BREAKTHROUGH MS
NEW RESEARCH
Fall 2018

Society Commits $12 Million for 40 New MS Research Projects

The National Multiple Sclerosis Society has just committed more than $12 million to support 40 new multi-year MS research projects.

This financial commitment is the latest in the Society's relentless research effort, investing a projected $35.8 million in 2018 alone to support new and ongoing studies around the world.

These new research projects strengthen the Society's comprehensive approach addressing critical research and scientific workforce priorities.

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

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

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

The 40 new projects seek answers to these questions. For example, New York University researchers are conducting a small clinical trial of **transcranial direct current stimulation** to assess its effectiveness for treating MS-related fatigue (p. 2). Researchers at the University of Southern California are identifying a reliable MRI marker that could be used to screen potential **therapies for progressive forms** of MS (p. 5). Researchers are investigating how eyesight is restored by **natural repair and rewiring processes** after optic neuritis in MS, for clues to rehabilitation strategies for people with MS with vision problems who do not show sufficient spontaneous recovery (p. 12).

INSIDE:

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

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

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Leigh Charvet, PhD
New York University Langone Medical Center
New York, New York
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $532,862
Title: A randomized controlled trial of remotely-supervised transcranial direct current stimulation (RS-tDCS) for the treatment of fatigue in multiple sclerosis
Summary: Researchers are conducting a small clinical trial of transcranial direct current stimulation to assess its effectiveness for treating MS-related fatigue.

This study may help to validate benefits of a novel, non-pharmaceutical treatment for improving MS fatigue

Background: Fatigue is common and one of the most difficult-to-treat symptoms experienced by people with MS. Transcranial direct current stimulation (tDCS) is a type of noninvasive brain stimulation that passes a mild electrical current through electrodes placed on the scalp. So far, this emerging therapy is well tolerated and it has shown preliminary benefit. Dr. Charvet and team are testing tDCS in an at-home setting.

The Study: Dr. Charvet and team are recruiting people with MS and fatigue to complete 30 treatment sessions across 6 weeks (five days per week), from home, of either active stimulation tDCS or a sham (placebo) tDCS. At the study's end, if someone has been assigned to the sham condition, they will be offered 10 active sessions. The team will measure how fatigue changes with tDCS treatment by measuring fatigue and associated symptoms for the length of the study. They will compare changes in fatigue between groups to determine benefits.

What's Next: This study may help to validate benefits of a novel, non-pharmaceutical treatment for improving MS fatigue.

Silvana Costa, PhD
Kessler Foundation Research Center
West Orange, New Jersey
Award: Research Grant
Term: 10/1/18-9/30/22 **Funding:** $476,609
Title: Keep an eye on the Symbol Digit Modalities Test
Summary: Investigators are analyzing aspects of a cognitive test commonly used in MS, to develop rehabilitation strategies.

Background: A commonly used 5-minute test to screen for cognitive issues, which can be common in people who have MS, is called the Symbol Digit Modalities Test (SDMT). It involves providing the person with a key or legend that enables them to substitute a geometric figure with a number. There are several functions that feed into the amount of time it takes an individual to do the test, but these have not been fully determined.

The Study: Dr. Costa and a team are conducting a four-year study to define precisely what contributes to SDMT performance. They are testing the idea that vision (the ability to see the stimulus), motor function (speech/eye movements and the ability to call out numbers), and executive thinking/thinking speed all play independent roles in contributing to test scores. The team will use sophisticated tools to test a group of people with and without MS.

What's Next: Results should provide insights that would allow more comprehensive and specific rehabilitation strategies for people with MS.

Deborah Backus, PT, PhD
Shepherd Center
Atlanta, Georgia
Award: Strategic Initiative
Term: TBD **Funding:** $75,000 (Pending)
Title: Comparative Effectiveness of an Exercise Intervention Delivered via Tele-rehabilitation and Conventional Mode of Delivery

Summary: The Society is supporting an extension of a clinical trial, funded by PCORI, to compare effectiveness of an exercise program done at home or in person in MS.

Background: Exercise can play a role in improving MS symptoms, function and quality of life, but it is not clear how to best get people engaged. Since traveling to a gym can be an impediment, effective at-home programs would broaden the availability of this approach to enhancing wellness.

