Society Commits $24.4 Million for 64 New MS Research Projects

The National Multiple Sclerosis Society has just committed $24.4 million in multi-year funding for 64 new MS research projects.

This financial commitment is the latest in the Society’s relentless research effort, investing an expected $35 million in 2019 alone to support 340 new and ongoing studies around the world.

These strategic research investments strengthen the Society’s comprehensive approach to addressing research priorities that will accelerate breakthroughs and build pathways to cures for MS.

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 64 new projects seek answers to these questions. For example, a phase II clinical trial is ongoing at Tisch MS Research Center of New York to see if stem cells derived from individuals' own bone marrow can inhibit immune mechanisms and augment repair of nerve-insulating myelin in progressive MS (p. 3); a University of Edinburgh team is attempting to enhance energy production in nerve cells to protect them from damage in MS (p. 29); scientists in Milan, Italy are analyzing how gut bacteria influence immune cell activity in the brain (p. 16); and Beth Israel Deaconess Medical Center researchers are asking whether treating sleep apnea can reduce MS-related fatigue (p. 10).

INSIDE:
New Projects: Neuroprotection/Repair........2
New Projects: Symptoms, Rehab, Wellness. 8
New Pilot Research Awards ......................12
New Projects: Risk Factors .......................14
New Projects: Pathology ..........................20
New Projects: Progression.........................26
Clinical Care/Research Fellowships...........30
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.

* * *

Gregory Duncan, PhD
Oregon Health & Science University
Portland, Oregon
Award: Postdoctoral Fellowships
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $177,243
Title: Mechanisms of neuronal adaptation to chronic demyelination
Summary: An Oregon team is determining how nerve cells may adapt to prevent themselves from being damaged in MS models, for clues to reducing damage and disease progression in MS.

Background: Progressive disability in MS is caused by damage to nerve cells and nerve fibers in the brain and spinal cord. This damage appears to occur after destruction of myelin, a fatty substance that wraps around nerve fibers. The extent to which nerve cells and fibers can adapt to resist damage following myelin loss is unclear.

The Study: Dr. Duncan and his team are investigating adaptive mechanisms in the nervous system. Following myelin loss in mice, they are examining changes in gene expression that may be involved in survival and maintenance of nerve cell function. They are also testing whether these adaptations they identified are necessary for nerve cell preservation by specifically turning on or off genes that are important in this process.

What’s Next: Increasing the natural ability of nerve cells to adapt to damage and protect themselves from further injury may be a novel therapeutic strategy in MS.

Kirsten Evonuk, PhD
Cleveland Clinic Foundation
Cleveland, Ohio
Award: Postdoctoral Fellowships
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $188,067
Title: Selective deletion of AMPA-type glutamate receptors on oligodendrocytes is neuroprotective in autoimmune demyelination
Summary: Researchers are seeking to discover how dysfunction of the nerve signaling chemical glutamate may block myelin repair in mice, for clues to promoting myelin repair in MS.

Background: In MS, myelin, the fatty substance that surrounds and protects nerve fibers in the spinal cord and brain, is damaged, leading to symptoms in people with the disease. Glutamate, a chemical in the brain that is important for brain cell communication, is elevated in regions of the brain where MS lesions are located.

The Study: Dr. Evonuk and her team are investigating the toxic effects of too much

(continued, p. 4)
National MS Society Funds New Clinical Trial of Individuals’ Own Stem Cells to Treat Progressive MS

Saud Sadiq, MD
Tisch MS Research Center of New York
New York, New York
Award: Strategic Initiatives
Category: Restore
Term: 4/1/2019-3/30/2023 Funding: $1,000,000
Title: Phase 2, Randomized, Double Blind, Placebo Controlled Study of Intrathecal autologous MSC-NP Cells in Patients With MS
Summary: The Tisch MS Research Center of New York is conducting a phase II clinical trial to see whether stem cells derived from individuals’ own bone marrow can inhibit immune mechanisms and augment tissue repair in progressive MS.

Background: Adult stem cells are being tested worldwide in clinical trials in MS. The individual’s own mesenchymal stem cells are isolated from the bone marrow or blood stream and multiplied in the lab, and then re-introduced in greater numbers into their body. Alternatively, the cells are sometimes treated prior to transfer to potentially enhance their ability to suppress nervous system damaging immune responses and/or promote myelin repair. Results were published in February 2018 from a small, open label, phase I stem cell trial at the Tisch MS Research Center of New York. The trial used 20 individuals’ own mesenchymal stem cells to derive more specific stem cells called “neural progenitor cells.” The cells were expanded in the laboratory and then injected into the space around the spinal cord (intrathecal). No serious adverse events were reported from the study. The Tisch MSRCNY team has launched a phase II trial of this therapy in progressive MS.

The Study: The Phase II is a placebo-controlled, FDA-approved trial that will involve 50 people with progressive forms of MS. The investigators will use the stem cell preparation protocol similar to what was used for the phase I trial. The neural progenitor cells will be infused into the spinal fluid in multiple doses. The stem cells are thought to release growth factors that may promote tissue repair as well as immune messengers that may inhibit immune responses. The trial will test whether participants show positive changes in measures of disability.

What’s Next: This phase II trial is the next step toward understanding potential benefits and risks of mesenchymal stem cells for the treatment of progressive MS. If it is found to be safe and beneficial, it would likely lead to a larger confirmatory trial. “There is an urgent need for more effective treatments for MS, particularly for those with more progressive forms of the disease,” said Dr. Bruce Bebo, National MS Society Executive Vice President, Research. “We believe that the potential of all types of cell therapies must be explored, and we are pleased to be a part of this clinical trial.”
glutamate and whether excess glutamate interferes with myelin repair. They are using mice that lack glutamate docking sites (receptors that bind glutamate and transmit its effects) in the cells that make myelin. The mice have the MS-like disease EAE, and the researchers are asking if recovery from EAE and myelin repair are better in mice without glutamate receptors compared to normal mice.

What’s Next: This study will help determine whether decreasing glutamate in the cells that make myelin may increase myelin repair in MS.

Jeffrey Huang, PhD
Georgetown University
Washington DC
Award: Harry Weaver Neuroscience Scholarships
Category: Restore
Term: 7/1/2019-6/30/2024 Funding: $758,838
Title: Amino acid induced microglia/macrophage-OPC crosstalk in CNS remyelination
Summary: A team is exploring a molecule that appears to be very active when myelin damage occurs, for clues to promoting myelin repair.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve cells. Normal myelin repair is less efficient as MS progresses. Increased understanding of factors that inhibit the process can provide new strategies for MS.

The Study: Dr. Huang has generated preliminary results showing that a molecule that transports amino acids (the building blocks of proteins) is present at high levels in inflamed MS brain lesions in mice, and his team is testing whether this molecule interferes with myelin repair. They are examining whether mice that do not make this molecule show reduced inflammation and better myelin repair compared to normal mice. They are testing whether a drug that targets this molecule improves myelin repair.

What’s Next? This study may reveal a new target for improving myelin repair and thus improving function in people with MS.

New Fast Forward Investments

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

Cashel Neural Inc. scientists are conducting laboratory studies to advance a compound that may promote the development of cells that make nerve-insulating myelin, which is destroyed in MS. Funding from Fast Forward is enabling the important lab studies needed to optimize this compound and advance its development towards human clinical trials aimed at repairing myelin in MS.

Term: 18 months; Grant Amount: $401,335

Researchers at Brigham and Women’s Hospital are creating and evaluating chemical cousins of an anti-anxiety drug to develop a therapy that can slow MS disease activity and promote repair. With funding from Fast Forward, the team will design, synthesize and evaluate potential benefits of these compounds, producing an agent that may reduce MS progression.

Term: 24 months; Grant Amount: $318,170

Through Fast Forward, the Society provides critical advice, drives connections, and directs vital funding to biotech companies and other small commercial entities.

Learn more at www.fastforward.org
Leandro Marziali, PhD
State University of New York at Buffalo
Buffalo, New York
Award: Postdoctoral Fellowships
Category: Restore
Term: 7/1/2019-6/30/2021 Funding: $188,067
Title: p38MAPKγ signaling in myelin biology: a novel molecular target to promote myelination and remyelination
Summary: A team is studying a protein that may inhibit myelin repair in people with MS, for clues to promoting myelin repair and recovery.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function properly and are vulnerable to destruction. The cells that make myelin are called oligodendrocytes and have the potential to repair myelin in people with MS. Certain molecules present in the brain may block the ability of oligodendrocytes to restore myelin.

