NEW RESEARCH

STOP. RESTORE. END.

Society Commits $13.8 Million for 40 New MS Research Projects

The National Multiple Sclerosis Society has committed $13.8 million to support an expected 40 new MS research projects. These are part of a comprehensive research strategy aimed at stopping MS, restoring function that has been lost, and ending the disease forever.

This financial commitment is the latest in the Society's relentless research effort, with 360 projects under active management. In 2017 alone the Society invested $40 million for new and ongoing studies.

The Society stimulates studies worldwide, leverages opportunities, fosters collaboration among foremost experts, and shapes the research landscape to address the urgent needs of people with MS. 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.

National Multiple Sclerosis Society

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

STOP: Investigators are leading the Network of Pediatric MS Centers in a study of how kids' diets impact MS relapses and progression. (see p. 2)

RESTORE: Researchers are investigating whether exercises to improve inner ear function can improve balance and vision stability in MS. (see p. 11)

END: Three new pilots are exploring the significance of genetic risk factors. (see page 13)

Inside...

STOP

A variety of therapies are effective for many people with relapsing MS, but for some people including those with progressive MS, finding a treatment that works is still elusive. The Society's comprehensive approach to accelerating the development and improvement of disease-modifying therapies includes: investigating the role of the immune system in the inflammatory attacks on myelin and the injury to nerve fibers that contributes to longer-term disability; supporting research leading toward clinical trials of new therapies; and understanding healthcare issues and advocating for policies that enable everyone with MS to access quality care and treatment.

STOP—Epidemiology

Emmanuelle Waubant, MD, PhD
University of California, San Francisco
San Francisco, CA
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $1,192,799
Title: Diet and relapse risk in pediatric MS
Summary: Investigators are leading the Network of Pediatric MS Centers in a study of how kids' diets impact MS relapses and progression.

Background: Environmental factors such as diet may modify the risk of MS relapse and disability progression. Very little is known about this topic. The Network of Pediatric MS Centers (NPMSC) was launched with Society funding to set the standard for pediatric MS care, educate the medical community about this underserved population, and create the framework to conduct critical research. Now the NPMSC is launching a study to confirm and expand their preliminary findings in children with the disease that a high proportion of calories from fat and low daily vegetable intake may increase the risk of having an MS relapse. In addition, they will study specific biological pathways that may contribute to MS progression.

The Study: Prof. Waubant and colleagues are enrolling children and adolescents with MS and asking them to complete food frequency questionnaires once a year. They also are collecting information such as relapse dates and the use of MS therapies. Finally, they are studying more in depth the biological pathways of an important amino acid, tryptophan, and its metabolites, and fatty acids, through dietary intake, blood levels, and gut microbiome, and how tryptophan and fatty acids relate to MS progression.

What's Next: This study will help us understand if diet alters the course of MS and may uncover new treatment strategies.

STOP—Nervous System Repair

Jianrong Li, PhD
Texas A&M AgriLife Research
College Station, TX
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $521,327
Title: Role of Galectin-9 in CNS Inflammation, Demyelination and Myelin Repair
Summary: Researchers at Texas A&M University are investigating a target for developing biomarkers and treatment strategies for progressive MS.

Background: MS involves an immune attack on the nervous system. Astrocytes and microglia are cells that modulate immune reactions in the brain. However, how they interact and regulate the immune T cells that cause damage in MS is not clear. Moreover, astrocytes and microglia also participate in regeneration but how and what signals regulate their beneficial functions are also not entirely clear. Dr. Li and colleagues have found that the protein "galectin-9" is produced by these cells and is significantly increased in the brain of people with secondary progressive MS.

The Study: The goal of this study is to determine the potential functions of galectin-9 in MS. Previous results suggest that galectin -9 is produced by astrocytes and microglia during inflammation and may directly blunt T cell responses and facilitate repair. This team is using genetic tools to selectively target galectin-9 in microglia and astrocytes. They also are inducing MS-like disease in mice to investigate how galectin-9 impacts brain inflammation and the repair of nerve-insulating myelin after damage.

What's Next: Galectin-9 levels in the cerebral spinal fluid may be useful as a biomarker for secondary progressive MS. This study may also uncover new therapeutic candidates for the future development of treatment and repair strategies for MS.

STOP—Preclinical Drug Development

Larry Sherman, PhD
Oregon Health & Science University
Portland, OR
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $575,556
Title: WE-thrombin for the treatment of inflammatory demyelination
Summary: Researchers are developing a novel agent that fights inflammation, which may protect the nervous system from damage in MS.

