August 2019 Newsletter

Accelerated Cure project for multiple sclerosis

Accelerating research towards a cure for multiple sclerosis

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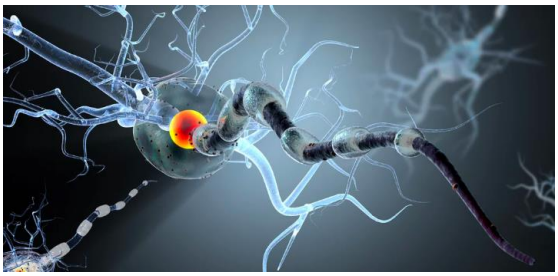
Regenerative Therapies for MS – How Close Are We?

All bodily functions are dependent on the conduction of nerve impulses through the central nervous system (CNS). Rapid conduction of signals through the CNS is dependent on the integrity of the myelin sheath (a fatty layer that surrounds nerve fibers). Multiple sclerosis (MS) is a disease that causes the immune system to attack, or erode, the myelin inside the CNS. This disrupts the signals from the brain to the rest of the body. Myelin production and repair is a very complex process that is naturally regulated in the body and is usually efficient. In MS, this process becomes less efficient over time and, in some people living with MS, stops working altogether, leading to mounting disability. There are currently 15 FDA-approved therapies for MS. Although these therapies are "disease-modifying," none can repair the damage done by the disease. Researchers are working hard to figure out the intricacies of remyelination and to develop more effective treatments. While the many steps, factors and pathways involved are challenging to understand, they offer many opportunities to intervene for better clinical outcomes. Myelin repair is a promising area of science that has the potential to improve function and quality of life for thousands of people living with MS and other demyelinating disorders.



One exciting area of focus in MS research is how to regrow myelin. Stem cell therapies have recently emerged as a possible regenerative approach to treating MS. A number of research teams are pursuing this line of study and have made exciting discoveries. As discussed in our April 2018 newsletter, stem cells can replicate and develop into every organ and tissue in the body. Mesenchymal stem cells are found in several places in the body (including the skin) and can differentiate into a variety of cell types. Researchers at Case Western Reserve School of Medicine have recently discovered how to turn ordinary skin cells into oligodendrocyte precursor cells (OPCs) through a process known as cellular reprogramming. When transplanted into mice created specifically to be deficient in myelin, these "induced" OPCs were successful in generating new myelin. The research team was able to quickly grow billions of these cells. This discovery may help scientists generate building blocks for myelin regrowth from readily abundant, common skin cells. It's important to note that, while this exciting research seems very promising in animal models, further research is necessary to demonstrate that the same cellular manipulation technique can be applied to human skin cells.

Athersys, Inc. is a biopharmaceutical company, established in 1995, that is developing a stem cell product for the treatment of MS called MultiStem. It is an "off the shelf" product that is manufactured from human stem cells obtained from non-embryonic tissue sources, such as bone marrow. It has the ability to form multiple cell types and the potential to deliver therapeutic benefit in several ways. In preclinical testing, MultiStem appears to stimulate production of cells that reduce inflammation, protect damaged or injured tissue, and promote myelin repair. More research in both animal models and the clinical setting is needed to fully understand the therapeutic benefit and risk profile of this product.

Other efforts to regrow myelin are also underway. Human growth hormone (HGH) helps control a number of body functions, including metabolism, as well as muscle and bone growth. It is also known to stimulate the immune system and may play a role in increasing inflammation in MS. HGH causes the production of insulin-like growth factor (a type of growth factor and a type of cytokine), which in turn facilitates OPC differentiation. Researchers in Germany recently conducted a pilot study with 25 MS patients on the inflammatory effect of HGH treatment and its potential to encourage myelin production.

Initial results from this investigation are promising, but more studies are necessary to draw definitive conclusions.

In 2010, fingolimod (Gilenya) was approved as the first oral treatment for people with relapsing remitting MS (RRMS). It works by preventing nerve inflammation. Researchers in Germany discovered it also appears to enhance peripheral nerve regeneration and remyelination in mice. Results show fingolimod can not only reduce nerve inflammation, but also promote nerve regeneration and improve myelin thickness. It does this by inhibiting the action of cell signaling molecules known to damage myelin. This newfound action appears to be independent of its anti-inflammatory characteristics. While further study is necessary to determine if the same is true in humans, this research suggests a powerful added therapeutic benefit for an FDA-approved treatment.