The Study: Dr. Marziali and his team are studying a molecule called p38γ, which may block myelin repair. Specifically, it may interfere with the ability of immature oligodendrocytes to mature into cells that can repair myelin. The team is using mice whose immature oligodendrocytes do not express p38γ to examine the role of this protein in myelin growth during development. They are also investigating other molecules that may regulate p38γ and conducting studies on the role of p38γ in myelin repair.

What’s Next: If these studies are successful, then p38γ may be a new molecular target for therapies that promote myelin repair in people with MS.

Booki Min, PhD
Cleveland Clinic Foundation
Cleveland, Ohio
Award: Research Grants
Category: Stop
Term: 4/1/2019-3/31/2022 Funding: $667,710
Title: The role of Foxp3+ regulatory T cells during glucocorticoid treatment of autoimmunity
Summary: Researchers are exploring how high-dose steroids used to treat MS attacks influence the activity of immune cells.

Background: The standard treatment for people with MS who develop acute relapses is high-dose steroids. While steroids reduce symptoms fairly well, long-term usage can cause adverse side effects. A key issue is that it is not specifically understood how steroids act on immune cells, especially T cells, which are involved in driving immune attacks in MS. The main goal of this research is to understand the role of T cells capable of turning off immune attacks, called regulatory CD4 T cells, during steroid-mediated control of inflammation.

The Study: In mice with the MS-like disease EAE, Dr. Min and team are systematically deleting regulatory CD4 T cells, both during the use of steroids and without the use of steroids. They are examining the impact of these manipulations on the inflammatory responses. Immune reactions and the genes that instruct them will be examined. They are utilizing a mouse model in which only regulatory T cells are not responding to steroid treatment. This will enable them to examine how steroids control regulatory T cells.

What’s Next: This research could lead to ways to improve the therapeutic potential of steroids while avoiding adverse side effects.
Pablo Paez, PhD  
The State University of New York at Buffalo  
Buffalo, New York  
Award: Research Grants  
Category: Restore  
Term: 4/1/2019-3/31/2022  
Funding: $492,314  
Title: Voltage-gated calcium channels in reactive astrocytes, a possible therapeutic target to reduce brain inflammation and promote remyelination in MS.  
Summary: Scientists are studying whether deleting tiny molecules that monitor calcium regulation in brain cells results can reduce inflammation and possibly promote repair.  
Background: Loss of myelin, the fatty substance that surrounds and protects nerve fibers, is a key feature in MS. Nerve fibers that have lost myelin do not work correctly, leading to symptoms and disability, and nerve fiber loss. Myelin repair is inefficient, and complete repair may be inhibited by cells that have reacted to the inflammatory state in the brain and spinal cord in MS.  
The Study: Dr. Paez’s team is studying cells, called astrocytes, which are the most abundant cells in the brain. During MS (and other neuroinflammatory diseases), astrocytes become “reactive” and play a role in preventing the normal repair of nerve-insulating myelin. The team is investigating the idea that molecules on these cells, called “voltage-gated calcium channels,” prolong their reactive state, preventing myelin repair. They are using mice that lack these channels to see if astrocyte reactivity is reduced and myelin repair improved.  
What’s Next: If this work succeeds, drugs that modulate calcium channels already approved for use in humans could be tested in people with MS.

Brian Popko, PhD  
University of Chicago  
Chicago, Illinois  
Award: Research Grants  
Category: Restore  
Term: 4/1/2019-3/31/2022  
Funding: $718,842  
Title: ZFP24 Control of the myelination program of oligodendrocytes  
Summary: Scientists are exploring molecules that may play a key role in the development of myelin-making cells, for clues to promoting repair in MS.  
Background: Myelin, a protective and insulating casing that wraps around nerve fibers, and the cells that make myelin in the brain and spinal cord (oligodendrocytes) are targets of immune attacks in MS. Prof. Popko’s team has identified a protein, ZFP24, that plays a critical role in myelin development and oligodendrocyte formation. In mice, oligodendrocytes that cannot produce ZFP24 are stuck in a premyelin-forming state, similar to cells in people with MS that fail to repair myelin. ZFP24 activity is regulated by one or more enzymes that alter its function. This research seeks to identify and characterize these enzymes, which are potential therapeutic targets for enhancing remyelination.  
The Study: ZFP24 controls oligodendrocyte maturation by activating genes that can instruct oligodendrocyte maturation and myelin formation. When ZFP24 is modified in certain ways, it can no longer activate genes. Prof. Popko’s team is analyzing mouse models and tissue isolated in the laboratory to explore the potential of manipulating ZFP24 in ways that may enhance myelin repair.  
What’s Next: Ultimately, information gained may serve as the foundation for developing therapies to enhance remyelination in MS.
Mariapaola Sidoli, PhD  
Stanford University  
Stanford, California  
**Award:** Postdoctoral Fellowships  
**Category:** Restore  
**Term:** 7/1/2019-6/30/2022  
**Funding:** $188,067  
**Title:** A new approach to analyze cAMP in oligodendrocyte development and myelination  
**Summary:** Stanford University researchers are analyzing a specific signal in the brain that stimulates the formation of myelin, for clues to harnessing the signal as a therapeutic target to promote myelin repair in MS.

**Background:** In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers that have lost their myelin do not function normally, and are vulnerable to destruction. Natural myelin repair in MS is inefficient, and therapies are needed to increase myelin repair.

**The Study:** Dr. Sidoli and her team are studying a molecule called “cAMP” that is important in promoting myelin development. The lab is able to visualize cAMP at a microscopic level, taking advantage of the transparency of zebrafish. The team can monitor myelin production when factors are added that increase or decrease cAMP. They are also investigating what genes cAMP turns on in the cells that make myelin.

**What’s Next:** Results from this project may identify new targets for drugs that increase myelin repair in people with MS.

Alessia Tassoni, PhD  
University of California, Los Angeles  
Los Angeles, California  
**Award:** Postdoctoral Fellowships  
**Category:** Restore  
**Term:** 7/1/2019-6/30/2021  
**Funding:** $127,386  
**Title:** Disability specific drug discovery for MS: Focus on Vision  
**Summary:** Novel technology is allowing a team from UCLA to analyze changes in the optic nerve of MS models, for clues to developing neuroprotective strategies in people with MS.

**Background:** Vision problems are one of the most common initial symptoms that lead to an eventual diagnosis of MS. Although most current disease-modifying therapies for MS reduce inflammation, they do not prevent tissue damage. Therapies for MS that protect the brain are needed to prevent disability including permanent vision loss.

**The Study:** Dr. Tassoni and her team are working to develop specific treatments to prevent or repair visual deficits in MS. They are taking advantage of recently developed technology that enables the detection of gene activity in specific cell types in the optic nerve, rather than in whole optic nerve tissue. This approach will allow the team to identify which molecules from which cells in the optic nerve drive the progression of visual disability in MS. They are testing this approach in mice with an MS-like disease called EAE, using healthy mice as a comparison.

**What’s Next:** If this study identifies molecular changes in MS-like disease, it could lead to better understanding of nerve degeneration in MS and uncover new targets for therapies that could protect or repair visual function in MS.
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.

* * *

Korhan Buyukturkoglu, PhD
Columbia University
New York, New York

Award: Postdoctoral Fellowships
Category: Restore
Term: 7/1/2019-6/30/2022 Funding: $194,456

Title: Building a Pattern Classifier to Distinguish Cognitive Phenotypes in MS

Summary: Columbia University researchers are bringing several different MRI methods together to see the ‘big picture’ of cognitive impairment in MS, to better evaluate and overcome this problem.

Background: Cognitive problems, such as slowed information processing, are common among people with MS. Imaging biomarkers that can diagnose or predict cognitive impairment in MS have not been identified, hampering treatment of this problem. Cognitive impairment is a consequence of multiple biological processes acting together and each of these processes can be pictured by different MRI methods.

