

NEW RESEARCH



STOP. RESTORE. END.

Society Commits Over \$21 Million for 78 New MS Research Projects

The National Multiple Sclerosis Society has committed over \$21 million to support an expected 78 new MS research projects. These are part of a comprehensive research strategy aimed at stopping MS, restoring function that has been lost, and ending the disease forever – for every single person with MS.

This financial commitment is the latest in the Society’s relentless research efforts to move us closer to a world free of MS, investing over \$53 million in 2015 alone to support more than 380 new and ongoing studies around the world. The Society pursues all promising paths, while focusing on the priority areas of progressive MS, nervous system repair, genes/the environment and wellness and lifestyle.

We are confident that with donor response to ongoing research successes, the crucial dollars needed to fund these and other research and clinical initiatives will be secured.

While we’re driving research to stop MS, restore function and end the disease forever, at the same time we’re identifying key interventions and solutions that can help people with MS live their best lives now.

The new projects include these, described in more detail in the following pages:



STOP:

- Commercial research projects focusing on developing compounds with potential to stop the progression of MS. (See p. 5)



RESTORE:

- Researchers at Brigham and Women’s Hospital are investigating the relationship between fatigue in people with MS and damage to a particular circuit in the brain using advanced imaging techniques. (See p. 18)



END:

- Investigators at Harvard Medical School are exploring whether exposure to air pollution could raise the risk of MS. (See p. 27)



National
Multiple Sclerosis
Society

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**STOP**

Stopping MS requires understanding the factors that contribute to MS disease progression, and finding ways to prevent damage to the nervous system. Stopping MS includes research on potential therapies, measuring disease activity, understanding how the immune system plays a role in triggering MS, and gathering data on health care issues to drive advocacy efforts for policies that enable everyone with MS to access quality care and treatment.

STOP—Health Care Delivery and Policy**Jared Bruce, PhD**

University of Missouri - Kansas City
Kansas City, MO

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/16; **Funding:** \$315,341

Title: Development of a treatment decision model in MS

Summary: Researchers at the University of Missouri are developing a model that will explain how people with MS weigh risks and benefits when deciding whether or not to take a disease-modifying therapy.

Background: Disease-modifying therapies (DMTs) are frequently prescribed to people with MS to reduce disease progression and flare-ups. However, 25-50% of people with MS choose not to take DMTs. Reasons include an immediate decrease in quality of life due to side effects and a delay in benefits. Although the effectiveness and risks of MS therapies are well-defined, relatively little is known about how these benefits and risks are perceived and weighed by people with MS. This benefit/risk trade-off is important for clinicians, industry, and regulators to understand when considering which therapies to develop, approve for clinical use, and recommend to people with MS. For these reasons,

the National MS Society released a targeted request for proposals on this topic.

The Study: Dr. Bruce and his team are studying 300 people with MS and asking them to indicate whether they would take hypothetical DMTs with various risk/benefit profiles. Participants will also complete questionnaires designed to assess social, clinical, and emotional factors associated with medication use. The team is using the data from these questionnaires to develop a mathematical model to explain how people with MS weigh risks and benefits when deciding whether or not to take a DMT. They are also determining what causes someone to change their mind from not taking to taking a DMT.

What's Next: Results from this study will increase our understanding of how people make medical decisions and how they weigh treatment benefits and risks. This increased understanding will be crucial in guiding the development and approval of future MS therapies.

Tanuja Chitnis, MD

Massachusetts General Hospital
Boston, MA

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$492,718

Title: Patient-family views on pediatric MS research needs, outcomes, and methods

Summary: Researchers at Massachusetts General Hospital are gathering opinions about research priorities related to pediatric MS from parents of children and teenagers with MS, and adults with pediatric-onset MS.



Background: Over the past 10 years there has been an increased awareness that MS occurs in children, and the National MS Society played a major role in the training of doctors and clinical centers able to care for children with MS by helping to establish the U.S. Network of Pediatric MS Centers (NPMSC). Several research studies have also started to better understand the causes of MS in children, and clinical trials have been launched to identify safe and effective treatments in children. Despite these advances, there has been limited information collected from people impacted by pediatric MS about their priorities, goals and thoughts about research studies.

The Study: The goal of this project is to gather the opinion on pediatric MS research priorities from parents of children with MS, teenagers with MS, and adults with pediatric-onset MS. Dr. Chitnis is developing an online questionnaire seeking views on specific research topics and priorities for research, and also will gather opinions with the help of patient and parent focus groups at three centers in the NPMSC. One focus of this study is the types of measures (or outcomes) that are the most meaningful for clinical trials in children with MS, and how a safe and effective treatment should be defined. The online survey will then be administered to 250 participants identified through the NPMSC. The team will review the results with the original focus groups, with the goal of gaining further insights on the responses.

What's Next: This study will give voice to people impacted by pediatric MS and help drive research priorities aimed at improving treatment and quality of life.

Marcia Finlayson, PhD

Queen's University
Kingston, Ontario, Canada

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/16; **Funding:** \$100,000

Title: Bone Mineral Density Screening and Fracture Risks in People with MS

Summary: Researchers at Queen's University are seeking to expand understanding of bone health in people with MS to develop programs and guidance to reduce osteoporosis and bone fractures.

Background: People with MS have a higher risk of low bone mineral density and osteoporosis compared to healthy adults. Because people with MS may fall often, fractures related to osteoporosis are a special concern. Fractures can lead to hospitalization, reduced quality of life, loss of mobility and independence, and nursing home admission. The World Health Organization has an assessment tool called FRAX[®] that is used to measure the risk of osteoporosis-related fractures and the need for medication to improve bone strength in adults. Past research suggests that FRAX may not work well for people with MS. This makes it difficult for health care providers to choose treatments to improve bone mineral density and reduce fracture risk in people with MS.

The Study: This team is seeking to expand knowledge of bone health in people with MS to improve bone health management in this population. They are using a repository of medical records of 1.2 million people in Manitoba, and a unique resource that includes information about all bone mineral density screening provided in Manitoba since January 1990. These records will be used to identify all people with MS and others who have received a bone mineral density screening test; to find out if age, gender, disability sta-



tus, history of fractures, medication use or a regular source of physician care influences if and when a person with MS receives a screening test; and to compare people with MS who were screened to people without MS who were screened. They will also examine whether FRAX can be improved to predict osteoporosis-related fractures in people with MS.

What's Next: The knowledge gained from this project will provide direction for future clinical practice guidelines on bone health management in MS, including the development of programs and services to prevent osteoporosis and fractures.

Robert Fox, MD

Cleveland Clinic Foundation
Cleveland, OH

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$416,686

Title: A Study of Benefit and Risk in People with MS

Summary: Researchers at the Cleveland Clinic are probing the perspectives of people with MS in terms of perceived benefits and risks of MS therapies to better inform the development and approval of future therapies.

Background: Although the effectiveness and risks of MS therapies are well-defined, relatively little is known about how these benefits and risks are perceived and weighed by people with MS and their care partners and loved ones. This benefit/risk trade-off is important for clinicians, industry, and regulators to understand when considering which therapies to develop, approve for clinical use, and recommend to people with multiple sclerosis. For these reasons, the National Multiple Sclerosis Society re-

leased a targeted request for proposals on this topic.

The Study: This project focuses on understanding patient perceptions and acceptance of benefits and risks of MS therapies. Dr. Fox and colleagues are administering a large-scale survey regarding preferences of various benefits/risks of MS therapies to people with MS and their care partners, clinicians, industry, and regulators. They will look for patterns of how people weigh risks and benefits based on their health status and other factors.

What's Next: Results should provide a deeper understanding of various perspectives concerning risks and benefits of MS therapies among the various stakeholders involved in the development of MS therapies: people with MS and their care partners, clinicians, industry, and regulators. This increased understanding will be crucial in guiding the development and approval of future MS therapies.