The Study: Deborah Backus and co-lead, Robert Motl, PhD (University of Alabama at Birmingham) will lead this clinical trial that examines the comparative effectiveness of an evidence-based exercise training program delivered via telerehabilitation (video conferencing) against the same program delivered on-site at a rehab facility for improving walking, mobility, symptoms, participation and quality of life in persons with MS with walking impairment. The four-month study will involve 500 participants.

What's Next: If an exercise program completed at home is as effective as the same program at an exercise facility, more people will be able to take advantage of this important activity.

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

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

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Anne-Louise Ponsonby, PhD
The Australian National University
Canberra, Australia
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $555,546
Title: Identifying epigenetic factors involved in MS onset: utilizing population-based studies with genetic and environmental measures.
Summary: Researchers at the Australian National University are studying a link between the environment and how genes are turned on and off to trigger the onset of MS.

Background: The cause of MS is complex and not fully understood, but is thought to involve the interaction between an individual's genes and environmental factors, such as exposure to sunlight, vitamin D or infections. This research will take advantage of a large population study (the Australian-based Ausimmune Study) that was established to track MS triggering factors.

The Study: Genes can be switched on or off, partly depending on whether the gene has a type of modification called "methylation." Methylation is a reversible change to the DNA that is influenced by environmental factors. Dr. Ponsonby and her team are using banked blood samples from the multi-center Ausimmune study to investigate methylation as a possible link between genetic and environmental factors.

They are examining the methylation status of many genes across the genome in people with the very first stages of an immune attack that may eventually be diagnosed as MS, and comparing it to people without neurologic disease. They hope to identify harmful methylation profiles that would trigger early MS. Importantly, this study's assets enable gene methylation profiles to be considered in the context of the underlying, stable genetic architecture.

What's Next: This study may uncover the early triggering events that lead to MS, providing new information on the underlying molecular mechanisms. It may lead the way for the development of therapies designed to switch genes on and off to turn off the early process of MS to prevent, stop or slow the disease.

Pathology: What is the cause of MS?

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

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Fast Forward

The Society launched Fast Forward to fill a critical gap in the development of new therapies and diagnostic tools for MS.

Read more

$20.3 Million

406 proposals reviewed

31 company projects and

12 academic projects funded

Christina Azevedo, MD, MPH
University of Southern California
Los Angeles, California
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $465,936
Title: Disentangling MS-Specific Brain Atrophy from Normal Aging
Summary: Researchers are identifying a reliable MRI marker that could be used to screen potential therapies for progressive forms of MS.

Background: In most cases, MS progression occurs over a long period of time. One of the reasons that there are few treatment options for progressive forms of MS is because there is no efficient way to detect slowing or stopping of progression in short-term trials.

The Study: This project uses brain atrophy (shrinkage) measurements from MRIs from over 500 people with MS and over 1300 adults without MS. Brain atrophy is part of normal aging, but it occurs faster in MS. Dr. Azevedo's team is developing a way to "subtract out" the brain atrophy that can be considered a normal part of aging, and focuses on the additional atrophy that occurs in MS. This project measures the MS atrophy in every brain region across adulthood (ages 22-89) using sophisticated statistical models to identify the regions that are most highly affected by MS. The most highly affected regions at each age will be further tested as possible MRI markers that could be used to screen new therapies in future studies.

What's Next: Success could provide an important tool for quickly testing potential therapies that slow or stop MS progression.

Bogoljub Ciric, PhD
Thomas Jefferson University
Philadelphia, Pennsylvania
Award: Research Grant
Term: 10/1/18-9/30/22 **Funding:** $584,056
Title: The role of CSF-1R and its ligands, CSF-1 and IL-34, in CNS autoimmunity.
Summary: Researchers are investigating regulators of specific immune cells involved in nervous system tissue damage in MS.

Background: In MS, destructive immune cells collectively known as myeloid cells infiltrate the brain and spinal cord and it is believed that these cells are responsible for the damage to tissues that drives disease progression. It's not completely understood what controls these cells and accumulation in the brain. Dr. Ciric and team are investigating myeloid cell regulators in MS.

The Study: Messenger factors, colony-stimulating factor 1 (CSF-1), interleukin 34 (IL-34), and their cellular receptor or docking site (CSF-1R), are known to play a role in regulating the survival of myeloid cells, and they haven't been tested for their role in MS. Dr. Ciric has preliminary evidence that blocking CSF-1 and CSF-1R in a mouse model of MS can suppress disease symptoms. The goal of this project is to investigate CSF-1R signaling in a mouse model of MS and to determine whether antibodies that block their signaling have potential as therapies to stop MS progression.

