

NEW RESEARCH



STOP. RESTORE. END.

Society Commits More than \$10.5 Million for 42 New MS Research Projects

The National Multiple Sclerosis Society has committed more than \$10.5 million to support an expected 42 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, investing a projected \$50 million in 2016 alone to support over 380 new and ongoing studies around the world. The Society pursues all promising paths to drive research breakthroughs in MS to fuel life-changing treatments and everyday solutions that are crucial for people to live their best lives.

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: Researchers at Imperial College, London, have pinpointed a molecule that may signal nerve cell death, and are investigating how to alter these signals to stop MS progression. (see p. 9)



RESTORE: University of Ottawa researchers are testing an intervention to increase physical activity, to determine if it can improve fitness and reduce vascular disease risk in people with MS. (see p. 12)



END: Researchers from Jewish General Hospital in Montreal are using advanced genetic tools to better understand the extent to which obesity and Epstein-Barr virus are linked with increased MS risk or MS progression. (see p. 18)

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National
Multiple Sclerosis
Society

**STOP**

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

STOP—Human Therapy Trials/Management of MS**Myla Goldman, M.D.**

University of Virginia
Charlottesville, Virginia

Award: Research Grants

Term: 10/1/2016-9/30/2020

Funding: \$624,604

Title: Assessment of the clinical importance of insulin resistance & steroid-associated hyperglycemia in relapsing MS

Summary: A team from the University of Virginia School of Medicine is exploring whether controlling blood sugar can decrease the severity and/or improve recovery from an acute MS relapse.

Background: An exacerbation of MS (also known as a relapse, acute attack or flare-up) causes new symptoms or the worsening of old symptoms. The standard treatment for a relapse is a course of intravenous (given in the vein) or oral steroids, but even with steroid treatment, some people experience poor recovery after a relapse. Research studies suggest that people with MS may be more likely to have “insulin resistance,” causing difficulties processing and appropriately using their body’s own blood sugar. Importantly, steroids

given to treat a relapse can, as a side effect, increase a person’s blood sugar levels – especially in those that are insulin resistant. Dr. Goldman’s team is exploring whether steroid-related blood sugar levels are associated with the severity of an MS relapse or degree of recovery.

The Study: Dr. Goldman and colleagues are recruiting 160 people with MS who are having an acute attack. They are evaluating blood sugar levels before, during, and after a standard course of steroid treatment. The team is determining how these factors relate to the degree of recovery, primarily by looking at differences between those who recover and those who do not fully recover from their relapse. They also are looking at whether people with high blood sugar have more severe relapses or lower chances of relapse recovery. Finally, they are looking at factors that contribute to high blood sugar, including obesity, elevated blood fats (lipids), and elevated blood pressure.

What’s Next: If blood sugar response is found to be relevant to relapse severity or recovery, this would represent a critically important discovery, since these factors are modifiable and may lead to treatment strategies that can reduce relapse severity and improve recovery, and possibly slow the accumulation of disability.



When Is It Safe to Stop MS Treatment?

Disease-modifying therapies (DMTs) approved in the United States to treat MS are anti-inflammatory and reduce the number of new relapses and MRI lesions, and may reduce the accumulation of disability. DMTs are used chronically, and there are currently no clear ways to determine at what point a DMT can be discontinued later in life. Now a team is collecting the necessary data to determine if and when DMTs should be discontinued, in a project cofunded by the Patient-Centered Outcomes Research Institute (PCORI) and the National MS Society. PCORI is an independent, nonprofit organization authorized by Congress in 2010, that seeks to determine the best healthcare options for each individual using patient-centered research.

John Corboy, MD (University of Colorado, Denver) received a PCORI grant of more than \$6,000,000 to conduct this study. Three hundred participants will be enrolled from MS centers across the United States, and they will be randomly chosen to continue or discontinue their DMT. The team is examining how this affects the risk of new relapses, disease activity on MRI scans, disability progression, and quality of life.

The Society has committed more than \$300,000 additional support, so that the study can be expanded to 15 sites. This would decrease the number of participants that each site needs to recruit, thus expediting the study. This study can provide the rigorous data necessary to allow individuals to determine when it may be appropriate to stop their MS therapy.

Ilana Katz Sand, M.D., Ph.D.

Icahn School of Medicine at Mount Sinai
New York, New York

Award: Research Grants

Term: 10/1/2016-9/30/2018

Funding: \$161,975

Title: Pilot study of a dietary intervention for MS

Summary: Researchers at the Icahn School of Medicine at Mount Sinai in New York are exploring the potential of a dietary approach to improving health and wellness in people with MS.

Background: People with MS often ask their health care providers whether changing their diet will help their MS. This question is not easy to answer because while there is an in-

creasing body of evidence regarding particular dietary components in animal models of MS, there is limited evidence in people with the disease. Scientifically robust clinical trials regarding diet are needed to establish the effects. This study aims to provide preliminary data to enable larger clinical trials of diet in the near future.