Background: One hallmark of the immune attack in MS is the dysfunction of the blood brain barrier, a system of blood vessels that controls what can enter the brain from the bloodstream. Dr. Sherman's team has found that a novel anti-inflammatory agent called WE-thrombin may inhibit this dysfunction. They have administered this agent to mice with a relapsing form of the MS-like disease

EAE, and found that disease severity and symptoms were reduced, along with damage to nerve-insulating myelin and nerve fibers in the spinal cord.

The Study: Prof. Sherman and team are determining whether WE-thrombin can reduce the severity and duration of a progressive form of EAE in mice, and whether this treatment is superior to steroid-based therapy. The team is also testing if WE-thrombin can prevent or reduce the severity of MS relapses in a relapsing-remitting model of EAE; and testing if WE-thrombin can either protect the nervous system or promote nervous system repair following MS-like attacks.

What's Next: WE-thrombin is already being tested for clinical use in other conditions. If this project is successful, it will provide the rationale to pursue additional studies aimed at testing whether WE-thrombin is effective and likely to be safe in people, with the eventual goal of testing WE-thrombin in clinical trials involving people with MS.

STOP—Health Care Delivery & Policy

Sarah Minden, MD
Brigham and Women's Hospital
Boston, MA
Award: Health Care Delivery & Policy Contract
Term: 10/1/2017-9/31/2019
Funding: $411,387
Title: What is the extent to which people with MS utilize complementary and alternative medicine (CAM)?

Summary: Investigators at the Brigham & Women's Hospital and collaborators are launching an extensive effort to understand complementary and alternative medicine use in MS.

Background: Some research shows that up to one third of people with MS use complementary and alternative types of medicine (CAM). High quality MS care may best be achieved through integrating CAM and conventional medicine, but we do not know much about the patterns of use and outcomes for people with MS who use CAM. Dr. Minden and collaborators at the Veteran's Administration MS Center of Excellence-East, Accelerated Cure Project, and Temple University are investigating this question.

The Study: The project has two main goals: 1) characterize the use of CAM and integrative medicine by individuals with MS and 2) provide the National MS Society with the evidence they need to advocate for improving access to integrative care. Dr. Minden and colleagues are using existing databases: the Sonya Slifka Study data collected from individuals with MS by telephone interviews since 2000 and the MarketScan® databases (a large collection of privately and publicly insured, de-identified patient data in the U.S.). The team is also conducting a survey of participants in the iConquerMS™ network and live focus groups and interviews with people with MS, CAM and conventional providers, and insurers and policymakers.

Can Lipoic Acid Stop MS Progression? New Clinical Trial Co-Funded by National MS Society

Investigators at Oregon Health & Science University are conducting a clinical trial to determine if the oral supplement, lipoic acid, is an effective treatment for progressive forms of multiple sclerosis.

Lead Investigator: Rebecca Spain, MD, MSPH
Oregon Health & Science University, Portland
Award: Strategic Initiative
Term: 10/1/17-9/30/20
Society's Share of Collaborative Funding: $1,180,578
Title: "Lipoic acid for the treatment of progressive multiple sclerosis"

Background: There are few treatment options that change the course of progressive forms of MS. The goal of this project is to determine if the oral supplement, lipoic acid, is an effective treatment for progressive forms of the disease. This work builds on a previous pilot trial that showed that lipoic acid slowed the rate of brain atrophy, or shrinkage, compared to placebo. Now this team wants to see if lipoic acid will slow clinical progression.

The Study: For this phase 2 clinical trial, which is being co-funded by the Veteran's Administration and the National MS Society, the team is enrolling 118 participants with primary progressive or secondary progressive MS across multiple sites. Participants will be randomly assigned to either lipoic acid or inactive placebo by mouth for 2 years. During the study, they will be monitored for changes in walking and falls, in their neurological exams, and brain atrophy observed on imaging scans. They will also be followed carefully to make sure lipoic acid is safe to take.

What's Next? If this widely available nutritional supplement proves to be beneficial, lipoic acid may become an inexpensive, safe and easily available treatment for people with progressive forms of MS.

* * *

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nationalmssociety.org/Research/Participate-in-Research-Studies

What's Next: The results of this study will help people with MS and their care providers make good decisions about use of CAM therapies.

STOP—Diagnostic Methods

Myriam Chaumeil, PhD
University of California, San Francisco
San Francisco, CA
Award: Research Grant
Term: 10/1/2017-9/31/2021
Funding: $566,618
Title: MR metabolic imaging of MS
Summary: Researchers are developing an imaging method to assess inflammation in the brain to develop new ways to stop MS.

