NEW RESEARCH

STOP. RESTORE. END.

Society Commits Nearly $19 Million for 54 New MS Research Projects

The National Multiple Sclerosis Society has committed another $18.8 million to support an expected 54 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 more than $50 million in 2014 alone to support 380 new and ongoing studies around the world. So that no opportunity is wasted, the Society pursues all promising paths, while focusing on three priority areas: progressive MS, nervous system repair, and wellness and lifestyle.

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

National Multiple Sclerosis Society

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:

- Exploring whether comprehensive care results in better outcomes for people with MS. (See p. 2)

RESTORE:

- Using video chatting to increase exercise in people with MS and decrease symptoms. (See p. 15)

END:

- Does a toxin derived from bacteria play a role in early MS damage? (See p. 23)

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STOP

Stopping MS requires understanding of 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—Epidemiology

William Culpepper, PhD
Veterans Administration Medical Center - Baltimore
Baltimore, MD

Title: What is the comparative effectiveness of comprehensive care vs. usual care for patients with multiple sclerosis?

Summary: Exploring whether comprehensive care results in better outcomes for people with MS.

Background: In general, patient care can be provided as either "comprehensive care" in which a team leader plus team members work together to treat a person's condition, or as "usual care" in which one health care provider cares for the patient and provides referrals for different types of treatment when needed. Previous studies have shown that comprehensive care is beneficial to people who have experienced strokes, but the effectiveness of comprehensive care vs. usual care for people with MS is assumed, but not known. This research project responds to a request for proposals on this priority question for the National MS Society's Health Care Delivery and Policy program.

The Study: William Culpepper, PhD, of the Veterans Administration Medical Center in Baltimore, received a research grant from the National MS Society to compare comprehensive care vs. usual care in people with MS. To perform this assessment, Dr. Culpepper and his team are obtaining information on clinical outcomes such as outpatient visits, inpatient admissions, costs, and other types of care from VA hospital databases, and analyzing whether these outcomes were better in people with MS who received comprehensive care or usual care.

What's Next? Improvements such as fewer inpatient admissions, lower costs, more appropriate use of medications, and fewer relapses or urinary tract infections would support the effectiveness of the comprehensive care model, and disseminating the results could have significant benefits to quality of life for people with MS.

STOP—Health Care Delivery and Policy

Malachy Bishop, PhD
University of Kentucky
Lexington, KY

Title: Optimizing MS care: Multiple sclerosis patients' perspectives and priorities for their MS Care

Summary: Understanding the healthcare priorities and preferences of people with MS.

Background: Previous studies have shown that healthcare works best when patients participate in its design and delivery. However, the healthcare priorities and preferences of people with MS are not well understood.

The Study: Malachy Bishop, PhD, of the University of Kentucky in Lexington has received a research grant from the National MS Society to increase our understanding of what people with MS want from healthcare. To do this, they are conducting a nationwide survey of 3,000 people with MS and National MS Society members to determine how well different healthcare settings and healthcare professionals are meeting the needs and expectations of Americans with MS. They are exploring whether people have different healthcare priorities and needs based on such characteristics as their age, general health, race/ethnicity, educational level, where they live, and type of MS. Dr. Bishop plans to provide the National MS Society with recommendations for optimizing MS healthcare through increased understanding of and attention to the priorities and preferences of people with MS. He is teaming up with researchers from the University of Illinois at Urbana-Champaign, University of Wisconsin-Madison, and Florida Atlantic University at Boca Raton.

What's Next? Findings from this study should inform the improvement of healthcare for people with MS.

Theresa Shireman, BSPharm, PhD
University of Kansas Medical Center - Kansas City
Kansas City, KS

Title: Effectiveness of Medicaid's home- and community-based services for persons with multiple sclerosis

Summary: Optimizing home- and community-based services to maintain the independence of people with MS.

Background: Many people with MS require care not only from family and friends, but also from paid health care workers. These home- and community-based services are sometimes paid for by Medicaid. The rules for qualifying for Medicaid for people with limited incomes vary from state to state, and the benefits of these services for people with MS are not completely understood.

The Study: Theresa Shireman, PhD, of the University of Kansas Medical Center in Kansas City, received a research grant from the National MS Society to review Medicaid re-

quirements in each state and to provide information to make Medicaid more accessible to people with MS. Dr. Shireman and her group are reviewing the rules for qualifying for Medicaid programs for all 50 state. They are also determining if people with MS use these services by reviewing billing records, and whether they benefit from these services in terms of reduced hospital stay.

What's Next? Optimizing the use of Medicaid-funded home- and community-based services will help people with MS remain independent, reduce caregiver burden, and reduce health care costs.

STOP—Neuropathology (Tissue Damage)

Wensheng Lin, MD, PhD
University of Minnesota
Minneapolis, MN
Title: Oligodendrocyte impact on neurodegeneration in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis
Summary: Seeking ways to protect myelin-making cells and nerve fibers from damage in MS.

Background: The disease process in MS leads to damage to nerve fibers, myelin (the fatty substance that surrounds and protects nerve fibers), and the cells that make myelin, called oligodendrocytes. When oligodendrocytes are exposed to stress such as an MS immune attack, they do not function or may die, affecting myelin and nerve fibers. To cope with stress, the body's natural defense mechanism called the "PERK pathway" can be turned on in oligodendrocytes, protecting them from further damage. In mice with the MS-like disease EAE, switching on the PERK pathway protects oligodendrocytes and nerve fibers and improves symptoms. The PERK pathway may work in part by increasing the amount of a protective factor called VEGF.

