PATHWAYS TO CURES

June 2023

Society Commits Over $19 Million for Research to Drive Pathways to Cures

The National MS Society has committed $19.4 million in multi-year funding to launch important new MS research projects. This is part of our ongoing effort to align the global MS research community around the most promising areas outlined in the Pathways to Cures roadmap to stop MS, restore function and end MS.

The new projects include 15 new research grants, 29 new fellowships and early career awards to support the MS workforce, and two strategic initiatives to extend knowledge to be gained from two clinical trials which leveraged $24 million in previous investments from the federal government.

These are part of the Society's annual investment of over $30 million to support more than 200 new and ongoing MS research studies around the world, including support and leadership for the International Progressive MS Alliance – a global effort to accelerate the development of effective treatments for people with progressive MS to improve quality of life worldwide.

Here are a few of the newly committed research projects:

STOPPING MS in its tracks:

• Researchers in Australia are looking for evidence of a role for diet in slowing MS progression. (See p.3)

RESTORING what's been lost:

• Researchers at the University of Colorado are testing whether electrical nerve stimulation can reduce fatigue in a clinical trial involving people with MS. (See p.19)

ENDING MS forever:

• Stanford University scientists are exploring novel technology with an eye toward developing a vaccine that may prevent the Epstein-Barr virus from triggering MS. (See p.30)

NEW PROJECTS SUMMARIZED INSIDE:Pathways to Cures:

Of Note:

Pathways to Cures: STOPPING MS

Stopping MS means achieving a state of no new disease activity or central nervous system injury, no worsening of daily living or quality of life, and no new manifestations of the disease. By doing this, we prevent disability, create an environment for myelin and axon repair and cultivate pathways that promote the restoration of function. The STOP pathway includes two major objectives: detecting MS early and precision medicine.

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Ana Anderson, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $396,000
Title: A TCF-1-Glucocorticoid regulatory axis underlies genetic susceptibility and steroid responsiveness in CNS autoimmunity
Summary: Brigham and Women's researchers are studying how immune molecules interact for clues to improving a standard treatment of MS relapses.

Background: The symptoms that people with MS experience are due to inflammation that leads to damage of nerve tissue in the brain and spinal cord. Immune cells that produce a protein called interleukin 17 (IL-17) are known to be involved. Further, IL-17-producing immune cells do not respond well to the steroids that are commonly used to shorten recovery time of MS relapses. This project addresses how to interfere with the damaging effects of IL-17-producing cells and how to improve their ability to respond to steroids to slow immune attacks on the nervous system in MS.

The Study: Dr. Anderson's team has identified two proteins that are linked to IL-17. Importantly, one of these proteins is instructed by a gene that has been linked to MS susceptibility in large-scale genetic studies. They are using advanced genetic tools and cutting-edge technologies to study how these two proteins work to influence the tissue-damaging and steroid-sensing capacities of IL-17 in mice with an MS-like disease, and in immune cells from people with and without MS.

What is the potential impact for people with MS? This information will inform the development of novel interventions to stop nerve tissue damage and improve responses to steroids during treatment of MS relapses.

Lucinda Black, PhD
Deakin University
Melbourne, Australia
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $480,128
Title: Elucidating the role of diet in MS to improve disease outcomes
Summary: Researchers at Deakin University in Australia are looking for evidence of a role for diet in slowing MS progression.

Background: Understanding the role of modifiable lifestyle factors, including diet, in MS disease progression is a high priority for people with MS. Specific aspects of a healthy diet, such as certain foods and nutrients, may help to slow disease progression, but there is a pressing need for high quality evidence. Such evidence would inform the development of dietary advice that is tailored for people with MS. Professor Black and colleagues are using information from a large Australian study to statistically test whether diet plays a role in slowing disease progression.

The Study: This study involves using information from more than 200 people with early MS followed for 15 years. At four time-points (onset, and five-, 10- and 15-year reviews), information on typical dietary intake was collected using a food frequency questionnaire. Blood samples from the same participants are available from the five-, 10- and 15-year reviews to measure nutrients that have been shown to be important for brain health. Face-to-face interviews included a neurological exam, interview with a study nurse, questionnaires, and a review of medical history. Professor Black's team is using advanced statistical methods to link dietary factors with measures of disease progression, such as relapse rate, disability, and MRI data.

What is the potential impact for people with MS? The findings of this research will potentially help all people with MS who are interested in modifying their diet to improve their disease outcomes and reduce the confusion caused by the conflicting online dietary advice marketed to people with MS.

Haritha Desu, PhD
University of Montreal Hospital
Montréal, Quebec
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $197,528
Title: Investigating T cell/oligodendrocyte interactions in MS: neuroprotective role of ICAM-1 signaling
Summary: A team at the University of Montreal Hospital is working to understand how immune T cells injure the cells that build nerve-insulating myelin and how to protect them to promote myelin repair.

Background: A hallmark of MS is the destruction of nerve-insulating coating (myelin) on nerve fibers by misdirected immune cells called T cells. It's not clear how T cells damage myelin and the cells that produce and repair it, called oligodendrocytes. Understanding the mechanisms involved should lead to therapies that can protect the central nervous system and promote the repair of myelin. Dr. Desu and team have recently shown in a mouse model of MS that T cells can directly contact oligodendrocytes in the brain and spinal cord through cell-to-cell "glue" molecules called ICAM-1.

The Study: This study involves the use of both human and mice samples to explore and potentially interrupt interactions between T cells and oligodendrocytes. One strategy is to examine T cell and oligodendrocyte interactions in tissue samples grown in lab dishes and determine if blocking ICAM-1 is protective. Another strategy involves deleting ICAM-1 from oligodendrocytes and seeing whether that protects against T cell-led damage in mice with an MS-like disease, and whether this limits direct contact between the oligodendrocytes and T cells.

What is the potential impact for people with MS? If the results of this study show that manipulating ICAM-1 molecules on oligodendrocytes is protective and can help restore function, the next step is to look for therapies that can do this in the brain and spinal cord, with the ultimate goal of developing treatments that can protect and restore neurological function in MS.

Josiah Gerdts, MD, PhD
University of California, San Francisco
San Francisco, California
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $618,056
Title: An engineered immune synapse detection circuit for T cell antigen discovery in autoimmune neurologic disorders
Summary: Researchers at UCSF are developing a technology to better identify the triggers that cause immune cells to attack the nervous system in MS and other disorders.

Background: In MS, something triggers immune cells, including T cells, to become misdirected and attack tissues in the brain and spinal cord. Scientists are still unclear what signals T cells to misbehave in MS. Identifying the molecular targets – called antigens -- of the immune cell attacks holds promise for improving MS diagnosis and therapies. However, identifying T cell antigens in MS has been difficult, owing to the large diversity of T cells in the body and the many potential antigens, such as components of nerve-insulating myelin, that could be involved in MS.

The Study: Dr. Gerdts has built a toolkit called "Immune Synapse Detection" (ISD) for discovering T cell antigens for immune-based neurologic disorders like MS using advanced cell engineering technology. In this system, the "handshake" between a T cell and the antigen creates a signal that allows identification of the antigen. Dr. Gerdts and team are using ISD technology to measure T cell responses to known antigens and T cells that recognize those antigens, then evaluate and refine ISD for measuring antigen discovery.

What is the potential impact for people with MS? Successful identification of MS-associated immune antigen targets could lead to many benefits for people with MS. These include improvements in diagnosis leading to starting therapy earlier, and new biomarkers of disease activity and prognosis that may create drug therapies tailored to the individual.