The Study: Dr. Buyukturkoglu and his group are analyzing different types of MRI brain scans collected from 185 people with MS and 35 people who don’t have MS. They are using computer-based methods called machine learning and pattern classification to combine and analyze large amounts of data present on multiple images. This analysis is expected to provide a comprehensive picture of what cognitive impairment in MS looks like on brain images.

What’s Next: Identifying imaging biomarkers of cognitive impairment will provide better ways of understanding and predicting this symptom and inform the development of rehabilitation strategies.
Kathryn Fitzgerald, ScD  
Johns Hopkins University  
Baltimore, Maryland  
**Award:** Career Transition/Research Grants  
**Category:** Restore  
**Term:** 7/1/2019-6/30/2022  
**Funding:** $412,500  
**Title:** The Melanopsin Pathway, Changes to Brain Structure and Depression in People with MS  
**Summary:** Because depression is common in MS, researchers are looking for early signs of brain and eye changes that may signal depression, for clues to identifying and preventing this symptom.

**Background:** Depression and other mood disorders are common in people with MS, and being depressed has been linked to increased disability, lower quality of life and more severe fatigue and pain symptoms. MS-related depression is not well understood, and there are few known factors that could increase or decrease the chance of developing depression.

**The Study:** First, the team is using brain MRIs to look for predictive markers of future increase or decrease in depressive symptoms. The team is using a combination of traditional statistical models and more novel methods that employ networks (how the brain’s regions might work together). Dr. Fitzgerald’s team will also test whether changes to a specific subpopulation of cells in the eye are involved with influencing mood. The cells help relay light information to the brain, and they may malfunction in people with MS. The team will use activity monitors to measure 24-hour biological rhythms of people with MS and see if the data relate to depression.

**What’s Next:** Being able to identify risk factors for depression in people with MS will help identify individuals earlier and optimize treatment.

Anna Kratz, PhD  
University of Michigan  
Ann Arbor, Michigan  
**Award:** Mentor-Based Postdoctoral Fellowships  
**Category:** Restore  
**Term:** 7/1/2019-6/30/2024  
**Funding:** $421,202  
**Title:** Training to Advance Rehabilitation Research in Multiple Sclerosis  
**Summary:** Researchers at the University of Michigan are training promising professionals to advance MS rehabilitation research.

**Background:** Chronic pain, fatigue, and cognitive problems are some of the most common and disabling symptoms experienced by people who have MS. Innovative and interdisciplinary research that increases understanding of the mechanisms that underlie these symptoms and the best approaches to treating them is important to helping people with MS to live their best lives.

**The Study:** The goal of this project is to train research fellows in rehabilitation research. An interdisciplinary team will be led by Anna Kratz, PhD, a clinical psychologist. The program will leverage hands-on research in an array of studies and clinical trials that are led by Dr. Kratz and collaborators. Studies include a trial of a web-based symptom self-management program, and data from a multi-site clinical trial of medication and/or behavioral therapy for fatigue in MS. These studies provide a rich learning environment that will enable fellows to gain a wide range of research competencies.

**What’s Next:** This mentor-based fellowship program will train rehab professionals how to conduct carefully controlled research studies with relevance to improving quality of life through rehabilitation.
Ivan Molton, PhD  
University of Washington  
Seattle, Washington  
Award: Research Grants  
Category: Restore  
Term: 4/1/2019-3/31/2023  
Funding: $1,147,727  
Title: Efficacy of a psychological intervention to improve ability to cope with uncertainty in MS  
Summary: University of Washington researchers are comparing traditional behavioral therapy with an alternate approach to determine how to better help people newly diagnosed with MS to cope with the uncertainty of the disease.  

Background: The symptoms and disease progression of MS are different in each person and difficult to predict over time. This uncertainty is often very stressful. However, people can improve their ability to tolerate uncertainty. Psychological counseling aimed at helping someone with MS cope with uncertainty may be very helpful.  

The Study: Dr. Molton and his team have developed a new one-on-one, six-session counseling intervention to help people newly diagnosed (within the last 3 years) with MS cope with the uncertainty of the disease. The program promotes acceptance of the uncertainty of MS, management of the associated anxiety, and full participation in life. Initial testing of this program showed promising results. They are now testing this program in a larger number of people with MS and comparing their outcomes to others who receive traditional cognitive-behavioral therapy and those who receive no counseling and only medical care for their MS. The team is looking for increases in acceptance of MS and decreases in anxiety.  

What’s Next: If this new approach to helping people cope with the uncertainty of MS is as beneficial or better than traditional approaches, it could become widely available by videoconference.  

Jacob Sloane, MD, PhD  
Beth Israel Deaconess Medical Center  
Boston, Massachusetts  
Award: Research Grants  
Category: Restore  
Term: 4/1/2019-3/31/2022  
Funding: $218,605  
Title: Role of sleep apnea in MS fatigue and disability  
Summary: Researchers at Beth Israel Deaconess Medical Center are exploring the prevalence of sleep apnea in people with MS and whether treating apnea can reduce MS-related fatigue.  

Background: Profound fatigue is a symptom commonly experienced by many people living with MS. Fatigue not only negatively impacts quality of life, but it may also affect disease activity and disability. People with MS have an increased risk of sleep apnea, where breathing stops and starts during sleep, and it is likely to play a role in fatigue.  

The Study: Dr. Sloane and his team are assessing how common obstructive sleep apnea is in a population of people with MS. They are also looking for a relationship between the presence of sleep apnea in these people and fatigue, sleep quality, and brain MRI results.  

What’s Next: Results may help clinicians better diagnose and treat fatigue in people with MS, and potentially MS itself.
Jacob Sosnoff, PhD
University of Illinois at Urbana-Champaign
Champaign, Illinois

Award: Mentor-Based Postdoctoral Fellowships
Category: Restore
Term: 7/1/2019-6/30/2024 Funding: $424,446
Title: Cognitive Motor Interference Rehabilitation in Multiple Sclerosis

Summary: Experienced mentors/researchers at the University of Illinois Urbana-Champaign are training promising rehabilitation professionals to conduct MS rehabilitation studies.

Background: Impairments in mobility and cognition are common in individuals with MS. Over the last decade a significant amount of research has demonstrated that these processes intersect. This “cognitive-motor interference” is associated with adverse events such as falls and reduced quality of life. Mobility and cognitive impairment may be best targeted with a combined rehabilitation intervention. The purpose of this mentor-based fellowship program is to build the workforce such that rehabilitation scientists examine predictors and consequences of cognitive-motor interference and design and implement successful rehabilitation studies to provide solutions for people with MS.

The Study: The MS rehabilitation research fellowship at the University of Illinois at Urbana-Champaign is a unique training program that will provide a hands-on learning environment combined with seminar participation, formal coursework, mentoring opportunities and a range of independent research projects. The training program focuses on teaching fellows the importance of systematically formulating and addressing a research question within a rehabilitation framework. The program will also extend beyond the lab and include aspects of professional development that are often overlooked in PhD programs, including lab/staff management, work/life balance and how to maximize teaching efforts and maintain research productivity.

What’s Next: This mentor-based fellowship program will train scientists in cutting-edge methods and enable them to apply these to clinical research projects with relevance to improving quality of life through rehabilitation.
14 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

Oscar Bizzozero, PhD (University of New Mexico, Albuquerque) is looking to inhibit a specific type of cell death in mice with MS-like disease, for clues to developing a strategy that might minimize damage and improve function in MS.

Asaff Harel, MD (The Feinstein Institute for Medical Research, Manhasset, NY) is exploring a possible alternative to using the tracing agent gadolinium in MRI scans, which may accumulate in the brain over time.

Christopher Hemond, MD (University of Massachusetts, Worcester) is investigating a specific subset of immune cells that may characterize highly inflammatory disease activity in people with MS.

Maria Savvaki, PhD (Foundation for Research and Technology-Hellas, Heraklion, Greece) is investigating whether a molecular process that helps cells to regenerate can protect nerve-insulating myelin from damage in MS.

Rebecca Straus Farber, MD (Columbia University, New York, NY) is testing two strategies for altering the gut microbiome in people with MS, in an effort to stop MS in its tracks.