The Study: The diet being tested in this pilot study was designed to include dietary components that have been suggested to be of benefit in MS through previous studies, and to exclude those that have been suggested to be detrimental. It is therefore rich in foods that are high in polyunsaturated fatty acids (particularly omega-3 fatty acids), polyphenols, antioxidants, and whole grains, and lim-



its meat, dairy, refined sugars and salt. Thirty people with MS are being randomly assigned to the dietary intervention or to a control group that is attending wellness meetings. Those assigned to the dietary intervention group will undergo an intensive educational program that will include menu suggestions, recipes, and grocery lists; regular meetings with a nutritionist; and e-mail updates/ phone calls. All participants will be followed for six months with various questionnaires, assessments, and bloodwork to determine adherence to the diet, potential effects on overall health and wellness (e.g., body mass index, blood sugar levels), health-related quality of life, fatigue and cognition.

What's Next: If this study suggests benefit from the diet, it would provide the necessary data to justify a larger trial of the dietary intervention to determine potential effects on MS disease course and symptom management.

STOP—Diagnostic Methods

Carlos Duarte, Ph.D.

University of Coimbra
Coimbra, Portugal

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$175,000

Title: Novel cerebrospinal fluid and serum biomarkers for MS

Summary: Investigators at the University of Coimbra, Portugal, are exploring whether proteins they have identified in the spinal fluid may be used as biomarkers or flags to help diagnose and track MS.

Background: Multiple sclerosis can be difficult to diagnose, and the symptoms, course and response to treatment vary among individuals and are unpredictable. There is no

specific diagnostic test for MS, so a combination of neurological exams, magnetic resonance imaging and evaluation of spinal fluid is most commonly used, with misdiagnosis occurring. Identifying reliable biomarkers that can distinguish MS from look-alike disorders would be highly desirable not only for diagnostic purposes, but also to help monitor disease activity and progression, and to evaluate response to treatment. Dr. Duarte's team recently scanned the proteome (entire set of proteins) in the spinal fluid of patients with MS compared with other neurologic diseases, and has identified a group of proteins that may set MS apart.

The Study: Now, this team is trying to validate the selected proteins that were identified in their original study. They will also determine whether the protein biomarkers identified are also valuable tools to characterize the disease when tested in blood samples, and follow participants to determine any correlation between the proteins and MS type.

What's Next: This project can help to identify a novel group of biomarkers to facilitate earlier diagnosis of MS, and to help distinguish different types of MS. Earlier diagnosis of MS may allow for earlier treatment and hopefully prevent nervous system damage and loss of function.



STOP—Health Care Delivery/ Policy

Daniel Hartung, M.P.H., Pharm.D.

Oregon State University
Corvallis, Oregon

Award: Health Care Delivery and Policy Research Contracts

Term: 10/1/2016-9/30/2018

Funding: \$411,151

Title: Costs, access, and value of MS disease-modifying therapies

Summary: Researchers at Oregon State University are investigating reasons for the escalating costs of MS treatments.

Background: The costs of medications for MS have increased dramatically in recent years. Currently, most therapies are priced over \$60,000 per year despite the increased number of therapies available. These costs often increase out-of-pocket co-pays or compel insurance companies to impose restrictions to access. Dr. Hartung's team is investigating the reasons for and implications of the escalating costs of MS treatments on patient care.

The Study: First, they are conducting interviews with pharmaceutical industry executives and analyzing pricing data. They also are acquiring Medicare data to examine trends in insurance company pharmacy benefits over time to see if they are associated with increasing MS medication prices. Finally, they will examine the effect of changes of pharmacy benefits on how individuals use MS medications.

What's Next: This research will help shed light on the drivers of MS therapy prices, and provide important information to help the National MS Society and others advocate for increased access to high quality healthcare for people with MS.

Surachat Ngorsuraches, B.S.Pharm., Ph.D.

South Dakota State University
Brookings, South Dakota

Award: Health Care Delivery and Policy Research Contracts

Term: 10/1/2016-9/30/2017

Funding: \$117,878

Title: Examining the cost-escalation and patient valuation of disease-modifying therapies

Summary: Researchers at South Dakota State University are investigating patient valuation of MS treatments.

Background: Despite the availability of disease-modifying treatments for MS, people still have limited access due to the escalating costs of these treatments. Insurers have asked patients to share more of these costs, which has been associated with lower adherence to the treatments. Understanding the ways in which people with MS perceive the values of these treatments has never been rigorously studied. For this reason, the National MS Society released a request for proposals to encourage investigators to apply for funding related to this issue. Dr. Ngorsuraches and colleagues are assessing how patients value disease-modifying treatments for MS.

The Study: This study will determine individuals' preference and willingness-to-pay, which reflects their value of disease-modifying treatment for MS. Treatment attributes—such as benefits, risks, and routes of administration—will serve as factors predicting the participants' preference. The team will calculate the willingness-to-pay for disease-modifying treatments from the preference.

