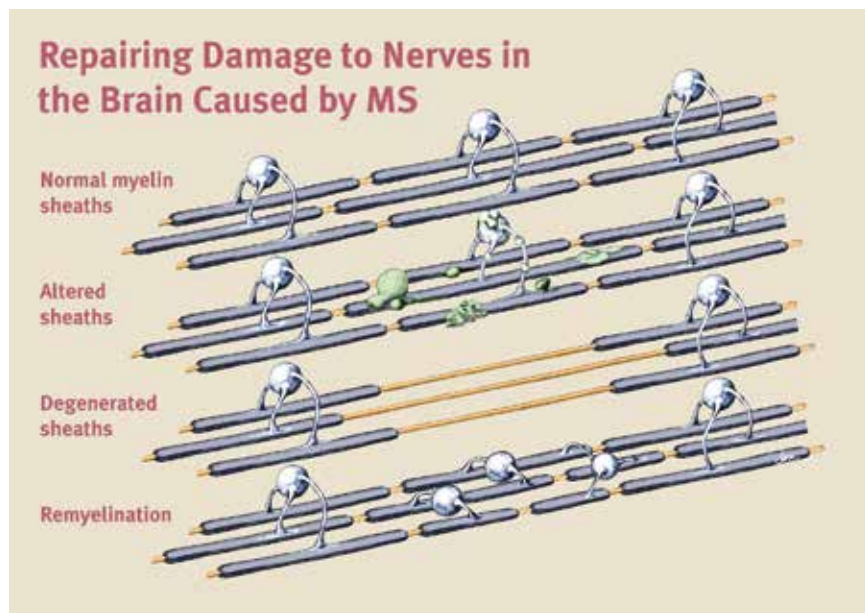


Getting at the Root of MS

Researchers focus on repairing myelin to treat multiple sclerosis symptoms.

BY TOM VALEO



In multiple sclerosis (MS), the immune system attacks a fatty white substance known as myelin, which coats the thread-like fibers known as axons that carry signals between brain cells. These attacks cause inflammation, which damages the myelin and disrupts the transmission of brain signals. Stop the inflammation, experts believe, and you'll probably stop the disease itself.

Unfortunately, no one has figured out how to do that, at least not completely. Luckily, the brain has a natural way of repairing damage to myelin. Stimulating that process could help keep symptoms at bay, and prevent one of the worst consequences of long-term MS—the degeneration and death of axons. Ramping up this remyelination process wouldn't cure the disease itself, but it would alleviate the numbness, weakness, and paralysis, as well as other MS symptoms.

Scientists are currently exploring a number of ways to promote remyelination. "This is a hot topic," says Steven Goldman, MD, PhD, chief

of the Division of Cell and Gene Therapy at the University of Rochester Medical Center and co-director of Rochester's Center for Translational Neuromedicine. Dr. Goldman is one of the leading researchers focused on ways to remyelinate brain cells. "The field is moving very quickly," he says, "and I'm hopeful that in a year or so this will be a very hot topic."

WHY IS MYELIN A TARGET?

Myelin is constantly renewed in the healthy human brain by cells known as oligodendrocytes. Once myelin is made, the oligodendrocytes wrap this new my-

elin around axons. When myelin is damaged, special cells in the brain known as oligodendrocyte progenitor cells move to the site and produce new oligodendrocytes that repair the damage.

Dr. Goldman has developed stem cells derived from a patient's own skin that can be transplanted into the brain, where they become oligodendrocyte progenitor cells capable of bolstering remyelination. This is a type of stem cell therapy.

The research would entail injection of oligodendrocyte progenitor cells into four sites at the front, back, and sides of the brain. Because progenitor cells are at an early stage of development, they can still migrate and spread throughout the brain on their own, ready to transform themselves into mature oligodendrocytes when remyelination of axons is needed.

"The idea is that if those patients have future demyelinating episodes, their brains would then have healthy progenitors capable of remyelinating axons if called upon to do so," Dr. Goldman says.

This strategy is unlikely to work well early in the disease process, when most patients experience sudden flare-ups of demyelination followed by remission of the disease. During this relapsing-remitting phase, stimulating remyelination might actually make matters worse by providing extra myelin for the immune system to attack.

However, it could be very useful for patients who go on to develop primary-progressive MS, which involves less inflammation but a gradual increase in disability. Patients with primary-progressive MS, which tends to appear later in life, often don't experience the sudden flare-ups of relapsing-remitting MS. Instead, their disease involves a steady decline toward disability. During the progressive phase, the immune system poses

"The first component of treatment involves **stopping the war**. You want to stop the invading immune cells from getting in and doing damage."