The Study: Wensheng Lin, MD, PhD, of the University of Minnesota, received a research grant from the National MS Society to investigate the role of VEGF in the PERK pathway. The team is using mice in which they can turn on and turn off aspects of the PERK pathway and VEGF. This will enable them to better outline the role of VEGF in the protective PERK pathway.

What's Next? Results from this study will suggest ways to design novel treatments that protect both oligodendrocytes and nerve fibers from damage in MS.

Don Mahad, MD, PhD
University of Edinburgh
Edinburgh, United Kingdom
Title: Mitochondria and mechanisms of axon degeneration in progressive MS
Summary: Exploring energy failure in cells as one possible cause of progressive MS.

National MS Society and Glialogix Collaborate to Develop Treatment for Progressive MS

The National MS Society has entered into a research collaboration agreement with Glialogix through Fast Forward to advance a new treatment for progressive MS.

The myelin sheath that surrounds and protects nerve fibers is damaged and destroyed in the brain and spinal cord by MS. Nerve fibers that have lost their myelin coating may also be damaged and destroyed, leading to long-term disability. An important unmet need in MS is finding ways to protect the nervous system from damage caused by MS. A normal brain chemical called glutamate may play a role in nerve damage in MS.

Glialogix has developed GLX1112, a compound that inhibits excess glutamate. GLX1112 is a reformulation of an FDA-approved therapy used to treat non-neurologic conditions, and is designed to improve its safety and effectiveness. The Society is providing Glialogix with funding for advanced preclinical and mechanistic studies of GLX1112. These data will be used to inform the design of clinical trials of GLX1112 and its future development as a treatment for progressive MS.

As an important part of the Society's research infrastructure, investments through Fast Forward continue to propel progress in significant ways. The Society will continue to boldly close the gap between promising discoveries and the commercial development necessary to get new treatments to people with MS.

Background: In progressive MS, neurological function continually declines, largely due to damage to nerve fibers. Current therapies target the immune system and do not directly target damage to nerve fibers. Therapeutic strategies to prevent damage to nerve fibers are an important unmet need. Nearly all cells including neurons (nerve cells) have structures inside them called "mitochondria" that make the energy needed by the cell. Mitochondria and the DNA they contain may be damaged in MS, leading to dysfunction of neurons and nerve fibers and symptoms in MS.

The Study: Don Mahad, MD, PhD, of the University of Edinburgh in Scotland, received a research grant from the National MS Soci-

ety to investigate the damage to mitochondria in neurons and their nerve fibers. They are examining mitochondria in neurons in tissue obtained from people with primary- and secondary-progressive MS and also relapsing-remitting MS, and from people without MS. They are also exploring associations between extent of mitochondrial energy failure and MS progression.

What's Next? Results from this study could lead to therapies that target mitochondria to stop the progression of MS.

STOP—Measuring MS Disease Activity

William Culpepper, PhD
Veterans Administration Medical Center
Baltimore, MD
Title: A Rasch-based comorbidity measure for use in patients with multiple sclerosis
Summary: Developing a tool for determining the impact of additional health conditions on outcomes for people with MS.

Background: Just as in the general population, people with MS sometimes have other health conditions, which are called "co-morbidities." Having other health conditions can make treating people with MS more difficult. The impact of these other diseases on the course of MS and its treatment and the subsequent outcomes are not known, but they are thought to contribute to MS progression.

The Study: William Culpepper, PhD, of the Veterans Administration Medical Center in Baltimore, received a research grant from the National MS Society to develop a detailed, quantitative measure that will increase our understanding of the impact of other health conditions on MS treatments and outcome. To do this, they are extracting data for about 18,000 people with MS who were seen at their Center of Excellence facility over about 4 years. They are analyzing these data to determine the importance of many types of additional conditions that occur in people with MS, and developing a formula for weighing their impacts on MS. They will then assess how well this new measure of co-morbidities predicts MS-related disability and disease progression.

What's Next? Results from this study could provide a new, comprehensive measure of the impact of additional conditions on people with MS, and may be useful for predicting clinical outcomes.

Yong Wang, PhD
Washington University School of Medicine
Saint Louis, MO
Title: Correlating MS cervical spinal cord pathologies defined by novel diffusion MRI with clinical measures
Summary: Improving imaging techniques to detect changes in the brain and spinal cord of people with MS.

Background: Both the brain and spinal cord are affected in MS. Physicians typically use a type of imaging called magnetic resonance imaging (MRI) to detect disease activity and damage to these areas. However, MRI has limitations in terms of the types of damage it can detect. For example, standard MRI is not good for differentiating myelin loss from the loss of nerve fibers, which is a type of damage associated with the progression of disability in MS.

The Study: Yong Wang, PhD, of Washington University School of Medicine in St. Louis, received a research grant from the National MS Society to investigate the usefulness of a new technique that may improve the ability to visualize damage in the spinal cord of people with MS. They are testing a new type of MRI called diffusion basis spectrum imaging (DBSI). Although MRI can see damage as a whole, DBSI may be able to visualize the different types of damage separately and may be especially useful for measuring nerve fiber loss. In this study, they are comparing DBSI results with examination of spinal cord tissue obtained via autopsy from 10 people with MS and 10 individuals without MS. They are also performing DBSI analysis of people with MS, people with other neurological disorders, and people without MS who had undergone MRI in a previous stud. They are comparing the DBSI data derived from MRI to physical ability and disability information for these people to see if DBSI accurately reflects disability progression.

What's Next? Improved imaging is important because it will help provide better tracking of MS progression and of the success of treatments aiming to stop MS progression.

STOP—Diagnostic Methods

Eun-Kee Jeong, PhD
University of Utah
Salt Lake City, UT
Title: Quantitation of axonal damage by diffusion and Bound-Pool-Fraction MRI
Summary: Exploring a new type of imaging to visualize nervous system damage in people with MS.

