

New MS Research Investments to Drive Pathways to Cures

Beyond the personal losses and economic disruptions caused by COVID-19, research into MS has been disrupted as the pandemic shut down laboratories and paused clinical trials around the world. But MS doesn't stop, and neither will the National MS Society. This spring the Society committed over \$16 million to support 50 new multi-year research projects and training fellowships, with global investments in research totaling \$65 million.

We're still here and committed to accelerating pathways to cures aimed at stopping MS, restoring function that has been lost, and ending the disease forever.

Just a few of the of the new cutting-edge research projects include researchers looking at immune cells from non-white individuals with MS to better predict and treat MS in diverse populations; a team exploring how diet and gut bacteria regulate functions of specific immune cells involved in MS; and several studies focusing on promoting repair of nerve-insulating myelin that is destroyed on MS.

Many of the new investments grow the MS research workforce by providing

immersive training at MS clinics, laboratories, and rehabilitation centers.

The Society is still the largest private funder of MS research in the world and is recognized as a global leader in driving MS research. We stimulate studies worldwide, leverage opportunities, foster collaboration, and shape the research landscape to find solutions for the urgent needs of 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?

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Symptoms, Rehab, Wellness: How do we reverse symptoms and promote wellness?

Emerging evidence suggests that wellness behaviors and lifestyle factors can influence the risk for developing MS, disease course, severity of symptoms and quality of life. Finding ways to understand and address the variable and unpredictable symptoms caused by MS will have a profound impact on people's quality of life. In addition, people with MS often live with other chronic medical conditions. Understanding how these other health conditions affect MS disease course and symptoms represents an important research opportunity. Opportunities to improve the design and conduct of clinical trials and providing strategies people can incorporate to enhance their wellbeing are a priority.

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Jared Bruce, PhD

University of Missouri - Kansas City
Kansas, Missouri

Award: Research Grants

Term: 10/1/2020-9/30/2024

Funding: \$756,059

Paid by the Marilyn Hilton MS Research Fund

Title: Development of a telehealth obesity intervention for patients with MS

Summary: A University of Missouri team is testing the effectiveness of an MS-specific weight loss/healthy living program delivered by phone, since obesity can profoundly worsen MS severity.

Background: Obesity increases the risk of developing MS. Moreover, obesity and MS are both associated with reduced mobility, increased fatigue, depression, and reduced quality of life. The goal of this study is to test a telephone treatment designed to help people with MS lose weight and exercise. Dr. Bruce will also determine whether losing weight in those who are obese is linked with improvements in depression, fatigue, mobility and other common MS symptoms.

The Study: Dr. Bruce is testing a telephone-delivered weight loss program in 70 people with MS. The intervention includes self-monitoring, goal setting, exercise, and social support. The program will be tailored to the special needs of people with MS, and may incorporate issues such as mobility/transportation difficulties, coping with relapse, mood disturbance, cognitive changes, and dealing with MS fatigue. After the study is completed, the team will determine whether weight loss leads to improvements in common MS symptoms.

What is the potential impact for people with MS? If this weight loss program is effective in helping people lose weight and reducing common symptoms, it can help to improve overall quality of life in people with MS.

Worldwide Research Effort to Improve Coronavirus Outcomes in People with MS

Collaborators around the world are implementing programs for collecting important information about the impacts and outcomes of COVID-19 infection in people living with MS and related disorders. These efforts will help healthcare providers identify the best way to handle this infection in people with MS, and will give people with MS the information they need to achieve the best outcomes.

For People with MS: For people living with MS, the iConquerMS™ online portal has created a survey so that people can share their experiences coping with the COVID-19 pandemic and what their personal experience has been with COVID-19. The results will be shared with an international initiative gathering data from healthcare providers and people with MS across the world. Join at <https://www.iconquerms.org/>

See this link for other COVID-19 Studies Recruiting People with MS:
[nationalmssociety.org/Research/Participate-in-Research-Studies/COVID-19-Studies-Recruiting-People-with-MS](https://www.nationalmssociety.org/Research/Participate-in-Research-Studies/COVID-19-Studies-Recruiting-People-with-MS)

For MS Healthcare Professionals: Collaborating organizations including the National MS Society and the Consortium of MS Centers have established the North American MS COVID-19 Clinical Database. Healthcare professionals caring for individuals with MS and other demyelinating diseases (Neuromyelitis optica or MOG antibody disease) who have confirmed or suspected COVID-19 are encouraged to report outcomes in a clinical data collection system. This effort is harmonized with other international COVID-19 data collection platforms. Access the case reporting tool at <https://www.covims.org/>

Brett Fling, PhD, BS, MS

Colorado State University
Fort Collins, Colorado

Award: Harry Weaver Neuroscience
Scholarships

Term: 7/1/2020-6/30/2025

Funding: \$752,710

Title: Split-belt treadmill training in the lab and sensory cueing in the real world to reduce limb asymmetries and improve gait

Summary: Colorado State specialists are studying whether a rehabilitation program that specifically addresses asymmetries that may exist between legs can improve walking in people with MS.

Background: People with MS often report significant asymmetries (inequalities) in strength and function between the legs which are associated with poor mobility,

falls, and a reduced quality of life. There is limited understanding as to why these limb asymmetries exist and what regions within the central nervous system contribute to these mobility-limiting issues. It is also unknown whether minimizing these lower limb asymmetries may improve mobility during activities of daily living. Through a novel gait neurorehabilitation program, this proposal aims to reduce gait asymmetries in people with MS, identify the neural mechanisms that accompany these reductions, and develop a system that could be used during daily activities to automatically monitor and improve movement when needed.

The Study: Dr. Fling's team will first determine the potential to use a split-belt treadmill, where the speed of each leg can be controlled independently, to reduce gait asymmetries and improve mobility in people with MS. Second, communication between the two sides of the brain hemispheres will be assessed by providing a stimulation to the brain with a machine called transcranial magnetic stimulation while individuals are making a voluntary contraction with the leg. Finally, they will implement a novel sensory feedback approach to transfer the split-belt treadmill paradigm to typical walking that people with MS can complete at home.

What is the potential impact for people with MS? This work will use a novel approach to transfer the laboratory-based treadmill training design into real-world, everyday living to improve function.

Wan-Yu Hsu, OTR, PhD

University of California, San Francisco
San Francisco, California

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$209,702

Title: Effects of non-invasive brain stimulation on cognitive function in patients with multiple sclerosis

Summary: UCSF researchers are investigating the potential benefits of non-invasive brain stimulation, called transcranial alternating current stimulation, to treat cognitive deficits in people with MS.

Background: MS symptoms include difficulties with thinking (such as processing information), even early in MS. These problems can have major impacts on a person's quality of life. Although disease-modifying therapies used to treat MS can sometimes stabilize these thinking problems, they generally do not provide improvement.

The Study: Dr Hsu will be working within the Bove Lab and with the collaboration of Neuroscape (a translational neuroscience center at UCSF) investigating an approach, called transcranial alternating current stimulation (tACS), which is a type of non-invasive brain stimulation that applies weak currents to the brain through the scalp. She will be testing the idea that tACS will improve thinking problems in people with MS, since this approach has been useful in people with other conditions that cause problems with thinking. The team is also determining whether certain people

with MS, such as those within a certain age group or those with a certain level of thinking function, will benefit most from this approach.

