

NERVOUS SYSTEM REPAIR

Restoring Function

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

The National MS Society has current, multi-year commitments of about \$33.8 million to support 53 research projects focusing on repairing the nervous system in MS.

Sylvia Christakos, PhD

University of Medicine and Dentistry of New Jersey
Newark, NJ

Area: New Jersey Metro Chapter

Award: Pilot Project

Term/Amount: 6/1/09-5/31/10; \$ 33,000

"Protection against experimental autoimmune encephalomyelitis by calbindin-D28K" Looking for a way to stop the progression of MS by preventing the death of nerve cells.

Myelin, the fatty material that surrounds and protects nerve fibers, is destroyed in the central nervous system (CNS – brain, spinal cord and optic nerves) in MS. Without their protective myelin, nerve fibers fail to conduct signals properly. In addition, damage to unprotected nerve fibers causes some nerve cells to die, contributing to the progression of MS. To date, there is no approved therapy aimed preventing nerve cell death.

In this pilot research project, Sylvia Christakos, PhD, is studying the effect of a protein known as "calbindin-D28K," or

CaBP28K, in mice with experimental autoimmune encephalomyelitis (EAE), an animal disease that resembles MS. CaBP28K binds or "buffers" calcium, one of the factors thought to be involved in the death of nerve cells in MS. There is some evidence that this protein is activated at sites of MS lesions in the brain, and this project asks the question of whether its activity can be ramped up to better protect vital nerve tissues in MS. Dr. Christakos is delivering the protein to the brain using an advanced "Trojan horse"-style approach to see whether "mopping up" more calcium before, during or after EAE can protect nerve cells.

Success in this preliminary step could lead to work toward a new approach to MS therapy that would prevent nerve cell death and progression of the disease.

Suhayl Dhib-Jalbut, MD

UMDNJ-Robert Wood Johnson Med. School
New Brunswick, NJ

Area: New Jersey Metro Chapter

Award: Research Grant

Term/Amount: 10/15/08-9/30/09; \$96,133

Paid in part by gifts from the Sayerville-Old Bridge Rotary and the Estate of Richard Stotwell to the NMSS New Jersey Metro Chapter
"BDNF-Engineered stem cell mediated neuroprotection in EAE" Testing the feasibility of using the body's own cells to deliver a key molecule to protect nervous system tissue from damage in MS.

MS damages the myelin insulation that coats nerve fibers in the brain and spinal cord, and the nerve fibers (axons) themselves are also damaged. While currently

approved immune-modulating drugs control attacks during the early phases of MS, they cannot prevent progressive loss of tissue. Therefore, novel neuroprotective strategies are needed.

Brain derived neurotrophic factor (BDNF) is a natural protein that supports the growth of axons. Suhayl Dhib-Jalbut, MD, is examining how BDNF might modulate axonal loss in mice with the MS-like disease EAE. His team also is testing the ability of bone marrow stem cells to deliver BDNF into the nervous system, and investigating whether increasing the activity of BDNF can protect axons.

These studies could identify new approaches for the prevention of disease progression in MS.

Marie Filbin, PhD

Hunter College

New York, NY

Area: New York City Chapter

Award: Research Grant

Term/Amount: 10/15/08-9/30/12; \$607,270

Paid in half by MS Hope for a Cure to the NMSS New York City Chapter

“MAG inhibits migration and induces death of Schwann cells” Investigating factors that may limit the ability of cells to repair MS damage to myelin, and ways to overcome those limits.

The immune attacks in MS cause damage to myelin, the insulation around nerve fibers, which slows or stops nerve impulses. Not only is myelin lost, but so also are the cells in the brain and spinal cord that make myelin, the oligodendrocytes. Many researchers believe that if myelin-making cells can be transplanted and widely dis-

tributed in the brain and spinal cord of people with MS, then these cells may re-form myelin and the nerves may re-gain their function.

Researchers have found that in laboratory studies, transplanting Schwann cells (myelin-making cells from the peripheral nervous system, outside the brain and spinal cord) into the brain can induce myelin repair, but these cells do not migrate well and so the repair is limited. Marie Filbin, PhD, and colleagues have identified a protein called MAG, found in the brain and spinal cord, that inhibits the migration of Schwann cells. Now they are seeking to identify the exact molecular mechanism that inhibits Schwann cell migration in cells isolated in the laboratory. Ultimately they are looking for ways to neutralize these factors and promote the migration of transplanted Schwann cells.

These studies should further the development of Schwann cell transplantation as a strategy for repairing damage in people with MS.