Background: One type of damage that occurs in MS is damage to nerve fibers, which leads to disability and disease progression. This makes it critical to monitor and prevent. The main technique for imaging disease activity and damage to the nervous system in people with MS is called magnetic resonance imaging (MRI). MRI has certain limitations, especially for visualizing damage to nerve fibers. Better imaging methods are needed to monitor damage and evaluate therapies that are designed to prevent nerve fiber damage in MS.

The Study: Eun-Kee Jeong, PhD, of the University of Utah in Salt Lake City, has received a research grant from the National MS Society to investigate the usefulness of

a new type of MRI (called "LoHi-B") that measures the amount of water in and near nerve fibers. They are now comparing Lo-Hi-B images of spinal cords from people with MS and people without MS. They are also performing imaging of people with MS to see if LoHi-B imaging information is related to their specific symptoms.

What's Next? This research could lead to non-invasive ways to track MS progression and benefits of therapies aimed at preventing nerve fiber damage and loss.

Sheng-Kwei (Victor) Song, PhD
Washington University School of Medicine
Saint Louis, MO
Title: Understanding the pathophysiology underlying MS progression
Summary: Improving the visualization of damage to the optic nerve in an MS model to better understand MS progression.

Background: Vision problems including optic neuritis (inflammation of the optic nerve) are common in people with MS. Determining the type of damage to the optic nerve and its relationship to vision problems is important. Damage to the optic nerve can be visualized with magnetic resonance imaging (MRI), but MRI has limitations.

The Study: Sheng-Kwei (Victor) Song, PhD, of Washington University School of Medicine in St. Louis, has received a research grant from the National MS Society to investigate two types of improvements in MRI to better visualize damage to the optic nerve in mice, to explore nerve damage as it occurs for clues to nerve degeneration and progressive loss of function in MS. One type of imaging called diffusion basis spectrum imaging (DBSI) can be used to individually visualize different types of damage (inflammation, loss of myelin, nerve fiber injury) in the optic nerve. The other is called diffusion functional MRI (diffusion fMRI), which can capture nerve cell activity as the subject undergoes visual stimulation. They are performing DBSI and diffusion fMRI in EAE mice with the MS-like disease and damage to the optic nerve, to determine how imaging data relate to vision problems.

What's Next? New types of imaging will allow better, understanding of damage to the nerves and functional loss in MS, and may lead to better ways to track benefits of therapies.

STOP—Biology of Glia

Oleg Butovsky, PhD
Brigham and Women's Hospital
Boston, MA
Title: Mechanism of regulation of CNS inflammation by microglia
Summary: Exploring how one type of brain cell is both harmful and helpful in MS.

Background: Microglia are one type of cell present in the brain. The function of these cells is to clean up cell debris, but whether these cells are helpful or harmful in MS is not clear and may change during different disease stages.

The Study: Oleg Butovsky, PhD, of Brigham and Women's Hospital/Harvard Medical School in Boston has received a research grant from the National MS Society to investigate how microglia function in rodents with an MS-like disease called EAE, and in tissue samples obtained from people with MS. The team is looking for the unique genetic instructions for these functions, and investigating how microglia are different in mice with relapsing-remitting (early disease stage) vs. progressive EAE (later disease stage). They are also looking for ways to change the function of microglia in EAE and in cells from people with MS. The overall goal is to identify markers of helpful vs. harmful microglia in the hopes of eventually manipulating these markers therapeutically in MS – either to turn on helpful functions or to turn off harmful functions.

What's Next? Understanding how microglia function normally and in MS can help to target these cells as part of a therapeutic strategy to restore proper function in MS. In addition, identifying the microglial "signature" may lead to developing new tools to monitor disease progression in MS.

STOP—Role of the Immune System

Xiaoxia Li, PhD
Cleveland Clinic Foundation
Cleveland, OH

Title: Cellular and molecular mechanisms of the inflammasome in CNS inflammation

Summary: Identifying potential targets for turning off immune attacks in MS.

Background: In MS, the immune system attacks components of the brain and spinal cord, causing damage that can lead to progressive disability. Many current therapies for MS are aimed at controlling the immune system, however, these treatments do not help everyone, and more specific therapies are needed.

The Study: Xiaoxia Li, PhD, of the Cleveland Clinic Foundation, received a research grant from the National MS Society to better understand the components of the immune system that are involved in a frequently used model for MS called EAE. Groups of proteins work together during the immune attack in MS and in mice with EAE. Dr. Li and colleagues are examining several groups of proteins more carefully to try to identify individual proteins that are important during this attic. These proteins are potential targets for the development of new therapies for MS. Specifically, they are looking at a protein called "ASC" that may be important in EAE and possibly MS. Along with other molecules, ASC affects the function of T cells, a type of immune cell that plays an im-

portant role in MS. Dr. Li and colleagues are investigating how ASC and other proteins work together during an immune attack to affect the function of T cells.

What's Next? Identifying proteins that are specifically involved in the immune attack in EAE and MS will help identify targets for new therapies to stop MS in its tracks.

Robert Lisak, MD
Wayne State University
Detroit, MI
Title: B cell secretory factors and neuronal and oligodendroglial toxicity
Summary: Studying toxic substances made by immune cells that may cause nervous system damage in MS.

Background: In MS, the immune system damages various components of the brain and spinal cord. Parts of the nervous system that are targeted in MS include nerve cells, the fatty substance that surrounds and protects the nerve cell fibers (called myelin), and the cells that make myelin (called oligodendrocytes). One type of immune cell called "B cells" appears to make toxic substances that may damage one or more of these brain components.

