2026 HIGH IMPACT GRANT

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Target-site Pharmacokinetics to Enable Precision Medicine in Neuro-Sjögren's: Getting the Right Dose to the Right Tissue

Abstract: Sjögren's Disease (SjD) is a systemic interferonopathy, and neuro-Sjögren's, particularly small fiber neuropathy (SFN), is a debilitating manifestation associated with substantial morbidity. Therapeutic outcomes remain suboptimal due to a one-size-fits-all dosing paradigm and lack of target-site biological data. Type I/II interferon (IFN) activity drives neuroinflammation and nociceptor sensitization in SFN, yet clinical trials have shown no clinical benefit with hydroxychloroquine (HCQ), despite its known IFN-modulating effects. Given HCQ's lipophilicity and tissue sequestration, a key limitation of these trials was the absence of data on tissue HCQ exposure, which prevents distinguishing true pharmacologic inefficacy from inadequate tissue concentrations. Thus, defining HCQ concentrations in skin—the target-site rich in small nerve fibers—is critical to assess mechanistic plausibility in SjD associated SFN. Tissue level target site pharmacokinetics (TPK) assays were not available to quantify HCQ skin concentrations until we developed a valid liquid chromatography-based method. Building on our team's expertise in TPK in lupus (Garg), IFN signaling in SjD (McCoy), this study will quantify HCQ concentrations and TPK of HCQ in skin biopsies, the site of neuroinflammation, in patients with SjD related SFN in Aim 1. Aim 2 will assess associations between target site HCQ concentrations, IFN gene signatures in skin, and pain responses. Aim 3 will correlate skin and blood HCQ concentrations across current HCQ dosing to enable personalized HCQ dosing. This study will provide the first direct quantification of HCQ at the SFN target site in SjD and a novel link between TPK and neuroinflammatory biology. Results will yield a PK grounded go/no go decision for HCQ in SFN by distinguishing inadequate target site HCQ exposure from true inefficacy. Overall, this work delivers the first target site-mapped framework to optimize dosing of HCQ, and other medicines, in SFN & SjD.