed that an inhibitor of these calcium channels prevents progression of the MS-like disease EAE in lab mice.

The Study: Now Dr. Kaufmann and her colleagues are testing this calcium channel in-

hibitor to determine if it prevents relapses in mice with EAE. They are also determining if the inhibitor will help repair myelin, a major component of the brain that is damaged by immune attacks in MS. They are also looking for other ion channels on T cells that may also play a role in causing or worsening of EAE, and by implication, MS in people.

What's Next: Using inhibitors of calcium and other types of channels is a possible therapeutic strategy for stopping MS disease activity and restoring nerve-insulating myelin.

Liliana Lucca, PhD
Yale University
New Haven, CT
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $178,467
Title: The role of the co-inhibitory receptor TIGIT in the immune deregulation of MS patients
Summary: Investigators are testing the idea that a molecule called TGIT, which is present on certain immune cells, turns down inflammation in healthy people but is unable to dampen inflammation in people with MS.

Background: The blood of people with MS and people without MS contains similar numbers of immune cells that are reactive to components of the brain and spinal cord, such as protein components of nerve-insulating myelin. However, only in people with MS do these immune cells attack the brain and spinal cord. These immune cells from people without MS have anti-inflammatory characteristics, but in people with MS, they are pro-inflammatory.

Dr. Lucca and her colleagues are investigating the molecules that cause immune cells to become anti-inflammatory or pro-inflammatory.

The Study: Dr. Lucca is investigating two molecules called TIGIT and CD226 that may play a role in the pro- vs. anti-inflammatory activity of immune cells. Previous studies have suggested that CD226 is pro-inflammatory and TGIT is anti-inflammatory. Dr. Lucca is testing the idea that an imbalance in TIGIT and CD226 function is present in people with MS, predisposing them to the disease. They are testing this idea using a relevant type of immune cell called CD4+ T cells, which are obtained from blood samples. They expect that in cells from people with MS, TIGIT will not be able to turn off inflammation, thus increasing the pro-inflammatory effects of CD226. They expect that in cells from healthy people, TIGIT will be able to turn off inflammation. They are also investigating how to manipulate TIGIT so that cells from people with MS will become anti-inflammatory, similar to cells from people without MS.

What's Next: There are therapies in development that influence the function of TIGIT, and the results of this fellowship research may lead to important information about their potential for turning off immune attacks in MS.

Hongwei Qin, MD, PhD
University of Alabama at Birmingham
Birmingham, AL
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $583,800
Title: Function of Protein Kinase CK2 in CD4+ T Cells and Autoimmune Disease
Summary: Researchers are investigating an immune molecule called CK2 that may be harmful in MS.

Background: MS involves immune attacks in the brain and spinal cord, and immune cells called T cells play a big role. In MS, T cells can either ramp up inflammation, which can be

harmful, or turn it down, which can be beneficial. Understanding how the balance in inflammatory function between these two types of T cells is achieved will likely be important for understanding MS and developing better therapies.

The Study: Dr. Qin and her team are investigating a molecule called CK2 that may work as a switch that controls the inflammatory function of T cells in MS. The group is testing the idea that CK2 increases the pro-inflammatory type of T cells and suppresses the anti-inflammatory type of T cells. Thus, CK2 activity may be harmful in MS. They are using different forms of a mouse model of MS called EAE, and are testing the idea that CK2 shifts the balance toward an inflammatory environment and is thus harmful in EAE. They are investigating the details of how CK2 works using mice that are deficient in CK2 in T cells, and they are using an inhibitor of CK2 to see if it improves EAE.

What's Next: This research may provide a deeper understanding of immune activities in MS-like disease, and offer a new approach to turning off immune attacks in MS.

A.M. Rostami, MD, PhD
Thomas Jefferson University
Philadelphia, PA
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $650,000
Title: IL-37, a novel therapeutic intervention for autoimmune neuroinflammation
Summary: Researchers are exploring a novel strategy for stopping the attack in MS.

Background: In multiple sclerosis, the brain and spinal cord are attacked and damaged by the body's own immune system. The damage occurs to myelin, a substance that acts as an insulating cover to surround and protect each nerve fiber of the brain and spinal cord. The immune system is made up of many different types of white blood cells. A newly discovered immune molecule called IL-37 can modulate immune cell function. Dr. Rostami's team recently found that IL-37 can suppress disease in a mouse model of MS, and reduces infiltration of inflammatory cells into the spinal cord.

The Study: The goal of this project is to improve understanding of how IL-37 reduces myelin damage in the mouse model of MS, for clues to developing a new therapy for MS. The team is continuing to study how IL-37 exerts its effects in mice that have an MS-like disease, specifically how IL-37 induces cells with immune suppressing functions. They also are assessing its effect on blood cells of people with MS, looking at which specific immune cells it affects.

What's Next: The results of this research will lead to better understanding of the processes by which IL-37 inhibits inflammation, and may offer a strategy for stopping the immune attack in MS.

Ryan Schubert, MD
University of California, San Francisco
San Francisco, CA
Award: NMSS-AAN Clinician Scientist Development Award
Term: 7/1/2017-6/30/2020
Funding: $269,394
Title: Using comprehensive phage display coupled with next-generation sequencing to define the evolution of autoantibodies and viral antibodies in the two years after a first demyelinating event
Summary: Researchers are looking for antibody "signatures" in fluid samples that can predict which of those individuals with a first neurological event will go on to develop MS.