The Study: Robert Lisak, MD, of Wayne State University in Detroit, received a research grant from the National MS Society to investigate the molecules made by B cells and the damage they inflict on nerve cells and other brain components. They previously observed that B cells taken from people with MS released molecules that could damage oligodendrocytes in lab dishes. They are now investigating the effects of B cells isolated from people with MS on human and rat nerve cells in lab dishes. Results are being compared to B cells obtained from people without MS. They are also working to identify the toxic substance(s) produced by B cells.

What's Next? Identifying toxic substance(s) made by B cells and their effects on the components of the brain targeted in MS may lead to the development of therapies that protect against MS damage.

Amy Lovett-Racke, PhD
Ohio State University
Columbus, OH
Title: Role of miRNA in defective Tregs in multiple sclerosis
Summary: Exploring ways to alter the immune responses to stop MS in its tracks.

Background: In MS, the immune system attacks and damages components of the brain, causing disability. Various subsets of a type of immune cell called "T cells" can be helpful or harmful. The genes that instruct T cells are controlled in part by a group of molecules called microRNAs, or "miRNA. " The levels of miRNAs are abnormal in T cells in people with MS. These abnormal levels may prevent the development of other T cells called Tregs that can turn off the immune response in MS.

The Study: Amy Lovett-Racke, PhD, of Ohio State University in Columbus, received a research grant to determine if abnormal levels of certain miRNAs tilt the balance toward development of harmful T cells in MS. The team is examining if altering miRNA levels affects the type of T cells that develop (helpful vs. harmful), what happens when these altered T cells are injected into mice with EAE (a model of MS), and whether restoring normal miRNA levels will restore the ability of Tregs to turn off immune attacks.

What's Next? A therapeutic strategy that alters the levels of certain miRNAs could restore levels of helpful T cells and stop immune attacks in people MS.

Ashutosh Mangalam, PhD
Mayo Clinic College of Medicine
Rochester, MN
Title: Therapeutic potential of combination therapy using human gut-derived commensal bacteria and conventional MS drugs
Summary: Testing the beneficial effects of gut bacteria in MS model.

Background: MS involves immune-system attacks against the brain and spinal cord. The gut, including the small and large intestine, is the largest immune organ in mammal. Each of us has trillions of "commensal" bacteria living within our gut. Most of these bacteria are harmless as long as they remain in the inner wall of the intestine. They play a critical role in our normal physiology, and accumulating research suggests that they

New research may lead to new oral treatments based on gut bacteria to stop damaging immune activity in MS

are critical in the establishment and maintenance of immune balance by the molecules they release. One species of bacteria found in the gut called Prevotella histicola may possess anti-inflammatory properties.

The Study: Ashutosh Mangalam, PhD, of the Mayo Clinic in Rochester, MN has received a research grant to investigate the beneficial effects of Prevotella histicola in modulating the immune system in mouse models of MS. Previous studies have shown that this bacteria suppresses the disease onset and severity of the MS model EAE. Dr. Mangalam and his team are now investigating the effects of Prevotella histicola alone and in combination with the currently approved MS therapies, interferon beta and glatiramer acetate.

What's Next? The results could pave the way for new oral treatments that can modulate the immune response in MS.

Barbara Osborne, PhD
University of Massachusetts Amherst
Amherst, MA
Title: The role of notch family members in the development of EAE
Summary: Are "Notch proteins" a possible new therapeutic target for treating MS.

Background: MS involves immune system attacks which damage components of the brain and spinal cor. One type of immune cells called T cells are especially important in causing the inflammation seen in MS as well as in rodents with the MS-like disease called EAE. A family of proteins called "Notch proteins" are required for T cells to exert their harmful functions in EAE and are important in the development of EAE.

The Study: Barbara Osborne, PhD, of the University of Massachusetts at Amherst, received a research grant from the National MS Society to determine which of the four individual members of the Notch family of proteins is responsible for the harmful effects of inflammatory T cells in mice with EAE. Dr. Osborne and her team are also working to determine how the Notch proteins work inside cells.

What's Next? Determining which of the four Notch proteins is important in the development of EAE may indicate that finding a therapeutic that blocks Notch function may be beneficial for stopping immune attacks in people with MS.

David Pleasure, MD
University of California, Davis
Sacramento, CA
Title: Minimizing axon loss in a murine multiple sclerosis model by conditionally deleting astroglial CCL2 (MCP-1)
Summary: Exploring how specific cells contribute to nerve damage and progression in a model of MS.

Background: In MS, chronic, progressive disability is due to the loss of wire-like nerve fibers which conduct nerve signals. Current therapies can reduce acute relapses but do not directly address this chronic disease process. Our understanding of how nerve fiber loss occurs is incomplete.

The Study: David Pleasure, MD, of the University of California at Davis, received a research grant from the National MS Society to investigate the cells involved in nerve fiber loss in mice with an MS-like disease called EAE. The team is testing the idea that two related types of immune cells called "monocytes" and "macrophages" are responsible for the nerve fiber loss seen in later, chronic phases of EAE. They are specifically deleting one cell population at a time in mice with EAE and looking to see if nerve fiber loss is prevented in the absence of one population or the other.

What's Next? Finding therapies that block the actions of monocytes and/or macrophages may be useful for slowing or preventing MS progression.

Mari Shinohara, PhD
Duke University Medical Center
Durham, NC
Title: Study on innate immune inflammation that enhances EAE
Summary: Understanding differences in response to MS treatment by looking at MS models.

Background: Treating MS is challenging because the response to treatment, including the response to the widely used interferon beta, can vary from person to person. Similarly, one of the main models for MS, called EAE, is not a single disease but seems to vary according to how inflammation is initiates. Understanding the different subtypes of EAE may lead to better understanding of the various types of MS and may allow more informed selection of treatment.

