BREAKTHROUGH MS

# NEW RESEARCH

Summer 2021

## New MS Research Workforce Investments to Drive Pathways to Cures

The National MS Society has approved funding for new awards in 2021 as part of our commitment to support the research workforce. This summer the Society committed over $8.7 million to support 29 new training fellowships, early career awards, and other special initiatives, and continued to lead and support efforts of the International Progressive MS Alliance.

The Society aligns the global MS research community around the most promising areas outlined in the Pathways to Cures Roadmap. We utilize our leadership, influence, and funding to drive progress and propel the next generation of research leaders.

The new research awards described in the following pages align with the roadmap's three Pathways: STOPPING MS disease activity, RESTORING function by reversing damage and symptoms, and ENDING MS by preventing new cases. Here are a few examples:

**STOPPING MS**:

• Researchers in Texas and collaborators are examining MS worsening to uncover predictors of disease progression and improve preemptive care (see p. 10).

**RESTORING what's been lost** by reversing symptoms and disability:

• Researchers in New York City are testing a telehealth program that may reduce the devastating effects of MS-related fatigue (see p. 17).

**ENDING MS**:

• Researchers in Florida are identifying genes that contribute to making Black and Hispanic/Latinx people susceptible to MS (see p. 19).

**NEW PROJECTS SUMMARIZED INSIDE:**

**Pathways to Cures:**



**Of Note:**



National Multiple Sclerosis Society

## Pathways to Cures: STOP/How do we stop disease activity and progression?

Stopping MS is defined as achieving a state of no new disease activity, no worsening of daily living or quality of life, and no change in disease manifestations or clinical activity in people living with either relapsing or progressive forms of MS. Two key objectives have been targeted for the next three years: to advance the STOP pathway: early detection before symptoms appear, and precision medicine for individualized treatment and lifestyle strategies to prevent further progression.

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**Christina Azevedo, MD, MPH**
University of Southern California
Los Angeles, CA
**Award:** Harry Weaver Scholar Award
**Term:** 7/1/21-6/30/26
**Funding:** $747,267
**Title:** Understanding Mechanisms of Deep Grey Matter Injury Using MRI in MS
**Summary:** Researchers are using advanced imaging techniques to understand damage that occurs in MS for clues to stopping it.

**Background:** Brain tissue damage and loss occurs through several mechanisms in MS. Unfortunately, no currently available MS medication directly targets this damage other than by addressing inflammation. This team aims to identify brain regions that undergo tissue damage and loss through mechanisms outside of inflammation. Based on work so far, they believe that regions in the deep gray matter warrant further study.

### New Alliance Funding

The International Progressive MS Alliance, in which the National MS Society plays a leading role, has launched funding of 19 Research Challenge Awards to identify new therapeutic targets that will lead to treatments that will slow or stop disability progression. The projects focus on several areas including identifying why nerve fibers are lost and molecular pathways that promote neuroprotection and myelin repair.

Read more on the Alliance's website

**The Study:** Dr. Azevedo will examine these regions using three sophisticated MRI techniques: diffusion tensor imaging (which detects damage by measuring water flow), powerful 7-Tesla imaging (which allows researchers to see with greater detail much smaller areas of the brain than conventional 3T scans), and a measure of iron deposits. Each of these techniques measures a different aspect of the MS disease process. The team will estimate how much each process contributes to the loss of brain tissue volume in the deep gray matter in two large groups of people with MS.

**What is the potential impact for people with MS?** This project will advance our understanding of why brain tissue loss occurs in MS, and could help identify new therapeutic targets that would address damaging disease processes resistant to current treatments.

# JDRF, Lupus Research Alliance, and National MS Society Join Forces to Decode Common Immune Mechanisms

JDRF International, the Lupus Research Alliance and the National MS Society joined forces to accelerate research and discovery in autoimmunity and are proud to announce the recipients of their first joint grants. Called Decoding Immune-Mediated Diseases - Novel Approaches for Therapeutic Insights, the new program will support the research of eight grant recipients from major academic centers around the world. This marks the first time these three organizations are jointly funding research projects looking at common underlying disease mechanisms.

Autoimmune and immune-mediated diseases are chronic disorders in which the immune system produces a harmful response against its own cells, tissues and/or organs that results in inflammation and organ damage. According to the NIH, some 24 million Americans live with more than 80 autoimmune diseases. Insufficient knowledge of how these diseases progress is a common challenge that this grant program aims to overcome. The 2021 awardees are examining possible common mechanisms that could cause or contribute to the development of at least two of the three autoimmune diseases. Ultimately, the researchers hope to find novel targets and strategies for disease therapies.