What's Next: Since antibodies that block CSF-1R and CSF-1 are already being tested in clinical trials for other diseases, these results may be quickly translated for progressive MS.

Michael Matise, PhD
Rutgers, The State University of New Jersey
Piscataway, New Jersey
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $523,634
Title: Role of Shh-responsive astrocytes in blood-brain barrier integrity
Summary: Researchers at Rutgers University are exploring the role of a molecule in maintaining and repairing the blood-brain barrier, which malfunctions in MS.

Background: The brain is normally protected from harmful cells and substances that are present in the blood thanks to a tight network of cells called the "blood-brain barrier" or "BBB". In MS, this barrier does not work properly early on in the disease course, and harmful immune cells and molecules can enter the brain and begin the processes that lead to MS. Thus, understanding how the BBB is maintained and repaired could be very important for preventing or treating MS.

The Study: A molecule called Hedgehog is involved in cells that make up the BBB and plays a critical role in maintaining BBB integrity. Hedgehog also plays a role in repair of the BBB in lesions in mice with MS-like disease. In their current studies, Dr. Matise and his team are turning off Hedgehog in mice and looking at the impact on BBB integrity and repair. The team is also testing if turning off Hedgehog makes mice more likely to develop MS-like disease (EAE).

What's Next: This work could eventually lead to new therapies that maintain or increase Hedgehog to stop MS.

Mohamed Oukka, PhD
Seattle Children's Hospital
Seattle, Washington
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $724,816
Title: Effects of Fingolimod on T cells
Summary: Researchers are exploring immune regulators to refine attempts to stop MS disease activity.

Background: Immune cells called regulatory T cells, or "Tregs," are capable of turning off immune attacks, and their numbers appear to be reduced in people with MS. The underlying mechanisms that govern their function are not fully known. One of the disease-modifying therapies for MS, called fingolimod (Gilenya), is thought to alter Treg function in a positive way, but it is not clear exactly how it is usually of benefit in treating relapsing MS, and why in rare cases it worsens disease activity.

The Study: Dr. Oukka's team is conducting a series of studies to explore Treg function. His team has engineered lab mice to explore further how Tregs work by deleting a particular docking site (S1P receptor) on these cells. This docking site is normally acted upon by fingolimod. The team is analyzing Treg function in these mice, and also studying Tregs from people with MS who are and who are not treated with fingolimod to deepen knowledge of Treg function, their impacts on immune activity, and also how fingolimod works.

What's Next: Understanding more about how Tregs function or malfunction could lead to the development of more specialized and safer therapies that stop MS in its tracks.

Stefano Pluchino, MD, PhD
University of Cambridge
Boston, Massachusetts
Award: Research Grant
Term: 10/1/18-9/30/20 **Funding:** $289,219
Title: Characterization and manipulation of the metabolic pathways driving neuroinflammation
Summary: Researchers are studying a molecule called succinate made by these cells, and its role in nervous system damage in progressive MS.

Background: The immune system plays a prominent and harmful role in causing the relapsing-remitting form of MS. Much less understood is the role of the immune system in progressive MS.

The Study: Dr. Pluchino suggests that a type of immune cell called mononuclear phagocytes (MPs) plays a critical role in progressive MS. These cells not only cause harmful inflammation in the brain but also produce a harmful small molecule, called succinate, while they produce and use energy. In a mouse model of MS, Dr. Pluchino and his team are studying MPs and are determining which population produces succinate. They will then delete the harmful type of cells from mice and examine whether progressive disease is prevented. The team is also exploring the intricate cell processes in MPs derived from induced pluripotent stem cells (iPSCs – which are reprogrammed from adult skin or other cells).

What's Next: Eliminating succinate or the cells that make it could be a novel approach to slowing or stopping MS progression.

20 New High-Risk Pilot Projects Take Aim at MS

One way the Society propels MS research is by funding high-risk, high-potential pilot projects to investigate untested ideas. These one-year grants allow researchers to quickly gather data to determine if their ideas are worth pursuing.

STOPPING MS

Aditi Das, PhD (Univ. of Illinois at Urbana-Champaign, IL) is exploring a strategy for stopping the immune attack using a naturally occuring molecule similar to cannabis.