Background: Inflammation in the brain is an important driver of disease progression in MS, but details of the inflammatory process cannot currently be seen with standard magnetic resonance imaging (MRI), a common way to scan MS disease activity in the brain.

The Study: Dr. Chaumeil and her team are developing a method to use MRI to obtain images of important inflammation-producing immune cells called "macrophages." This method will also be able to distinguish between a harmful type of macrophage that makes MS worse, and a helpful type that aids in the repair of damage. To do this, they are using a mouse model of MS and a second mouse model that shows destruction of myelin, the fatty substance that surrounds and protects nerve fibers that is attacked and destroyed in MS.

What's Next: Understanding the status of macrophages in the brain and spinal cord will be very important for diagnosis, prognosis, and assessment of how well new therapies are working in MS.

Joel Pachter, PhD
University of Connecticut Health Center
Farmington, CT
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $671,350
Title: Extracellular vesicles and MSCs as novel tools to aid in the diagnosis and treatment of secondary progressive MS
Summary: Investigators are exploring the therapeutic potential of stem cells and a novel method of tracking the course of secondary progressive MS in mice.

Background: While most people with MS initially have the relapsing-remitting form of the disease, many will eventually transition to secondary progressive MS. There are few treatment options for this type of chronic MS. A contributing factor is failure to diagnose the condition in a timely manner. Finding a way to make an accurate and timely diagnosis of the transition to secondary progressive MS could pave the way for better treatment approaches. One of those approaches being explored is different types of stem cells, which may both reduce immune attacks and encourage regeneration.

The Study: Using a mouse model of MS that exhibits a similar course of relapsing-remitting transitioning to secondary progressive disease, Prof. Pachter and colleagues are evaluating a novel stem cell product (mesenchymal stem cells) shown to have a therapeutic effect in another animal model of MS. The objective is to see whether these stem cells prevent transition to secondary progressive disease or limit its severity. The team is also analyzing blood samples from mice throughout the course of their disease to identify certain RNA molecules (these molecules show what genes are active) that correlate with the onset of secondary progressive disease. Such RNA molecules could potentially serve as clinical 'biomarkers' that inform physicians when a change in treatment may be necessary. These RNA molecules will also be analyzed to see if their disappearance correlates with effective stem cell therapy.

What's Next: This study may yield novel methods for both tracking and treating secondary progressive MS.

STOP—Immunology

Estelle Bettelli, PhD
Benaroya Research Institute
Seattle, WA
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $497,819
Title: Cell type specific modulation of STAT1 signaling to prevent the development of CNS autoimmunity
Summary: Researchers are studying a signaling pathway with the goal of protecting the nervous system from MS damage.

Background: In MS, different components of the immune system attack and destroy myelin, the fatty substance that surrounds and protects nerve fibers. Most immune research related to MS has focused on adaptive immune cells called T cells and B cells. However, these cells are activated by other immune cells called innate immune cells. In addition, predicting who will respond to interferon beta, a common treatment for MS, is difficult.

The Study: Dr. Bettelli and her team are focusing on a factor called STAT1, which modulates adaptive and innate immune cells and is essential to drive the activity of interferon beta. They are testing the idea that STAT1 has complex and antagonistic roles on adaptive and innate immune cells. Specifically, they are investigating whether changing STAT1 signaling can control the activity of innate immune cells, and thus harmful T cells, and can protect brain and spinal cord

tissues that are injured in MS. STAT1 also controls how interferon beta works. The team is testing the idea that by understanding how STAT1 and interferon beta work together, they can better predict who will and will not respond to interferon therapy.

What's Next: Better understanding of the effects of STAT1 may allow better control of the activation of harmful immune cells, protection of the nervous system, and prediction of who will respond to interferon beta. Results will also help in the development of better therapies for people with MS.

Gregory Owens, PhD
University of Colorado Denver
Denver, CO
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $705,938
Title: Mechanisms of CNS injury in MS antibody-mediated demyelination
Summary: Researchers are investigating how antibodies found in the cerebrospinal fluid of people with MS cause damage in mice, and the implications for treating MS.

Background: The fluid obtained from a spinal tap, called cerebrospinal fluid, contains cells that produce a type of immune protein called antibodies. For most people with MS, there is a specific signature of antibodies in the spinal fluid, termed oligoclonal banding, that is often used to help with MS diagnosis.