**The following investigators are receiving funding from the Society and JDRF.**

**Investigator: Amit Bar-Or, MD,** University of Pennsylvania, Philadelphia, PA
**Title:** "Linking multiple disease compartments in T1D and multiple sclerosis"
**Term:** Two years
**Grant Amount:** $250,000 from the National MS Society, plus co-funding from JDRF
University of Pennsylvania researchers are developing immune cell profiles at the sites of immune attack targets, in lymph nodes, and in blood to find better ways of detecting disease activity in MS and Type 1 diabetes.

**Investigator: Kevan Herold, MD,** Yale University, New Haven, CT
**Title:** "Analysis of antigen specific T cells in response to immune therapies in MS and T1D"
**Term:** 2 years
**Grant Amount:** $246,376 from the National MS Society, plus co-funding from JDRF
Yale University researchers are analyzing immune cells to uncover insights into how to stop immune attacks against the body's own tissues in MS and in Type 1 diabetes.

**Visit DecodingAutoimmunity.org to learn more**

**Pavan Bhargava, MBBS, MD**
Johns Hopkins University
Baltimore, MD
**Award:** Harry Weaver Scholar Award
**Term:** 7/1/21-6/30/26
**Funding:** $630,502
**Title:** Understanding the contributions of metabolic dysfunction to MS pathophysiology
**Summary:** Researchers are exploring how byproducts of energy processes in immune and brain cells may contribute to MS.

**Background:** People with MS may have abnormalities in the way certain brain and immune cells process energy and other maintenance activities (metabolism). Dr. Bhargava's team previously found that levels of toxic metabolites (substances involved in metabolism) were related to the severity of MS. Interestingly, these metabolic toxins are known to contribute to heart disease and diabetes risk in certain populations. How these altered levels of metabolites contribute to MS disease course or risk is currently not known.

**The Study:** Dr. Bhargava and colleagues will test the effects of four specific metabolite toxins, identified in prior studies, on the functioning of different kinds of immune and brain cells in a dish. They will test a variety of concentrations of these metabolic toxins to assess whether they skew immune cells towards a more inflammatory state, or directly affect the functioning of cells in the brain and spinal cord. They will also test the effects of administering these metabolic toxins in a rodent of MS to observe their impacts on immune cells and the nervous system.

**What is the potential impact for people with MS?** This study could identify new avenues for the treatment of MS, through eliminating or supplementing metabolites.

**Yanan Chen, MD, PhD**
Northwestern University
Evanston, IL
**Award:** Career Transition Fellowships
**Term:** 7/1/21-6/30/26
**Funding:** $605,649
**Title:** Enhancing the unfolded protein response as a protective therapy for MS
**Summary:** Northwestern scientists are exploring a novel strategy for protecting myelin-making cells and promoting myelin preservation and repair in MS.

**Background:** MS involves an immune system response in the brain and spinal cord that damages myelin, a fatty substance that is essential for proper nerve signaling and function. Oligodendrocytes, the cells that make myelin, also are lost. Normally, a protective response is triggered to help oligodendrocytes cope with stress during inflammatory attacks. During this protective response the body shuts down myelin production and prompts the oligodendrocyte to produce beneficial proteins to help remove the abnormal myelin. In MS, however, oligodendrocytes severely ramp up production to repair all the damaged myelin, but the cell can't keep up and dies in the process.

**The Study:** Dr. Chen and colleagues are measuring the therapeutic effects of small chemical compounds that are designed to enhance this protective response in mouse models of MS. They are also exploring the mechanism by which the oligodendrocytes die, called autophagy, during MS-like inflammatory attacks. They will then treat the mice with MS-like disease with an inhibitor to determine whether it can promote myelin preservation and repair.

**What is the potential impact for people with MS?** Similar inhibitors are in trials for other diseases, so this study can lead to novel MS therapies that provide direct protection to myelin and oligodendrocytes in the brain and spinal cord.

**Blake Dewey, MSc (pending)**
Johns Hopkins University
Baltimore, MD
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24
**Funding:** $190,752
**Title:** Validating spinal cord imaging outcomes for evaluating patient progression
**Summary:** Researchers are exploring novel strategies for tracking the transition of people to progressive MS.

**Background:** Currently, it is difficult to predict the worsening of symptoms, or the transition of people to progressive MS. The goal of this study is to test the use of automated analysis of spinal cord imaging, and compare these data to outcomes from neurological testing and novel data from wrist-worn activity trackers. This will allow the team to see if measurements from spinal cord MRI are useful in predicting if a person will get worse over time.

**The Study:** Dr. Dewey and colleagues are collecting data from three large ongoing studies. These studies will provide over 10,000 individuals and over 25,000 MRI scans. They will use a software package called the Spinal Cord Toolbox to automatically extract the measurements and compare them between scan types and between different sites to make sure the measurements are consistent. After testing, they will collect data on a subset of 255 people, obtaining MRI scans of the brain and spinal cord at the beginning of the study and after two years, then comparing this to wrist-worn activity data and neurological tests.