What is the potential impact for people with MS? This study will provide evidence to help determine if tACS is a viable, non-pharmacological approach to treating thinking problems in people with MS.

Abbey Hughes, MA, PhD

Johns Hopkins University
Baltimore, Maryland

Award: Mentor-Based Postdoctoral Fellowships

Term: 7/1/2020-6/30/2025

Funding: \$447,217

Title: Advancing Psychosocial Wellness in Multiple Sclerosis Through Mentored Training in Rehabilitation Research

Summary: Rehabilitation researchers at Johns Hopkins have received funding to train promising rehabilitation professionals to conduct MS rehabilitation research.

Background: Addressing psychosocial aspects of MS is critical to effective MS rehabilitation. Psychosocial issues affect people with MS and their loved ones and include cognitive changes, depression, anxiety, disrupted sleep, pain, caregiver stress, and disparities in health care. Research focused on assessing psychosocial challenges is vital to improving quality of life and functioning in MS. There remains a great need for training in research focused on psychosocial aspects of MS rehabilitation.

The Study: This project will establish a five-year mentored postdoctoral fellowship program in MS rehabilitation research that focuses on psychosocial aspects of rehabilitation. To meet the need for advanced training in psychosocial rehabilitation research, this fellowship will focus on three aspects of psychosocial wellness: (1) developing and using technology to increase access to psychosocial assessment and interventions; (2) integrating pharmacologic and non-pharmacologic approaches to treat cognitive and emotional MS symptoms; and (3) engaging underserved people with MS to reduce systemic racial, ethnic, and socioeconomic disparities in disease outcomes.

What is the potential impact for people with MS? This program will train rehab professionals how to conduct carefully controlled research studies with relevance to improving quality of life.

Robert Motl, PhD

University of Alabama at Birmingham
Birmingham, Alabama

Award: Mentor-Based Postdoctoral
Fellowships

Term: 7/1/2020-6/30/2025

Funding: \$485,553

Title: Training in Physical Activity
Promotion for Multiple Sclerosis

Summary: Rehabilitation researchers at the University of Alabama at Birmingham have received funding to train promising rehabilitation professionals to conduct MS rehabilitation research.

Background: There is substantial evidence for the benefits of engaging in physical activity among persons with MS, yet their participation in health-promoting physical activity remains low. Prof. Motl's team is addressing this issue by training and mentoring postdoctoral fellows on ways to promote physical activity in MS through research that targets adherence and sustainability of physical activity interventions, to optimize long-term behavioral changes.

The Study: The postdoctoral fellows will receive training in the design of behavioral interventions that can be delivered in-person or through other channels (such as Web-based, telephone, or newsletter) for immediate and long-term physical activity behavior change. This will be supplemented by training in methods of quantifying physical activity and its outcomes and theories of behavioral change and determinants of physical activity. This

training will develop postdoctoral fellows who continue research on how to promote physical activity in people with MS.

What is the potential impact for people with MS? This program will train rehab professionals how to conduct carefully controlled research studies with relevance to improving quality of life.

Joshua Sandry, PhD

Montclair State University
Montclair, New Jersey

Award: Research Grants

Term: 10/1/2020-9/30/2023

Funding: \$451,216

Title: Neuroimaging of Hippocampally Mediated Memory Dysfunction in Multiple Sclerosis

Summary: A team at Montclair State is exploring changes in brain structure that underlie memory and cognitive problems in people with MS.

Background: Difficulty remembering new information is a common problem experienced by individuals living with MS. There is an urgent need to develop effective treatments to restore lost memory functioning, which will be more successful with increased knowledge about the underlying cognitive and brain processes responsible for memory problems.

The Study: This project will establish the best method for measuring and tracking brain activity underlying memory problems in people with MS. Using advanced imaging techniques, the team will investigate links between working memory changes and structure and damage to an area of the brain called the hippocampus. They will track people with MS who have memory problems compared to those who do not have memory problems, and they will also compare findings in people without MS. This will enable them to evaluate how cognitive processes change and relate to memory problems as a function of MS.

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What will be the impact for people with MS? This effort will provide preliminary data and help establish methods likely to yield informative results in a subsequent study that will involve more participants. The information gained from this line of research will provide a strong foundation for future treatments to restore lost memory functioning.

12 New High-Risk Pilot Projects Take Aim at MS

One way the Society propels MS research 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 their ideas are worth pursuing.

STOPPING MS

Jennifer Graves, MD, PhD (University of California San Diego) is exploring whether cells involved in aging are associated with disease severity in people with MS.

Guanshu Liu, PhD (Hugo W. Moser Research Institute at Kennedy Krieger, Inc., Baltimore) is testing novel imaging to determine how immune factors enter the brain in MS.

Easing the financial burden of MS

Gelareh Sadigh, MD (Emory University) and colleagues are exploring whether a cost information program can decrease financial burden and increase compliance with care in people with MS. People with MS are at high risk for financial burden because of expensive medications, potential for disability and losing income at a young age. Increased financial burden is associated with stopping medications and checkups. The goal of this pilot study is to evaluate whether informing people with MS of their out-of-pocket costs and optimizing those costs through a centralized cost information program is feasible, and if it is effective in improving financial burden and increasing compliance with MS care.

Jorge Oksenberg, PhD (University of California, San Francisco) is testing whether aging cells are related to progression of MS-like disease.

Darren Perkins, PhD (University of Maryland, Baltimore) is testing whether a therapy already in clinical trials can be applied to the immune response in MS.

Gelareh Sadigh, MD (Emory University, Atlanta) is exploring whether a cost information program can decrease financial burden and increase compliance with care.

Peter Stys, MD (University of Calgary, Alberta, Canada) is investigating a role for immune B cells in MS progression.

Stephen Tomlinson, PhD (Medical University of South Carolina, Charleston) is testing whether inhibiting immune system components affects progression of MS-like disease.

RESTORING WHAT'S BEEN LOST

Carlos Camara Lemarroy, MD (University of Calgary, Alberta, Canada) is exploring a novel strategy for promoting myelin repair.

Erin Gibson, PhD (Stanford University, Palo Alto) is exploring whether alterations in circadian rhythms in MS-like disease contributes to a failure in the natural capacity for myelin repair.

Walking to music

Eric Klawiter, MD (Massachusetts General Hospital) and colleagues are testing a method of walking to a beat or music to see if it improves walking in people with MS. Many people with MS report difficulty walking as one of their most debilitating symptoms. This team is testing whether a technique called Rhythmic Auditory Stimulation (RAS) can help 20 people with MS improve their walking abilities. RAS has previously been shown to improve walking characteristics such as speed, stride length and rhythm in other populations. In RAS, a person walks to a metronome beat or to familiar music. Depending on the person's goals, the tempo of the rhythm is either increased or decreased a little with each walk. The results collected from this small study can be used to power future larger studies that aim to treat walking dysfunction in MS.

Eric Klawiter, MD (Massachusetts General Hospital, Boston) is testing a method of walking to a beat or music to see if it improves walking in people with ms.

