Title: Targeting the Endocannabinoid System for Headache

Migraine is one of the most common, yet under studied, neurological syndrome, contributing to the 116 million Americans (14.2% of US adults) experiencing chronic pain. The complex symptoms of migraine include intense headache, disturbed vision, vomiting, and sensitivity to light, sound and smell. Despite a large prevalence and severe symptoms, there are few anti-migraine therapeutic strategies with moderate effectiveness, limited tolerability, and serious long-term side-effects. The endocannabinoid system (ECS) recently received attention linking attenuation of pain, including migraine, to endocannabinoid signaling. Components of the endocannabinoid system include the bioactive lipid compounds named endocannabinoids (eCB), their metabolic enzymes (e.g., mono- and di-acyl glycerol lipase, MAGL and DAGL, serine hydrolase ABHD6), and their receptors, the CB1 and CB2. Recent clinical experiments support the idea of Endocannabinoid Deficiency (CED) as a potential mechanism of migraine in patients. However biochemical studies providing strong evidence for the potential efficacy of eCBs in migraine are limited. To date, no study has investigated the changes in levels and function of each ECS component in headache. This proposal will tackle this major gap in migraine pathology by elucidating the role of endocannabinoids in migraine, using an integrated approach of analytical chemistry, molecular biology, systems neuropharmacology and functional expression analyses.

Monoacylglycerol lipase and ABHD6 are key enzymes in the hydrolysis of the endocannabinoid, 2-arachidonoylglycerol (2-AG), whereas DAGL is the major enzyme generating 2-AG in the central nervous system. Preliminary data suggest overactivity of MAGL and loss of DAGL expression in regionally distinct areas of the trigeminal pain axis with temporal dynamics following cortical injection of KCl. We postulate that pathogenic remodeling of the 2AG endocannabinoid signaling system plays a critical role in the generation of headache pain that can be targeted therapeutically. Our proposal seeks to validate increasing eCB tone by targeting either MAGL and/or ABHD6 as unique, and not yet studied, targets for migraine therapy using selective inhibition and activation, respectively. Successful completion of this project will enhance our understanding how endocannabinoid system regulates pain in headache disorders and lay the foundation for a comprehensive drug discovery program to develop novel migraine therapeutics.