**What is the potential impact for people with MS?** This project will be the first to include this kind of data in looking at the transition of people to progressive MS, and may yield breakthroughs on how to identify MS progression in important clinical trials dealing with MS progression.

**Jordan Dworkin, PhD**
Research Foundation for Mental Hygiene, Inc.
New York, NY
**Award:** Biostatistics/Informatics Junior Faculty Award
**Term:** 7/1/21-6/30/24
**Funding:** $256,999
**Title:** Mapping multi-modal relationships among lesions and clinical outcomes in MS
**Summary:** Researchers at Columbia are using advanced methods to understand and predict how the locations of MS brain lesions link to symptoms and outcomes.

**Background:** MRI scans are important for detecting brain lesions, or spots of MS disease activity and damage. However, much remains unknown about how the specific characteristics of a lesion, like its texture and location, manifest as symptoms or behaviors in people with MS.

**The Study:** Dr. Jordan Dworkin is collaborating with Columbia University MS experts to develop a better understanding of the complex relationships between lesions and symptoms. He will be developing new statistical methods for uncovering and predicting these pathways. The team is also investigating whether other brain processes potentially bridge the gap between lesions and symptoms, and whether these processes can improve individuals' resilience to lesion damage. They will then build tools that will enable researchers, MS healthcare providers, and people with MS to incorporate this new knowledge to enhance understanding of MS, to better predict future symptoms, and to improve individualized treatment plans.

**What is the potential impact for people with MS?** This project aims to provide the MS community with new statistical tools to predict MS symptoms and improve treatment outcomes.

# 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 studies, they cannot proceed. Seeing this need, the Society established the Sylvia Lawry Physician Fellowship, named in honor of its founder. This program provides formal clinical trial training with established investigators. Six new trainees have been awarded this fellowship in 2021:

**Christina Gaudioso, MD,** Washington University in St. Louis
Dr. Gaudioso will be exposed to all types of MS at all stages of disease. She will receive additional training experiences in pediatric MS rehabilitation, neuro-ophthalmology, and pediatric immunology. Dr. Gaudioso will participate as an active investigator in numerous clinical trials taking place at the MS center. She will also obtain a Master of Science in Clinical Investigation.

**Kimystian Harrison, MD,** Johns Hopkins University, Baltimore, MD
This fellowship will provide Dr. Harrison with specialized training to conduct clinical trials and also to evaluate, diagnose, and care for people with MS. Dr. Harrison will learn to utilize and interpret advanced neuro-imaging, an essential element in diagnosing MS and in clinical trials. She will pursue formal education in clinical research, in epidemiology and statistics.

**Victoria Levasseur, MD,** Washington University in St. Louis
To develop clinical proficiency, Dr. Levasseur will spend time caring for new and follow-up patients. She will be an active investigator in numerous clinical trials, participating as an examining physician in several trials, and learning clinical study outcome measures. Dr. Levasseur's experience will be augmented through a Master's degree with coursework in biostatistics, trial design, and ethics.

**Neda Sattarnezhad Oskouei, MD,** Stanford University, Stanford, CA
This fellowship will focus on the diagnosis, treatment, and monitoring of the disease through outpatient encounters at the MS clinic. Dr. Sattarnezhad will also receive formal research training by completing a Master's degree in Epidemiology and Clinical Research, and will participate in numerous, multi-phase clinical trials, gaining hands-on experience in trial design and conduct.

**Alexandra Simpson, MD,** Johns Hopkins University, Baltimore, MD
Dr. Simpson will gain experience in all aspects of MS clinical trials. She will have varied roles within clinical trials. Dr. Simpson will supplement this hands-on experience with formal coursework in epidemiology, biostatistics, and trial design. She will participate in direct patient care to learn the intricacies of chronic management of MS, including management of troublesome symptoms.

**Jorge Torres, MD,** Massachusetts General Hospital, Boston
Dr. Torres will gain clinical trial experience through NeuroNEXT, a network supported by the NIH for making neurology trials more efficient.He will be involved trial design and implementation from the start, as biomarker and therapeutic trials are proposed to the network. Dr. Torres is completing a Master of Medical Science in Clinical Investigation degree.

**Alexander Gill, MD, PhD**
Johns Hopkins University
Baltimore, MD
**Award:** NMSS-ABF Clinician Scientist Award
**Term:** 7/1/21-6/30/24
**Funding:** $293,307
**Title:** Targeting Neurotoxic Inflammatory Glia and NLRX1 in MS/EAE
**Summary:** Scientists at Johns Hopkins are targeting a protein in MS-like disease with an eye toward developing therapies to stop MS.