Another approach to regenerative therapy is examining the key molecules that are important to oligodendrocytes (ODs) that may also serve as therapeutic targets for promoting myelin repair. The ReBUILD Trial is the first randomized clinical trial of a treatment to restore myelin damage in MS. Clemastine fumarate is an antihistamine that is commonly used to relieve symptoms of allergy, hay fever and the common cold. The groundbreaking results from this study show this over-the-counter drug can also improve the demyelinating optic neuropathy in patients with RRMS. This effect was sustained, suggesting that the observed improvement was not due to a transient effect of medication on transmission, but rather a persistent structural change induced by treatment. Results also suggest that myelin repair can be achieved even following prolonged damage. Clemastine treatment was associated with fatigue, however no serious adverse events were reported during the trial. Although clemastine is an over-the-counter medication, it's important to note that doses in this trial exceeded the maximum recommended dose. More research with larger numbers of people is needed before doctors can recommend this as a treatment for people with MS.

Researchers at the Mayo Clinic developed an antibody (a protein produced by the immune system to fight against infection) called rHIgM22 that binds to the surface of ODs and facilitates the clearance of myelin debris from damaged axons. rHIgM22 treatment

resulted in improved brain remyelination and motor function in preclinical studies (in mice). Phase I clinical testing of this antibody is underway. Results of the first phase I study (done in subjects with stable MS) show a single dose of rHIgM22A is well tolerated, has a long duration of action (3 to 4 days), and crosses the blood-brain barrier. Investigators conducted a second Phase I trial, the results of which are still pending, to determine if a single dose of rHIgM22 is safe and tolerable during relapse. Phase II clinical trials with this antibody are planned for the future.

Endece is a biopharmaceutical company based in Wisconsin. Their lead investigational product, NDC-1308, is being developed to promote myelin repair in people with secondary progressive MS. It is intended for use either as a mono-therapy or in combination with other disease-modifying therapies. The molecule works by inducing differentiation of OPCs. NDC-1308 facilitates remyelination and shows a neuro-protective effect in animal models. This treatment crosses the blood-brain barrier and is well tolerated in mice. Further testing is needed to determine its safety, tolerability and efficacy in humans. Endece hopes to initiate a Phase I clinical trial in the near future.

Longevity Biotech, Inc. is a preclinical-stage biopharmaceutical company working to develop a synthetic peptide (a small protein) called LBT-3627. This product is a potential disease modifying therapy for MS, Parkinson's Disease and other neurological disorders. Vasoactive intestinal peptide (VIP) is a well-known anti-inflammatory agent. LBT-3627 targets the VIP family of receptors, which plays multiple roles in neuroprotection. The hope is that LBT-3627 will bolster the immune response for neuroprotection while potentially also promoting the growth and maturation of OPCs. LBT-3627 has demonstrated a significant neuro-protective effect in animal models. Longevity Biotech is actively progressing this program through preclinical development and toward clinical trials.

Current MS research is also focused on potential therapies that will protect the nervous system in order to allow natural myelin repair to occur. For example, Ibudilast is a medication used in mainly in Japan to treat asthma and stroke. In a recent study, Ibudilast

reduced the progression of brain atrophy or shrinkage in those with progressive MS by nearly 50 percent. More research is needed to determine why and how this drug works in progressive MS, before it can be made available to people with this stage of the disease. Lipoic acid is an antioxidant available as an over-the-counter supplement. In animal models of MS, it has been shown to reduce inflammation and degeneration of the optic nerve and spinal cord. Results of a Phase II clinical trial, published in September 2017, showed lipoic acid reduced brain atrophy in subjects with SPMS by 68 percent, suggesting a clinical benefit for this form of the disease. Phenytoin is an anticonvulsant, commonly used to manage seizures in epilepsy. It is also used to help manage pain in MS. Subjects with optic neuritis (ON) who took phenytoin as part of a Phase II clinical trial had 30% less damage to the retina compared with those taking a placebo. This suggests that phenytoin is neuro-protective in patients with acute ON. Estriol is an estrogen that naturally increases to high levels in serum during the last half of pregnancy (a time when MS relapse rates typically decrease). Estriol treatment is anti-inflammatory and neuro-protective in animal models. Clinical studies demonstrate a similar effect in humans. For example, results of a small study of people with MS indicate that estriol reduces the number of gadolinium-enhancing lesions. A 2016 study also shows Copaxone treatment combined with estriol provides a protective effect on the brain.

Protecting and repairing the nervous system, in particular myelin, holds significant promise as a strategy to develop treatments that will not only stop or reduce MS progression, but also restore the function that the disease steals. While the development of therapies that encourage myelin repair is gaining more traction in the MS research community, many questions remain. Scientists from around the globe are focused on this compelling area of research. The Accelerated Cure Project's mission is to facilitate research like this toward a meaningful and significant impact for those living with MS.