

## MYELIN BIOLOGY

### 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 \$16.7 million to support 56 research projects focusing on myelin biology in MS.

#### **Jonah R. Chan, PhD**

University of Southern California  
Los Angeles, CA

Area: Southern California Chapter

Award: **Harry Weaver Neuroscience Scholar**

Term/Amount: 7/1/09-6/30/14; \$452,200

**"Reconstructing microenvironments to control oligodendrocyte differentiation"**

Looking for ways to encourage the growth of new myelin-forming cells to repair damage in MS.

Myelin, the protective wrapping of nerve fibers, is damaged and destroyed in MS. The myelin coating enables nerve fibers to carry signals rapidly; when it is damaged, nerve signals are disrupted. Cells called oligodendrocytes manufacture and maintain myelin in the central nervous system (CNS: brain, spinal cord and optic nerves). Oligodendrocyte precursor cells (OPCs) develop

(differentiate) into oligodendrocytes in the growing CNS, and some OPCs remain in the adult as a source of new oligodendrocytes. These OPCs do not differentiate into oligodendrocytes rapidly enough to repair myelin damage in MS.

Jonah Chan, PhD, is studying factors that cause OPCs to develop into oligodendrocytes using nerve cells and OPCs grown together in the laboratory. This procedure allows Dr. Chan to study individual factors, such as how densely OPCs are packed or where they are located with respect to nerve cells, and to look at how different combinations of factors affect OPC differentiation.

This research will provide new information about what causes OPCs to develop into oligodendrocytes, and should offer clues to how to make OPCs yield more oligodendrocytes to repair myelin damaged by MS.

#### **Dale Edberg, PhD**

Mayo Clinic College of Medicine  
Rochester, MN

Area: Minnesota Chapter

Award: **Postdoctoral Fellowship**

Term/Amount: 7/1/09-6/30/10; \$54,191

**"Organotypic cerebellar slices as a model to study CNS remyelination"** Developing a sophisticated new tool for screening factors that can increase myelin repair, for clues to new repair therapies for MS.

Repairing the nervous system damage that results from immune attacks in multiple sclerosis is critical to restoring function and preventing further damage to the wire-like axons that relay nerve signals. To a certain extent, the body can repair the myelin coat-

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ing on axons in MS, but at some point during the disease this process fails.

Dale D. Edberg, PhD, is focusing on learning more about the vast array of signals and factors that are responsible for healing damaged myelin (also known as remyelination) and compounds that may ramp up myelin repair. He has been working on an elegant new lab model of remyelination that involves cultivating slices of brain tissue from rats. The resulting three-dimensional tissues allow him to rapidly assess factors naturally involved in myelin repair, and also to tease out the most important by introducing specific inhibitors and then measuring repair.

Dr. Edberg's refinement of this powerful tool should provide a fast and cost-effective way to discover the molecules that have the most relevance to remyelination. These could have potential for developing into therapies aimed at restoring function in people with MS.

**Alexander Gow, PhD**

Wayne State University  
Detroit, MI

Area: Michigan Chapter

Award: Research Grant

Term/Amount: 7/1/09-6/30/13; \$635,358

**"Non-immune models of neurodegeneration"** Investigating the cells that make nerve-insulating myelin and factors that may impede the normal repair of myelin during the course of MS.

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 loss 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") becomes activated. Dr. Gow's team has identified a protein that may be important in this process, called Tribbles3, although it is not clear whether this protein promotes cell death or survival. They now are investigating this protein further, and are developing a new mouse model for studying how oligodendrocytes are lost during disease processes such as MS.

Finding a way to interrupt the loss of oligodendrocytes in people with MS may help preserve their natural ability to repair myelin and reverse symptoms.

**Judith B. Grinspan, PhD**

Children's Hospital of Philadelphia  
Philadelphia, PA

Area: Greater Delaware Valley Chapter

Award: Research Grant

Term/Amount: 10/15/08-9/30/11; \$495,799

*Funded by the NMSS Greater Delaware Valley Chapter*

**"Dorsal signaling and oligodendrocyte development"** The role of a family of proteins that may inhibit the natural repair of myelin, and ways to counteract their influence in MS.

Following the destruction of nerve fiber-insulating myelin that is a hallmark of MS, new growth of replacement myelin fails to keep up with the damage. This is despite

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the presence of oligodendrocyte precursors – immature cells that are capable of differentiating into new myelin-producing cells.

