Multiple Sclerosis (MS) is a disease of the central nervous system (CNS) that commonly affects individuals 20–40 years old. MS is thought to be an autoimmune disease in which T cells attack and destroy the myelin sheath surrounding neurons. Demyelinated neurons have a reduced capacity to transmit electrical impulses, causing symptoms from loss of muscle control to memory loss. One protein thought to play a role in MS, B7-2, a member of a family of proteins that regulate T cell functions expressed by antigen presenting cells (APC). Generation of an immune response by T cells requires two signals: binding of the T-cell receptor to the antigen/MHC complex on APC and binding of B7-1 to CD80 on the T cells. B7-2 is thought to be involved in suppression of the T cell response through binding to CTLA-4. Research using the mouse model of MS, experimental autoimmune encephalomyelitis (EAE), demonstrated that injection of B7-2 specific antibodies resulted in a more severe disease course. These data suggest that B7-2 plays a role in negative regulation of the immune response during EAE, possibly by binding CTLA-4. To investigate how B7-2 interacts with CTLA-4, we created a physical model of B7-2 based on its crystal structure (1ncn.pdb) using 3D printing technology that highlights the protein’s β-sheet structure and amino acids thought to be important in CTLA-4 binding. This work was supported by a grant from NIH-NCCR-SEPA as part of the SMART team program at Milwaukee School of Engineering.

In MS, most patients have a relapsing-remitting disease course in which their symptoms spontaneously resolve. The mechanisms leading to this recovery are largely unknown, but have been investigated using the animal model of MS, (EAE). One possible mechanism is the downregulation of the T cell response by the binding of B7 with CTLA-4 on the T cells, delivering a negative signal (Fig. 2). To examine this possibility, EAE was induced by immunization with self-antigen in adjuvant with pertussis toxin and administered blocking reagents for B7 and CTLA-4 (Fig. 4A). Blocking of CTLA-4 (Fig. 4B) or B7-2 (Fig. 4C) resulted in more severe EAE, suggesting that this interaction is important in controlling autoimmunity in the CNS.

The immune system is composed of many cell types, which are thought to contribute to the onset of MS. The most important being a CD4 T cell. CD4 T cells develop in the thymus and recognize foreign antigens such as bacteria and self-antigens by a process known as antigen presentation. During antigen presentation, antigens are taken up by APC, degraded into small protein fragments called peptides, which are presented on their cell surface bound to MHC molecules. The CD4 T cell binds to the peptide/MHC complex via their cell surface T cell receptor (TCR) (Fig. 1A). For a T cell to become fully activated or responsive (+ signal) to the antigen it must receive a second costimulatory signal delivered by binding of CD28 to one of two B7 (B7-1 or B7-2) molecules expressed by the APC (Fig. 2A).

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Once activated, T cells enter the CNS and those with the ability to recognize self-antigens expressed by oligodendrocytes become reactivated and initiate an inflammatory response that results in the formation of lesions containing accumulations of numerous immune cells (Fig. 3A) and demyelination (Fig. 3B).

Due to the regulatory role that B7-2 appears to play in regulating CNS autoimmunity, as seen in MS, understanding the structure of B7-2 binding to CTLA-4 on T cells may be critical for the development of therapeutics for MS and other autoimmune disorders. In addition, understanding this ligand/receptor binding may lead to new insights into the structural basis for the signal transduction that occurs intracellularly when B7-2 binds to CTLA-4. We have developed a physical model for the crystal structure of the CTLA-4 receptor binding domain of B7-2 that highlights the amino acid residues in the B7-2 protein shown to play an important role in ligand receptor binding.