What's Next: This study will provide better understanding of factors explaining patient valuation of treatments for MS. It will allow the use of treatments to reflect the quality of care based on how patients value them.



STOP—Role of the Immune System

Robert Axtell, Ph.D.

Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma

Award: Research Grants

Term: 10/1/2016-9/30/2018

Funding: \$422,400

Title: Role of B cells in Th17 induced neuro-inflammation

Summary: Researchers from Oklahoma Medical Research Foundation are investigating an immune modulating treatment for possible clues to stopping MS progression.

Background: Recent research suggests a previously unexpected role of immune cells known as “B cells” in driving disease activity in MS. Therapies that inhibit the CD20 molecule on B cells and decrease their numbers have been shown to be effective in reducing disease activity in MS clinical trials. Therapies that block another immune molecule, BAFF, also decrease B cells. But in clinical trials of BAFF-blockers, relapsing MS worsened. These different results demonstrate that the function of B cells is highly nuanced in multiple sclerosis and not well understood.

The Study: Dr. Axtell’s team has developed different versions of the MS-like model disease EAE that may illuminate the beneficial and detrimental aspects of B cells. They are using these models to examine how blocking BAFF affects the immune attack. In particular, the team is looking at cells called “neutrophils” that may help to drive an inflammatory B cell response. Interestingly, these cells have been implicated in the development of secondary progressive MS.

What’s Next: These studies will help determine why BAFF-blockers failed to benefit MS, and could tease out whether a certain subset of people with MS could benefit from using BAFF-blockers as a treatment.

Thomas Forsthuber, M.D., Ph.D.

The University of Texas at San Antonio
San Antonio, Texas

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$660,269

Title: NETs and lipid peroxidation as drivers of progressive EAE

Summary: University of Texas at San Antonio researchers are exploring how to stop nervous system damage, for clues to developing treatments that stop MS progression.

Background: In MS, the immune system attacks the brain and spinal cord, including the myelin that protects and insulates nerve fibers. Prof. Forsthuber’s team and others have suggested this immune attack results in oxidative stress, a process wherein “free radicals,” normal by-products of bodily processes, cause tissue injury. This may result in unwanted changes to lipids (fat molecules) that comprise myelin. The team believes that these changes snowball, resulting in MS progression. They have new information that a class of white blood cells called neutrophilic granulocytes may contribute to the modification of these lipids and therefore may play an important role in MS progression.

The Study: This project investigates how neutrophils drive the modification of the lipids in the brain, and how these modified lipids may drive disease progression. The study consists of two parts. In the first part Prof. Forsthuber and colleagues will study how these modified lipids are generated, and, importantly, how they can be removed and neutralized, in mice



with an MS-like disease called EAE. The second part of the work will investigate how neutrophils contribute to the generation of these modified lipids and how this process contributes to progression of EAE.

What's Next: Treatment with antioxidants such as green tea has shown potential benefit in some people with MS, but not others. These studies can provide important information to better understand the disease mechanisms that need to be targeted to make treatments such as antioxidants successful. If lipid modification turns out to be a critical factor that drives MS progression, then targeting its prevention may be a new approach to treating or preventing MS progression.

Dimitry Kremmentsov, B.S, Ph.D.

University of Vermont
Burlington, Vermont

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$552,845

Title: Mechanisms of sex-specific p38 MAPK-mediated pathogenesis in CNS autoimmunity

Summary: University of Vermont researchers are exploring immune system activity that may explain why MS affects women more than men, and may yield a strategy for stopping the immune attack.

Background: MS affects women two to three times more often than men. Why this happens is not well understood. There is evidence that sex hormones, like estrogen and testosterone, maybe involved in the immune attack. This sex difference may represent a window into better understanding the disease process, and could provide an opportunity to develop gender-specific therapies. Dr. Kremmentsov and colleagues have identified a gene and molecule – p38 alpha – that

can be targeted to improve MS-like disease in mouse models. Interestingly, this only works in females, and seems to be related to sex hormones.

The Study: Now this team is exploring hormonal regulation of p38 further, by examining the cell types affected by p38 alpha signaling. They also are looking at p38 alpha in MS-like disease in mice in which sex hormones are deactivated, or in which hormone replacement therapy is administered.

What's Next: These studies are aimed at providing a detailed understanding of p38 alpha in MS-like disease. Eventually, treatments targeting p38 alpha may be used to treat people with MS. Such treatments have already begun to be tested in other human diseases

Francisco Quintana, Ph.D.

Brigham and Women's Hospital
Boston, Massachusetts

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$624,082

Title: Therapeutic and environmental control of astrocyte function during autoimmune neuroinflammation

Summary: Researchers at Brigham & Women's Hospital are exploring an immune mechanism that may contribute to MS progression and may open doors to wellness strategies aimed at stopping progression.