The Study: Dr. Owens and his team are investigating the types of damage caused by MS-related antibodies in the spinal fluid. The team has observed that some antibodies found in the cerebrospinal fluid from people with MS bind to nervous system tissue and produce MS-like damage when introduced into mouse nervous system tissue. The team is studying how these antibodies cause myelin loss, including the role of an immune process called complement activation. The team is also working to identify what molecules are specifically targeted by these antibodies and the frequency of these antibodies among individuals with MS.

What's Next: Determining how antibodies are involved in MS could lead to the development of new therapies that block these harmful processes.

David Scott, PhD
Henry M. Jackson Foundation
Bethesda, MD
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $485,942
Title: Engineering human CNS-specific T regulatory cells
Summary: Researchers at the Uniformed Services University are investigating a way to specifically turn off components of the immune system that are harmful in people with MS.

Background: Immune cells called "T cells" are important to the MS disease process. These cells "recognize" a variety of proteins in the brain, driving harmful immune attacks. Some other types of T cells can turn off these same attacks. Eliminating the ability of these immune cells to recognize these proteins may be a beneficial treatment approach to stop MS.

The Study: Professor Scott and his team are working to dampen this harmful process using an approach called Chimeric Antigen Receptor (CAR) therapy that has shown recent success in a type of leukemia. They have engineered their own, specific type of CAR T regulatory cells and are testing whether these cells can dampen harmful T cells in lab dishes and in mouse models. They are also analyzing if they can regulate the harmful T cells taken from the bloodstreams of people with MS.

What's Next: If successful, the next step would be a clinical trial of this new approach to turn off harmful immune attacks in people with MS.

Scott Zamvil, MD, PhD
University of California, San Francisco
San Francisco, CA
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $632,348
Title: Negative selection regulates development of pathogenic AQP4-specific T cells
Summary: Researchers are investigating abnormal immune cell development in a disease called neuromyelitis optica that resembles MS in some ways.

Background: A disease called neuromyelitis optica (NMO) is distinct from MS, but resembles MS in some ways. Sometimes, making a diagnosis of NMO vs. MS is difficult. An accurate diagnosis is necessary because some therapies are beneficial in only one of the two conditions. Understanding the differences in the immune system between NMO and MS will help doctors make a more accurate diagnosis and treatment recommendations. In NMO, the immune system incorrectly targets a brain protein called AQP4.

The Study: Prof. Zamvil and his team are investigating the development of a type of immune T cell that targets AQP4. They are testing the idea that development of these T cells, which occurs in the thymus gland, happens incorrectly and produces cells that mistakenly target AQP4. Normally, immature T cells that enter the thymus die if they recognize a "self" protein like AQP4, but Prof.

Zamvil believes that this does not occur in NMO, and that these T cells that recognize AQP4 escape this process, and survive to launch immune attacks. The team is using genetically manipulated mice to test this idea.

What's Next: A better understanding of the underlying cause of NMO, and the ability to distinguish NMO from MS, will lead to better diagnosis and treatment for both.

STOP—Measuring MS Disease Activity

Sheng-Kwei Song, PhD
Washington University School of Medicine
St. louis, MO
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $648,976
Title: How Does Optic Neuritis Impact Nerve Function and Its Assessment?
Summary: Researchers are developing a method to specifically image damage to the optic nerve to better understand MS disease processes.

Background: Visual symptoms caused by inflammation of the nerve serving the eyes (optic neuritis) are often the earliest hint that a person is developing MS. Current methods for looking at vision problems reflect the overall damage to the visual system, and are not specific to damage that may be happening to the optic nerve. Better imaging methods will increase understanding of how MS-mediated disease processes affect the optic nerve.

The Study: Prof. Song and colleagues are using novel imaging methods to better examine damage in the optic nerves of mice with EAE, a model of MS. They are using "diffusion basis spectrum" imaging and "diffusion functional MRI" to consider only the optic nerve, and not other vision-related structures, in their analysis. They are also directly examining the optic nerve tissue to calibrate what the imaging captures with what is going on in the body. In this way, their findings can then be translated to use in people in a non-invasive way.

What's Next: This work represents the first steps toward a method of diagnosing and evaluating optic nerve damage in people with MS, and also assessment of changes to the optic nerve in response to treatment.

RESTORE

As MS progresses, function is lost, depriving people of moving, thinking and feeling their best. We must deepen our understanding of what specifically causes nervous system damage in MS as well as find ways to protect the nervous system from injury and to repair damage. Accelerating research breakthroughs to restore function will provide life-changing advances for people with MS. It could allow us to restore neurological function, address unpredictable symptoms for people with all types of MS, and provide people with proactive strategies to maintain optimal function and improve quality of life.

