BREAKTHROUGH MS
NEW RESEARCH
Fall 2019

Society Commits $14.6 Million for 43 New MS Research Projects

The National Multiple Sclerosis Society has just committed more than $14.6 million to support 43 new multi-year MS research projects.

This financial commitment is the latest in the Society's relentless research effort, investing a projected $36 million in 2019 alone to support new and ongoing studies around the world.

These new research projects strengthen the Society's comprehensive approach addressing critical research 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 43 new projects seek answers to these questions.

For example, a study at Harvard's Brigham and Women's Hospital is focusing on stopping MS progression by identifying the role of "astrocyte" brain cells; a University of Melbourne, Australia study is testing whether immune cells of the brain can **increase the repair** of nerve-insulating myelin damaged by MS; a study at Rutgers University is examining whether a high-fiber supplement can **normalize the composition of gut bacteria** that can be abnormal in MS; and a study at UCLA is testing whether a small protein produced in the brain can **protect the nervous system** from MS damage.

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 lives. In addition, people with MS often live with other chronic medical conditions. Understanding how these other health conditions affect MS disease course and symptoms represents an important research opportunity. Opportunities to improve the design and conduct of clinical trials and providing strategies people can incorporate to enhance their wellbeing are a priority.

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Jared Bruce, PhD
University of Missouri - Kansas City
Kansas City, Missouri
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2020
Funding: $203,382
Title: Development of a telehealth obesity intervention for patients with MS
Summary: A team is testing a telephone-delivered treatment designed to help people with MS lose weight, and seeing if weight loss is linked to reduced symptoms.

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

Can losing weight by those who are obese improve depression, fatigue, mobility and other common MS symptoms?

The Study: During this pilot phase, Dr. Bruce will take first steps toward planning a telephone-delivered weight loss program and test-drive it in a small number of people with MS in preparation for conducting a larger trial. The planned intervention includes self-monitoring, goal setting, exercise, and social support. The program will be tailored to the special needs of people with MS, and may incorporate issues such as mobility/ transportation difficulties, coping with relapse, mood disturbance, cognitive changes, and dealing with MS fatigue. The team will determine whether weight loss leads to improvements in MS symptoms.

What's Next: If this weight loss program is effective and reduces common symptoms, it can help to improve quality of life in MS.

Michelle Cameron, MD, PT, MCR
Oregon Health & Science University
Portland, Oregon
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $534,358
Title: A Randomized Controlled Trial of a Multicomponent Walking Aid Program for People with MS
Summary: Oregon Health & Science University researchers are testing whether a standardized program provided by physical therapists, that helps to select, fit, and train in using walking aids, can prevent falls in people with MS.

Background: Research suggests that about half of people with MS will experience a fall or falls. Falling has both physical and psychological impacts. People with unsteady gait often use walking aids such as a cane, walker, or crutches to try to prevent falls but these people often still fall. Improper selection, fitting, and use of walking aids may be part of why they continue to fall.

The Study: Dr. Cameron and her team have developed a program that optimizes walking aid selection, fitting and use, called the Assistive Device Selection, Training and Education Program (ADSTEP). Preliminary testing of ADSTEP suggested that the program reduces the likelihood of falling. This study is a larger, controlled trial to definitively determine if ADSTEP prevents falls in people with MS. People who walk with walking aids and have fallen in the past year will be randomly assigned to ADSTEP or to a control group. Those in the ADSTEP group will work with a physical therapist who selects the best walking aid for them, fits the walking aid, and then trains the person on how to use it. The control group will receive brochures about fall prevention and will be allowed to enroll in ADSTEP at the end of the trial. The team is comparing falls, walking performance, and patient-reported outcomes in the two groups.

What's Next: If this study confirms that ADSTEP reduces falls, it could quickly be translated to improve quality of life for people living with MS.

Kouichi Ito, PhD
Rutgers, The State University of New Jersey
Piscataway, NJ
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $673,908
Title: Gut dysbiosis-mediated CNS autoimmunity
Summary: Scientists are examining whether a specially designed high-fiber supplement can reduce changes in gut bacteria associated with MS.

Background: MS involves immune-system attacks on the brain and spinal cord. Differences between people with MS and people without MS have been observed in the composition of gut bacteria, and other studies have hinted that these differences, known as gut dysbiosis, may play a role in MS disease activity.

