Many people consider the New Year as the “next chapter” in their lives, a time to focus on new beginnings and possibilities. Continuing this theme, our January newsletter focuses on another chapter, and what could be a new frontier, in MS research – remyelination. Myelin is a fatty substance that coats, or insulates, the nerve fibers of the brain and spinal cord and helps speed the conduction of electrical impulses along them. MS is a disease that causes the immune system to attack, or erode, the myelin in the central nervous system. This disrupts the signals from the brain to the rest of the body. Virtually all bodily functions depend on the transmission of nerve signals. When MS disrupts these pathways, multiple symptoms can occur. Remyelination is the process of creating new myelin sheaths. Scientists all over the world are working to better understand the many steps, pathways, and factors involved in myelin production and repair. Our first article covers the intricacies of this regenerative process, many of which have the potential to be exciting new therapeutic targets.

All of the FDA-approved treatments for MS are designed to slow the rate of relapse and the accumulation of disability. None of them can undo the nerve scarring that occurs in MS. 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. Learn more about where we stand with regenerative therapies for MS.

Dr. Ben Barres was an acclaimed Stanford neuroscientist whose research revolutionized our understanding of the structure and function of the brain. His landmark exploration of the role of glial cells in neurodegenerative brain diseases seeded an entirely new and exciting field of research in this area. As a result, researchers now have a better understanding of the mechanism of myelin destruction and repair, making the discovery of a regenerative therapy for MS more plausible. Ben Barres not only changed the course of neuroscience, he also
cared deeply about other people and touched many lives. His influential life was cut short when Barres lost his fight with pancreatic cancer in 2017. We hope you enjoy the remarkable story of his life and accomplishments.

Our Repository Spotlight focuses on the work of Dr. Terrence Fisher at Vaccinex, Inc. Semaphorin 4D is a protein expressed by immune cells known to promote immune activation and inhibit myelination. Dr. Fisher is working on the development of an antibody-based therapy that would suppress this protein’s activity and potentially promote remyelination.

Our iConquerMS Spotlight is on a study, brought to us by Jon Strum in his podcast series, RealTalk MS, that reveals an exciting association between exercise, treatment with clemastine fumarate (a commonly used antihistamine), and faster remyelination rates in mice. We at iConquerMS are pleased to collaborate with Jon to communicate relevant research activities and results such as these to the MS community.

We would like to express our heartfelt thanks for the many ways that our partners, donors and volunteers have given of their time, talents and resources. If you haven’t already done so, it’s not too late to make a donation! Every contribution brings us closer to our goal and makes a significant difference in ACP’s success. We hope you enjoy our newsletter and encourage you to share it with anyone you think may be interested in learning more about ACP.

The Accelerated Cure Project Team

Unlocking the Mystery of Remyelination

Myelin is a fatty substance that coats the nerve fibers of the central nervous system (CNS), the brain and spinal cord. It insulates the nerves and helps speed the conduction of electrical impulses along the spinal cord to and from the brain. 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. These damaged areas in the myelin sheath, seen with magnetic resonance imaging (MRI), are called plaques or lesions. Virtually all bodily functions depend on the transmission of nerve signals. When MS disrupts these pathways, multiple symptoms can occur. For example, depending on where the damage occurs, a person with MS may experience a variety of symptoms, including numbness, pain, vision loss, cognitive impairment, trouble with bowel and bladder function, difficulty with speech, or paralysis.

Cell signaling is part of the communication process that governs the basic activities of cells. Cell to cell signaling involves the transmission of a chemical signal from a sending cell to a receiving cell. These chemical signals, which are proteins or other molecules produced by a sending cell, are often secreted from the cell and
released into the extracellular space. They then float over to neighboring cells. Not all cells can “hear” a particular chemical message. In order to detect a signal (or be a target cell), a neighbor cell must have the right receptor for that signal. When a signaling molecule binds to its receptor, it alters the shape or activity of the receptor, triggering a cascade of biochemical reactions inside the cell, called a signaling pathway. After the first molecule in the pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function is carried out.