Background: Many people experience acute MS relapses and then periods of recovery. Later in the course of MS, many transition to the "secondary progressive" phase, which involves worsening of disabilities with or without occasional relapses. There is an unmet need for therapies to prevent the accumulated loss of function. Dr. Quintana's team is in-



investigating immune mechanisms operational during progressive disease, and seeking to develop innovative therapeutic strategies targeting astrocytes, the largest cell population in the brain and spinal cord. They have identified a novel mechanism operational in astrocytes which involves type I interferons (such as interferon-beta, or IFN-beta). Preliminary results show that this mechanism can be targeted specifically to treat MS-like disease in mice and prevent the chronic accumulation of neurological deficits.

The Study: Now the team is studying this mechanism further. First, they are evaluating the effects of IFN-beta signaling on astrocytes in mice. Preliminary results indicate that IFN-beta signaling activates a molecule called “AhR” in astrocytes. AhR is a sensor that is switched on when certain molecules attach to it, specifically, molecules from the diet, the gut microbiome, and the metabolism. In a second step, they are evaluating the effects of AhR in astrocytes during MS-like disease using mouse strains that lack AhR in astrocytes. They are then activating AhR through special diets and antibiotic treatments to influence the gut as well as the metabolism. In a third aim, they are evaluating these mechanisms for the treatment of MS-like disease in acute and chronic mouse models, as well as treating human astrocytes isolated in the laboratory.

What’s Next: These results may help to define a mechanism that contributes to MS progression, and may reveal how food, the gut microbiome, or pollutants may affect the outcome of MS. The results might lead to treatments and wellness strategies aimed at stopping the progression of MS.

STOP—Measuring MS Disease Activity

Jiwon Oh, M.D., Ph.D.

Johns Hopkins University
Baltimore, Maryland

Award: Research Grants

Term: 10/1/2016-9/30/2018

Funding: \$500,000

Title: Leptomeningeal inflammation in MS: a prospective MRI study

Summary: Researchers are exploring a novel imaging finding that may yield clues to understanding and stopping MS progression.

Background: Recently, advanced imaging technology has enabled the visualization of a finding known as “leptomeningeal enhancement” (LME), or inflammation of the layers of tissue (meninges) surrounding the brain, in a significant portion of people with MS. This finding is novel and surprising, as it was previously thought that it was not possible to visualize inflammation in the meninges using MRI in people with MS. One recent study demonstrated that this finding is more likely to occur in people with progressive disease, and in people with more severe neurological disability. These observations are intriguing, and may provide needed insight into MS disease mechanisms, and what sort of tissue changes cause neurological disability.

The Study: Dr. Oh and colleagues are assessing how common LME is in a large, combined group of people with MS, and are looking at what sort of pathological changes LME causes in the brain. They are recruiting about 100 people with MS currently being followed at the Johns Hopkins MS Clinic, and 100 from a group currently followed at the National Institutes of Health. Participants will undergo annual MRIs of the brain, and detailed clinical assessments over two years. Dr. Oh’s team is assessing how clinical disability relates to the



presence of LME, and whether LME and associated tissue changes are related to the development and progression of clinical disability in MS. Finally, in an existing clinical trial assessing the efficacy of rituximab administered into the spinal fluid, they are assessing how LME changes with rituximab administration, and whether observed changes in LME correspond to treatment response.

What's Next: Ultimately, this study will increase understanding of the role that inflammation of the meninges plays in MS, especially progressive MS, and will enable the development of LME for use in clinical practice and in clinical trial settings.

STOP—Neuropathology

Richard Reynolds, Ph.D.

Imperial College London
London, United Kingdom

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$646,187

Title: The role of meningeal inflammation induced cytokine signaling and mitochondrial dysfunction in neurodegeneration in progressive MS

Summary: Researchers have pinpointed a molecule that may signal nerve cell death, and are investigating how to alter these signals to stop MS progression.

Background: The loss of nerve cells (neurons) plays a central role in driving MS progression. However, the processes underlying this loss remain poorly understood. Prof. Reynolds has brought together an international team from the United Kingdom and the Netherlands, and has identified a number of molecules that are being made by immune cells trapped within the brain space that might be damaging neurons in MS. Recent work indicates that

one such molecule, TNF, has the potential to kill neurons.

The Study: Now, this team is examining brain tissue obtained from people with MS to see whether machinery within neurons responds to a signal from TNF that induces cell death. They are studying whether TNF acts by damaging the powerhouses of the cells, the mitochondria, so that the neurons die due to an inability to produce energy. They are trying to stop this type of cell death using a variety of small drug-like molecules that are already available. The next stage will be to test whether TNF can produce the same kind of neuronal death in a rat model of MS and whether the approaches used to inhibit this in neurons in a dish will also work in rats.

What's Next: If this is successful, then these studies will prepare the way for early pre-human testing of therapeutic approaches that may stop clinical progression in MS.

STOPPING MS PROGRESSION

In an unprecedented global effort to end progressive MS, the International Progressive MS Alliance has awarded three \$4.7 million Collaborative Network Awards for a total investment of \$14.1 million toward accelerating the pace of progressive MS research.