National MS Society Collaborates Commercially to Develop Treatments for Progressive MS

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

Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada
Grant Amount: $838,300, *Funded in part by the MS Society of Canada*

The Centre for Addiction and Mental Health ("CAMH") and the University of Aberdeen are focused on developing a neuroprotective therapy to prevent nervous system damage and progression in MS. In studies funded by research grants from the National MS Society and MS Society of Canada, the CAMH team made the novel observation that blocking the interaction between two proteins that form a complex (GluR2 and GAPDH) provides neuroprotection by preventing excitotoxicity (nerve tissue damage caused by too much of the neurotransmitter glutamate). Many attempts to prevent excitotoxicity in the past have impaired normal communications in the brain. The CAMH team has identified two chemically distinct early lead compounds which reduce excitotoxicity. The teams in Toronto and Aberdeen are now seeking to make new molecules with optimal properties for drug development and plan to test the most promising in MS models. These studies are necessary to refine this potential treatment approach in advance of possible early-stage testing in people with MS.

Background: Whether a person who experiences neurologic symptoms from a first demyelinating event will go on to develop a definite diagnosis of MS is difficult to predict. Making such a determination is important so that these individuals can receive the best care and early treatment. Tests that are currently used to try to predict development of MS are limited.

The Study: Dr. Schubert and his team are working to increase the accuracy of MS diagnostics by examining antibodies in blood and spinal fluid. Antibodies are molecules produced by immune cells that specifically recognize foreign molecules (such as viruses) or those from the body's own tissues (called "self" molecules). Dr. Schubert's mentor, Dr. Hauser, is conducting a study called EPIC II in which people with an initial demyelinating event provide blood and spinal fluid samples at different times after the initial event. Dr. Schubert is testing samples from the study participants at different times during the disease process to identify all antibodies that recognize viruses and self molecules. They

are then looking for a "signature" set of antibodies that can separate participants who went on to develop MS from those who did not get MS.

What's Next: The ability to predict who will and will not eventually develop MS will enable earlier treatment decisions and the potential for better outcomes.

Rodolfo Thome, PhD
Thomas Jefferson University
Philadelphia, PA
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $184,654
Title: The role of IL-7 in pathogenesis of Experimental Autoimmune Encephalomyelitis
Summary: Researchers at Thomas Jefferson University are investigating the role of an immune molecule that may drive damaging inflammation in MS.

Background: MS involves damaging immune attacks on the brain and spinal cord. Immune cells produce many different types of cytokines, which are messenger molecules that induce changes, such as increased or decreased inflammation. One cytokine that promotes inflammation is called interleukin-7 (IL-7). Different genetic forms of the immune cell docking site (receptor) for IL-7 are implicated in MS, yet the effects of IL-7 on some cell types are not fully understood. Dr. Thome and colleagues are examining the role of IL-7 on cells in the brain.

The Study: Dr. Thome and colleagues are investigating IL-7 using mice with the MS-like disease EAE. To explore how IL-7 affects "dendritic cells" (immune cells that present fragments of foreign molecules to other immune cells), the team is engineering mice so that they do not have the IL-7 receptor. They will look at the course of EAE in these mice compared to normal mice that have the receptors intact. The team is also examining the effect of IL-7 on astrocytes, which are cells that perform multiple important functions in the brain, and microglia, which clear away debris in the brain. The team is growing these cells in a dish, treating them with IL-7, and testing what other pro-inflammatory molecules are produced. They are also investigating mice with EAE that lack the IL-7 receptor specifically in astrocytes or microglia and comparing them with normal mice with EAE.

What's Next: Increased understanding of the role of IL-7 in EAE and in MS may allow the development of more precise treatments that turn off only the immune activity that is damaging in MS, leaving the rest of the immune system intact.

Chao Wang, PhD
Brigham and Women's Hospital
Boston, MA
Award: Career Transition Fellowship
Term: 7/1/2017-6/30/2022
Funding: $587,079
Title: Regulation of TH17 cell function by CD5Like
Summary: Researchers at Brigham and Women's Hospital in Boston are exploring how a recently discovered molecule may be used to develop a strategy for stopping the immune attack in MS in its tracks.

Background: Multiple sclerosis involves an immune attack launched on the brain and spinal cord. Th17 cells are a type of immune cell shown to induce inflammation, but they also are present in the healthy gut, where they play a protective role. A therapy that targets Th17 cells had remarkable clinical success in treating psoriasis, an immune system-mediated skin disease. Now Dr. Wang's re-

search aims to identify factors that can distinguish pathogenic Th17 cells in the brain and spinal cord from those protective Th17 cells in the gut.

The Study: Dr. Wang has discovered that a novel molecule, called CD5L, is naturally made by only protective Th17 cells but not pathogenic Th17 cells. To determine the therapeutic effects of CD5L, Dr. Wang and colleagues are studying its effects in a mouse model of MS. They have developed novel biologic tools to study CD5L and the molecules that it may interact with, for clues to developing a targeted therapy for MS.

What's Next: The results of these studies should provide insights on a novel molecule that seems able to regulate the immune system, and may have promise for developing an approach to stopping MS in its tracks.

STOP—Measuring MS Disease Activity

Joo-won Kim, PhD
Icahn School of Medicine at Mount Sinai
New York, NY
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $184,654
Title: Assessing Microstructural Integrity of Cervical Spinal Cord Gray and White Matter with Ultra-High Field Diffusion MRI for Progressive MS
Summary: Researchers at the Icahn School of Medicine at Mount Sinai are using advanced imaging to evaluate damage to the spinal cord in people with progressive MS to allow better ways to predict and treat progression.

Background: Gray matter (the tissue in the brain that contains mainly nerve cells and appears gray) and white matter (the tissue in the brain that contains mainly nerve fibers covered in myelin and appears white) in both the brain and spinal cord are damaged in MS. MRI (magnetic resonance imaging) scans of the brain is a standard way for physicians to track an individual's disease activity. However, the spinal cord is fairly small, and imaging it is difficult with conventional imaging methods.