The Study: Studies suggest that a diet high in fiber can promote the growth of healthy bacteria in the gut. Dr. Ito's team is examining whether a specially designed high-fiber supplement, added to a standard MS disease-modifying therapy, causes beneficial changes to immune system activity and to gut bacteria composition, intestinal tissue and inflammation. The team will also transplant fecal samples from people with MS who are, or are not, on the high-fiber diet to see if there are positive impacts on a mouse model of MS (EAE).

What's Next: This study will provide preliminary clues as to whether a clinical trial of a high-fiber supplement in people with MS is justified.

Ilana Katz Sand, MD, PhD
Icahn School of Medicine at Mount Sinai
New York, New York
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2021
Funding: $299,679
Title: The Effect of Dietary Factors on Disease Outcomes in Multiple Sclerosis
Summary: Researchers are following up on a previous study of diet in people with MS, to validate their findings and determine whether additional dietary factors are important.

Background: Rigorous research studying associations between diet and MS disease outcomes is lacking but important. This team has recently completed a small trial of a modified Mediterranean dietary intervention in MS. Before they proceed with a larger study, they need more certainty about which type of diet they should be studying and what type of impact they should expect. Previous data collected on a group of people with early MS preliminarily suggests that the level of intake of certain food groups and nutrients is linked to measures of neurodegeneration in MS (gray matter atrophy) and with MS-related disability. Now they are expanding this work in the same group to validate these findings and evaluate whether specific dietary factors are important.

The Study: Dr. Katz Sand and colleagues are continuing their research on dietary factors in approximately 180 participants with MS who are part of the NYC Reserve Against Disability In Early MS cohort (led by Dr. James Sumowski) by collecting additional dietary data and biospecimens at

the 3-year follow up mark. Participants have already undergone an MRI and a clinical evaluation at the time of study entry; this evaluation will be repeated at the 3-year mark. The team also will use statistical analyses to look at whether particular dietary factors are associated with changes in MRI measures or clinical disability, and to study relationships with body weight (BMI) and blood cholesterol levels.

What's Next: This project will provide much-needed data to allow the team to design a larger clinical trial on diet in MS, and in the meantime may provide preliminary recommendations on dietary practices that may be of benefit in MS.

Robert Motl, PhD
University of Alabama at Birmingham
Birmingham, Alabama
Award: Strategic Initiatives
Category: Restore
Term: 7/1/2019-6/30/2022
Funding: $157,646
Title: Supplemental Funding for MSSC Feinstein Study: Improving Cognition In People With Progressive Multiple Sclerosis
Summary: Supplemental funding to support imaging to detect brain plasticity for an international trial comparing the benefits of exercise and cognitive rehabilitation in people with MS.

Background: Cognitive dysfunction is considered an "invisible" symptom that impacts many people with MS. It can have significant impact on employment, relationships, and activities of daily living. The Multiple Sclerosis Society of Canada has launched a $5 million, multicenter, international clinical trial to investigate if cognitive rehabilitation and aerobic exercise can improve cognition in people with progressive MS.

The Study: Robert Motl, PhD, is receiving supplementary funding from the Society to conduct expanded brain imaging (MRI and other types) aspects of the study. This additional funding would permit the addition of imaging outcomes with 30 cognitively-impaired persons with progressive MS. This would substantially increase the ability of this study to capture the effects of the interventions on plasticity.

What's Next: This landmark study may provide a treatment option for people with progressive MS and cognitive dysfunction.

Phillip Rumrill, PhD
Kent State University
Kent, Ohio
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $657,842
Title: A Two-Phase Examination of Labor Force Participation, Employment Concerns, and Workplace Discrimination among Latinas/os and African Americans with Multiple Sclerosis
Summary: Researchers are investigating the employment experiences of Hispanic/Latinos and African Americans with MS.

Background: This project investigates the employment experiences of the growing numbers of Hispanic/Latinos and African Americans with MS. The research represents an important extension of a project funded by the National MS Society in which Dr. Rumrill's team examined the employment concerns and discrimination experiences of Americans with MS. Results revealed that the employment concerns facing Hispanic/Latinos and African Americans were different from those of the Caucasian group.

The Study: For this study, Dr. Rumrill is conducting a national survey of employment concerns and experiences utilizing random samples of Caucasians, Hispanic/Latinos, and African Americans with MS (1,000 in each group). Studies comparing the two minority groups to the Caucasian group are planned to identify predictors associated with return to work optimism for unemployed participants, factors associated with turnover intention for employed participants, and patterns in the use of workplace accommodations among employed participants.

What's Next: With a better understanding of these issues, MS professionals can improve the employment rates of Hispanic/Latinos and African Americans with MS.

