National Multiple Sclerosis Society

NEW RESEARCH

31 New Research Projects Begin

The National MS Society has just committed over $14 million to support 31 innovative MS research projects. These exciting new studies were selected for their scientific merit and high relevance to the fight against MS, out of 122 reviewed by our volunteer panels of scientific advisors.

When the National MS Society makes research commitments such as these, the money is not in hand to meet them: The Society now has over $90 million in current- and future-year commitments to meet. Contributions to the Society to help support these committed projects are essential to helping ensure that this important research proceeds in future years.

The new projects are part of a comprehensive research program slated to invest over $46 million this year alone to propel MS research forward, including funding over 380 new and ongoing MS investigations in the U.S. and abroad. By the end of fiscal year 2008, the Society will have invested nearly $600 million since its founding to support basic and clinical research aimed at preventing, treating and curing multiple sclerosis.

Inside…

Following are brief summaries of the new research grants, grouped according to major avenues of MS investigation. In addition, 44 new "high-risk, high potential" pilot projects aimed at testing innovative ideas were awarded over the last six months. These appear on pages 8-10.

REHABILITATION
Maximizing Abilities

Rehabilitation regimens that can help people with MS achieve maximal physical, psychological, social and vocational potential have gained increasing acceptance in recent years. But to convince doctors and insurers that rehabilitation really does help, there needs to be scientific evidence that can only come from carefully designed and conducted studies. The National MS Society has current, multi-year commitments of $4.5 million to support 20 research projects focusing on rehabilitation in MS, including the following two new ones.

Robert Motl, PhD
University of Illinois at Urbana-Champaign
Urbana, IL
NMSS Area: Greater Illinois Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/12; $696,628
"Do symptoms predict reduction of physical activity across time in MS?" Understanding factors that may lead to reduced physical activity in persons with MS.

Having MS may often lead to a substantial reduction in physical activity. Inactivity in people with or without MS can result in numerous conditions such as heart disease, muscle weakness, and decreased bone density.

Very little is known about the factors that are associated with reduced physical activity in MS. Robert W. Motl, PhD, is examining whether the frequency and severity of MS-related symptoms influence physical activity. His team is tracking changes in activity over three years in 250 individuals with relapsing-remitting MS, a course of MS characterized by flare-ups followed by complete or partial remissions. Physical activity is being measured by an accelerometer, a device worn around the waist that measures movements throughout the day. The results are being correlated with clinical measures of disease activity and patient reports of symptoms.

This study could substantially improve our knowledge of the factors leading to reduced physical activity in people with MS, and help design programs to increase it.

Richard Van Emmerik, PhD
University of Massachusetts
Amherst, MA
NMSS Area: Central New England Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/11; $474,269
"Dynamic balance control and fatigue in multiple sclerosis" Identifying factors involved in balance problems in posture and walking experienced by people with MS to find better ways to intervene.

A common problem faced by people with multiple sclerosis is poor balance control during standing and walking. Richard E. Van Emmerik, PhD, and colleagues are aiming to better understand these disturbances.

Dr. Van Emmerik's team is investigating gait and balance in multiple groups of individuals: 20 people with MS without walking problems, 20 people with MS and walking problems (but who do not use mobility aids) and 20 people without MS. They are assessing posture, gait initiation and walking using state-of-the-art electronic motion tracking systems.

Given the essential role that balance and gait play in daily life, a more thorough understanding of these mechanisms is essential for developing effective rehabilitation intervention programs for people with MS.

MEASURING DISEASE ACTIVITY
Tracking the Course of MS

Advances in imaging technology are allowing us to view disease activity in MS more clearly than ever before. Such advances may lead to ways to predict the course of disease in an individual, and may also help more quickly determine whether experimental treatments are working. Researchers are also seeking noninvasive ways to track nerve fiber damage that may result in disease progression, and differentiating nerve fiber damage from damage to the fiber's myelin coating. The Society is currently supporting 38 research projects on measuring disease activity, with total multi-year commitments of $9.3 million.

Anne Cross, MD
Washington University
Saint Louis, MO
NMSS Area: Gateway Area Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $395,562
"Directional diffusivity as a window into the pathology of MS" Testing a non-invasive imaging method for its ability to detect damage to nerve fibers in MS.

Researchers now recognize that loss of the wire-like projections from nerve cells, called axons or nerve fibers, may be the main cause of long-term disability in people with MS. Although magnetic resonance imaging (MRI) is a useful tool for many aspects of MS diagnosis and treatment, it cannot differentiate between damage to the myelin that insulates axons and damage to the axon itself.

Anne Cross, MD, and colleagues have found that an imaging technique called diffusion tensor imaging (DTI) can identify these two types of damage in several animal models of MS. In this project, the Washington University team is using MRI and DTI images collected during a clinical trial of an MS drug to study DTI's effectiveness in predicting the development of axon injury. The team is also determining whether DTI findings correlate with clinical dysfunction, and using a year's series of images of those who are newly diagnosed to see if early findings on DTI predict future findings.

The development of a safe and accurate assessment tool of axon injury would lead to improved clinical trial evaluations and more effective management of people with MS.

HEALTH CARE DELIVERY/ POLICY
Improving Care Standards

What if the cure were found today but insurers refused to pay for it? Access to care is one of many issues tackled by the Society's Health Care Delivery and Policy Research Program, providing data that can serve as the basis for influencing public policy, and offering people with MS and their families practical ways for improving the quality of their lives.

With the help of its volunteer Health Care Delivery and Policy Research Advisory Committee, the Society establishes priority areas each year and releases a request for proposals from investigators in the field. The following two projects responding to

those priorities were recently awarded.

The priority areas for 2008 focus on: 1) Comprehensive analysis of the direct and indirect costs of MS; 2) Comprehensive survey and analysis of long-term care services, including home-based services, in MS; and 3) Abuse of persons with MS by caregivers. In addition, the Society has opened up its HCDPR program to accept investigator-initiated health policy studies in MS on any pertinent topic.

Read more about the Society's Health Care Delivery and Policy research at: http://www.nationalmssociety.org/HealthResearch

Carol Simon, PhD
Abt Associates Inc.
Cambridge, MA
NMSS Area: Central New England Chapter
Award: Health Care Delivery & Policy contract
Term/Amount: 7/1/07-6/30/09; $384,233
"Financial modeling of multiple sclerosis medical care" Analyzing how the costs and financing of MS health care influences the quality of that care and the ability of people to access care.

This project is designed to better understand the organization and financing of MS care. Carol Simon, PhD and colleagues will attempt to identify misalignment between costs and reimbursements, and ascertain its impact on access to and quality of care.