The Study: Dr. Kim, along with his mentors, Dr. Xu and Dr. Matilde Inglese, are using an advanced type of imaging called ultra-high field diffusion MRI to scan gray and white matter tissue integrity of the spinal cord. The team is comparing MRI measurements in people with progressive MS compared to people without MS. They are also comparing people with MS who have different levels of disease severity. These non-invasive imaging methods will allow more precise monitoring of damage to the spinal cord in people with progressive MS.

What's Next: Figuring out a good way to image MS damage in the spinal cord would open up the ability to use spinal cord imaging in larger studies and clinical trials, and allow more accurate assessment of damage to test therapies designed to treat MS.

New Collaborative MS Research Award Takes Novel Approach to Repair Damage in MS

Title: "Novel approaches to understanding progression and repair using viral MS models"
Term: 4/1/17-3/31/22 **Grant Amount:** $ 825,000
Lead investigators: Thomas Lane, PhD, Robert S. Fujinami, PhD, John W. Rose, MD, Noel G. Carlson, PhD, Ryan M. O'Connell, PhD, June L. Round, PhD, Eun-Kee Jeong, PhD, University of Utah, Salt Lake City

Background and Details: In MS, harmful immune cells enter the brain and cause damage. One major harmful event in MS is called "demyelination," which is damage to and loss of myelin, the fatty substance that surrounds and protects nerve fibers. The body's natural repair of damaged regions begins but is ultimately incomplete. Viruses have long been considered possible agents that trigger MS in certain people. Dr. Lane and his team of collaborators are using mouse models of MS that are the result of viral infection. Damage caused by these viruses is worse than that seen in other models and therefore has great potential to increase understanding of the disease processes and myelin repair strategies.

The Study: Dr. Lane is overseeing this project and is working to understand if stem cells programmed in the laboratory from adult skin cells (induced pluripotent stem cells – iPSCs) are beneficial for repair of nervous system damage in these virus-induced models. Dr. Lane is taking advantage of the expertise of several collaborators. **Dr. Fujinami,** who has decades of experience in MS models and pathology in the brain caused by viruses, is investigating the possible effectiveness of a new therapy to improve repair and protect the brain in the virus-induced models. **Dr. Carlson** has extensive experience in studying inflammation in the brain with the various methods that are being used in this project. **Dr. Rose** is a clinician/scientist who played a role in moving the drug daclizumab from preclinical studies in the lab to an FDA-approved therapy for MS. He and Dr. Carlson are collaborating to investigate the role of one of the cell types in the brain that may play a role in myelin repair. **Dr. O'Connell** is a new investigator to the MS field, and is an expert in microRNAs, molecules that regulate whether or not various types of proteins are made. He is investigating how microRNAs affect inflammation in the brain and myelin loss. Immunologist **Dr. Round** is also new to the MS field, and is investigating how the bacteria that are normally present in the gut affect immune responses and disease progression in these virus-induced models. **Dr. Jeong,** an expert in imaging in MS and its models, is preforming the required imaging in this study.

What's Next: The results emerging from this collaboration—which combines the expertise of established MS scientists with investigators who have expertise in cutting edge methods—will be necessary for developing innovative new therapies to promote repair in MS.

Jennifer Linden, PhD
Weill Cornell Medical College
New York, NY
Award: Career Transition Fellowship
Term: 7/1/2017-6/30/2022
Funding: $588,436
Title: Using Endothelial Microparticles to Study Real-Time Blood Brain Barrier Permeability in Multiple Sclerosis Patients
Summary: Investigators at Weill Cornell Medical College in New York are studying a molecular "signature" found in blood that may indicate the status of the blood-brain barrier, which normally protects the brain by keeping harmful cells and molecules out of the brain.

Background: The brain is normally protected from potentially harmful cells and molecules present in the blood by the "blood-brain barrier" or BBB. However, in diseases such as MS, the BBB does not function properly, and harmful immune cells enter the brain. In MS, abnormal BBB permeability appears to play a role in the destruction of myelin (the fatty substance that surrounds and protects nerve fibers), nerve cell injury, the formation of MS lesions, and progression. Persistent BBB permeability may also contribute to failed repair of damage. The processes involved in BBB permeability are not well understood.

The Study: Dr. Linden and her mentors are developing a method to study BBB permeability in people with MS in real time. The BBB is formed by cells called endothelial cells that line the inside of blood vessels. When injured, these cells release small "packets" of molecules that reflect the properties of the endothelial cells. These packets can be considered a "signature" of what is happening to the BBB. The team is isolating the packets from blood samples and comparing the signature in people with MS with the signature found in people who don't have MS. They are also comparing differences in the signature over two years with changes in brain lesions (damaged areas) detected with brain imaging. Differences in the signature are expected to help explain how BBB permeability occurs in MS.

What's Next: Development of therapies designed to reduce BBB permeability may be a treatment strategy in MS.

Shiv Saidha, MBBCh, MD, MRCPI
The Johns Hopkins University
Baltimore, MD
Award: Research Grant
Term: 4/1/2017-3/31/2019
Funding: $494,401
Title: In-vivo investigation of trans-synaptic neurodegeneration in multiple sclerosis
Summary: Researchers at Johns Hopkins University are testing new methods of assessing nerve cell damage, involving the visual system, to determine its value for predicting more severe MS.

Background: MS involves an immune system attack that results in damage and loss of myelin, the protective insulation surrounding wire-like nerve fibers. This results in injury and destruction of the nerve fibers and nerve cells from which these fibers originate, and is actually the main cause of disability of MS. Yet, strategies to accurately track and predict the loss of nerve cells in MS are lacking. The visual pathways run from the eyes to the back of the brain, and inflammation of the optic nerves (optic neuritis) carrying messages from the retina to the visual system is a frequent occurrence in MS. Imaging techniques such as optical coherence tomography (OCT) and non-conventional MRI allow assessment of retinal tissue and the brain tissue that processes visual information. This study is assessing whether optic neuritis results in the loss of

nerve tissue deep in the retina and in the back of the brain (distant from the sites of initial inflammation and injury), and whether this damage helps predict more severe MS.