Sterling Ortega, PhD (University of Iowa, Iowa City) is studying a unique population of immune cells that may help reverse nervous system damage in MS.

ENDING MS FOREVER

Aaron Carlson, MD (University of Colorado, Denver) is using an extensive database to study people with MS and MS care in that state.

Risk Factors: Why do some people get MS and others don't?

Although tremendous progress has been made in identifying key biological pathways that contribute to MS risk, the cause is still unknown. Preventing MS for future generations requires a deep understanding of what triggers MS, how triggers lead to the development of the disease, and how to protect against it.

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Lisa Barcellos, PhD, MPH

University of California, Berkeley
Berkeley, California

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$540,708

Title: Identification of Genetic Contributions to Pediatric-Onset MS Using a Multi-Omics Approach

Summary: UC Berkeley scientists are studying pediatric MS for insights into the genes and other factors that determine a person's risk for developing MS.

Background: There is very strong evidence supporting the association between both low vitamin D status and childhood obesity and increased risk of developing pediatric MS. Some major advances in understanding the genetic component of these two important pathways have recently been made. This team will utilize this new information in a well-designed study to further understand the underlying biology of how low vitamin D and childhood obesity contribute to developing MS in children.

The Study: Prof. Barcellos and colleagues will study 1,000 children/adolescents with MS, 1,000 children/adolescents without MS, and 16,000 additional controls. They are using state-of-the-art genomic tools including methods that will help them to learn where in the genome (the full complement of hereditary information) vitamin D affects the expression (turning on or off) of other genes. They also are studying cells isolated in lab dishes to help identify areas of the genome in immune cells that are known to play a role in MS. By employing sophisticated methods of statistical analysis, they will determine the vitamin D- and obesity-related gene candidates that are most likely to be involved in MS.

What is the potential impact for people with MS? The results will have implications for prevention, diagnosis and prognosis, and ultimately selection of disease therapy in all types of adult and childhood MS.

Mahmoud Pouladi, MSc, PhD

Agency for Science, Technology and
Research (ASTAR)

Connexis, Singapore

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$554,374

Title: Ermin in Multiple Sclerosis

Summary: Researchers in Singapore are doing lab studies to understand how a rare gene mutation related to myelin may influence the risk of developing MS.

Background: Genetic factors are known to influence the risk of developing MS.

Identifying these factors and understanding how they influence biological processes related to MS may suggest novel approaches to treat or stop MS. Advances in genetic analysis techniques have made it possible to identify rare gene variations that cause disease. This team has discovered one such possible variation in a family of people with MS. Because little is known about the gene, they are studying the consequences of this variation in a mouse MS model.

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The Study: Dr. Pouladi's team is creating a mouse model carrying the specific genetic variation identified in the family of people with MS. They are using multiple timepoints to look at the effects of aging with this mutation. They will then study the impact of the gene on brain pathology and neurological functions. The team will study how the specific variation affects immune reactions and also damage to and repair of myelin, the coating that surrounds nerve fibers in the brain, which are key processes in the pathology of MS.

What is the potential impact for people with MS? The knowledge gained will improve our understanding of the underlying cause of MS, and the model developed may help identify potential new approaches for treating MS.

Neuroprotection/Repair: How do we repair the damage caused by MS?

The hopes of people living with MS today rest on finding a way to stop disease worsening by preventing neurodegeneration and reversing the damage to restore lost function. The brain can repair myelin and also rewire itself around damaged areas, but in order to significantly impact disease, this natural ability needs to be enhanced. In addition to developing treatment strategies, there is a crucial need for non-invasive ways to determine quickly whether neuroprotective and repair strategies are working.

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Riley Bove, MD, MSc

University of California, San Francisco
San Francisco, California

Award: Harry Weaver Scholar Award

Term: 7/1/2020-6/30/2025

Funding: \$708,972

Paid by the Marilyn Hilton MS Research Fund

Title: Trials for remyelination in MS: from bench to bedside to home

Summary: Researchers are testing a novel molecule that may repair myelin in women with MS ages 45-60, using a home-based trial that employs digital tools.

Background: Research studies that can be performed in the home, such as home-based clinical trials, are becoming more common. This approach is promising for people living with MS because it could allow people who do not usually have access to research (e.g.,

due to competing demands on their time, or geographic distance from clinic) the opportunity to contribute to, and benefit from, scientific advances. Advances are especially needed in the repair of nerve-insulating myelin, which is damaged in MS. Unfortunately, myelin repair has largely been measured through the visual system, limiting the pool of research participants to those with visual injury. Home-based trials using digital tools that assess other aspects of a person's function could accelerate testing of promising repair strategies.

The Study: Dr. Bove's team will test a promising therapy for myelin repair. In laboratory work, they have found that a specific selective estrogen receptor modulator (SERM) promotes myelin repair in lab animals. This SERM has an excellent safety profile along with other desirable effects such as improved bone health. They will test the SERM in both clinic and home-based settings. The home-based trial will involve 50 women with MS between the ages of 45 and 60. The team will recruit, enroll, evaluate and treat participants entirely using electronic questionnaires, televideo interviews, and other digital tools. In parallel, they will run a traditional in-clinic trial with the same medication in another group of 50 women.

What is the potential impact for people with MS? The goal is to accelerate the pipeline from discovery to treatment by improving access and finding new ways to conduct clinical trials and test a promising new agent for promoting repair in MS.

Monica Langley, PhD

Mayo Clinic Rochester
Rochester, Minnesota

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$196,309

Title: Targeting CD38 to Enhance Myelin Regeneration Following Diet-induced Mitochondrial Deficits

Summary: Mayo Clinic scientists are looking at the consumption of high fat diet as a risk factor and/or modifier of disease progression in an MS model.

Background: Research suggests that having a high body mass index may contribute to causing MS, along with other factors. The inflammation associated with MS or a high fat diet depletes a molecule called NAD⁺, which is necessary for proper function of mitochondria (the energy producers in the cell). NAD⁺ is also needed for survival of cells that make and repair myelin, the fatty substance that surrounds and protects nerve fibers destroyed in MS.

The Study: To understand how a high fat diet may have a harmful effect in MS, Dr. Langley and her team are looking at the consumption of a high fat diet as a risk factor and/or modifier of disease progression in a mouse model of myelin loss and repair. They are assessing NAD⁺ and mitochondrial function in the brain of mice consuming a high fat diet and how this influences loss of cells that make myelin and repair myelin. They are also examining the therapeutic potential of a drug that prevents the breakdown of NAD⁺.

What is the potential impact for people with MS? Results from this study may suggest a new treatment strategy for myelin repair based on blocking NAD⁺ breakdown in the brain and spinal cord.

Hyun Kyoung Lee, PhD

Baylor College of Medicine
Houston, Texas

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$656,739

Funded in part by the Donald C. McGraw Foundation

Title: Deciphering the Daam2-VHL signaling axis in oligodendrocyte remyelination in multiple sclerosis

Summary: Baylor researchers are focusing on understanding interactions of molecules to find a way to promote the repair of myelin that has been damaged by MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function properly, and are also made vulnerable to further damage and loss. Although some myelin repair does occur in MS, it is often not adequate to keep up with the damage. The cells that make myelin in the brain are called oligodendrocytes. These are mature cells that are derived from a pool of immature oligodendrocyte “precursors.”