**Background:** The neurologic deficits that people with MS experience result from damage to nerve cells and the coating (myelin) on nerve wires in both the brain and the spinal cord. Glial cells, such as astrocytes and microglia, reside in the brain and spinal cord and normally support nerve cell and myelin health, but may be activated during MS and become toxic. A protein called NLRX1 normally can turn down inflammation, but if it stops working, glial cells may be activated into an inflammatory, neurotoxic state. The goal of this project is to understand the role, and potential therapeutic targeting, of NLRX1 in mouse models of MS.

**The Study:** Dr. Gill's team is developing a mouse model where NLRX1 is absent only in astrocytes or microglia. They will use these mice to specifically address how loss of NLRX1 in these cell-types affects damage to neurons and myelin in mice with MS-like disease. Dr. Gill is also determining the potential of a compound, called NX-13, which can activate NLRX1 and possibly limit inflammation and neuronal injury. For some of these studies the team is focusing on the nerve layer in the back of the eye, utilizing a lab model that mimics the optic nerve injury commonly seen in people with MS.

**What is the potential impact for people with MS?** This research should provide important information about how astrocytes and microglia participate in MS disease activity, and clues to whether targeting NLRX1 has therapeutic potential to turn off immune activity that leads to MS progression.

**Yoon-Chul Kye, PhD**
Brigham and Women's Hospital
Boston, MA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24 **Funding:** $193,789
**Title:** The role of immune checkpoint molecules on B cell in CNS autoimmune diseases
**Summary:** Researchers at Brigham and Women's Hospital are determining how to optimize and improve upon therapies that target immune B cells in people with MS.

**Background:** A recent approach in MS therapies is targeting B cells, a type of immune cell involved in the immune responses underlying MS. Evidence suggests that there are two distinct subpopulations within B cells: one is a regulatory B cell (Breg) that suppresses inflammation and the other is a pro-inflammatory B cell that promotes development of MS. However, there is still much to learn about these subtypes of B cells in terms of the development and progression of MS.

**The Study:** Dr. Kye and colleagues have generated mouse models that lack the genes that instruct molecules on the surface of B cells. Using these models, they are seeking to identify which gene in B cells is essential for the regulation of MS-like disease in mice, and which molecule may be a promising target candidate for turning off immune attacks in MS. In addition, the team is using state-of-the-art computational analysis to identify novel molecules on B cells to aid their explorations.

**What is the potential impact for people with MS?** These findings may improve and optimize B cell-targeting therapies in people with MS, and help to develop new treatment strategies to stop MS in its tracks.

**Frederike Oertel, MD**
University of California, San Francisco
San Francisco, CA
**Award:** Postdoctoral Fellowships
**Term:** 7/1/23-6/30/24
**Funding:** $66,226
**Title:** Dissecting selective vulnerability of neurons and axons using the afferent visual system in animal models of demyelination and inflammation
**Summary:** UCSF Researchers are exploring why some nerve cells are more susceptible to damage in MS, for clues to preventing MS progression.

**Background:** Damage to nerve cells (neurons) and nerve fibers (axons) – is a hallmark of disability progression in MS. Some neurons are more susceptible to damage than others in MS. The goal of this project is to understand what makes some neurons more vulnerable to MS-related damage than others. This might allow us to develop better strategies to protect these nerve cells and fibers to prevent progression.

**The Study:** This team will characterize selective damage patterns in the visual systems of MS rodent models after acute and chronic nerve degeneration, using a combination of laboratory techniques such as tissue analysis and high-resolution microscopy. They will also use non-invasive imaging, including optical coherence tomography (OCT, which can evaluate nerve tissue layers at the back of the eye) and functional measurements to determine the consequences of neuronal vulnerability or resilience.

**What is the potential impact for people with MS?** Understanding the vulnerability of different components of the brain will allow the team to identify targets for enhancing neuronal survival, and preventing progression of disability in MS.

**Amber Salter, PhD, MPH**
University of Texas Southwestern Medical Center
Houston, TX
**Award:** Biostatistics/Informatics Junior Faculty Award
**Term:** 7/1/21-6/30/24
**Funding:** $222,759
**Title:** Investigation of MS Disease Progression Using a Multifactorial Approach
**Summary:** Researchers at UT Southwestern and collaborators are examining MS worsening to uncover predictors of disease progression and improve preemptive care.

**Background:** It's not clear why some people with MS can experience a mild course of disease and others experience disease worsening and progression. There are likely many factors that play a role in any one person's disease course, making it difficult to predict the optimal therapy or future severity. Dr. Amber Salter and collaborators are applying sophisticated data analysis tools to better understand the factors that drive disability worsening and the development of progressive MS.

**The Study:** The team is examining MS disease worsening across a wide array of data, including the novel brain Diffusion Basis Spectrum Imaging and MS treatment clinical trial data. They are also applying novel statistical methods to identify different disability worsening courses and what factors describe those who are included in each group using data from MS PATHS, a large, multi-institution dataset that tracks information from clinic visits. They will examine links between comorbidities (MS plus other disorders in an individual) and outcomes from completed MS treatment clinical trials. Finally, Dr. Salter will develop tools to harmonize multiple data sources on disability so that results from multiple studies can be combined to shed greater light on MS progression and its treatment.