The Study: Dr. Saidha and colleagues will utilize an existing cohort of 20 people with MS who have been tracked for one year after experiencing optic neuritis. They will also recruit 20 more people with MS within one month of optic neuritis onset. All participants will be tracked for three years, undergoing MRI annually and neurological evaluations every 6 months. Participants will also undergo detailed eye examinations at study entry, and the back of their eyes will be scanned with OCT and a retinal function imager. This new device allows the investigators to see and quantify blood flow in retinal blood vessels.

What's Next: This study will provide important information that will help predict who is at greatest risk for losing nerve tissue from optic neuritis and MS, and who may benefit from aggressive therapy, potentially from early in the disease course.

Afsaneh Shirani, MD
Washington University School of Medicine
St. Louis, MO
Award: NMSS-AAN Clinician Scientist Development Award
Term: 7/1/2017-6/30/2020
Funding: $198,894
Title: Predicting clinical progression in multiple sclerosis patients using a novel imaging biomarker targeted at differentiating and quantifying the underlying pathologies
Summary: Researchers at Washington University School of Medicine are developing a new type of brain imaging to allow detection and prediction of different types of damage that occur in people with MS.

Background: Damaging activity in MS includes inflammation, destruction of myelin (the fatty substance that surrounds and protects nerve fibers), and destruction of the nerve fibers. Comprehensive assessment of the disease process requires the ability to track each of these types of damage. Current imaging methods are best suited to tracking one type of damage at the expense of others, and more than one scanner is needed if multiple imaging methods are to be applied at the same time. A novel imaging technique called diffusion basis spectrum imaging was developed at Washington University and has shown promise for detecting these three types of damage in animal models. Dr. Shirani and colleagues will take the next step and test the usefulness of this imaging method in people with MS.

The Study: Dr. Shirani and colleagues are using diffusion basis spectrum imaging to scan 60 participants, 15 each with relapsing-remitting MS, secondary progressive MS, and primary progressive MS, as well as 15 volunteers without MS. Scans are being performed at 1-year intervals. Measurements taken from these images are being compared to clinical outcomes and standard imaging methods.

What's Next: Results of this study will not only provide important information to better understand the underlying disease processes responsible for MS, particularly the sequence of changes in the brain over time, but also allow more precise assessment of the effects of treatments for people with MS.

Ian Tagge, PhD
Oregon Health & Science University
Portland, OR
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2019
Funding: $113,047
Title: Phenotyping leptomeningeal pathology in MS using DCE MRI
Summary: Researchers at Oregon Health and Science University are using advanced imaging methods to visualize MS activity in the "leptomeninges," which covers the outer surface of the brain.

Background: Disease activity in MS is ongoing, even in the absence of new symptoms. One place in the brain where persistent inflammation occurs is called the leptomeninges, which is a thin layer of tissue that surrounds the outer surface of the brain. Leptomeningeal inflammation is related to breakdown of the blood-brain barrier, an abnormal event that occurs in MS that allows substances and cells in the bloodstream to enter the brain that would normally be excluded. Inflammation of the leptomeninges may play a role in both early and later stages of MS, and assessment of this type of inflammation may be important in predicting and monitoring of disease progression. However, routine imaging of this type of inflammation has not been established.

The Study: Dr. Tagge and his colleagues, which includes mentor Dr. Rooney and co-mentor Daniel Reich, MD, PhD (National Institutes of Health), are using an advanced type of imaging called contrast-enhanced MRI to detect inflammation of the leptomeninges. People with MS with leptomeningeal inflammation are undergoing imaging, and Dr. Tagge is developing methods to improve visualization of inflammation. This imaging will increase understanding of the nature and importance of leptomeningeal inflammation and the associated breakdown of the blood-brain barrier.

What's Next: This new method of assessing disease activity may provide important ways of understanding the underlying disease mechanisms in MS and tracking the effectiveness of new treatments for MS.

STOP—Neuropathology

Ben Clarkson, PhD
Mayo Clinic Rochester
Rochester, MN
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $184,654
Title: Role of ISGylation in MS Synaptopathy
Summary: Researchers at the Mayo Clinic are investigating a process called "ISGylation" that may play a role in the cognitive problems experienced by many people with MS.

Background: In addition to causing damage to nerve-insulating myelin in the brain and spinal cord, MS also damages nerve fibers and their connections, called synapses. Destruction of myelin and damage to nerves in MS can cause cognitive impairment, which includes problems with memory, learning, attention, and other mental processes. The specific causes of cognitive impairment in MS are unclear, and there are few reliable treatment approaches to address these problems.

The Study: Dr. Clarkson and colleagues previously showed that immune system molecules can turn on genes within nerve cells (neurons), and that this may contribute to nerve injury. In mouse models of MS and models of synapse injury, the team previously identified a series of genes that modify a process called "ISGylation" in neurons. The team

is now testing the idea that ISGylation affects synapses - the points of communication between two nerve cells. They are exploring if decreasing ISGylation prevents damage to synapses, and testing whether increasing ISGylation promotes inflammation and synapse damage. The team is also measuring ISGylation in brain specimens from people with MS to see if levels of ISGylation are related to nerve injury, disability, or cognitive problems.

What's Next: If ISGylation plays a role in synapse injury and cognitive problems in MS, therapies that target this process could be developed to treat cognitive impairment in people with MS.

STOP—Preclinical Drug Development

Matthew Bellizzi, PhD
University of Rochester Medical Center
Rochester, NY
Award: Research Grant
Term: 4/1/2017-3/31/2018
Funding: $210,049
Title: Modulating microglial activation for gray matter neuroprotection in multiple sclerosis
Summary: Researchers are investigating drugs that may protect nerve connections in the brain from the damage that occurs in MS.