Read more on our website:

[http://www.nationalmssociety.org/About-the-Society/News/Progressive-MS-Alliance-Brings-Together-Resear-\(1\)](http://www.nationalmssociety.org/About-the-Society/News/Progressive-MS-Alliance-Brings-Together-Resear-(1))



17 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

Shing-yan Chiu, PhD (University of Wisconsin-Madison) is exploring a strategy for stopping a toxic process that damages nerves and contributes to MS progression.

Francesca Fallarino, PhD (University of Perugia, Perugia, Italy) is investigating a novel target for stopping the immune attack in MS.

Yulin Ge, MD (New York University School of Medicine) is investigating whether measuring pH levels in the brain is linked to MS progression or tissue injury.

Muru. Gopal, PhD (Brigham and Women's Hospital, Boston, MA) is investigating a novel strategy for stopping the immune attack in MS.

Varghese John, PhD (University of California Los Angeles, Los Angeles, CA) is developing a quick test for assessing treatment success in people with relapsing MS.

PILOT SPOTLIGHT-Tracking MS in Saliva

Batia Kaplan, PhD (Sheba Medical Center, Ramat Gan, Israel) is developing a non-invasive laboratory test for diagnosis and follow-up of MS. A saliva sample is taken to analyze the presence of a special class of molecules, “immunoglobulin free light chains” (FLC). In a healthy state, the amount of FLC is small, but people with active MS show abnormal levels and distribution of FLC. In this study, saliva samples will be compared among people with MS, healthy controls, and people with other neurological diseases. This novel finding opens new opportunities for developing a way of diagnosing and monitoring MS by a non-invasive and inexpensive way.

Robyn Klein, MD, PhD (Washington University School of Medicine, St. Louis, MO) is exploring a strategy for promoting recovery from the immune attack in a mouse model of MS.

Daniel Ontaneda, MD (Cleveland Clinic Foundation) is exploring extensive data to determine the feasibility of a trial testing vitamin D in people with progressive MS.



RESTORE

Peter Altenburger, PhD (Indiana University, Bloomington, IN) is testing a novel method of improving walking in people with progressive MS.

K. Bo Foreman, PhD (University of Utah, Salt Lake City) is studying the effectiveness of balance training to improve the ability of people with MS to prevent themselves from falling.

PILOT SPOTLIGHT-Acupuncture for MS Symptoms

Although persons with MS have tried acupuncture, and many claim to have benefitted from it, little research has specifically examined the effects of acupuncture on MS symptoms. **Herbert Karpatkin, DSc** (Hunter College, NY) is testing an acupuncture treatment that is a combination of a typical treatment suggested by Chinese Medicine textbooks, combined with treatment that is individualized to the needs of people with MS. They are looking at the effects of acupuncture on specific symptoms of MS such as walking, balance, strength, sensation, fatigue, and mood. Thirty people with MS are being randomly assigned to receive acupuncture (twice a week for four weeks) or no acupuncture. The results can provide preliminary information about whether acupuncture is a useful treatment for persons with MS, and if so, for which specific symptoms.

Trevor Kilpatrick, PhD (Florey Institute of Neuroscience and Mental Health, Parkville, Australia) is exploring a therapeutic target that may enhance myelin production in MS.

Eun-Jeong Lee, PhD (Illinois Institute of Technology, Chicago) is examining the impact of a possible source of workplace discrimination for clues to improving employment in MS.

Brahim Nait-Oumesmar, PhD (INSERM, Paris, France) is developing a novel mouse model for evaluating myelin repair strategies in MS.

Brian Popko, PhD (University of Chicago) is using advanced genetic tools to understand how myelin-making cells develop and are affected in MS, for clues to repair strategies.

Lauren Strober, PhD (Kessler Foundation Research Center, West Orange, NJ) is testing a comprehensive intervention that may help people with MS to stay employed.



END

Gang Li, PhD (Brigham and Women's Hospital, Boston, MA) is pinpointing the genetic variations associated with the cause of MS.



STOP—Neurophysiology

Maarten Kole, M.Sc., Ph.D.

Netherlands Institute for Neuroscience
Amsterdam, Netherlands

Award: Research Grants

Term: 10/1/2016-9/30/2020

Funding: \$449,340

Title: Mechanisms and consequences of synapse elimination in secondary progressive MS and the cuprizone model

Summary: Researchers at the Netherlands Institute for Neuroscience are exploring a strategy for improving learning and memory in secondary progressive MS by addressing damage in a specific area of the brain associated with these functions.

Background: Many people with MS experience cognitive impairments such as problems in remembering events or reduced ability to learn. These symptoms may result from damage to a region of the brain called the hippocampus, which is known to be responsible for the control of memory and learning. One of the major changes occurring in the hippocampus during MS is the loss of synapses, the contact points between cells necessary for transferring and encoding information in the brain. His colleague, Valeria Ramaglia, PhD, has recently shown that components of the immune system, proteins called C1q and C3, are involved in the removal of synapses in the MS hippocampus.

