Experimental allergic encephalomyelitis (EAE) is an inflammatory disease of the central nervous system (CNS) that resembles human multiple sclerosis (MS). EAE and MS develop when proteins of the myelin sheath that covers axons are released and encounter cells of the immune system such as T lymphocytes. Activation of these lymphocytes will trigger inflammation that destroys the myelin leading to clinical signs that manifest mostly in the form of motion impairment and muscle paralysis. Inactivation of myelin specific lymphocytes is currently viewed as a means to halt immune attack against the brain and reverse the course of disease. In this study we devised an antigen specific approach against EAE and tested its efficacy in an advanced genetic setting, which would better represent the human genetic polymorphism. Therefore, we have created an F1(SJL/J x Bl/6) mouse for analysis of the reversal of compatible as well as “in trans” EAE where the disease is induced by a peptide restricted to one parent and the treatment uses a fusion protein carrying a peptide restricted to the other parent. The results indicate that the effectiveness of the treatment depends on the method of disease induction and the genetic makeup of the mouse.