**Glial cells** (also called glia) are non-neuronal cells in the CNS, accounting for 90 percent of the brain’s cells and more than half its volume. They surround neurons and provide support for and insulation between them. **Oligodendrocytes** (OD) are a type of glial cell responsible for production of myelin. They are primarily found in the brain, but also in smaller numbers in the spinal cord. ODs are formed from **oligodendrocyte progenitor cells** (OPCs), also known as oligodendrocyte precursor cells. OPCs have “stem cell-like” properties, such as the ability to differentiate into specific cell types and the ability to self-renew. Remyelination is the process of generating OPCs to form ODs, which then create new myelin sheaths. This regenerative process occurs in two major phases – OPC migration and differentiation. OPCs migrate to the damaged axon and then differentiate into mature ODs, which can wrap damaged axons with new myelin sheaths.

While it is a vast improvement, the myelin formed from remyelination is structurally abnormal. These nerve coverings are typically shorter and thinner than usual and, as a result, have reduced conduction velocity compared to normal myelinated axons. This is often observed in MS patients by physical exam or evoked potentials.

Remyelination is a very complex process with a myriad of contributing elements. Listing all of them would require an entire scientific volume. To name a few, a number of signaling pathways are known to impact OPC differentiation. The **LINGO1**, **Hyaluronan** and **Wnt** pathways have an inhibitory effect (therefore hindering remyelination). The **RXR** pathway has a beneficial effect, which accelerates remyelination. The **Notch1** pathway affects remyelination in both directions. On the one hand, it inhibits OPC differentiation. On the other, it also appears to facilitate OPC migration. A variety of other factors influence this regenerative process. One such factor is **Reticulon 4** (also known as neurite outgrowth inhibitor, or Nogo). Nogo is a protein known to inhibit neuronal growth. There are three variants – Nogo A, B, and C, each with a unique function. Blocking Nogo-A during a demyelinating attack is thought to help to protect or restore damaged neurons. Researchers in Switzerland recently found that antibodies against Nogo-A enhanced neuronal regeneration and remyelination in two animal models of MS. Another protein thought to inhibit neuronal growth is **EphrinB3**. A recent study reveals EphrinB3 also inhibits OPC differentiation. In a rat model of MS, investigators demonstrated infusion of EphrinB3 inhibits remyelination and masking EphrinB3 using antibodies promotes remyelination.
Gene expression is another important factor in remyelination. DNA (deoxyribonucleic acid) determines the structure and function of every cell and is responsible for characteristics being passed on from parents to their children. DNA is transcribed into RNA (ribonucleic acid), which is then translated into a sequence of amino acids, the building blocks of proteins. Proteins make many of the structures and all of the enzymes in a cell or organism. Transcription is the process where a gene’s DNA sequence is copied (or transcribed) into an RNA molecule. Proteins called transcription factors play a central role in regulating transcription. They can activate or repress the transcription of a gene, which determines whether the gene functions (is “turned on”) at a given time. Gene expression is currently a hot topic in MS research. A number of transcription factors have been shown to be important in remyelination. Recently, investigators at the University at Buffalo discovered a transcription factor called PRRX1 in human OPCs. They found that activating the PRRX1 gene disrupted myelin repair by blocking OPC proliferation, thereby disabling myelin production. As more genes involved in myelin regeneration are found and cross-linked more will be understood about the process.

The immune system is the body’s defense against infections and other intrusions. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade body systems and cause disease. In MS, abnormal activity of the immune system results in inflammation, which in turn causes myelin damage. The current clinical therapies for MS primarily focus on inhibiting the immune response. Cytokines are a group of proteins secreted by cells of the immune system that act as chemical messengers to help control the immune system and fight disease. They are cell-signaling molecules that help cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Chemokines are a type of cytokine that stimulate movement of cells. Scientists believe chemokines play a role in both the migration and differentiation of OPCs.

Interestingly, the immune system has a conflicting effect on myelin repair. Research shows acute inflammation is a key signal that activates adult OPCs to mobilize and mature (thereby facilitating remyelination), however long-term inflammation can be toxic to OPCs (which inhibits the regeneration process). Further study indicates that key cytokines responsible for the destruction of myelin may also mediate the process of myelin...
regeneration and repair. For example, interleukins (ILs) are thought to be involved in both processes. Researchers also believe the environment surrounding cells plays a key role in remyelination. MS lesions often contain myelin and OD debris. Data from a 2006 study indicate this material may inhibit the differentiation of OPCs, thereby decreasing the efficiency of remyelination. Cytokines mediate the inflammatory responses that promote pathogen and debris clearance from the damaged axon.