Using information from sources such as care private providers, MS clinics and Medicare payments, the investigators will identify principal diagnostic and therapeutic procedures required by people with MS. They will then ascertain costs incurred by care providers and the sources and amounts of payment for their services, and determine any gaps between costs for services rendered and payments received.

This study will provide data to guide improvements in the structure and processes of MS care, and suggest strategies to help care providers negotiate appropriate reimbursement of medically necessary services. It should also provide the National MS Society with important data with which to advocate for improvements to improve the quality of care available for people with MS.

Barbara Vickrey, MD, MPH
VA Greater Los Angeles Healthcare System
Los Angeles, CA
NMSS Area: Southern California Chapter
Award: Health Care Delivery & Policy contract
Term/Amount: 7/1/07-6/30/10; $487,570
"Development of indicators for multiple sclerosis" Defining what constitutes quality MS health care and how to measure it to establish better standards of medical care for people with MS.

Multiple sclerosis (MS) is a complex neurological disorder that can cause a wide spectrum of symptoms. There is currently no set of tools for measuring whether persons who have MS are receiving high-quality health care. Barbara Vickrey, MD, MPH, is leading a team of MS specialists and social scientists to analyze the medical evidence and to gather input from key stakeholders, including patients, clinicians, insurers, and administrators, as to what constitutes high quality MS care.

The researchers will then draft a set of quality indicator measures and obtain rat-

ings from a stakeholder group on each measure's importance and impact. The final set of MS quality indicators will be field-tested in a wide range of practice settings, so that the indicators can be ready for widespread use.

Future applications include use of the indicators in studies to test new ways of delivering high-quality MS care, and to help clinicians and healthcare systems in evaluating the quality of the MS care they are providing.

NERVOUS SYSTEM REPAIR
Restoring Function

Decades of research into nerve physiology and the biology of glial cells – the numerous brain cells that support nerve cells – have been laying the groundwork for finding ways to restore normal function in individuals with MS.

Nervous System Repair and Protection teams funded by the Society's Promise:2010 campaign are taking this research to the next level, with a goal of placing nerve tissue-protective treatments in clinical trials by the year 2010. Other research on this topic focuses on the microenvironment of the brain and conditions conducive to stimulating natural repair, and the potential for cell therapies. The Society is currently funding 61 investigations focusing on central nervous system repair, including the following 5 new ones, for a total multi-year commitment of $38 million.

Gareth John, VetMB, PhD
Mount Sinai School of Medicine
New York, NY
NMSS Area: New York City Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $497,320
"Astrocyte regulation of CNS remyelination"
Studying a new role for brain cells called astrocytes, which may contribute to myelin repair in MS.

Once myelin—the insulating coating of nerve fibers in the brain and spinal cord—is damaged in MS, it is only poorly repaired by oligodendrocytes, the brain cells that make and maintain myelin. Recent evidence suggests that factors produced locally within myelin-damaged areas (called lesions or plaques) play an important role in determining the success or failure of myelin repair. Gareth John, DVM, PhD, is studying brain cells called astrocytes, which are found in abundance in MS lesions, may contribute to myelin regeneration.

Astrocytes release a cytokine, or signaling chemical, called IL-11. Preliminary studies indicate that IL-11 promotes the survival and maturation of oligodendrocytes and increases their production of myelin. Giving IL-11 to mice protects them from developing MS-like disease. Dr. John's team is now tracing the signals and pathways activated by IL-11 that lead to myelin formation. They are also examining tissue samples of MS lesions to detect evidence of IL-11 activity in areas where myelin has been repaired.

This research may yield significant information about the role of IL-11 in myelin repair, and may open a therapeutic avenue to promote oligodendrocyte survival and myelin repair in people with MS.

Jeffery Kocsis, PhD
Yale University
New Haven, CT
NMSS Area: Greater Connecticut Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $463,696
"Therapeutic potential of cellular transplantation into a focal model of EAE" Determining the relative value of two types of adult stem cells in protecting and repairing MS-like injuries to the spinal cord.

Multiple sclerosis can injure nerve fibers and their insulating myelin sheaths in the brain and spinal cord. While therapies exist to dampen the immune attack underlying the disease, cell-based therapies are being explored to protect nerve fibers and to repair myelin. In EAE, an MS-like disease studied in animal models, inflammation is scattered throughout the brain and spinal cord, making it difficult to target a consistent site for cell transplantation.

To combat this difficulty, Jeffery Kocsis, PhD, and colleagues are using a model in which EAE is targeted to the rat spinal cord, causing focal nerve fiber loss and myelin damage that is more amenable to studying the effectiveness of cell transplantation. They are now transplanting two types of cells – those that produce myelin for the nerves outside the central nervous system and stem cells found in bone marrow. These cells have shown therapeutic potential in several models of MS-like damage, but not yet in models that mimic MS as well as EAE.

These experiments should add to the base of information needed for considering cell-based therapies in people with MS.

Stefano Pluchino, MD, PhD
Fondazione Centro San Raffaele del Monte Tabor
Milano, Italy
Award: Research Grant
Term/Amount: 10/1/07-9/30/09; $278,452
"Central vs. peripheral immunomodulation in neural stem cell transplant for MS" Exploring mechanisms at work in the phenomena in which cell transplants can reduce brain inflammation and enhance nervous system tissue repair.

In recent years, scientists have been exploring alternative ways to repair the damage of brain and spinal cord tissues that occurs during the course of the immune attack in MS. The San Raffaele Hospital team and others have been investigating transplantation of neural stem cells. These cells have been shown to move to distant sites of injury within the brain upon intravenous injection. Further, transplanted neural stem cells may either develop into various functional types of brain cells—including neurons and myelin-forming cells—or eventually significantly suppress the burden of inflammation in specific areas of the brain.

Stefano Pluchino, MD, PhD, and colleagues recently observed that neural stem cells injected into mice with the MS-like disease EAE accumulate and persist, not only in the brain and in the spinal cord, but also in areas of the immune system, even up to 100 days after transplantation. Now they are tracking these cells more closely in EAE models to determine how they accumulate, persist, and affect the immune response.

These findings are critical to the rational design and development of clinical trials for cell transplantation in people with MS.

Timothy Vartanian, MD, PhD
Beth Israel Deaconess Medical Center
Boston, MA
NMSS Area: Central New England Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $606,177
"Innate immune mechanisms of axonal injury in MS" Exploring a novel approach to why nerve fibers are damaged and why natural repair mechanisms eventually fail in MS.

Over the past decade, the idea that injury to axons—the fibers that conduct nerve signals from one nerve cell to another—may account for significant disability in MS has gained acceptance. Understanding how this injury occurs is a major focus of MS research. In this project, Timothy Vartanian, MD, PhD, is investigating a potential molecular mechanism for axon damage involving receptors, or docking proteins, on axons that may be mistakenly activated in MS.