The Study: Using mouse models of MS, now this team will measure hippocampal changes and find out whether these changes are responsible for cognitive impairments. They also are relating the observations made in the model to MRI scans of brain tissue from people with MS, and cognitive information from their medical records. Importantly, the team

will test whether a novel treatment, that targets C1q in the hippocampus, can improve clinical outcome in mice with MS-like symptoms.

What's Next: This research will deliver important basic information about how changes in the hippocampus affect cognition in MS, and will help identify potential targets, such as C1q, that might be blocked to prevent cognitive deficits.



RESTORE

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

RESTORE—Lifestyle/Wellness

Lara Pilutti, Ph.D. (Transfer in process)

University of Ottawa
Ottawa, Ontario, Canada

Award: Research Grants

Term: 10/1/2016-9/30/2018

Funding: \$TBD

Title: Lifestyle physical activity intervention for improving cardiorespiratory fitness and vascular comorbidity risk in MS

Summary: Researchers are testing an intervention to increase physical activity to determine if it can improve fitness and reduce vascular disease risk in people with MS.

Background: Vascular conditions such as high blood pressure, diabetes and cardiovascular disease are common among people with MS, and can negatively impact the diagnosis, treatment, and progression of MS.



Physical inactivity is one of the leading causes of vascular disease in the general population, and has been suggested as one explanation for the increased risk of vascular conditions in people with MS. It is possible that increasing physical activity levels might lead to reductions in vascular disease risk factors by improving fitness in people with MS. Dr. Pilutti and colleagues have developed, refined, and tested a lifestyle physical activity intervention that has been shown to increase physical activity in people with MS.

The Study: Now this team is conducting a clinical trial to test if this intervention can improve fitness and reduce vascular disease risk. Sixty adults with MS will be randomly assigned into either a lifestyle physical activity intervention or a general wellness intervention for six months. The lifestyle physical activity intervention involves visiting a website and engaging in one-on-one video chat sessions with a behavioral coach to increase day to day physical activity. Participants will be given a pedometer (step counter) to monitor and record their daily activity. The “general wellness intervention” involves providing information on self-managing MS consequences through methods other than physical activity. The team will test the same set of outcomes before, immediately after the intervention, and after a 6-month period without the intervention, to determine if there are changes in cardiorespiratory fitness and vascular disease risk factors.

What’s Next: This study will set the stage for the design of a future, larger Phase-III trial of effectiveness of the lifestyle physical activity intervention for improving vascular disease risk factors in adults with MS. If it proves effective, this intervention may improve quality of life for people with MS and reduce their risk for complications from vascular disease.

Ruchika Prakash, Ph.D.

Ohio State University
Columbus, Ohio

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$631,261

Title: A physical activity-based tracking intervention to enhance cognitive and neural plasticity

Summary: Researchers are testing whether increasing physical activity through the use of simple accelerometers can improve cognitive functioning in MS.

Background: Cognitive problems are common among people with MS, but there are currently few treatments to reduce or improve these problems. Previous investigations involving people with MS have shown an association between higher levels of physical activity and cognition, particularly on tasks that require individuals to quickly manipulate information. Dr. Prakash and colleagues are seeking to establish a cause and effect relationship between increased physical activity and improved cognitive functioning.

The Study: One hundred participants will be randomly assigned to either a step-count tracking (using a wearable accelerometer) or a water intake-tracking control group. Step-count tracking, such as what is provided by common accelerometers like “Fitbits,” provides feedback and accountability that has been shown to increase physical activity of the wearer. Assessments will include paper and pencil tasks of cognitive function, and functional MRI scans that provide high-resolution data on brain activity during actual tasks. After all data have been collected, the team will determine the impact of the step-count tracking intervention, compared with the water-intake tracking intervention, on measures of cognition and brain functioning.



What's Next: If proven effective, step-count tracking will represent a low-cost intervention for increasing levels of everyday physical activity in people with MS, with subsequent gains for cognitive health. Data gathered through this study, along with the easy availability of low-cost step-count monitoring devices, will allow clinicians to prescribe these as cognitive rehabilitation tools for people with MS who live with cognitive issues.

RESTORE—Nervous System Repair

James Salzer, M.D., Ph.D.

New York University School of Medicine
New York, New York

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$610,536

Title: Role of adult neural stem cells in remyelination

Summary: Researchers at New York University are exploring how to stimulate the brain's own stem cells to promote the repair of nerve-insulating myelin.

Background: An important goal in MS research is to enhance repair of the myelin sheaths around nerve fibers that have been damaged in the course of the disease. A major strategy to enhance remyelination—and the focus of this proposal—is to improve the ability of immature myelin-making cells, which are known to exist in significant numbers in the adult brain, to form new sheaths. Prof. Salzer has found that adult nerve stem cells are capable of repairing myelin, and that inhibiting a specific protein (called Gli1) in these cells improves their recruitment to and subsequent formation of new myelin sheaths in mouse models.