RESTORE—Rehabilitation

Lee Dibble, PhD
University of Utah
Salt Lake City, UT
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $436,220
Title: Gaze and postural stability in persons with MS at risk for falls: Characterizing deficits and response to treatment
Summary: Researchers at the University of Utah are investigating whether exercises specifically designed to improve inner ear function can improve balance and vision stability in people with MS.

Background: Normal inner ear function is needed for balance and vision stability. Nerve damage in the areas of the brain that process signals from the inner ear can lead to dizziness, balance problems, and an increased risk of falling. It is not known to what extent the loss of nerve-insulating myelin in brain areas that process inner ear signals creates dizziness in people with MS, and whether specific exercises can improve balance and reduce the risk of falls in people with MS.

The Study: Professor Dibble and his team are performing a study in which people with MS will perform one of two types of exercise. The first is specifically designed to improve balance function and vision stability, and the second (with which to compare) is designed to improve strength and endurance but will not affect the inner ear. Comparing the two groups will help determine the effectiveness of the inner ear/vision stability treatment approach.

What's Next: The study will show if exercises targeted at balance and vision function are effective at reducing problems with dizziness, eye movement stability, and balance in people with MS. Such information will provide important guidance for therapists working with people with MS who have these problems.

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

Lisa Barcellos, PhD (University of California, Berkeley, CA) is applying cutting edge technology to study immune cells in people with MS.

Oscar Bizzozero, PhD (University of New Mexico, Albuquerque) is investigating how failure to launch an antioxidant response may contribute to MS damage.

Sara Colpitts, PhD (Geisel School of Medicine, Hanover, NH) is investigating how antibiotic treatment may induce a regulatory immune response in MS-like disease in mice.

Hannes Devos, PhD (University of Kansas Medical Center, Kansas City) is testing a novel method of assessing cognitive function through measuring the pupil in MS.

Alexander Gow, PhD (Wayne State University, Detroit, MI) is exploring a novel facet of the myelin that insulates nerve fibers, for clues to how it is targeted in the MS attack.

PILOT SPOTLIGHT-Why Doesn't the Antioxidant Response Work in MS?

When cells and tissues are exposed to oxidants they normally mount an antioxidant response that reduces or contains the damage. However, this defense mechanism does not seem to work properly in MS. **Oscar Bizzozero, PhD** (University of New Mexico, Albuquerque) is exploring whether this is due to low amounts of a protein called Nrf2, which is the major regulator of the antioxidant response. Now they are seeking to identify small molecules called microRNAs that could inhibit Nrf2 synthesis and thus lower the Nrf2 levels in MS-like disease models. Results from this study will help discover potential targets for developing a new therapeutic approach to treat MS.

John Lindsey, MD (University of Texas Health Center at Houston) is exploring whether virus proteins stimulate an immune response similar to that which occurs in MS.

David Jay Mock, MD (University of Rochester Medical Center, Rochester, NY) is determining whether a virus plays a role in preventing myelin repair in an MS model.

Chunying WU, PhD (Case Western Reserve University, Cleveland, OH) is developing a novel imaging method for identifying changes to myelin in models of MS.

RESTORE

Jason Franz, PhD (University of North Carolina at Chapel Hill) is studying how virtual reality might be used to accurately identify balance problems in people with MS.

Nora Fritz, PhD (Wayne State University, Detroit, MI) is testing the effectiveness of telephone-delivered exercise to improve fatigue in people with relapsing-remitting MS.

PILOT SPOTLIGHT-Reducing Complications from Breathing Problems

Complications from breathing problems are the most frequent reason for critical illness and intensive care in people with MS, particularly as the disease progresses. Exercises of the respiratory muscles have the potential to improve breathing in people with MS. **Min-Hui Huang, PhD** (Regents of the University of Michigan, Flint) is examining the effects of a 10-week respiratory muscle exercise program on respiratory muscle strength, fatigue, activity level, and respiratory infection rates in 40 people with advanced MS. They will assess whether the participants improve after the training, and whether the effects can be maintained after the training ends. These results will help to reduce complications from respiratory problems, and improve function in people with advanced MS.

Helen Genova, PhD, (Kessler Foundation Research Center, West Orange, NJ) is examining the effects of an intervention aimed at improving emotional processing abilities in MS.

May Han, MD (Stanford University, Stanford, CA) is understanding how brain cells known as astrocytes may both promote and inhibit myelin repair in a novel MS model.