Background: Not only white matter, but also gray matter, is damaged in the brain of people with MS. Gray matter is the tissue in the brain that includes nerve cells. Once nerve cells are damaged or die, they are not readily replaced. Thus, strategies to treat gray matter damage in MS are primarily focused on protecting nerve cells from harm. One type of immune cell normally found in the brain, including in the gray matter, is microglia, which normally function to clean up debris in the brain.

The Study: Dr. Bellizzi and his team are investigating drugs that may help microglia protect nerve cells from degeneration. In particular, they are looking at the effect of these drugs on synapses, the specialized point of communication between nerve cells. They are using a mouse model of MS called EAE to test whether these drugs can protect synapses from damage, restore synaptic function after damage, and improve learning and memory, which are processes that rely on healthy synapses.

What's Next: This study will help determine which drug or drugs should be tested further, and represents an important first step to developing therapies that can protect the brain from MS injury and stop progression of MS.

Daniel Kaufman, PhD
University of California, Los Angeles
Los Angeles, CA
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $595,449
Title: Preclinical studies aimed at repurposing a clinically safe drug to help treat MS
Summary: Researchers are testing a molecule for its ability to limit inflammation in MS, to stop the disease in its tracks.

Background: MS occurs when an immune attack is launched on the brain and spinal cord. Dr. Kaufman's group has shown that immune cells have docking sites for the amino acid GABA and that GABA binding to these sites limits autoimmune responses. GABA, however, does not pass through the barrier that separates the brain from the blood. Prof. Kaufman and colleagues have been working with a GABA-like molecule that passes through this barrier and has a track record of safe use in people.

18 New High-Risk Pilot Projects Take Aim at MS

One way the Society propels the knowledge to end MS is by funding high-risk, high-potential pilot projects to investigate untested ideas. These one-year grants allow researchers to quickly gather data to determine if ideas are worth pursuing

STOP

Paola de Candia, PhD (Fondazione MultiMedica ONLUS, Milan, Italy) is investigating molecules that may contribute to the immune attack in MS for clues to stopping the attack.

Goetz Ehrhardt, PhD (University of Toronto, Toronto, Ontario, Canada) is studying newly discovered antibodies to obtain new knowledge on the immune attack in MS.

Naiman Khan, PhD (University of Illinois at Urbana-Champaign, Champaign, IL) is testing whether dietary factors play a role in vision problems in MS.

Priya Narayanan, PhD (Georgia Regents University, Augusta, GA) is exploring a possible source of vision problems in mouse models of MS, for clues to restoring function in MS.

David Rowitch, MD, PhD (University of California, San Francesco, San Francisco, CA) is using cutting edge technology to explore a mechanism for MS damage.

Justin Rubio, PhD (University of Melbourne, Melbourne, Australia) is studying nerve cells for clues to stopping MS progression.

Tarun Singhal, MD (Brigham and Women's Hospital, Boston, MA) is using advanced imaging to explore a novel pathway for the worsening of MS and its symptoms.

PILOT SPOTLIGHT-

Approximately half of persons with MS develop memory impairment, but there are currently no validated treatments. **James Sumowski, PhD** (Icahn School of Medicine at Mount Sinai, New York, NY) and colleagues are performing a trial of atomoxetine — a non-stimulant medication FDA-approved for use in persons with ADHD — versus placebo to improve memory in 30 people with MS and memory impairment. Evidence indicates that atomoxetine improves memory by targeting brain mechanisms responsible for memory function, so this might be a solution for memory problems in MS.

Ameer Taha, PhD (University of California, Davis, Davis, CA) is exploring a role for lipid molecules in the progression of MS and cognitive changes.

Seema Tiwari-Woodruff, PhD (University of California, Riverside, Riverside, CA) is investigating why seizures occur in some people with MS for clues to reducing this symptom.
Harley Tse, PhD (Wayne State University, Detroit, MI) is testing a method of generating powerful immune cells to stop the attack in MS models.
Ai-Hong Zhang, PhD (Henry M. Jackson Foundation, Bethesda, MD) is testing a therapeutic strategy for stopping the immune attack without compromising immune protection in MS.

RESTORE

PILOT SPOTLIGHT-

Chronic pain is one of the most common and interfering symptoms experienced by people living with MS. **Kevin Alschuler, PhD** (University of Washington, Seattle, WA) and his team are seeking a new way to help people with MS who also experience pain. To date, most treatments for pain have been "reactive" treatments that are used only after a person is having significant difficulty due to pain. These interventions are helpful, but most research suggests they are not helpful enough. This team is developing and testing an intervention that targets a key part of coping with pain, called pain catastrophizing (excessive negative thoughts and emotional responses to pain) in 40 people with MS. They are intervening early and delivering the intervention remotely by videoconference so that it is easier to participate. The findings may make life better for people with MS and pain.

Meghan Beier, PhD (Johns Hopkins University, Baltimore, MD) is developing a web-based tool for assessing cognitive changes in people with MS.
Jeffrey Huang, PhD (Georgetown University, Washington, D.C.) is testing a novel strategy for repairing myelin in a mouse model.
Farrah Mateen, MD, PhD (Massachusetts General Hospital, Boston, MA) is conducting a trial testing whether light therapy reduces fatigue in people with MS.

END

Arnold Stromberg, PhD (University of Kentucky, Lexington, KY) is developing novel genetics technology to assess the numerous genetic interactions that contribute to MS.
Jeff Wall, PhD (University of California, San Francisco, San Francisco, CA) is exploring a new model for MS.