Michael Halpern,

University of Arizona
Tucson, AZ

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/16; **Funding:** \$99,614

Title: Secondary Analysis of Existing Data Sets: Patient-Reported Reasons for Changes in DMT Use and Subsequent Treatments and Clinical Outcomes

Summary: Researchers at the University of Arizona are exploring the factors that help determine treatment choices and treatment switching to develop a framework for guiding decisions and improving outcomes.

Background: Treatment options for individuals have expanded as new disease modifying therapies (DMTs) have become available for relapsing forms of MS. However, there are no



National MS Society Collaborates Commercially to Develop Treatments for Progressive MS

Getting treatments to people with MS requires bold leadership, tenacity and investment at every stage of the research process. The Society continues to propel promising new therapies by breaking down barriers to commercial development through funding mechanisms like Fast Forward. We drive connections of all the resources necessary to ensure that promising treatments don't languish on a dusty shelf., including these most recent collaborations to develop treatments for people with progressive MS:

Io Therapeutics, Inc., Santa Ana, CA

Io Therapeutics is a privately held biopharmaceutical company focused on advancing novel treatments for cancers, neurodegenerative diseases, and autoimmune diseases. Their lead compound is IRX4204, a small molecule developed for treatment of cancers, and has been shown to promote myelin repair in MS models.

Funding: \$204,000 to support further preclinical study of the ability of IRX4204 to promote myelin repair, to prepare for phase I studies in people with progressive MS.

Kadimastem, Ltd., Ness Ziona, Israel

Kadimastem is a biotechnology company that specializes in the development of stem cell-based medical solutions. They have developed a screening platform to identify compounds that promote the maturation of neural stem cells into functional myelin-making oligodendrocytes.

Funding: \$152,400 to test and validate a potential drug discovered through this screening platform for people with progressive forms of MS.

New York University, New York, NY

With funding from the National MS Society and others, Prof. James Salzer, Dr. Jayshree Samanta (a former Society postdoctoral fellow) and colleagues found an unexpected subtype of stem cells in the brain that become activated and transform into myelin-making oligodendrocytes in response to myelin damage. Blocking or eliminating a molecule, called Gli1, stimulated the cells to repair damaged myelin more effectively.

Funding: \$598,950 to continue preclinical development of better Gli1 blockers for use as a treatment to repair myelin in people with MS.



widely used guidelines to help physicians or patients choose appropriate DMTs based on patient preferences and characteristics, or switch to a new DMT after stopping a DMT because of side effects, progression of MS, costs, or other reasons. Also, little information is available about what factors influence whether a person stops using one therapy and how they choose a new one. It is important to consider how patient characteristics, reasons for stopping a DMT, and the choice of a new DMT affect clinical and quality of life outcomes for individuals with MS.

The Study: With the goal of providing guidance to help physicians and individuals with MS select the DMT that best meets their preferences and provides the best outcomes, Dr. Halpern will analyze data from the Sonya Slifka Longitudinal MS Study. This National MS Society-sponsored study interviewed individuals with MS to collect information on switching DMTs, including reasons for stopping a DMT, the new DMT started, and clinical outcomes and quality of life after starting the new DMT. The team will explore how the many factors involved in stopping or switching may affect changes in clinical outcomes and quality of life for individuals with MS. Using this information, they will develop a “DMT Choice Framework” to help guide treatment choices and improve outcomes for people with relapsing MS.

What’s Next: The DMT Choice Framework can help MS physicians and people with MS discuss what is important to consider when switching to a new DMT, and ensure that the perspectives of patients are included in this discussion. Better DMT choices may improve how well a treatment works, decrease the chance of serious side effects, and lead to better outcomes for individuals with MS.

Heather Kane, MA, PhD

RTI International

Research Triangle Park, NC

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$214,840

Title: To what extent are nurse practitioners and physician assistants utilized in MS and what impact do they have on costs, clinical outcomes, and patient satisfaction?

Summary: Researchers at RTI International and University of Arizona are exploring how nurse practitioners and physician assistants may assist neurologists in providing access to care for individuals with MS.

Background: A study by this team, funded by the National MS Society, indicated shortages of neurologists who provide care for individuals with MS; these shortages will likely worsen in the future. Advanced Practice Providers (APPs, that is, nurse practitioners and physician assistants) can assist neurologists in supporting treatment and disease management for individuals with MS. In particular, APPs can initiate MS therapies, educate patients and families, monitor disease progression, and provide social support. Because MS treatment requires long-term disease management, APPs may complement neurologist-provided care by serving as the “hub” for day-to-day care and addressing unmet needs for individuals with MS. This is why the National MS Society released a request for proposals targeting this question.

The Study: First Drs. Kane, Michael Halpern, and colleagues are conducting focus groups with APPs to explore factors affecting their career choices and the challenges they faced in choosing careers providing care for individuals with MS. Information from the focus groups will be used to develop a national survey of APPs to collect information on APP training, the types of MS patient care services



they provide, and the characteristics of the neurology practices where APPs work. The team will analyze the responses to explore how APPs may be able to offer additional assistance to neurologists in providing care for individuals with MS, and how training for APPs may be improved to enhance opportunities for health care professionals to learn more about MS earlier in their career.

What's Next: Results will be used in combination with a second, parallel study being conducted on this topic to help formulate policy and advocacy efforts by the National MS Society and others, and to develop programs aimed at providing better access to high quality comprehensive MS care to all people with MS.

Deborah Miller, PhD

Cleveland Clinic Foundation
Cleveland, OH

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$545,144

Title: Assessing Access, Change, Concerns, and Consequences of People with MS Regarding Four Types of Personal Insurances

Summary: Researchers at Cleveland Clinic are evaluating the availability and concerns around available insurance coverage for individuals with MS and their families.

Background: Many individuals with MS leave the workforce due to progressive worsening of their condition. As access to personal insurance, including health, disability income, long-term care, and life insurance, is largely employer-based or purchased out-of-pocket from earnings, unemployment can lead to significant distress regarding health, financial security, and the future. Even those continuing in the workforce can face worries regarding the cost and coverage of their healthcare plans.

The Study: Dr. Miller's team is evaluating access issues and related concerns that individuals with MS and their families experience regarding health, disability, long-term care, and life insurances. They seek to better understand the worries, stress, and health consequences that people with MS experience related to limited access to insurances or concern that their current insurance may be reduced or eliminated. They will administer a survey to a subset of individuals with MS registered with the North American Research Committee on Multiple Sclerosis (NARCOMS).

What's Next: This survey can yield crucial information on specific concerns faced by individuals with MS in acquiring and maintaining personal insurance, and whether this has an impact on their health. This can help guide the design of programs to ease these concerns.

Brant Oliver, PhD

MGH Institute of Health Professions
Boston, MA

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$244,175

Title: Understanding the impact of nurse practitioners and physician assistants in multiple sclerosis care: A three part study of utilization, quality, and patient experience.

Summary: Researchers at Massachusetts General Hospital are exploring how nurse practitioners and physician assistants may be able to assist neurologists in providing access to care for individuals with MS.

Background: There is a high demand for specialized MS care and there are not enough physicians (neurologists) available to meet this need. The cost of MS care is al-



so very high, which can limit access to care. This creates a need to find ways to deliver high quality care more efficiently. This is why the National MS Society released a request for proposals targeting this question. Dr. Brant Oliver's team is focusing on how Advanced Practice Providers (APPs, that is, nurse practitioners and physician assistants) are used and how often, how much the care they deliver costs, the quality of that care, and the patient experience of that care.

The Study: Dr. Oliver's team is studying APP cost, quality and patient experience outcomes in MS care using three different methods: (1) a study of billing claims data from a large national billing claims data bank, which will yield information on APP care utilization and cost; (2) a study of the North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry to study quality outcomes of APP care; and (3) a patient survey, using My Healthcare Journey (www.healthcarejourney.com), an online MS patient wellness and education community, to learn more about patient satisfaction and experience with MS care delivered by APPs.