Min-Hui Huang, PhD (Regents of the University of Michigan, Flint) is testing a method of improving breathing and reducing complications of breathing problems in advanced MS.

Sonya Kim, PhD (New York University School of Medicine, New York) is developing an instrument that measures the partner's responses to the impact of MS.

Mia Minen, MD, MPh (New York University Langone Medical Center, New York) is testing a method of reducing pain from migraine and MS.

END

Farren Briggs, PhD (Case Western Reserve University, Cleveland, OH) is exploring how genetic risk factors may be related to age at onset of MS.

Kathleen Burns, MD, PhD (The Johns Hopkins University, Baltimore, MD) is determining the significance of a sequence of genetic material inherited by people with MS.

Stephen Francis, PhD (University of Nevada, Reno) is studying a specific genetic feature that may confer susceptibility to MS.

Laura Rice, PhD
University of Illinois at Urbana-Champaign
Champaign, IL
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $570,217
Title: Validation of a Fall Prevention Program Among Non-Ambulatory Wheeled Mobility Device Users with MS
Summary: Researchers are developing a program designed to help prevent falling for people with MS who are wheelchair users.

Background: Research suggests that about half of people with MS fall at least once during a 6-month period. Falls can cause injuries, and fear of falling can prevent people from participating in social activities. Although some research has been done in ways to prevent falls in people with MS who can walk, little is known about preventing falls in people with MS who are full-time wheelchair users.

The Study: Dr. Rice and her team are developing a comprehensive therapeutic program designed to educate this group of people with MS about how to prevent and recover (get up) from falls. Participants will be assessed to determine how often they fall, and then will be randomly assigned to either a 6-week program that will provide comprehensive education about risk factors associated with falls, or to a wait-listed control group who will continue their normal activities. All participants will monitor their fall frequency for 24 weeks after the education period ends, and be revaluated immediately and 12 weeks later to examine the immediate and long-term impacts of the education.

What's Next: A program designed to prevent falling in people with MS could be implemented worldwide, improving quality of life and reducing injuries.

RESTORE—Nervous System Repair

Fraser Sim, PhD
The State University of New York at Buffalo
Buffalo, NY
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $579,899
Title: Targeting extracellular sulfatases to accelerate oligodendrocyte progenitor-based myelin repair and regeneration
Summary: Researchers are attempting a new strategy to improve the ability of cells to repair of nerve-insulating myelin.

Background: In MS, the fatty substance that surrounds and protects nerve fibers, called myelin, is attacked and destroyed. Nerve fibers that have lost their myelin do not function properly and are also vulnerable to damage, leading to symptoms in people with MS. Repairing myelin is an important goal in MS, but the body's natural myelin repair is generally incomplete in people with the disease. The cells that make myelin are called "oligodendrocytes," and they are derived from immature precursor cells that reside in the brain.

The Study: Dr. Sim and colleagues are testing the idea that an enzyme called sulfatase is involved with inhibiting ongoing repair, and that blocking sulfatase will increase the ability of immature oligodendrocyte precursor cells to mature and begin to repair myelin. This may help both precursor cells that are already present in the brain as well as cells that could be transplanted. The team is performing experiments in mice lacking sulfatase enzymes and determining how an inhibitor of sulfatases works.

What's Next: If these studies produce promising results, sulfatase inhibitors could be tested as a way of improving myelin repair in people with MS.

RESTORE—Health Care Delivery & Policy

Michael Halpern, MD, PhD, MPH
Temple University
Philadelphia, PA
Award: Health Care Delivery & Policy Contract
Term: 10/1/2017-9/31/2019
Funding: $359,411
Title: What are the barriers preventing access to rehabilitation services, particularly maintenance services among people with MS and what are some of the potential solutions to these barriers?
Summary: Researchers are examining how to improve access to rehabilitation services for people with MS.

Background: Rehabilitation services – including physical and occupational therapy, cognitive counseling, and therapeutic recreation – can assist people with MS to function better at home and work, improve thinking and memory, and enhance participation in leisure activities. However, there is very little known about which individuals with MS are able to obtain rehabilitation services, and what barriers may exist to receiving these services.

The Study: To help improve quality of life outcomes among people with MS, this team has developed the Philadelphia MS Consortium, a group of MS and rehabilitation science researchers and clinicians at three large health care systems: Temple University, Drexel University, and Einstein Medical Center. Together, they are reviewing electronic medical records of people with MS to determine how frequently individuals are referred for rehabilitation services, the types of services they receive, and whether there are difficulties in getting these services. The team is convening focus groups to get more detailed information from people with MS on problems they have had in receiving rehabilitation care, and using the information to develop a national survey. Using all of these findings, the team will then develop a program to help people with MS get needed rehabilitation services.