**What is the potential impact for people with MS?** Ultimately, this study should advance our ability to identify predictors of disease worsening, which would allow for more personalized treatment for individuals and improve the way clinical trials of treatments for progressive MS are conducted.

**Elif Sozmen, MD, PhD**
University of California, San Francisco
San Francisco, CA
**Award:** NMSS-ABF Clinician Scientist Award
**Term:** 11/1/21-6/30/24
**Funding:** $222,856
**Title:** Study the Role of Fibrinogen in Autoimmune Responses in Multiple Sclerosis
**Summary:** UCSF researchers are exploring a therapeutic strategy targeting fibrin, a protein associated with damage in MS.

**Background:** Several studies have provided evidence that blood protein fibrinogen may trigger damage to regions of the brain in MS, including pioneering work by Professor Dr. Katerina Akassoglou, who is serving as a mentor to Dr. Sozmen. The main goals of this project are to determine how fibrinogen interacts with the immune system in people with MS, and to discover the fibrin-mediated

immune responses that may be detrimental. This may identify a novel target for therapeutics in MS.

**The Study:** Dr. Sozmen will analyze how the immune system in MS patients interacts with fibrinogen and will identify how fibrinogen may be attracting and activating these immune cells. Next, she will characterize immune reactions that may be unique to people with MS.

**What is the potential impact for people with MS?** Ultimately, this project will provide new insights into why the immune system attacks the brain and spinal cord in MS, and ways it might be prevented or stopped.

**Elizabeth Sweeney, PhD (pending)**
Weill Cornell Medical College
New York, NY
**Award:** Biostatistics/Informatics Junior Faculty Award
**Term:** 7/1/21-6/30/24
**Funding:** $315,539
**Title:** Evaluation of and Automated Image Analysis Tools for a QSM Rim Positive Multiple Sclerosis Lesion Biomarker
**Summary:** Developing new, automated ways to analyze brain scans to better detect the benefits of MS therapies against chronic inflammation.

**Background:** Conventional MRI scans are used in the clinic to help determine whether an individual's MS disease-modifying therapy is working to curb damaging immune attacks. However, they are not good at predicting longer-term outcomes or detecting the chronic inflammation thought to underlie progressive stages of MS. Dr. Elizabeth Sweeney aims to address this unmet need by developing new analysis tools to detect chronic inflammation and the impact of therapies on that inflammation.

**The Study:** Dr. Sweeney and collaborators are using a novel type of MRI, called quantitative susceptibility mapping (QSM), to detect a rim of chronic inflammation present within some MS brain lesions (QSM rim+ lesions). At the early stage of QSM rim+ lesions, the inflammation is high, and over time the inflammation will slowly decrease and the lesions become a late stage scar. The team is developing an automated way to detect these lesions, and then will develop a new statistical method to determine the stage of inflammation of each QSM rim+ lesion. Finally, they will use this information to compare the impact of two disease-modifying therapies on these lesions.

**What is the potential impact for people with MS?** The results of this study should contribute to our understanding of progressive MS and may offer a new tool to detect whether specific disease-modifying therapies are working to prevent progression in individuals.

**Ceren Tozlu, PhD (pending)**
Weill Cornell Medical College
New York, NY
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24
**Funding:** $204,814
**Title:** Mapping multi-modal brain features to impairment severity in people with MS using machine learning
**Summary:** Researchers are using advanced technology to streamline the process of diagnosing and tracking MS.

**Background:** It is challenging for clinicians to accurately predict an individual's MS course using clinical, biological, and imaging data. Having access to an accurate prognosis is essential to the development of individualized treatment plans. The aim of this study is to identify clinical and MRI biomarkers of disease activity that predict an individual's disease course.

**The Study:** Dr. Tozlu and colleagues are using existing data from 150 people with MS, including multi-modal MRI scans and EDSS scores (a clinical measure of physical disability). Machine learning will be used to create a model that can take a person's clinical and imaging data and to predict disability level. This will provide insight as to why some people are resilient to progression while others are not. A second aim is to create a model that can take a person's baseline clinical and imaging metrics and predict their disability scores three years later. These models will also allow the team to identify the brain regions which are most important to predict the disability level. Eventually healthcare providers could use this algorithm to tailor an individual's treatment depending on predicted severity of their disease.

**What is the potential impact for people with MS?** Understanding why some patients develop impairment while others do not has the potential to open new horizons for therapies that boost this mechanism in MS.

**Liwei Wang, PhD**
New York University Langone Medical Center
New York, NY
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24
**Funding:** $204,814
**Title:** Investigation of novel ion channels as potential next-generation therapeutic targets for MS
**Summary:** A team is exploring the potential of a therapeutic strategy for MS based on proteins on cell surfaces and inside of cells known as ion channels.