Protecting Myelin from Damage

“Autophagy” comprises a major mechanism which engulfs, removes, and recycles unwanted cell material. It plays a protective role in cell survival and its dysregulation has been linked to several disorders. Maria Savvaki, PhD (Foundation for Research and Technology-Hellas, Heraklion, Greece) is investigating whether autophagy dysregulation contributes to myelin damage such as that which occurs in MS. The team is stopping autophagy in nerve cells isolated in the laboratory and in mouse models, and then checking myelin formation. They also are screening a library of FDA-approved molecules known to promote autophagy for effects on myelin formation. This research aspires to provide significant insights in disorders interfering with myelin decline such as MS.
**RESTORING WHAT’S BEEN LOST**

**Drew Adams, PhD** (Case Western Reserve University, Cleveland, OH) is exploring how cholesterol-like molecules may act to promote myelin repair, for clues to targeting these molecules in MS repair strategies.

**Michael Bemben, PhD** (University of Oklahoma, Norman) is testing a modified weight training program for clues to increasing physical function and improving quality of life in MS.

**Riley Bove, MD** (University of California, San Francisco) is testing whether sleep problems improve in people with MS with the use of melatonin.

**Leigh Charvet, PhD** (New York University Langone Medical Center, New York, NY) is testing whether virtual reality techniques can reduce pain in people with MS.

**Evan Cohen, PhD** (Rutgers, The State University of New Jersey, New Brunswick) is testing whether providing rest intervals throughout walking rehabilitation efforts improves their effectiveness in people with MS.

**Akiko Nishiyama, MD, PhD** (University of Connecticut, Storrs Mansfield) is exploring whether immature myelin-making cells secrete molecules that are important for the formation of myelin, for clues to repair strategies for MS.

**Richard Van Emmerik, PhD** (University of Massachusetts, Amherst) is testing tai chi and mindfulness meditation training for their ability to improve balance in MS.

**ENDING MS FOREVER**

**Shannon Dunn, PhD** (University Health Network, Toronto, Ontario, Canada) is using a model of MS to unravel the biology of the effects of smoking on MS.

**Deanna Saylor, MD** (Johns Hopkins University School of Medicine, Baltimore, MD) is working with healthcare providers in sub-Saharan Africa to improve diagnosis and tracking of MS, for clues to factors that lead to development of this disease worldwide.
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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Kirsten Anderson, PhD
University of California, San Francisco
San Francisco, California
Award: Postdoctoral Fellowships
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $188,067
Title: Killer immunoglobulin-like receptor polymorphism associations with Multiple Sclerosis: Bioinformatics approach to understanding the genetic impact on disease phenotypes, disability progression and clinical outcomes

Summary: UCSF researchers are studying genes that instruct certain immune cells in people with MS, because differences in these genes may impact why some people have more MS relapses and or experience MS progression sooner.

Background: People with MS experience differences in disease severity and progression. Genetic differences among individuals may in part explain these variations. Natural killer cells are immune cells that recognize and kill damaged or infected cells. Natural killer cells have docking sites (receptors) on their surface that recognize their targets. These receptors, called KIRs, are highly variable among people and are encoded by genes that are highly variable. Although the role of natural killer cells in MS is not entirely clear, decreased numbers of natural killer cells in the blood are associated with more brain lesions in people with MS.

The Study: Dr. Anderson and her team are working to determine if the genetic variations in KIRs are associated with MS relapse rates and disease progression. By examining data from a group of people with MS who have undergone both clinical examination and genetic sequencing, Dr. Anderson and her team are studying the relationship between KIR variations and MS disease progression, disease type, and markers of disease activity seen on MRI.

What’s Next: Results may help predict how severe an individual’s MS may become, which could influence treatment decisions. This study will also clarify the role of natural killer cells in MS.
Theron Casper, PhD  
University of Utah  
Salt Lake City, Utah  

**Award:** Strategic Initiatives  
**Category:** Stop  
**Term:** 7/1/2019-6/30/2022  
**Funding:** $3,490,520  

**Title:** The Network of Pediatric MS Centers  
**Summary:** The Society is supporting a one-of-a-kind, expanding network for research to advance knowledge and understanding of the triggers and impacts of MS in both children and adults.

**Background:** The Network of Pediatric MS Centers (NPMSC) was launched with Society funding in 2006 to set the standard for pediatric MS care, educate the medical community about this underserved population, and create the framework to conduct critical research — both to understand childhood MS and to unlock the mysteries of MS in adults. This special initiative was funded through the Society’s Promise: 2010 campaign, laying the groundwork for current studies by the NPMSC to measure clinical and cognitive manifestations of early-onset MS, and track environmental and genetic triggering factors.

**The Study:** The Society’s renewed investment supports research activities of 11 member clinics and the University of Utah Data Coordinating and Analysis Center, which is responsible for managing the patient registry and fostering collaboration. Funding for the network provides essential infrastructure and leverage to facilitate research and to gain additional funding sources. Over the last term, the team has focused on searching for the cause of MS by studying risk factors for the disease in children, close to the time of exposure. The team’s current priorities relate to defining the causes of cognitive dysfunction in pediatric MS, identifying what determines whether disability will accrue in pediatric MS, and identifying mechanisms that underlie tissue injury and repair to improve treatment. The Network of Pediatric MS Centers currently includes Children’s Hospital Boston, Cleveland Clinic, Massachusetts General Hospital, Mayo Clinic College of Medicine, New York University Langone Medical Center, Texas Children’s Hospital, University of Alabama at Birmingham, University of California San Francisco, the University of Colorado, and Washington University in St. Louis.

**What’s Next:** This strategic investment provides the infrastructure and research support needed to keep this unique network — with the largest group of well-characterized pediatric MS cases in the world — moving forward.
**Marika Falcone, MD, PhD**
Fondazione Centro San Raffaele
Milan, Italy
**Award:** Research Grants
**Category:** Stop
**Term:** 4/1/2019-3/31/2022 **Funding:** $335,544
**Title:** Assessing the immune regulatory role of gut microbiota in brain autoimmunity and disease activity in RRMS patients
**Summary:** Researchers in Milan, Italy are analyzing how gut bacteria influence immune cell behavior in the brain, and how alterations in those bacteria may reduce or exacerbate MS disease activity.

**Background:** A person’s diet can affect the population of bacteria present in their intestines, and these changes in bacterial populations have been shown to regulate inflammation in distant organs like the brain. Furthermore, gut bacteria are altered in people with MS and correlate with worse disease activity.

**The Study:** Dr. Falcone and her team are studying tissue samples from the intestines of people with relapsing-remitting MS. Her team is looking for a link between gut bacteria and changes in the intestinal immune cells that might trigger attacks of the central nervous system that cause MS relapses.

**What’s Next:** Nutritional interventions designed to decrease harmful bacteria and reduce generation of dangerous immune cells in the gut may improve MS in conjunction with current MS therapies.

**Adil Harroud, MD**
University of California, San Francisco
San Francisco, California
**Award:** Clinician Scientist Development Award
**Category:** Stop
**Term:** 7/1/2019-6/30/2021 **Funding:** TBD
**Title:** The genetic basis of progression in multiple sclerosis
**Summary:** UCSF researchers are analyzing genetic material from people with MS to determine the role that genes may play in MS progression.

**Background:** Individuals living with MS often experience a gradual loss of abilities. This is called MS progression. People with progressive MS show highly varied disease, with some remaining quite functional and others experiencing severe disability. Although much is known about relapsing-remitting MS and ways to treat it, less is known about what drives MS progression and there are fewer therapies available to slow it.

**The Study:** Dr. Harroud and his team are seeking a genetic explanation for progressive courses of MS. They are analyzing the genes of 10,000 people over age 55 who have had MS for at least 10 years and who have different severities of progressive MS. The goal is to identify genetic differences that may explain some of the variability. They are also asking if people who are genetically predisposed to be obese have worse progressive MS.

**What’s Next:** This work may identify biological reasons for progression and suggest ways to slow or stop it.
Dominique Kinnett-Hopkins, PhD
Northwestern University Feinberg School of Medicine
Evanston, Illinois
Award: Postdoctoral Fellowships
Category: Stop
Term: 7/1/2019-6/30/2020 Funding: $58,476
Title: Disease characteristics and healthcare utilization patterns in advantaged and disadvantaged patients with multiple sclerosis
Summary: Researchers at Northwestern are examining how people with MS access healthcare, and how residing in a disadvantaged area, racial identity, and distance to medical services may impact their use of the healthcare system.