What's Next: Results will be used in combination with a second, parallel study being conducted on this topic to help formulate policy and advocacy efforts by the National MS Society and others, and to develop programs aimed at providing better access to high quality comprehensive MS care to all people with MS.

Bianca Weinstock-Guttman, MD

The State University of New York at Buffalo
Buffalo, NY

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/16; **Funding:** \$99,468

Title: Investigation of factors related to stable disease in an aging MS sample as indicators of reduced burden of disease. Priority 5: Secondary analysis of existing datasets

Summary: Researchers at the University of Buffalo are investigating what factors contribute to disability progression in people with MS who are age 60 or over.

Background: The symptoms of disability a person with MS may experience vary greatly from person to person and this unpredictability has led to the search for possible predictors of disease severity. Recent studies have found that older age is a strong predictor of greater disability, but the aging MS population has been inadequately studied. With disability worsening closely related to aging, and with the aging population continuously increasing in number, it is of great importance to investigate what factors contribute to disability stability or progression for people with MS who are age 60 or over.

The Study: Prof. Weinstock-Guttman and colleagues are investigating people with MS who are 60 and over and have been diagnosed for at least 15 years. Data will be obtained from the New York State Multiple Sclerosis Consortium (NYSMSC) registry, with data captured for 10,000 people with MS. They are analyzing a sample of approximately 500 people for whom there is follow-up information for 5 years or more. The team is looking at history of medication use, additional medical conditions, type of



How Many People in the United States Have MS?

There has not been a scientifically sound, national study of the prevalence of MS in the United States since 1975. The National MS Society convened a group of experts to determine the best way to develop a scientifically sound and economically feasible estimate of the number of people in the U.S. who have multiple sclerosis.

After careful investigation, the team determined that the best approach is to develop a method of sampling administrative databases (such as those maintained by insurers, health maintenance organizations, Medicare, Medicaid, Veterans Health Administration, and the U.S. military). Mitchell T. Wallin, MD, MPH (Baltimore Veterans Affairs Medical Center/University of Maryland) is leading this \$1.3 million research project to develop this method. This effort will not only determine how many people in the U.S. have MS, but will also provide prevalence estimates by age, sex, race, and regions. Another aim is to understand how people with MS utilize health care and costs involved. Ultimately the team will determine a strategy to re-assess MS prevalence at regular intervals in the future.

This project will provide a sound estimate of the number of people who have MS in the U.S. and critical information about other social and economic characteristics of the disease, which will inform research, programs and advocacy that will help people with MS live their best lives.

MS, and disability changes over time. Important characteristics that are being examined include gender, race, living environment, employment history, insurance status, marital status and educational status. They also are gathering the participants' reports on their perception of physical disability, activities of daily living and psychosocial function, to help identify modifiable events that could be changed through health care referrals or interventions.

What's Next: The knowledge gained from this research study may have a substantial impact by aiding MS advocates and policy makers to understand and act on issues affecting quality of life and care in the aging MS population.



STOP—Neuropathology (Tissue Damage)

Douglas Feinstein, PhD

University of Illinois at Chicago

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$659,100

Title: Neuroprotective effects of the CRMP2 activator lanthionine ketimine ester in EAE

Summary: Researchers from the University of Illinois are testing the possibility that a natural brain molecule called lanthionine ketimine can prevent neurodegeneration in a mouse model of progressive MS.

Background: In MS, the immune system attacks various components of the brain, including myelin, the fatty substance that surrounds and protects nerve fibers. Nerve cells and their fibers are also damaged in MS. A protein called CRMP2 has been shown to play a role in the health of nerve cells, and also in reducing inflammation and stimulating myelin-making cells to produce myelin. Prof. Feinstein's team is looking at a factor that naturally occurs in the brain and appears to regulate the activities of CRMP2. This factor is called lanthionine ketimine (LK), which they have altered to produce LKE, which more easily enters cells. They have found that LKE reduces inflammation and nerve cell damage in mice with EAE, a model for MS disease.

The Study: The team is testing if LKE reduces neurodegeneration in a chronic model of MS that resembles progressive stages of MS. They are treating mice at times when neurodegeneration begins, using different doses of LKE to find the dose that gives the best benefit, and then testing that dose at a later time when there is greater neurodegeneration. Since one of the known targets of LKE is the protein CRMP2, they are measuring changes in levels of CRMP2 and related proteins during the course of EAE, and will test if LKE pre-

vents those changes. They will test the role of CRMP2 in EAE by using mice that have reduced or increased CRMP2 activity. To determine how LKE and CRMP2 work, they will carry out studies using nerve and myelin-making cells isolated in laboratory dishes.

What's Next: If successful, the results will provide the scientific justification for developing LKE-related compounds for their potential for treating progressive MS.

James Waschek,

University of California, Los Angeles
Los Angeles, CA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$497,802

Title: Molecular dissection of neuroprotective and immunoprotective actions of PACAP signaling in the retina in murine EAE

Summary: Researchers at the University of California, Los Angeles are investigating a molecule called PACAP to see if it has potential for protecting the visual system from damage caused by MS.

Background: In MS, the immune system attacks and destroys components of the brain and often the related visual system as well. However, the nervous system has natural ways to protect itself from inflammation. This study is examining a molecule that may play a role in protecting the nervous system from damage caused by the immune system in MS.

The Study: Prof. Waschek and his team are examining a naturally occurring molecule called PACAP that may protect the nervous system. Using a mouse model of MS called EAE with damage in the visual system, this group is examining if PACAP can provide protection from injury by blocking inflammation and nerve damage to the visual system.



The team is also deleting one of the targets of PACAP to see if it becomes unprotective. If elimination of this target worsens the eye damage, it will show that the particular target normally provides protection. Therapies can then be designed to activate this target to halt the neurological decline in MS.

What's Next: The use of PACAP or activation of the molecules it acts upon may be a therapeutic strategy for reducing the effects of inflammation and protecting the brain, spinal cord, and visual system from damage in people with MS. The biotechnology industry and academic laboratories are working to stabilize and increase the bioavailability of molecules that target PACAP docking sites in anticipation of future clinical trials.

STOP—Diagnostic Methods

Seth Smith, PhD

Vanderbilt University
Nashville, TN

Award: Research Grant

Term: 10/1/15-9/30/17; **Funding:** \$818,004

Title: Quantitative and Longitudinal MRI Characterization of Spinal Cord Damage in Patients with MS

Summary: Imaging specialists at Vanderbilt University are developing and implementing new, high-resolution MRI methods to better visualize and track MS disease activity and damage in the spinal cord.

Background: The spinal cord is responsible for sending and receiving information from the brain and is often damaged in multiple sclerosis. Radiologists are good at detecting and characterizing MS using MRI scans of the brain, but the spinal cord is more challenging to image and has not received the same attention. Spinal cord MRI shows some damage in MS, but as in brain MRI, the areas showing

damage are sometimes poorly related to the neurological problems that some people with MS experience. With current advancements in MRI hardware, software, and design, researchers now can examine the spinal cord structure better than ever before to see more lesions, appreciate more fully disease-related tissue damage, and examine the biochemical changes that may occur before the spinal cord tissue is destroyed.

The Study: Dr. Smith and colleagues are developing and implementing a new, high-resolution MRI method to better visualize MS lesions in the spinal cord. They also are developing novel MRI methods that can see inside the spinal cord tissue to examine the nerve-insulating myelin and biochemistry of the spinal cord. They will relate these new MRI methods to the sensory and motor problems associated with spinal cord damage, with the goal of seeing which combinations of new MRI methods might be able to predict improvement or worsening of symptoms, and potentially offer a new tool for evaluating whether or not therapies are effective. To do so, the team is obtaining spinal cord imaging scans in 25 healthy volunteers and 50 people with MS.

What's Next: If this team can show that this new, rapid, non-invasive method is better than the standard MRIs, this has the potential to improve the care and management of MS and speed clinical translation and trials of new therapies.