Dr. Vartanian has located immune receptors called "toll-like receptors" (TLRs) on axons. TLRs are activated when a ligand, a specific substance that precisely fits their unique configuration, binds to them. Activation of axonal TLRs by synthetic ligands inhibits axon growth and causes axons to deteriorate. It has also been noted that RNA, a genetic molecule, can act as a TLR ligand to turn off axon growth. Dr. Vartanian is currently testing the idea that RNA released from dying cells during inflammation in MS activates axonal TLRs, leading to axon damage and degeneration.

Elucidating the mechanism behind axon damage is the first step in developing new drugs and other protective strategies to preserve axon function in MS.

Howard Weiner, MD
Brigham and Women's Hospital
Boston, MA
NMSS Area: Central New England Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $479,312
"Neuroprotection in EAE using novel fullerene based compounds" Preclinical testing of a novel compound that has potential to protect nervous system tissues from MS inflammation.

Currently, few treatment options exist for progressive MS, the most severe form of the disease. The disability seen in progressive MS is thought to be caused by degeneration of nerve cells. Howard Weiner, MD, is continuing his studies of a new drug called ABS-75 that has shown to be effective in treating progressive forms of EAE, the MS-like disease of mice.

Some research suggests that overproduction of a nerve chemical called glutamate by immune cells may cause the nerve degeneration characteristic of progressive MS. Dr. Weiner is testing the effects of ABS-75 on glutamate synthesis and on the activation of immune cells called astrocytes, which have been implicated as key players in the MS immune response. ABS-75 is also being administered to mice with EAE to study potential side effects and dosing requirements, as well as to analyze how the drug works with the immune system to protect nerve cells.

Determining the mechanisms by which ABS-75 exerts its nerve-protecting effects in mice with EAE is an important first step in studying this agent for its potential use as a future treatment for people with MS.

44 New Pilot Grants Test Innovative Ideas

Over the last six months, 44 new grants were awarded through the Pilot Research Program. These projects are aimed at quickly exploring new, untested ideas and generating preliminary data needed to apply for full grant support.

Therapy/Management of MS

Malachy Bishop, PhD "Adherence to disease modifying therapy in multiple sclerosis" University of Kentucky, Lexington, KY, **$44,000**, 9/1/2007-8/31/2008

Kottil Rammohan, MD "Induction of B cell tolerance to interferon using Ig-interferon complexes" Ohio State University, Columbus, OH, **$44,000**, 5/1/2007-4/30/2008

Rehabilitation

Scott Davis, PhD "Baroreflex modulation of sympathetic nerve activity in MS patients" University of Texas Southwestern Med. School, Dallas, **$44,000**, 9/1/07-8/31/08

Slobodan Jaric, PhD "A novel device to test hand function in multiple sclerosis" University of Delaware, Newark, DE, **$44,000**, 7/1/2007-6/30/2008

Psychosocial Aspects of MS

David Shucard, PhD "Variability of the ERP as an index of cognitive neural efficiency in MS" Buffalo General Hospital, Buffalo, NY, **$44,000**, 5/1/2007-4/30/2008

Diagnostic Methods

Thomas Barry, PhD "Exploration of extra-neural MS tissue for mycoplasma DNA sequences" National University of Ireland, Galway, Ireland, **$40,000**, 8/1/2007-7/31/2008

CNS Repair

Ernesto Bongarzone, PhD "Mobilization of neural precursor cells in the blood of MS patients" University of Illinois at Chicago, Chicago, IL, **$44,000**, 6/1/2007-5/31/2008

Douglas Feinstein, PhD " Regulation of BMPs and noggin in astrocytes" University of Illinois, Chicago, IL, **$44,000**, 9/1/2007-8/31/2008

Marie Filbin, PhD "MAG and myelin inhibit Schwann cell migration" Hunter College, New York, NY, **$44,000**, 8/1/2007-7/31/2008

Martin Grumet, PhD "Functions of olfactory ensheathing cells and their precursors" Rutgers University, Piscataway, NJ, **$44,000**, 4/1/2007-3/31/2008

Lori Isom, PhD "Expression of Na + channel B2 subunits in human MS" University of Michigan, Ann Arbor, MI, **$44,000**, 7/1/2007-6/30/2008

Gary Matthews, PhD "Novel mechanisms of ion channel targeting in myelinated axons" State University of New York at Stony Brook, **$44,000**, 4/1/2007-3/31/2008

Ralph Puchalski, PhD "Construction of mouse spinal cord gene expression atlas" Allen Institute for Brain Science, Seattle, WA, **$44,000**, 6/1/2007-5/31/2008
Moses Rodriguez, MD "Effect of statins on central nervous system remyelination" Mayo Clinic College of Medicine, Rochester, MN, **$44,000**, 5/1/2007-4/30/2008

Biology of Glia
Roumen Balabanov, MD "Generation of PLP/dnIRF-1 transgenic mouse" Rush University Medical Center, Chicago, IL, **$44,000**, 9/1/2007-8/31/2008
Manzoor Bhat, PhD, Med.ScD. "Disorganization of axonal domains in multiple sclerosis" University of North Carolina at Chapel Hill, **$44,000**, 5/1/2007-4/30/2008
Jeffrey Dupree, PhD "Differential neurofascin 155 glycosylation in multiple sclerosis" Virginia Commonwealth University, Richmond, VA, **$44,000**, 9/1/2007-8/31/2008
Hitoshi Komuro, PhD "Role of pituitary adenylate cyclase-activating polypeptides on oligodendrocyte migration" Cleveland Clinic Foundation, **$44,000**, 9/1/2007-8/31/08
Qing Lu, PhD "Genome-wide analysis of transcription factors for CNS myelinogenesis" UT Southwestern Medical Center at Dallas, **$44,000**, 5/1/2007-4/30/2008
Sean Ryder, PhD "Regulation of alternative splicing in oligodendrocytes by QKI" University of Massachusetts, Worcester, MA, **$44,000**, 7/1/2007-6/30/2008
Sara Szuchet, PhD "Is RhoBTB2 a player in the events that stage CNS myelination" University of Chicago, Chicago, IL, **$44,000**, 9/1/2007-8/31/2008
Chengji Zhou, PhD "The role of Wnt signaling in oligodendrocyte lineage" University of California, Davis, Sacramento, CA, **$44,000**, 8/1/2007-7/31/2008

Epidemiology
Ilya Kister, MD "Prevalence and significance of migraines and other headaches in MS" New York University, New York, NY, **$44,000**, 9/30/2007-9/30/2008

Human Genetics
Brigitte Huber, PhD "HERV-K18 as risk factor in multiple sclerosis" Tufts University, Boston, MA, **$44,000**, 9/1/2007-8/31/2008