Mario Galgani, PhD (Consiglio Nazionale delle Ricerche - CNR, Napoli, Italy) is studying a previously unexplored regulatory t cell population and its involvement in MS.

Stefan Gold, PhD (Charité - Universitätsmedizin Berlin, Berlin, Germany) is seeking to understand basic MS mechanisms and how they might differ between men and women.

Daniel Harrison, MD (University of Maryland, Baltimore, Baltimore, MD) is developing automated methods for evaluating tissue damage in people with MS.

Predicting Treatment Response

Differences in genes may help explain why some people get very low white blood cell counts while taking the MS treatment dimethyl fumarate (making them prone to infections), while others do not. **Helen Tremlett, PhD** (University of British Columbia, Vancouver, British Columbia, Canada) is aiming to identify these important genetic markers using a simple saliva (spit) test. They are studying this possibility in 225 people who have taken dimethyl fumarate for MS. These markers may help to predict who is likely to get this adverse reaction even before they start treatment.

Andres Herrada, PhD (Universidad Autónoma de Chile, Temuco, Chile) is examining how immune cells enter the brain and spinal cord during MS-like disease in mice.

Lior Mayo, PhD (Tel Aviv University, Tel Aviv, Israel) is studying immunological mechanisms that contribute to MS progression and their therapeutic potential.

Daniel Pelletier, MD (University of Southern California, Los Angeles, CA) is developing an optimal method to image cortical lesions in MS using strong MRI technology.

Hao Zhu, PhD (University of Kansas Medical Center, Kansas City, KS) is studying high dose biotin therapy and pioglitazone in models of progressive MS.

RESTORING WHAT'S BEEN LOST

Dagmar Amtmann, PhD (University of Washington, Seattle, WA) is improving questionnaires about sexual function so that they are relevant for people with MS.

Roberta Brambilla, PhD (University of Miami, Miami, FL) is testing molecules that may be candidates for promoting neuroprotection and myelin repair in MS.

Frank Dinenno, PhD (Colorado State University, Fort Collins, CO) is seeking to determine whether reduced muscle blood flow is a potential cause of lower exercise capacity in MS.

Ekaterina Dobryakova, PhD (Kessler Foundation Research Center, West Orange, NJ) is examining impediments that might prevent people with MS from adapting socially.

Reducing Emotional Distress in People with MS and Their Carepartners

Emotional distress is a common symptom experienced by individuals with MS, as well as their carepartners. One specific type of cognitive-behavioral approach focuses on improving skills to improve emotion regulation, reduce depression and anxiety, and improve relationships with others. **Abbey Hughes, PhD** (Johns Hopkins University, Baltimore, MD) is testing the efficacy of a unique group-based intervention for improving emotion regulation in people with MS and their carepartners. The intervention consists of 12 weekly therapy and skills training sessions to improve emotion regulation, interpersonal effectiveness, and distress tolerance. These data will provide a foundation for conducting a larger definitive clinical trial.

Simon Gandevia, MD, PhD (Neuroscience Research Australia, Sydney, Australia) is investigating the effectiveness of a strategy to improve bowel function in MS.

Mark Petersen, MD (University of California, San Francisco, San Francisco, CA) is determining if fibrinogen's inhibitory effects on myelin repair can be overcome.

Yannick Poitelon, PhD (Albany Medical College, Albany, NY) is investigating a possible reason why new myelin fails to wrap around nerve fibers in MS.

David Schulz, PhD (University of Missouri-Columbia, Columbia, MO) is understanding the underlying changes in the bladder circuitry that can cause bladder symptoms in MS.

Susan Smedema, PhD (University of Wisconsin-Madison, Madison, WI) is determining if specific character strengths protect people with MS from reductions in quality of life.

Christine Stadelmann, MD (University Medical Center Goettingen, Germany) is determining how cell communication may be important for efficient myelin repair.

Mari Shinohara, PhD
Duke University Medical Center
Charlotte, North Carolina
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $638,583
Title: Study on innate immune inflammation that enhances EAE
Summary: Duke University researchers are exploring how immune system activity leads to nerve degeneration, for insights into ways to prevent nerve loss and MS progression.