The Study: The team is now studying the effectiveness of this GABA-like molecule at more advanced stages of MS-like disease in mice, and testing it in combination with some MS therapies for relapsing-remitting MS. They are studying mechanisms by which the activation of the GABA docking sites on immune cells can turn off MS-like disease in mice.

What's Next: Because of the treatment's safety record, if these mouse studies are successful, they could lead to a new therapy for MS.

Eve Kelland, PhD
University of Southern California
Los Angeles, CA
Award: Research Grant
Term: 4/1/2017-3/31/2021
Funding: $645,623
Title: Assessment of the neuroprotective activity of angiotensin 1-7 and its potential role in demyelinating disease
Summary: Researchers at the University of Southern California are exploring whether a drug can be repurposed to protect myelin-making cells (oligodendrocytes) from death in MS models.

Background: MS damages the insulating covers of nerve cells, called myelin, in the brain and spinal cord. The cells that make myelin (oligodendrocytes) are also damaged and die. Although it's not known what causes the initial damage to oligodendrocytes, research suggests that it is likely due to the immune system. Many of the approved therapies for MS modify the immune response in the hopes that it will protect the remaining oligodendrocytes, but none of the current treatments are able to directly protect the oligodendrocytes. Early studies from Dr. Kelland's team have shown that a novel therapy, called angiotensin 1-7 (A1-7) might be used to protect oligodendrocytes in MS.

The Study: To explore this possibility, the team is growing oligodendrocytes in lab dishes to see if treating them with A1-7 protects the cells when they are exposed to inflammatory stress factors. They are also testing A1-7 in several mouse models. One disease model targets oligodendrocytes with a toxin, and the second model triggers the immune system to target and kill oligodendrocytes. Dr. Kelland and colleagues will treat the mice with A1-7 to see if the drug can protect the oligodendrocytes.

What's Next: If A1-7 can protect oligodendrocytes in models of MS, this will bring research one step closer clinical trials for people with MS. Since A1-7 has already been given to people with other ailments, it may shorten the timeline for its development in MS.

RESTORE

As MS progresses, loss of function grows; this disability deprives people from moving, thinking and feeling their best. Comprehensive efforts and substantial research investments over the past decade have driven significant progress towards understanding how the nervous system is damaged in MS. Accelerating research breakthroughs to restore function could allow us to repair this damage, address unpredictable symptoms for people with all types of MS and provide people with proactive rehabilitation and wellness strategies to maintain optimal function and improve quality of life.

RESTORE—Lifestyle/Wellness

John DeLuca, PhD
Kessler Foundation Research Center
West Orange, NJ
Award: Mentor-Based Postdoctoral Rehabilitation Fellowship
Term: 7/1/2017-6/30/2022
Funding: $404,698
Title: MS Fellowship in Neuropsychological Rehabilitation
Summary: Rehabilitation researchers at Kessler Foundation have received funding to train promising rehabilitation professionals to conduct MS rehabilitation research.

Background: The majority of people with MS experience cognitive problems that can interfere with everyday functioning. It is important to have trained scientists and clinicians who can conduct rigorous studies of potential interventions designed to improve cognitive functioning and improve everyday life. The Mentor-Based Postdoctoral Fellowship in MS Rehabilitation Research recruits and trains talented clinician-scientists in neuropsychology, cognitive rehabilitation and cognitive/translational neuroscience. A highly individualized Research Training Plan is designed by the trainee in close collaboration with his/her mentors.

The Study: Each individual fellow's areas of interests are nurtured so that they can develop their own line of research. Fellows are guided through the process of research starting from an idea, design, and submitting a proposal, to data collection, analysis, data presentation and publication of a research manuscript. All fellows are required to apply for a federal grant, submit at least one manuscript for publication for each year of training, and present their research at a minimum of one national professional conference. Individualized courses based on the training needs of the specific fellow are included.

What's Next: Trainees who complete this program emerge with enthusiasm for rehabilitation research and the skills and methodology they need to be competent and competitive investigators.

Victoria Leavitt, PhD
Columbia University
New York, NY
Award: Mentor-Based Postdoctoral Rehabilitation Fellowship
Term: 4/1/2017-3/31/2021
Funding: $389,211
Title: Cognitive Rehabilitation in MS: From Neuroscience to Clinical Practice
Summary: An award supporting training of promising young candidates in cognitive rehabilitation for people with multiple sclerosis.

Background: Cognitive impairment is prevalent in MS, even at early stages of the disease. Its impact is felt on the personal and professional level, as individuals struggle to maintain responsibilities and functions. Research is needed to gather evidence for programs that can address cognitive symptoms. One way to enhance research is to train rehabilitation specialists in the proper ways to conduct rehabilitation research. That's the purpose of the National MS Society's Mentor-Based Fellowship in Rehabilitation.

The Study: Fellows selected for this training program will become involved in one of the active human subjects research projects currently taking place in Dr. Leavitt's lab. Close co-mentorship between Dr. Leavitt and Dr. Yaakov Stern (head of the Cognitive Neuroscience Division) will ensure that each fellow develops a meaningful project within cognitive rehabilitation, alongside some of the

most prominent investigators in the field. Dr. Leavitt believes that research must be meaningful and readily adaptable for real-life use by persons with MS. This motivates a focus on modifiable lifestyle factors that protect brain function (such as diet, exercise, or intellectual enrichment). Not only do these have scientific evidence to support their efficacy for protecting/improving cognition, but they can be readily employed by people with MS. Dr. Leavitt and her team are clinician-scientists who strive to ask questions that are clinically meaningful while also lending themselves to formal scientific inquiry.

What's Next: The mentor-based fellowship enables training of promising candidates for successful careers in cognitive rehabilitation research in MS.

