
Betty Soliven, MD

University of Chicago
Chicago, IL

Area: Greater Illinois/Midwest

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

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"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-

ing injury.

To test the possibility that ACPD may enhance myelin regrowth after injury, Dr. Dreyfus's team treated mice that were subjected to myelin damage with ACPD. They found that ACPD enhanced expression of traits associated with mature oligodendrocytes, and also increased a growth factor known to increase proliferation and differentiation of oligodendrocytes. The team is now following up these preliminary results to explore whether and how ACPD protects against myelin damage and stimulates myelin repair.

They believe that understanding the actions of this small molecule will provide insights to optimize maintenance and repair of oligodendrocytes that deteriorate in MS.

Gareth John, VetMB, PhD

Mount Sinai School of Medicine
New York, NY

Area: New York City-Southern NY/Northeast
Term/Amount: 10/1/10-9/30/13; \$448,405

"Reactive astrogliosis regulates blood-brain barrier permeability" Tracing events leading to the breakdown of the barrier that restricts immune cells from entering the brain, to find ways to minimize lesion formation and relapses in MS.

A structure called the blood-brain barrier (BBB) separates the central nervous system – the brain and spinal cord – from the blood and maintains the environment to facilitate nerve impulse transmission. Breakdown of the BBB is an early and prominent event in an MS relapse, allowing entry of immune cells and proteins that exacerbate nervous system function and restrict repair. However, the mechanisms underlying BBB breakdown in people with MS relapses are not fully understood.

Dr. John's team has identified a novel mechanism for BBB breakdown in MS. Cells within the BBB use structures called tight junctions to restrict permeability, and the properties of these junctions are determined by proteins called claudins and occludin. Dr. John has found that a specific molecule called VEGF-A disrupts the activity of these proteins. Now they are testing this possible mechanism in BBB cells isolated in the laboratory and in models of MS-like disease.

The goal of this work is to minimize the breakdown of BBB permeability and prevent relapses in people with MS.

Samia Khoury, MD

Brigham and Women's Hospital
Boston, MA

Area: Greater New England/Northeast
Term/Amount: 10/1/10-9/30/13; \$497,521

"Regulation of EAE through the PDL1/PDL2 pathway" Studying signals in immune system cells that control the attack on nerve-insulating myelin, seeking ways to turn off the attack in MS.

MS and one of its animal models, EAE, result from the destruction of myelin – the material that surrounds and protects nerve fibers – in the central nervous system (CNS: brain, spinal cord and optic nerves), and damage to the nerve fibers themselves. In both MS and EAE, the nervous system damage is caused by the immune system. Immune system behavior is complex, because of the large number of cell types and because of the large number of molecules the cells use to communicate with each other and coordinate their activity.

Although many of the communication molecules the immune system uses are released into the blood or tissue fluid, Samia

Khoury, MD, and her colleagues are studying molecules that stay on the surfaces of cells. When these signaling molecules on adjacent cells touch, they activate signals in the "PDL1/PDL2 pathway" inside the cells that "turn off" an immune response.

The results of this research will lead to greater understanding of how immune system activity is controlled, and could provide new ways to turn off the immune system attack in MS.

ENDING MS FOREVER

Seeking Infectious Triggering Factors

Because MS is thought to occur in people whose genes make them susceptible, researchers have been exploring the possibility that viruses or bacteria could act as disease triggers for MS.

The National MS Society has current, multi-year commitments of about \$3 million for research projects focusing on specifically on identifying possible infectious triggers. Many immunology projects are closely related to this effort as well.

Byung Kim, PhD

Northwestern University
Chicago, IL

Area: Greater Illinois/Midwest

Term/Amount: 10/1/10-9/30/13; \$485,904

"Pathogenic mechanisms of virus-induced demyelinating disease" Studying how viruses can trigger immune attacks against nerve tissue to understand how a virus might trigger MS.

MS involves a mistaken attack by the immune system, which normally protects the body from infections, against myelin, the material that surrounds and protects nerve fibers, in the central nervous system (CNS: brain, spinal cord and optic nerves). Other tissues including nerve fibers and myelin-making cells are also destroyed. Destruction of myelin (demyelination) by the immune attack interferes with the ability of nerve fibers to carry signals properly, leading to the symptoms of MS. It is not known what causes the immune system to attack myelin, but one possibility is that a viral infection may help trigger the attack.

Byung Kim, PhD, is studying mice infected with a virus that can result in demyelination by the immune system, producing symptoms similar to MS. Dr. Kim and colleagues are looking at how viral infection of some cells in the CNS stimulates the development of immune system cells that attack myelin, and are attempting to find ways to reduce or eliminate the cells that cause demyelination.

This research will improve our understanding of how virus infections may trigger MS, and could lead to new avenues to prevent a virus from triggering the disease.