—TASSIE COLLINS, PHD, MD

less of a threat to myelin.

Another challenge to this therapy, which Dr. Goldman and many other scientists are trying to solve, is that the brain's ability to remyelinate axons declines over time. As a result, axons die, producing an array of permanent debilitating symptoms.

Although stimulating the remyelination of damaged axons is not a cure, it has the potential to transform MS from a life-altering disability into a manageable disorder. If remyelination preserves the function of axons and spares them from death, MS symptoms might all but disappear, or at least progress more slowly.

"Remyelination is the single most important neuroprotective event that can happen in the MS brain, or in any other brain in which there has been demyelination," says Richard Ransohoff, MD, who recently left the Cleveland Clinic to become a senior research fellow in neuroimmunology at Biogen Idec, a biotechnology company that has a remyelinator drug in development.

"Even though remyelinated sheaths are thinner and shorter, they are fully protective against axon degeneration," says Dr. Ransohoff, who is also a Fellow of the American Academy of Neurology (FAAN). "Where there is remyelination there is no degeneration, and conversely, where there is no remyelination there is degeneration. Therefore, anything that can promote remyelination by even a little bit is exceptionally important."

While at the Cleveland Clinic, where he was director of the Neuroinflammation Research Center, Dr. Ransohoff studied CXCR2, a protein involved in the development of oligodendrocytes. He found that blocking CXCR2 produced more efficient remyelination.

"We're not clear about why that works, but the fact is it does work," he says. "A drug that blocks CXCR2 and promotes remyelination would be a

game-changer for MS."

But testing such a drug would require a technique to monitor changes in myelin in the brain—a daunting task since the brain is full of the stuff, making the detection of small changes extremely difficult. Fortunately, various technological improvements in brain imaging are bringing us closer to that goal, according to Dr. Ransohoff. This will spur the development of therapies for MS and other disorders such as cerebral palsy, certain types of stroke, spinal cord injury, and perhaps even dementia.

THEAPIES IN THE PIPELINE

The Myelin Repair Foundation (MRF), which is dedicated to finding treatments that protect and renew myelin, is collaborating with the National Institutes of Health to study MRF-008, a drug already approved to treat hypertension. The drug appears to stimulate remyelination in animal models of MS.

"Unlike current therapies for multiple sclerosis, which all suppress the immune system, MRF-008 may help protect oligodendrocytes in the brain from damage," says Jay Tung, PhD, the MRF's chief research officer.

Tassie Collins, PhD, vice president of translational medicine for the MRF, compares MS to a war within the body. Rogue immune cells enter the brain to attack and destroy myelin. Then, oligodendrocytes and other cells help clean up the damage and rebuild.

"The first component of treatment involves stopping the war," says Dr. Collins. "You want to stop the invading immune cells from getting in and doing damage."


That is the goal of the drugs currently prescribed to treat MS. All are designed to chase away the "warriors" sent by the immune system. Once the attacks cease, the patient's own body rebuilds the damaged myelin, but not perfectly.

"There's a certain amount of resiliency in myelin formation, but most MS patients say they're left with some loss in sensation or some other reduction of nerve function," Dr. Collins says. "That's the component that's missing. There aren't any drugs that help the rebuilding process. Ideally you would want to do both—stop the ongoing damage but also speed up the rebuilding of myelin. That's the focus of the Myelin Repair Foundation—to find a way to protect tissue and to rebuild it."

THE IMPACT OF AGING

The ability of the brain to remyelinate axons declines with age, but the freshness of the damage, known as a lesion, also determines how efficiently it can be repaired, according to V. Wee Yong, PhD, co-director of the Hotchkiss Brain Institute Multiple Sclerosis Program at the University of Calgary.

"Remyelination tends to be more robust early in lesion development," says Dr. Yong. "A new lesion tends to be in a better position to be repaired than an older lesion in younger and older individuals. Maybe the environment is still conducive to the repair of myelin. Maybe some degree of inflammation is necessary for the repair process."

Whatever the reason, axons that are successfully remyelinated seem to be better protected against subsequent injury, perhaps because of better signaling between the oligodendrocytes and the axons, says Dr. Yong. "When an axon is remyelinated, this exchange of information seems to protect the axon. That is what is driving us in the remyelination field right now—protecting the axon." 

FOR MORE INFORMATION:

- ▶ To learn more about research in the pipeline for myelin repair, visit the website for the Myelin Repair Foundation (www.myelinrepair.org).