What's Next: Information from this study can improve access to rehabilitation, help restore function and improve quality of life .

Mitchell Wallin, MD, MPH
Institute for Clinical Research, Inc.
Washington, DC,
Award: Health Care Delivery & Policy Contract
Term: 10/1/2017-9/31/2019
Funding: $441,744
Title: Multiple Sclerosis Telehealth Utilization Project
Summary: Researchers nationwide are collaborating to investigate the use of technology to deliver specialty care remotely to people with MS,

Background: MS is a complex disease that is best dealt with by doctors who specialize in its treatment. "Telehealth" is the use of communication technologies to provide clinical care to individuals who live far from their doctors. It's currently not known to what extent telehealth is being used to provide MS specialty care to people with MS, and what might prevent broader use of telehealth for people with MS.

The Study: Dr. Wallin is using large electronic databases to determine the use of telehealth by people with MS across the U.S. The team is also doing a survey to collect personal experiences about the use of telehealth from people with MS, physicians, and insurance providers. They are also conducting focus groups of people with MS and health care providers to understand what factors permit the use of telehealth and what factors prevent it.

What's Next: Better understanding and availability of telehealth could enable people with MS to access MS specialty care regardless of where they live, which would likely improve their treatment and outcomes.

RESTORE—Biology of Glia

Ethan Hughes, PhD
University of Colorado Denver
Denver, CO
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $586,687
Title: Mechanisms and Dynamics of Cortical Remyelination
Summary: Researchers are investigating methods to improve and visualize repair of nerve-insulating myelin, ultimately to restore function for people with MS.

Background: Progressive MS is associated with shrinking of a region of the brain called the cortex, which is associated with higher brain functions. Shrinkage is due in part to destruction of myelin, the fatty substance that surrounds and protects nerve fibers. Finding a way to stop myelin destruction and stimulate its repair is urgently needed to prevent progression and restore function.

The Study: Dr. Hughes and his team are using advanced imaging techniques in mouse models of MS to evaluate methods to improve myelin repair, particularly focusing on the cortex. These imaging techniques can be used to visualize myelin and the cells that

make myelin in live mice, and the team is also observing these repair processes as they happen. They are also trying to improve myelin repair with different interventions.

What's Next: The study will show ways to improve myelin repair and methods to monitor repair so that treatments to restore function to people with MS can be developed and improved.

Akiko Nishiyama, MD, PhD
University of Connecticut
Storrs Mansfield, CT
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $610,077
Title: Neuronal activity-dependent regulation of remyelination and chromatin remodeling
Summary: Researchers from the University of Connecticut and University of Paris are using cutting-edge technology to explore a novel possibility for restoring damaged nerve-insulating myelin.

Background: An axon is an extension of a nerve cell surrounded by a protective sheath called myelin. This sheath has a role in the survival of the axon and allows for the fast transmission of information between different parts of the brain and spinal cord. People with MS experience a progressive loss of myelin, which causes a deterioration of the transmission of nerve signals. Recent studies suggest that there is cross-talk between the cells that make myelin and the axons that they surround, and that the production of myelin is greater when axons are active and transmit electrical signals.

The Study: Professor Nishiyama and her co-investigator Dr. Maria Cecilia Angulo (University of Paris) are assessing whether this cross-talk, in areas of myelin damage in mice, promotes the production of myelin by increasing the number of new myelin-making cells. They are using "optogenetics," an advanced technique that combines the activity of a protein in mouse axons that is sensitive to light, and an optical system to control and direct the light. This technique enables the team to study the activity of axons and myelin in mice that have experienced myelin damage.

What's Next: This work could provide a new avenue toward promoting myelin repair in people with MS. These new treatment possibilities would help protect the axons from further damage and could diminish the devastating effects of nerve loss.

Athena Soulika, PhD
University of California, Davis
Sacramento, CA
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $652,581
Title: Novel lipid-mediated mechanism controls oligodendrocyte maturation
Summary: Investigators are exploring a new strategy for repairing nerve-insulating myelin and restoring function in MS.

Background: Nerve cells transmit information to one another through wire-like axons, which are insulated by a sheath of proteins and lipids (fatty substances) known as myelin. Within the brain and spinal cord, myelin is produced by mature cells called oligodendrocytes. In people with MS, mature oligodendrocytes can die, and as a result axons lose their protective myelin. Dr. Soulika's team has identified a process that may contribute to the inability of oligodendrocytes to mature and form new myelin in people with MS.