Erin Gibson, PhD
Stanford University
Stanford, California
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $591,289
Title: Targeting circadian mechanisms of degeneration in myelin disorder
Summary: Stanford scientists are exploring whether alterations in circadian rhythms in MS-like disease contribute to a failure in the natural capacity for myelin repair.

Background: MS is a neurological disorder in which the immune system attacks the brain and spinal cord. One target is the myelin that wraps around nerve fibers, as well as the oligodendrocytes, cells that make myelin. Precursor oligodendrocytes called OPCs are available to replace damaged myelin, but myelin repair diminishes in MS. The majority of people with MS report sleep or circadian abnormalities. Circadian rhythms are approximate 24-hour cycles generated at the molecular, cellular and behavioral levels, including sleep and wakefulness. Little is known about the role of circadian rhythms in the process of myelin formation, specifically, the life cycle of the OPC.

The Study: Dr. Gibson's team is monitoring circadian 24-hour rhythms and OPC dynamics in a mouse model of MS. They are creating models with intact and deficient circadian clocks, and observing whether the change results in any differences in OPC dynamics. They also are exploring whether repairing circadian function when myelin is damaged serves to increase repair.

What is the potential impact for people with MS? These findings may provide new therapeutic avenues targeting circadian control of myelin-forming cells to enhance myelin repair in MS.

Myla Goldman, MD, MSc
Virginia Commonwealth University
Richmond, Virginia
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $259,921
Title: Validation of a Clinical Outcome Measure of Demyelination: Physiologic, MRI, and Biomarker correlates of 6MW gait speed trajectory
Summary: Researchers at Virginia Commonwealth University are testing whether a new walking test can better identify myelin damage in people with MS, which may help to improve the success rate of clinical trials of repair strategies.

Background: Despite several promising treatments studied for promoting the repair of myelin (the nerve fiber insulation that is damaged in MS), there has not been a successful clinical trial to support approval of a repair strategy. Dr. Myla Goldman believes these trials may be failing because of difficulties in selecting participants and measuring successful repair. It is difficult to identify the presence of myelin damage and to see repair without invasive testing. Her team is testing whether a walking test they have developed may help to resolve this problem and help move repair strategies forward.

The Study: This team is enrolling 93 people with MS. Approximately one third will be Black people with MS, so that the

Strategic Initiatives: Boosting Impact of Trials

The National MS Society is providing strategic funding to leverage impact of two clinical trials, hoping to yield results that can stop MS in its tracks.

Robert Fox, MD, Cleveland Clinic Foundation, $1,224,590
Dr. Fox and collaborators conducted the SPRINT-MS study 10 years ago, testing ibudilast in people with progressive MS, finding positive outcomes on MRI measures that detect shrinkage (atrophy) of the brain. Now they are comparing the extensive brain imaging they collected a decade ago with participants' current condition. They aim to find early signals that predicted outcomes. This study could identify an imaging biomarker that will more easily and cost-effectively predict whether a therapy can slow MS progression.

Daniel Ontaneda, MD, PhD, Cleveland Clinic Foundation, $1,072,882
An international team is extending a clinical trial originally funded by PCORI to determine whether early, highly effective treatments are the better approach to preventing future disability in people with relapsing MS. There is much to be learned about how the participants feel about their quality of life, and the actual clinical and MRI outcomes farther down the road.

results can be generalizable to a broader and larger number of individuals. Enrolled participants will be asked to complete three 6-minute walks with 15-minutes of rest between walks. During these walks, Dr. Goldman and colleagues will measure the distance a participant is able to cover during each minute of the 6-minute walk. The results of this walk test will be compared with evoked potentials, a way of measuring the speed of nerve signals to detect myelin integrity.

What is the potential impact for people with MS? This study has the potential to find a low-cost, readily accessible tool to identify people with MS most likely to benefit from myelin repair strategies.

Jennifer Graves, MD, PhD
University of California San Diego
San Diego, California
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $630,870
Title: Biological Age in the Pediatric MS Population
Summary: A team at the University of California, San Diego is studying biological aging in children with and without MS for clues to stopping the effects of premature aging on the course of MS.

Background: Age has emerged as a factor that contributes to the severity of MS – both the natural aging process, and an accelerated aging that may occur as a result of the disease process. Research is ongoing to understand this accelerated aging and how it might be slowed. To best separate the effects of natural vs accelerated aging, Dr. Graves and colleagues are looking at children and adolescents with MS. If children with MS, who have very young chronological ages, have evidence of accelerated aging this would strongly support the idea that MS drives premature aging.

The Study: The team is measuring "biological age" (which may differ from chronological age) through multiple genetic markers in a large group of children and adolescents with MS, and comparing these with children without MS. They are using blood samples previously provided by 300 kids who were diagnosed with MS during childhood/adolescence and 150 kids without MS. All samples were previously stored for future research. Dr. Graves will perform state-of-the-art experiments to get the markers needed to estimate biological age.

What is the potential impact for people with MS? Studying biological aging in children may help clarify the pathways of aging that may worsen MS and identify new therapeutic strategies for stopping the effects of aging on the course of MS.

Jing-Ping Lin, PhD
National Institutes of Health/National Institute of Neurological Disorders and Stroke
Bethesda, Maryland
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $606,065
Title: Identifying signaling modules that drive glial senescence in a model of MS
Summary: NIH researchers are studying the involvement of specific brain cells in the destruction and restoration of nervous system tissues during aging and in MS-like inflammation for clues to stopping disease activities and enhancing repair.

Background: The brain contains various types of cells called glia, which play vital roles in the nervous system, such as supporting nerve cells and building protective insulation around them. However, the function of these cells can decline prematurely due to inflammation or aging, referred to as senescence.

The Study: The objective of this study is to improve our understanding of how various types of glial cells interact in specific areas of the brain and how they are affected by aging and inflammation. Dr. Lin and her team are comparing the activity of glial cells in healthy laboratory animals to those with age-related decline or MS-like inflammation to investigate the interactions that initiate senescence. These studies aim to provide valuable insights into the workings of glial cells during development, normal aging, and accelerated aging due to inflammation such as what is seen in MS.

What is the potential impact for people with MS? Better pinpointing the causes of nervous system damage and repair will significantly expand our knowledge of how to stop MS disease activity and lead to better treatments to restore function.

Elina Misicka, PhD
Case Western Reserve University
Cleveland, Ohio
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2025
Funding: $132,101
Title: Metabolomic biomarkers of risk, severity, and progression of MS
Summary: Researchers at Case Western are looking for biomarkers associated with MS risk, severity and progression to promote better treatment and prevention.

Background: To understand how MS causes disability, scientists need to better understand the processes that are occurring within the body. Advanced technology called metabolomics enables an automated way to evaluate the millions of substances that are made or used when the body breaks down food and other substances to create energy. There may be substances that can be detected in the blood that may be different, depending on a person's environment, sex, or level of MS disability. These differences could

serve as the basis of biomarkers to help diagnose and predict the course of MS.

The Study: Dr. Misicka and her team are investigating the biological mechanisms underlying MS by comparing the metabolomic "fingerprints" between people with MS and people without MS, as well as those with relapsing MS compared to progressive MS, and men and women. This research is attempting to better understand chemical processes that underlie MS and how it impacts people differently.