STOP—Biology of Glia

Richard Daneman, PhD

University of California, San Diego
San Diego, CA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$780,002

Title: Mechanisms of blood-brain barrier disruption during neuroinflammation

Summary: University of California, San Diego researchers are studying how the barrier between the blood vessels and the brain becomes leaky, a condition in MS that allows potentially harmful cells and molecules to enter the brain from the bloodstream.

Background: Unlike other parts of the body, the blood vessels in the brain have a tight barrier that inhibits molecules and cells from moving freely out of the blood and into the brain. Damage to this “blood-brain barrier” or “BBB” allows harmful immune cells and molecules to enter the brain and cause damage during MS. Pericytes, a type of cell adjacent to blood vessels, are involved with maintaining the integrity of the BBB by modulating the presence of a group of four genes collectively called “EHDs.”

The Study: Dr. Daneman and his team are testing the idea that in MS, pericytes may not correctly modulate the presence of EHDs or interact properly with blood vessels, leading to a leaky BBB. Studying mice in which EHDs are overrepresented in blood vessels in the brain, they are analyzing how increased expression (presence) of EHDs leads to a leaky BBB. They are also studying mice with the MS-like disease EAE that are lacking active EHDs in the blood vessels, and monitoring disease severity and immune cell infiltration into the brain. Finally, they are determining the details of how EHD expression is controlled.

What’s Next: Increasing our understanding of what leads to a leaky blood-brain barrier in MS will contribute to the development of new approaches to stop or limit the severity of MS.

Gareth John, PhD

Icahn School of Medicine at Mount Sinai
New York, NY

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** TBD
Co-funded with the National Institutes of Health

Title: Reactive astrocytes control leukocyte and humoral trafficking into the CNS

Summary: Researchers are investigating cells and proteins that control entry of harmful immune cells and molecules into the brain for clues to stopping this influx in MS.

Background: Various harmful immune cells and immune messengers enter the central nervous system in MS, damaging tissues and driving relapses. New therapies are needed to limit entry of these harmful components into the brain and spinal cord. Such therapies are expected to limit the development and progression of disability. Cells and molecules present in the blood must pass through two barriers to enter the brain: first, the blood-brain barrier (BBB) and second, the glia limitans (GL).

The Study: In previous studies, Dr. John’s laboratory examined factors that mediate harmful opening of the BBB. In this current study, Dr. John and his team are focusing on the GL. A type of brain cell called reactive astrocytes appear to mediate the integrity of the BBB and the GL. Using mice in which individual proteins can be deleted, Dr. John’s team is testing the idea that different proteins present in reactive astrocytes selectively mediate entry of immune messengers or im-



Illinois Lottery Pilot Projects

The MS lottery ticket is one of five specialty scratch-off tickets in Illinois that benefit charitable causes/organizations. Proceeds go to the MS Research Fund within the Illinois Department of Public Health's budget. Since the first ticket was sold in 2008, more than \$7 million has been raised for MS research. Research grants are distributed from the fund to neurologists, scientists, and other medical professionals at statewide institutions whose work is focused on MS.

Awardee	Location	Project Title
David Everly, PhD	Rosalind Franklin University	Association between viral load and encephalitogenic T cell activation in MS
Makio Iwashima, PhD	Loyola University – Chicago	Monocyte-based immune tolerance for MS
Curtis Johnson, PhD	University of Illinois at Urbana-Champaign	Evaluating subcortical degeneration with MR elastography and its relation to cognition and aerobic fitness in MS
Gopal Thinakaran, PhD	University of Chicago	Deciphering the role of BIN1 in MS

immune cells into the brain through the GL. Finally, they are using mouse models of MS to test the importance of these astrocyte proteins and GL barrier integrity on disease severity. These studies address mechanisms for controlling tissue damage in MS.

What's Next: This project will help determine the importance of the GL as a critical second barrier that may be a target for stopping the entry of harmful components into the brain in MS, and may have broader implications for delivering therapeutic molecules into the brain.

STOP—Infectious Agents

Katharine Whartenby, PhD

Johns Hopkins University
Baltimore, MD

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$671,997

Title: Mechanisms of Increased Morbidity and Mortality of Influenza Infections in People with MS

Summary: Researchers at Johns Hopkins University are studying mice with MS-like disease that are infected with flu virus to investigate why flu is dangerous for people with MS.



Should dose and timing of flu vaccines be calibrated specifically for people with MS ?

Background: People with MS appear to be more susceptible to infections than people of similar ages without MS, independent of immune-suppressive therapies, and the lungs are particularly vulnerable. The lung is a site of inappropriate activation of the immune system in people with MS, and this may damage the lung and worsen MS and infections.

The Study: Dr. Whartenby and her team are investigating why people with MS are more susceptible to viral infections such as influenza, and what might be done to address it. To gain an understanding of what happens to people with MS, they are examining mice with EAE, a model of MS, that are infected with the flu virus. People with MS report being sicker or that their MS relapses after having the flu. Therefore, Dr. Whartenby and her team are examining whether mice with both EAE and influenza have worse EAE symptoms and/or worse flu-like symptoms than mice with only one disease. The team is also investigating the role and timing of flu vaccines to determine whether dose and timing should be calibrated specifically for people with MS in terms of disease activity.

What's Next: This study will add to our understanding of why people with MS are more vulnerable to infection, and may lead to the development of guidance around the timing and use of vaccines.

STOP—Role of the Immune System

Gabriela Constantin, MD, PhD

University of Verona
Verona, Italy

Award: Research Grant

Term: 10/1/15-9/30/17; **Funding:** \$140,000

Title: The role of neutrophil trafficking mechanisms in the pathogenesis of animal models of multiple sclerosis

Summary: Researchers at the University of Verona are examining immune cells called neutrophils in mice with an MS-like disease for clues to their possible role in MS inflammation and progression.

Background: Neutrophils represent the most abundant immune-related cells in the blood, and are essential for clearing away foreign microbes during infections. Neutrophils can release several inflammatory messengers and toxic products, and they can directly or indirectly interact with other immune cells, promoting or regulating their functions. Neutrophils may also produce collateral tissue damage via inflammation, and a detrimental role for neutrophils has been discovered in brain trauma, epilepsy and stroke. Preliminary evidence suggests a damaging role for neutrophils in MS and the MS model EAE, but their role in disease onset and progression is unclear.

The Study: Dr. Constantin's team is examining how neutrophils leave the blood and enter the brain and spinal cord during EAE, and the interactions these cells have once they are within the central nervous system. The team's preliminary findings indicate that within the brain, neutrophils interact with other immune cells called microglial cells, possibly influencing their activation and behavior including the type of inflammation seen during progressive stages of MS. The team has evidence



that neutrophils gain access to the brain using a new mechanism of cell adhesion under inflammatory conditions. To further explore this mechanism, they are investigating activities of neutrophils in early and chronic phases of EAE.

What's Next: The insights the team gains about mechanisms that allow neutrophils to gain access to the brain and possibly drive inflammation and progression may open up new approaches and targets for stopping MS.

Youhai Chen, MD, PhD

University of Pennsylvania
Philadelphia, PA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$676,829

Title: MS and the Transcription Factor c-Rel

Summary: Researchers are testing whether compounds that block a key molecule in the MS immune attack are effective in blocking disease activity in cells obtained from people with MS.

Background: MS involves an immune system response that damages the brain and spinal cord. Several large-scale studies of genetic risk factors for MS have established that a molecule called "c-Rel," which instructs the activity of genes (known as a transcription factor) is a risk factor for MS and other diseases that involve the immune system. Mice that are genetically designed to lack c-Rel are resistant to developing MS-like disease.

The Study: This team believes that treatments that target c-Rel might be effective for treating MS. To test this theory, they have identified two classes of small molecules that specifically inhibit c-Rel function by preventing it from binding to DNA. Preliminary studies in mice indicate that these compounds are highly effective in diminishing the severi-

ty of EAE, an MS-like disease. Now Prof. Chen's team is seeking to understand how c-Rel regulates immune responses in people by testing the effect of compounds that block c-Rel in immune cells from people with MS.