The Study: Mari Shinohara, PhD, of the Duke University Medical Center in Durham, NC, is investigating treatment response in different subtypes of EAE. Dr. Shinohara and colleagues have established mice with two different types of EAE, one that responds to interferon beta and one that does not. They are studying these mice to understand the immune molecules that may be responsible for the differences in response.

What's Next? Understanding treatment response in mouse models may help increase our understanding of such responses in MS and allow physicians to predict the best therapy for each person with the disease.

Lawrence Steinman, MD
Stanford University
Palo Alto, CA
Title: Recombinant crystallins for treatment of multiple sclerosis-tip of an iceberg of guardian amyloids including crystallins, prion, tau, amyloid beta and others
Summary: Developing a new class of therapeutics for possible application in MS.

Background: While the immune system normally protects the body from foreign invaders, such as viruses or bacteria, in MS, the immune system attacks and damages tissues in the brain and spinal cord. In earlier studies, proteins found in and around MS lesions, such as "alpha B crystallin," were thought to be damaging in MS. But recent work by Dr. Steinman's team suggests, intriguingly, that alpha B crystallin reduces immune cell activity in the laboratory, and improves the clinical condition of mice with EAE, a disease similar to MS.

The Study: Lawrence Steinman, MD, now has a research grant from the National MS Society to investigate this and related proteins further in mouse models of relapsing and progressive MS. They will also investigate antibodies that are raised to alpha B crystallin for clues to preventing these antibodies from neutralizing its positive effects.

What's Next? This work could open an important new approach to treating MS.

Anette van Boxel-Dezaire, PhD
The Cleveland Clinic Foundation
Cleveland, OH

Title: The gut-brain axis and blood-brain barrier damage in multiple sclerosis

Summary: Exploring how the brain and gut barriers are disrupted in MS.

Background: In the normally functioning brain, molecules and cells in the blood are inhibited from entering the brain due to the "blood-brain barrier" which keeps these molecules and cells inside blood vessels. In MS, this barrier breaks down, and potentially harmful cells and molecules in the blood are able to enter the brain and damage it. A similar barrier exists in the gut, and disruption of the gut barrier leads to various symptoms experienced in MS.

The Study: Anette van Boxel-Dezaire, PhD, of the Cleveland Clinic Foundation, received a research grant to investigate a possible link between impaired function of the brain and gut barrier. They are using two different systems in which cells are grown in a dish and form a brain-like barrier or a gut-like barrier. They are using these barrier models to test if various immune molecules implicated in making MS worse can damage the barrier, allowing potentially harmful molecules and cells to cross it. They are also testing inhibitors of barrier damage.

What's Next? Understanding these barriers and keeping them intact in MS may suggest ways to prevent or treat MS.

Scott Zamvil, MD, PhD
University of California, San Francisco
San Francisco, CA

Title: Characterization of novel MOG T cell epitopes shared in EAE and MS

Summary: Studying how harmful immune cells involved in MS attacks recognize proteins in nerve-insulating myelin.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fiber. Loss of myelin leads to symptoms in people with the disease. One component of myelin, a protein called myelin oligodendrocyte protein or "MOG," appears to be specifically recognized by immune "T cells" in MS in a mouse model of MS.

The Study: Scott Zamvil, MD, PhD, of The University of California at San Francisco has received a research grant to understand the specific parts of MOG that are recognized by T cells. They are using a mouse model of MS called EAE that is induced by MOG or pieces of MOG to investigate the T cell-directed attack of myelin.

What's Next? Understanding exactly what components of myelin are recognized and attacked by T cells may lead to highly specific therapies to block only the harmful T cells and to leave the function of helpful T cells untouched.

Hao Zhang, PhD
Medical College of Wisconsin
Milwaukee, WI
Title: Therapeutic implications of KYC, a novel myeloperoxidase inhibitor, in multiple sclerosis
Summary: Can blocking free radicals in an MS model provide clues to stopping disease progression in people with MS.

Background: The events that drive progression of MS are poorly understood. One event that may worsen the disease is production of a group of molecules called "free radicals," which are byproducts of bodily processes. Free radicals are harmful to nerve cells in the brain, and damage to nerve cells is associated with the progression of disability in MS. Thus, blocking free radical production may be a novel therapeutic strategy for stopping MS progression.

The Study: Hao Zhang, PhD, of the Medical College of Wisconsin in Milwaukee, has received a research grant from the National MS Society to investigate an inhibitor of free radical production, called "KYC," in rodents with an MS-like disease, EAE. Dr. Zhang and colleagues are looking closely at how KYC works and are checking for any signs that KYC might be toxic, as a prelude to eventually testing this in people with MS.

What's Next? KYC could potentially be useful for protecting nerve cells from damage and for stopping the progression of disability in MS.

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

Robert Motl, PhD
University of Illinois at Urbana-Champaign
Urbana, IL
Title: Project BIPAMS: Behavioral intervention for increasing physical activity in MS
Summary: Using video chatting to increase exercise in people with MS and decrease symptoms

Background: In addition to being essential to general health and well-being, exercise is helpful in managing many MS symptoms. In a previous pilot study, University of Illinois at Urbana-Champaign researchers funded by the National MS Society showed preliminary success using an Internet intervention combined with video-chat sessions by a behavioral change coach to improve the results of a 6-month physical activity program. They found significant improvements in increasing physical activity – as well as reducing fatigue, depression and anxiety – among those participating in the internet-delivered program versus controls who were not in the

program. The program also improved cognitive function and body composition.