What is the potential impact for people with MS? Identifying and understanding biomarkers could help in earlier diagnosis of MS and MS at different stages and may point to biological processes relevant to MS risk, disability or progression. The researchers also hope that their work will lead to new treatments for MS and possibly even its prevention.

Serhat Okar, MD
National Institutes of Health/National Institute of Neurological Disorders and Stroke
Bethesda, Maryland
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $233,334
Title: Evaluation of Diagnostic and Disease-Monitoring Performance of Portable Ultra-low Field (64 mT) Magnetic Resonance Imaging in Patients with MS and Progressive Multifocal Leukoencephalopathy
Summary: NIH researchers are testing the ability of portable MRI scanners to lower costs and improve diagnosis and monitoring of people with MS.

Background: Magnetic resonance imaging (MRI) is essential to help diagnose and monitor disease activity in MS. In recent years MRI scanners for brain scans have become smaller, portable and easier to use. Now scientists want to determine if "MRI-on-wheels" can provide information equivalent to conventional MRI machines about the brain and potential complications associated with MS.

The Study: Dr. Okar and his team are collecting and analyzing scans from portable and conventional MRI from adults with MS and age- and sex-matched volunteers without MS. The team's goals are to evaluate the diagnostic performance of portable MRI in MS compared to conventional clinical MRI and

to evaluate how well portable MRI can detect disease-related brain changes in MS. They also intend to create an algorithm, or formula, that uses baseline portable and conventional MRI scans to improve the accuracy of follow-up portable MRI scans.

What is the potential impact for people with MS? Using portable MRI scanner technology in MS care should make MRI more available and cheaper for people with MS, especially those who live in areas where conventional MRI may be harder to access, especially people who have disability that makes it harder for them to travel long distances. This will enable easier follow-up and more precise decisions on possible therapies, especially for people living with advanced MS. It may also improve the diversity of clinical trials of new MS medications.

Novalia Pishesha, PhD
Boston Children's Hospital
Boston, Massachusetts
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $610,812
Title: Engineering the modularity of single domain antibody fragment that target Class II MHC for inducing antigen-specific tolerance
Summary: Researchers at Boston Children's Hospital are modifying certain proteins that can affect the immune system as a strategy for turning off immune attacks in MS.

Background: Certain immune system responses, both beneficial and harmful, start by engaging a type of immune cell called an antigen presenting cell. This helps immune cells identify what to attack, which in MS means attacks on components of the brain and spinal cord. In mouse models of MS, antigen presenting cells both change the course of the disease and reduce the severity of symptoms.

The Study: Using mouse models, Dr. Pishesha and her team are modifying proteins that can affect the immune system with tiny antibody fragments called nanobodies. These modifications are designed to make the nanobody useful in dampening antigen presentation and stopping the MS disease process. The nanobody compounds they are developing may also be useful for tracing the behavior of immune cells within the body.

What is the potential impact for people with MS? This novel approach may lead to the development of new ways to turn off MS immune attacks and may also lead to nanobody-based imaging agents that may one day be used to track disease progression and the response to treatment.

Carmen Sato-Bigbee, PhD
Virginia Commonwealth University
Richmond, Virginia
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $600,000
Title: Nociceptin role in the progression of MS
Summary: Researchers at Virginia Commonwealth University are targeting a protein that may promote MS progression, for clues to stopping MS in its tracks.

Background: A small protein molecule, called Nociceptin, may play a role in MS progression. Dr. Sato-Bigbee and colleagues have found that increasing levels of toxic molecules in both MS and in the aging nervous system may produce elevated amounts of Nociceptin. This molecule may then inhibit cells that make nerve-insulating myelin, thereby preventing repair in people with progressive MS.

The Study: The team is looking at Nociceptin levels in samples of blood and spinal fluid, paying special consideration to differences related to age, sex, and race. State-of-the-art microscopic examination and molecular biology techniques will be used to identify the type of brain cells that produced higher Nociceptin levels in tissue samples from people with MS and in people without MS. Therapeutic treatments to stop and reverse symptoms of progressive MS will be investigated by blocking Nociceptin actions in two different mouse models that are representative of different forms of MS.

What is the potential impact for people with MS? These studies may provide new targets for the development of treatments to specifically prevent and reverse the progression of MS.

Luke Schwerdtfeger, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $205,470
Title: Role of novel microbes and their metabolites identified in progressive MS in driving CNS autoimmunity
Summary: Researchers at Brigham and Women's Hospital are examining compounds made by intestinal microbes to see if and how they may be involved in MS disease activity.

Background: The gut microbiome (the mass of microbes, including bacteria, fungi and viruses, that naturally live in our intestines) plays an important role in health and disease and has been found to be substantially altered in people living with MS. Some specific strains of bacteria may have inflammation-reducing qualities and others may worsen inflammation.

The Study: This project aims to understand the influence of intestinal microbes on MS disease activity and whether selected microbes affect MS, either harmfully or

possibly beneficially. Dr. Schwerdtfeger is examining gut bacteria from people with progressive MS and determining what products they secrete that may be harmful or beneficial. The team will test these products in lab dishes and in mice with MS-like disease and observe their impacts. They hope to identify beneficial products that could become the basis of a therapy to stop MS disease activity.

What is the potential impact for people with MS? The identification of gut bacteria products able to reduce disease activity in MS will open a new arena of potential therapies based on probiotics or dietary supplements.

Syed Suhail, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $205,470
Title: Role of TIM-3 on myeloid cells in regulating neuroinflammation and neurodegeneration
Summary: Researchers at Brigham and Women's Hospital/ Harvard Medical School are studying how an immune molecule called TIM-3 affects immune responses in the brain and spinal cord in progressive MS.

Background: Damage to the brain and spinal cord in MS is thought to happen when certain immune cells react to myelin (the protective and insulating coating on nerve fibers). While a number of therapies that regulate immune responses have been effective in treating relapsing MS, fewer options are available for people with progressive MS. Scientists are looking into how specific immune cells are activated, along with their role in tissue damage.

The Study: Levels of an immune molecule called TIM-3 are reduced in the brain and spinal fluid of people with MS. Dr. Suhail and team are exploring how reduced TIM-3 may ramp up damaging immune activity. One way they are testing this is by engineering mice to lack TIM-3 and observing the impacts during MS-like disease. The team is also using a variety of advanced technologies to further explore how TIM-3 may reduce inflammation in search of interactions that could potentially be targeted by experimental therapies in the future.

What is the potential impact for people with MS? This study may lead to finding specific targets in the immune system that can be used to develop therapies for people with progressive MS for whom there are few treatment choices.

Tomokazu Sumida, MD, PhD
Yale University
New Haven, Connecticut
Award: Harry Weaver Scholar Awards
Term: 7/1/2023-6/30/2028
Funding: $624,377
Title: Pathogenic Programs Driving Regulatory T Cell Dysfunction in MS
Summary: Yale researchers are working to find what causes immune cells to enter and attack the nervous system in MS.

Background: A recent investigation of MS and 20 other autoimmune or immune-mediated diseases found that most of the genetic risks associated with autoimmune disease are linked to changes in DNA caused by environment and lifestyle, such as diet and exercise. These factors can affect the function of certain immune T cells called Tregs that play a role in regulating immune system defenses. However, there is no biomarker or test that could detect these immune system changes to predict a person's disease course or response to a particular therapy.