Joshua Sandry, PhD
Montclair State University
Montclair, New Jersey
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2020
Funding: $200,782
Title: Neuroimaging of Hippocampally Mediated Memory Dysfunction in Multiple Sclerosis
Summary: Researchers are measuring memory-related abilities in individuals with and without MS for clues to how such cognitive processes change in MS.

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

The Study: This one-year pilot project will establish the best method for measuring and tracking brain activity underlying memory problems in people with MS. Using advanced imaging techniques, the team will investigate links between working memory changes and structure and damage to an

area of the brain called the hippocampus. They will track people with MS who have memory problems compared to those who do not have memory problems, and they will also compare findings in people without MS. This will enable them to evaluate how cognitive processes change and relate to memory problems as a function of MS.

What's Next? This one-year pilot effort will provide a strong foundation for future treatments to restore lost memory function.

E. Yeh, MD
Hospital for Sick Children
Toronto, ON, Canada
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $665,469
Title: Physical Activity, Quality of Life and Disease Outcomes in Youth with Multiple Sclerosis: the ATOMIC (Active Teens With Multiple Sclerosis) Physical Activity Research Program
Summary: A team is testing if a smartphone app that provides tailored physical activity info/coaching can increase physical activity in pediatric MS.

Background: Prof. Yeh and colleagues have previously shown that children and teens with MS tend to be very inactive, and that vigorous physical activity is associated with higher levels of well-being and lower MS disease activity in youth. Her team has taken input from kids with MS to create a smartphone-based app (the ATOMIC - Active Teens with MS - App) and now will evaluate the effectiveness of this tool for increasing physical activity in kids with MS in a multi-center, controlled trial.

The Study: Fifty-six young people with MS (aged 11-21 years) will take part in a six-month study. The participants will be randomly assigned to either an app and coaching-based physical activity intervention or a nutritional information program. Those receiving the intervention will be given an activity monitor (Fitbit) that directly syncs with the ATOMIC app. A physical activity coach will communicate by text with participants in the intervention group weekly and speak to them on the phone biweekly as a means to support, motivate and encourage adherence to the program. The research team will measure the effect of the program on physical activity, mediators and moderators of physical activity, depression and quality of life.

What's Next: This intervention, if successful, has the potential to be disseminated more broadly and could have long-term impacts on the lives of young people living with MS.

Progression: How do we stop MS progression?

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

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Bonnie Dittel, PhD
Versiti Wisconsin, Inc.
Milwaukee, Wisconsin
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $723,641
Title: B cell regulation in EAE/MS
Summary: A Wisconsin team is exploring a newly identified subset of immune cells for clues to developing a cell-based therapy to stop the immune attack in MS.

Background: In MS, immune cells attack components of the brain and spinal cord, leading to symptoms and tissue loss in people with the disease. Current MS therapies modify the immune system, but more precise therapies are needed that stop disease progression but also allow the immune system to perform its normal role in fighting off infection. Dr. Dittel and her team have discovered a novel subset of immune B cells that can regulate the activity of other immune cells important for the suppression of autoimmunity.

The Study: The team is now characterizing the function of these B cells and evaluating their therapeutic potential in MS. They are manipulating immune genes of mice with the MS-like disease EAE to track specific immune reactions. They are determining whether these B cells generate antibodies, which are proteins that fight off infection. They are also assessing where in the body the B cells are located, and testing whether these cells can turn off immune attacks.

What's Next: Understanding how this novel B cell works could open up new therapeutic strategies for MS that more precisely dampen only a part of the immune system, leaving the rest intact.

Society Helps Fund ChariotMS Trial in People with Advanced MS

Research suggests that long-term disability in people with MS depends in part on the length of the wire-like nerve fibers. Longer nerves, such as those that send and receive messages to and from the legs have a higher chance of being damaged than shorter nerves, such as those that serve the hands. This can lead to earlier loss of lower limb function, while shorter nerves may still be able to be treated. A clinical trial is getting under way that will involve people with advanced MS, who are rarely included in trials.

The National MS Society is helping to fund this placebo-controlled, Phase 2 clinical trial that will test whether cladribine (in generic form, delivered by injection under the skin) can preserve or improve hand/upper limb function. This trial will be done at multiple medical centers across the United Kingdom. In addition to evaluating manual dexterity, the trial will measure safety, fatigue, imaging, cognition and quality of life.

If the trial is successful, it may eventually lead to a generic therapy that can help protect or improve hand and upper limb function in people with MS.