Background: Disadvantaged groups are people who have a higher risk of poverty, discrimination, and violence than other groups. Disadvantaged groups may also have more problems receiving good health care because of less access to health care, having less money and fewer available resources near their homes.

The Study: Dr. Kinnett-Hopkins and colleagues are analyzing electronic health records from three hospitals that served advantaged and disadvantaged people with MS in the Chicago area between the years 2011 and 2016. They are using a statistical analysis to group together people who use healthcare services in similar ways, and then examining those groups to see if where they live, what racial identity they have, and the distance to healthcare services impacts the way they use healthcare services.

What’s Next: This project should highlight barriers to health care access in disadvantaged communities, allowing for approaches that improve health outcomes for people with MS.

Matthew Lincoln, MD, Dphil
Yale University
New Haven, Connecticut
Award: Career Transition Fellowships
Category: End
Term: 7/1/2019-6/30/2024 Funding: $412,500
Title: Genetic and molecular heterogeneity of MS
Summary: A team at Yale is seeking to fine tune MS genetic studies using a novel framework that combines MS genetics data with similar data from related diseases, for insight into disease mechanisms and possible gene regulation.

Background: People with MS may have very different symptoms, disease courses and response to therapy. The biological and genetic reasons for such differences are not well understood. Over 200 common gene variants have been shown to be involved in the risk of MS.

The Study: Dr. Lincoln and his team are working to determine the genes that correspond to these 200 genetic variants and in what cell types, such as immune cells or brain cells, these genes are switched on or off. They are combining MS genetic data with similar data from several other autoimmune diseases that share basic disease processes. The team can use these shared processes to better identify the genes and mechanisms that contribute to MS. They will then examine how these genetic variants work in the cells and if these variabilities explain differences in MS symptoms, response to therapy, and disease progression.

What’s Next: Results should contribute substantially to understanding the cause of MS, and may help clinicians understand how to provide personalized care to each person with MS.
Averil Ma, MD  
University of California, San Francisco  
San Francisco, California  
Award: Research Grants  
Category: End  
Term: 4/1/2019-3/31/2022  
Funding: $658,766  
Title: Ubiquitin Mediated Prevention of Multiple Sclerosis  
Summary: A UCSF team is testing whether changes to a potent inflammation-reducing protein contribute to the onset of MS-like disease in mice, for clues to developing new therapies to stop MS.

Background: The cause of MS is unknown, but certain genes, which encode proteins, likely play an important role. A protein called A20 modulates a process called ubiquitination and likely plays an important role in reducing susceptibility to MS by decreasing inflammation.

The Study: Dr. Ma and his team are testing the idea that A20 prevents an MS-like disease called EAE. They are using mice with EAE that do not make A20 in certain immune cells. They are investigating whether that loss of A20 increases susceptibility of mice to EAE. They are also determining what cell types are involved in the actions of A20 and how A20 works biochemically to prevent EAE.

What’s Next: This research may help identify a genetic risk factor for developing MS, and may offer new insights into whether therapies that increase A20 may help prevent MS.

Rosella Mechelli, PhD  
Università Telematica San Raffaele Roma  
Rome, Italy  
Award: Research Grants  
Category: Stop  
Term: 4/1/2019-3/31/2021  
Funding: $100,000  
Title: EBV genotyping in MS  
Summary: Investigators in Rome, Italy are confirming and clarifying the possible role of specific strains of Epstein-Barr virus as a triggering factor in MS.

Background: Although infection with Epstein Barr virus (EBV) may play a role in triggering MS, the details are not clear. Many people are infected with EBV, but comparatively few of these people develop MS. Different types of EBV exist.

The Study: Dr. Mechelli and her team are investigating the idea that the particular strain of EBV is what is important in triggering MS. They previously identified certain types of EBV that are more common in people with MS and other types that are more common in people without MS. They are extending this observation by analyzing a group of 400 people with relapsing-remitting MS and 400 age- and sex-matched individuals without MS, with different genetic backgrounds and different locations to determine the importance of possible MS-associated EBV types.

What’s Next: Understanding EBV variants that may be involved in triggering MS may help identify ways to prevent the disease and develop better treatments.
Nikos Patsopoulos, MD, PhD  
Brigham and Women’s Hospital  
Boston, Massachusetts  
**Award:** Harry Weaver Neuroscience Scholarships  
**Category:** End  
**Term:** 7/1/2019-6/30/2024  
**Funding:** $779,428  
**Title:** Omic-based precision medicine strategies in multiple sclerosis  
**Summary:** Researchers at Brigham and Women’s Hospital are refining a system to better predict an individual’s risk for developing MS.

**Background:** A family history of MS increases a person’s risk of developing the disease, and over 200 genetic variants have been identified as increasing MS risk. A “genetic risk score” based on these variants can help determine a person’s risk, but this approach is relatively new and not well understood.

**The Study:** Dr. Patsopoulos and team are using genetic and non-genetic data from more than 100,000 people with and without MS to more carefully understand genetic links in MS. They are evaluating genetic risk scores using real-life clinical information to test if they can be used for diagnosis and predicting outcomes in MS.

**What’s Next:** Results from this study may allow family members of a person with MS to better understand and predict what their risk of developing MS may be and what actions they may take to reduce that risk.

Andrew Steelman, PhD  
University of Illinois at Urbana-Champaign  
Champaign, Illinois  
**Award:** Research Grants  
**Category:** Stop  
**Term:** 4/1/2019-3/31/2022  
**Funding:** $566,732  
**Title:** Upper-respiratory infection, glial activation and disease exacerbation  
**Summary:** Researchers at the University of Illinois are exploring how upper respiratory infections may trigger MS attacks, by studying immune reactions to infection in mice with an MS-like disease.

**Background:** A substantial proportion of people with MS who sustain upper respiratory infections go on to have an MS relapse, and the timing of the two events and other data suggest that they are linked. Finding a way to block processes that lead to MS relapses such as these may improve quality of life and reduce MS progression.

**The Study:** Dr. Steelman’s team is determining how a viral infection in the respiratory system can activate cells that cause inflammation within the brain. His preliminary data has also suggested that upper-respiratory infection may slow the repair of nerve-insulating myelin, and his team is trying to determine why. His team is using powerful tools to explore biological pathways in the brain that are impacted by infections. The team will also test whether an antiviral medication can decrease MS-like disease onset or relapses in mice.

**What’s Next:** If these studies are successful and the antiviral medication inhibits the occurrence of disease and disease relapses in mice, then clinical trials could be initiated to determine whether this approach would stop MS relapses in people.
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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Omer AL-Louzi, PhD
National Institutes of Neurological Disorders and Stroke
Bethesda, Maryland
Award: NMSS/ABF Clinician Scientist Development Award
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $276,697
Title: Characterizing the central vein sign in MS using advanced magnetic resonance imaging techniques and pathology correlations
Summary: NIH imaging specialists are using advanced MRI to determine whether a central blood vessel in brain lesions (areas of damage) can distinguish MS from similar disorders, and thus expedite the process of diagnosing MS.

Background: MS can be challenging to diagnose because other diseases can closely resemble many aspects of MS. Accurate diagnosis of MS is necessary so that therapy can be given early in the disease course, which leads to the best outcomes. Likewise, ruling out MS in someone without the disease is important so that the person does not receive unnecessary MS therapy.

The Study: Dr. Al-Louzi and his team are using advanced imaging methods to look for a feature called the “central vein sign” (CVS). The CVS is a light-colored, tube-shaped area within an MS lesion (damaged area) in the brain. This tube is a blood vessel. Lesions with CVS are more frequent in MS than in non-MS conditions. The team is investigating how CVS lesions change over time, the best ways to image these lesions, and how CVS relates to MS pathology.

What’s Next: The presence of CVS lesions in MRI scans may help physicians distinguish people with MS from those without the disease, improving diagnosis and treatment.
Clare Baecher-Allan, PhD  
Brigham and Women’s Hospital  
Boston, Massachusetts  
Award: Research Grants  
Category: Stop  
Term: 4/1/2019-3/31/2022  
Funding: $625,788  
Title: Are CD20+ T cells dysfunctional in Multiple Sclerosis?  
Summary: A team at Brigham and Women’s Hospital is studying blood samples from people with MS to determine whether a novel set of immune cells drives MS, for clues to developing a therapeutic strategy for stopping the disease.