The Study: Dr. Soulika and her collaborators have identified a group of lipid-derived molecules that act as regulators of the oligodendrocyte maturation process, and believes that these molecules are overproduced in people with MS as a result of continuous inflammation. Now they are examining this possibility in oligodendrocytes isolated in the lab, and in models of MS. They are exploring the molecular pathways that are activated in oligodendrocytes in response to the lipid molecules, and also examining whether inhibiting the molecules promotes myelin formation and restores neurological function.

What's Next: This work may yield a new class of therapeutics that promote myelin repair and restore function in MS.

RESTORE—Human Genetics

Paul Tesar, PhD
Case Western Reserve University
Cleveland, OH
Co-Investigator: Olivia Corradin, PhD
Whitehead Institute, Boston, MA
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $654,444
Title: The impact of chemical and genetic dysregulation of transcriptional pausing on oligodendrocyte generation and myelination in MS
Summary: Investigators are researching underlying factors that hinder stem cells in the brain from replacing myelin in MS.

Background: In MS, the body mistakenly treats the protective layer of myelin that wraps nerve cells as foreign and destroys it. This leaves nerve cells exposed and causes symptoms and MS relapses. The brain has cells called oligodendrocyte progenitor cells (OPCs) that are capable of regenerating myelin. However, in people with MS, these cells often fail to perform this task. Dr. Tesar's and Dr. Corradin's teams have identified genetic differences in people with MS that may contribute to decreased myelin repair capacity.

The Study: Dr. Tesar and colleagues have developed a method that allows them to generate large quantities of oligodendrocytes to better study the process of myelin repair in the laboratory. They already have tested thousands of molecules to identify the factors that block the process of myelin

formation, and are proceeding to investigate how these factors block myelin formation, using models of MS as well as brain tissue obtained from people with MS via autopsy. They also are testing if inhibitors of myelin formation originate from genetic variants known to be associated with susceptibility to MS.

What's Next: This research should provide novel insights into factors that interfere with myelin repair in MS, and identify future therapeutic avenues that aim to restore function and reverse neurological symptoms.

RESTORE—Measuring MS Disease Activity

Bing Yao, PhD
Kessler Foundation Research Center
West Orange, NJ
Award: Research Grant
Term: 10/1/2017-9/31/2020
Funding: $558,314
Title: Investigating the Correlation between Cognitive Fatigue and Brain Iron Deposition in Basal Ganglia in Multiple Sclerosis
Summary: Investigators are exploring whether iron in certain areas of the brain contributes to cognitive fatigue in people with MS.

Background: Fatigue is a common, disabling symptom for many people with MS. Dr. Yao's team is exploring cognitive fatigue, which refers to individuals' perception that cognitive functioning temporarily declines during an extended period of cognitive effort. Studies have shown that cognitive fatigue results from dysfunction of an area deep in the brain called the basal ganglia. The basal ganglia is associated with abnormal iron deposits. This study will examine the link between iron deposition and the severity of cognitive fatigue in people with MS. A better understanding of mechanisms of cognitive fatigue in MS may lead to effective treatments for it.

The Study: Dr. Yao's team is recruiting 80 individuals with relapsing-remitting MS and 40 people who don't have MS. Each participant will be tested for general fatigue and cognitive fatigue. Participants will also undergo a series of high-resolution MR scans. These images will quantify the iron deposition in the basal ganglia, and will be correlated with the severity of participants' fatigue.

What's Next: The findings from this research should greatly improve our knowledge of mechanisms underlying cognitive fatigue in MS, and may lead to new approaches for treating this problematic symptom.

Key Questions That Drive the Society's Research

Many people with MS are living without effective treatment options and face the prospect of progressive disability. Despite tremendous progress toward understanding MS, there are vital questions that must be answered to change the world for people with MS.

To stop MS in its tracks, restore what has been lost, and end MS forever, there are still critical questions we must answer that drive the Society's research priorities:

- Why does MS affect certain people and not others?
- What is the cause of MS?
- How do we stop MS progression?
- How do we repair the damage caused by MS?
- How do we reverse symptoms and promote wellness?

Accelerating Breakthroughs

The National MS Society is the largest private funder of MS research in the world and is recognized as a global leader in driving MS research. The Society stimulates studies worldwide, leverages opportunities, fosters collaboration among foremost experts, and shapes the research landscape to address the urgent needs of people with MS. The complexity of MS necessitates a comprehensive approach to address our most pressing research priorities and to accelerate research breakthroughs.

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