Daniel Hawiger, MD, PhD
Saint Louis University
St. Louis, Missouri
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $756,300
Title: Dendritic cells-orchestrated and Hopx-mediated homeostasis of regulatory T cells blocking autoimmune neuroinflammation
Summary: Scientists are exploring the mechanisms by which certain cells can regulate immune attacks in MS, for clues to developing targeted therapies to stop MS.

Background: Immune system cells normally undergo a process in which they become "tolerant" and ignore the body's own "self" tissues. Maintaining this tolerance is orchestrated by immune cells called Tregs. Research suggests that Treg function is abnormally low in people with MS, which may lead to immune attacks against the brain and spinal cord. Another type of immune cell, called a dendritic cell, has a key role in controlling the autoimmune process and Treg functions.

The Study: Dr. Hawiger and his team are working to understand how different subsets of dendritic cells control different types of Tregs under inflammatory conditions in mice with MS-like disease. They are also investigating the importance of a protein called Hopx, which is involved in transcribing genetic information in Tregs and may thus control their function.

What's Next: Results may suggest ways to develop targeted MS therapies that only disable cells that do not tolerate "self."

Amber Salter, PhD, MPH
Washington University School of Medicine
St. Louis, Missouri
Award: Strategic Initiatives
Category: Stop
Term: 9/9/2019-10/31/2020
Funding: $113,691
Title: MS Metadata Collective: A Collaborative Effect of North American Observational Studies in MS
Summary: A team is aiming to establish a metadata catalogue and to increase the feasibility of harmonizing disability measures across registries.

Background: A plethora of observational studies, including registries, have captured information about MS progression. However, these studies have different objectives and different methods of data collection, limiting the ability to combine or compare findings across studies. A recent meeting hosted jointly by the National MS Society and Consortium of MS Centers sought to address these issues. The objective of this proposal is to establish a metadata catalogue and to increase the feasibility of harmonizing disability measures across registries.

The Study: Up to 18 North American registries will be invited by Dr. Salter and the team to provide their study metadata (descriptions of each registries' data). Each registry will work with Maelstrom Research group to create a metadata catalogue, to be stored and searchable on a website. Then, the group will characterize measures of disability progression used by these various registries including their method of administration, reliability and sensitivity.

What's Next: This project will leverage extensive research on progressive MS to help launch collaborative studies that can stop MS progression in its tracks.

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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Brenda Banwell, FRCP, MD
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $627,223
Title: Does Recreational Marijuana Exposure Increase Cognitive Impairment and MRI Measures of Brain Injury in Youth and Young Adults with Multiple Sclerosis?
Summary: A team is studying the effect of recreational marijuana use on the brain and cognition in teenagers with MS.

Background: The onset of MS in childhood and adolescence can have negative impacts on learning, memory, planning, and other mental tasks, as well as on normal brain growth. Many adults with MS use marijuana. Although marijuana use in adults can have negative effects on memory and brain volume, its effects on adolescents are not known. Many teens, including those living with MS, use marijuana. This may impact brain development and their ability to perform mental tasks even further.

Results from this study will suggest how to counsel teens with MS about the cognitive risks of using marijuana.

The Study: Dr. Banwell and her team are working to understand whether recreational marijuana use by teenagers with MS impairs mental abilities and harms the brain. They are comparing teens with and without MS who report using marijuana and who report not using marijuana (30 per group). Each teen will perform tests to measure his/her mental abilities and will undergo MRI of the brain to assess any abnormalities. Results from all groups will be compared to detect any particular differences in teens with MS who use marijuana.

What's Next: Results from this study will suggest how to counsel teens with MS about the risks of using marijuana.

Jorge Oksenberg, PhD
University of California, San Francisco
San Francisco, California
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $830,155
Title: The role of Ataxin1 in autoimmune demyelination
Summary: A team at UCSF is seeking to understand the contribution of a gene known as "ATXN1" to MS risk and clinical course.

Background: The cause of MS is unknown, but genetic factors contribute to susceptibility to the disease. One gene that may play a role is called ATXN1.

The Study: Prof. Oksenberg and his team are working to understand how ATXN1 affects MS risk and MS disease course. The AXTN1 protein, which is encoded by the ATXN1 gene, plays previously unknown important roles in certain immune cells. The team is using statistical analysis to investigate which variants of the ATXN1 gene are important in MS risk. They are also using mice that have mutant forms of ATXN1, which have an MS-like disease called EAE, to determine how ATXN1 may impact immune function in MS.