Janet Shucard, PhD
The State University of New York at Buffalo
Buffalo, NY
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $608,859
Title: The Effects of Working Memory Training on Brain Function, Structure, and Cognition in MS
Summary: Investigators at The State University of New York at Buffalo, Jacobs School of Medicine and Biomedical Sciences, are testing two training programs for improving cognitive function in people with MS.

Background: Cognitive difficulties are common in people with MS, and they can impact an individual's quality of life, employment, and disease-related outcomes. Two areas affected in MS are working memory and processing speed. Working memory allows you to hold and manipulate information in memory for a brief period of time, such as adding numbers together or remembering a shopping list. It is a core function that affects many other areas of cognition. Processing speed is the rate at which information is efficiently used. The research team is examining whether training of working memory vs. training of processing speed differentially affect brain structure and function, and cognitive performance in MS.

The Study: Dr. Shucard's team is studying 90 people with MS. Thirty participants will train on a working memory task for about 20 minutes a day, 4-5 days a week, for 4-5 weeks. Another 30 will train on a processing speed task for the same amount of time, and a third group of 30 will be assigned to a control group and not receive any intervention. All will be tested on a broad range of cognitive abilities. The team also is using a range of imaging and electrophysiological measures to examine how training results in changes in the structure and function of different brain areas, as well as the connections between these brain areas. Changes in the structure and function of the brain will be related to changes in cognitive performance.

What's Next: The results of this study would provide extensive and important information about the nature and value of training-related changes in brain structure and function, and cognitive performance in MS.

RESTORE—Nervous System Repair

Dennis Bourdette, MD
Oregon Health & Science University
Portland, OR
Award: Research Grant
Term: 4/1/2017-3/31/2021
Funding: $598,082
Title: Promoting remyelination in animal models of multiple sclerosis with a selective thyromimetic prodrug

Summary: Researchers are exploring a novel strategy for repairing myelin and restoring function in laboratory models of MS.

Background: In MS, immune cells destroy the insulating material, called myelin, on nerve fibers in the brain and spinal cord. Myelin can be naturally repaired by the brain, but in MS this tends to fail as the disease progresses, resulting in disabilities. There are no treatments for MS that promote myelin repair. High doses of thyroid hormone stimulates myelin repair in lab models of MS. These doses can't be used in people with MS, however, because this would cause serious cardiac side-effects and osteoporosis. This team has synthesized a new compound, "proU-sobetirome," that has some thyroid-like effects but does not have cardiac side-effects.

The Study: Now Dr. Bourdette and colleagues are studying the effects of proU-sobetirome in three mouse models of MS. They are administering proU-sobetirome or an inactive placebo to mice to evaluate its ability to stimulate myelin repair and restore function. Importantly, the team is using a new model of MS that involves paralysis due to widespread myelin damage. This will allow them to test the compound's ability to not only stimulate myelin repair but also to reverse paralysis.

What's Next: If Dr. Bourdette's team demonstrates that proU-sobetirome is highly effective at promoting myelin repair in three different models of MS, they will have a strong reason for developing this compound as a possible treatment to restore function in MS.

Mahboobeh Fereidan-Esfahani, PhD
Mayo Clinic Rochester
Rochester, MN
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2019
Funding: $110,388
Title: New Technologies to Characterize Therapeutic Human Antibodies for Demyelinating Disease
Summary: Researchers are investigating characteristics of an antibody that may promote repair of some types of damage that occur in progressive MS.

Background: Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS, and the cells that make myelin are also damaged. Natural repair of myelin in MS occurs, but can be minimal. In addition, axons, which are the long nerve fiber extensions from nerve cells, are damaged, especially in progressive MS. Therapeutic strategies to repair damage to myelin and axons are needed to improve function in people with MS.

The Study: Dr. Fereidan-Esfahani, Dr. Rodriguez, and their team are investigating a human immune antibody called "rHIgM12." This antibody has positive effects in an animal model of myelin loss that shares features of progressive MS. They are determining how this antibody promotes myelin and possibly nerve repair by characterizing the binding of the antibody to nerve cells, as well as how it promotes growth of nerve cell extensions called "neurites."

What's Next: Results from this study could support the development and testing of rHIgM12 in a phase I clinical trial to determine if it can promote myelin and axon repair in people with MS.

Teng-Wei Huang, PhD
Baylor College of Medicine
Houston, TX
Award: Postdoctoral Fellowship
Term: 7/1/2017-6/30/2020
Funding: $172,507
Title: The role of Sox9 in remyelination after white matter injury
Summary: Researchers are exploring a novel pathway to understand why myelin repair fails in people with multiple sclerosis, for clues to a possible repair strategy.

Background: MS involves an immune system attack on the central nervous system, leading to the loss of a fatty layer called the myelin sheath that helps the function and survival of nerve cells. Failure to repair the myelin sheath causes symptoms of MS to build up over time in patients. Repair involves cells called astrocytes, which aid in myelin sheath recovery during acute phases of MS injury, but can inhibit the repair process during later phases. Clinical treatments that can regulate the production of these astrocytes may improve myelin repair. A gene called Sox9, which is very important for astrocyte development, is also present at high levels within MS lesions (areas of damage) in brain samples from MS patients.

The Study: First, the team is determining the role of Sox9 in myelin repair. They are deleting Sox9 specifically in myelin-making cells and in astrocytes in mice and observing the effect that has on myelin repair. These studies will reveal where and how Sox9 functions in MS lesions. Then they are looking into the relationship between Sox9 and another protein called B4GALT6. Preliminary data note that Sox9 influences B4GALT6, and B4GALT6 regulates astrocyte behavior in mouse models of chronic MS. Now they will further investigate this relationship during myelin repair.

What's Next: These findings may help uncover what causes myelin repair to fail in MS, and to evaluate the therapeutic potential of targeting the Sox9-B4GALT6 pathway.

