

by disease severity.

This study and the resulting recommendations will provide critical information for the Society and other stakeholders to address MS physician shortages and help ensure optimal care for all people with MS.

## 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 about \$14 million to support research projects focusing on myelin biology in MS.

### Roumen Balabanov, MD

Rush University Medical Center  
Chicago, IL

Area: Greater Illinois/Midwest

Term/Amount: 10/1/10-9/30/13; \$557,137

**Paid by special funds by the Illinois Lottery**

**"Role of IRF-1 in oligodendrocytes"** Looking for ways to protect the cells that make nerve-protecting myelin from damage in MS.

MS involves immune system damage to myelin, the fatty material that surrounds and protects nerve fibers (axons) in the central nervous system (CNS: the brain, spinal cord and optic nerves). Oligodendrocytes, the cells that manufacture and maintain myelin in the CNS, are also damaged. Some immune system cells release a chemi-

cal known as interferon gamma (IFN-gamma), which may contribute to myelin damage by preventing oligodendrocyte growth and repair of myelin.

In this research project, Dr. Balabanov is investigating how a molecule called interferon regulatory factor 1 (IFR-1), found inside oligodendrocytes, may play a role in the damage caused by IFN-gamma. Preliminary data indicate that suppressing the action of IFR-1 may protect oligodendrocytes from IFN-gamma, and Dr. Balabanov will test this idea using mice that have had their genetic make-up altered so that their oligodendrocytes do not produce IFR-1. The research will compare the severity of the MS-like disease EAE in IFR-1 deficient mice with normal mice to better discern the role of IFR-1 in tissue damage.

This research could lead to new understanding of how IFN-gamma damages oligodendrocytes, and provide a clue for developing new ways to prevent myelin damage in MS.

### Ben Barres, MD, PhD

Stanford University Medical Center  
Palo Alto, CA

Area: Northern California/West

Term/Amount: 10/1/10-9/30/13; \$496,237

**"Signaling mechanisms that control the blood-brain barrier"** Determining how the protective barrier between the bloodstream and the brain and spinal cord breaks down in MS.

The capillaries, or tiny blood vessels, of the brain have a layer around them called the blood-brain barrier (BBB). By controlling what can move from the blood into the tissue of the brain, the BBB protects the

## Up Close: Research Fellow Angela Hahn, PhD



Making sure we attract the best and brightest minds to conduct MS research is a major goal of the National MS Society's research programs. This summer the Society made it possible for dozens of energetic young doctors and scientists to get the training they need to make MS the focus of their careers. Meet one of them.

Angela Hahn, PhD (University of California at San Francisco) is going after myelin – a major target of the immune attack in MS – and it's personal. While in graduate school, Dr. Hahn was diagnosed with multiple sclerosis.

“At the time, my knowledge of neurobiology was limited to what I had learned in a few courses,” she says. “What was a topic of interest became a topic of utmost importance.” Dr. Hahn is now completing her training through a postdoctoral research fellowship from the National MS Society. Her project focuses on finding a way to rebuild myelin at sites of damage by stimulating oligodendrocytes (myelin-making cells).

Dr. Hahn's emotions about having MS fuel her studies. “As a patient, MS frustrates me,” she says. “After decades of research there is no cure, just a handful of treatment options; no drug to repair the damage already inflicted; and no way of knowing what the progression of my illness will be. “As a scientist, MS intrigues me because I can logically separate myself from the “no's” that frustrate me to see the fascinating biological problems behind them.”

Jonah Chan, PhD – Dr. Hahn's mentor – says that her emotion will serve her well in these experiments. “Angela possesses great dreams for the future,” he says. “She has a vision for the ‘big picture’ concerning MS research and – more importantly –her life. While most researchers and scientists focus on the details of the experiments, Angela has the unique ability to bring a touch of humanity into scientific research.” Dr. Chan is a former fellow himself, whose independent research career was launched with funding from a National MS Society Harry Weaver Neuroscience Award.

Dr. Hahn will spend the majority of her fellowship in the laboratory conducting and designing experiments, learning new techniques of studying brain cells and new microscope technologies. In the short-term, she is learning the ropes of neurobiology, but her long-term goal is to better the lives of people with MS – like herself. “By understanding the mechanisms involved in how oligodendrocytes make myelin, I want to help discover a treatment to repair the damage, and also the physical and emotional stress caused by MS.”

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brain from many toxic substances. In MS, the BBB breaks down, allowing molecules and the immune system cells that cause tissue damage to move into the brain.

In an attempt to understand what factors contribute to the health and proper functioning of the BBB, a team led by Ben Barres, MD, PhD, has been studying its development in growing animals. Dr. Barres found that pericytes – cells that wrap around small blood vessels – act in concert with the cells of the capillaries and with other brain cells known as astrocytes to form the BBB. In this research project, the team is studying how the signaling mechanisms, or communication pathways, among these cell types are altered to make the BBB “leaky” in EAE, an animal model of MS.

This research project will lead to better understanding of how the BBB breaks down in MS, and may open new avenues for preventing that breakdown to halt MS.

### **Maria Givogri, PhD**

University of Illinois at Chicago  
Chicago, IL

Area: Greater Illinois/Midwest

Term/Amount: 10/1/10-9/30/13; \$375,507

**Paid by special funds by the Illinois Lottery**

### **“Regulation of neurogliogenesis in health and multiple sclerosis by sulfatides”**

Studying molecules that limit myelin repair and looking for ways to improve myelin repair in MS.

In MS, the immune system, which normally protects the body from infective agents such as viruses and bacteria, attacks and damages myelin. Myelin is the material that surrounds and protects nerve fibers, and the oligodendrocytes that make and repair myelin can also be lost. Cells that are capable

of developing into oligodendrocytes – neural stem cells (NSCs) and oligodendrocyte precursor cells (OPCs) – exist in brain but they fail to produce new oligodendrocytes rapidly enough to keep up with their destruction in MS.

