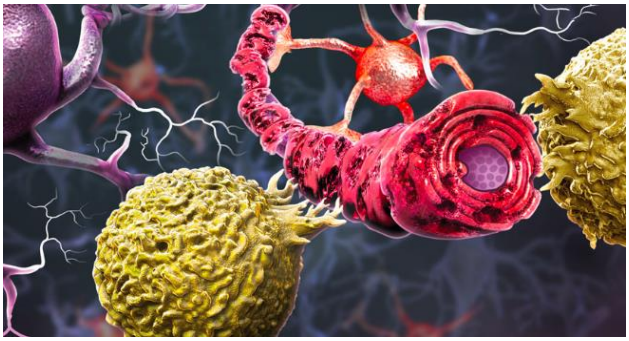
August 2021 Newsletter

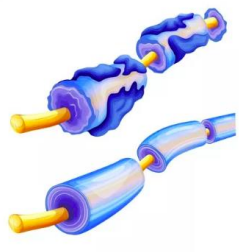
Unlocking the Mystery of Remyelination



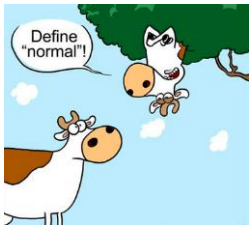
Myelin is a fatty substance that coats the nerve fibers of the central nervous system (CNS), the brain and spinal cord. It insulates the nerves and helps speed the conduction of electrical impulses along the spinal cord to and from the brain. Multiple sclerosis (MS) is a disease that causes the immune 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.



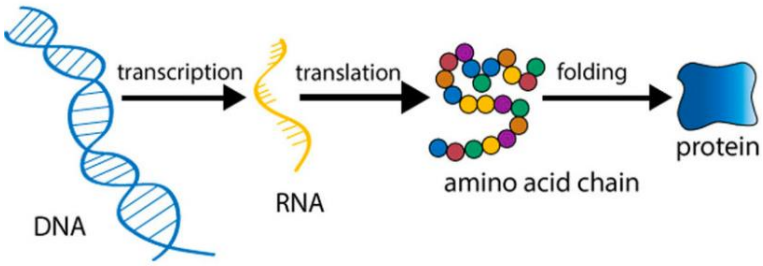
Glial cells (also called glia) are non-neuronal cells in the CNS, accounting for 90 percent of the brain's cells and more than half its volume. They surround neurons and provide support for and insulation between them. Oligodendrocytes (OD) are a type of glial cell responsible for production of myelin. 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.



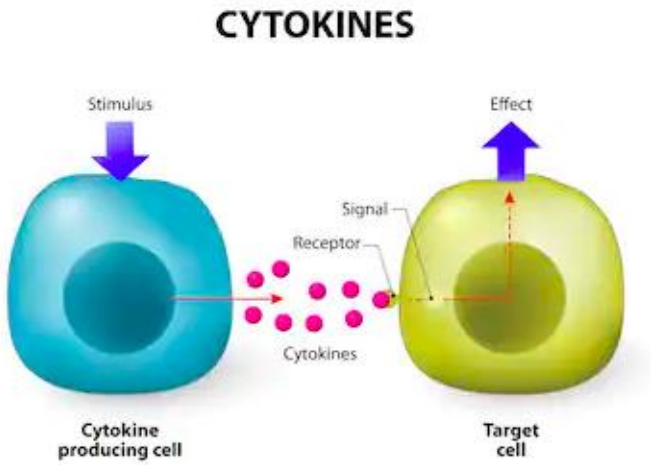
While it is a vast improvement, the myelin formed from remyelination is structurally abnormal. These nerve coverings are typically shorter and thinner than usual and, as a result, have reduced conduction velocity compared to normal myelinated axons. This is often observed in MS patients by physical exam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

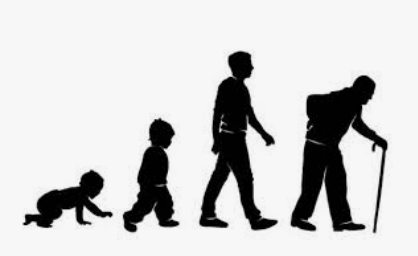


The immune system is the body's defense against infections and other intrusions. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade body systems and cause disease. In MS, abnormal activity of the immune system results in inflammation, 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.