The Study: Dr. Lee is investigating key molecular signals involved in getting oligodendrocyte precursors to mature into myelin-making oligodendrocytes. In particular, she is exploring the interaction of molecules involved in this maturation process, including “Daam2.” Daam2 appears to interact with other processes to inhibit the natural maturation and repair process. The team will examine Daam2 activity in samples of MS brain lesions and mouse models, and test whether a signaling cascade that blocks the Daam2 pathway can promote myelin repair.

What is the potential impact for people with MS? Further understanding of how a specific molecule inhibits normal myelin repair can lead to the design of strategies to overcome this mechanism to promote repair as a treatment for MS.

Jiaxing Li, PhD

Oregon Health & Science University
Portland, Oregon

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$196,309

Title: Investigating synapse assembly and disassembly in oligodendrocyte precursor cells

Summary: OHSU scientists are focusing on how myelin-making cells and nerve cells communicate, and how this knowledge may be used to promote myelin repair in MS.

Background: Synapses are the points of communication between nerve cells and between nerve cells and other cells. In MS,

myelin, the fatty substance that surrounds and protects nerve cells, is attacked and destroyed. The cells that make myelin are called oligodendrocytes, and nerve cells communicate with oligodendrocytes and their precursors through synapses; however, these synapses are not well understood. Synapses are lost in MS, but how this may affect MS progression and myelin repair is not known.

The Study: Dr. Li and his team are working to understand the physical properties of synapses through which neurons and oligodendrocyte communicate. The team is focusing on how the connections are established and modified, and what MS-related genes may be important. They are addressing these questions using zebrafish, which have myelin similar to that in mammals, but develop faster than mammals. Zebrafish embryos are transparent, allowing easy visualization of synapse structures in real time in living fish.

What is the potential impact for people with MS? Knowledge about how oligodendrocytes and nerve cells communicate and how this communication affects myelin formation may identify new ways to enhance myelin repair in MS.

Mathilde Pruvost, PhD

Research Foundation of CUNY-ASRC
New York, New York

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$196,309

Title: Promoting remyelination by investigating the nuclear mechanisms induced by neuronal stimulation in adult oligodendrocyte progenitors.

Summary: Researchers at CUNY-ASRC are exploring how nerve signals stimulate myelin-making cells for clues to promoting myelin repair in MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve cells. Nerve cells that have lost their myelin do not function properly, leading to symptoms in people with the disease. The brain can repair myelin, but repair is incomplete. Treatments are needed that enhance the body's natural ability to repair myelin.

The Study: Dr. Pruvost and her team are investigating how stimulation of nerve cells sends a message to myelin-making cells and how this may increase myelin repair. They are investigating how the signal from the nerve cells changes the DNA in myelin-making cells. These changes to the DNA do not change the sequence of the DNA but they likely affect what genes are turned on or off. After damage occurs to myelin in mice, the team is using sophisticated techniques to activate nerve cells and then

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explore how the myelin-making cells' DNA changes and if/how myelin repair is impacted. They are also determining what genes are affected by nerve cell activation to improve myelin repair.

What is the potential impact for people with MS? Results may identify new targets that can be used for the development of novel therapies leading to efficient repair of myelin in people with MS.

Progression: How do we stop MS progression?

MS progression often occurs early in the disease, even while the brain compensates for injury and even in people successfully treated for relapses. Progression is not easily measured and usually happens over long periods of time, making it hard to quickly detect whether a therapy is impacting the course of disease. This has made the development of therapies for progressive stages of MS a challenge. Diagnosing progressive disease based on biomarkers, in addition to clinical presentation, would enable the testing of therapies earlier, promising better ways of protecting the nervous system from MS injury.

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Peter Calabresi, MD

Johns Hopkins University
Baltimore, Maryland

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$840,246

Title: Validation of Serum Neurofilament Light Chain as a Biomarker in Multiple Sclerosis: Subtypes and controls

Summary: Johns Hopkins researchers are determining whether blood levels of a neurofilament, released when nerves are damaged, can be validated as a blood test to monitor MS and predict its course.

Background: There is presently no blood test that can allow health care providers to assess MS disease activity and progression. Progress has been made in developing a blood test to measure a molecule (neurofilament light chain) that is released when nerves are damaged in MS. However, in order to determine what is an abnormally high level in people with MS, we need to know what is normal for age, sex, and race; and the effects of other medical problems such as diabetes and high blood pressure, since these processes could alter neurofilament levels.

The Study: Dr. Calabresi's team plans to establish reference ranges for neurofilaments in the blood using 3,000 healthy control samples chosen to mirror the US population, and from which they know medical histories and illnesses. Once they have established normal values, they will examine if elevated levels predict worsening of clinical and MRI measures in 5,000 people with MS.

What is the potential impact for people with MS? These results will enable meaningful interpretation of sNFL in clinical practice and facilitate adoption as a tool for disease management.

Peter Calabresi, MD

Johns Hopkins University
Baltimore, Maryland

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$694,510

Title: Mechanisms of complement component 3 mediated neurodegeneration in MS and EAE

Summary: Johns Hopkins researchers are exploring sex differences in specific immune activity and whether blocking it has potential for protecting the nervous system in MS.

Background: Currently, there are no therapies that are specifically nerve-protecting or can substantially slow the progress of nerve damage and progressive disability in people with MS. Previously, Dr. Calabresi's team found that there are different versions of a gene called complement component 3 (C3) that appear to be associated with faster rates of nerve damage in the back of the eye (retina). This study will help to determine the potential for blocking C3 as a strategy to protect the nervous system and slow disability progression in people with MS.

The Study: The team is studying C3 in an animal model of MS called EAE. They have discovered that C3, already known to be important in immune functions, is also found in brain cells called astrocytes, and is important in causing nerves in the brain to die. When the C3 gene is deleted from mice, nerve cells in the retina are protected in female but not male mice. Now they are

conducting a series of tests in which they eliminate the C3 gene from astrocytes or immune cells in male and female mice to determine how this protects the cells from dying.

What is the potential impact for people with MS? The results of this study may help influence companies to try existing C3 inhibitors in clinical trials, which could facilitate the development of neuroprotective therapies for people with progressive MS. This study may also shed light on the disparate effects of MS on females compared to males.

Training Trial Specialists: The Sylvia Lawry Fellowship

Without clinical trials, there would be no disease-modifying therapies for MS – these are how new treatments are tested. Without clinicians trained in conducting these complex studies, they cannot proceed. Seeing this need, the Society established the Sylvia Lawry Physician Fellowship Program, named in honor of its founder. This program provides physicians with up to 3 years of formal training, under the tutelage of established investigators, in designing and conducting clinical trials in MS. Five new fellows are on their way to developing the skills involved in designing, implementing, and analyzing clinical trials in MS:

John Ciotti, MD, Washington University in St. Louis, Missouri

Dr. Ciotti is seeking to pursue additional fellowship training to enhance his expertise in the clinical management of MS and as an MS clinical investigator. The fellowship at the John L. Trotter MS Center has a long tradition of training successful fellows who go on to obtain faculty positions at highly regarded academic institutions.

