



2026 HIGH IMPACT GRANT

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Cerebrospinal Fluid Indicators of Cognitive Dysfunction in Patients With Sjögren's Disease

Abstract: Sjögren's disease (SjD) is a heterogeneous disease impacting ~4 million people in the United States that drives a significant reduction in patients' quality of life. According to the Living with Sjögren's patient survey outcomes reported on the Sjögren's Foundation website, ~62-82% of patients experience brain fog and forgetfulness, termed cognitive impairment (CI). Microglia are a brain-resident macrophage population that establish permanent residence during embryonic development and serve as first responders to neuronal damage to restore and maintain homeostasis. However, when perturbed, these cells can contribute to the damage underlying neurodegenerative diseases. Our preclinical work in another autoimmune rheumatologic disease, neuropsychiatric lupus (NPSLE), suggests that there is marked increase in a disease-associated subset of microglia (DAM), originally identified in Alzheimer's disease, that corresponds to NPSLE-associated CI. Our translational work also suggests a detectable increase in a DAM-like subset in cerebrospinal fluid (CSF) of NPSLE patients. While a recent report implicates immune-mediated processes as an underlying mechanism of SjD-associated CI, immune cell-mediated, particularly DAM-mediated, underpinnings, of SjD-associated CI have yet to be defined. Thus, we hypothesize that a pattern of cellular changes, specifically increasing numbers of DAM-like cells, within the CSF of SjD patients will serve as an indicator of SjD-associated CI. CI in SjD remains understudied; the hope is to utilize the infrastructure we have created for NPSLE patient assessment to interrogate underlying mechanisms of this aspect of SjD. The proposed studies herein mark the start of this endeavor.

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