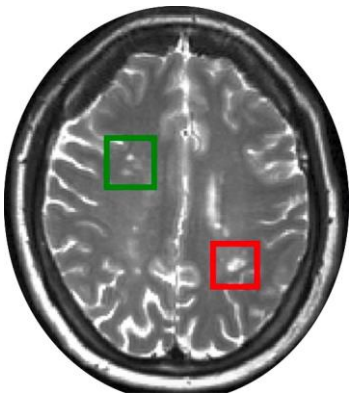
Interestingly, the immune system has a conflicting effect on myelin repair. Research shows acute inflammation is a key signal that activates adult OPCs to mobilize and mature (thereby facilitating remyelination), however long-term inflammation can be toxic to OPCs (which inhibits the regeneration process). 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.



Brain MRI - The red box contains 1 demyelinated lesion. The green box contains 3 shadow plaques (remyelinated lesions).

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.

Understanding and Living With MS Fatigue

According to the National MS Society, 80% of people with MS experience fatigue, and over half rank it as one of their most troubling symptoms. Nearly everyone feels overtired or overworked from time to time and such instances of languor usually have an identifiable cause and a likely remedy, such as a good night's sleep. Fatigue is an unrelenting exhaustion that lasts longer, is more intense and isn't relieved by rest. It's a nearly constant state of weariness that develops over time. Fatigue can be either physical or cognitive, or both at the same time. Physical fatigue may affect an individual's energy and motivation. Limbs may feel heavy and hard to use and, as a result, individuals may feel the need to lie down immediately. Cognitive fatigue, on the other hand, could affect one's concentration. Individuals with cognitive fatigue may have difficulty following a conversation or thinking of words or numbers. In either case, fatigue negatively impacts the functioning and quality of life of the majority of people living with MS.

MS fatigue is complex, with many layers and contributing factors. In some cases, fatigue is "secondary" to an underlying cause and may be effectively addressed by treating the source. For example, many people with MS struggle with depression. Depression itself can manifest with fatigue, so it is often difficult to distinguish it from between the two. In addition, other symptoms of depression, such as lack of motivation, are often mistaken for fatigue. Research shows a direct association between fatigue and depression, even considering the overlap between the two conditions. In instances where depression and fatigue occur concurrently, fatigue may be effectively addressed by treating the underlying depression. Investigators also found a direct relationship between fatigue and disease severity (subjects with more disability were more likely to experience fatigue). In addition, subjects with progressive MS appeared to have higher fatigue scores (experience more fatigue) that those with RRMS. However, this difference may be attributable to the differences in disability among the types of MS. By the same token, people with MS may have sleep disorders that interfere with restful sleep. In fact, researchers at the University of Washington found the prevalence of sleep problems in people with MS is significantly higher than in the general population, particularly in women living with the disease. Exhaustion from a lack of restful sleep is considered to be a contributing, if not a causative, factor in MS fatigue. Medications used to treat MS and its symptoms have the potential to cause fatigue. For example, fatigue is a side effect of some disease modifying treatments, including interferons (Avonex, Betaseron and Rebif), Tysabri and Novantrone. Drugs taken for MS symptoms like spasticity (baclofen or diazepam) or nerve pain (gabapentin), to name a few, can also contribute to fatigue. In some cases, a medication adjustment can help with fatigue, however anyone considering such a change should first consult with their healthcare team. Sometimes, people with MS have other medical conditions, such as infections, anemia, or thyroid conditions, which can also increase fatigue.

Beneath these secondary causes is "primary" MS fatigue, called lassitude, the cause of which is unknown. Lassitude has a number of specific characteristics that help distinguish it from secondary MS fatigue. Lassitude generally occurs on a daily basis. It is considered more severe than secondary MS fatigue, and is more likely to interfere with daily responsibilities. Lassitude often occurs early in the morning, even after a restful night's sleep. This type of fatigue comes on easily and suddenly, tends to worsen as the day progresses and is often aggravated by heat and humidity. No matter what form of fatigue an individual with MS may experience, this overwhelming tiredness can affect anyone with MS, regardless of physical disability, and occur at any time in the course of the disease. Even though it is more likely in those with higher levels of disability, it is not always the case. Fatigue can also be the most prominent symptom in a person who otherwise has minimal physical limitations. People with MS may also find that fatigue worsens their other MS symptoms.