Measuring MS Disease Activity
Kailash Chadha, PhD "Proteomic analyses of interferon-inhibitory protein" Roswell Park Cancer Institute, Buffalo, NY, **$44,000**, 7/1/2007-6/30/2008
Joseph Herbert, MD "Validation of a new severity-based MS classification system using the Sylvia Lawry database" Hosp. for Joint Diseases, NY, **$44,000**, 9/1/07-8/31/08
Sharon Lynch, MD "Glutathione as a measure of oxidative stress in MRS in brains of MS patients" U. of Kansas Medical Center, Kansas City, **$44,000**, 8/1/2007-7/31/2008
Frederick Munschauer, MD "The role of advanced glycation end-products in multiple sclerosis" Buffalo General Hospital, Buffalo, NY, **$44,000**, 5/1/2007-4/30/2008

Horea Rus, MD, PhD "RGC-32 as a potential marker of disease activity in multiple sclerosis" University of Maryland, Baltimore, MD, **$44,000**, 9/1/2007-8/31/2008

Immunology

Bonnie Dittel, PhD "Regulation of autoreactive T cell effector function in CNS by the cannabinoid system" Blood Ctr of Wisconsin, Milwaukee, **$44,000**, 8/1/07-7/31/08
Zsuzsanna Fabry, PhD "Cerebral trauma and CNS autoimmunity" University of Wisconsin-Madison, Madison, WI, **$44,000**, 8/1/2007-7/31/2008
Kouichi Ito, PhD "Generation of MBP-Tg mice to investigate the development of MBP-specific tregs" UMDNJ, Piscataway, NJ, **$44,000**, 7/1/07-6/30/08
David Kaplan, MD, PhD "High resolution immunophenotyping in the study of MS" Case Western University Hospital, Cleveland, OH, **$44,000**, 5/1/2007-4/30/2008
Hans Lassmann, MD "Feasibility of microarray studies in archival paraffin embedded MS tissue" Medical University of Vienna, Austria, **$40,000**, 8/1/2007-7/31/2008
Steven LeVine, PhD "The functional role of histamine receptors on lymphocytes from MS patients" University of Kansas, Kansas City, **$44,000**, 7/1/2007-6/30/2008
Minnie McMillan, PhD "Mass spectrometry study of a toleragenic peptide for treating MS" University of Southern California, Los Angeles, **$44,000**, 4/1/07-3/31/08
Thomas Petro, PhD "Effect of resveratrol on development of EAE" University of Nebraska Medical Center, Lincoln, NE, **$44,000**, 7/1/2007-6/30/2008
Christine Rohowsky-Kochan, PhD "Il-17 and SOCS expression in multiple sclerosis" UMDNJ, Newark, NJ, **$44,000**, 9/1/2007-8/31/2008
Philip Stork, MD "The role of the small G protein Rap1 in the EAE model of MS" Oregon Health & Science University, Portland, OR, **$44,000**, 5/1/2007-4/30/2008

Infectious Agents

Walter Atwood, PhD "Stem cell model of JCV-induced CNS disease" Brown University, Providence, RI, **$44,000**, 8/1/2007-7/31/2008
Jan Lunemann, MD "Epstein Barr virus infection and autoimmunity in multiple sclerosis" The Rockefeller University, New York, NY, **$44,000**, 9/1/2007-8/31/2008

Neuropathology

David Herrmann, MD " Is there a peripheral contribution to neuropathic pain in MS? A skin biopsy study" University of Rochester, NY, **$44,000**, 5/1/2007-4/30/2008
Aaron Johnson, PhD "Comprehensive assessment of antigen specific CD8 T cell mediated axonal damage" University of Cincinnati, **$44,000**, 5/1/2007-4/30/2008
Jacqueline Orian, PhD "Early grey matter changes in murine multiple sclerosis-like disease" La Trobe University, Australia , **$40,000**, 9/1/2007-8/31/2008

IMMUNOLOGY
Why The Immune System Goes Awry

Better treatments, prevention and a cure are the ultimate goals of MS research, and perhaps no branch of investigation has borne more fruit toward these goals than the study of the immune system. Current therapies for MS emerged from our growing understanding of how the immune system works and how it can be manipulated to suppress or regulate immune attacks. This work continues, as the investigators working in this area strive to pinpoint the cells and molecules that spur on the immune attack and those that can turn it off. These efforts are geared toward developing treatments that target specific aspects of the immune attack, possibly alleviating the side effects of more general immunosuppressive therapies.

The National MS Society has current, multi-year commitments of $43 million to support 135 research projects focusing on the immunologic underpinnings of MS.

Konstantin Balashov, MD, PhD
UMDNJ-Robert Wood Johnson Medical School
New Brunswick, NJ
NMSS Area: Mid-Jersey Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $445,220
"Plasmacytoid dendritic cells in MS" Understanding how viral infections may trigger immune attacks in MS by exploring immune cells that monitor for viruses in the body.

Researchers have long speculated that viruses play a role in triggering the immune response that causes MS. In support of this idea is the observation that symptom relapses often follow a viral infection in people with the disease. Konstantin Balashov, MD, PhD, is investigating a possible scenario involving immune cells called plasmacytoid dendritic cells (PDCs) to explain how viral infections may lead to MS exacerbations.

PDCs function as viral "sentinels" and are activated when a specific viral molecule binds to a receptor, or docking protein, called TLR-9. Dr. Balashov is collecting PDCs from people with MS currently experiencing a relapse and determining whether the cells have been activated and if so, whether TLR-9 has been engaged. In addition, one class of treatment for MS, interferon beta, is being studied to determine whether it prevents PDC activation as part of its ability to modulate disease activity.

This research may contribute to our understanding of a possible link between viral infection and MS relapses, and may suggest use of TLR-9 blockers to treat relapses.

Brian Evavold, PhD
Emory University
Atlanta, GA
NMSS Area: Georgia Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $489,426
"Mechanisms of tolerance against autoimmune disease using MHC variant peptides" Administering altered pieces of myelin proteins to mice with MS-like disease in efforts to turn off the immune attack.

The immune system normally responds only to foreign, or "non-self" proteins (called "antigens"), such as those belonging to the flu virus. Immune cells called T cells bind to these non-self antigens and initiate an immune response against them. Sometimes, T cells interpret "self" proteins, such as those belonging to the nerve-insulating tissue called myelin, as foreign. Usually the body is able to correct this mistake and prevent an immune response. But in MS, this fail-safe system malfunctions, and the immune system unleashes an attack against myelin.