What's Next: Information generated from these studies will help determine the role of c-Rel as a risk factor for MS, and help develop novel c-Rel blocking compounds that may have future potential for treating MS.

Bonnie Dittel, PhD

BloodCenter of Wisconsin
Milwaukee, WI

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$706,686

Title: Characterization of a novel regulatory B cell subset that attenuates EAE

Summary: Researchers are investigating how a subset of immune "B cells" reduces inflammation, for clues to harnessing this power to stop MS.

Background: In MS, the immune system damages tissues in the brain and spinal cord, and finding a way to reduce or stop this immune response, which includes inflammation, may be key to stopping MS in its tracks. The immune system has its own mechanisms for reducing inflammation. One of these mechanisms is mediated by an immune cell type called B cells. B cells are best known for their ability to produce antibodies that can clear microorganisms. However, certain B cells, called regulatory B cells ("Bregs") can control inflammation. In preliminary findings this team has shown that Bregs promote the expansion of another regulatory immune cells called regulatory T cells ("Tregs"). Tregs have been shown to be essential for turning off immune attacks in MS.



The Study: Dr. Dittel's team is seeking to understand how Bregs communicate with Tregs in mice with EAE, an MS-like disease. They will use antibodies that bind to specific proteins on the surface of B cells to identify B cell subsets, looking for Bregs that drive Treg expansion and drive recovery from EAE. In order to translate these findings in mice to human MS, they must determine whether the same population of Breg exists in people, and will obtain human B cells to do this.

What's Next: Identifying and knowing more about B cells capable of turning off inflammation will help determine how this power can be harnessed to stop MS, and better inform research on B cell-depleting therapies such as ocrelizumab, now in clinical trials in MS.

Christopher Jewell, PhD

University of Maryland - College Park
College Park, MD

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$598,715

Title: Harnessing intra-lymph node controlled release to promote myelin-specific tolerance

Summary: Researchers at the University of Maryland are investigating a strategy that may help turn off the harmful aspects of the immune system that occur in MS while leaving beneficial functions of the immune system intact.

Background: In MS, the immune system incorrectly recognizes components of the nervous system as foreign and mounts a harmful immune response. These harmful responses are directed against components of myelin, the fatty substance that surrounds and protects nerve fibers. Nerve fibers and nerve cells are also damaged. Current therapies for MS broadly decrease the activity of the immune system, often leaving people vulnerable to

infection. An unmet need in MS is to have more specific ways to decrease the harmful aspects of the immune system while leaving helpful functions intact.

The Study: Dr. Jewell and his team are using specially designed polymer particles they believe will reprogram the immune system not to attack myelin components. To test this idea, the group is using two mouse models of MS, one mimicking aspects of relapsing-remitting MS and a second that mimics aspects of progressive MS – a stage of disease with particularly limited treatment options. The team is using degradable polymer particles to introduce regulatory immune signals directly into lymph nodes – the tissues that control immune function. The studies will track the impacts on disease course, immune activity, tissue damage, and safety. They are also determining how specific the response is to see whether the ability to fight off other infections is retained.

What's Next: Results from this study may suggest ways to correct or suppress harmful immune responses to myelin components without suppressing the entire immune system. This may lead to improved treatments for people with all forms of MS.

Jonathan Kipnis, PhD

University of Virginia
Charlottesville, VA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$660,000

Title: The role of meningeal lymphatics in EAE/MS

Summary: University of Virginia researchers are exploring the role of a previously unknown path of immune cells for clues to stopping MS.



Background: MS is thought to involve immune-system attacks on the brain and spinal cord, but there are many facets of this immune response that are not well understood. This team has recently uncovered evidence of a previously unknown path of immune cells from the brain and the spinal cord directly into the deep cervical lymph nodes (the draining lymph nodes of the brain and spinal cord), where the initial phases of immune activation are taking place. These are called meningeal lymphatic vessels. Professor Kipnis and his team proposes that these vessels ensure that T cells remain silent and do not attack the brain, but when this mechanism fails, attacks ensue. The team is now investigating the possible involvement of these vessels in MS models.

The Study: Prof. Kipnis and colleagues are investigating the initiation of immune attack in the meninges, which is a layer of tissues surrounding the brain and the spinal cord. In mouse models of relapsing and progressive MS (EAE), the team is studying the circulation of cells between the meninges and the deep cervical lymph nodes and assessing when and how the signal that triggers and activates destructive immune T cells is being delivered. Using pharmacological, genetic and biochemical approaches, the team will focus on understanding the role of the meningeal lymphatic system in regulating immune responses, and how it impacts the initiation, progression and severity of MS-like disease in mice. They will also attempt to manipulate this system to interrupt the disease process.

What's Next: Better understanding of how lymphatic vessels that are potentially controlling inflammation in the brain will open the door to targeting these vessels therapeutically to interfere with the course of their action (or restore their lost action) to stop MS.

Booki Min, DVM, PhD

Cleveland Clinic Foundation
Cleveland, OH

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$614,018

Title: IL-27-conditioned Foxp3+ regulatory T cells, a novel Treg therapy to treat autoimmune inflammation in the CNS

Summary: Researchers are exploring a novel way of reducing the immune attack on the brain and spinal cord that occurs in MS.

Background: MS involves immune system attacks on the brain and spinal cord. Certain T cells, called Tregs, are known to play a role in balancing immunity and turning off attacks. Increasing evidence suggests that MS may involve decreased Treg numbers or function, so finding a way to correct the Treg defect is a strategy being investigated to treat MS. This team is taking a novel approach utilizing an immune messenger protein known as interleukin-27 (IL-27) to improve Treg function. They have found that pre-stimulating Tregs with IL-27 dramatically enhances their function so that they can reduce disease activity in mouse models of MS.

The Study: Dr. Min and colleagues have engineered a new mouse model in which Tregs are unable to receive IL-27 signals. The team is now testing the importance of IL-27 stimulation of Tregs for controlling inflammation in mice with MS-like disease. They are identifying the cellular mechanisms by which Tregs execute a regulatory role during the immune attack and how IL-27 controls those processes, and testing the practical application of IL-27 stimulation to treat inflammation in the brain/spinal cord.

What's Next: This study should help to determine the therapeutic potential of Treg transfer therapy for treating MS in the future.



RESTORE

Research related to restoring what's been lost in MS focuses on understanding how nerves and their protective myelin coating work normally, and how repair of these critical tissues and cells can be facilitated. Research on restoring function also focuses on lifestyle/wellness approaches, including exercise, diet, and rehabilitation strategies.

RESTORE—Lifestyle/Wellness

Ekaterina Dobryakova, PhD

Kessler Foundation Research Center
West Orange, NJ

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$408,836

Title: The Effect of Feedback Presentation on the Fronto-Striatal Network Activity and Fatigue in Individuals with MS.

Summary: Researchers at the Kessler Foundation are investigating whether a rehabilitation technique known as “feedback presentation” can relieve fatigue experienced by people with MS.

Background: Many people with MS experience unusually severe physical and mental fatigue. A technique called feedback presentation informs individuals about how successful they are at performing a particular task. Feedback presentation has been shown to affect the activity of the “fronto-striatal network” of brain areas that has been suggested to be compromised in individuals with fatigue. The activity of this network increases during positive feedback presentation (such as receiving food or money) and decreases during negative feedback presentation (omission of expected food or money).

The Study: Preliminary data from Dr. Dobryakova's team indicates that feedback presentation during a gambling task alleviates fatigue in individuals with MS. This current study extends these findings to a learning environment that is more representative of rehabilitation settings. The team is conducting a study where individuals with MS and without MS undergo a brain scan while performing a learning task with two feedback conditions (monetary and non-monetary feedback) and a no-feedback condition. During the feedback conditions, participants will be presented with either positive or negative feedback. Self-reported fatigue ratings will be acquired at intervals during the scan to determine which types of feedback may be capable of reducing fatigue.