Myelin production and repair is naturally regulated in the body and is usually efficient in a healthy CNS. A variety of factors can interfere with myelin production, including a diet high in sugar content, poor sleep quality, alcohol, nutrient deficiencies, and hormonal imbalances. Many regenerative processes become less efficient with increasing age, including remyelination. This is particularly relevant for diseases like MS, which can span decades. Aging brings about intrinsic changes in OPCs and their signaling, both of which impact myelin repair. Compounding this aging effect, the repair process becomes increasingly incomplete in people with MS. Most, if not all, nerve function can be restored early in the disease. However, the repair process becomes less efficient over time, and disability mounts. When axons are left bare (without myelin), their conduction velocity goes down. In addition, a naked axon is much more likely to degrade completely, resulting in complete loss of function. Once a nerve fiber is degenerated, it cannot regenerate. This loss of axons because of a lack of protection is a significant factor in the debilitating effects of MS.

Although myelin repair is typically limited in people with MS, it does occur in a significant percentage of MS patients, in all stages and manifestations of the disease, including primary progressive MS. These repaired lesions are frequently referred to as shadow plaques. It isn’t clear what prevents remyelination in lesions that occur in early stages of the disease. Scientists believe it could relate to abnormal inflammatory activity or dysfunction of ODs. In either case, nerve repair may begin within a month or two after the damage occurs. ODs can survive a demyelinating attack and may contribute to subsequent regenerative attempts. However, decreased numbers of ODs over time (after repeated attacks) may make remyelination impossible in late stage disease. In advanced MS, myelin repair seems to only occur at the edge of MS lesions, suggesting that the forces regulating nerve repair are insufficient to reach the lesion core. In lesions containing more ODs, impaired OPC differentiation appears to be the primary obstacle to efficient myelin repair.

Pathology studies show remyelination is found in both inactive lesions, and in lesions with ongoing demyelinating activity. One study demonstrates that older age at death and longer disease duration were associated with significantly more remyelinated lesions. According to these data there is no relationship between the capacity for remyelination and one’s age of disease onset. Investigators found that the location of lesions plays a role in the remyelination process, with nerves in
subcortical or deep white matter lesions more likely to regenerate than those in periventricular lesions. Another study concludes that remyelination may be more efficient in females (who are at higher risk of developing MS) than males. This could be due to the differential effects of sex hormones on OD proliferation and maturation, as well as on the neuroinflammatory process.

All of the FDA-approved drugs are designed to slow the rate of relapse and the accumulation of disability. None of them can undo the nerve scarring that occurs in MS. Several signaling pathways and other complex factors have been shown to impact remyelination, representing possible exciting new therapeutic targets. Scientists all over the world are working to better understand the intricacies of this regenerative process in order to determine how to repair myelin and restore function to those living with MS.

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 rHlgM22 that binds to the surface of ODs and facilitates the clearance of myelin debris from damaged axons. rHlgM22 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 rHlgM22A 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 rHlgM22 is safe and tolerable during relapse. Phase II clinical trials with this antibody are planned for the future.

Endece Neural 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 Neural 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.
Dr. Ben Barres was an acclaimed Stanford neuroscientist whose research revolutionized our understanding of the structure and function of the brain. He not only changed the course of neuroscience, but he also cared deeply about other people and touched many lives. He was a beloved mentor to dozens of students and trainees, working nonstop on their behalf. As a result of his personal struggle with gender identity, and eventual gender transition, he was a passionate advocate for women in science. Along the way he also became a hero for people from gender and sexual minorities. His influential life was cut short when Barres lost his fight with pancreatic cancer at the age of 63.

Ben was born Barbara Barres, one of four children in West Orange, NJ. His interest in science first manifested itself as a fascination with the mad scientist in the 1941 Superman cartoon. Dr. Barres decided he wanted to be a scientist before reaching his 5th birthday. As a child, he loved mathematics and science over dresses and jewelry. His parents simply saw him as a tomboy, but even as a very young child Ben felt that he was assigned the wrong gender. In his words, “Internally I felt strongly that I was a boy. This was evident in everything about my behavior.”