The Study: Now Prof. Salzer's team is proposing to learn more about the functional capability of these stem cells in repair, and how they interact with another pool of repairing cells and other cells in the brain. They also are exploring further how Gli1 limits the capabilities of nerve cells. To this end, they are using mouse models of myelin damage and repair. They are genetically manipulating cells in these lab models to discover more about the basic principles that govern myelin repair.

What's Next: These studies will provide new insights into the contribution of stem cells to repair. It also will provide information on factors that regulate stem cell effectiveness, to help guide therapeutic efforts at promoting myelin repair.

RESTORE— Myelin Biology

Thanh Nguyen, Ph.D.

Weill Cornell Medical College
New York, New York

Award: Research Grants

Term: 10/1/2016-9/30/2020

Funding: \$897,374

Title: Quantitative MRI of lesion iron and myelin repair

Summary: Weill Cornell Medical College researchers are testing and validating a novel imaging technique for use in determining how iron in MS lesions in the brain may affect myelin repair.

Background: Finding a way to repair the myelin that protects nerve fibers is currently an active area of research in MS, with the goal of improving recovery after relapses and potentially preventing loss of nerve cells. There are likely multiple factors that limit natural myelin repair in people with MS. Iron deposits within areas of damage (lesions) is one potential factor limiting repair. Dr. Nguyen's team has de-



National MS Society Collaborates Commercially to Develop Treatments for Progressive MS

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

University College London (UCL)

Researchers at University College London previously identified a molecule—VSN16R—that relieves spasticity in mice without causing side effects such as muscle weakness, sedation, or alteration in mood, which can occur with current treatments. With support from the National MS Society through Fast Forward, the toxicity studies necessary to bring this molecule to human testing were completed and VSN16R is now being tested in a phase II trial to see if it can improve MS-related spasticity. During preclinical studies the UCL team uncovered a potential neuroprotective effect of VSN16R. They are now doing further preclinical testing to determine if molecules similar to VSN16R can be developed into well-tolerated, neuroprotective therapeutic strategies for relapsing and progressive MS.

Funding: (\$553,725) to support identification of new neuroprotective compounds to prevent or delay neurodegeneration in progressive MS, and test compounds in mouse models.

veloped two brain imaging methods (Quantitative Susceptibility Mapping and Myelin Water Imaging) to accurately evaluate the amount of iron within lesions and to assess the influence of iron on myelin recovery.

The Study: Now the team is working to improve the accuracy of these techniques and to shorten brain scanning time. This will improve comfort for people undergoing these scans. They plan to overlap both imaging techniques to accurately determine the amount of myelin and iron present within lesions. They are validating this approach in a rat spinal cord model of MS by comparing

MRI measurements with actual tissue damage. Then they will use the technology to study people with MS who have new lesions, looking at early changes in myelin and iron within lesions and how this influences myelin repair 12 months later.

What's Next: This research can determine the exact role of iron in myelin damage and its influence on myelin repair, for clues to fostering the development of novel myelin repair strategies to restore function in people with MS.



Adan Aguirre, Ph.D.

State University of New York at Stony Brook
Stony Brook, New York

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$446,024

Title: Role of TGF-beta in oligodendrogenesis and myelin repair

Summary: Researchers at the State University of New York, Stony Brook, are exploring the role of a molecule in stimulating myelin-making cells to repair nerve-insulating myelin in MS.

Background: In the brain, cells known as “oligodendrocytes” form myelin, a fatty coating that insulates nerve fibers. This protective coat enables rapid transmission of nerve signals. In MS myelin is destroyed, and nerve fibers and nerve cells are damaged as well. In response to myelin damage, successful natural myelin repair is achieved by immature oligodendrocytes. However, this repair does not succeed in keeping up with the damage.

The Study: Dr. Aguirre’s team has shown that a molecule called transforming growth factor beta (TGFb) may provide signals that promote oligodendrocyte development and the process of repair. Now they are studying how critical TGFb signaling is to myelin repair in mouse models and using models of myelin damage, and also are exploring whether manipulating these signals affects myelin repair and functional recovery. They are also examining tissue obtained from people with MS for evidence of TGFb activity.

What’s Next: The team hopes to identify crucial molecules that are good candidates for designing treatments to promote myelin repair and restore neurological function in people with MS.

Babette Fuss, Ph.D.

Virginia Commonwealth University
Richmond, Virginia

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$196,705

Title: ATX: a regulator of CNS myelination

Summary: Researchers are studying a signaling pathway to determine its potential for stimulating immature myelin-making cells to mature and form new myelin to restore function in MS.

Background: Myelin, the sheath that insulates nerve fibers, is a key target of the immune attack in MS. Researchers are working on therapeutic approaches that stimulate immature myelin-making cells (known as oligodendrocytes) to mature and form new myelin, but need more information about the molecular mechanisms involved in this process. Dr. Fuss and colleagues are investigating a novel idea that signaling via the molecule LPA, which is generated through the activity of another molecule, namely autotaxin) has the capacity to promote maturation of oligodendrocytes. Importantly, signaling by these molecules seems to be impaired in MS.