Brian Evavold, PhD, has been researching a way to harness this fail-safe system to prevent T cells from reacting against myelin proteins. His team has constructed variants of two myelin proteins that bind loosely to T cells. This loose binding activates a mechanism that shuts off T cell activity and dampens their ability to mount an immune response. Dr. Evavold is now investigating the molecular signals generated by this mechanism and testing whether the two variants can suppress T cell reactions against other myelin proteins.

Information gained in this research could lead to the design of an MS therapy that directly targets myelin-reactive T cells, thus reducing the risk of side effects of drugs that target the entire immune system.

Vijay Kuchroo, PhD, DVM
Brigham and Women's Hospital
Boston, MA
NMSS Area: Central New England Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $456,555
"Role of TIM-1 in the induction and regulation of EAE" Focusing on the complex balance of immune factors that regulate the immune attack that underlies MS.

In multiple sclerosis, the myelin that insulates nerve fibers is the target of an immune attack resulting in neurological symptoms. Recent studies implicate a new type of immune cell – Th-17 cells – in this immune attack. Th-17 cells produce an inflammation-promoting messenger protein called IL-17, and appear to be more harmful than the long-recognized aggressive "Th1" immune cells. Meanwhile, regulatory T cells exist that can offset the harmful effects of Th1 and Th17 cells.

Vijay K. Kuchroo, DVM, PhD, and colleagues have identified a cell surface molecule, TIM-1, that appears to play an important role in regulating the balance of aggressive (Th1 and Th-17 cells) and regulatory T cells. Whereas auto-aggressive cells induce tissue inflammation, regulatory T cells protect against inflammation and maintain tolerance. Now they are studying in detail the mechanisms by which TIM-1 regulates this balance between auto-aggressive disease-inducing and protective regulatory T cells.

A thorough understanding of natural

processes that can turn off the immune attack and re-balance the immune system will provide critical information on the immune response in MS, and may provide us with avenues to create better therapies.

Mark Mannie, PhD
East Carolina University
Greenville, NC
NMSS Area: Eastern No. Carolina Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $414,548
"Antigen-specific inhibition of EAE" Designing a potential therapy for MS that traps and kills destructive immune cells that target nerve-insulating myelin.

T cells are the immune cells that initially sense when a pathogen, such as a parasite or virus, has invaded the body. T cells alert other immune cells to begin an attack that eventually destroys the invader. But in MS, T cells seek out and destroy myelin, one of the body's own brain and spinal cord tissues. T cells capable of reacting against myelin are normally deleted during immune system development. Researchers speculate that for unknown reasons, this elimination process fails to take place in people with MS.

Mark Mannie, PhD, has been investigating a strategy that lures these myelin-reactive cells into a trap that turns off their ability to target myelin. The "bait" consists of fusion proteins comprised of a myelin protein and an inhibitory immune chemical called a cytokine. When a myelin-reactive T cell recognizes the myelin protein and binds to it, the inhibitory cytokine deactivates the T cell. Several of Dr. Mannie's fusion proteins appear to protect rats from MS-like disease. He is now investigating the cellular and molecular mechanisms that the proteins use to target self-destructive T cells.

These experiments may provide a foundation for future research into the use of these fusion proteins as vaccines in the treatment and prevention of MS.

Vincent K. Tuohy, PhD
Cleveland Clinic Foundation
Cleveland, OH
NMSS Area: Ohio Buckeye Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $501,105
"Regulated gene-based therapy for CNS demyelinating disease" Developing a novel gene therapy that would provide therapeutic levels of interferon beta from a single injection of DNA so that the repeated injections currently required for this therapy would be precluded.

Interferon-beta, an approved therapy for MS, is rapidly cleared from the system, necessitating frequent injections to compensate. In addition, frequent, repeated injections can be associated with side effects including inflammation at sites of injection and liver toxicity, which can make people less likely to comply with their prescribed therapy.

Vincent K. Tuohy, PhD, is investigating the possibility of developing a one-time interferon-beta treatment delivered via genetic material, or DNA. His team has shown that they can reduce relapses and progression of experimental autoimmune encephalomyelitis (EAE), an MS-like disease, in mice after a single injection of DNA that instructs the production of interferon-beta. Now they are investigating ways to improve

upon this approach by providing more complete control over the regulation of interferon-beta output by the injected gene.

These studies may ultimately lead to the production of a novel strategy for improving current MS therapy and may form the basis for future delivery of therapeutic gene products.

Xiaoli Yu, PhD
University of Colorado Health Science Ctr.
Denver, CO
NMSS Area: Colorado Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $428,175
"Identification of peptide epitopes/mimotopes relevant to multiple sclerosis"
Attempting to determine the exact targets of immune antibodies found in the spinal fluid of people with MS for insights into its cause.

The spinal fluid of most people with MS contains increased amounts of a type of antibody called IgG. Antibodies are immune proteins directed against an immune trigger, or "antigen." IgG antibodies are present almost exclusively in infectious and inflammatory disorders and are usually directed against the disease-causing agent. However, previous attempts to identify the antigens to which these antibodies are targeted in MS have failed.

Xiaoli Yu, PhD, has devised a new approach that may pinpoint the specific target of these antibodies in MS. Antibody-producing cells from the spinal fluid of people with MS are isolated in the lab, and the antibodies that they make are reconstructed from the cells' DNA. These "recombinant antibodies" (rAbs) are then used to screen a large number of peptides (small pieces of protein) to see if any antibodies react against any particular peptide. Peptides that provoke a rAb reaction are then tested to see if they are recognized by actual antibodies present in spinal fluid from people with MS. Reactive peptides from this final group are undergoing further study to determine if they belong to known antigens.

Knowing the specific antigen or antigens that trigger MS should help researchers better understand the cause of this disease and design better treatments.

MYELIN AND GLIAL BIOLOGY
What Makes Myelin Tick?

Exploring glia, which include cells in the nervous system that make nerve-insulating myelin, is a cornerstone of MS research. Myelin appears to be the main target of the immune attack in MS. The cells that make myelin – oligodendrocytes – also are lost in MS. Researchers in this area study aspects of myelin that make it an immune target, and ways that some brain cells can contribute to the immune attack. They are also looking at factors that are important to the growth and development of oligodendrocytes and myelin, to find ways of promoting myelin repair.

The Society is funding 72 projects in glial cell/myelin biology, for a total multi-year commitment of some $22 million.

Ben Barres, MD, PhD
Stanford University Medical Center
Palo Alto, CA
NMSS Area: Northern California Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $535,128
"Signaling mechanisms that control the blood-brain barrier" Exploring the early development of the blood-brain barrier, the screen that normally prevents most immune cells from entering the brain but which breaks down in MS.

Normally, the brain is protected by a network of blood vessels and cells called the blood-brain barrier (BBB). The BBB shields the brain from toxic chemicals and potentially harmful immune cells. However, in MS, the BBB breaks down, allowing the influx of immune cells that lead to an attack on brain and spinal cord tissues.