At school, the then Barbara Barres repeatedly requested, but was denied, access to courses in science and engineering. A summer science program with no gender restrictions at Columbia University finally allowed access to these subjects, and led him to pursue a Bachelor of Science degree (BS) in biology at the Massachusetts Institute of Technology (MIT), which he earned in 1976. In 1979, Barres completed a medical degree at Dartmouth College, followed by a neurology residency at Weill Cornell Medicine. While studying pathology specimens in the course of his studies, he was struck by the observation of large numbers of irregular-appearing glial cells near lesions in the brain. Prior to this, researchers believed these cells merely supplied stability and nutrients to the brain’s neurons. He was intrigued that so many of the diseases that impair brain and nervous-system function involve glial cells, yet so little was known at the time about their biology. Frustrated at physicians’ inability to provide cures or even to understand the causes of complex degenerative brain diseases, Barres left medicine to study glial cells further and, in 1990, earned a doctorate (Ph.D.) in neurobiology at Harvard Medical School.
As Barbara and as Ben, Barres’ research led to numerous landmark discoveries. He had an almost superhuman work ethic, often working 18–20 hours per day. He was known by many in the neuroscience community as the “godfather of glia” for his pioneering research that inspired an entire field of scientists studying glia. During a postdoctoral fellowship at University College London, Barres worked with a team that was using immunological techniques to isolate three classes of glial cells. Working in this lab, Barres made new discoveries about the best-known class of glial cells, oligodendrocytes. These fat-filled cells were already understood to wrap themselves around neurons, a process called myelination, providing electrical insulation and significantly increasing the transmission speed and reliability of neuronal impulses. Barres showed, among other things, that electrical activity in neurons was necessary for their myelination. In 1993, he joined the faculty of Neurobiology at the Stanford School of Medicine and started his own lab. In 2008, he was appointed as the Chair of Neurobiology. At Stanford, Barres turned his attention to a second less understood class of glial cells known as astrocytes. With his colleagues, he discovered astrocytes are key to the formation and activation of the connections in the brain responsible for learning and memory. Barres and colleagues also discovered that astrocytes cooperate with microglia (a third type of glial cell) in pruning those connections so the most useful ones remain. Barres’ most recent research showed that astrocytes contribute to the death of injured neurons and other glia and these “destructive” astrocytes are more common in degenerative brain diseases like Alzheimer’s, Parkinson’s, MS, and Lou Gehrig’s disease (ALS). This important discovery, published while Barres was undergoing chemotherapy, may provide opportunities for the development of new treatments for these diseases.

In his early work, Dr. Barres used samples from the ACP Repository for a study that focused on the role of the blood brain barrier (which prevents materials in the blood from entering the brain) in both the cause and progression of MS. He shared ACP’s collaborative approach to research. Rather than jealously guarding his methods and data, he went to great lengths to make this information widely available to others working in the same area. In 2011, Dr. Barres co-founded a biotechnology company, Annexon Biosciences, to translate these findings into drugs that could someday succeed in retarding or preventing the progression of neurodegenerative disorders.

Over the course of his career, Barres published 167 peer-reviewed papers. He organized and chaired numerous meetings, won many awards and served on the editorial boards of a number of distinguished journals, such as Science, Neuron, the Journal of Neuroscience, Glia, and Current Biology. He was elected to membership in the American Association for the Advancement of Science, the American Academy of Arts and Sciences and the National Academy of Medicine. In 2013, Ben Barres was the first openly transgender scientist to be elected to the National Academy of Sciences.
For the first three decades of his life, Barres struggled with the knowledge that he was a man living in a woman’s body and became increasingly uncomfortable in his own skin. In 1997 (at the age of 43), Barres transitioned from female to male. He came out to his friends and family in an email, saying “I’m still going to wear jeans and t-shirts and pretty much be the same person I always have been, it’s just that I’m going to be a lot happier.” He wrote a letter to his colleagues at Stanford University, signed his birth name, Barbara Barres, making it clear that he wished to be known as Ben from that point forward. His friends, family and coworkers responded with unwavering support. Barres’ pioneering research continued to move forward after he came out as Ben. However, his transition caused some unexpected ripples.

Barres, as Barbara, faced many challenges in the course of his academic and early scientific career, often stemming from being a female in a male-dominated field. For example, as an MIT undergraduate he solved a hard math problem that had stumped the rest of his virtually all-male class, only for his professor to suggest that his boyfriend must have done the work. While working on his Ph.D., he lost a fellowship competition to a male student who had published a sixth as many papers. During his decades as Barbara, Barres had known what this unfairness felt like, but he was unprepared for the drastically different treatment he got once he presented as a man. All of a sudden, fellow researchers began addressing him more collegially and treated him with more respect. On one occasion, after Barres gave a talk as Ben, he even heard an audience member remark, “Ben Barres gave a great seminar today, but then his work is much better than his sister’s.” He was angered by the chauvinism in many scientific institutions. Having lived both gender roles, he understood the pervasiveness of sexism and had a unique perspective on how to effect change.