Jamie McDonald, MD, MS, Stanford University, Stanford, California

Dr. McDonald will complete a two-year fellowship in MS and neuroimmunology. She will be trained in clinical evaluation, diagnosis, counseling, and treatment as part of a multidisciplinary team focused on improving the well-being of persons living with MS.

Daniela Pimentel Maldonado, MD, Johns Hopkins University, Baltimore, Maryland

Dr. Pimentel Maldonado will be trained in MS clinical research at the Johns Hopkins MS Precision Medicine Center of Excellence. She will also pursue a Masters of Science in Clinical Research at the Medical University of South Carolina, where she will obtain formal training in disciplines such as epidemiology, clinical trial design, and biostatistics.

Lindsay Ross, MD, Cleveland Clinic Foundation, Cleveland, Ohio

During this fellowship, Dr. Ross will be involved in a number of different research projects at the Mellen MS Center at the Cleveland Clinic, in order to gain the experience needed to be an independent MS researcher.

Neha Safi, MD, Icahn School of Medicine at Mount Sinai, New York, New York

Dr. Safi will work with MS experts to create comprehensive treatment plans for individuals with MS, including neuroradiologists who have access to state of the art imaging technology to understand the various subtypes of MS and to distinguish MS from other conditions. She will work with research coordinators to recruit people with MS for clinical trials, collect data, analyze results, and generate novel conclusions to improve MS care.

Laura Piccio, MD, PhD

Washington University School of Medicine
St. Louis, Missouri

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$652,160

Title: Cerebrospinal fluid-biomarkers-based diagnostic and prognostic models for Multiple Sclerosis

Summary: Washington University researchers are using powerful technology to measure spinal fluid proteins to develop biomarker profiles to predict MS course and response to treatments.

Background: Currently, the diagnosis of MS is mainly based on the neurological exam, the evaluation of symptoms, and MRI findings. Diagnosing MS can be complex, and there is no single laboratory test that can confirm it. New technical advances allow researchers to study the characteristics of the spinal fluid (CSF) that could assist with disease diagnosis and to predict how fast a person with MS will progress. This can help the clinician and the patient to decide whether they should choose more or less aggressive treatment.

The Study: Dr. Piccio, Dr. Bielekova, and a team of collaborators at multiple sites are confirming the accuracy of previously published MS diagnostic and predictive tests based on the measurement of more than 1000 CSF proteins in an independent population of people with MS. They are also determining if these biomarkers can predict MS course and validate new pathways that may be targeted by future MS treatments.

What is the potential impact for people with MS? These studies may allow more accurate MS diagnosis and a better understanding of the disease process in each individual. This could allow more personalized selection of treatments and faster demonstration of the effectiveness of future treatments for progressive MS.

Milos Simic, PhD

University of California, San Francisco
San Francisco, California

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$196,309

Title: Development of cellular immunotherapies for multiple sclerosis
Summary: A UCSF team is engineering immune cells as a strategy to deliver a payload to the nervous system to decrease damaging immune activity and provide healing growth factors.

Background: One type of immune cell, called a B cell, plays important roles in the immune attacks in MS. Therapies that deplete B cells have proved to be an effective approach for treating relapsing forms of MS. However, this approach has so far not proved effective for treating progressive MS, at least in part because in progressive MS it is thought that B cells have moved into the brain and spinal cord (collectively called the central nervous system or CNS), where the B-cell depleting therapies do not penetrate. One question is whether developing a B cell depleting therapy that can enter the CNS would be effective against progressive MS.

The Study: Dr. Simic and his team are engineering immune cells that can enter the CNS and deliver a therapeutic payload that is designed to decrease the number of B cells in the CNS, decrease the ongoing inflammation, and deliver beneficial factors that protect nerve cells and that could help restore neurologic functions. They are testing these experimental treatments in mice with an MS-like disease called EAE.

What is the potential impact for people with MS? Results from this study may lead to development of a new approach capable of delivering therapies to the brain and spinal cord where they are needed, and sparing other parts of the immune system. More specific, less toxic therapies for MS may be the final result.

Elias Sotirchos, MD

Johns Hopkins University
Baltimore, Maryland

Award: Career Transition Fellowships

Term: 7/1/2020-6/30/2025

Funding: \$550,000

Paid by the Marilyn Hilton MS Research Fund

Title: Prediction of risk of disability worsening and inflammatory disease activity in MS utilizing multimodal predictive algorithms

Summary: Johns Hopkins University researchers are studying multiple factors in large numbers of people with MS to provide insight into which factors are associated with a more severe disease course.

Background: People with MS show an unpredictable disease course, ranging from mild to severe disease. Although various factors have been proposed to be useful for predicting disease course in groups of people, more work is needed to bring these predictions to the individual level. This information is valuable because it can be used to guide treatment decisions. Studies in large numbers of people with MS can provide further insight into which factors are associated with a more severe disease course.

The Study: Dr. Sotirchos and his team are using data from a large number of people with MS (more than 15,000 from 10 MS centers) to develop a computer model that can predict disability worsening, attacks, and new brain lesions. To develop this model, which could be used for an individual person with MS, they are using “machine learning” and combining multiple predictive factors including demographics, clinical characteristics, imaging data, a marker in the blood called neurofilament light chain, and other factors.

What is the potential impact for people with MS? Ultimately the goal is for the predictive models being developed to be available as online tools and/or within electronic medical records for use by doctors and people with MS to accurately assess the risk of future disease worsening, enabling personalized risk assessments and therapeutic decision-making.

Biao Xiang, PhD

Washington University School of Medicine
St. Louis, Missouri

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$185,284

Title: Using a Novel MRI technique to Measure Evolution of tissue damage in Progressive Multiple Sclerosis

Summary: Investigators are testing the ability of an imaging technique to detect and track progressive MS.

Background: Although MRI techniques are effective to monitor MS lesions in relapsing-remitting MS, there are few ways to reliably track disease-related changes in primary and secondary progressive MS. This hinders the development of effective therapies because it takes longer to confirm therapeutic effect on progressive MS.

The Study: Dr. Xiang and his team are using a novel type of MRI called simultaneous multi-angular relaxometry of tissue (SMART) to measure MS disease progression. They are analyzing SMART images that were acquired every 9 months from 24 people with progressive MS. The team is looking at changes in the images that distinguish progressive MS from non-progressive MS, changes in brain regions that are related to disability, and changes that occur over four years.

What is the potential impact for people with MS? Developing better imaging biomarkers for progressive MS is expected to accelerate the development of therapies.

Weiquan Zhu, PhD

University of Utah
Salt Lake City, Utah

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$688,500

Title: Stabilizing the Blood-Central Nervous System Barrier to Treat Multiple Sclerosis

Summary: A team is studying the role of a protein in the onset and progression of MS lab models, and whether blocking it has potential for treating MS.