What's Next: Understanding the role of ATXN1 in MS could help predict or treat MS.

Pathology: What is the cause of MS?

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

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Dritan Agalliu, PhD
Columbia University Medical Center
New York, New York
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $635,264
Title: Endothelial Wnt signaling in CNS neo-angiogenesis and blood-brain barrier in EAE/MS
Summary: Researchers are exploring blood vessel abnormalities in MS to develop therapies that prevent the influx of immune cells and protect the nervous system in MS.

Background: The "blood-brain barrier" is formed by small blood vessels in the brain and spinal cord. This barrier limits the molecules, antibodies and immune cells that are able to move from the blood into the brain. In MS and a similar animal model for the disease known as EAE, the blood-brain barrier is disrupted, allowing immune

cells, antibodies and substances that damage myelin, the protective material around nerve fibers, to enter the brain and spinal cord.

The Study: Dritan Agalliu, PhD, is investigating the role of a complex signaling process, the "Wnt/beta-catenin pathway," that normally contributes to the formation of the blood-brain barrier during brain development, in abnormal formation of new "leaky" vessels and the mechanisms that prevent the repair of the blood-brain barrier in disease. His team is using both MS animal models and tissue obtained from people with MS via autopsy in combination with molecular, cellular and single cell RNA sequencing approaches to examine the degree of abnormal vessel formation during disease. Moreover, they are activating or inhibiting molecules in this pathway to assess how it may contribute to formation of new "leaky" blood vessels, blood-brain barrier function and disease activity in MS or its animal models.

What's Next: Restoring barrier function offers the possibility of preventing disease flare-ups or speeding remission in people with MS.

Francesca Bagnato, MD, PhD
Vanderbilt University Medical Center
Nashville, Tennessee
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2023
Funding: $840,182
Title: 7T-rings as a biomarker of disease severity in MS
Summary: Researchers are testing whether an indicator found using powerful imaging tools can – if found early – serve to predict and ultimately prevent more severe MS.

Background: Predicting whether a person with MS will do well or progress rapidly is not possible because predictive biomarkers of disease progression are not available. People with MS who are predicted to experience rapid worsening would need to receive more aggressive treatment.

The Study: Dr. Bagnato is developing a predictor of MS disease course using a special type of MRI called susceptibility-based MRI using a powerful magnet (7 tesla) that provides much better visibility of MS lesions than those typically used during standard MS checkups. The team is using this tool to scan 80 people with MS early in their disease, who will be followed for two years. They are looking for a type of MS lesion called 7T-rings. These lesions get bigger over time. The team is looking at whether 7T-rings are present at the onset of MS and how they are related to the person's disability and disease activity over time.

What's Next: This study may provide an important tool for predicting disease severity and informing treatment choices.

John Chen, MD, PhD
Massachusetts General Hospital
Boston, Massachusetts
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $764,935 *Funded in part by a generous donor*
Title: Targeting the ubiquitous oxidative aldehyde acrolein in MS
Summary: Researchers are testing advanced imaging to track changes in MS disease activity, and test a novel treatment targeting inflammation and oxidative stress.

Background: A sensitive and specific imaging method to monitor and predict MS disease progression is needed. One possible solution is to track the body's ability to eliminate normal by-products of cell processes, which if left unchecked can cause "oxidative stress" and can be toxic to cells. One of these toxic molecules, called acrolein, is present in the environment and is made by the body. Acrolein causes and increases inflammation and has been shown to be elevated in people with MS.

The Study: Dr. Chen and his team are developing an imaging procedure that uses positron emission tomography, or PET scanning, to monitor the reduction of molecules like acrolein. They are testing this imaging procedure in mice with EAE, an MS-like disease. They are then using PET to track the state of oxidative stress and inflammation after treatment of mice with drugs that reduce acrolein.

What's Next: This may justify and validate the further testing of PET to monitor MS progression.

Dimitry Krementsov, PhD
University of Vermont
Burlington, Vermont
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $615,377
Title: Next generation systems analysis of pathogenetic mechanisms underlying CNS autoimmunity using the Collaborative Cross
Summary: A team is seeking to identify and validate genes that may underlie a person's susceptibility to MS.

Background: The cause of MS is unknown but likely involves a combination of multiple genetic and environmental factors. Researchers do not know exactly how genes work with other factors to trigger MS, how or whether genes cause different forms of MS, or why MS is more common in women.

