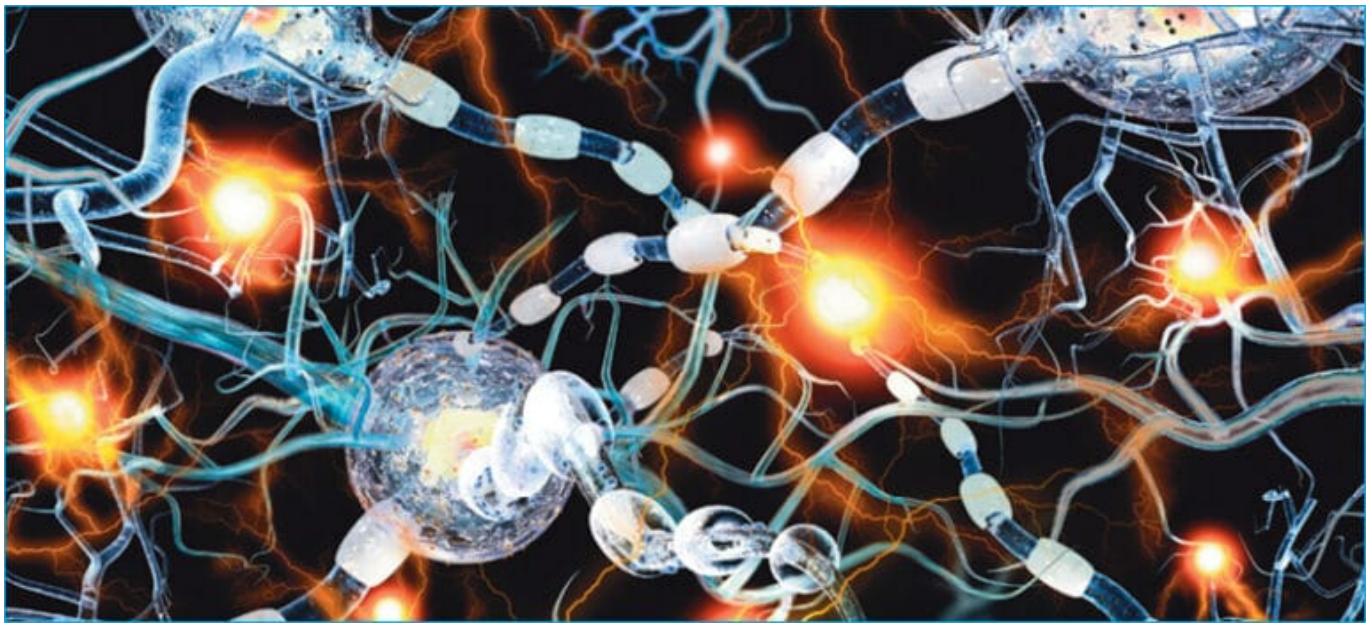
Repair and restore



Researchers study ways to reduce neurological symptoms of MS.

by Lori De Milto

Researchers are studying different ways to restore or repair myelin in hopes of developing new treatments for multiple sclerosis.

Myelin is the protective coating around the nerve fibers in the central nervous system, which comprises the brain, spinal cord and the optic (eye) nerve. Cells called oligodendrocytes make myelin. When myelin is damaged, the electrical signals that send messages between your brain and your body slow down or stop, causing neurological symptoms like problems with seeing, thinking, remembering and moving. Doctors and researchers also think that myelin loss makes the underlying nerve fiber (axon) more vulnerable to injury.

Four research teams are trying to stimulate natural myelin repair capabilities and are studying drugs to treat MS and models for myelin repair. “In the initial stages of MS, the body can repair itself. As the disease progresses, that ability fails,” says Meredith Hartley, PhD, a National MS Society postdoctoral fellow at Oregon Health & Science University in Portland, Oregon, who is a member of one of the teams.

Dr. Bruce Cree. Photo courtesy of Dr. Bruce Cree

Dr. Bruce Cree, a neurologist who also has a doctorate in biochemistry and a master's in advanced studies in clinical research, is conducting clinical trials to test therapies in people living with MS and neuromyelitis optica. Cree is the George A. Zimmermann Endowed Professor in Multiple Sclerosis and a professor of clinical neurology at the University of California, San Francisco (UCSF). He is also the clinical research director of the UCSF Weill Institute for Neurosciences.

