Project Summary/Abstract

Lyme disease is a multisystem infection, caused by bacteria of the *Borrelia burgdorferi* species complex and transmitted by *Ixodes* ticks. The initial skin rash may be followed by complications affecting joints, heart, and the nervous system, all of which usually respond well to antibiotic treatment. However, some patients report persistence of chronic pain, fatigue, and difficulties with concentration and memory despite recommended treatment and in the absence of objective evidence of infection. The condition, variably referred to as post-Lyme disease syndrome (PLDS) and chronic Lyme disease, is associated with considerable impairment in the health-related quality of life in the affected patient population. However, few clues to the cause(s) of the symptoms have emerged. Lack of biomarkers to aid in the diagnosis and follow up of patients has also compounded the problem of understanding the disease and finding suitable therpaies. Preliminary data within this proposal show the presence of significant differences in the immune system response between PLDS patients and post-Lyme healthy individuals, including 1) elevated levels of antibodies to nervous system antigens; 2) increased antibody reactivity to specific proteins of *B. burgdorferi*; and 3) differential antibody response towards specific membrane-proximal epitopes of the VlsE protein. The central hypothesis of the proposed experiments is that the humoral immune system response in PLDS patients differs significantly from post-Lyme healthy individuals, which can be utilized to understand the disease mechanism and identify novel biomarkers. Our goal is to investigate the specificity and pathogenic relevance of the observed differential immune response in PLDS, with the following specific aims: 1) To characterize the specificity and pattern of reactivity of the observed antibody response to autoantigens; 2) To determine the specificity and cross-reactivity of the discovered differential immune response to *B. burgdorferi*; and 3) To assess the pathogenic relevance of the observed differential antibody response by examining its effect on neural cell viability and function. Successful completion of the proposed experiments will provide a better understanding of the specificity and significance of the differential immune response in PLDS, yield new insights into the pathogenic mechanism of PLDS that may suggest novel approaches to its treatment or prevention, and offer potentially useful biomarkers for the diagnosis and follow-up of patients.