The Study: Dr. Sumida is working to find out what leads to dysfunction of certain T cells in MS and to identify potential molecules that could be targeted by a therapy. To find cell changes in MS, he is examining blood samples people who are newly diagnosed and not yet treated for MS, as well as from age- and sex-matched controls who don't have MS. Understanding functional changes of Tregs may allow the team to figure out how to slow or even prevent disease onset and progression, as well as develop biomarkers that could personalize treatment options and help design effective therapies.

What is the potential impact for people with MS? The results generated by this work will provide important insights into what drives immune dysfunction in MS. In the long term, when combined with genetic studies, this work should prove valuable in eventually stopping the progression of MS as well as facilitating the development of precision medicine.

Tyler Titcomb, PhD
The University of Iowa
Iowa City, Iowa
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $603,625
Title: Registered Dietitians, Nutritional Risk, and Dietary Patterns in MS
Summary: A team is seeking evidence for the idea that including a registered dietitian nutritionist on MS care teams can improve the course of MS.

Background: People with MS who are interested in diet and nutrition may turn to internet sources (that likely are not based on scientific evidence) to obtain this information. Including a registered dietitian nutritionist on the MS healthcare team may help to inform both people with MS and their healthcare providers about the impacts of diet. This project aims to provide direct evidence that including a

registered dietitian nutritionists on the healthcare team can reduce fatigue and relapse rates, and improve quality of life for people living with MS.

The Study: The North American Research Committee on MS (NARCOMS) is a voluntary registry for people with MS that includes over 45,000 participants enrolled since 1996. In 2003, a survey of alternative medicine use was conducted and indicated that at that time, 24% of the survey respondents indicated seeing a registered dietitian or nutritionist within the previous 12 months. Participants will be split into two groups: those who did see a registered dietitian or nutritionist and those who did not. Then fatigue, quality of life, and risk of relapse will be compared between the groups to determine if seeing a registered dietitian or nutritionist is linked with better health and disease outcomes. Two literature reviews will also be performed to determine how common nutritional risks are and whether dietary patterns are linked to better outcomes among people with MS.

What is the potential impact for people with MS? The results from this series of studies should provide justification for the inclusion of registered dietitian nutritionists on the MS healthcare team. This would provide people who are interested in diet a way to get evidence-based information on diet as part of their care, and enable the use of diet to improve wellness.

Danwei Wu, MD
Stanford University
Stanford, California
Award: NMSS-ABF MS Clinician Scientist Award
Term: 7/1/2023-6/30/2026
Funding: $301,086
Title: Targeting CNS myeloid population through bone marrow transplantation in EAE mouse model
Summary: Stanford researchers are investigating aspects of bone marrow transplant in mice to enhance its ability to protect the nervous system and slow progression.

Background: Despite advancements in treatments, some people with MS do not respond to current therapies. A type of bone marrow transplant called autologous hematopoietic stem cell transplantation (aHSCT) has been shown to be beneficial in resetting the immune system in people with aggressive forms of MS or who don't respond well to available treatments. Researchers have recently discovered that following aHSCT, some of the bone marrow cells, called circulation-derived myeloid cells (CDMCs), can enter the brain and spinal cord. These cells are able to remain in the brain and spinal cord long-term and may protect from inflammation.

The Study: Dr. Wu and team are exploring a strategy that enables CDMCs to enter the brain and spinal cord more efficiently and reach all parts of the nervous system. Using a mouse model of MS, the team is working to understand how CDMCs suppress inflammation and to better understand how bone marrow transplant works to slow down the progression in people with MS who have benefited from this treatment.

What is the potential impact for people with MS? This research may lead to a way to improve the benefits of aHSCT therapy for MS, as well as potentially develop a stem cell-based method to deliver genes or proteins to the brain and spinal cord to help repair the nervous system.

Dandan Yang, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $212,153
Title: Glucocorticoid biosynthesis and sensing of Th17 cells in CNS autoimmunity
Summary: Researchers at Brigham and Women's Hospital are investigating why steroids work better for some people with MS than others and to make them more effective in quelling attacks on the nervous system.

Background: Glucocorticoids (GCs) are potent steroid hormones that serve as a standard therapy to shorten the recovery time from MS relapses. Unfortunately, not everyone has a beneficial response to GCs. Part of the explanation might be that certain immune cells produce a protein called interleukin-17 (IL- 17), which is responsible for the inflammation that leads to damaging relapses in MS. There are two types of IL-17-producing cells, one that causes nerve tissue damage and one that doesn't; the first type is less sensitive to steroids.

The Study: Dr. Yang and her team have developed genetic tools to study, in an animal model of MS, the role of steroid response and steroid production in cells that produce IL-17. They have also identified a protein that can increase steroids' effectiveness against the damaging type of IL-17–producing cells. Dr. Yang will compare blood samples from people with relapsing MS and people without MS to determine the effect on steroid response of IL-17–producing cells.

What is the potential impact for people with MS? Figuring out why some MS patients do not respond to steroids and increasing the ability of IL-17-producing cells to respond to steroids has the potential to stop damaging relapses more quickly and may lead to the development of improved treatments for MS relapses.

Yevgeniy Yuzefpolskiy, PhD
Benaroya Research Institute
Seattle, Washington
Award: Postdoctoral Fellowships
Term: 9/1/2023-8/31/2026
Funding: $212,153
Title: Role of B cells in Modulating Metabolic Pathways of Pathogenic CD4 T cells in Murine Model of MS
Summary: Researchers at Benaroya are focusing on how disease-causing immune T cells form and are affected by B cells with the aim of deleting them or preventing them from forming in the first place.

Background: The immune system is made up of many types of cells, among them T cells and B cells, which are believed to be involved in triggering destruction in the brain and spinal cord of people with MS. This causes the loss of functions such as coordination, mobility and vision in MS. While many disease-modifying therapies are available that can decrease the frequency and intensity of flareups in people with relapsing MS, so far none can cure the disease. That cure may come about when scientists understand how T cells are triggered to cause damage and how to neutralize them.

The Study: Dr. Yuzefpolskiy is aiming to decipher the mechanisms that drive the onset and progression of MS. Cells in the body, like all living things, require food for energy to perform their functions. Cells use a wide variety of food types depending on their function and location in the body. This team believes that by understanding the energy that is used by disease-causing immune cells, they can devise a way to starve them and prevent them from causing disease. Working first on a mouse model of MS, Dr. Yuzefpolskiy will then analyze the most promising targets in human blood samples in a search for future therapies.

What is the potential impact for people with MS? Results from this study will provide the fundamental building blocks for better understanding the role of T cells and B cells in causing MS. Results may also suggest new, more diverse and adaptable therapies that target harmful T cells and B cells.

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. Four new trainees have been awarded this fellowship in 2023:

Karla Gray-Roncal, MD, Johns Hopkins University, Baltimore, Maryland
Dr. Gray-Roncal will participate in weekly clinics where she will learn more about careful diagnosis and management of disease and symptoms. She will assume the roles of treating physician and evaluating neurologist in ongoing clinical trials and be involved in trial design, analysis of research data and dissemination of results. She will complete formal courses in epidemiology and statistics through Bloomberg School of Public Health. She will gain expertise in magnetic resonance imaging and optical coherence tomography, which are fundamental to MS management.

Nara Michaelson, MD, Massachusetts General Hospital, Boston, Massachusetts
Dr. Michaelson will study how physical therapy influences nerve fiber density and nerve cell firing patterns within the brain using advanced MRI imaging. She will also look at whether dalfampridine, an add-on medication used in MS, can improve physical and cognitive disabilities. She will be intimately involved in all aspects of clinical trial design and implementation. Dr. Michaelson will complete Harvard Medical School's Master of Medical Science in Clinical Investigation degree.