Although some research suggests that BBB development is led by brain cells called astrocytes and takes place after birth, Dr. Barres has preliminary evidence that the barrier is constructed during prenatal development by cells called pericytes, which line the interior walls of the barrier's blood vessels. His team is further investigating this by exploring cell to cell interactions, and is also exploring whether a protein released from pericytes functions as the signal to begin building the BBB in early development.

Understanding how the BBB initially develops may suggest strategies to rebuild the barrier in diseases like MS in which it is compromised. These studies may also uncover a mechanism by which the barrier could be transiently lifted to deliver MS drugs directly to brain tissue.

Wenbin Deng, PhD
University of California, Davis
Sacramento, CA
NMSS Area: Northern California Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $453,255
"Mechanisms of microglial activation underlying EAE" Exploring how the antibiotic minocycline inhibits destructive immune activity of brain cells called microglia for clues to new therapeutic targets for MS.

Minocycline is an available antibiotic and anti-inflammatory drug that also demonstrates beneficial effects in animal models of MS and in preliminary clinical trials in people with MS. However, its mode of action in MS and MS-like disease is unknown. Wenbin Deng, PhD, is assessing the possibility that minocycline acts on proteins associated with immune cells called microglia using both laboratory-grown cells and mice with the MS-like disease EAE.

Microglia normally help rid the nervous system of harmful invaders. But in MS, microglia participate in the immune response that leads to the destruction of nerve-insulating myelin. Preliminary studies indicate that minocycline directly targets two proteins called PARP-1 and p38 MAPK. Dr. Deng is now searching for evidence that active forms of these proteins are produced by activated microglia, and determining what roles the proteins play in myelin and nerve damage and the death of myelin-making cells.

This research may reveal valuable information about the role of microglia in MS and more importantly, contribute knowledge about a potentially effective drug to treat MS.

Catherine Faivre-Sarrailh, PhD
Jean Roche Institue
Marseille, France
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $255,000
"Role of cell adhesion molecules in building axo-glial junctions" Studying glue-like molecules that are vital for proper nerve signaling and whether they are potential targets of the immune attack in MS.

The myelin sheath that insulates nerve fibers is not continuous; rather, it is separated by bare areas called nodes of Ranvier. Tiny channels clustered around the nodes regulate the flow of sodium and potassium molecules that generate the nerve impulse. Flanking each node is a region called the paranodal junction, where the nerve fiber makes contact with oligodendrocytes, the cells that produce myelin. Recent studies indicate that when myelin is destroyed in MS, the paranodal junction is also disrupted, suggesting that paranodal disturbance may contribute to the signs and symptoms of the disease.

Catherine Faivre-Sarrailh, PhD, is studying the function of glue-like "cell adhesion molecules" that act as contact points between nerve fiber and oligodendrocyte. One experimental goal is to learn details about how the molecules travel to and cluster at the paranodal junction. A second goal is to test whether an immune response directed against adhesion molecules occurs in MS and contributes to disease severity.

Understanding the structure and function of contacts between nerve fibers and oligodendrocytes may yield insight into the MS disease process and approaches to restore normal nerve conduction.

Yue Feng, MD, PhD
Emory University
Atlanta, GA
NMSS Area: Georgia Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $497,317
"Regulation of QKI in CNS myelination and repair" Studying whether enhancing the presence of a protein in immature myelin-making cells can stimulate their maturity and promote myelin repair.

One reason MS symptoms are long-lasting is because myelin, the material that covers nerve fibers and helps conduct nerve impulses, is only inadequately repaired following the immune attack that precipitates the disease. Oligodendrocytes, the cells that produce myelin, are also lost during this immune attack. Finding a way to facilitate myelin repair may prevent damage to the underlying nerve fibers and the progression of disability.

Genetically altered mice called "quaking mice" are born with abnormally low amounts of myelin. These mice have a defect in a gene that researchers have named "qkI." Studies by Yue Feng, MD, PhD, have shown that qkI regulates several genes for oligodendrocyte growth and myelin production. Dr. Feng is now determining how qkI itself is switched on and suspects that its activation may be through an unusual mechanism. In addition, her team will also investigate a way to force the activation of qkI in order to turn on myelin-making genes and thus promote myelin repair.

Uncovering the pivotal players in oligodendrocyte development and myelin growth is a critical step in constructing approaches that can repair myelin in MS.

Vittorio Gallo, PhD
The Children's National Medical Center
Washington, DC
NMSS Area: National Capital Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $501,669
"A novel regulator of oligodendrocyte development" Exploring factors that influence the development and survival of replacement cells capable of repairing damaged myelin in MS.

MS is a disease in which myelin, the insulating sheath that covers nerve fibers, is destroyed. Although some myelin-making cells called oligodendrocytes replace lost myelin, it is not enough to restore normal nerve functioning. Vittorio Gallo, PhD, suspects that myelin repair ultimately fails in MS because the there is impaired development of oligodendrocyte replacement cells. This project is exploring this process in detail to learn where failures may occur.

Oligodendrocytes develop from immature precursor cells (OPCs). During early development, OPCs proliferate and migrate to the correct areas in the brain and spinal cord, and differentiate to mature, myelin-making cells. The mature cells then provide the requisite amount of myelin. Dr. Gallo is testing a molecule called endothelin 1 (ET-1) for its ability to influence the first two steps in oligodendrocyte development and for its involvement in preventing the third step, cell differentiation and myelination. The team is also exploring the role of ET-1 in myelin repair.

Defining the molecular regulators of the myelin-making process may lead to therapies that influence myelin repair to restore function in people with MS.

Jeffrey Loeb, MD, PhD
Wayne State University
Detroit, MI
NMSS Area: Michigan Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/08; $143,765
"Axoglial communication through regulated release of neuregulin" Understanding chemical signals and growth factors provided by nerve fibers to the insulating myelin that wraps them, and how this signaling is impacted by MS.

The nerve-insulating material called myelin that is attacked in MS is made by brain cells called oligodendrocytes. These cells (also known as one type of "glial cell") wrap around the nerve fibers, producing the multilayered myelin sheath that allows for efficient nerve signal transmission. One limitation in developing MS repair therapies comes from a lack of understanding of the molecular interactions that occur at the interface (known as the axoglial junction) between the nerve fiber and the oligodendrocyte during myelin production.

Jeffrey Loeb, MD, PhD, is investigating how neuregulin 1 (NRG1), a key protein implicated in oligodendrocyte growth and survival, is regulated in the nervous system. Released by axons, NRG1 is found in high concentrations at axoglial junctions. Dr. Loeb's team is studying the molecular signals sent out by glial cells that trigger neuregulin release, and how NRG1 becomes concentrated at the axoglial junction. Included in these studies is an experiment that tests a possible therapeutic use for NRG1's axoglial targeting mechanism. Identifying factors controlling oligodendrocytes may help restore myelin in MS.