**Background:** Ion channels are proteins located at the surface of all cells as well as inside of cells in the human body, including nerve cells and immune cells. They transport charged particles like calcium and potassium into the cell, which is essential for normal cell function. Ion channels have long been known to regulate the function of neurons (nerve cells). Growing evidence shows that some ion channels are also required for the ability of immune cells to induce immune attacks that lead to MS. The ultimate goal of this project is to identify ion channels that may be promising targets for better MS therapies.

**The Study:** Dr. Wang and colleagues have designed and performed a genetic screen of immune cells of mice. This screening effort identified novel ion channels that may control the development and severity of MS-like disease (EAE) in mice, and possibly in people. They are now selectively "deleting" the genes for these ion channels in immune cells and analyzing how their absence impacts EAE and immune function. They will also analyze tissue obtained from people with MS to determine if the identified ion channels are abnormally regulated, and if deleting them affects the inflammatory function of human immune cells.

**What is the potential impact for people with MS?** These studies will show whether ion channels are promising targets for the next generation of therapies to stop MS.

**Cory Willis, PhD**
University of Cambridge
Cambridge, UK
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24
**Funding:** $193,789
**Title:** Exploring the role of ASTROcytic succinate recepTOR in neuroinflammation (ASTRO_TOR)
**Summary:** Researchers at the University of Cambridge are exploring how certain brain cells may drive MS progression.

**Background:** Astrocytes are a type of brain cell that work as waste collectors, clearing away the buildup of harmful substances to maintain a safe working environment for other brain cells. Growing evidence from animal disease models and cells isolated from people with MS suggest that astrocytes may contribute to the persistent inflammation that drives MS progression. This team is studying the biological processes underlying disrupted astrocyte function in lab models that mimic progressive MS.

**The Study:** Dr. Willis will first investigate the role of a molecule (succinate receptor) on the surface of astrocytes in shaping their response to chronic inflammation, which has been implicated in progressive stages of MS. The team will manipulate this molecule on human astrocytes using state-of-the-art gene-editing technologies, to determine how it impacts the ability of astrocytes to respond to inflammation. Then they will use lab models of progressive MS to identify how the presence or absence of this molecule on astrocytes affects inflammation in the late stages of the disease.

**What is the potential impact for people with MS?** Findings from this work should lead to the identification of relevant and critical targets for the development of improved therapies for people with progressive MS.

**Soumya Yandamuri, MS, PhD**
Yale University
New Haven, CT
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/24
**Funding:** $193,789
**Title:** Isolation and characterization of myelin oligodendrocyte glycoprotein monoclonal antibodies
**Summary:** Researchers at Yale are exploring a mechanism for the damage that occurs to nerve-insulating myelin in MS.

**Background:** MS is a disease that involves damage to myelin, the crucial insulation that helps nerve cells quickly relay signals. Myelin oligodendrocyte glycoprotein (MOG) is one of the proteins of myelin, and immune proteins (antibodies) targeting MOG have been detected in individuals with MS. Studying these antibodies may provide insight into how and why myelin is damaged in MS.

**The Study:** Dr. Yandamuri is focusing on understanding why antibodies to MOG exist in people with MS, and how they damage oligodendrocytes, the cells that produce myelin. This team is assessing a large number of immune cells in people with MS using a cutting-edge technique. They aim to find at least 15 patient-derived cells that produce MOG antibodies and analyze the genes that instruct them. They will then use advanced tools to understand whether the production of the antibodies was a result of defects in the cells, and whether and how these antibodies damage oligodendrocytes.

**What is the potential impact for people with MS?** This work should bring to light new mechanisms that contribute to myelin damage in MS, yielding clues for repairing damage and restoring function.

## Pathways to Cures: RESTORE/How do we reverse symptoms and recover function?

Multiple sclerosis can result in many different symptoms, including vision loss, pain, fatigue, sensory loss, impaired coordination, mobility, and cognitive changes. Translation of knowledge from basic mechanisms to functional impact is needed to optimize treatment, manage symptoms, and ultimately restore function for people living with both relapsing and progressive forms of MS. Two key objectives have been targeted for the next three years to advance the RESTORE pathway: remyelination and restoration of function.

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**Katrina Adams, PhD**
The Children's National Medical Center
Washington, District of Columbia
**Award:** Career Transition Fellowships
**Term:** 7/1/21-6/30/26
**Funding:** $610,298
**Title:** Elucidating molecular mechanisms of neural stem cell-derived gliogenesis in remyelination
**Summary:** Researchers at Children's National Hospital are exploring how myelin-making cells derived from stem cells might be used to repair myelin in MS models.