Maria Givogri, PhD, is investigating a group of molecules known as sulfatides. Sulfatides are released from damaged myelin, and Dr. Givogri and colleagues have found that these molecules prevent neural stem cells from making OPCs, and thus reduce the number of oligodendrocytes available to repair myelin. Now Dr. Givogri is looking at how sulfatides act on NSCs in laboratory dishes, and will also determine how prevalent they are in the brains of people with MS.

This research could provide new clues about why myelin repair is deficient in MS and how to improve myelin repair to restore function in people with MS.

### **Carlos Parras, PhD**

INSERM U711

Paris, France

Term/Amount: 10/1/10-9/30/13; \$274,423

**Paid by the National MS Society South Central Region**

**“Promoting remyelination from endogenous oligodendrocyte precursors”** Studying genes inside the body’s spare cells that are capable of maturing into myelin-forming cells to find ways to stimulate nervous system repair in MS.

Myelin, the material that surrounds and protects nerve fibers enabling them to carry nerve signals rapidly, is damaged and destroyed in the central nervous system (CNS: brain, spinal cord and optic nerves) in MS. Myelin is made and maintained in the CNS by cells known as oligodendrocytes. In developing animals, oligodendrocytes are gen-

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erated by oligodendrocyte precursor cells (OPCs). Some OPCs remain in the adult brain and are able to replace damaged oligodendrocytes, but this repair process fails to keep up with the damage in MS.

Dr. Parras is modifying genes that are active in OPCs in mice to determine how the genes influence the ability of the OPCs to form oligodendrocytes. In addition, he is applying the modified genes to demyelinated mice, to see how they influence the repair of myelin (remyelination).

The results of this research could provide a basis for developing ways to foster myelin repair that would restore functions in people with MS.

### **David Pleasure, MD**

University of California, Davis  
Davis, CA

Area: Northern California/West

Term/Amount: 10/1/10-9/30/13; \$433,947

**"Corticospinal tract degeneration in EAE: role of endolysosomal TLRs"** Exploring the role of specific immune reactions in nerve fiber damage and testing ways to block them to protect the nervous system in MS.

While many of the early symptoms of MS are caused by the failure of nerve fibers to carry signals properly after their protective myelin sheath is damaged, long-term progressive disability is caused by the death of nerve cells. The destruction of nerve cells that supply the "corticospinal tract" – essentially a group of nerve fibers, similar to a bundle of wires – running from the brain into the spinal cord, leads to weakness of muscles in the arms and legs.

David Pleasure, MD, is investigating the role of a group of molecules known as "endolysosomal TLRs" found inside nerve cells. These TLRs become active when nerve cells are damaged, and seem to be involved in self-destruction by the damaged cells. Looking at mice with the MS-like model EAE, which has corticospinal tract degeneration similar to that seen in MS, Dr. Pleasure and colleagues are investigating how the TLRs cause the loss of nerve cells, and studying whether drugs that block their action can prevent the loss of nerve cells in MS.

This work has great potential for developing new therapies to prevent the progressive loss of function experienced by many people with MS.

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## Betty Soliven, MD

University of Chicago  
Chicago, IL

Area: Greater Illinois/Midwest

Term/Amount: 10/1/10-9/30/12; \$319,778

**Paid by special funds by the Illinois Lottery**

### **"Lysosphingolipid receptors and growth factors in oligodendroglial regeneration"**

Studying how FTY720, a potential oral treatment for MS, protects against injury and /or promotes repair of myelin.

The first oral disease-modifying therapy for MS, fingolimod (Gilenya) was recently approved by the U.S. FDA for the treatment of relapsing forms of MS. Aside from the effect of fingolimod on inhibiting immune attacks in MS, its actions on glial cells and neurons in the central nervous system (CNS) have also been an area of exciting research. Dr. Soliven and other investigators have found that fingolimod and related agents that act on "sphingosine-1-phosphate (S1P) receptors" regulate the survival, proliferation, and differentiation of cells that make myelin in the CNS. These cells are called oligodendrocytes.

The goal of this research project is to investigate further the CNS effects of fingolimod and other S1P receptor modulators. Her team will study the mechanisms underlying the protective and stimulating action of these compounds on oligodendrocytes and immature oligodendrocytes. They will also examine whether fingolimod exerts any effect on nerve fibers, which would lead to a change in neurological symptoms or in disease progression.

These studies will provide useful information on the potential long-term CNS effects of drugs that act on S1P receptors, which is highly relevant to future therapeutic use of fingolimod in MS.

## RESTORING FUNCTION

### Nervous System Repair

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 \$28 million to support research projects focusing on finding ways to repair the nervous system and restore lost function in people with MS.

## Cheryl Dreyfus, PhD

University of Medicine and Dentistry of NJ  
Piscataway, NJ

Area: NJ Metro/Northeast

Term/Amount: 10/1/10-9/30/13; \$448,215

**Paid by the National MS Society South Central Region**

**"The role of glial cell-derived factors in a cuprizone model of MS"** Investigating factors that enhance the repair activity of myelin-making cells, for clues to restoring function in people with MS.

In MS, the oligodendrocyte (a cell that produces a supportive and insulating myelin sheath around axons) may become a target of the immune attack and die. Many groups are searching for molecules that reverse this destruction. Recent results indicate that one molecule that may play such a role is a specific stimulator (called ACPD) of a docking site or receptor for a neurotransmitter. This stimulator is being shown to play protective roles in a number of models of brain disease. Importantly, receptors for ACPD are increased in active chronic MS lesions, suggesting that the role of the stimulator may impact the disease and be enhanced follow-