Background: MS is known to involve immune attacks against brain and spinal cord tissues. Less understood is the relationship between initial immune activity and progressive neurodegeneration, and how the innate immune system (which is the first line of defense against foreign invaders such as viruses) participates in progressive MS. Dr. Shinohara has developed a mouse model of MS that undergoes progressive nerve degeneration after immune attacks, similar in some respects to progressive MS in people.

The Study: Using this model, Dr. Shinohara's team is deciphering the sensors and signaling that the innate immune system uses to launch chronic inflammation and nerve degeneration in the brain and spinal cord. They are deleting or enhancing specific mouse genes and analyzing the results on innate immune activity and nerve loss. The team is also using a Nobel Prize-awarded technology, super-resolution microscopy. This will help them to deeply analyze steps in the nerve-degeneration process for the first time.

What's Next: This study will help identify key steps involved in nerve loss in MS.

Scott Zamvil, MD, PhD
University of California, San Francisco
San Francisco, California
Award: Research Grant
Term: 10/1/18-9/30/20 **Funding:** $312,771
Title: Single cell transcriptomic profiling and clonal analysis of CD8+ T cells in MS
Summary: Researchers are working to identify unique genes that are turned on in CD8+ T cells from people with MS compared to people without the disease.

Background: In MS, the immune system attacks the brain and spinal cord, leading to tissue damage and neurological symptoms in people with the disease. One type of immune cell, called the CD8+ T cell, has been found in MS lesions, or areas of disease activity or damage. However, their complete role in MS is not clear.

The Study: Prof. Zamvil and his team are obtaining samples of blood and cerebrospinal fluid from people with MS and people with other neurological disorders. Using sophisticated technology, they are working to identify genes that are turned on in individual CD8+ T cells present in these samples from people with MS, in contrast to those from people without MS. They are also looking at CD8+ T cells that are directed against myelin, a component of the brain and spinal cord that is targeted by immune cells in MS. This work will allow identification of unique genes that are turned on in CD8+ T cells in MS but not in other neurological disorders.

What's Next: This work should provide insights into what's going wrong in MS, and may offer new clues for novel therapies.

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

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

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Stephen Crocker, PhD
University of Connecticut Health Center
Farmington, Connecticut
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $608,036
Title: Cellular Senescence in Neural Progenitor Cells Limits CNS Remyelination
Summary: Investigators are exploring the reasons why repair of nerve-insulating myelin fails in MS, and seeking ways to reverse the problem.

Background: MS attacks the brain and spinal cord, damaging myelin, the protective sheath that encases nerve fibers. The nervous system can normally repair myelin but at some point this fails in MS. Dr. Crocker has preliminary evidence that this failure may be due to premature aging of the cells, also called senescence.

The Study: To understand why remyelination in MS fails, Dr. Crocker's team has collected blood from people with different types of MS, and also from their spouses or siblings. Using a technology called induced pluripotent stem cells (or iPS cells), they transformed the blood cells into stem cells, and then into brain stem cells called neural progenitor cells (NPCs), which are found in areas of the brain damaged by MS. They are using these cells to study cellular senescence in MS, looking for any differences among different types of MS, exploring the types of signaling chemicals they give off, and whether reversing the process of senescence can enable NPCs from people with MS to promote myelin-making oligodendrocytes to mature and repair myelin.

What's Next: This novel study should provide answers about why myelin repair can fail in MS, and identify targets for the development of therapies that can reverse senescence and restore myelin repair.

You Can Advance MS Research

You can share your research ideas, give DNA for genetic studies, register to indicate your future interest, and/or participate in clinical trials and research studies.

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

Tanja Kuhlmann, MD
University Hospital Münster
Münster, Germany
Award: Research Grant
Term: 10/1/18-9/30/20 **Funding:** $337,352
Title: Effect of age on human oligodendroglial differentiation and (re-)myelination
Summary: Researchers are determining the factors that may limit the repair of myelin damaged during the course of MS.

Background: MS attacks the brain and spinal cord, damaging myelin, the protective sheath that encases nerve fibers. The nervous system can normally repair myelin with reserve cells that reside in the brain, called oligodendrocyte progenitor cells, but at some point the process often fails in MS. Dr. Kuhlmann is following up studies suggesting that myelin repair may be influenced by age or by inhibiting conditions in MS brain lesions.