The exact cause of MS-related fatigue is still unknown. However, researchers are working to figure out this mystery. There is evidence that fatigue is related to the general activation of the immune system that occurs in MS. As discussed in our January 2019 newsletter, cytokines are chemical messengers that are secreted by certain cells in the immune system. Researchers in Germany found pro-inflammatory cytokines are significantly higher in MS subjects with fatigue, compared to MS subjects not experiencing fatigue. This suggests that fatigue is at least partially mediated through activation of these cytokines. Another study showed that the levels of the hormone dehydroepiandrosterone (DHEA) are lower in MS subjects with sustained fatigue when compared to those without fatigue, suggesting the endocrine system may play a role. The fact that many people with MS report increased energy while taking corticosteroids as treatment for their neurologic symptoms further supports a possible hormonal influence. However, it's important to note that, because of the chronic nature of fatigue and risks of long-term steroid use, steroids are not recommended as treatment for fatigue. Other studies suggest that MS fatigue stems from damage to the central nervous system caused by demyelination. Specifically, one study suggests that a reduced transmission of electrical signals in the brain could play a role and another study points to nerve loss as a contributing factor.

In some cases, drugs may be used in treating fatigue. However, medication is not a solution to fatigue on its own. Because different factors can cause or add to MS-related fatigue (such as depression or sleep disorders), anti-fatigue medications should be used in conjunction with treatment for these factors (when applicable). It's also important for people with MS to see their physician regularly to ensure their disease is under the best control possible. Modafinil (Provigil) is a medication used to increase wakefulness in individuals with the sleep disorder, narcolepsy. It is used off-label in MS to treat fatigue and sleepiness. Studies suggest that low dose modafinil (200 mg daily) significantly improves both, and is well tolerated in people with MS. Armodafinil (Nuvigil) is a medication that is similar to modafinil and is also prescribed for the treatment

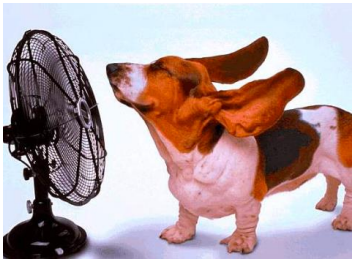
of MS fatigue. Amantadine (Symmetrel) is an antiviral medication used in Parkinson's disease. It has also been used in the treatment of MS fatigue since the 1980s, although its benefit in this regard is not well documented. Methylphenidate (Ritalin) is a central nervous system stimulant used for treatment of attention deficit disorders. In some cases, it is also helpful in reducing MS fatigue. Studies are underway to confirm this benefit. Dextroamphetamine (Dexedrine) is also a stimulant medication. Its effects on MS fatigue are similar to those of methylphenidate. A recent study suggests that aspirin may lessen fatigue in people with MS (among other benefits). While aspirin usage is relatively common in the general population, its use by people with MS also has the potential for negative effects on specific components of MS disease process (for example, further decreasing mitochondrial function, which is a cause of nerve degeneration MS). Further studies are needed to confirm the potential benefits, as well as the risks, of aspirin treatment for people with MS.

A number of alternative therapies may provide some benefit for MS-related fatigue. Some people with MS find that caffeine (in moderation) can be helpful in managing fatigue. Unfortunately, caffeine is an irritant to the bladder, and can exacerbate urgency and frequency. Individuals with MS should speak with their healthcare team about their caffeine intake to be sure they are not exceeding levels that are appropriate for them. Acetyl-L-carnitine (ALCAR) is a dietary supplement that appears to reduce MS-related fatigue, however research to support this benefit is mixed. A small study of 36 subjects, done in 2004, suggests ALCAR is well tolerated and more effective than amantadine for the treatment of MS-related fatigue. Other studies claim there is insufficient evidence to support this benefit. As discussed in our February 2019 newsletter, some herbs are used to help relieve fatigue. These include ginkgo biloba, valerian, St. John's wort, as well as Siberian and Asian ginseng. As we mentioned last month, many of these herbs have problematic side effects that should be carefully considered before use. Some people with MS turn to Tai chi and yoga for relief of their MS fatigue. A recent review of studies conducted on Tai chi practice and MS concluded the evidence to support a benefit with regard to improving fatigue is inconclusive. However, researchers found Tai chi significantly improves quality of life and functional balance in people with MS.