The Study: To follow up these findings with a larger study, Robert Motl, PhD, of the University of Illinois at Urbana-Champaign, received a research grant from the National MS Society to test this intervention in a group of 280 people with MS. For 6 months, one group will participate in an internet-based approach that includes use of a website and video chats with a behavioral coach and specifically aims to increase physical activity. The other group will receive internet-based attention and social contact that is not specifically designed to increase physical activity. After 6 months of these interventions, the two groups will be examined to measure their levels of physical activity, walking ability, fatigue, depression, pain, and quality of life.

What's Next? If successful, video chatting to increase physical activity could become an important addition to regular care for people with MS to improve symptoms.

Jacob Sosnoff, PhD
University of Illinois at Urbana-Champaign
Urbana, IL
Title: Fall risk and incidence reduction in multiple sclerosis
Summary: Testing an exercise program to reduce the risk of falling in older people with MS.

Background: Falling is common in people with MS and can lead to injuries such as cuts, broken bones, and head injuries, which in turn can lead to decreased physical activity and reduced participation in life activities. Falls may be especially devastating in older adults. It is not clear which strategies to prevent falling for people with MS are useful, although supervised exercise programs may be effective.

The Study: Jacob Sosnoff, PhD, of the University of Illinois at Urbana-Champaign, received a research grant from the National MS Society to test if a 6-month home-based, unsupervised exercise program designed to improve balance and increase lower body strength will reduce the frequency of falls, improve quality of life, and improve participation in life activities in older adults. He and his research group are enrolling 100 people with MS over 50 years of age and will divide them into two groups, each receiving a different intervention program. After 6 months, they will assess the two groups for falls, quality of life, participation in life activities, strength, balance, and walking abilities.

What's Next? Finding an exercise program that reduces falls would go far to improve quality of life for people living with MS.

RESTORE—Nervous System Repair

Ben Emery, PhD
Oregon Health Science University
Portland, OR (Transfer Pending)
Title: A transcriptional approach to myelin repair
Summary: Testing a strategy for increasing myelin repair in MS by manipulating a major gene in myelin formation.

Background: In MS, myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed by the immune system. The body's ability to repair myelin by itself is incomplete. Myelin formation is genetically controlled, and a gene called "myelin regulatory factor" (Myrf) appears to play a critical role by acting as a master controller of other genes involved in myelin formation.

The Study: Ben Emery, PhD, who recently relocated to the Oregon Health Science University, along with collaborator Ranjan Dutta, PhD, of the Cleveland Clinic, has received a research grant from the National MS Society to understand how Myrf works in the cells that make myelin in the brain, which are called oligodendrocyte. They are investigating whether Myrf can speed up myelin repair in rodents with myelin loss similar to that which occurs in MS, and looking at Myrf activity in tissue from people with MS.

What's Next? If Myrf is indeed a master controller of myelination, therapies that increase Myrf activity may ultimately be used to increase natural myelin repair in people with MS.

Stephen Fancy, DVM, PhD
University of California, San Francisco
San Francisco, CA
Title: Remyelination failure in MS – mediators and control mechanisms of pathological Wnt activity
Summary: Exploring why myelin is not well repaired in MS and targeting a protein as a strategy to promote myelin repair.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Current treatments for MS focus on suppressing the immune system and do not directly address myelin repair. The cells in the brain that make myelin are called oligodendrocytes. Myelin repair requires maturation of immature oligodendrocytes to mature, myelin-making cells. This maturation process is controlled by a protein called "Wnt. "

The Study: Stephen Fancy, DVM, PhD, of the University of California at San Francisco, received a research grant from the National MS Society to explore why myelin repair fails in MS. Dr. Fancy and his team are investigating how Wnt controls the maturation of oligodendrocyte. They are examining areas of damage within tissue samples obtained from people with MS, looking for evidence of abnormal Wnt activity. They also are

studying oligodendrocytes in mice to understand how Wnt is turned on and off, for clues to therapies that may manipulate Wnt to improve myelin repair in people with MS.

What's Next? If Wnt controls oligodendrocyte maturation and thus myelin repair, manipulating Wnt could be a therapeutic approach that will promote myelin repair and improve disability in people with MS.

Jeffrey Huang, PhD
Georgetown University
Washington, DC
Title: Role of retinoic acid synthesis in CNS remyelination
Summary: Exploring the role of a molecule in myelin repair and its potential as a target for restoring function in people with MS.

Background: In MS, the immune system attacks and destroys a fatty substance called myelin, which surrounds and protects nerve fibers. Nerve fibers also are damaged, leading to symptoms and disability in people with MS. One strategy to treat MS is to find a way to promote repair of myelin in the brain. The cells in the brain that make myelin are called oligodendrocytes.

The Study: Jeffrey Huang, PhD, of Georgetown University in Washington, DC, has received a research grant from the National MS Society to explore how a molecule called "Raldh2" functions in oligodendrocytes during myelin formation. Raldh2 is active in oligodendrocytes after loss of myelin and may be required for myelin repair. To explore its role, Dr. Huang and his team are using mice in which Raldh2 is genetically modified to test if it is required for successful myelin repair.

What's Next? If it is required for myelin repair, finding a way to promote Raldh2 may be a strategy for increasing repair in MS.

Gareth John, DVM, PhD
Icahn School of Medicine at Mount Sinai
New York, NY
Title: Kruppel-like factor-6 signaling in myelin formation and repair
Summary: Exploring the importance of a protein called Klf6 in the MS repair.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds nerve fibers. Nerve fibers are damaged as well. Myelin is made in the brain by cells called oligodendrocytes, which are derived from an immature population of cells. A protein called Krüppel-like factor-6 (Klf6) may be very important in promoting the maturation of oligodendrocytes that are capable of myelin repair. Because myelin repair stalls in people with MS, strategies for promoting the maturation of cells that are capable of repair may be promising for restoring function to people with MS.