Christopher Orlando, MD, MPH, University of Southern California, Los Angeles, CA
Dr. Orlando will contribute to care for a highly diverse population. He will also complete a Graduate Certificate in Clinical Translational Research. He will participate in multiple clinical trials with a particular emphasis on people of different races and ethnicities who are underrepresented in clinical trials. His role will include recruiting participants, conducting focus groups, assessing symptoms, and disseminating results.

Karlo Toljan, MD, Cleveland Clinic Foundation, Cleveland, Ohio
This program combines experience in clinical trials, coursework in clinical research on track for a PhD degree, and ongoing patient care. Dr. Toljan will become familiar with all aspects of trial design and conduct. His research will focus on imaging markers for use in clinical trials. He will also dedicate time to patient care to become proficient in all clinical aspects of MS care, including being able to accurately diagnose MS.

Pathways to Cures: RESTORING FUNCTION

Restoring what has been lost means reversing MS symptoms and recovering function. While disease-modifying therapies (DMTs) can limit relapses and delay disease progression, they do not truly restore cognitive or physical abilities. By focusing on an integrated approach to regeneration and remyelination, as well as better understanding how wellness and lifestyle choices affect symptoms, those living with MS can have an improved quality of life free from the burden of MS symptoms. The RESTORE pathway includes two major objectives: regeneration and restoration of activity.

* * *

Korhan Buyukturkoglu, PhD
Columbia University
New York, New York
Award: Harry Weaver Scholar Awards
Term: 7/1/2023-6/30/2028
Funding: $730,849
Title: Thalamus Derived Radiomic Features to Explore Cognitive Impairment in People with Multiple Sclerosis and At-Risk Individuals
Summary: Researchers at Columbia are using advanced technology to find a way to leverage clinical MRIs in screening for cognitive problems in MS.

Background: Individuals with MS commonly encounter cognitive difficulties that can interfere with their daily activities and overall well-being, including memory problems and challenges with attention and information processing. While various MRI findings have been linked to these issues, there are no definitive brain imaging indicators that fully explain the underlying cause of cognitive impairment in MS. Moreover, it remains difficult to accurately predict which individuals with MS will experience cognitive impairment and which specific cognitive functions will be impacted.

The Study: Dr. Buyukturkoglu is currently researching the use of a rapidly developing technique called "radiomics," which has already been effectively utilized in cancer imaging, to gain a deeper understanding of cognitive impairment in MS. Radiomics research aims to extract vast amounts of data from medical images, such as MRI scans. With the help of sophisticated machine learning algorithms and statistical models, radiomics enables researchers to pinpoint significant patterns in MRI scans that may not be readily observable to the human eye. The team is investigating the thalamus, a brain structure that when damaged has been linked to cognitive impairment, in individuals with MS from diverse racial and ethnic backgrounds. They are also analyzing MRI measures and radiomics in people with a family history of MS to predict the cognitive status of this group, who are at a higher risk of developing MS.

What is the potential impact for people with MS? Findings of this study would help to develop clinically relevant, repeatable and non-invasive MRI biomarkers that may predict cognitive impairment in MS at its earliest stages and potentially inform screening, prevention and treatment strategies.

Roger Enoka, PhD
University of Colorado - Boulder
Boulder, Colorado
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $589,207
Title: Reducing fatigue in people with MS by treatment with transcutaneous electrical nerve stimulation
Summary: A team at the University of Colorado is testing whether electrical nerve stimulation can reduce fatigue in a clinical trial involving people with MS.

Background: The prevalence of fatigue increases with disease progression and eventually becomes a primary concern for most people with any type of MS. Fatigue is difficult to treat and manage because its severity fluctuates over time. Professor Enoka and colleagues are testing a novel method with potential for improving fatigue.

The Study: The team is conducting a trial involving 40 people with MS who will participate in an 11-week study comparing effective and sham doses of transcutaneous electrical nerve stimulation (TENS) applied to leg muscles. The electrical current will be set at an intensity to elicit slight muscle contractions for the effective dose, whereas it will be set at a lower intensity that can just be felt for the sham dose. TENS will be delivered through electrodes placed on the skin of lower leg and thigh muscles of both legs. The stimulation will be applied while participants perform light exercises, which is expected to stimulate nerve cells in the spinal cord. The team will determine the impact of the TENS treatment on self-reported measures of fatigue, and then compare these with objective assessments of walking and measures of mobility.

What is the potential impact for people with MS? This study may reveal a low-cost method for reducing fatigue and will help to lower the barrier for individuals to become more engaged in physical activity programs and to reap the benefits that an active lifestyle affords.

Lindsay Festa, PhD
University of Pennsylvania
Philadelphia, Pennsylvania
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $610,065
Title: Regulation of the oligodendrocyte actin cytoskeleton by the lysosomal cation channel TRPML1
Summary: Researchers at UPenn are working on strategies that enhance repair and restoration of myelin, the nerve coating that is damaged in MS.

Background: One of the hallmarks of MS is the immune-system assault against myelin, the casing that insulates and nurtures nerve fibers. Myelin is produced by brain cells called oligodendrocytes. These are generated from immature cells called oligodendrocyte precursor cells (OPCs). While there are currently no therapies approved to successfully promote the repair of myelin, researchers have been working to identify proteins that could do this.

The Study: A protein called transient receptor potential mucolipin 1 (TRPML1) has been found to be decreased in MS brain lesions. Dr. Festa has previously shown that activating this protein in OPCs results in cells that can better generate myelin. Now, using OPCs in lab dishes and in a mouse model, she is working to confirm the role of TRPML1 in generating oligodendrocytes and myelin. The team is also determining if TRPML1 activity is disrupted when myelin is injured and monitoring how much myelin is generated from these cells and its quality.

What is the potential impact for people with MS? Results of Dr. Festa's work could potentially lead to the development of therapies that target the TRPML1 protein to promote myelin repair and thus stop an individual's disease from advancing.

Brett Fling, PhD
Colorado State University
Fort Collins, Colorado
Award: Mentor-Based Postdoctoral Fellowships
Term: 7/1/2023-6/30/2028
Funding: $497,901
Title: From bench to bedside - mobility control and neurorehabilitation in people with multiple sclerosis
Summary: Experienced mentors/researchers at Colorado State University are training promising professionals to conduct MS rehabilitation research.

Background: Most people with MS eventually develop balance and gait (walking) problems. Dr. Fling's team believes that successful rehabilitation for these problems requires a better understanding of the nervous system's contributions to mobility impairment in each individual, so that specific, directed therapies can be applied.

The Study: Under the direction of experienced researchers, fellows will learn the neuroscience underlying posture, balance, and walking, and how dysfunction occurs over the course of MS. They will also learn how to translate this scientific understanding into designing improved methods for assessing gait and balance, as well as rehabilitation interventions that can restore function to people with MS. Mentors will meet monthly with fellows to review plans and accomplishments and help with interpretation of the fellow's results. Fellows will be exposed to rehabilitation, systems neuroscience, statistics, clinical research, bioengineering, and neurology via meetings with mentors and collaborators at Colorado State and the University of Colorado.

What is the potential impact for people with MS? This program will train rehabilitation professionals to conduct rigorous, well-controlled research studies with the potential to improve mobility and quality of life for people living with MS.