With support from the National Multiple Sclerosis Society, three other scientists are delving into how myelin is repaired and ways to stimulate that process. Hartley has a PhD in biological chemistry. Ethan G. Hughes, an assistant professor of cell and developmental biology and the Boettcher Investigator at the University of Colorado School of Medicine in Aurora, Colorado, has a doctorate in neuroscience. Babette Fuss is a professor of anatomy and neurobiology at Virginia Commonwealth University in Richmond, Virginia. Her doctorate is in neurobiology.

Drugs to repair or restore myelin

Cree has been participating in several completed or ongoing research studies of experimental therapies that could help repair or restore myelin. The ReBUILD study, conducted from January 2014 to April 2015, used clemastine, an existing oral antihistamine. This study showed that clemastine promotes oligodendrocyte development and wrapping of myelin. The other studies are testing an experimental drug called elezanumab, given intravenously. UCSF and the Rachleff family supported the study of clemastine, while the pharmaceutical company AbbVie, Inc. is supporting the studies of elezanumab. These are all phase 2 studies in which researchers study a drug's effectiveness and safety.

The ReBUILD study, conducted at UCSF studied 50 people with relapsing-remitting MS who have chronic damage to the optic nerve. Half of the participants received clemastine first and then a placebo. The other half received a placebo first and then clemastine.

Jonah Chan, PhD.
Photo courtesy of Jonah Chan, PhD

Researchers found that clemastine modestly improved the speed of electrical signals in the optic nerve. “The study findings suggest that myelin can be repaired, even following prolonged damage,” Cree says. The results were published in Lancet in 2017.

The use of clemastine was based on the work of Jonah Chan, a professor of neurology at UCSF. Chan tested thousands of compounds (ingredients that could be made into drugs) and FDA-approved drugs looking for any that might stimulate myelin repair and restoration. He identified clemastine as a possible treatment. The Society awarded him the first Barancik Prize for Innovation in MS Research in 2013.

Another phase 2 two study of clemastine is underway at UCSF, led by Dr. Ari Green. This study is testing clemastine in people with acute optic neuritis, an inflammation that can lead to vision loss. Vision problems are often the first symptom of MS.

An experimental therapy under study by Cree is elezanumab (ABT-555), a monoclonal antibody that is engineered to target a specific molecule. Studies of elezanumab in lab models showed that it enables axons to regrow and begin to transmit nerve messages again. Elezanumab also reduced inflammation and showed some ability to grow myelin.

A phase 1 safety study of elezanumab conducted by Cree showed that elezanumab did not cause serious side effects or discomfort, or lead to consistent symptom worsening. Twenty people living with MS participated: 18 had relapsing-remitting MS and two had secondary progressive MS. Cree presented results at an American Academy of Neurology meeting in 2018.

Based on the phase 1 safety study, Cree is now conducting two phase 2 studies of elezanumab, one in people with relapsing-remitting MS and the other in people with progressive forms of MS. Both studies compare two different doses of elezanumab to placebo, an inactive, nondrug compound that’s designed to look just like elezanumab. In both

trials, elezanumab is used as an add-on therapy to existing anti-neuroinflammatory medications that participants already may be taking. “This is very good news for patients because the product has the potential to be useful in both relapsing and progressive forms of MS,” Cree says. UCSF is one of dozens of locations in the United States and Canada that are part of these studies.

For more information, visit ClinicalTrials.gov:

- Study in relapsing MS
- Study in progressive MS

A new compound and a new model

Under a postdoctoral fellowship from the Society, Hartley is part of a research team at the lab of Thomas Scanlan, PhD, at Oregon Health & Science University. The team has discovered a compound that stimulates myelin repair. Hartley was the lead author on an article with study results published in JCI Insight (“Myelin repair stimulated by CNS-selective thyroid hormone action,” April 2019).

Meredith Hartley, PhD.
Photo courtesy of Meredith Hartley, PhD

This research tested an orally active thyroid hormone-like drug called sobetirome, discovered in the Scanlan Lab. Thyroid hormone naturally stimulates myelin production in infants and improves myelin repair in models of MS. But high levels of thyroid hormone aren’t safe in people.