The Study: Gareth John, VetMB, PhD, of Mount Sinai School of Medicine in New York, has received a research grant from the National MS Society to understand how Klf6

works to promote oligodendrocyte maturation. Klf6 appears to be a link between signals from outside the cell that influence immature oligodendrocytes and initiation of the maturation "program" that works inside these cell. They are now testing the importance of Klf6 in myelin repair using mice that do not have Klf.

What's Next? Determining how Klf6 works in myelin repair may suggest new strategies for repairing myelin and restoring function in people with MS.

One idea for promoting myelin repair is to transplant cells that make myelin to provide more replacement cells to the brain.

Marius Wernig, PhD
Stanford University
Palo Alto, CA
Title: Generation of transplantable myelinating glia from human fibroblasts
Summary: Can skin cells be used to produce cells that will repair damage in MS.

Background: In MS, the immune system attacks and destroys myelin, the fatty substance that surrounds and protects nerve fibers. Promoting myelin repair is a major strategy in MS treatment research. One idea to promote myelin repair is to transplant cells that make myelin, called oligodendrocytes, to provide more replacement cells to the brain.

The Study: Marius Wernig, MD, of Stanford University in Palo Alto, has received a research grant to devise ways to generate sufficient numbers of oligodendrocytes that can be transplanted into the brain to repair myelin. Dr. Wernig, along with collaborator Dr. David Rowitch (University of California, San Francisco) and team are exploring two strategies to grow enough oligodendrocytes in lab dishes for transplantation. Although the strategies are different, both of these methods start with skin cells, which can be coaxed to become oligodendrocytes. The team is using human skin cells to produce oligodendrocytes and testing their fate when transplanted into mice. They will compare characteristics of the two methods to determine the optimal strategy. The possibility of using skin cells has several possible advantages. For example, if skin cells are isolated from the same person that will receive the oligodendrocytes for transplantation, the body may not reject them.

What's Next? Results from this study could ultimately lead to a way to restore myelin and thus function in people with MS.

RESTORE— Measuring Disease Activity

Lauren Strober, PhD
Kessler Foundation Research Center
West Orange, NJ
Title: Standardization and normative data of the symbol digit modalities test-oral version
Summary: Improving a test that measures cognitive function.

Background: Cognitive problems are common in people with MS, with difficulties in thinking speed being the most common. One measure that can be used to measure thinking speed is the Symbol Digit Modalities Test (SDMT). Performance on the SDMT has proven to be sensitive to changes in cognitive function in MS as well as predictive of changes in activities such as driving and employment. However, the SDMT has limitations, including the fact that what is considered "normal" in the general population is outdated, and it is not clear what would be considered a meaningful change in performance on the SDMT over time

The Study: Lauren Strober, PhD, of the Kessler Foundation in West Orange, NJ, received a research grant from the National MS Society to improve the use of the SDMT by updating what is considered "normal. " To accomplish this goal, her research team will administer the SDMT to a large sample of healthy individuals and analyze the data taking into account age, gender, and education. The end result will be an updated set of normal results, or norms, that will allow for better interpretation of results obtained when examining cognitive function in MS.

What's Next? Improving the SDMT will allow for more confident interpretation of test results and will allow physicians to identify meaningful change in performance on the SDMT in people with MS, which will ultimately allow for better treatment selection.

RESTORE—Biology of Glia

Jonah Chan, PhD
University of California, San Francisco
San Francisco, CA
Title: A functional high-throughput screen for remyelination: Muscarinic receptors regulate oligodendrocyte differentiation and myelination
Summary: Screening large numbers of molecules that may be useful for stimulating myelin repair in MS.

Background: In MS, myelin, the fatty substance that surrounds and protects nerve fibers, is attacked and destroyed. Myelin is required for nerve fibers to function properly and it may protect them from damage caused by MS attacks. Thus, strategies to repair myelin, a natural healing process that is generally inefficient, are likely to improve function in people with MS.

20 New Pilot Projects Take Aim at MS

These new, high-risk, high-potential, one-year projects explore untested ideas.

STOP

Daniel Kirschner, PhD (Boston College) is examining myelin architecture using novel technology, to address how nerve impulse conduction goes awry in MS.

Athena Soulika, PhD (University of California, Davis) is studying an enzyme that may affect myelin-making cells in MS.

Magdalena Zoledziewska, PhD (Istituto di Ricerca Genetica e Biomedica) is comparing gut bacteria from people with and without MS, for clues to the immune attack.

Dennis Ko, MD, PhD (Duke University) is studying genes that instruct an anti-inflammatory protein, IL-10, in people with MS, for clues to an association with MS risk.

Gregory Konat, PhD (West Virginia University) is testing whether inflammation induced by viruses triggers exacerbations in a mouse model of MS.

Joseph Harding, PhD (Washington State Univ.) is testing a neuroprotective compound.

RESTORE

Melissa Brown, PhD (Northwestern University) is investigating molecules that may direct immune cells to enter the brain and launch MS immune attacks.

Jonathan Campbell, PhD (University of Colorado) is estimating the prevalence and incidence of MS in the commercially insured US population.

Chung-Yi Chiu, PhD (University of Illinois at Urbana-Champaign) is developing an intervention for increasing activity and decreasing sedentary behavior in people with MS.

John DeLuca, PhD (Kessler Foundation Research Center) is testing whether a well-known psychostimulant can treat cognitive fatigue in MS.

Charles Howe, PhD (Mayo Clinic) is generating nerve stem cells from skin cells in the lab.

Wei Liu, PhD (Auburn University) is exploring a strategy for improving walking in MS.