The Study: Dr. Kuhlman and team are conducting a series of studies to tease out which factors are largely responsible for myelin repair failure. They are using newer technology to turn skin cells into stem cells that can then turn into OPCs and mature oligodendrocytes. They are generating oligodendrocytes from skin cells of people with and without MS, and transplanting the cells in lesions of young and old mice to determine whether aging influences repair.

What's Next: The results of this study will help determine what are the constraining factors for continued myelin repair in MS, and will suggest the development of treatment strategies that overcome these constraints.

Netta Levin, MD, PhD
Medical Research Fund of Hadassah Medical Organization
Jerusalem, Israel
Award: Research Grant
Term: 10/1/18-9/30/20 **Funding:** $147,360
Title: Temporal reorganization to overcome monocular demyelination – unique plasticity mechanism in MS – A renewal application
Summary: Researchers are investigating how eyesight is restored by natural repair and rewiring processes after optic neuritis in MS.

Background: When nervous system damage occurs in MS, the recovery of function depends whether the body's natural tissue repair processes were successful and also whether the brain changed its "wiring" to compensate for unrepaired damage to return function. This compensation process is called "cortical adaptation," and it may be especially important for restoration of visual function after damage to the optic nerve during optic neuritis, which is often the first sign of MS.

The Study: Prof. Levin and her team are investigating how cortical adaptation works to restore binocular vision (vision in both eyes). They are examining people with early MS or pre-diagnosed MS who have optic neuritis, compared to people who don't have MS and have normal vision. The team is performing various types of brain imaging and behavioral studies to look at the different ways that the parts of the brain involved in vision change to compensate for damage and improve vision.

What's Next: These studies may suggest rehabilitation strategies for people with MS and vision problems.

Caterina Mainero, MD, PhD
Massachusetts General Hospital
Boston, Massachusetts
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $916,045
Title: Multimodal imaging of neuro-inflammation and its contribution to cortical demyelination and regeneration in MS
Summary: Researchers are developing methods to monitor cells called microglia that likely play a role in myelin repair in MS.

Background: In MS, an important component of the brain and spinal cord called myelin is attacked and destroyed. Myelin is a fatty substance that insulates and supports nerve fibers. Nerve fibers that have lost their myelin do not function normally, leading to symptoms in people with the disease. The body can naturally repair myelin, although only partially. Understanding natural myelin repair processes may help promote repair.

The Study: "Microglia" are a type of immune cell in the brain that may play a role in myelin repair, in part by cleaning up debris. However, observing microglia during myelin repair in people is challenging. Dr. Mainero and her team are developing advanced imaging techniques that combine position emission tomography (PET) with an MRI scanner that is much stronger than those typically used in hospitals. With this scanner, they are studying 30 people with a new diagnosis of MS for one year to trace natural myelin repair and determine whether microglia participate.

What's Next: These studies may form the basis for designing studies to test novel therapies that promote repair.

Teresa Wood, PhD
Rutgers, The State University of New Jersey
Piscataway, New Jersey
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $788,614
Title: Cooperative Functions of mTOR and TrkB/Erk Signaling in Remyelination
Summary: Researchers are studying two molecular pathways that may work together to maintain and repair myelin in mice.

Background: In MS, the immune system attacks the brain and spinal cord, targeting myelin, a fatty insulator that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function normally and are vulnerable to destruction, producing symptoms in people with MS. Myelin is made by cells called oligodendrocytes. The brain has immature cells that can turn into oligo-dendrocytes to restore myelin after damage, but this natural repair is interrupted in MS.

The Study: Prof. Wood, with her co-investigator, Prof. Cheryl Dreyfus (Robert Wood Johnson Medical School, Rutgers), and their teams are exploring mechanisms responsible for myelin synthesis in oligodendrocytes in mice. They are investigating two signaling pathways, one called "mTOR" and one called "TrkB/ERK," that may work together to play a role in oligodendrocyte maturation, myelin maintenance, and repair. They are deleting components of one or both pathways and observing how repair is affected.

What's Next: Targeting components to enhance these pathways with new or existing therapies could promote myelin repair in MS.

Progression: How do we stop MS progression?

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

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David Hafler, MD
Yale University School of Medicine
New Haven, Connecticut
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $825,000
Title: Longitudinal, single-cell assessment to define the mechanism of B cell depletion therapy in Multiple Sclerosis
Summary: Yale University researchers are investigating the role of immune B cells in MS and what happens to the immune system in people with MS who are taking B cell-depleting therapies.