The Study: Dr. Krementsov and his team are identifying genes in mice with EAE, a laboratory model that resembles some aspects of MS, to overcome some aspects of genetic study that would be impossible in people. They are working to identify genes that may control MS disease course such as progressive or relapsing MS, and genes that could affect women more than men, and vice versa. To do this, they are using a new genetic model of mouse with a highly diverse genetic make-up, which has not been applied to the study of MS. Their findings may complement and augment new discoveries being made by human geneticists studying MS genes.

What's Next: Identification of genes that control aspects of MS could lead to preventative or therapeutic strategies.

Francisco Quintana, PhD
Brigham and Women's Hospital
Boston, Massachusetts
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $642,070
Title: Molecular control of astrocytes in CNS inflammation
Summary: Brigham and Women's researchers are seeking to Identify a role for "astrocyte" brain cells in MS progression, for clues to stopping progression in its tracks.

Background: Multiple Sclerosis involves immune system attacks on tissues in the brain, spinal cord and optic nerve (central nervous system – CNS). This team has discovered a novel mechanism in brain cells called astrocytes that boosts CNS inflammation and is activated by environmental pollutants. Preliminary evidence suggests that blocking this pathway using genetic approaches and drugs already approved for use in humans reduces inflammation and nerve degeneration. With this project, Professor Quintana and colleagues aim to deepen their understanding of this pathway to develop effective and safe treatments for progressive MS.

The Study: Prof. Quintana's team will analyze this specific signaling pathway in mouse models of MS and human cells isolated in the lab. In a second step, they will determine whether proteins that are being targeted as a new approach to treat MS synergize with this signaling pathway to boost astrocytes' disease-promoting capabilities. They also will evaluate pharmacological inhibitors approved for human use to see if they can improve disease in acute and chronic MS models.

What's Next: This project has both basic and clinical implications. It will define mechanisms that control astrocyte function and consequently inflammation and neurodegeneration, while illuminating new approaches for treating progressive MS.

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

The hopes of people living with MS today rest on finding a way to stop disease worsening by preventing nerve degeneration 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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Charles Abrams, MD, PhD
University of Illinois at Chicago
Chicago, Illinois
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2021
Funding: $136,115
Title: Role of Connexin 47 in oligodendrocytes
Summary: University of Illinois researchers are generating a mouse model to study the role of a protein in the development and maintenance of myelin, for clues to targeting this protein in myelin repair strategies 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 properly, and are also made vulnerable to further damage and loss. The cells in the brain and spinal cord that make myelin are called oligodendrocytes. "Connexin 47" is a protein that allows oligodendrocytes to communicate with other oligodendrocytes and with other cell types. Mice that lack connexin 47 are susceptible to EAE, an MS-like disease. In addition, people with MS have reduced amounts of connexin 47.

The Study: To more carefully study the role of connexin 47 in EAE, and its potential implications in MS, Dr. Abrams and his team are creating a mouse model that lacks connexin 47 specifically in myelin-making oligodendrocytes and at specific times of interest. This will give the team clues about how the loss of connexin 47 at different timepoints contributes to the severity of MS-like disease.

What's Next: Having this mouse model will be an important tool for the research community to understand the role of connexin 47 in the maintenance and repair of myelin.

New Fast Forward Investment

The National MS Society, through its Fast Forward drug development program, is investing in one new project, with additional investments expected soon:

Researchers at Clene Nanomedicine Inc. are currently conducting a clinical trial in people with MS to see if a compound called Biocatalytic Nanocrystalline Gold (CNM-Au8) can protect the nervous system from damage and promote myelin repair by providing supportive energy to brain cells. With this Fast Forward investment, the team will measure and track blood markers in trial participants to help determine whether the compound is facilitating myelin repair and neuroprotection.

Identifying and validating blood biomarkers will not only advance CNM-Au8 as a potential treatment for MS, but also expand the biomarker repertoire available to the MS field as new drugs for remyelination and neuroprotection are developed.
Term: 24 months; **Investment Amount:** $339,232

Learn more about Fast Forward

Trevor Kilpatrick, MBBS, PhD
Florey Institute of Neuroscience and Mental Health
Melbourne, Australia
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $403,830
Title: Modulating microglial activity for treatment of demyelinating diseases of the CNS
Summary: Researchers are testing whether the transplant of modified microglia – immune cells of the brain – can improve repair of myelin in an MS model.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Finding ways to promote myelin repair could help protect the underlying nerve fibers from loss and restore nerve signaling.