Steven A. Goldman, MD, PhD

University of Rochester Medical Center
Rochester, NY

Area: Upstate New York Chapter

Award: Research Grant

Term/Amount: 7/1/09-6/30/12; \$522,257

“Progenitor cell-based myelination of the dysmyelinated central nervous system”

Testing the ability of transplanted cells to grow or repair nerve-insulating myelin in animal models as a prelude to cell transplantation in people with MS.

MS involves a misguided immune attack against myelin, the insulating coating that surrounds nerve fibers, in the central nervous system. One of several possibilities being explored for repairing the resulting damage is to transplant replacement myelin-making cells, called oligodendrocytes, that may have the capability to restore myelin.

Steven A. Goldman, MD, PhD, and colleagues have conducted previous studies to establish methods for extracting progenitor, or immature, oligodendrocytes from human brain tissue and transplanting them to repair tissue damage in mice. They have shown – in mice that normally make no myelin – that transplanting oligodendrocyte progenitor cells into these mice results in almost complete restoration of their previously lost neurological function. Now they are further exploring these methods in other mouse models, including a model that resembles progressive MS.

This highly focused effort is likely to move this approach quickly toward the ultimate goal of testing the ability of cell transplantation to restore function in persons who have MS.

Zhigang He, PhD

The Children's Hospital
Boston, MA

NMSS Area: Central New England Chapter

Award: Research Grant

4/1/2008-3/31/2012; \$ 702,007

“NAD-based neuroprotection in models of multiple sclerosis” Understanding mechanisms involved in a natural nerve protection mechanism and seeking ways to enhance it to stop nervous system injury in MS.

MS injures axons, the fibers that conduct nerve signals, as well as the myelin that insulates them. The injury to axons in the brain and spinal cord is thought to be a major contributor to long-term disability in MS. Zhigang He, PhD, has been studying how axons are injured in MS and in this project is investigating a possible protective mechanism.

Dr. He's previous studies suggest that the level of a natural chemical called nicotamide adenosine diphosphate (NAD) in nerve cells is critical for protecting axons. NAD functions as an energy-transfer molecule in many of the body's biochemical processes. Dr. He has found that increasing NAD levels reduces axonal degeneration and symptoms in mice with an MS-like disease. This current study focuses on defining the molecular mechanisms underlying this protection. Additional experiments are determining how to increase NAD levels by manipulating the levels of a chemical that participates in NAD formation.

This research may provide insights into the cause of axonal damage in MS as well as suggest a preventive strategy to preserve long-term nerve function.

Gianvito Martino, MD

Fondazione Centro San Raffaele
Milano, Italy

Award: Research Grant

4/1/2008-3/31/2010; \$ 292,636

“The role of endogenous neural stem/precursor cells in multiple sclerosis” Exploring natural nervous system repair processes for insights into restoring function in MS.

The insulating coating on nerve fibers, called myelin, is damaged by repeated immune attacks in MS. Often this damage shows signs of natural repair, especially early in the disease, but at some point this repair is thwarted by unknown factors.

In this study, a team led by Gianvito Martino, MD, is focusing on factors that influence the capacity of resident adult neural stem/precursor cells (called endogenous cells) to migrate within damaged areas and promote brain repair through several mechanisms, such as cell replacement, myelin regrowth, and neuroprotection. The team is exploring reserves of precursor cells in an area of the brain called the sub-ventricular zone (SVZ) in mouse models of progressive MS, and examining how specific manipulations of SVZ cells have consequences “downstream” in terms of the cells’ abilities to proliferate, mature, migrate and repair damaged myelin.

This study should provide important insights for future clinical trials of tissue repair strategies in MS.

Debra A. Mayes, PhD

Cincinnati Children's Research Hospital
Cincinnati, OH

NMSS Area: Ohio Valley Chapter

Award: Postdoctoral Fellowship

Mentor: Nancy Ratner, PhD

7/1/2008-6/30/2011; \$ 150,800

“NF1 and Ras activation in oligodendrocyte progenitor cell development and myelination” Seeking insights into the molecular events that control the available population of brain cells that have potential to repair damage that occurs in MS.

Oligodendrocytes are cells that make and maintain myelin in the brain and spinal cord. Myelin surrounds and protects nerve fibers, and enhances their ability to conduct nerve signals. In MS, the myelin is damaged, interfering with nerve signals and leading to the symptoms of MS. Cells known as “progenitor” or “stem” cells in the brain can develop into new oligodendrocytes which could repair myelin, but for unknown reasons they fail to keep up with myelin repair in MS.