Background: Therapies that target and kill immune B cells, such as Ocrevus, have demonstrated effectiveness in treating MS, but how they alleviate disease is not understood, since the role of B cells in MS activity has not been fully investigated. Dr. Hafler's team is focusing on how immune activity is altered by B cell depletion therapy as a way to understand the role of B cells in MS.

The Study: Prof. Hafler's team is applying cutting-edge technology to evaluate the immune systems of people with MS before and after B-cell depleting therapy, studying the immune system at the level of individual cells. One tool tells them about what cell types are present and what their function may be. The team will study individuals' immune system shifts over time, and also trace what happens to immune cells that target myelin, which are thought to be critical mediators of disease.

What's Next: Understanding the mechanisms underlying MS will aid in the development of new therapies that have more defined targets. This study should also provide new insights into what goes wrong with the immune system in MS.

Robyn Klein, MD, PhD
Washington University School of Medicine
Saint Louis, Missouri
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $736,586
Title: Interferon lambda as a biomarker and target for Diseases Progression in MS
Summary: Investigating the role of interferon lambda in progressive forms of MS.

Background: Progressive forms of MS, which may occur at the onset of MS or secondary to relapsing-remitting MS, are characterized by degeneration of nervous tissue. Effective treatments for all progressive forms of MS are urgently needed.

The Study: Prof. Klein and her team are investigating a molecule called interferon lambda, which may play an important role in progressive forms of MS. In mice, her team is examining the role of interferon lambda in maintaining inflammation and causing tissue damage within the brain and spinal cord. They are testing the idea that interferon lambda signaling is important for continued activation of the immune system and promotion of nerve fiber injury. They are also investigating whether interferon lambda levels within the brain and spinal cord of people with progressive forms of MS may be a marker of disease progression and/or a target for therapies to promote recovery.

What's Next: Successful completion of these studies may lead to the development of strategies for blocking interferon lambda as a treatment for progressive forms of MS.

Researchers are testing whether oral Miltefosine can turn off immune attacks in MS-like disease in mice; Miltefosine is currently used to treat a parasitic disease

Vipin Kumar, PhD
University of California San Diego
San Diego, California
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $625,486
Title: Targeting lysophospholipid-reactive type II NKT cells for potential oral therapeutic in multiple sclerosis

Summary: Researchers at the University of California, San Diego are investigating the usefulness of an oral therapy already in use for another purpose for its ability to reduce MS-like disease in a mouse model.

Background: In MS, immune cells including T cells set off attacks on the brain and spinal cord, causing symptoms in people with the disease. Normally T cells are regulated by other immune cells that can turn off these attacks. Finding a way to harness the ability to turn off immune attacks could lead to a way to turn off MS.

The Study: Prof. Kumar and his team are studying the ability of an oral therapy called Miltefosine to turn off immune attacks in MS-like disease in mice. Miltefosine is currently used to treat a parasitic disease. The team is conducting a series of tests to see if this therapy can block the activity of destructive T cells and thus reduce the severity of the MS-like disease in these mice. They are also identifying the cells and molecules that are involved in this process.

What's Next: This research represents a new approach to turning off MS disease activity, and if successful, next steps could include clinical studies to test whether Miltefosine can be used as a novel treatment for MS.

Yisong Wan, PhD
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
Award: Research Grant
Term: 10/1/18-9/30/21 **Funding:** $621,351
Title: Targeting T cell function to halt MS/EAE development
Summary: Researchers at the University of North Carolina at Chapel Hill are studying a factor that appears to be important in abnormal activation of immune cells that are harmful in MS.

Background: In MS, the immune system is abnormally activated and attacks components of the brain and spinal cord, causing tissue damage and a variety of symptoms in people with the disease. In particular, T cells, a type of immune cell, are abnormally activated and play a harmful role in MS.

The Study: Dr. Wan and his team are studying factors that are involved in abnormal T cell activation. They previously identified a factor called "VprBP" that is essential for growth and activation of T cells. Blocking VprBP in mice reduces an MS-like disease called EAE. The team is now exploring the details of how VprBP works during the development of EAE, and by implication, MS. They are also testing how VprBP works in human T cells, knowledge that will be important for designing future treatments for people with MS.

What's Next: This study should provide new insights into ways to stop the immune attack in MS.

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