Stephen Miller, PhD (Northwestern University) is testing a treatment approach that combines immune regulation and myelin repair in a model of MS.

Robert Motl, PhD (University of Illinois at Urbana-Champaign) is surveying people with MS to develop a program to promote exercise and physical activity behavior in persons with MS.

Claire Riley, MD (Columbia University) is studying brain growth &primary-progressive MS.

Maria Schultheis, PhD (Drexel University) is studying cognitive function and sleep in MS.

Sarah Morrow, MD (University of Western Ontario) is exploring walking in MS.

Manning Sabatier, PhD (Emory University, Atlanta, GA) is exploring slope walking as a way to enhance spinal function and reduce spasticity in MS.

Betty Soliven, MD (University of Chicago) is looking at why making myelin cells fail in MS.

Jacob Sosnoff, PhD (University of Illinois at Urbana-Champaign) is investigating a rehabilitation technique for improving the ability of a person with MS to walk and think at the same time.

The Study: Jonah Chan, PhD, of the University of California at San Francisco, received a research grant from the National MS Society to refine and enhance technology that provides a rapid method to screen for substances that promote myelin repair. With the first generation of this technology, the team identified a group of candidate molecules capable of promoting myelin growth. The team is further refining the screening method and then investigating how the identified candidates work in mice with myelin damage, to identify ideal characteristics and versions of these candidates for future testing in people with MS.

What's Next? Identified compounds that promote myelin repair are candidates for new therapies that could be clinically tested for their ability to repair myelin in people with MS. Currently Dr. Ari Green, Clinical Director of the MS Research Group at UCSF, has initiated a clinical trial for remyelination in relapsing-remitting MS with a compound identified by the screen (reBUILD, http://multiplesclerosi. ucs. edu/research/rebuild).

Laura Feltri, MD
The State University of New York at Buffalo
Title: Characterization of a novel inhibitor of myelination: MAPK12/P38MAPKgamma
Summary: Does a natural inhibitor of nerve-insulating myelin have potential as a target for myelin repair in MS.

Background: In MS, the immune system attacks and destroys the fatty substance called myelin that protects nerve fiber. Nerve fibers are damaged as well, causing symptoms and disability in people with the disease. For unknown reasons, myelin repair – which can occur naturally – is inefficient in people with MS. Currently approved treatments target the immune system but do not directly promote myelin repair.

The Study: . Laura Feltri, MD, of The State University of New York at Buffalo, received a research grant to study a potential inhibitor of myelin repair. Dr. Feltri and her team have identified a protein called "P38MAPKgamma" that blocks myelin formation in mice. This protein may be one of the reasons why myelin repair in MS is inefficient. They are examining how P38MAPKgamma works in mice with EAE, a model of MS, and in mice with toxin-induced myelin damage. The team is examining myelin formation in mice that lack P38MAPKgamma.

What's Next? If P38MAPKgamma is an important inhibitor of myelin synthesis, blocks this protein could be an important new way to promote myelin repair in people with 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.

Marc Horwitz, PhD
University of British Columbia
Vancouver, BC, Canada

Title: How latent gammaherpesvirus enhances EAE pathology: implications on EBV's role in the etiology of MS

Summary: Studying the role of Epstein-Barr virus in a model of MS for clues to a possible MS trigger.

Background: MS is thought to occur when people whose genes make them susceptible encounter something in their environment that triggers this immune-based neurological disease. Although many infectious agents have been investigated at various times as possible triggers of MS, no single virus or bacterium has been proved to cause MS. However, previous studies have suggested that the risk of MS is increased in persons who have had a history of infectious mononucleosis (caused by the Epstein-Barr virus, or "EBV") or who have high levels of blood serum antibodies against EBV, which indicate past exposure to the virus.

Investigating how a viral infection is related to MS-like disease in mice may lead to clues for developing strategies to prevent MS.

The Study: Marc Horwitz, PhD, of the University of British Columbia in Vancouver, Canada, received a research grant from the National MS Society to investigate the role of EBV in mice with the MS-like disease called EAE. His team has discovered that mice infected with an EBV-like virus and induced to develop EAE develop a more severe form of disease that is highly similar to MS. Now Dr. Horwitz and colleagues are testing this model further, specifically investigating the immune cells and molecules involve. They also are studying how this virus infection might be blocked.

What's Next? Investigating how virus infection is related to MS-like disease development in mice may lead to clues for developing strategies that can prevent MS.

Timothy Vartanian, MD, PhD
Cornell University Medical College
New York, NY

Title: Modeling nascent lesion formation in multiple sclerosis

Summary: Does a toxin derived from bacteria play a role in early MS damage?

Background: Some tissue damage occurs within hours of symptom onset in MS. This damage may include the loss of oligodendrocytes (the cells that make myelin, the fatty substance that surrounds and protects nerve fibers) and leaky blood vessels. However, some research suggests that early on, myelin is not yet destroyed and no inflammation is seen. The lack of inflammation in early lesions suggests the possibility that MS begins as a result of something present in the environment such as a toxin or virus, rather than because of a dysfunctional immune response. However, no specific toxin or virus has been identified as a cause of MS.

The Study: Timothy Vartanian, MD, PhD, of Cornell University Medical College in New York City, has received a research grant to investigate whether a toxin called epsilon toxin might be responsible for this early damage. Using mouse models, his team is testing whether epsilon toxin, which is derived from the commonly occurring bacterium Clostridium perfringens, can cause the same changes in the brain that are found in new MS lesions, including loss of oligodendrocytes and leaky blood vessel.

What's Next? Identifying a toxin as possible MS trigger could lead to therapeutic strategies to kill the bacteria and/or neutralize the toxin.

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