NIH Award from the National Institute of Neurological Disorders and Stroke

Principal investigator: William John Karpus, pathology, Feinberg School of Medicine

- **Project:** The Role of Chemokines in Autoimmune Encephalomyelitis
- **Start Date:** September 15, 2009
- **Total Award Amount:** $38,940

**How the results of this project will benefit society:**
Experimental autoimmune encephalomyelitis (EAE) is a relapsing-remitting demyelinating disease of the central nervous system (CNS) that serves as an animal model for multiple sclerosis (MS). These studies will help to understand the immunopathogenesis of MS and provide a basis for the development of novel chemokine and chemokine receptor therapies for treatment of ongoing disease.

**The problem the project is trying to solve:**
Disease induction is accompanied by CNS histopathology characterized by mononuclear cell infiltrates, consisting of T cells, macrophages, and B cells. The CNS infiltration by macrophages, T cells, and B cells results in chronic relapsing remitting paralysis similar to what has been seen in a subset of MS patients. One of the major goals of this application is to address the role of chemokines and chemokine receptors in PLP-induced EAE, including determining the chemokines that are important in regulating macrophage, microglia, and dendritic cell trafficking and biology in EAE pathogenesis.

**How the project will work:**
We hypothesize that specific chemokines and chemokine receptors regulate macrophage, microglia, and dendritic cell trafficking in the development and progression of EAE. Furthermore, these cell types can produce chemokines that also play a regulatory role in the progression of EAE. The following specific aims will be addressed to test our hypothesis: 1) Determine the role of macrophage and microglial chemokine receptor expression in the regulation of disease progression. This will be accomplished by testing the contribution of various receptors in CNS macrophage migration and microglia positioning through the use of specific chemokine receptor gene knockouts and small molecular weight antagonists; 2) Determine the role of CCR6 and its ligand CCL20 (MIP-3alpha) in the regulation of dendritic cell trafficking to the CNS during ongoing disease as well as dendritic cell migration to peripheral lymphoid tissue to stimulate autoreactive T cells. The use of CCR6 knockout mice and in vivo anti-CCL20 treatment will be employed to determine the mechanism of this ligand-receptor combination in disease regulation. 3) Determine the role of CCL22 and its receptor CCR4 in the regulation of EAE remission and relapsing disease. This will be accomplished by utilizing CCR4 knockout mice and in vivo anti-CCL22 treatment at appropriate time points to reveal the mechanism of this chemokine in disease progression.

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