What's Next: This study should help determine whether a feedback technique can alleviate MS fatigue without medication, which would represent a major step forward for people with MS.

Charles Guttman, MD

Brigham and Women's Hospital
Boston, MA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$595,326

Title: Neurogenic Determinants of Fatigue in MS

Summary: Researchers are investigating the relationship between fatigue in people with MS and damage to a particular circuit in the brain using advanced imaging techniques.

Background: Fatigue is a common symptom experienced by people with MS. Fatigue is defined as an overwhelming sense of tiredness, lack of energy or feeling of exhaustion. It affects not only physical but mental performance. This project aims to study the relationship between fatigue in MS patients and



Adult Day Programs: Finding the Best Solution

MS Adult Day Programs are emerging as an important source of support for people with MS in carrying the activities of daily living and improving access to respite services for family members who are taking care of people with MS. For participants, these programs offer life-enhancing services, including medical care, rehabilitation therapies, nutrition therapy, social interaction, and stimulating activities, keeping people engaged in their communities. However, these services are not consistently available through insurance coverage, and there is insufficient documentation of their impact.

For these reasons, the Conrad N. Hilton Foundation and the National MS Society joined forces to release a request for research proposals targeting an evaluation of the cost effectiveness and other impacts of these programs. As a result of this request, Joseph Gasper, PhD, Christine Borger, PhD (Westat, Inc.) and colleagues are funded to collect responses and outcomes in people involved in MS adult day programs at 16 different sites around the country, and compare them with those from people with MS who are not participating in such a program. Their evaluations will focus on whether participation in an MS Adult Day Program reduces health care utilization and long-term health care costs, compared to non-participants. The team will also determine if participation improves emotional and cognitive well-being, both for people with MS and caregivers.

This study will provide critical information needed to make MS Adult Day Programs more widely available and improve their funding from insurers and other sources.

damage to a particular circuit in the brain called the fronto-striatal pathway. This pathway links the front part of the brain to deeper structures of the brain, and plays an important role in both motor and cognitive functions. In particular, the team is seeking to understand whether people with significant damage to these brain structures are less able to treat their fatigue with medication or other interventions, such as exercise.

The Study: Dr. Guttmann is enrolling three groups of participants: people with MS with sustained fatigue that is unresponsive to therapy, people who had fatigue in the past but are currently able to manage it, and people who never experienced fatigue. They are measuring the brain structures of interest by outlining them on available MRI exams, and will then relate these measurements to fatigue levels. Participants also will undergo more advanced MRI exams, allowing a more



detailed look at the nerve fibers that connect the brain structures within this pathway. They also are asking participants to record their sleep patterns and to answer detailed questions about their fatigue and any medications they are taking.

What's Next: This study should improve our understanding of MS fatigue, help predict who might benefit from available fatigue treatments, and point the way for future solutions to fatigue in people with MS.

Robert Motl, PhD

University of Illinois at Urbana-Champaign
Urbana, IL

Award: Healthcare Delivery & Policy Contract

Term: 10/1/15-9/30/18; **Funding:** \$403,312

Title: Project COMPLETE: Coordinated Multiple Sclerosis Exercise Toolkit

Summary: Researchers at the University of Illinois at Urbana-Champaign are developing a set of tools to promote physical activity in people with MS, which is expected to reduce disability and improve quality of life.

Background: People with MS who have mild to moderate levels of disability can benefit greatly from exercise and physical activity. However, most do not engage in regular exercise. It is currently unclear what people with MS want and need to engage in regular exercise, or what healthcare providers may be able to do to meet the needs and wants of their patients regarding exercise behavior.

The Study: Prof. Motl and his team are developing a conceptual model (i.e., conceptual representation of a real-world phenomenon) that will guide the promotion of exercise in people with MS through interactions between the individual and his or her healthcare provider. Based on this model, they will then develop a "tool kit" that will

provide methods to put this model into practice to promote exercise-minded behavior. The team will eventually evaluate the effectiveness of this tool kit to promote increased physical activity in people with MS.

What's Next: Successful development of an approach to increase people's engagement in exercise would be widely disseminated for its potential for reducing disability and improving quality of life for people with MS.

RESTORE—Nervous System Repair

Sue Barnett, PhD

University of Glasgow
Glasgow, Scotland

Award: Research Grant

Term: 10/1/15-9/30/16; **Funding:** \$407,332

Title: Mesenchymal stem cells (MSCs) isolated from the olfactory mucosa as a source of cells for treatment of MS

Summary: Researchers are investigating if adult stem cells from the nose can dampen harmful aspects of the immune system and improve myelin repair.

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, leading to symptoms in people with MS. One strategy for treating MS is to both repair myelin and reduce the harmful effects of the immune system. Previous studies have shown that a type of adult stem cell resident in the body, called "mesenchymal stem cells" (MSCs), can help repair the nervous system. MSCs are usually obtained from bone marrow but are found in other tissues.



The Study: Prof. Barnett and her team are investigating whether MSCs obtained from inside the nose may be a more viable source of repair cells than MSCs obtained from bone marrow. Her group is isolating MSCs from bone marrow and from the nose and growing separate populations of these cells in a dish. Using mice with myelin damage, they are asking which population of MSCs influences immune cells so that they cause less damage, and which increases cells that repair myelin.

What's Next: MSCs can be easily obtained from the nose without major surgery, and injecting these cells into patients with spinal cord injuries has been found safe. If necessary research continues to be positive, nose-derived stem cells may ultimately be tested for their benefits in treating people with MS.

Benjamin Deneen, PhD

Baylor College of Medicine
Houston, TX

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$669,948

Title: The role of NFIA in reactive astrocytes after white matter injury

Summary: Researchers are investigating a protein that may play a role in myelin repair and replacement of lost nerve cells, two events that may improve progressive MS.

Background: In MS, the myelin sheath, which is the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed. Nerve cells and nerve fibers are also damaged. Myelin destruction triggers a cascade of natural events that attempt to repair myelin and limit damage. One component of this repair response is a type of brain cell called "reactive astrocytes." These cells are abundant in MS lesions and recent research suggests that they may be involved in facilitating the repair of myelin and may also even help restore damaged nerves in MS lesions.



Researchers are investigating if adult stem cells from the nose can dampen harmful aspects of the immune system and improve myelin repair.

The Study: Dr. Deneen and his team are studying a protein called "NFIA" that is produced in reactive astrocytes. This protein appears to control their production, and impacts myelin repair. The team is investigating NFIA in reactive astrocytes in MS lesions, and identifying its role in new and longer-term areas of myelin damage in mice. They are also looking at the possibility that interfering with NFIA may cause reactive astrocytes to turn into new nerve cells, which could hold promise for replacing nerve cells lost in MS.

What's Next: If this research is successful, it could someday lead to the development of a therapy that stimulates the natural ability of reactive astrocytes to repair the brain.



Ian Duncan, BVMS, PhD, FRSE

University of Wisconsin-Madison
Madison, WI

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$648,468

Title: Remyelination following global demyelination and its promotion in a novel animal model

Summary: Researchers are exploring factors controlling the repair of myelin and ways to non-invasively detect and enhance repair.

Background: Myelin, the nerve-insulating coating that promotes nerve signaling in the brain and spinal cord, is damaged in MS and often the body's natural repair processes cannot keep up, leaving nerve fibers vulnerable and unable to send signals properly. One possible way of protecting nerves from destruction in MS is to facilitate myelin repair.

The Study: Professor Duncan and team are studying myelin damage and repair in a model that provides opportunities to study myelin at many stages of damage and recovery. The team is studying sources of repair cells in the brain, the timing of their activity, and the ability of restored myelin to protect against nerve loss. They are examining repair in the optic nerve and also the spinal cord to see what may account for differences. The team is also using advanced MRI in this model to visualize changes in myelin non-invasively with an eye toward developing standard ways of examining myelin repair in people with MS.