Background: Although it has long been believed that MS is primarily mediated by immune “T cells,” the effectiveness of ocrelizumab – a therapy that targets CD20, a protein on B cells – has made it clear that B cells are also involved. It was recently found that CD20 is active on a subset of T cells as well. Dr. Baecher-Allan and her team are addressing the possibility that these CD20+ T cells may help to drive MS.

The Study: The team is isolating cells from blood samples donated from people with MS and from donors without MS, for comparison. They will separate out CD20+ T cells and conduct tests to determine if the cells isolated from people with MS secrete unusual combinations of pro-inflammatory proteins, or have altered responses to inhibitory proteins and immune cells.

What’s Next: These studies will indicate whether a novel subset of immune cells may play a role in maintaining or advancing disease activity in MS, and potentially lead to the identification of new targets for therapies that can stop MS in its tracks.

Claudia Cantoni, PhD  
Washington University School of Medicine  
Saint Louis, Missouri  
Award: Career Transition Fellowships  
Category: Stop  
Term: 7/1/2019-6/30/2024  
Funding: $589,886  
Title: MiR-223: a new potential therapeutic target to modulate myeloid cells in multiple sclerosis  
Summary: Researchers at Washington University are exploring the possibility that a subset of immune cells in the blood may be impaired in MS, for clues to how these cells might be manipulated to suppress disease activity.

Background: In MS, immune system cells attack components of the brain and spinal cord, causing damage and leading to symptoms in people with the disease. One type of immune cells, called T cells, has been identified as playing a damaging role in MS. Another type of immune cell, called myeloid-derived suppressor cells (MDSCs), blocks the activity of these harmful T cells. MDSCs are present in lower numbers in the blood of people with MS compared to people without MS.

The Study: Dr. Cantoni and her team are studying how MDSCs work and why their numbers are lower in people with MS. Specifically, they are studying a molecule called miR-223, which they believe controls the function of MDSCs. Using a mouse model of MS called EAE, they are investigating how miR-223 controls the immune-suppressing effects of MDSCs and are testing the effects of blocking miR-223. They are also analyzing miR-223 in people with MS compared to people who do not have MS.

What’s Next: If this research confirms a role for MDSCs, it could uncover leads to new therapies to turn off immune attacks to stop MS.
**Dimitrios Davalos, PhD**  
Cleveland Clinic Foundation  
Cleveland, Ohio  
**Award:** Research Grants  
**Category:** Stop  
**Term:** 4/1/2019-3/31/2022  
**Funding:** $643,008  
**Title:** Gliovascular Mechanisms of Blood-Brain Barrier Disruption in Multiple Sclerosis  
**Summary:** Cleveland Clinic researchers are using novel techniques to explore mechanisms involved in early immune cell infiltration into the nervous system in MS-like disease, for clues to stopping immune attacks in MS.

**Background:** The special architecture of blood vessel walls in the healthy brain and spinal cord (collectively called the central nervous system) tightly regulates the access of immune cells and molecules from the bloodstream to these vital organs. This architecture is called the blood-brain barrier (BBB). In MS, the BBB becomes leaky early on, and potentially harmful immune cells and molecules enter the nervous system and trigger immune attacks that drive disability.

**The Study:** Dr. Davalos and his team are using a mouse model of MS called EAE to investigate early changes in damaged blood vessels and entrance of immune cells into the spinal cord when the BBB is compromised. They are using an advanced imaging technology called two-photon microscopy to study changes in blood vessels in real time. They are imaging blood vessels, microglia (immune cells that normally reside in the brain), and blood-derived immune cells after the BBB has been damaged in EAE, and following the interactions among these immune cells and blood vessels over time, as disease develops. They are also examining a possible role for molecules that they have found to be possible mediators of harmful changes, and are testing if targeting them can prevent disease progression.

**What’s Next:** The imaging studies will shed much needed light in deciphering the sequence of events driving MS. If this research confirms a role for the investigated molecules, drugs that target them and are already available to treat other conditions could potentially be tested as a treatment for MS at its early stages.

**Jordon Dunham, MS, PhD**  
Cleveland Clinic Foundation  
Cleveland, Ohio  
**Award:** Postdoctoral Fellowships  
**Category:** Stop  
**Term:** 7/1/2019-6/30/2022  
**Funding:** $181,754  
**Title:** Neuronal morphology and expression profiles in a novel sub-variant of MS  
**Summary:** Scientists at the Cleveland Clinic are studying mechanisms of damage in some people with MS who seem to have injury to nerve cells but not to nerve-insulating myelin typically seen in MS.

**Background:** Researchers previously assumed that all individuals with MS have damage and loss of myelin, the fatty substance that surrounds and protects nerve fibers. The nerve fibers themselves are also damaged. Cleveland Clinic researchers recently identified a rare sub-variant of MS by examining autopsied tissue, which they called myelocortical MS. Individuals with this subtype do not show signs of myelin damage in the brain’s white matter region, but they have nerve cell injury that appears to occur independently of the inflammation that is seen in typical MS. Currently there is no way to detect myelocortical MS in living individuals.
**The Study:** Dr. Dunham and his team are working to understand how nerve cells are damaged in myelocortical MS. They are analyzing the sequence of expressed genes in autopsy specimens from people who had typical MS compared to samples from people with myelocortical MS. They are also assessing differences between the two types of MS at the point where one nerve cell communicates with another (called a synapse). They are testing the idea that synapses and the proteins located at the synapses will be different in the two MS subtypes.

**What’s Next:** This work will help further understanding of this subtype of MS, and may help identify new therapeutic targets to treat myelocortical MS.

**Jeff Dunn, PhD**  
University of Calgary  
Calgary, Canada  
**Award:** Research Grants  
**Category:** Stop  
**Term:** 4/1/2019-3/31/2022  
**Funding:** $369,028  
**Title:** Using light based technology to identify the extent of hypoxia in the cortex of patients with MS  
**Summary:** University of Calgary researchers are using new technology to detect and investigate whether and how reduced levels of oxygen in parts of the brain may impact people with MS.

**Background:** MS disease activity in the brain may lead to reduced levels of oxygen in brain areas. This may make symptoms, inflammation, and loss of brain tissue worse.

**The Study:** Dr. Dunn and his team are determining how many people with MS have low oxygen levels in the brain and if this relates to relapses or symptoms, including fatigue and depression. They are also testing whether low brain oxygen changes over time. They are using a new, non-invasive technology that uses light to look at brain oxygen levels in people who are visiting the clinic for a regular check-up for their MS. They are investigating the relationship between their new light-based data with information collected during the normal clinical visit.

**What’s Next:** If depleted oxygen levels are reliably detected with this new technology, it should bring new insights into MS pathology and new treatment approaches.
Shailendra Giri, PhD
Henry Ford Health System
Detroit, Michigan
Award: Research Grants
Category: Stop
Term: 4/1/2019-3/31/2022 Funding: $577,672
Title: Impaired DHA metabolism in multiple sclerosis
Summary: Researchers at Henry Ford Health System are looking at whether people with MS have abnormalities in their ability to process polyunsaturated fatty acids -- dietary components that may fight inflammation.

Background: Inflammation plays a major role in MS relapses. The body uses molecules called omega-3 and omega-6 polyunsaturated fatty acids (PUFAs, “good fats”) to help reduce inflammation. A clinical trial showed that PUFA supplements did not help people with MS, although they helped individuals with other types of inflammatory diseases.

The Study: Dr. Giri and his team are investigating why PUFAs did not help people with MS. They are testing the idea that people with MS do not use PUFAs effectively. The team is using specialized equipment to examine the levels of various molecules that result from breaking down PUFAs to see if there are differences between samples from people with MS and people without MS. Also, they are testing the idea that other good fats may decrease the activity of harmful immune cells from people with MS.

What’s Next: The results of this study may show that supplementation with other, non-PUFA good fats may be beneficial to people with MS by reducing inflammation and relapses.

