2026 HIGH IMPACT GRANT

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Decoding Neuro-Sjögren's In A Dish: Multi-Neural Subtype Screening And Gut-Derived Extracellular Vesicle Mechanisms On An Innervated Microphysiological Platform

Abstract: Neurological manifestations affect 10–60% of primary Sjögren's Disease (SjD) patients, including small fiber neuropathy, dysautonomia, and cognitive impairment, yet the cellular and molecular mechanisms driving neuro-Sjögren's remain poorly understood. A critical barrier to progress is the absence of controllable, human-relevant models capable of isolating neural responses to SjD-specific serum factors across gut-brain axis (GBA) compartments in real time. Building on Sjögren's Foundation Pilot Grant, our laboratory developed a dual-chip microphysiological system (MPS) incorporating human iPSC-derived neurons and gut organoid epithelium evaluated on microelectrode arrays (MEAs). The platform measures electrophysiological and morphological responses to disease-relevant stimuli with high sensitivity, demonstrated by robust responses to neurotransmitters. We will deploy a two-chip GBA architecture (1) an innervated gut chip (enteric neurons + iPSC-derived organoid epithelium) and (2) a blood-brain barrier (BBB) chip (endothelial cells + astrocytes + forebrain neurons) to pursue three aims: (1) screen SjD patient serum across both compartments to define disease-specific electrophysiological and phenotypic fingerprints; (2) isolate and characterize gut epithelial-derived factors and extracellular vesicles (EVs) under SjD conditions including microbial stimulation; and (3) test whether SjD-conditioned EVs cross the BBB to induce neuroinflammatory changes in forebrain neurons. Patient samples stratified by ESSDAI, autoantibody profile (anti-SSA/Ro, anti-SSB/La), and seronegative status will be provided by clinical collaborator Dr. Sara McCoy. We hypothesize that gut-derived EVs under SjD conditions carry neuroinflammatory cargo that crosses the BBB and induces CNS neural dysfunction, providing the first mechanistic evidence of an EV-mediated gut-to-brain axis in SjD and laying the groundwork for therapeutic target identification and biomarker discovery.

For more information, please contact the Sjögren's Foundation at research@sjogrens.org.