The Study: Prof. Kilpatrick and his team are investigating a type of immune cell called microglia that plays an important role in cleaning up myelin debris, a necessary step for more efficient myelin repair. They are focusing on a protein called Mertk, and testing the impacts on myelin repair when the protein is deleted from microglia (which should increase inflammation and reduce myelin repair) or added to microglia (which should increase clearance of myelin debris and promote repair).

What's Next: If increasing Mertk in microglia is successful in the mouse model, it would be a step toward using this approach to increase repair in MS.

18 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

Onur Afacan, PhD (Boston Children's Hospital, Boston, MA) is testing novel scanning techniques to improve the ability to diagnose and monitor MS in children.

Jonathan Baell, PhD (Monash University, Melbourne, Australia) is developing and testing a form of a natural brain protein that may protect nerves from damage in MS.

Farrah Mateen, MD, PhD (Massachusetts General Hospital, Boston, MA) is testing if an electronic pill bottle cap can improve treatment adherence in people with MS.

Ipek Oguz, PhD (Vanderbilt University, Nashville, TN) is developing an approach that would enable computerized recognition of types of MS brain lesions.

Nikos Patsopoulos, MD, PhD (Brigham and Women's Hospital, Boston, MA) is testing the use of cutting-edge technologies to study brain cell mechanisms to understand MS.

Steven Roth, MD (University of Illinois at Chicago, Chicago, IL) is engineering a novel approach to reducing inflammation to prevent nerve tissue damage in an MS model.

Pilot in Focus: Intestinal Viruses and Gut Bacteria

There has been growing interest in research on how bacteria in the intestines may influence the risk of getting MS or making it more severe. Intestinal viruses are important components of the gut microbiome, but have not yet been well studied in MS. **Yanjiao Zhou, MD, PhD** (University of Connecticut Health Center, Farmington, CT) is focusing on differences in gut viruses in people with and without MS, treated and untreated. The team also is interested in understanding if the viruses, particularly those that infect bacteria, contribute to the changes of the bacteria in the gut in MS.

Nisarg Shah, PhD (University of California San Diego, San Diego, CA) is testing a way to speed the regeneration of immune system cells after bone marrow transplantation in MS.

Russell Shinohara, PhD (University of Pennsylvania, Philadelphia, PA) is exploring whether insurance type impacts MS progression or disease activity.

RESTORING WHAT'S BEEN LOST

Brynn Adamson, PhD (University of Illinois at Urbana-Champaign, Champaign, IL) is testing a novel community-based exercise program to increase physical activity in MS.

Stephen Crocker, PhD (University of Connecticut Health Center, Farmington, CT) is investigating the link between bladder problems and the loss of myelin in MS.

Elizabeth Hubbard, PhD (Berry College, Berry, GA) is looking at the impact of individualized arm and leg exercises on fatigue, depression and other MS symptoms.

Igal Ifergan, PhD (Northwestern University, Evanston, IL) is exploring cell interactions in the brain in search of molecular triggers for promoting myelin repair.

Maria Mendoza, MD (University of Washington, Seattle, WA) is testing two hypnosis techniques for their ability to reduce fatigue in spanish-speaking people with MS.

Pilot in Focus: Exercise Program for Wheelchair Users

Exercise training has a number of benefits for people with MS, however, most of these benefits have been reported in people with mild to moderate disability. There is little information or recommendations about exercise for people with MS who use wheelchairs (i.e., non-ambulatory). **Lara Pilutti, PhD** (University of Ottawa, Ottawa, Ontario, Canada) is assessing a single bout of adapted exercise (arm-cycle, recumbent stepper, and functional electrical stimulation cycle) in 20 non-ambulatory people with MS. If effective, there is potential for improving participation and quality of life for people with MS who use wheelchairs.

Isobel Scarisbrick, PhD (Mayo Clinic Rochester, Rochester, MN) is investigating the role of a protein in the repair of nerve-insulating myelin, and how to promote repair in MS.

Aaron Turner, PhD (Seattle Institute for Biomedical and Clinical Research, Seattle, WA) is examining veterans with MS for clues to the risks involved in administering opioids for pain.

Feng Yang, PhD (Georgia State University, Atlanta, GA) is testing whether training people with MS with controlled falling experiences can build skills to prevent falls.

Kelly Monk, PhD
Oregon Health & Science University
Portland, Oregon
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $738,270
Title: Molecular and Genetic Regulation of Myelin Capacity in the CNS
Summary: Researchers are studying how two genes function so that they may be targeted to promote myelin repair in MS.