Larissa Jank, MD
Johns Hopkins University
Baltimore, Maryland
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $205,470
Title: Indole-3-lactate – a novel metabolic modulator of oligodendroglial function and a potential remyelinating agent for MS
Summary: Researchers are exploring the effect of a molecule produced in the gut on the brain and whether taking related dietary supplements may help restore nerve-insulating myelin.

Background: The molecule Indole-3-lactic acid (ILA) is produced by bacteria in the gut when breaking down certain dietary proteins. Scientists have found that ILA levels are lower in people with MS. On the other hand, elevated ILA levels in people with MS have been associated with lower disability. This makes ILA supplementation of interest as a potential therapy to promote the regeneration of myelin, the nerve fiber coating that is attacked by the immune system in MS.

The Study: Using both animal models of MS and laboratory cell cultures, Dr. Jank is investigating how ILA may promote the maturation of myelin-making cells so that they are ready to generate myelin. The team is determining whether ILA treatment can help overcome some mechanisms that block myelin repair especially during progressive phases of MS.

What is the potential impact for people with MS? This research may help explain the relationship between changes in gut-bacteria-derived molecules and disease progression. ILA, and possibly other similar molecules derived from gut bacteria, may potentially play a role in restoring myelin-making cells, which could stop MS disease progression and restore lost function. These molecules might also be used to assess the risk of disease progression and to individualize treatments.

Jennifer Orthmann Murphy, MD, PhD
University of Pennsylvania
Philadelphia, Pennsylvania
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $653,875
Title: The role of microglia in cortical remyelination
Summary: A team at the University of Pennsylvania is investigating features of brain cells called “microglia” that could be manipulated to enhance myelin repair.

Background: Immune attacks on the brain and spinal cord during MS cause damage to nerve-insulating myelin, and the loss of the cells that make myelin, the oligodendrocytes. The nerve cells can also be damaged. We do not yet understand what factors interfere with complete replacement of myelin and oligodendrocytes in the cortex, the outermost layer of the brain. Microglia are a specialized type of immune cell in the brain that contribute to myelin formation during early development. In adult brains, microglia respond to injury and disease, including during the course of MS. Dr. Orthmann-Murphy’s team is using new tools that can characterize in detail how microglia respond to myelin loss to determine whether damage to myelin causes some microglia to become dysfunctional and prevent myelin repair and oligodendrocyte replacement.

The Study: These studies will use lab mice that have a fluorescent protein in microglia and oligodendrocytes, which will be used to visualize them in the living brain and measure their interactions and behavior. The genetic makeup of microglia will be examined in cells isolated in the laboratory, to define all the different ways microglia change after myelin is damaged. The results should help to determine whether altered microglia support or prevent replacement of myelin and oligodendrocytes.

What is the potential impact for people with MS? Changes in microglia that are successfully manipulated to promote or support myelin repair can then be translated to treatment trials to repair myelin in people with MS.

Lindsay Osso, PhD
University of Colorado Denver
Denver, Colorado
Award: Postdoctoral Fellowships
Term: 7/1/2025-6/30/2026
Funding: $68,588
Title: Determining the mechanisms underlying remyelination by surviving oligodendrocytes
Summary: Researchers are investigating how myelin-building cells that survive attacks can contribute to the repair of myelin, the protective nerve coating that is damaged in MS.

Background: In multiple sclerosis, the immune system destroys the protective nerve fiber insulation called myelin, which can interfere with nerve signal conduction and leave nerve fibers and cells vulnerable to damage. Creating new myelin (remyelination) is the primary way to restore function. While myelin repair can occur naturally, in MS it is often limited, so new strategies to increase myelin restoration are needed to improve function.

The Study: Research suggests that myelin-building brain cells called oligodendrocytes that survive immune attacks can participate in myelin repair. In MS, the formation of new oligodendrocytes that can restore myelin is sometimes blocked. Using mouse models, Dr. Osso is investigating the mechanisms that regulate the capacity of surviving oligodendrocytes to restore myelin.

What is the potential impact for people with MS? Understanding the mechanisms that regulate myelin repair is a critical step towards being able to develop therapies to promote recovery of myelin and neurological function. An approved therapy for myelin repair would be transformative for those living with MS.

Vaibhav Patil, PhD
Northwestern University
Evanston, Illinois
Award: Postdoctoral Fellowships
Term: 9/1/2025-8/31/2026
Funding: $70,619
Title: Role of m6A mRNA methylation in CNS remyelination and inflammation
Summary: Northwestern University scientists are working to expand the possibilities for repairing myelin, the protective nerve coating that is damaged in MS.

Background: The cells (oligodendrocytes) that produce myelin, a coating that insulates and protects nerve fibers are highly sensitive to the immune system attacks and inflammation that are the hallmarks of MS. Researchers trying to understand how to protect oligodendrocytes recently discovered that a biological mechanism called “mRNA methylation” is responsible for the development and maintenance of cells. This mechanism could play a critical role in the survival of oligodendrocytes and their capacity to produce new myelin.

The Study: While mRNA methylation is critical in the development of myelin-producing oligodendrocyte cells, it's not clear if it plays a role in myelin repair in MS. Dr. Patil and team are studying mRNA methylation in process of myelin repair using mouse model. One model is a mouse that was engineered to lack a molecule related to mRNA methylation, to understand how its absence influences oligodendrocyte health and myelin repair. The study should provide useful information on whether the survival of oligodendrocyte cells can be enhanced to protect against inflammation and damage in MS.

What is the potential impact for people with MS? These studies should inform efforts to protect oligodendrocytes and promote myelin repair to restore function for people with MS.

Lachlan Rash, PhD
The University of Queensland
Brisbane, Australia
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $584,878
Title: Target validation of acid-sensing ion channel inhibitors to stop disease progression and manage pain in MS
Summary: Researchers at The University of Queensland in Australia are developing an inhibitory molecule that may help to protect the nervous system and prevent symptoms such as pain in people with MS.

Background: Despite good progress in our understanding of the mechanisms of MS and development of new therapies, injury to nerve cells is an aspect of the disease that remains poorly treated. A protein called acid sensing ion channel 1 (ASIC1) is found on nerves and on inflammatory cells in the body, and its role is to detect and respond to damage. When ASIC1 is over-activated in nerves, it can cause damage or death of nerve cells and increased pain signaling, contributing to the symptoms experienced by people with MS. ASIC1 might be a novel drug target to help treat MS.

The Study: Dr. Rash and colleagues have developed an inhibitor of ASIC1. Now they are testing the ability of this compound to protect mice with an MS-like disease from nerve cell injury. They also are investigating whether the compound can reduce pain, a common symptom of MS. Finally, they are looking to make sure it does not increase the activity of immune cells that might be harmful in people with MS.

What is the potential impact for people with MS? The results of this study will help to understand a potential new treatment strategy for stopping nerve damage and reducing pain in people with MS.

Sumire Sato, PhD, PT
University of Florida
Gainesville, Florida
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding: $200,689
Title: Identifying brain biomarkers in MS walking function to enhance rehabilitation outcomes: examining brain white matter after accounting for "free-water" fluid
Summary: Researchers at the University of Florida are focusing on using MRI imaging to understand how mobility declines with age and in people with MS.

Background: Recent advances in MRI (magnetic resonance imaging) techniques make it possible to measure the movement of water molecules in the brain, called diffusion weighted MRI. This technique can bring insights into damage and inflammation in the brain and how this damage relates to walking and balance. The immune system attacks in MS against the brain and spinal cord can alter the results from diffusion weighted MRI.