What's Next: This research will enhance our understanding of factors controlling the repair of nerve-insulating myelin and suggest new approaches to stimulating repair to restore function in people with MS.

Brian Popko, PhD

University of Chicago
Chicago, IL

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$629,322

Title: Investigating the role that ZFP191 phosphorylation state plays in regulating oligodendrocyte maturation

Summary: University of Chicago researchers are studying a molecular "switch" that may be a key to turning on the repair processes of nerve-insulating myelin to restore function to people with MS.

Background: Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS. Although the brain has an inherent ability to make new myelin, myelin repair in MS is often insufficient. People with advanced MS have a reduced ability to repair myelin, and this inability leads to persistent symptoms. The cells in the brain and spinal cord that make myelin are called oligodendrocytes. In people with MS, oligodendrocytes appear to be "stuck" in an immature state in which they cannot make new myelin. Increasing our understanding of factors that can push oligodendrocytes to fully mature so they can make new myelin is important for developing strategies to repair myelin and restore function in multiple sclerosis.

The Study: Prof. Popko and his team are studying a factor called ZFP191 that may act as a "switch" in the oligodendrocyte maturation process. ZFP191 binds to DNA near myelin-related genes and controls the activity (expression) of those genes. The team has preliminary evidence of the molecular process (phosphorylation) that turns on and off ZFP191 activity. In this study, Dr. Popko and his team are identifying the enzymes that are involved in this on and off activity to find a



way to activate oligodendrocyte maturation and myelin repair.

What's Next: Because the activity of enzymes that interact with ZFP191 may be controlled with drugs, the results from this study may suggest therapeutic strategies to improve myelin repair in people with MS.

RESTORE—Biology of Glia

Carlos Parras, PhD

INSERM - Institut National de la Santé et de la Recherche Médicale
Paris, France

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$675,977

Title: Chd7 chromatin remodeler function in myelination and remyelination

Summary: Researchers at INSERM in Paris are examining MS lesions and mouse models to investigate the role of a protein called CHD7 in chromatin remodeling, which is required for oligodendrocyte maturation and subsequent myelin repair.

Background: Myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed in MS. Nerve fibers and cells are also damaged. Although the brain is able to repair myelin, repair is incomplete, and the myelin repair ability decreases as MS progresses. Nerve fibers that have lost their myelin and failed to repair it do not function properly, leading to symptoms in people with MS. The cells in the brain that make myelin are called oligodendrocytes. These cells must change from an immature to a mature state to myelinate. Oligodendrocytes in MS brains appear to be “stuck” in an immature state. Therapies to push these cells into a mature state may improve myelin repair and thus symptoms in people with MS.

The Study: The process of oligodendrocyte maturation involves a step called “chromatin remodeling.” Chromatin refers to the DNA inside cells plus proteins that the DNA is wound around. When chromatin is densely packed, the genes on the DNA cannot be accessed and thus cannot be turned on. When an oligodendrocyte matures, the chromatin unwinds in a process called chromatin remodeling so that the genes that must be expressed for myelin synthesis can be turned on. A protein that may be important for chromatin remodeling in oligodendrocytes is called CHD7. Dr. Parras and his team are using mice in which CHD7 can be specifically deleted in oligodendrocytes, and are looking at myelin repair after injury. They are also looking at CHD7 in active and chronic MS lesions, and looking at what genes CHD7 controls.

What's Next: Determining the genes and mechanisms controlled by CHD7 in myelin formation/repair and developing ways of increasing the activity of CHD7 may be a therapeutic strategy to improve myelin repair ability in people with MS.

Xianhua Piao, MD, PhD

Boston Children's Hospital
Boston, MA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$103,250
Co-funded with the National Institutes of Health

Title: The role of GPR56 in CNS myelination and myelin repair

Summary: Investigators at Boston Children's Hospital are studying a protein involved in the growth of nerve-insulating myelin as a possible mechanism for stimulating myelin repair in MS.

Background: Myelin is the fatty insulation that covers nerve fibers and allows for the



31 New Pilot Projects Take Aim at MS

One way the Society propels MS research forward 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 ideas are worth pursuing. Grants begin October 1, 2015.



STOP

Konstantin Balashov, MD, PhD (Rutgers, The State University of New Jersey, New Brunswick) is understanding the role of B cells in the immune attack in MS.

Paul Bollyky, MD, PhD (Stanford University, Stanford, CA) is exploring a novel immune pathway that may lead to recurrent relapses in MS.

Bogoljub Ciric, PhD (Thomas Jefferson University, Philadelphia, PA) is exploring an immune protein's role in driving the immune attack in MS-like disease in mice.

Daniel Harrison, MD (University of Baltimore, Baltimore, MD) is exploring whether inflammation is present in progressive MS using high field MRI.

Jeff Hill, PhD (University of New Mexico, Albuquerque, NM) is exploring immune system events that may prevent repair in MS.

Ilana Katz Sand, MD (Icahn School of Medicine at Mount Sinai, New York, NY) is conducting a trial to determine whether a salt-lowering treatment affects MS progression.

Eric Klawiter, MD (Massachusetts General Hospital, Boston) is assessing an advanced MRI technique for the ability to track nerve fiber damage, disability and cognitive function in MS.

Sarah Minden, MD (Brigham and Women's Hospital, Boston, MA) is exploring the effectiveness of telehealth for improving access to care for people with MS.

Robert Naismith, MD (Washington University School of Medicine, St. Louis, MO) is evaluating a novel method of assessing optic nerve damage and repair.

Maiken Nedergaard, MD, DMSc (University of Rochester Medical Center, Rochester, NY) is investigating a novel aspect of the immune attack in MS for clues to stopping the attack.

Ruben Papoian, PhD (University of Cincinnati, Cincinnati, OH) is examining a possible mechanism for the effects of vitamin D3 in MS.

Steven Patrie, PhD (The University of Texas Southwestern Medical Center, Dallas) is using advanced technology to monitor proteins over time to determine their role in MS progression.

Laura Piccio, MD, PhD (Washington University School of Medicine, St. Louis, MO) is examining people treated with Tecfidera to see how certain white blood cells are affected.

Leonid Pobeziński, PhD (University of Massachusetts Amherst, Amherst, MA) is exploring a novel strategy for stopping the T cells that drive the immune attack in MS.



Joseph Reynolds, PhD (Rosalind Franklin University, Chicago, IL) is exploring the role of a certain signal in activating the immune attack in MS.

Erik Shapiro, PhD (Michigan State University, East Lansing, MI) is evaluating the capability of novel imaging technology to pinpoint immune system activity early in the course of MS.

Larry Sherman, PhD (Oregon Health and Science University, Portland, OR) is testing a compound for its effects on disease progression in MS models.

Olaf Stuve, MD, PhD (The University of Texas Southwestern Medical Center, Dallas, TX) is investigating the role of a possible environmental trigger in worsening MS.

Howard Weiner, MD (Brigham and Women's Hospital, Boston, MA) is determining whether a hormonal therapy approved for menopausal symptoms provides benefit in women with MS.

RESTORE

Leigh Charvet, PhD (NYU School of Medicine, New York, NY) is testing an at-home method of delivering mild electrical stimulation to improve MS symptoms.

Ruth Defrin, PhD (Tel Aviv University, Tel Aviv, Israel) is investigating a source of chronic pain in MS, for clues to treatment strategies for reducing pain.

Alban Gaultier, PhD (University of Virginia, Charlottesville, VA) is investigating whether the composition of gut bacteria contributes to depression in people with MS.

Stefan Gold, PhD (Charité - Universitätsmedizin Berlin) is exploring how MS affects brain circuits that are important for the processing of emotional and social information.

Jeffery Hebert, PT, PhD (University of Colorado, Denver, Denver, CO) is determining whether a computerized test is able to predict falls in persons with MS.

Victoria Leavitt, PhD (Columbia University, New York, NY) is administering aspirin to people with relapsing MS, to see if treatment can lower brain temperature, and reduce fatigue.