Qing Lu, PhD
UT Southwestern Medical Center at Dallas
Dallas, TX
NMSS Area: Lone Star Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/08; $158,212
"The role of Zfp488 in oligodendrocyte differentiation" Exploring the role of molecules that may control the development of myelin-making cells for clues to stimulating repair of nerve-insulating myelin in MS.

The production of myelin—the sheath of insulating material that surrounds nerve fibers—is a complex process involving many chemical and genetic signals. The myelin-making cells in the brain and spinal cord, called oligodendrocytes, develop from immature cells called precursors. They then specialize, or differentiate, into mature cells and activate the genes that direct myelin production. Qing Lu, PhD, has identified genes called Olig1 and Olig2 that act as an "on-switch" for myelin-making genes. In this project, Dr. Lu is focusing on a newly identified protein called Zfp488, made by a different gene, which is regulated by Olig1.

Results of preliminary studies indicate that Zfp488 participates in myelin formation through its interaction with Olig2. In this study, Dr Lu's team is researching the function of Zfp488 in the early development and differentiation of oligodendrocyte precursors in special mouse strains. One strain overproduces Zfp488 during brain development, while the other lacks the protein altogether. Analysis of oligodendrocyte and myelin formation in these mice will reveal the influence of the protein on these activities.

The information gained in this research may lead to the discovery of new targets that in the future could be manipulated to promote myelin repair in people with MS.

Elior Peles, PhD
Weizmann Institute of Science
Rehovot, ISRAEL
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $402,966
"Cell adhesion molecules in CNS myelination" Examining the crucial role of molecules that influence how nerve fibers are wrapped by insulating myelin to repair damage caused by the MS immune attack.

The myelin sheath that insulates nerve fibers, or axons, in the brain and spinal cord is produced by cells called oligodendrocytes. Each oligodendrocyte "arm" spirals around an axon, forming the multilayered structure that allows the efficient conduction of nerve signals. The development and maintenance of myelin requires constant communication between oligodendrocytes and their associated axons. Little is known about the molecules that mediate this interaction, a knowledge gap in efforts to design treatments to repair myelin in people with MS.

Elior Peles, PhD, is working with a molecule family called Necl that appears to mediate signaling between axons and myelin-making cells in the peripheral nervous system, the nerve network that extends throughout the body. Dr. Peles has now found that two Necl molecules are also associated with oligodendrocytes in the

brain and spinal cord. This study is tracing the functions of the molecules in developing oligodendrocytes grown in the lab as well as in mice. Myelin production in mice genetically altered to lack these two molecules is also being analyzed to highlight the exact point at which Necl molecules are needed in the process of normal myelin development.

This research may provide important information about how myelin is built and maintained and may suggest strategies to repair myelin in MS.

Jack Rosenbluth, MD
New York University Medical Center
New York, NY
NMSS Area: New York City Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $290,235
"Analysis of a new dysmyelinating mutant" Studying a naturally occurring mutant mouse that has abnormal myelin to better understand how myelin components contribute to nerve conduction.

Many of the symptoms of MS are caused by damage to myelin, the insulating sheath on nerve fibers essential for efficient nerve-signal conduction. The myelin sheath is a highly complex structure. Because of this complexity, it is not completely understood which myelin sheath components are damaged in MS, and the relationship between the severity and location of myelin sheath damage and neurological symptoms remains unclear.

To answer these and other questions, Jack Rosenbluth, MD, is studying a new experimental mouse called "shaking." These "mutant" mice have a genetic alteration that causes severe myelin abnormality. However, the mutant mice display only mild neurological symptoms. Dr. Rosenbluth is identifying specific structural defects in the myelin sheaths of shaking mice and characterizing the exact gene responsible. The structural abnormalities are also being compared with those of other mouse mutants used in MS research, including a strain in which comparable myelin abnormality results in much more severe neurological disability.

This research should lead to a better understanding of the effects of specific myelin sheath abnormalities on nerve function in MS and give researchers greater insight into how specific myelin sheath components normally function.

Bridget Shafit-Zagardo, PhD
Albert Einstein College of Medicine
Bronx, NY
NMSS Area: New York City Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $510,665
"The impact of rhgas6 on oligodendrocyte survival and myelination" Testing the ability of a molecule to stimulate the growth of nerve-insulating myelin for clues to repairing nervous system damage in MS.

In MS, repeated immune-system attacks destroy the insulating myelin that coats wire-like nerve fibers and interrupts nerve signaling in the brain and spinal cord. The nerve fibers themselves, and the cells that make myelin, called oligodendrocytes, can also be destroyed. Although some myelin is naturally repaired, especially early in the

disease, the extent of this repair is thought to be limited.

As MS progresses, immature oligodendrocytes, called oligodendrocyte precursors, may die, reducing the population of cells capable of repairing myelin. Bridget Shafit-Zagardo, PhD, is investigating the myelinating process using myelin-coated nerves growing in culture dishes. Her team is refining this culture system to allow the testing of growth factors and other compounds that may have promise for stimulating tissue repair. They are also testing the ability of a factor called growth factor growth arrest-specific protein 6 (rhgas6) to enhance the survival and maturation of oligodendrocyte precursors and myelin repair.

These studies will provide insight into signaling processes that protect oligodendrocytes and aid in remyelination. Ultimately they could lead to a new approach to reversing the damage caused by MS.

Betty Soliven, MD
University of Chicago
Chicago, IL
NMSS Area: Greater Illinois Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $504,577
"Lysosphingolipid receptors and growth factors in oligodendroglial regeneration"
Does blocking a molecule present on immune cells, which is the action of the experimental MS therapy FTY720, impact myelin-making cells that also carry this molecule?

FTY720 is a drug currently undergoing investigation as an oral therapy for MS. Acting on certain receptors, or docking proteins, called S1P receptors, FTY720 is thought to prevent immune cells from attacking myelin, the insulating coating of nerve fibers that comes under attack in MS. But S1P receptors are also found on oligodendrocytes, the cells that produce myelin. Betty Soliven, MD, is investigating the actions of these receptors in oligodendrocyte growth and survival. Her research could reveal whether FTY720 encourages myelin regrowth in addition to its immune-suppressing effects.

One set of experiments is focusing on the interaction between oligodendrocyte S1P receptors and the activation of growth factors known to promote oligodendrocyte growth. A second set is studying mice that lack S1P receptors to determine the receptors' impact on oligodendrocyte development and myelin production.