Background: The blood vessels in the brain (called the blood-brain barrier) are normally tightly sealed, preventing movement of most cells and molecules into the brain from the blood. However, in MS, the blood vessels can become leaky, which allows harmful cells and molecules to enter the brain and spinal cord. Dr. Zhu and her team discovered a molecule called ARF6 that is activated in MS and promotes leaking of blood vessels.

The Study: Dr. Zhu and her team are using mouse models of MS and testing whether deleting the gene that controls ARF6, or inhibiting ARF6 with a drug, can prevent leaking of blood vessels and therefore reduce or reverse MS-like disease. They are also examining the effects of ARF6 inhibition in human brain blood vessel cells grown in a lab dish.

What is the potential impact for people with MS? These studies should show whether ARF6 is a potential therapeutic target for treating MS.

Pathology: What is the cause of MS?

Much has been learned about immune system activity in the relapsing-remitting phase of MS and this knowledge has led to the development of effective disease-modifying therapies. Less understood is the relationship between initial immune activity and progressive neurodegeneration and how other immune factors participate in the progressive phase of MS. Identifying the causes of MS, and the underlying mechanisms and biological pathways involved in MS injury to the brain and spinal cord, will expose new targets for the development of treatments to stop the damage that causes disability.

* * *

Nozha Borjini, PhD

Cleveland Clinic Foundation

Award: Postdoctoral Fellowship

Term: 7/1/2020-6/30/2023

Funding: \$189,883

Title: “Study of Blood Brain Barrier Disruption in Neuroinflammatory Disease”

Summary: Dr. Borjini will train with a Cleveland Clinic team which is exploring mechanisms at early stages of MS-like disease that enable immune cells to enter the brain and spinal cord, and possible ways to stop them.

Background: The blood vessels in the brain and spinal cord are normally tightly sealed, preventing unwanted cells and molecules in the bloodstream from entering the brain and spinal cord. In MS, however, these

blood vessels, collectively called the blood-brain barrier, can leak and allow entry of harmful cells and molecules; this is thought to be one of the first events in the course of MS.

The Study: Dr. Borjini and her team are working to determine what causes these early disruptions to the spinal cord’s blood vessels and how immune cells in the blood are recruited to these leaky blood vessels. They are using advanced real-time imaging methods to observe changes in the blood vessels of the spinal cord in mice with the MS-like disease called EAE. The team is also examining whether a molecule called endothelin is important in these processes. Finally, they are testing whether an FDA-approved drug for high blood pressure that blocks endothelin can prevent damage to blood vessels in mice with EAE.

What is the potential impact for people with MS? These studies will help determine whether blocking endothelin may be a potential therapeutic approach to stopping MS at very early stages of progression.

Mary Catanese, PhD

Massachusetts General Hospital
Boston, Massachusetts

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$196,309

Title: In vivo neuroimaging of histone deacetylases in Multiple Sclerosis

Summary: Researchers at Mass General are using imaging to explore the role of a protein in MS-related damage to the nervous system, for clues to developing better therapies.

Background: We hypothesize that dysregulation of enzymes called histone deacetylases, or HDACs, likely occurs in MS. These enzymes play important roles in the health of myelin, the fatty substance that surrounds and protects nerve fibers and becomes damaged and destroyed in MS. HDACs are well-studied in animal models of MS, however, not much is known about the potential dysregulation of HDACs in people with MS.

The Study: Dr. Catanese and her team are measuring the levels of HDACs in the brains of people with MS using a novel HDAC-specific radiotracer for neuroimaging. People with MS and healthy controls are undergoing positron emission tomography (also called PET scanning) with this tracer to detect HDACs, as well as simultaneously acquired brain MRIs to identify lesions and evaluate white matter health. The team is measuring HDAC protein levels in MS brain lesions, non-lesioned white matter and across the entire brain, including the cortex,

where lesions are also found, to compare changes in people with MS to people who do not have MS. They will also be evaluating if HDACs are related to loss of overall white matter health and if changes in HDACs are related to MS symptoms.

What is the potential impact for people with MS? Inhibiting HDACs decreases MS-like symptoms in lab models but we do not yet understand how HDACs may become dysregulated in people with MS. Understanding HDACs in people may ultimately help guide strategies for the development of therapeutic approaches for people with MS.

Laura Ghezzi, MD

Washington University in St. Louis
St. Louis, Missouri

Award: Postdoctoral Fellowships

Term: 7/1/2020-6/30/2023

Funding: \$209,702

Paid by the Marilyn Hilton MS Research Fund

Title: Characterization and quantification of Mucosal Associated Invariant T cells in patients with Multiple Sclerosis at time of diagnosis and in response to different disease modifying therapies

Summary: Researchers are exploring how diet and the gut microbiota may regulate the number and function of a specific type of immune cell.

Background: An improperly functioning immune system plays a key role in initiating and continuing MS. The immune system includes many types of cells. One type of immune cell called mucosal associated

invariant T (MAIT) cells constitutes a specific subset of white blood cells. MAIT cells, which are found in MS lesions in the brain, normally mature in the gut. This supports the idea that what a person eats may impact the immune system.

The Study: Dr. Ghezzi and her team are characterizing MAIT cells and their products in the blood and in spinal fluid of people with MS before treatment and in response to different MS therapies. They are also investigating the effect of diet and gut microorganisms on MAIT cells by following over time a group of people with MS who are undergoing intermittent fasting or consuming a regular diet.

What is the potential impact for people with MS? A more comprehensive study of immune cells including MAIT cells in MS could suggest treatments that combine conventional therapy with dietary interventions.

Murugaiyan Gopal, PhD

Brigham and Women's Hospital
Boston, Massachusetts

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$502,140

Title: The pathogenic role of miR-92a in the regulation of T helper cell responses in MS

Summary: A Brigham and Women's Hospital team is exploring the role of a molecule linked to harmful immune activity, and whether inhibiting it has promise for treating MS.

Background: In MS, immune cells called Th1 and Th17 cells can rev up inflammation and are thought to be harmful. Other immune cells called Tregs are anti-inflammatory and thus considered beneficial. Molecules called microRNAs (miRNAs) control which genes are turned on and off, and are important in numerous diseases including MS. One miRNA, called miR-92a, controls inflammatory immune cells and Tregs in MS and in an MS-like disease called EAE in mice. Research shows that removing miR-92a reduces the severity of EAE.

The Study: Dr. Gopal and his team are determining how miR-92a regulates the disease-causing functions of inflammatory T cells and disease-preventing functions of Tregs in EAE and MS. They are also evaluating the therapeutic potential of drugs that inhibit miR-92a in several MS animal models, including models of relapsing-remitting and progressive MS. They are also examining miR-92a and immune cells from people with MS compared to people who do not have MS, for clues to its potential role in MS.

What is the potential impact for people with MS? These studies may show that inhibiting miR-92a is a promising treatment approach that warrants further development for people with MS.

Elena Herranz Muelas, PhD

Massachusetts General Hospital
Boston, Massachusetts

Award: Career Transition Fellowships

Term: 7/1/2020-6/30/2025

Funding: \$604,628

Title: Novel imaging tools for assessing spinal cord inflammatory activity in vivo in multiple sclerosis, its clinical relevance and correlation with brain pathology

Summary: Researchers at Massachusetts General Hospital are applying novel imaging technology to study the spinal cord in people in the early stages of MS.