**Background:** The myelin wrapping that surrounds nerve fibers in the brain and spinal cord is a prime target for immune attacks in MS. Natural myelin repair occurs, but at some point it fails, leaving nerve fibers exposed. One source of new myelin-making cells (oligodendrocytes) is neural stem cells, which have been shown to contribute to myelin repair in mouse models of MS. Dr. Adams and team are studying how oligodendrocytes derived from neural stem cells differ from other oligodendrocytes. In addition, this project seeks to understand the molecular mechanisms that regulate the generation of oligodendrocytes from neural stem cells, with the goal of identifying signals that could be targeted in people with MS to promote myelin repair.

**The Study:** This project uses advanced techniques to characterize oligodendrocytes derived from neural stem cells and other oligodendrocytes in the brains of two MS mouse models, and in brain tissues obtained from people with MS. The team also is using mouse genetic tools to determine the mechanism of a signaling molecule called Endothelin-1 that has previously been shown to play a role in myelin repair.

**Potential Impact for People Living with MS:** The results should provide critical insight into the role that neural stem cells might play in repair of MS-related myelin damage, and their potential as a therapy for promoting myelin repair.

# New Fast Forward Investment

The National MS Society, through its Fast Forward drug development program, is investing in one new project:

People with MS often describe feeling alone in their MS journey. Support groups deliver tangible benefits, but the logistics of getting to a traditional support group can be insurmountable. The goal of the company is to deliver the benefits of support groups to people with MS in a novel, convenient way. Harnessing the power of online connection, this team has developed "eSupport," private, face-to-face professionally moderated support groups that people with MS can join from the safety and comfort of home. With a pilot grant from the Society, Dr. Leavitt showed that this program was feasible and reduced depression and loneliness in a pilot clinical trial of people with MS. Based on the study results, Dr. Leavitt launched eSupport Health, a public benefit corporation delivering private, secure, video link-enabled group-based workshops and support moderated by a licensed coach with knowledge of MS.

This funding from the Society through Fast Forward will support the SUNRISE study, a clinical trial establishing benefits of eSupport groups delivered to Black and Latinx individuals with MS. Individuals from these groups are historically underrepresented in research studies, and historically undertreated for mental health. This funding will help to launch a solution that has the potential to improve mood, brain health, and overall quality of life for people with MS.

**Term:** 18 months; **Investment Amount:** $300,000

**Learn more about Fast Forward**

**Valerie Block, DSc., PT**
University of California, San Francisco
San Francisco, CA
**Award:** Career Transition Fellowships
**Term:** 7/1/21-6/30/26
**Funding:** $591,128
**Title:** Moving MS bladder dysfunction into the 21st Century: developing novel and accessible ways to treat, predict and prevent dysfunction in the home
**Summary:** A team is developing a solution for bladder problems in people with MS.

**Background:** Bladder problems impact many people with MS over the course of their disease, affecting quality of life, mood, social participation, and doing physical activity and exercise. Bladder symptoms typically only come to light when they are already moderately severe, and more difficult to treat and stabilize. Then, testing for bladder dysfunction and following it over time is performed using either patient reports, or invasive testing. Many barriers to evaluation and care exist: these include sensitivity of the topic, transport, cost, time, and access to trained specialists.

**The Study:** Dr. Block and team are assembling a toolkit to evaluate, and eventually treat, bladder dysfunction in people with MS in their own homes. To do this, they are using existing data from a large cohort of people with MS with up to 15 years of follow-up. From this information, they will create a risk-factor profile for bladder dysfunction. Next, they will determine which remote technology tools would be most appropriate for bladder monitoring, testing, and treating in the home. They will gain input from people with MS, as well as experts in MS and bladder dysfunction. Finally, they will test these tools in the home and optimize the toolkit selected.

**What is the potential impact for people with MS?** This research should lead to a new, economical and non-invasive solution for bladder dysfunction in people with MS.

**Elizabeth Gromisch, MA, PhD**
Mount Sinai Rehabilitation Hospital
Hartford, CT
**Award:** Harry Weaver Scholar Awards
**Term:** 7/1/21-6/30/26
**Funding:** $700,467
**Title:** Development and Feasibility of a Fatigue Self-Management mHealth Program for Persons with Multiple Sclerosis
**Summary:** Researchers are testing a program that may reduce the devastating effects of MS-related fatigue.

**Background:** While cognitive behavioral therapy and energy conservation strategies on their own have been shown to be effective for managing the fatigue that so many people with MS experience, it has been suggested that including both of these approaches into a fatigue self-management program would be beneficial. This study aims to develop a fatigue self-management program for persons with MS that includes both cognitive behavioral and energy conservation strategies, and is available as a new mobile device telehealth application called "mHealth" Managing My MS My Way (M4W).