The Study: Dr. Sato is using a technique that corrects for the changes that MS can cause in diffusion weighted MRI to better understand how damage to specific areas of the brain influence movement disability in people with relapsing MS. To gain further insights, she is comparing diffusion weighted MRI data from people with relapsing MS to data from older adults ages 60 to 80 who either do or don't have difficulty with walking and balance.

What is the potential impact for people with MS? This study should provide important information on using MRI to pinpoint damage that underlies movement problems. Further studies may lead to improvements in recovering function.

Larry Sherman, PhD
Oregon Health & Science University
Portland, Oregon
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $599,999
Title: Role of Hyaluronan in MS Cognitive Dysfunction
Summary: Researchers at Oregon Health & Science University are exploring whether a molecule called hyaluronan contributes to problems with cognition in MS, and whether blocking its activity can improve memory in lab models.

Background: Many people living with MS experience problems with memory. Prof. Sherman's team has found that a molecule found outside of cells in areas of the brain involved with learning and memory, called hyaluronan, can influence both the activity of nerve cells and formation of new nerve cells. Disrupting hyaluronan signaling can result in memory problems in mouse models that are similar to memory problems experienced by people with MS. So the team is investigating strategies to alter hyaluronan signaling in hopes of improving memory.

The Study: Prof. Sherman's group will utilize novel drugs to altering hyaluronan levels in the brain to test if these drugs can improve memory in mice with EAE, a model of MS. They are also exploring this approach in tissues obtained from people with MS. First, they will assess how hyaluronan activity changes as disease progresses. Then, they will test how hyaluronan affects memory in mice with EAE, and finally, if blocking an enzyme that breaks down hyaluronan can improve memory in mice with EAE. They are specifically looking at whether the effects of hyaluronan on nerve cells may be more pronounced in older individuals.

What is the potential impact for people with MS? These studies will determine the role of hyaluronan in learning and memory dysfunction in an MS-like animal model, and have the potential to define novel therapies that can be developed to restore cognitive dysfunction in people with MS.

Seema Tiwari-Woodruff, PhD
University of California, Riverside
Riverside, California
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $589,499
Title: Functional recovery of Visual Pathway by modulating inflammation, inducing remyelination, and mitigating axon damage.
Summary: Researchers at University of California, Riverside are exploring how one molecule may contribute to nerve damage in MS for clues to restoring function.

Background: There are no effective therapies that directly protect nerves from damage in people with MS. This damage contributes to the progression of disability. Prof. Tiwari-Woodruff and colleagues are focusing on an enzyme called "SARM1" that, when activated, leads to depletion of energy molecules and destruction of nerve cells, so specifically blocking it therapeutically could be beneficial.

The Study: Measuring visual function is a useful method to assess nerve health and function over the course of disease, because the eye contains unique nerve cell sub-types within a small area. This team will use various mouse models of MS and axon (nerve fiber) damage, in which they can specifically label these cells. This will enable them to observe the role of SARM1 on nerve cell health, and the effects of chemical SARM1 blockers on ongoing nerve cell damage.

What is the potential impact for people with MS? These results will advance our understanding of how nerves are damaged in MS and may yield a strategy for protecting against this damage and reversing it to restore function and prevent MS progression.

Ceren Tozlu, PhD
Weill Cornell Medical College
New York, New York
Award: Career Transition Fellowships
Term: 7/1/2023-6/30/2028
Funding: $607,777
Title: Multi-modal neuroimaging and cognitive assessment of females with multiple sclerosis across different stages of menopause
Summary: Researchers at Weill Cornell are exploring how menopause affects thinking and memory in women with MS.

Background: The effects of menopause on memory and thinking (cognition) are relatively unstudied, both in the general population and in women who have MS. Research in the general population suggests that cognitive decline occurs in the period just before menopause but returns to normal after menopause. However, the recovery might be lower for women with multiple sclerosis due to existing tissue damage in the brain compared to those who don't have MS.

The Study: Dr. Tozlu is looking at cognitive decline in older women by assessing mental processes in women ages 45 to 55 with relapsing MS at different stages of menopause (before, during, and after) and age-matched women who don't have MS. She is collecting MRI scans of the brain, blood samples, cognitive tests, and other information from participants to look for differences between the women in such biomarkers as brain structure, function, and metabolism.

What is the potential impact for people with MS? Identifying more clearly the biological underpinnings of impairment in cognition in people with MS, particularly around the time of menopause, will help scientists better understand the role and impact of hormonal changes in MS. By understanding the mechanics of cognitive decline or resiliency, personalized treatments and hormonal therapies that can reduce impairment in middle-aged and older people with MS will be more possible.

Barbara Willekens, MD, PhD
Antwerp University Hospital
Antwerp, Belgium
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding: $546,156
Title: MACSIMISE-BRAIN: Metformin Add-on Clinical Study in Multiple Sclerosis to Evaluate Brain Remyelination and Neurodegeneration
Summary: A team is testing the ability of metformin – a therapy approved for diabetes – to stop progression and restore function in people with progressive MS.

Background: Despite many treatments being approved to treat MS, people with MS still experience progression of disability and no treatments enhance the repair of nerve-insulating myelin or to protect nerve cells and fibers from damage. Several studies in animal models have shown that metformin – an approved treatment for diabetes – has properties that can reduce inflammation, protect nerves, and promote myelin repair. Previously a small, early study of metformin in people with MS did not demonstrate significant adverse events.

The Study: This trial is a collaborative effort of Dr. Willekens and colleagues at University Hospital Ghent, AZ Sint-Jan Brugge, NMSC Melsbroek, UMSC Hasselt, the University of Antwerp and University Hospital Brussels. The team is testing the effectiveness of metformin compared to placebo in 120 people with progressive MS who do not have signs of active inflammation. Participants will be followed for two years and will be monitored with neurological exams and MRI scans. Individuals also will be invited to participate in a sub-study where blood samples will be collected to examine potential biomarkers that could inform other research teams about progressive MS. During the entire duration of the project, special attention will be paid to communicating with participants, in close collaboration with a stakeholder/advisory committee.

Fast Forward Funding

Researchers at Clene Nanomedicine have been testing an experimental therapy called Biocatalytic Nanocrystalline Gold (CNM-Au8) in people with relapsing MS and have found suggestions that it can facilitate myelin repair and nerve protection. Previous funding from Fast Forward enabled the company to measure blood biomarkers that may help detect nervous system protection and repair. New funding from Fast Forward is enabling the company to deeply examine a small group of people with progressive MS using very powerful brain scanning. The participants are being given CNM-Au8 for several weeks and are being scanned before, during, and after taking the compound. This research can determine whether CNM-Au8 is a viable strategy for stopping progressive MS.

What is the potential impact for people with MS? If this study is successful, an already approved treatment may be an available pathway toward stopping MS progression and restoring function in people with progressive MS.

Pathways to Cures: ENDING MS

Ending MS means no one else hears the words, "you have MS." There is growing evidence that MS may be preventable. The two main objectives of the END pathway are preventing MS in the general population and identifying MS in its earliest (prodromal) stages to delay or prevent the onset of signs or symptoms, defined as secondary prevention.

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Natalia Drosu, PhD
Massachusetts General Hospital
Boston, Massachusetts
Award: Postdoctoral Fellowships
Term: 7/1/2023-6/30/2026
Funding**:** $197,528
Title: CD4+ T cell responses to immunodominant HLA-DRB1*15:01-restricted Epstein-Barr virus antigens in patients with multiple sclerosis with potential cross-reactivity to myelin
Summary: Researchers at Mass General Hospital are examining how environmental and genetic sensitivity to the Epstein-Barr virus may work together to trigger MS.