Background: Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS. Researchers believe that a key way to protect nerve fibers from damage is to restore lost myelin. Although the body has its own repair processes, these often fail in MS.

The Study: The teams of Prof. Monk and Dr. Ben Emery are investigating the function of two genes that control the construction of myelin: one drives myelin synthesis and one inhibits it. They are exploring how the loss of the myelin-inhibitory gene causes increased myelin formation, and whether loss of this gene can promote myelin repair. The team is also studying the function of these two genes in normal myelin synthesis during development. They are using two types of animal models for these studies. One is zebrafish, which are transparent and make it easy to visualize myelin growth and manipulate genetically. They are also using mice that undergo myelin loss.

What's Next: Therapies are needed to promote myelin repair in people with MS, and one or both of these genes may be targets for such a novel therapy.

Isobel Scarisbrick, PhD
Mayo Clinic
Rochester, Minnesota
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $740,036
Title: Protease Activated Receptor Targets for Myelin Regeneration
Summary: A team is exploring whether specific molecules can be "switched off" to promote nervous system repair in MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers, and natural myelin repair processes often fail. Nerve fibers that have lost their myelin cannot send their signals properly and are vulnerable to damage and loss. Understanding how myelin destruction and repair is controlled is important.

The Study: A molecule called PAR1 is found on the surface of cells. The FDA has approved medications that target PAR1, and these are being tested in clinical trials to treat people with other diseases. Dr. Scarisbrick and her team are investigating the importance of PAR1 and associated molecules in myelin destruction and repair. In lab studies, they have discovered that blocking PARs promotes myelin production. Now they are seeking to determine if these PARs can be turned off to promote myelin repair in two different lab models of myelin injury, and they are testing inhibitors of PARs in mice and in human cells.

What's Next: If PAR1 is important for protection and repair of myelin, it could potentially be repurposed to test in MS.

Seema Tiwari-Woodruff, PhD
University of California, Riverside
Riverside, California
Award: Research Grants
Category: Restore
Term: 10/1/2019-9/30/2022
Funding: $482,269
Title: Reprogramming proinflammatory responses to increase CXCL1 levels and axon remyelination in EAE
Summary: Researchers are determining how compounds that connect with estrogen docking sites work to promote repair of nerve-insulating myelin in MS models.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects the nerve fibers, and the nerve fibers can also be damaged. Available therapies for MS are mostly aimed at dampening the immune system. However, a therapy that modifies the immune response to be protective, directly promotes repair of myelin and protects and nerve fibers is also necessary. The sex hormone estrogen has been shown in rodent studies to protect the brain, but estrogens impact the reproductive system and have been linked to cancers. An estrogen-like therapy that specifically protects the brain without affecting the female reproductive system is desired, and could even be used in both men and women.

An estrogen-like therapy could protect the brain without affecting the female reproductive system

The Study: Professor Tiwari-Woodruff is testing estrogen-like compounds that act on estrogen docking sites in the brain and may provide nervous system protection, without impacting the reproductive system. They are testing what impact these compounds have on a specific immune messenger protein that seems to stimulate the survival and production of myelin-making cells. To do so, the team is testing mouse models of myelin damage and also cells isolated in the laboratory.

What's Next: This research may yield a novel approach to developing a therapy that promotes myelin repair and protects the nervous system from damage in MS.

James Waschek, PhD
University of California, Los Angeles
Los Angeles, California
Award: Research Grants
Category: Stop
Term: 10/1/2019-9/30/2022
Funding: $646,509
Title: Preservation of axon integrity by neural PACAP/PAC1 signaling in a chronic EAE model
Summary: A team is testing a new approach for protecting nerves from damage in MS.

Background: The physical and cognitive disabilities that can develop over time in people with MS are likely due to loss of nerve cells and their connections to other nerve cells. A small protein produced in the brain, called PACAP, can protect nerve connections after inflammation and injury.

The Study: Prof. Waschek and his team are determining how PACAP is protective in mice that have the MS-like disease EAE by deleting the gene that controls its docking site (receptor). This receptor binds PACAP and transmits PACAP's actions. They are testing the idea that deleting the receptor will remove the beneficial effects of PACAP. They are also testing whether delivering PACAP into the brain can reduce the severity of EAE and prevent the loss of nerve connections.

What's Next: This project will provide important information that will help determine whether PACAP, or stimulating its brain receptors, is a promising strategy for developing a therapy to protect the nervous system from MS damage.

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