Barres devoted much of his last decade to publicly describing the challenges he had faced as female in science, and offering ways to correct a system that he viewed as fundamentally biased against women and minorities. He worked relentlessly to improve the representation of women in all areas of science. He fought tirelessly for policies to protect women from sexual harassment and refused invitations to institutions with extremely poor gender ratios. He frequently interrupted his own keynote speeches about glia to talk about the inherent prejudice in science and barriers that keep such groups from succeeding in their careers.

Barres was a brilliant scientist who made it possible for others to shine. Barres considered his students and postdocs as if they were his children. Seeing them flourish and succeed was one of his greatest sources of joy. He went out of his way to mentor dozens of students and postdocs, stepping aside so they could blaze their own trails without having to compete with him. Barres’ lab meetings were legendarily intense and well attended, often lasting more than three hours, during which he covered a wide variety of topics and encouraged open, spontaneous discussions. Ben’s devotion to his trainees is evidenced by the fact that he spent the final days of his life writing and updating dozens of letters of recommendations for them in anticipation of their future career developments after his death.
In April 2016, Ben was diagnosed with advanced pancreatic cancer. He was remarkably brave and philosophical about his illness and his life. In his words, “I lived life on my terms: I wanted to switch genders, and I did. I wanted to be a scientist, and I was. I wanted to study glia, and I did that too. I stood up for what I believed in and I like to think I made an impact, or at least opened the door for the impact to occur. I have zero regrets and I’m ready to die. I’ve truly had a great life.” Barres succumbed to his illness in December 2017. His memoir, The Autobiography of a Transgender Scientist, documents his extraordinary life story.

Much of the book is rightfully devoted to Ben’s scientific achievements, punctuated by intensely difficult moments. Also included is an account of Barres’ dogged advocacy, both for mentoring young scientists and helping women in science. One section of Barres’ memoir lists his trainees along with the positions they held in 2017. Many of them went on to be leaders in their fields, which is a testimony to the powerful impact of Barres’ efforts on their behalf.

Ben Barres left behind what some describe as a “towering legacy of goodness.” Many doors have been opened, thanks to his keen insight, humanity and courage. He was a beloved mentor to more than 40 trainees. His heartfelt efforts to promote equity and diversity in science touched many lives. His landmark work inspired an entirely new field of research into the role of glial cells in neurodegenerative brain diseases. As a result, researchers now have a better understanding of the mechanism of myelin destruction and repair, making the discovery of a regenerative therapy for MS more plausible.

**Repository Spotlight - Dr. Terrence Fisher, Vaccinex Inc.**

Vaccinex, Inc. is a biotechnology company, based in Rochester, NY, working on the development of antibody-based therapies to treat neurodegenerative diseases. Semaphorin 4D (SEMA4D) is a protein expressed by immune cells that promotes immune activation and inhibits myelination. Suppression of this protein’s activity would hypothetically promote remyelination. As part of their work to develop a SEMA4D antibody for both the diagnosis and treatment of MS, Dr. Fisher and his team analyzed 200 ACP Repository samples to see if SEMA4D levels are elevated during active disease. This work could provide important information regarding this protein’s possible role as a biomarker in MS. Dr. Fisher’s study is just one of more than one hundred studies using ACP Repository samples to advance and accelerate research into MS.
iConquerMS™ Spotlight – Enhancement of Remyelination by Exercise

RealTalk MS is a podcast series (established by Jon Strum), which offers a wealth of information and encouragement to people affected by MS. Recently, Jon reported on a study that explored the effect of exercise on the rate of remyelination in a mouse model of MS. Mice with toxin-induced lesions were given free access to either an open or a locked running wheel (thereby controlling whether or not they could exercise). Results showed that the physically active mice experienced faster remyelination. The research team then investigated the combined effect of exercise and treatment with the over-the-counter anti-histamine, clemastine. Investigators concluded treatment with clemastine further enhanced remyelination over exercise alone. While further research is necessary to demonstrate these findings in humans, this study represents significant progress in identifying factors that may affect myelin repair. We at iConquerMS and Jon are working together to communicate relevant research activities and results such as these to the MS community.