Glenn Matsushima, PhD
University of North Carolina at Chapel Hill
Chapel Hill, NC
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $500,259
Title: Function of microglia during remyelination
Summary: Researchers are exploring a novel strategy for promoting the natural capacity of the brain to repair the damage in MS.

Background: This project addresses why the process of repairing the myelin that surrounds nerve fibers fails in MS. During MS, the immune attack can interfere with the ability of brain cells to perform functions that keep the brain healthy and working properly. Normally, when a myelin-making cell (oligodendrocyte) dies, the brain has a process of removing the dead cell and replacing it with a new one that can form new myelin. This process is not fully understood, but Dr. Matsushima's team believes that cells of the immune system known as macrophages or microglia may serve to recognize the dying cells and may trigger myelin repair by ushering in new oligodendrocytes under normal circumstances.

The Study: Now they are manipulating certain proteins and controlling their activity to provide clues to what those proteins do to the macrophages or microglia that make them behave in a beneficial way. They are studying mice that are engineered to lack these proteins, and contrasting them to mice that have the proteins. They are looking for any changes or differences associated with

repairing damaged areas. The investigators will also try therapies that may help resolve the problem by replacing the protein that does not function properly. These studies should provide mechanistic insights for the importance of macrophages or microglia during repair and they hope novel proteins that benefit oligodendrocytes will be uncovered.

What's Next: If successful, then this research could lead to new targets to repair myelin damage and restore function in MS.

RESTORE— Myelin Biology

Holly Colognato, PhD
State University of New York at Stony Brook
Stony Brook, NY
Award: Research Grant
Term: 4/1/2017-3/31/2020
Funding: $582,278
Title: Signaling pathways that regulate myelin repair
Summary: Researchers are exploring a strategy for stimulating signals that promote myelin repair in MS.

Background: MS therapies can slow disease activity, but they don't directly promote the repair of nerve-insulating myelin damaged by MS. More knowledge about the inner workings of myelin-forming cells is needed to develop therapies that stimulate myelin repair. Dr. Holly Colognato and colleagues have discovered that when myelin-forming cells lack an enzyme called "Csk," myelin formation is enhanced. This occurs both during normal brain development and during myelin repair in mouse models of myelin damage.

The Study: The team is further investigating the effect of Csk loss to learn what cellular signals are altered that permit the cells to augment myelin repair. They are examining how signals change in the absence of the Csk enzyme by generating mice that lack Csk. They are also testing the idea that Csk influences the function of AMPK, a cell energy sensor that appears to be increased in the absence of Csk. They are also stimulating myelin-forming cells with an FDA-approved drug that can turn on AMPK activity to learn if this drug promotes myelin repair.

What's Next: By learning more about the cellular signals that can enhance myelin repair, this team can harness these signals to help stimulate myelin repair in people with MS.

Stephen Fancy, DVM, PhD
University of California, San Francisco
San Francisco, CA
Award: Harry Weaver Neuroscience Scholar
Term: 7/1/2017-6/30/2022
Funding: $776,122
Title: Oligodendroglial-vascular interactions control successful remyelination in MS
Summary: Researchers are exploring interactions between blood vessels and myelin-making cells for clues to promoting myelin repair in MS.

Background: In MS, myelin sheaths that insulate nerve fibers are damaged, and so are myelin-making cells called oligodendrocytes. These myelin sheaths can be regenerated in a process called remyelination. Remyelination by immature oligodendrocyte precursor cells (OPCs) is critical to recovery, but fails in MS, contributing to disease progression. Remyelination involves two stages: First, OPCs are recruited to migrate into the area of damage (lesion) from surrounding brain tissue, and then the OPCs develop ("differentiate") into mature oligodendrocytes within the lesion and start to make myelin. This team proposes that interactions with blood vessels influence an OPC's ability to migrate and differentiate.

The Study: Dr. Fancy's team is imaging the remyelination process in mice to explore the possibility that OPCs use the blood vessels in the brain as a climbing frame to crawl around on and gain access to areas of damage. They are assessing how contact with blood vessels and factors secreted from blood vessels may directly affect OPC's, exploring contact between OPCs and blood vessels during remyelination, to determine what goes wrong in MS. They are also examining this possibility in brain samples from people with MS.

What's Next: Opening a research focus on the understudied area of the interactions between blood vessels and oligodendrocytes may help to identify therapeutic targets for promoting myelin repair in MS.

END

Ending MS means no one will ever get this disease again. Although progress has been made in identifying key risk factors and biological pathways that contribute to MS susceptibility, the cause is still unknown. Preventing MS for future generations requires a deep understanding of what triggers MS, how triggers lead to the development of the disease, and how to protect against it.

END—Myelin Biology

David Pitt, MD
Yale University
New Haven, CT
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Funding: $311,752
Title: NFκB-related MS risk variants drive excessive activation of astrocytes in MS
Summary: Researchers are exploring a novel pathway by which newly discovered genetic variants may yield clues to ending MS.
Background: Genetic studies on people with MS have resulted in a list of genetic variants that increase the risk for developing MS. The mechanisms through which genetic risk variants predispose a person to developing MS are currently unknown. Dr. David Pitt and colleagues are studying how some of these genetic risk variants change the cellular functions of brain cells and how this may result in increased risk for developing MS.

The Study: Dr. Pitt and his team will employ a novel technology to transform skin cells from people with MS first into stem cells and then into astrocytes, a type of brain cell that is important for inflammatory reactions in the brain. These cultured cells are genetically nearly identical to the astrocytes in the brain and will be used to examine how risk variants alter cellular function. In addition, the team is testing whether the effect of the risk variant can be reversed with existing medications.

What's Next: Genetic risk variants may be associated with overactivation of certain pathways. Thus, people with MS who carry specific variants might benefit from medication that blocks associated pathways. This study provides a basis for individualized medicine.

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