Background: In MS, activated immune cells called microglia produce inflammation and are present in areas of damage to the brain and spinal cord. Damage to the spinal cord is an important determinant of physical disability. Detecting the presence of these cells in the spinal cord would provide better information about the state of a person's MS and response to treatment. Current imaging methods such as MRI can detect only some of these immune cells.

The Study: Dr. Herranz Muelas and her team are using two novel types of imaging, with a focus on the spinal cord. The first combines MRI and positron emission tomography (PET), and the second is an advanced type of MRI called ultra high field 7 Tesla (T) MRI. During MR-PET, they are using a marker to visualize activated microglia. Ultra high field 7 T MRI is being used to visualize very small structures in detail. People with early stages of MS are undergoing MR-PET and 7 T MRI, in

addition to neurological and neuropsychological assessments, and they will be followed up 2 years later. The team hopes to learn whether the extent of inflammation and the presence of inflammatory microglia in the spinal cord, as seen with these two types of imaging, are associated with brain inflammation, shrinkage of the brain, and worse physical disability.

What is the potential impact for people with MS? Results from this study may help identify new ways of predicting outcomes and efficiently screening for potential therapies in people with early stages of MS.

Dan Hu, PhD

Brigham and Women's Hospital
Boston, Massachusetts

Award: Research Grants

Term: 4/1/2020-3/31/2021

Funding: \$46,752

Title: Characterization of heat shock proteins in Multiple Sclerosis

Summary: Researchers at Brigham and Women's Hospital are exploring the role of specific proteins in the immune activity that underlies MS, for clues to developing new therapies.

Background: Multiple sclerosis involves an immune response that results in damage to the brain and spinal cord. One type of immune cells – Th17 cells – are particularly linked to inflammation in MS, but some Th17 cells are actually protective. The basic immune mechanism underlying the development and function of Th17 cells in

the development of MS is not well understood. This team has found that heat shock proteins – proteins produced by cells in response to stressful conditions – may be linked to Th17 cell function.

The Study: Dr. Hu and colleagues are studying these proteins further, to determine whether altered expression of heat shock proteins is associated with Th17 cells taking on an inflammation-promoting role. They will measure heat shock proteins in people with MS who have been treated with disease-modifying therapies and in those who have not been treated. They will look at people with MS at different clinical stages to determine whether the activity of heat shock proteins in Th17 cells links to progression and response to therapy.

What is the potential impact for people with MS? This work could potentially pin down new targets for regulating inflammation in MS and sparing protective immune cells.

Mihir Kakara, M.B.B.S.

University of Pennsylvania
Philadelphia, Pennsylvania

NMSS-ABF Clinician Scientist Award

Term: 7/1/2020-6/30/2023

Funding: \$209,702

Funded with support from the Nerney Family Foundation

Title: Epstein-Barr virus salivary shedding and immune responses in multiple sclerosis following B-cell depletion

Summary: Scientists at the University of Pennsylvania are exploring the role of a virus specifically in people with MS who are undergoing treatment with B cell-depleting therapy.

Background: The cause of MS is unknown, but the disease may be triggered by environmental factors in genetically susceptible people. One likely environmental factor that triggers MS is the Epstein-Barr virus (EBV). More than 95% of healthy people are positive for EBV, but their healthy immune system keeps the virus in check. In people with MS, the immune system is abnormal, and EBV may not be properly controlled. A drug called ocrelizumab depletes immune cells called B cells, where EBV is located, and can successfully treat MS.

The Study: Dr. Kakara and his team are investigating how the immune system reacts to EBV when B cells are depleted. B cells interact with another type of immune cell called T cells, and both cell types are involved in MS. The team is investigating what happens to T cells when B cells are removed by studying these cells from people with MS who responded well versus poorly to ocrelizumab. EBV is present in saliva, and the team is also exploring possibly using the levels of EBV in saliva as a marker for good response to ocrelizumab.

What is the potential impact for people with MS? This study will provide information about improper functions of the immune system in people with MS and how EBV is involved. This knowledge may allow earlier selection of people who respond to ocrelizumab and earlier switching of non-responders to another treatment, thus improving outcomes.

Dzung Pham, PhD

Henry M. Jackson Foundation
Bethesda, Maryland

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$532,850

Title: Harmonizing of Heterogeneous MRI Data in MS

Summary: Henry M. Jackson scientists are developing tools that will enable the pooling of MRI images to enhance understanding of MS and to track changes in an individual's MS over time.

Background: Magnetic resonance (MR) imaging plays a critical role in the diagnosis of MS, as well as for monitoring disease progression and response to therapies. Computer automated techniques for detecting brain lesions and quantifying brain volumes from MR imaging have shown great promise in facilitating both research studies and clinical evaluations of MS. However, inconsistencies arise due to scanner changes, software upgrades, and continually improving imaging protocols. This team is developing tools to harmonize both longitudinal and cross-sectional MR imaging data acquired from people with MS.

The Study: Dr. Pham and colleagues are developing and validating algorithms for robust, consistent analysis of large multi-site datasets involving mixed MRI protocols. They are applying machine learning techniques to ensure that data across scanners and sites are consistently and robustly analyzed, thereby providing improved statistical power in longitudinal or cross-sectional group analyses and clinical trials. They will test and refine the techniques by analyzing MS imaging data acquired at two different sites, involving imaging data spanning over a decade.

What is the potential impact for people with MS? By the end of the project, the team will have developed a suite of tools for robust image harmonization and analysis that will be freely distributed to the scientific community. These tools will facilitate large clinical trials, and enable detailed tracking of MS disease activity over time.

Farinaz Safavi MD, PhD

National Institutes of Health
Bethesda, Maryland

Award: NMSS-ABF Clinician Scientist Awards

Term: 7/1/20-6/30/23

Funding: \$289,351

Title: Role of B cells in development of meningeal tertiary lymphoid structures

Summary: A team at National Institutes of Neurological Disorder and Stroke is exploring the role of an important enzyme in immune cells in MS disease activity and progress.

Background: In MS, one of the proposed reasons for chronic inflammation and nerve cell damage is the activation of immune cells and their toxic effects on nerve cells. Recently, suppression of an enzyme called Bruton Tyrosine Kinase (BTK) demonstrated an ability to control inflammation in MS. However, the exact function and specific pathways contributing to this process are not well understood. The goal of this study is to determine how BTK suppression affects inflammatory function in immune cells and their effects on nerve cells.

The Study: This team is studying immune cells from both people and mouse models of MS to determine how BTK inhibition or a lack of BTK affect immune cells. They will investigate the role of BTK in immune cell-mediated damage to nerve cells and how BTK inhibition may reduce nerve cell injury. Additionally, the role of BTK will be evaluated in immune cells that reside in the

brain and their function. Finally they will use mouse model of MS to deeply study the effect of BTK inhibitor on an organized cluster of immune cells in the meninges -- tissue that covers the brain and spinal cord.

What is the potential impact for people with MS? This research will expand knowledge about immune cells and will open a window to the development of new targeted medications with fewer side effects and greater efficiency in the treatment of MS.