In this postdoctoral research project, Debra Mayes, PhD, is studying the effects of a signaling molecule, “NF1,” a protein that helps to regulate the development of oligodendrocytes. By a combination of work with mice that lack the gene for NF1 and studies of oligodendrocyte progenitor cells grown in the laboratory, Dr. Mayes hopes to determine the exact role of NF1 and find out whether myelin repair can be increased by altering the amount of NF1 in the brain. The results of this line of work could lead to new ways to enhance myelin repair, which could restore nerve function and reduce disability in people with MS.

Jayshree Samanta, PhD

New York University Medical Center
New York, NY

NMSS Area: New York City Chapter

Award: Postdoctoral Fellowship

7/1/08-6/30/11; \$150,800

“Role of sonic hedgehog in remyelination”

Investigating a molecule that may be key to the brain’s recruitment of cells to repair damage caused by MS.

The myelin sheath wraps around the nerve fibers (axons) in the brain and spinal cord. Myelin provides the insulation needed for rapid conduction of impulses, and may promote the integrity of the axon. In MS, myelin is damaged by immune attacks, resulting in blocked nerve messages and ultimately leading to the loss of axons.

Myelin is made by cells called oligodendrocytes (OL). After myelin is damaged, normally new OLs are generated by adult stem cells resident in the brain, but in MS this process remains incomplete or cannot keep up with the damage. The stem cells require a molecule called Sonic Hedgehog (Shh) for their survival and also for generating OLs, but details of its role following myelin damage are not known.

Jayshree Samanta, PhD, is examining whether Shh-responsive stem cells produce myelin-repairing OLs, and whether Shh signaling is necessary for remyelination. These studies will provide new insights into the role of Shh in regulating activation and recruitment of OL progenitors in MS. Understanding the origin of remyelinating cells and the signals that trigger their activation, migration and differentiation also has major implications for developing repair strategies to restore function in MS.

Jacob A. Sloane, MD, PhD

Beth Israel Deaconess Medical Center
Boston, MA

NMSS Area: Central New England Chapter

Award: Research Grant

4/1/2008-3/31/2011; \$ 474,920

“Remyelination in MS: negative regulation by hyaluronan and Toll-like receptors”

Molecules that may inhibit natural myelin regeneration in MS, and possible strategies to overcome them to restore function.

MS causes the destruction of myelin, the multilayered sheath of fats and proteins that insulates axons, the nerve fibers that conduct nerve signals. Myelin is produced by cells called oligodendrocytes. Although some immature oligodendrocytes (called progenitors) have been found in areas of myelin damage, they are unable to mature into myelin-repairing cells. Jacob Sloane, MD, PhD, proposes that hyaluronan, a building block molecule present in many areas of the body, may prevent maturation of progenitors and inhibit myelin repair in MS.

Dr. Sloane is investigating whether hyaluronan activates special receptors, or docking sites, on oligodendrocytes. These “toll-like receptors (TLRs)” are part of the body’s innate alarm system that warns of a threat. Dr. Sloane is detailing the effects of TLR activation by hyaluronan on oligodendrocyte survival and myelin production in mice with an MS-like disease called EAE. Mice without TLRs are also being tested to determine the exact contribution of these receptors to oligodendrocyte inhibition.

This research may suggest a means of interrupting TLR activation by hyaluronan, which may result in a strategy to restore normal nerve function in people with MS.

Riqiang Yan, PhD

Cleveland Clinic Foundation

Cleveland, OH

NMSS Area: Ohio Buckeye Chapter

Award: Research Grant

4/1/2008-3/31/2011; \$ 486,057

“The role of BACE1 in myelination” The role of a molecule in the repair of nerve-insulating myelin, and whether blocking its activity blocks repair.

Many researchers are looking for ways to prompt the repair of myelin -- the nerve-fiber covering that is destroyed by an autoimmune response in MS -- as a means of restoring normal nerve function in people with the disease. These efforts have led to the discovery of many proteins that play a role in the complex process of myelin production. Riqiang Yan, PhD, is investigating one such protein called BACE1, which has already been implicated in the production of amyloid peptides that are believed to cause dementia in Alzheimer disease.

Dr. Yan has found that mice genetically engineered to lack BACE1 have abnormally low amounts of myelin. Other studies suggest that BACE1 may aid in the processing of neuregulin, a key initiator of myelination. This study is elucidating the exact mechanisms by which BACE1 regulates myelin production. One experiment is looking at whether myelination is stopped when a BACE1-inhibiting drug is given to mice.

This research is timely because BACE1 inhibitors are being investigated as potential therapies for cognitive dysfunction, a symptom of many diseases including MS. It is important to know whether these inhibitors slow or stop myelination and should thus be avoided by people with MS.