March 2–8 marked Multiple Sclerosis (MS) Awareness Week in the United States. MS is a chronic, often debilitating disease of the central nervous system (CNS), affecting more than 2 million people worldwide. As recently as 25 years ago, a diagnosis of MS came with no hope for course-altering treatment options, and researchers had only a very limited understanding of the mechanistic underpinnings of disease onset or progression.

The etiology of the disease is still not completely understood—although we do know that MS is effectively an autoimmune disease, whereby the immune system launches an attack on the protective myelin sheath surrounding nerve cells. Loss of myelin prevents nerves from signaling to each other normally, which in turn affects the ability of the brain to send instructions to the body. This may lead to a wide range of symptoms and outcomes of variable severity—including numbness or weakness in one or more limbs, loss of normal motor function, and emotional and cognitive effects. Most MS patients will initially experience a relapsing–remitting form of the disease (RRMS), whereby sporadic flare-ups of symptoms are followed by periods of remission. A proportion of MS patients experience one of several progressive forms of the disease characterized by worsening symptoms without periods of remission—either from the onset of diagnosis, or after an initial period of RRMS.

Why do the immune systems of patients with MS malfunction? Although this is not entirely clear, and the initial antigen responsible for triggering the immune response—whether it be of self- or foreign pathogen-origin—has not been identified, we do know that genetic and environmental factors are contributing factors to the disease. Genome-wide association studies have recently identified at least 100 gene polymorphisms associated with MS risk—and most genes identified seem to be related to immune system function. However—as with other diseases with complicated etiology—genetics do not provide absolute causality, and it seems environmental factors including, for example, Epstein–Barr virus infection and smoking may also affect MS risk.

We know that T cells are involved in regulating the pathology of MS. However, the precise roles of different T helper (Th) cell subtypes (such as Th17 cells and regulatory T cells) and how these cells are themselves regulated is not very clear. B cells are also thought to be involved: several trials using B-cell blocking antibodies (such as ocrelizumab and ofatumumab) have shown a reduction in disease severity for RRMS and/or primary-progressive forms of MS. Questions remain, however, regarding how B cells may be contributing to disease—for example whether they may be presenting specific antigens or whether antibody production may play a role.

The immune system and the regulatory factors that affect immune-mediated inflammation are central factors in MS. Many treatment approaches for RRMS that are now available have focused on modulating the immune system and blocking or reducing CNS inflammation. In the early 1990s, interferon-β (IFN-β) was approved by the Food and Drug Administration as one of the first treatment options for relapsing MS, and follow-up studies have indicated a reduction in relapse rates as well as disease severity for a proportion of IFN-β-treated MS patients. However, IFN-β treatment outcomes are variable among populations, and we still have little mechanistic understanding of how this and other immune modulators currently in use (such as glatiramer acetate and dimethyl fumarate) ameliorate MS disease symptoms. Today, in addition to the immune modulators listed above, several biologics and small molecules are in use or undergoing trials for the treatment of MS. Examples include natalizumab and fingolimod, which both block the traffic of T cells into the CNS by different mechanisms, and which appear to be some of the more efficacious therapeutics available. Alemtuzumab, which depletes lymphocytes, has also recently been approved for RRMS. However, as this antibody will remove several types of immune cells non-specifically, it is difficult to pinpoint exactly how it is working to reduce relapse rates.

Other clinical approaches to treating MS are focusing on addressing the neurodegenerative component of the disease. For example, several clinical trials are currently underway using a patient’s own stem cells to help repair damaged neurons, and to help ameliorate disease symptoms. Other researchers are also working to identify molecules or biomarkers that may help to stimulate the repair of the myelin sheath.

Despite this encouraging progress, better insight into the cellular mediators and regulators of MS disease onset and progression is needed in order to provide greater therapeutic specificity, to improve response rates, and to help minimize adverse effects, which—for some treatments—can potentially be quite severe. There is a pressing need in particular for insight into pathological mechanisms underlying the progressive form of MS, as most available treatment options in use or under development are targeted toward relieving the relapsing form of disease. However, one of the major challenges facing basic researchers in this field is the fact that—although powerful and widely used—the most frequently used animal model system, experimental autoimmune encephalomyelitis (EAE), does not fully recapitulate the complex biology seen in human MS. The EAE disease model therefore comes with some substantial caveats for probing disease mechanisms and predicting the success of therapeutic interventions. Better, more accurate, disease models are therefore needed.

There is also an urgent need for biomarkers which will help clinicians easily diagnose MS, monitor disease progress, and responses to treatment. Although a large number of biomarkers have been proposed for MS, very few have been rigorously validated or applied to clinical practice.

We have come a long way in just the past few decades in both understanding the basic molecular and cellular basis of disease, as well as in developing several treatment approaches to managing disease severity. A diagnosis of MS now comes with some hope for disease-altering treatment. But we still have a long way to go.