Carmen Melendez-Vasquez, PhD (Hunter College, New York, NY) is investigating novel technology for tracking myelin repair.

Robert Motl, PhD (University of Illinois-Urbana-Champaign, Champaign, IL) is determining factors that contribute to sedentary behavior in people with MS.

Lara Pilutti, PhD (University of Illinois at Urbana-Champaign, Urbana, IL) is testing a cycling program for reducing vascular conditions that affect people with MS.

Prudence Plummer, PhD (University of North Carolina-Chapel Hill) is conducting a clinical trial of Ampyra combined with physical therapy for improving walking and cognition in MS.

Alex Strongin, PhD (Sanford-Burnham Medical Research Institute, La Jolla, CA) is exploring whether a specific molecule is related to pain levels in people with MS.

Stella Tsirka, PhD (State University of New York at Stony Brook, Stony Brook, NY) is investigating a strategy for both battling inflammation and improving repair in MS.



If air pollution is associated with increased risk of MS, this could provide evidence for advocating for pollution reduction policies.

nervous system to function properly. In the brain and spinal cord, cells known as oligodendrocytes make the myelin sheath. MS damages myelin, causing debilitating symptoms. Repair occurs, but often fails to keep up with the damage. This team is studying a protein related to myelin growth as a possible mechanism for repairing myelin in MS. They are seeking to learn more about the protein, called GPR56, in normal myelin formation during development and during repair.

The Study: Dr. Piao and colleagues are studying how GPR56 regulates oligodendrocyte development using a mouse model where the GPR56 gene is deleted. They are exploring the effects of deleting GPR56 for clues to its function during myelin growth and repair. They also are looking at what type of cells produce GPR56 in brain tissue derived from people with MS, as well as what GPR56 binds to in the brain to promote myelin formation.

What's Next: This study should shed light on whether GPR56 can be considered as a target for future therapeutic strategies to repair myelin and restore function to people with MS.

Carmen Sato-Bigbee, PhD

Virginia Commonwealth University
Richmond, VA

Award: Research Grant

Term: 10/1/15-9/30/18; **Funding:** \$792,413

Title: The mu-opioid/nociceptin-orphanin FQ receptor system in oligodendrocyte development and remyelination

Summary: Researchers are investigating newly discovered docking sites that may be key to stimulating natural repair of nerve-insulating myelin.

Background: MS involves damage and loss of myelin in the brain and spinal cord. Myelin insulates and protects nerve fibers, and finding a way to stimulate repair of myelin is a possible way of stopping damage to nerve fibers and cells. The brain contains resident cells that can transform into mature myelin-making cells (oligodendrocytes) that can regenerate myelin. These often fail to keep up with myelin damage in MS.

The Study: Dr. Sato-Bigbee's team has found two docking sites that work together to control the generation of oligodendrocytes. These docking sites interact with endorphin and nociceptin, two molecules that are present at different levels in the brain and spinal cord. The team is now investigating how these docking sites are involved in remyelination, and whether they would be good targets for the development of a therapy to stimulate myelin repair. The team will also examine cerebrospinal fluid and brain tissue samples obtained from people with relapsing-remitting, secondary-progressive, and primary-progressive MS to understand the activities of these docking sites during disease.

What's Next: This study may lead to the development of new pharmaceutical approaches to stimulating repair of myelin in MS.

**END**

Ending MS forever means finding the cause of MS, what triggers it, and what may protect against it so that we can prevent MS for future generation. Research into ending MS includes studies to identify MS-related genes, because genes make people susceptible to MS. Another research area is to better understand factors in the environment that influence whether a person gets MS, and identifying possible infectious triggers for MS.

END—Epidemiology**Natalia Palacios, ScD**

Harvard T.H. Chan School of Public Health and Harvard Medical School
Boston, MA

Award: Research Grant

Term: 10/1/15-9/30/16; **Funding:** \$76,554

Title: Air Pollution and Risk of Multiple Sclerosis

Summary: Investigators are exploring whether exposure to air pollution is associated with risk of MS.

Background: The cause of MS remains subject to intense investigation, and environmental factors are believed to contribute strongly to MS risk and progression. Exposure to air pollution has been implicated in a wide variety of diseases, such as heart disease and stroke. However, the effects of air pollution on diseases of the central nervous system have been little explored. Although some research has linked air pollution to higher rates of MS relapse, no study has answered the question of whether air pollution could affect the risk of developing multiple sclerosis.

The Study: Dr. Palacios will address the question of whether exposure to air pollution contributes to MS risk by evaluating data from two large groups of women enrolled in the

Nurses' Health Studies, which include hundreds of thousands of female nurses followed over the last several decades. All of the nurses report their residential addresses throughout the study, and their health status – including whether they developed MS – is also captured. Air pollution measures for each woman in the study are derived from their residential address using a geographical information system (GIS). The investigators will link individual places of residence at different ages with location-specific air pollution levels, and examine whether air pollution levels are related to risk of developing MS.

What's Next: If air pollution is associated with increased risk of MS, this could provide further scientific evidence for advocating for pollution reduction policies, and also contribute to research to understand the cause of MS.

END—Genetics**Trevor Kilpatrick, MBBS, PhD**

Florey Institute of Neuroscience and Mental Health
Melbourne, Australia

Award: Research Grant

Term: 10/1/15-9/30/17; **Funding:** \$539,341

Title: Understanding the Role of MERTK in the Aetiology and Pathogenesis of MS

Summary: Researchers at the University of Melbourne in Australia are investigating the function of an immune cell protein which is abnormal in some people with MS, to understand its potential role in MS.

Background: Both genetic and environmental factors play a role in causing MS, but the details are not clear. Dr. Kilpatrick and his team previously identified a gene called "MERTK" as being associated with increased susceptibility to MS. An abnormal form of



MERTK is found in about 10% of people with MS. The protein whose manufacture is instructed by the MERTK gene is found on the surface of specific immune cells and regulates how the cells respond to inflammation.

The Study: Dr. Kilpatrick and an international team of collaborators are testing the idea that abnormal MERTK in some people with MS leads to an abnormal response of immune cells to inflammation. Through a series of studies, they are examining the details of the effects of abnormal MERTK proteins on immune cell function, and comparing its presence and activity in people who have different strengths of the MERTK gene. They are also exploring MERTK presence in brain tissue from people who had MS in their lifetimes, armed with information about their clinical course.

What's Next: The results should increase our general understanding of immune cell function and dysfunction in MS, and provide a potential target for therapeutic strategies.

END—Role of the Immune System

Elizabeth Blankenhorn, PhD

Drexel University
Philadelphia, PA

Award: Research Grant

Term: 10/1/15-9/30/16; **Funding:** \$210,240

Title: Refining the genetic basis of EAE in B6 mice to establish a model for MS-GWAS testing

Summary: Researchers are using mouse models to specifically identify risk genes and the role of gut bacteria in MS development.

Background: The genes that a person inherits contribute to a person's risk of developing MS. Rodent models can aid genetic studies of people because they exhibit similar disease traits as people with MS, and their genome

(complete set of DNA) is remarkably similar to that of humans. This team is using a specialized mouse model in which they have already narrowed down the genome locations linked to disease susceptibility and resistance.

The Study: Prof. Blankenhorn's team is breeding mice that inherit smaller and smaller regions of a chromosome that still make them resistant to EAE, an MS-like disease. They will continue to breed generations until the region is small enough to identify specific genes that prevent the mice from getting sick. Data so far suggest that the type of bacteria the mice possess in their gut is critical to whether or not they develop disease. This line of research into gut bacteria is also an emerging area of interest in people with MS. The team is comparing the type of bacteria in the gut of mice depending on where they were raised and whether or not they show disease characteristics.

What's Next: If successful, this work will identify genes and gut bacteria in mice that control the onset of MS-like disease. This information can be used to investigate whether the same factors influence MS in humans.

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