The development of oligodendrocytes and myelin is controlled by a series of growth factors. Judith Grinspan, PhD, and colleagues have been studying one family of factors, the bone morphogenetic proteins (BMPs). They have found that large amounts of BMPs can inhibit myelin formation, and that BMPs are present in increased quantity in a mouse model of MS. However, a total lack of BMPs results in not enough myelin, suggesting that the amount of BMPs must be tightly controlled during development. Dr. Grinspan's preliminary data suggest that BMPs work closely with another growth factor family, the "Wnts." Now her team is determining how Wnts modulate oligodendrocyte development both in tissue culture models and in mouse models.

This research will aid in our understanding of the factors required for proper myelin formation, and how to capitalize on these factors to develop myelin repair strategies for MS.

### **Qing R. Lu, PhD**

UT Southwestern Medical Center at Dallas  
Dallas, TX

Area: Lone Star Chapter

Award: Research Grant

Term/Amount: 10/15/08-9/30/11; \$463,132  
*Funded in full by the NMSS Lone Star Chapter*

**"Zfp488 in oligodendrocyte differentiation"** Determining the role of a molecule and how it influences formation of brain repair cells for clues to reversing damage in MS.

The production of myelin – the sheath of insulating material that surrounds nerve fibers, and which is thought to be a primary target of MS attacks – 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. At this point the genes that direct myelin production are activated. Qing Richard Lu, PhD, has identified genes called Olig1 and Olig2 that act as the "on" switch for myelin-making genes.

In this project, Dr. Lu plans to focus 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. 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 should reveal the influence of the protein on these activities.

This research may lead to the discovery of new targets that could be manipulated to promote myelin repair in people with MS.

**Angeliki Mela, PhD**

Columbia University  
New York, NY

Area: New York City Chapter

Award: **Postdoctoral Fellowship**

Mentor: James E. Goldman, MD, PhD

Term/Amount: 7/1/09-6/30/12; \$156,515

**“Kai1/CD82 regulates oligodendrocyte progenitor migration and differentiation”** Studying a protein that may play a critical role in nerve tissue repair.

MS involves immune system attacks against brain and spinal cord myelin, the tissue that surrounds nerve fibers. After myelin is injured, some repair occurs by resident immature cells called oligodendrocyte precursor cells (OPCs). The mechanisms that promote the movement and maturation of OPCs so that they commence myelin repair are not yet clear.

Dr. Mela is exploring a protein, CD82, that may play a critical role in this process. This protein has not been previously described in oligodendrocytes, although it is known to regulate movement of cancer cells. Preliminary results suggest that CD82 restricts OPC cell migration. To study how CD82 might regulate migration and maturation of OPCs, Dr. Mela is performing a series of experiments in cell cultures of OPCs and in rodents in which she is increasing and decreasing CD82 activity.

This work should contribute to our un-

derstanding of myelin repair and may be helpful in the search for new repair strategies for the treatment of MS.

**Mengsheng Qiu, PhD**

University of Louisville  
Louisville, KY

Area: Kentucky/SE Indiana Chapter

Award: Research Grant

Term/Amount: 7/1/09-6/30/12; \$426,617

**“Developmental regulation of axonal myelination by Necl molecules”** Investigating the role of specific molecules in the growth of nerve-insulating myelin and prospects for stimulating repair in MS.

Oligodendrocytes are the cells in the brain and spinal cord that form myelin sheaths around axons (nerve fibers) to ensure the transmission of electrical signals among nerve cells. Injury or degeneration of these cells may be a chief cause of impairment of nerve function in MS. Myelin formation requires the close contact between oligodendrocytes and axons. However, exactly how this interaction occurs is not yet known.

Mengsheng Qiu, PhD, and his team are studying Necl1 and Necl4, proteins that mediate the interaction of myelin-making cells and axons in the peripheral nervous system. They are examining whether the genes for these proteins play a similar role in myelin formation in the brain and spinal cord (the central nervous system, or CNS) by studying CNS cells in laboratory tissue cultures and in animal models.

Results should significantly enhance our understanding of the molecular pathways governing myelin formation in the CNS, and offer novel approaches for stimulating myelin repair in people with MS.