Timothy Vartanian, MD, PhD

Weill Cornell Medical College
New York, New York

Award: Research Grants

Term: 4/1/2020-3/31/2022

Funding: \$314,666

Title: Defining ancestry associated B-cell inflammation in treatment naïve Multiple Sclerosis

Summary: Weill Cornell researchers are investigating immune cell differences in racially and ethnically diverse individuals to better predict and treat MS in non-white populations.

Background: African Americans and Latino Americans with MS more often experience a severe disease course compared to Caucasian Americans. Better understanding why may improve care for people of races and ethnicities who may be predisposed to an aggressive MS disease course. A previous study found a higher concentration of immune antibodies in the spinal fluid of African Americans and Latino Americans with MS compared to Caucasian Americans. Dr. Vartanian's team is asking whether B cells, which make antibodies, are present in greater numbers or have a greater inflammatory function in African Americans and Latino Americans with MS.

The Study: Prof. Vartanian's team is obtaining blood samples from African American, Latino American, and Caucasian American people with relapsing remitting MS as well as from people who do not have MS. They will use an advanced technique called flow cytometry to identify and count

Researchers are investigating immune cell differences in racially and ethnically diverse individuals to better predict and treat MS in non-white populations.

specific B cell types. They will isolate B cells from blood samples and stimulate them in different ways to measure production of inflammatory molecules. The team will also use techniques that measure genetic variants that are especially prevalent among people from different geographic regions around the world.

What is the potential impact for people with MS? This work can more specifically describe why people of specific races and ethnicities with MS tend to experience more aggressive disease, and better inform treatment strategies for this population.

Howard Weiner, MD

Brigham and Women's Hospital
Boston, Massachusetts

Award: Research Grants

Term: 4/1/2020-3/31/2023

Funding: \$661,446

Title: The role of B cells in CNS autoimmunity

Summary: A team at Brigham and Women's Hospital is exploring subsets of immune B cells and their contribution to MS onset and disease activity.

Background: B cell-depleting therapies have demonstrated striking efficacy in relapsing forms of MS, indicating that B cells play a crucial role in the immune response in MS. Professor Weiner and colleagues have found that certain subsets of B cell isolated from the circulation of healthy donors increase, while others reduce, immune activation, and that these subsets do not function similarly when isolated from people with MS. Now the team is focusing on identifying the specific B cell populations that are dysfunctional in MS.

The Study: Professor Weiner's group is studying how B cells that rev up or reduce inflammation contribute to the development of disease, and the mechanisms that contribute to their abnormal activity. They will also perform studies on similar B cell subsets in several mouse models. The team is using a highly novel technique to identify how cells differ between people with MS and people without MS.

What is the potential impact for people with MS? These studies may provide a rationale for supporting early treatment with B cell-depleting therapy, and may help differentiate which of the B cell therapies being developed may or may not be beneficial.

Sebastian Werneburg, M.Sc., PhD

University of Massachusetts Medical School
Worcester, Massachusetts

Award: Career Transition Fellowships

Term: 7/1/2020-6/30/2025

Funding: \$595,418

Title: Molecular Dissection of Neural Circuit Disassembly by Reactive Glia in Demyelinating Disease

Summary: A team at UMass is studying the fate of synapses -- the points of communication between two nerve cells -- throughout the course of MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve cells. Nerve cells that have lost their myelin do not function properly and myelin loss can also cause to the degeneration and death of nerve cells, both leading to symptoms in people with the disease. Recently, Dr. Werneburg and colleagues identified profound loss of synapses, the points of communication between nerve cells, during early disease stages in multiple MS animal models. This synapse loss impaired brain function and appeared to occur before other nerve cell degeneration, suggesting that it might be an early feature of progressive disease. However, not

enough is known about what happens to synapses during other stages of MS.

The Study: Dr. Werneburg and his team are using different mouse models of MS to monitor what happens to synaptic connections during multiple stages of the MS-like disease course, including phases of recovery and myelin repair. In addition, they are investigating how microglia, immune cells in the brain, contribute to the regulation of synaptic connections in the course of the disease. They are also determining how changes in synapses, including synapse loss and regeneration, affect brain function, and they are testing whether therapies that promote myelin repair will restore synaptic connections and brain functions and improve disability in these mouse models.

What is the potential impact for people with MS? Synapse loss and microglia are important targets for the development of new therapies for people with MS with the goal of stopping and reversing disease progression, improving brain function and reducing disability.

Yuyi You, MD, PhD
Macquarie University
Sydney, Australia

Award: Research Grants

Term: 4/1/2020-3/31/2024

Funding: \$543,272

Title: Investigating the role of demyelination in anterograde transsynaptic degeneration in MS

Summary: University of Sydney researchers are studying the contributions of myelin loss to nerve degeneration, which can lead to MS progression.

Background: In MS, degenerative changes usually occur in specific regions of the brain but can then spread, leading to large-scale degeneration and worsening of clinical symptoms. This spreading is believed to be associated with MS disease progression. When myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS, nerve fibers do not function properly, leading to many symptoms. Loss of myelin may worsen the spreading of degeneration in the brain.

The Study: Dr. You and his team are using the visual system as a model to study this degeneration. They are looking at the role of myelin loss and repair on spreading of degeneration in mouse models. The team is asking whether myelin loss comes before the loss of the connections between nerve cells in people with MS who have optic neuritis, which is inflammation of the optic nerve that affects vision. In mice, they are testing whether myelin repair protects the brain from the spreading of degeneration.

What is the potential impact for people with MS? Results from this study could extend the importance of developing therapies to improve myelin repair in people with MS.

National MS Society Funds Clinical Care and Clinical Research Fellowships

2020 Clinical Care Fellowships

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

Awardee	Location	Mentor
Sarah Conway, MD	Brigham and Women's Hospital	Tanuja Chitnis, MD
Francisco Gomez, MD	University of Alabama at Birmingham	John Rinker, MD
Torge Rempe, MD	University of California San Diego	J. Graves, MD, PhD
S. Satyanarayan, MD	Icahn School of Medicine at Mt. Sinai	Fred Lublin, MD
Tyler Smith, MD	New York U. Langone Medical Center	Ilya Kister, MD
Chen Yan, MD	Cleveland Clinic Foundation	Jeffrey Cohen, MD

“It is undoubtedly thrilling to enter a field at the advent of momentous therapeutic advancements, but most of all, it is the strength, resilience, and resolution of my patients that inspired me to pursue a fellowship in multiple sclerosis and neuroimmunology.

- *Dr. Sammita Satyanarayan*

2020 Institutional Clinician Training Awards

Consistent with its effort to ensure that people affected by MS have access to comprehensive, high quality health care, the Society offers the Institutional Clinician Training Award, a five-year award to mentors and institutions to provide training for board-certified/eligible neurologists and physiatrists in MS specialist care. The goal is for fellows to acquire the skills and knowledge necessary to provide the highest quality of care for individuals with MS.

Lead Mentor	Location
Lilyana Amezcua, MD	University of Southern California
Jeffrey Gelfand, MD	University of California, San Francisco
Scott Newsome, DO	Johns Hopkins University