Joseph Sabatino, MD, PhD
University of California, San Francisco
San Francisco, California
Award: Research Grants
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $61,875
Title: Characterization of myelin-reactive CD8+ T cells in Multiple Sclerosis
Summary: UCSF researchers are analyzing immune cells in the blood and spinal fluid from people with MS and other neurologic diseases to determine if unique cell populations drive the immune response in MS.

Background: In MS, various types of immune cells attack components of the brain and spinal cord, causing damage and producing symptoms in people with the disease. While certain features of the immune response are better understood in MS, little is known about the potential role of CD8+ T cells, also called killer T cells. CD8+ T cells from MS lesions appear to be expanded in response to an unclear stimulus within the central nervous system.

The Study: Dr. Sabatino and his team are comparing samples of blood and spinal fluid from people with MS and people with other neurological disorders. They are studying whether certain CD8+ T cells are enriched in MS compared to other disorders. They are also using these samples to determine what components in the brain these cells are directed to attack.

What’s Next: These results could lead to new therapeutic strategies for MS, and may also identify potential biomarkers that could help diagnose MS and predict its severity.
Naresha Saligrama, PhD
Stanford University
Stanford, California
Award: Career Transition Fellowships
Category: Stop
Term: 7/1/2019-6/30/2024 Funding: $598,908
Title: Understanding T cell receptor diversity and specificity in Multiple sclerosis and Experimental autoimmune encephalomyelitis
Summary: A Stanford team is using advanced and technologies to analyze a novel subset of immune cells in people with MS during relapses, remissions, and after treatment, for clues to what activates and sustains the immune response.

Background: In MS, different types of immune cells attack components of the brain and spinal cord, causing damage and producing symptoms in people with the disease. T cells are a type of immune cell that plays a harmful role in MS.

The Study: In collaboration with Stanford Neurologists, Dr. Saligrama is analyzing samples of blood and spinal fluid from people with MS. They are looking for overlap in T cells found in blood and spinal fluid because immune cells in the blood may represent immune cells in the spinal fluid, which is harder to obtain from people. They are also examining T cells in people with MS who take the MS immune-modifying therapy glatiramer acetate to understand how this therapy affects T cells. In another step, they are studying T cells in mice with an MS-like disease called EAE to understand which T cells are important in disease.

What’s Next: These results could identify new targets for MS therapies that are more specific and safer than current medications.

Hengameh Shams, PhD
University of California, San Francisco
San Francisco, California
Award: Postdoctoral Fellowships
Category: Stop
Term: 7/1/2019-6/30/2021 Funding: TBD
Title: Characterization of interplay between T and B lymphocytes in MS using functional proteomics
Summary: A UCSF team is using advanced technology to study links between immune function and disease status in people with MS.

Background: MS involves dysfunction of the immune system, and damage to the brain and spinal cord. It is not yet clear what leads the immune system to launch MS and the progressive disability that can occur over time. Communication between immune cells is complex and key for all immune functions in both health and disease. This team is using state-of-the-art techniques to decode critical interactions between two immune cell types, T and B cells.

The Study: Proteins are fundamental biological molecules that form the structure of cells and mediate cell function. Dr. Shams and colleagues are breaking down immune cells into their protein constituents and measuring each protein in different cell types. Then, they will use sophisticated computing to integrate this information to understand how immune cells communicate with each other. They are doing this in cells obtained from people newly diagnosed with MS who have not yet received immune-modifying therapies, and also in treated people.

What’s Next: Ultimately, this work may generate novel therapeutic targets and fine-tune current MS therapies so that treatment results in greater benefits and less adverse effects.
Gregory Wu, MD, PhD
Washington University School of Medicine
Saint Louis, Missouri
Award: Research Grants
Category: Stop
Title: Formation of ectopic lymphoid tissue in autoimmune encephalomyelitis and MS
Summary: Washington University researchers are exploring a novel feature of the immune system that may prevent therapies that target immune B cells from being effective in some people with progressive MS, for clues to better management of MS progression.

Background: B cells are a type of immune cell that has been implicated in playing a role in MS attacks. Therapies that delete B cells have shown benefit in MS. However, B cells are sometimes protected from therapies when they are lodged in areas called “ectopic lymphoid tissue” or ELT. Regions of ELT also promote inflammation and damage to the brain in MS.

The Study: Dr. Wu and his team are investigating what genes are turned on in B cells that are found in ELT. He is looking at whether another type of immune cell causes B cells to move into ELT, researching where B cells receive the energy they need to form ELT and to promote inflammation. The team has developed a mouse model of ELT and are also using tissue samples from people with MS to inform several of these studies.

What’s Next: These studies may provide information on how to precisely and more successfully target B cells as a therapy for 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.

Erin Beck, MD, PhD
National Institute of Neurological Disorders and Stroke
Bethesda, Maryland
Award: Career Transition Fellowships
Category: Stop
Term: 7/1/2019-6/30/2024 Funding: $601,176
Title: Evolution of cortical pathology and its relation to meningeal inflammation in multiple sclerosis
Summary: Researchers are using advanced imaging to look at specific areas of damage in the brains of people with MS that are linked with progression, for clues to developing treatments that can stop the disease.
Background: Recent efforts have uncovered MS lesions in the “gray matter,” areas of the brain that contain mostly cell bodies. People with progressive MS may have more lesions in cortical gray matter than those with relapsing MS.

The Study: Dr. Beck and her team are developing advanced MRI methods to understand how cortical lesions develop and change over the course of disease, and the relationship between cortical lesions and cognitive problems, disability, and the transition from relapsing-remitting to progressive disease. They are also investigating the relationship between signs of inflammation in the spinal fluid and cortical lesions.

What’s Next: The new MRI techniques and information gained from their use may help better monitor disease progression in people with MS, and better guide new and existing therapies.

Mingnan Chen, PhD
University of Utah
Salt Lake City, Utah
Award: Research Grants
Category: Stop
Term: 7/1/2019-6/30/2021 Funding: TBD
Title: Understanding and utilizing the role of programmed death 1-positive (PD-1+) cells in multiple sclerosis
Summary: A team is developing a therapy that targets specific immune cells, and testing it in MS mouse models to see if it can stop MS-like attacks without affecting normal immune function.

Background: During the course of multiple sclerosis, the immune system attacks and damages the brain and spinal cord. This team is developing a new approach that targets a special population of immune cells (lymphocytes) that are major players in this attack. The approach should leave the majority of lymphocytes intact and, it is hoped, preserve normal immunity. Their preliminary data has shown that depleting cells that presented a specific molecule – known as PD-1 -- cured mice with severe MS-like disease. Mice that had received this treatment were able to mount full-strength immune responses.

The Study: Now Dr. Chen and colleagues are developing a compound that is selectively toxic to cells presenting PD-1. They are testing the capability of this compound to reverse or delay progression of MS-like disease using two mouse models that mimic two common clinical courses of MS – progressive MS and relapsing-remitting MS. The team also will examine whether the healthy immunity of mice is fully functional after treatment with the experimental compound.

What’s Next: If depletion of PD-1-positive cells is an effective approach in mouse models, it could lead to testing this approach in people.

Sasha Gupta, MD
University of California, San Francisco
San Francisco, California
Award: Clinician Scientist Development Award
Category: Stop
Term: 7/1/2019-6/30/2022 Funding: $201,197
Title: Use of anti-CD19 CAR-T cells in treatment of CNS autoimmune demyelinating disease in mice
Summary: A team is testing a therapy used to target immune B cells in cancer for clues to whether this treatment can slow MS progression.

Background: Certain immune cells, including B cells, are involved in MS development in both the blood and the brain. Current treatment approaches to eliminate B cells only remove
Establishing an MS Biobank

**Strategic Initiative:** The National MS Society is leveraging PCORI-funded clinical trials to support an MS biobank as a shared resource for researchers searching for biomarkers.