While proper treatment can help control fatigue, changes in lifestyle can also prove beneficial. Strategies to conserve energy are often helpful. An analogy can be made for people with MS between bank accounts and energy levels. Both benefit from the same rule of thumb – less money, or energy, used now means more will be available later on. In other words, doing too much early in the day can burn through all energy stores and leave an individual feeling tapped out. Energy rationing is especially important for people with MS, who tend to start the day with lower energy levels than the average person. For some, a brief rest is very helpful to recharge and scheduling breaks (alternated with periods of activity) is useful to avoid becoming too tired too quickly. If a task is too much to handle at one time, it may be helpful to divide it into smaller parts or ask for help if this isn't possible. Planning one's activities can also help, for example to avoid going up and down the stairs more often than necessary. Listing activities in their order of importance can be

useful to see what needs to done first and what can wait until another day, should all energy be used up before reaching the end of the list. Those with limited energy often need to accept the fact that not everything will necessarily be completed when and how one prefers them to be done.

Efficiency while performing household duties is also useful in battling fatigue. Whenever possible (when cooking or cleaning, for example), arrange supplies in advance to minimize the amount of time spent standing. With respect to meals, selecting menus in advance with easy recipes can help preserve stamina. Having food delivered (rather than shopping) is the most time and energy efficient option. If that's not an option, make a list of all necessary ingredients for the week's meals before shopping for food. Being familiar with a local store and the aisles where individual items are located can assist with saving time and energy as well. Whenever possible, prepare double portions of a meal and freeze leftovers for another day. This provides extra meals that require little time to prepare.



It's important for people with MS to recognize and avoid environmental factors that may cause fatigue. For example, many find it helpful to avoid extremes in heat (long, hot showers or baths, for example) because it drains their energy. On a hot summer day, it may be useful to cool down with a fan or spray bottle or stay in air-conditioning when possible. As mentioned in our May 2018 newsletter, the Multiple Sclerosis Association of America's Cooling Distribution Program offers cooling vests, smaller products to wear under clothing and other accessories to help people with MS keep cool.

Other basic principles of healthy living can also be helpful in managing MS fatigue. Eating a well-balanced, healthy diet can help boost energy levels. Decreased physical activity can lead to tiredness and lack of energy. Regular, moderate exercise can decrease these feelings, as well as improve strength and foster a more positive attitude. Any person with MS who is considering a new exercise program should consult with a physician before starting, and throughout, their regimen. An exercise program needs to fit the capabilities and limitations of the individual and it may need to be adjusted as changes in MS symptoms occur. Periods of exercise should be carefully timed to avoid the hotter periods of the day. Many people with MS find exercising in water to provide exceptional benefits as it is not only cool, but water helps them move in ways they may not be able to on land. Finally, managing stress can play an important role in combating fatigue. This can be done in a variety of ways. Adjusting expectations and limiting daily to-do lists will likely bring a sense of accomplishment that can go a long way toward reducing stress. Educating family and friends about MS fatigue may also help. Given that fatigue is an "invisible symptom" of MS, they might not understand it and may be more helpful if they appreciate its full impact. Some people with MS find support groups to be a source of comfort and camaraderie, as well. Others rely on relaxation techniques to help reduce stress.

Fatigue management has many dimensions and often requires a team effort between family, caregivers, healthcare providers, and many other members. Physicians and other healthcare providers can prescribe and monitor medications, as well as provide education and help develop strategies. Family and caregivers can help provide for physical needs, or with moral support. Perhaps more than with any other symptom

of MS, the key player in coping with fatigue is the person with MS. He or she has the ultimate responsibility for implementing any suggested game plan and making adjustments based on its effectiveness. Managing fatigue involves both trying to keep energy levels up and using energy efficiently. Finding the right balance may be a learning process that requires trial and error. As an individual with MS goes through this process, it's important for them to have a support system (team) to lift them up when they may falter. Through this team effort, it's possible for individuals with MS to function, participate in extracurricular activities and have the best quality of life possible.

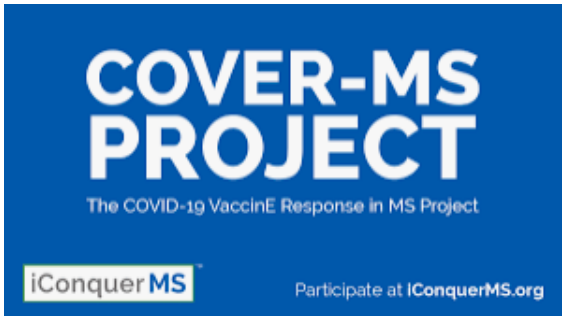
August 2021 iConquerMS Spotlight

Power COVID-19 Vaccine Research With Your Data!