**The Study:** This study will be conducted in two stages: the development of this fatigue intervention in the M4W application, and evaluating the benefits of the intervention in a small clinical trial. First Dr. Gromisch and team will engage 30 people living with MS who experience fatigue. They will provide input on the content of the program and technology needs, review a pre-release version of the application to provide feedback, and field-test a functioning version. Then Dr. Gromisch will do a clinical trial to determine potential benefits for managing fatigue.

**What is the potential impact for people with MS?** This project will help to understand if M4W is feasible and can reduce the impact of MS-related fatigue on daily life.

**Matthew Plow, PhD**
Case Western Reserve University
Cleveland, OH
**Award:** Mentor-Based Postdoctoral Fellowships
**Term:** 7/1/21-6/30/26
**Funding:** $451,374
**Title:** Training Nurse Scientists to Improve the Outcomes of Rehabilitation Interventions in People with Multiple Sclerosis
**Summary:** Researchers are training scientist nurses how to conduct MS research aimed at reversing symptoms and restoring function.

**Background:** Rehabilitation interventions promote skills, behaviors, and/or exercises that can reduce the negative impact of multiple sclerosis. Nurse scientists have the needed expertise to conduct research that improves rehabilitation interventions but have few opportunities to receive the necessary advanced training to focus their research on rehabilitation specific to MS.

**The Study:** Through a collaborative partnership between Case Western Reserve University and Cleveland Clinic, Dr. Plow and colleagues are implementing a novel program that will increase the number of highly trained, PhD-prepared nurse scientists who are well prepared to improve the effectiveness of rehabilitation among people with MS. The proposed training program consists of several integrated activities including coursework, seminars/journal clubs, and mentored research. At the completion of the program, the nurse scientists will have the requisite training to launch independent projects in 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 reversing symptoms and improving quality of life for people living with MS.

## Pathways to Cures: END/How do we prevent MS?

Ending MS is defined as no new cases of MS. Two key objectives have been targeted for the next three years to advance the END pathway: primary prevention and secondary prevention. Primary prevention involves limiting exposures to MS risk factors in the general population. Secondary prevention focuses on individuals at high risk for MS and developing and deploying interventions in the period prior to preclinical/clinical stages of disease to reduce or eliminate the risk for developing MS.

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**Ashley Beecham, PhD**
University of Miami
Miami, FL
**Award:** Postdoctoral Fellowships
**Term:** 7/1/21-6/30/23
**Funding:** $127,563
**Title:** Utilizing a multi-omics approach to identify genetic contributors to multiple sclerosis in a multi-ethnic population of Hispanics and African Americans
**Summary:** Researchers are seeking genes that contribute to making Black and Hispanic/Latinx people susceptible to MS.

**Background:** In people of European ancestry, more than 200 DNA segments have been identified which contain a genetic variant that occurs more often in people with MS than in people without MS. However, these DNA segments can be quite large, and the exact location of the susceptibility variant is unclear. This project aims to narrow the width of the 200 DNA segments that have previously been identified (a process known as fine-mapping), identify the susceptibility variants within each segment, and determine how these variants contribute to risk of MS. The team is specifically conducting these studies in underrepresented populations, where the genetic diversity will enhance the ability to narrow the segments and identify MS susceptibility variants.

**The Study:** Dr. Beecham and colleagues will perform targeted genotyping to identify genetic variants within the previously identified DNA segments for 2500 Hispanics/Latinx people with MS and 1500 Black people with MS. They also will use advanced genetics technology to assess how these variants are related to MS outcomes.

**What is the potential impact for people with MS?** Identifying genes that predispose a person to the risk of MS, and understanding how they act, will enable more targeted treatment strategies that benefit a variety of ancestral backgrounds.

# National MS Society Funds Clinical Care Fellowships

**2021 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 |
|---|---|---|
| Sidarth Dasari, MD | University of Vermont | Andrew Solomon, MD |
| Ghazal Lashgari, MD | Cedars-Sinai Medical Center | Nancy Sicotte, MD |
| Ahmad Mahadeen, MD | Cleveland Clinic Foundation | Jeffrey Cohen, MD |
| Gina Perez Giraldo, MD | Northwestern University | Roumen Balabanov, MD |
| Dan Michael Pineda, MD | Cleveland Clinic Foundation | Le Hua, MD/ Carrie Hersh, DO |
| Shuvro Roy, MD MCR/Scott Newsome, DO | Johns Hopkins University | Ellen Mowry, MD, |
| Laura Saucier, MD | Massachusetts General Hospital | Tanuja Chitnis, MD/ Mark Gorman, MD |
| Zuleyma Toledo-Nieves, MD | University of South Florida | Derrick Robertson, MD |
| Amy Yu, MD | Columbia University | Claire Riley, MD |

Dr. Toledo-Nieves is passionate about teaching underserved Spanish-speaking people with MS. “I am looking forward to working hand-in-hand with my patients in a clinical setting and to continue learning from them, aiding them in decision-making and helping them to fully understand their disease,” she says.

**Read more about MS Research**