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## RESTORING FUNCTION

### Myelin's Growth, Injury and Repair

Myelin insulates the wire-like extensions of nerve cells, speeding nerve conduction and protecting the nerve from harm. Because myelin is thought to be the main target of the immune attack that underlies MS, it's vital that we understand its development, function and repair.

The National MS Society has current, multi-year commitments of \$17.8 million to support research projects focusing on myelin biology in MS.

#### **Ben A. Barres, MD, PhD**

Stanford University Medical Center  
Stanford, CA

Area: No. California Chapter/Region G

Award: Research Grant

Term: 10/1/09-9/30/12

Funding Required: \$487,716

**"How does thyroid hormone promote CNS myelination?"** Identifying mechanisms by which a natural hormone impacts myelin formation, for clues to stimulating myelin repair in MS.

The development of therapies designed to promote the regeneration of lost myelin – the nerve-ensheathing substance that is a main target of the immune attack in MS – is currently a major unmet need in MS treatment. Oligodendrocytes are the cells that produce myelin in the brain and spinal cord, and the generation of oligodendrocytes from immature oligodendrocyte "precursor" cells (OPCs) is a required preliminary step for myelin regeneration.

Dr. Barres is investigating how a thyroid hormone known as "T3" – which, if reduced,

results in decreased myelin formation – might be affecting the development of oligodendrocytes. His team is studying what genes that instruct the development of OPCs are affected by T3. The team is using gene chips – tiny slides on which investigators can track activity of thousands of genes simultaneously – and mouse models which permit the study of the effects of T3 on myelin formation.

The genes identified in this project might someday be used to stimulate myelin repair in people with MS.

#### **Narayan R. Bhat, PhD**

Medical University of South Carolina  
Charleston, SC

Area: Mid Atlantic Chapter/Region C

Award: Research Grant

Term: 10/1/09-9/30/10

Funding Required: \$157,288

**"A promyelinogenic function of p38 MAP kinase in oligodendrocytes"** Identifying molecular signals that control the activity of cells capable of repairing myelin damaged by MS.

MS destroys myelin – the material that protects nerve fibers – and also damages the nerve fibers themselves. The cells that make myelin in the brain and spinal cord are called oligodendrocytes. These are present in the adult brain and they perform some myelin repair but cannot keep up with the MS damage. Dr. Bhat is studying the signals that trigger oligodendrocytes to become mature myelin –making cells during early development in search of clues to triggering these cells to promote repair.

His team's preliminary data point to signals from an enzyme known as p38 MAP kinase, which seem to play a pivotal role in

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inducing oligodendrocytes to form myelin. Now they plan to explore this possibility further by analyzing what genes in myelin are activated by this protein, and also using a mouse model in which this pathway is "knocked out" to detect its role and function.

Identifying the signals that control myelin-making cells can enhance their use in therapeutic strategies to repair damage in MS.

**Anthony T. Campagnoni, PhD**

University of California, Los Angeles  
Los Angeles, CA

Area: Southern California Chapter/Region G

Award: Research Grant

Term: 10/15/09-9/30/12; \$ 471,689

*Funded by the NMSS Southern California Chapter*

**"Golli-MBP gene expression in the nervous system"** Searching for new ways to encourage the repair of myelin, the material damaged in MS.

Myelin, the material that surrounds and protects nerve fibers, is made in the brain and spinal cord by cells known as oligodendrocytes, and is the target of the immune attack in MS. Oligodendrocytes develop from a type of stem cell called oligodendrocyte precursor cells (OPCs). Potentially, OPCs could replace damaged myelin in MS, but for reasons that are still unclear, they cannot keep up with the damage.

In this research project Anthony Campagnoni, PhD, hopes to determine how proteins known as "golli-myelin basic proteins (goli-MBP) act in OPCs. The golli-MBP proteins are apparently involved in the movement of OPCs and production of myelin as the cells develop into mature

oligodendrocytes. Dr. Campagnoni will apply cutting-edge biochemical and microscopic techniques to cells from mice in which the genes for goli-MBP proteins have been modified to pinpoint their role in OPC development.

This work could provide important clues about how to stimulate OPCs to better repair damaged myelin and restore nerve function in people with MS.

**Babette Fuss, PhD**

Virginia Commonwealth University  
Richmond, VA

Area: Central Virginia Chapter/Region B

Award: Research Grant

Term: 10/1/09-9/30/12

Funding Required: \$ 496,697

**"The role of focal adhesion kinase (FAK) in CNS myelination"** Investigating how to enhance the capacity for myelin repair to restore function in MS.

In MS, the myelin that protects nerve fibers in the central nervous system (CNS: brain and spinal cord and optic nerves), is damaged and although cells that can develop into myelin-making cells persist in the brain they do not seem capable of making enough myelin to repair the damage in MS. Myelin is made and maintained by cells known as oligodendrocytes. During early development of the CNS, oligodendrocytes extend long arm-like processes that search around for a nerve fiber. When they contact a nerve fiber, they wrap around it and begin to make myelin, a process known as myelination.

In this research project Babette Fuss, PhD, aims to determine the role of a molecule called "focal adhesion kinase" (FAK) in promoting myelination by oligodendrocytes. In lab rodents that lack FAK, the amount of

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A cascade of events damage the wire-like axons extending from nerve cells, along with the myelin sheathing that wraps around them. Identifying these events is crucial to protecting and repairing the nervous system in MS

myelin on nerve fibers in the CNS is greatly reduced. In addition, there is evidence that there is less FAK in the damaged CNS areas for some people with MS compared to the CNS of people who don't have MS. Dr. Fuss will study the effects of FAK on oligodendrocytes grown in lab dishes, as well as in mice that have been modified so that the gene responsible for making FAK can be turned off at various stages of development.

This work should provide important clues about how to make the myelin-forming cells more effective, thus improving myelin repair and restoring nerve function in MS.

## RESTORING FUNCTION

### The Nervous System in Health and Injury

The immune attack in MS unleashes a cascade of events that damage the wire-like arms of nerve cells (axons) and the protective tissue (myelin) that wraps around axons, disrupting nerve signal transmission. Understanding these processes is crucial to efforts to protect and repair the nervous system. The National MS Society has current, multi-year commitments of \$7.7 million to support investigators focusing on neuropathology and neurophysiology.

#### Elliot Frohman, MD, PhD

University of Texas SW Medical Center  
Dallas, TX

Area: Lone Star Chapter/Region E

Award: Research Grant

Term/Amount: 10/1/09-9/30/10; \$185,000

*Funded by the NMSS Lone Star Chapter*

#### **"Modeling the pathophysiology of Uthhoff's phenomenon in multiple sclerosis"**

Developing a system for studying the temperature-related changes in nerve function that occur in people with MS.

Many people with MS experience a temporary worsening of their symptoms when the weather is very hot or they run a fever, get overheated from exercise, or take very hot showers or baths. For example, some people notice that their vision becomes blurred when they get overheated—a phenomenon known as Uthhoff's sign. These temporary changes can result from even a very slight elevation in core body temperature (as little as one-quarter to one-half of a degree) because it