These studies may ascribe to FTY720 an as-yet undiscovered beneficial effect on myelin-making oligodendrocytes. Because oligodendrocytes are destroyed in the MS immune attack, promoting their growth and survival in people with MS may lead to the restoration of normal myelin structure and function.

NEUROPATHOLOGY
Nervous System Injury

MS involves immune-mediated injury, not just to the myelin coating that insulates nerve fibers in the brain and spinal cord, but also to the nerve fibers themselves. Investigators are working to determine how and when nerve fibers get damaged, and how to protect them.

The National MS Society is currently funding 9 research projects in neuropathology, for $3.6 million.

Alexander Gow, PhD
Wayne State University
Detroit, MI
NMSS Area: Michigan Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $464,845
"Molecular mechanisms of stress induced oligodendrocyte cell death" How an immune messenger chemical prominent in MS immune attacks may damage myelin-making cells and impede myelin repair.

Oligodendrocytes are the cells that make myelin, the sheath that insulates nerve fibers. In MS, an immune response that normally targets only harmful invaders, such as bacteria, instead targets myelin and leads to its destruction and also to the eventual death of oligodendrocytes. The exact mechanism underlying the demise of oligodendrocytes in MS is unknown, but Alexander Gow, PhD, believes that MS causes oligodendrocytes to experience "metabolic stress." As a result, a pathway that causes the cell to self-destruct (known as "apoptosis") is suddenly activated. Interrupting this process may help preserve oligodendrocytes—and the ability to repair myelin—in people with MS.

Dr. Gow is exploring a possible protective role for a molecule called CHOP in oligodendrocyte cell stress and apoptosis. CHOP acts as a molecular switch for certain processes, and some research suggests that it can make oligodendrocytes more resistant to apoptosis. Dr. Gow is exploring the effect on oligodendrocyte survival when mice produce excess amounts of CHOP. The role of CHOP inhibitors is also being studied to determine whether they make oligodendrocytes more susceptible to apoptosis.

The information gained in this study may guide development of drug therapies that block oligodendrocyte destruction and reduce the severity of MS signs and symptoms.

John Rose, MD
VA Medical Center
Salt Lake City, UT
NMSS Area: Utah State Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $563,475
"The role of COX-2 in oligodendrocyte death and demyelination" Understanding the potential role of an inflammatory protein called COX-2 in the destruction of myelin-making cells in MS.

In MS, a misdirected immune response attacks myelin, the insulating material of nerve fibers in the brain and spinal cord. In addition, the brain cells that manufacture myelin, called oligodendrocytes, can also be destroyed in MS, and eventually the body cannot repair the damaged myelin. Understanding the causes of oligodendro-

cyte loss may lead to the design of therapeutic interventions that restore myelin production and function.

John Rose, MD, is studying the role of an inflammatory protein called COX-2 in oligodendrocyte death. COX-2 is produced during inflammation and is involved in other immune-related diseases, such as arthritis. Preliminary studies reveal that COX-2 is present in oligodendrocytes in MS brain lesions and in animal models of MS. Dying oligodendrocytes also produce COX-2. Dr. Rose's team is investigating the contribution of COX-2 to oligodendrocyte death, myelin damage, and symptom severity in mice with an MS-type disease. They are also testing the effectiveness of COX-2 inhibitors in protecting oligodendrocytes and reducing inflammation.

COX-2 inhibitors are already available and widely used for treating pain. These studies may lay the groundwork for subsequent clinical investigations of COX-2 inhibitors for the treatment of MS.

TISSUE/DNA BANKS
Vital Resources

The National MS Society supports several facilities to provide resources for researchers studying multiple sclerosis. These include three MS tissue banks that provide brain tissue for researchers studying the pathology of MS—its nature, cause, and effects on the brain – and a DNA bank that fuels research to understand the genetic basis of MS.

A large number of participants in these banks are needed to accelerate discovery. Such facilities depend upon the generous pledges of tissue or blood donors who recognize how important their "gifts" are to propelling MS research forward.

Stephen Hauser, MD
University of California, San Francisco
San Francisco, CA
NMSS Area: Northern California Chapter
Award: Research Grant
Term/Amount: 4/1/08-3/31/12; $878,962
"Support of a core DNA repository for MS"
Banking genetic material from individuals and families with MS as a shared resource for studies searching for genes that confer susceptibility to MS.

Multiple sclerosis is not inherited in the classic sense of the word, but there is evidence that multiple genes can confer susceptibility to MS. Dr. Stephen Hauser was among the first MS researchers in the United States to recognize the need for genetic studies to understand genetic influences in MS, and has been at the forefront in organizing collaborative studies with geneticists at Harvard and Duke uni-

versities. These and additional investigators are now part of the International MS Genetics Consortium, collaborating to map the genome (all of the genetic material within humans) of MS.

With funding from the National MS Society, Dr. Hauser established a DNA bank to extend these studies and better pinpoint the MS genes. Dr. Hauser's group gathers and stores a large number of blood samples (from which DNA is derived) from people with MS, including those with no family history of the disease and those whose families have multiple members with the disease.

These samples are used by Dr. Hauser's research team and are also shared with researchers around the world studying MS susceptibility. By assisting researchers in genetic studies of MS, this "library" of DNA could be instrumental in finding the underlying cause of MS. This knowledge would set the stage for developing therapies aimed at preventing or reversing the disease.

Howard Lipton, MD
University of Illinois at Chicago
Chicago, IL
NMSS Area: Greater Illinois Chapter
Award: Research Grant
Term/Amount: 10/1/07-9/30/10; $425,958
"Establishing a multiple sclerosis tissue repository at the University of Illinois" Gathering and banking MS tissue samples to serve as a resource for MS researchers seeking to understand this disease and how to cure it.

This is a new satellite facility of one of two tissue banks supported by the National MS Society for many years. A tissue bank is very close to what it sounds like: an area set aside in a laboratory or medical center where tissue specimens are "deposited" and stored for later "withdrawal" and use. These banks represent a true partnership between persons with MS and the researchers seeking the cause of, and cure for, the disease.

Brain and spinal cord tissues, spinal fluid and other specimens from persons who had MS during their lifetimes are frozen or otherwise preserved very soon after the death of the donors. The specimens are sent to the established tissue bank at the University of California, Los Angeles for actual banking. The banked tissues are carefully catalogued with information about the donor's medical history. This ready and crucial resource is available to any legitimate investigator seeking clues to multiple sclerosis.

Index of New Research Projects, by National MS Society Chapter

NOTE: Index does not include Pilot Projects, listed on pages 8-10.

"New Research" is produced twice a year by the National Multiple Sclerosis Society, Research & Clinical Programs, 733 Third Avenue, NY, NY 10017-3288. For more information about multiple sclerosis research, call **1-800-344-4867** or visit our Web site: **http://www.nationalmssociety.org**.