Background: The Epstein-Barr virus (EBV) is a well-known risk factor that in the presence of other susceptibility factors can trigger MS. Yet exactly how that occurs is still unclear. Nearly everyone in the world has been exposed to EBV, usually in childhood and without symptoms. However, a small percentage of people who were exposed to EBV get MS later in life. Researchers have also found that a common gene variant involved in immune system function (HLA-DRB1*15:01) gives people a much higher risk of getting MS. This gene presents bits of proteins from cells and tissues to the immune system, which signals it to attack if it detects something foreign. Researchers are trying to figure out if this gene may present pieces of EBV to the immune system, causing it to respond to EBV differently in people with MS compared to those without MS.

The Study: This study is an extension of Dr. Drosu's doctoral research at MIT in screening antiviral drugs that target EBV for possible use in clinical trials in MS. The experiments proposed in this work address the HLA-DRB1*15:01 gene and EBV, the two most significant environmental and genetic risk factors for MS. She aims to understand how they are linked to trigger MS and what might be different between people with MS and those without MS in their immune responses to EBV.

What is the potential impact for people with MS? This work holds the potential for understanding key triggering factors for MS and provides biomarkers of EBV immune activity, which could be used to predict who may get MS before diagnosis as well as how to design more effective treatments with fewer side effects.

Theodore Jardetzky, PhD
Stanford University
Stanford, California
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding**:** $571,058
Title: Targeting EBV entry glycoproteins for vaccine and therapeutic development
Summary: Stanford scientists are exploring novel technology with an eye toward developing a vaccine that may prevent the Epstein-Barr virus from triggering MS.

Background: The Epstein-Barr virus (EBV) is a leading trigger of MS. This virus is easily passed between people and most people have already been exposed, usually in childhood. There are vaccines in development that, if proven safe and effective, may eventually be tested in people who are at higher risk for MS, such as people with close family members with MS.

The Study: Prof. Jardetzky's team is seeking to determine whether they can produce a highly protective EBV vaccine using a unique protein – called the EBV gB protein – which can adopt multiple shapes that impact its recognition by the immune system's antibodies. Developing a vaccine using this protein may be a way to prevent EBV from entering cells in people with MS. Dr. Jardetzky is developing unique models in which his team will test whether this nimble protein can stimulate a more protective antibody response.

What is the potential impact for people with MS? Although EBV likely does not act alone in the development of MS, a vaccine that can stop its effects is one pathway to ending MS forever.

Dalia Rotstein, MD, MPH
St. Michael's Hospital
Toronto, Canada
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding**:** $151,000
Title: When does MS begin after infectious mononucleosis?
Summary: A team in Toronto is using a novel dataset to map out the earliest steps of MS in people who had mononucleosis, for clues to developing strategies that can end MS by prevention.

Background: Mounting evidence suggests that Epstein Barr virus (EBV) infection, which can lead to mononucleosis and other disorders, is a trigger for MS in the context of other MS risk factors. Other research has shown that MS likely starts years before the first attack or typical symptoms. Studies have demonstrated that there is a period called the "MS prodrome," marked by non-specific symptoms and increased health service use that starts 5 to 10 years in advance of the recognized onset of MS.

The Study: Dr. Rotstein and colleagues are using health billing claims data generated from hospital and physician visits. They have identified 2,780 people who had

mononucleosis followed by MS, which is a very large group compared to previous studies. They will analyze the average time from mononucleosis to onset of MS, and any variation in time caused by factors such as sex, age, socioeconomic status, and immigrant status. They also will compare people with mononucleosis who later developed MS to people who did not. They will use health claims to evaluate when health service use starts to rise after mononucleosis in the people who later developed MS. This will give evidence of the average time from mononucleosis to onset of the MS prodrome, and the duration of the prodrome.

What is the potential impact for people with MS? If we can map out the earliest onset of MS and its prodrome, it may be possible to develop strategies for stopping the development of MS or even preventing it.

Timothy Vartanian, MD, PhD
Weill Cornell Medical College
New York, New York
Award: Research Grant
Term: 4/1/2023-3/31/2026
Funding**:** $616,671
Title: Harboring the Initial Trigger of MS
Summary: A team at Weill Cornell Medical College are determining whether bacteria that have been associated with MS are related to changes in disease activity, for clues to developing a therapy that targets these bacteria and possibly prevent MS activity.

Background: Studies support the idea that MS is triggered when people with the right combination of genes and other risk factors are exposed to some trigger in the environment. However, no specific toxin or virus has been identified as the single trigger. Prof. Timothy Vartanian and colleagues have found evidence that the commonly occurring bacterium Clostridium perfringens is more common in the MS gut microbiome (the collection of microorganisms that live in the intestines) and that people with MS tend to have a higher abundance of this bacterium.

The Study: To provide clear evidence of this association they are now conducting a study over time and in more than one geography. The team is enrolling people with MS and control subjects without MS from Seattle and New York. The study includes control subjects from the same household as the person with MS, to differentiate the impact of genetic and environmental factors. This team also has developed a sophisticated method to separate the bacterium from fecal samples, an important step for culturing bacterial strains.

What is the potential impact for people with MS? Identifying a possible MS trigger could lead to therapeutic strategies to stop MS or to end it by prevention.

Funding Clinical Training to Improve Care

2023 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.

Fellow	Mentors	Institution
Jenna Brunn, MD	Tiffany Braley, MD, MS Andrew Romeo, MD	University of Michigan
Natasha Choudhury, MD	Roumen Balabanov, MD	Northwestern University
Luis Compres Brugal, MD	Derrick Robertson, MD Natalie Moreo, MD	University of South Florida
Kimberly DiMauro, DO	Jeffrey Cohen, MD Daniel Ontaneda, MD, PhD	Cleveland Clinic Foundation
Aisha Elfasi, MD	Scott Newsome, DO Bardia Nourbakhsh, MD	Johns Hopkins University
Alec Friedman, MD	Claire Riley, MD Rebecca Farber, MD	Columbia University
Jennings Gyedu, DO	Fred Lublin, MD	Icahn School of Medicine at Mount Sinai
Kayla Jacques, MD	Revere Kinkel, MD Jennifer Graves, MD, PhD	University of California San Diego
Carynn Koch, MD	Siddharma Pawate, MBBS Subramaniam Sriram, MBBS	Vanderbilt University Medical Center
Molly Moehlman	Teri Schreiner, MD, MPH Robert Gross, MD	University of Colorado Denver
Zachery Rohm, MD	Siddharma Pawate, MBBS Subramaniam Sriram, MBBS	Vanderbilt University Medical Center
Carol Swetlik, MD	Jeffrey Cohen, MD Daniel Ontaneda, MD, PhD	Cleveland Clinic Foundation
Rachel Zolno, MD	Tanuja Chitnis, MD Mark Gorman, MD	Massachusetts General Hospital

2023 Institutional Clinician Training Awards

These awards go to mentors and institutions to provide training for board-certified/eligible neurologists and physiatrists in MS care.

Mentors	Institution
Tiffany Braley, MD	University of Michigan Multiple Sclerosis Fellowship Program

NOTE: This document is not an official record and any errors do not reflect official changes to research award agreements. Some grants listed do not have final signed agreements.