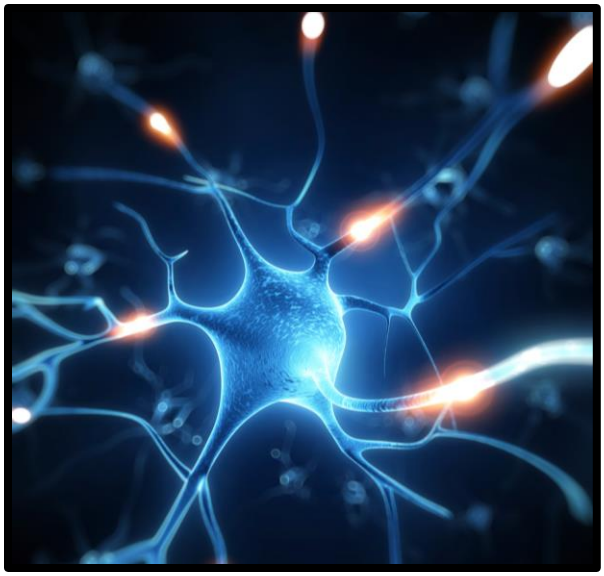
Fix My Myelin

In a recent conversation with a long-time friend of ACP who has MS, we asked her what she would most like MS researchers to study. Her answer was swift and unequivocal. "Fix my myelin," she demanded. She might also have added, "and repair my neurons," since the two are closely related.

While therapies that reverse the processes of demyelination and neurodegeneration in people with MS are not yet available, the hunt is on. Scientists have identified multiple targets that could potentially affect remyelination and others that could attenuate or reverse neurodegeneration. They have tested some in animal models and a few others in early stage clinical trials.

Background



According to the National MS Society, "In people with MS, damage to the myelin in the central nervous system (CNS) and eventually to the nerve fibers themselves, interferes with the transmission of nerve signals between the brain and spinal cord and other parts of the body." How this happens varies, depending on the type of MS an individual has. People with relapsing forms of MS experience cycles of inflammatory attacks that cause demyelination, followed by periods of recovery characterized by remyelination. The currently approved disease modifying therapies (DMT's) for MS address the inflammatory process. They reduce the frequency and severity of inflammatory episodes and give the body a break, providing the opportunity to self-repair. The time between relapses, the severity of each relapse and its location in the brain and spinal cord all determine the degree to which the body repairs its own myelin.

Over time, these repair mechanisms become less effective, resulting in the lasting degeneration of myelin and nerves that characterizes progressive forms of MS. There are not yet any DMT's to slow, stop or reverse neurodegeneration in humans, and the

neurodegeneration that eventually results from demyelination plays a significant role in MS disability.

The human nervous system is divided into two parts: the central nervous system (CNS), which consists of the brain and spinal cord, and the peripheral nervous system (PNS), which consists of cranial and spinal nerves along with their associated ganglia. Different parts of the human nervous system react differently to injury. Our peripheral nervous system consists of the nerve fibers that branch off from the spinal cord and extends to all parts of the body, including the neck and arms, torso, legs, skeletal muscles and internal organs. It has the ability to regenerate, such as in patients who have had parts of limbs reattached after an accident. Our central nervous system lacks this same capacity for self-repair.

In addition to understanding how myelin is lost, scientists who are trying to repair myelin and maintain neural integrity are focusing on three areas of investigation:

1. Discovering ways to boost myelin repair.
2. Knowing how to prevent neuro*de*generation
3. Understanding how to stimulate neuro*re*generation.

Myelin repair

Myelin is formed by cells in the central nervous system known as oligodendrocytes, which "insulate axons by wrapping the myelin around them in thin sheets like rolled up paper."[1] The structure of the myelin coating, which includes periodic gaps along the length of the axon, helps to increase the speed of signals sent through the nerve. In addition, oligodendrocytes "feed" axons via channels within the myelin. Therefore, demyelination not only strips axons of their ability to conduct information, it starves them to death and hastens neurodegeneration. Any therapy that successfully boosts myelin repair will also potentially prevent neurodegeneration.

An example of a drug that holds promise for remyelination is **clemastine**. It is actually an old drug – an antihistamine- that looks like it may perform new tricks in people with MS. A group of researchers at the University of California San Francisco using a laboratory assay found that clemastine helped oligodendrocytes to develop and make myelin. When tested in 50 people whose relapsing-remitting MS also included chronic demyelinating optic neuropathy, it revealed measurable improvement in the speed with which electrical signals traveled from the eye to the brain and back. This suggests that myelin repair occured, and at a faster speed than would have occurred without the drug. While it's not a slam dunk for researchers, they regard it as one step down the path. A great deal more about this promising therapy can be found in an issue of MS Discovery Forum from April, 2016 here. Other drug-discovery efforts are focused on the identification of molecules that can stimulate the maturation of oligodendrocyte progenitor cells into new myelin-producing cells.

[1] MS Encyclopedia, at www.mult-sclerosis.org.

Another example of a drug aimed at boosting remyelination is NDC-1308, a new molecule from the company Endece that is currently undergoing lab testing. It's thought to activate genes in precursor cells that encourage them to mature into oligodendrocytes and make myelin. Depending on the outcome of the lab tests, this drug may also enter the human clinical trial stage.

Axonal regeneration

LINGO-1 is a protein that exists in the brain and spinal cord. Research in rodent models of MS has revealed that LINGO-1 blocks axonal regrowth in the CNS. As a result, scientists have searched for mechanisms to block Lingo. **Opicinumab** is an anti- LINGO-1 monoclonal antibody[2]. When tested on mice, opicinumab increased axonal regeneration. A controlled randomized trial had a recent setback but is still proceeding to test the effect of this monoclonal antibody on humans. Further research is ongoing to answer questions on safety, tolerability and efficacy of the therapy.

Other scientists are searching for alternative cell types that might be capable of contributing to the replacement of damaged neurons. The adult brain comprises at least two places, known as "niches" where new neurons are generated. These niches harbor life-long adult neural stem cells (NSCs). An increasing number of investigations are beginning to examine these cells under pathological conditions, to try to gauge the potential of neural stem cells to replace lost neurons in MS.

Diagnostics

Finally, some scientists are hoping to improve ways of monitoring disease progression by developing blood tests that can monitor the processes of demyelination and neuronal loss in patients. These approaches may not only result in diagnostics to measure disease progression, they may also yield new drug targets. For an example of work being done in this area read here.

While definitive ways to fix myelin and stop nerves from degenerating do not yet exist, these examples demonstrate that there is promise. To date, ACP has played a role in advancing this research, by supplying samples and data to some of the scientists doing the important work. We hope to do even more in the future, as progress occurs and interest in the study of these topics grows.

[2] Antibodies are natural proteins that fight disease. Monoclonal antibodies are produced from single cells. They can be produced in the laboratory and are therefore, of great importance to immunology.