The Study: To define autotaxin-LPA signaling as an important regulator of oligodendrocytes, Dr. Fuss is assessing its signaling in cells isolated in lab dishes and in zebrafish, a good model of this process because the fish are literally transparent. The team is also exploring the signaling in mice that experience myelin damage and repair.

What’s Next: The proposed research will provide important basic information on mechanisms that may stimulate oligodendrocytes to mature and repair myelin. The findings can lead to the development and testing of novel therapies to stimulate myelin repair in MS.

**Vittorio Gallo, Ph.D.**

The Children's National Medical Center
Washington, D.C.

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$538,351

Title: Signaling mechanisms underlying Sox17-mediated oligodendrocyte generation and repair

Summary: Researchers at Children's National Medical Center in Washington, DC, are investigating a molecule that influences the development of cells that make nerve-insulating myelin, for clues to promoting nervous system repair in MS.

Background: In multiple sclerosis, the myelin that insulates nerve fibers and oligodendrocytes (myelin-forming cells) are damaged and lost in the brain and spinal cord. The natural process of myelin repair, initiated through the recruitment and maturation of immature oligodendrocytes, may begin in people with MS, but remains insufficient or incomplete. Nerve fibers are damaged as well, and this manifests as progressive disease. This project analyzes how a molecule, known as Sox17, activates signals that promote the development of oligodendrocytes, enhance oligodendrocyte replacement and repair, and reduce tissue damage.

The Study: Prof. Gallo's team is studying the function of Sox17 during the process of myelin damage and spontaneous repair in two mouse models: one engineered to produce high levels of Sox17 protein, and another engineered to be deficient in Sox17. They are doing a series of studies to help establish what biochemical signals are required for normal control of adult oligodendrocytes, how these become disrupted after myelin damage, and how they might be restored by Sox17.

What's Next: These studies will provide important information about Sox 17 in myelin repair, and also establish a platform for analyzing small-molecule agents for their ability to promote Sox 17 signals to effectively induce myelin repair.

Jaime Grutzendler, M.D.

Yale University
New Haven, Connecticut

Award: Research Grants

Term: 10/1/2016-9/30/2019

Funding: \$330,000

Title: Local astrocyte contributions to myelin repair

Summary: Yale University researchers are exploring how cells called astrocytes contribute to the repair of nerve-insulating myelin and implications for promoting myelin repair.

Background: Myelin is a crucial component found in the brain that acts as insulation for the electrical transmission of signals between different brain regions and individual cells. In MS, the immune system attacks the brain and spinal cord, and myelin is a key target of the attack. One of the main impediments to developing effective treatments for myelin repair involves our incomplete understanding of the mechanisms by which myelin-making cells of the brain and spinal cord, called oligodendrocytes, develop and produce myelin.

The Study: Dr. Grutzendler's team is investigating astrocytes, a particularly abundant supporting cell in the nervous system that may contribute locally to the development and function of myelin-making oligodendrocytes following myelin damage. The team is studying mice with myelin damage to characterize the timing and key features demonstrated by immature oligodendrocytes as they develop and eventually form myelin sheaths. Next, they are examining how astro-



cytes establish interactions, because these interactions are believed to be important for various functions, including facilitating the flow of nutrients to developing oligodendrocytes.

What's Next: This set of experiments can provide a novel viewpoint on the role of astrocytes in myelin formation and how these cells can be manipulated to encourage repair.



END

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

END—Risk Factors

Brent Richards, M.D.

Jewish General Hospital
Montreal, Quebec

Award: Research Grants

Term: 10/1/2016-9/30/2018

Funding: \$128,000

Title: The effect of obesity and EBV on the risk and progression of MS: A Mendelian randomization analysis

Summary: Researchers from Jewish General Hospital in Montreal are using advanced genetic tools to better understand the extent to which obesity and Epstein-Barr virus are associated with increased MS risk or progression.

Background: While the cause of MS is still not known, scientists believe that the interaction of several different factors may be involved. Previous studies have linked higher levels of body mass index (BMI) and previous

infection with the Epstein-Barr virus (EBV) with increased risks of developing MS.

The Study: Dr. Richards and colleagues are taking a new approach to studying BMI and EBV on the risk of MS and MS progression. The team is first identifying genes associated with BMI and/or EBV that have been pinpointed by large scale genetics studies involving hundreds of thousands of people. Next, they are investigating to what extent these genes are associated with increased MS risk, or MS progression, in the genetics data accumulated by the International MS Genetics Consortium in tens of thousands of people with MS. Dr. Richards is using Mendelian Randomization, a technique that can help to tease out whether BMI and EBV play a causal role in MS.

What's Next: Since obesity and EBV represent risk factors that can be targeted by health interventions, a better understanding of these factors would help to inform the development of new strategies that could potentially prevent MS or stop onset and progression.

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