**Title:** “Establishing an MS biobank, leveraging two comparative effectiveness clinical trials supported by PCORI”

**Term:** 4/1/19-3/31/22  
**Grant Amount:** $534,669 (Hopkins) and $378,797 (Cleveland Clinic) = $913,466

**Principal Co-Investigators:** Ellen Mowry, MD, MCR and Scott D. Newsome, DO (Johns Hopkins)  
Daniel Ontaneda, MD, MS (Cleveland Clinic) and Nikos Evangelou, MD, DPhil (Univ. of Nottingham)

**Background:** There is a critical need in MS for “biomarkers” that can detect disease activity without waiting for symptoms to occur. Researchers are seeking biomarkers that can provide early readouts about disease course, and predict an individual’s response to therapy. The Society is capitalizing on two important clinical trials to develop a biobank for biomarker discovery research.

**Project:** The Patient Centered Outcomes Research Institute (PCORI) has invested $24 million for two multicenter clinical trials focused on understanding the comparative effectiveness of early, intensive therapy versus step-wise escalation therapy in relapsing MS. Drs. Ellen Mowry and Scott Newsome of Johns Hopkins are leading the “TREAT-MS” trial, and Dr. Daniel Ontaneda of Cleveland Clinic and Dr. Nikos Evangelou of the University of Nottingham are leading the “DELIVER-MS” trial. Since the two studies are similar, the researchers are collaborating to establish a unified biobank that will collect serum, cells, and DNA from participants in both studies to be used as a community resource for biomarker discovery studies. The biobank will be hosted at the University of Alabama-Birmingham, led by Dr. Chander Raman, and the expense for processing and storage of samples will be covered by philanthropic contributions already in place. The United Kingdom samples will be held at the University of Cardiff, under the direction of Dr. Emma Tallantyre.

**Impact:** This unique resource will likely provide insights that will greatly advance our understanding of MS for years to come.

B cells in the blood and not the brain. Removal of these B cells from the brain may be needed to further improve therapies for MS.

**The Study:** Dr. Gupta and her team are investigating a possible method to eliminate harmful B cells from both the blood and the brain using CAR-T cells. CAR-T cells are human immune cells engineered to target and kill cells on which a specific protein is active, and they have been successful in treating certain human cancers. Dr. Gupta will be testing CAR-T cells designed to target a protein active in B cells in mice with two types of an MS-like disease called EAE.

**What’s Next?** Because CAR-T cells are already used in people with cancer, positive results from this study could lead to rapid turnaround testing of this strategy in people with MS.
Don Mahad, MD, PhD  
University of Edinburgh  
Edinburgh, Scotland  
Award: Research Grants  
Category: Stop  
Term: 4/1/2019-3/31/2021  
Funding: $169,493  
Title: Targeting mitochondria to protect axons in progressive MS  
Summary: A team is attempting to enhance energy production in nerve cells, to protect them from damage in MS.

Background: In MS, the fatty substance that surrounds and protects nerve fibers, called myelin, is destroyed. MS brain tissue obtained at autopsy shows an increased number of mitochondria, the main energy producer in cells, in regions of the nerve cells that had lost their myelin. Increasing the ability of damaged nerve cells to produce energy may be protective of the brain and spinal cord in MS.

The Study: Dr. Mahad and his team are investigating how cells are able to increase energy production following myelin loss. Mitochondria located near the nucleus of the cell appear to move down the length of the nerve fiber and merge with the mitochondria in regions of myelin loss. To understand this process in greater detail, the team is imaging mitochondria in mice and in nerve cells grown in a dish that were treated with a toxin that damages myelin. They are also using genetic manipulation and drugs to increase the production and transport of mitochondria to sites of myelin loss and are asking whether these actions are protective.

What’s Next: Finding ways to increase energy production of nerve cells may be a viable strategy for protecting the nervous system in MS.

Bardia Nourbakhsh, MD  
Johns Hopkins University  
Baltimore, Maryland  
Award: Research Grants  
Category: Stop  
Term: 4/1/2019-3/31/2022  
Funding: $397,248  
Title: Evaluating the effects of short-term B-cell depletion on long-term disease activity and immune tolerance in relapsing multiple sclerosis  
Summary: Researchers are exploring the longer-term impacts of short-term use of B-cell depleting therapy on the immune system and MS.

Background: Ocrevus is an MS disease-modifying therapy that targets and destroys immune cells called B cells. This medication is typically given to people with MS every 6 months for an indefinite period of time. The effect of B cell-targeting medications may last well beyond the 6-month reinfusion period.

The Study: With the goal of reducing undesirable and long-term side effects, Dr. Nourbakhsh and his team are testing whether the short-term use of Ocrevus can stop MS flare-ups and new lesions on MRI for a long period of time. They are treating 10 people with relapsing-remitting MS with two courses of Ocrevus and then following them for 2.5 years or longer to check for a long-lasting reduction in flare-ups and new lesions. The normal role of B cells is to produce antibodies. Dr. Nourbakhsh is also testing blood samples from these 10 people to examine whether short-term use of Ocrevus changes B cell production of antibodies against “self” tissues, a process that is harmful in MS.

What’s Next: Less frequent administration of medications such as Ocrevus may reduce side effects and costs while benefiting MS.
### National MS Society Funds Clinical Care and Clinical Research Fellowships

#### 2019 Clinical Care Fellowships
The awards provide one year of post-residency training with experienced mentors to optimize access to quality care and solutions for people with MS.

<table>
<thead>
<tr>
<th>Awardee</th>
<th>Location</th>
<th>Mentor</th>
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<tbody>
<tr>
<td>Justin Abbatemarco, MD</td>
<td>Cleveland Clinic Foundation</td>
<td>Jeffrey Cohen, MD</td>
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<tr>
<td>Horacio Chiong-Rivero MD, PhD</td>
<td>University of Southern California</td>
<td>Lilyana Amezcua, MD &amp; Daniel Pelletier, MD</td>
</tr>
<tr>
<td>Kristin Galetta, MD</td>
<td>Brigham and Women's Hospital</td>
<td>James Stankiewicz, MD &amp; Tanuja Chitnis, MD</td>
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<tr>
<td>Nicholas Lannen, MD</td>
<td>University of Virginia</td>
<td>Myla Goldman, MD</td>
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<tr>
<td>Erica Parrotta, DO, MS</td>
<td>NYU Langone Medical Center</td>
<td>Ilya Kister, MD</td>
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<tr>
<td>Stephanie Taylor, MD</td>
<td>Vanderbilt University Medical Ctr.</td>
<td>S. Pawate, MBBS, and S. Sriram, MBBS</td>
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#### 2019 Sylvia Lawry Physician Fellowships
As part of the Society’s effort to propel knowledge to end MS, the promising young doctors receiving training from a Sylvia Lawry Physician Fellowship learn from top MS experts who mentor their initiation into the complex methods of designing and conducting clinical trials in persons with MS.

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<thead>
<tr>
<th>Awardee</th>
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<th>Mentor</th>
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<tr>
<td>Carolyn Goldschmidt, DO</td>
<td>Cleveland Clinic Foundation</td>
<td>Jeffrey Cohen, MD</td>
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<tr>
<td>Elaine Su, MD</td>
<td>Stanford University</td>
<td>Jeffrey Dunn, MD</td>
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<tr>
<td>Yinan Zhang, MD</td>
<td>Icahn School of Medicine at Mount Sinai</td>
<td>Fred Lublin, MD</td>
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#### 2019 Institutional Clinician Training Awards
Consistent with its effort to ensure that people affected by MS have access to comprehensive, high quality health care, the Society offers the Institutional Clinician Training Award, a five-year award to mentors and institutions to provide training for board-certified/eligible neurologists and physiatrists in MS specialist care. The goal is for fellows to acquire the skills and knowledge necessary to provide the highest quality of care for individuals with MS.

<table>
<thead>
<tr>
<th>Lead Mentor</th>
<th>Location</th>
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<tr>
<td>Brenda Banwell FRCP, MD</td>
<td>Children's Hospital of Philadelphia</td>
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<tr>
<td>Jeffrey Cohen, MD</td>
<td>Cleveland Clinic Foundation</td>
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<tr>
<td>Myla Goldman, MD, M.Sc.</td>
<td>University of Virginia</td>
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<tr>
<td>Andrew Goodman, MD</td>
<td>University of Rochester Medical Center</td>
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<tr>
<td>Fred Lublin, MD</td>
<td>Icahn School of Medicine at Mount Sinai</td>
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<tr>
<td>Vijayshree Yadav, MD</td>
<td>Oregon Health &amp; Science University</td>
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