On August 23, 2021, the U.S. Food and Drug Administration (FDA) approved the Pfizer-BioNTech vaccine for the prevention of COVID-19 disease in individuals 16 years of age and older. The vaccine, which will now be marketed as Comirnaty, continues to be available under emergency use authorization for individuals 12 to 15 years of age and for the administration of a third dose in people who are not expected to have a normal or adequate immune responses after two doses of the vaccine, such as people with MS on certain disease modifying therapies.

The National MS Society recently updated its COVID-19 vaccine guidance as follows, "People with MS age 12* and older who are fully vaccinated with an mRNA vaccine may be eligible to receive an additional vaccine dose now. Talk with your healthcare provider to determine the best time to get your additional dose." (* Only the Pfizer/BioNTech

vaccine is authorized for age 12 and older.) The Society's guidance is based on available data from studies (which are ongoing) and the opinions of MS experts.



The COVER-MS study (COVID-19 VaccinE Response in MS) is underway to collect data from iConquerMS members about their experience with the COVID-19 vaccines. All adults affected by MS are eligible (21 or older) and welcome to participate. Participants will be asked to complete a few short surveys on the iConquerMS portal at different timepoints. These surveys contain questions about demographics, MS characteristics, COVID-19 infection, COVID-19 vaccines received, reactions to them, and any MS symptoms experienced before and after vaccination. The data collected will provide a better understanding of the short- and longer-term effects of the vaccines in the MS population. A third round of surveys will soon be released for those fully vaccinated individuals that elect to receive a booster shot. Stay tuned!

Real-world data from COVER-MS will complement the available guidance and provide additional assurance for those with MS who are planning to get vaccinated. If you are an iConquerMS member that has received a COVID-19 vaccine, please login today and share your experience by clicking on "Participate in the COVID-19 Vaccination Study." Forgotten to report your experience with your second shot? It's not too late! If you're not yet a member of iConquerMS, please join the network and start powering MS research with your data today!

August 2021 Research Spotlight

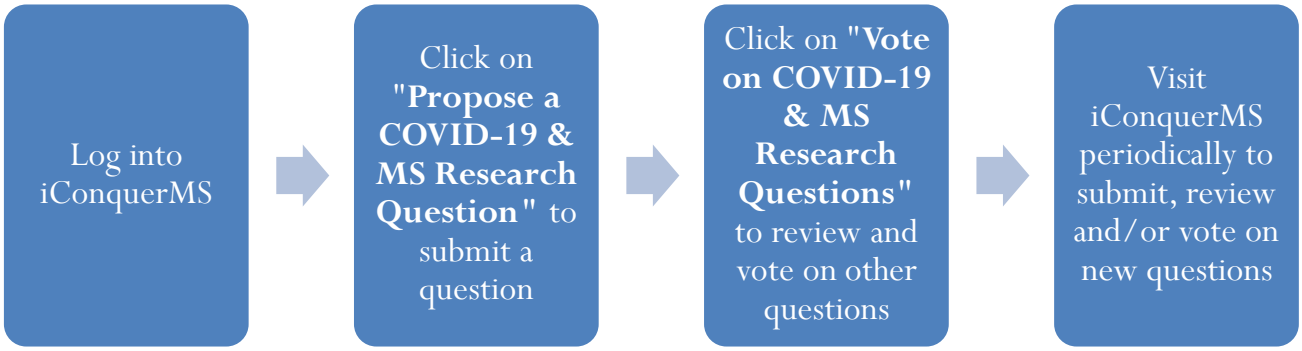
RESEARCH OPPORTUNITIES

Power MS Research With Your Questions and Priorities!

iConquerMS is leading the movement to include the patient perspective in every step of MS research. Now, network members can play a larger role than ever before in initiating and collaborating with researchers on studies that will expand knowledge in areas that matter most to people affected by MS.

iConquerMS members have always been able to submit research questions to the initiative. It's now possible to comment and vote on questions submitted by the community through the newly launched **Our Questions Have Power** program. Questions that are high priority for the iConquerMS community will be shared with researchers, who will work in collaboration with the iConquerMS community to develop them into research studies.

Participation is easy!



If you are not already a member, please consider joining iConquerMS, the only people-powered research network for MS. Add your voice to those working together to improve MS care and bring us closer to a cure!