“We demonstrated that sobetirome can stimulate myelin repair and saw improvements in motor abilities and the amount of myelin,” Hartley says. Sobetirome repaired myelin without the potentially severe side effects of high-dose thyroid hormone therapies.

To translate sobetirome from mice to people, Oregon Health & Science University has

licensed the technology to Llama Therapeutics Inc., which is currently working on preclinical development. If results are promising, clinical trials will be the next step.

The team has also developed a new lab model for studying myelin repair. The model involves mice genetically engineered to mimic MS. “This model provides opportunities for better studying the effects of myelin repair therapeutics,” Hartley says.

Along with Hartley’s postdoctoral fellowship, this research was also supported by the National Institutes of Health, the Race to Erase MS and the Oregon Health & Science University Laura Fund for Innovation in Multiple Sclerosis. In 2020, Hartley plans to start a research lab focused on myelination and re-myelination at the University of Kansas, where she’ll be an assistant professor of chemistry.

A new way to see myelin repair and test treatments

Hughes and his team are focusing on the brain’s cortex, where thinking begins. MS causes cells in the cortex, the outermost layer of the brain, to shrink. This is partly due to destruction of myelin. While oligodendrocytes can repair or make some new myelin, this natural repair process is slow and incomplete.

Ethan G. Hughes, PhD.
Photo courtesy of Ethan G. Hughes, PhD

Under a research grant from the Society, Hughes is using two-photon microscopy to see and study oligodendrocytes in the brains of mice before and after damage to myelin. Two-photon microscopy uses lasers that produce long wavelength light to see deeper into the brain than other types of microscopy. This produces clear images of individual cells in living animals (“in vivo”). Hughes and his team at the University of Colorado School of Medicine are looking at the myelin repair process as it happens naturally and after the mice receive a behavioral intervention such as learning a new motor skill.

“Our in vivo imaging approach allows us to test interventions in a different manner than has

been done before. Now, we can watch how individual cells repair myelin in living animals," Hughes says.

The results of the research grant, which continues through September 2020, may provide new information on the role of oligodendrocytes in myelin repair that other researchers can study. Eventually, this line of research could lead to new therapies to repair or restore myelin. "I'm excited by the possibility that myelin repair could be a therapeutic approach for patients," Hughes says.

The role of cells in myelin repair and restoration

Fuss and her team at Virginia Commonwealth University are focusing on how oligodendrocytes differentiate and form new myelin. Their research is funded by a grant from the Society. They are exploring the potential of a signaling pathway called autotaxin-LPA to promote oligodendrocytes differentiation and restore myelin in MS. In general, a signaling pathway describes a group of molecules within a cell that work together to control one or more cell functions, in this case oligodendrocyte differentiation. Identification and characterization of individual components of such signaling pathways is important, since it has the potential to lead to the development of therapeutic drugs.

Babette Fuss, PhD.
Photo courtesy of
Babette Fuss, PhD

Fuss and her team are studying the ability of autotaxin-LPA signaling to promote oligodendrocyte differentiation in a variety of model systems: cultures of oligodendrocytes, the developing zebrafish, and mice in which myelin damage and repair can be investigated in both the absence and presence of autotaxin-LPA signaling. So far, the group was able to demonstrate that myelin repair is attenuated in the absence of autotaxin-LPA signaling, and they were able to identify a set of receptors that are important in activating the autotaxin-LPA signaling pathway in oligodendrocytes.

In its basic definition, a receptor describes a cell surface molecule that interacts with a

specific ligand, in this case LPA, to activate cellular responses, which may be different in different cell types. In the case of LPA binding receptors, some receptors have been shown to participate in tumor formation. Thus, Fuss and her team are focusing their research on those receptors that specifically promote oligodendrocyte differentiation without causing adverse effects.

“We hope to be able to stimulate an individual receptor toward a signaling cascade that causes oligodendrocytes to repair myelin without causing negative side effects,” says Fuss.

The ultimate goal of this research is to develop a synthesizable ligand that can be used to promote oligodendrocyte differentiation and myelin repair in MS patients. Since responses to individual therapeutic drugs may vary from person to person, Fuss and her team are also studying other ways to stimulate myelin repair and growth. “We need to identify more than one good strategy, since different therapeutic approaches may be needed for different populations of patients,” she says.

Lori De Milto is a Sicklerville, New Jersey-based freelance writer.

Learn more about repairing what’s been lost.