Development of Brain-Penetrant FABP5 inhibitors to Treat Opioid Addiction

Overview/Abstract

Addiction is a relapsing brain disorder characterized by compulsive drug seeking and total loss of control over drug intake. The past decade has witnessed a catastrophic increase in opioid addiction, culminating in nearly 83,000 overdose deaths this past year alone. The lack of effective treatment options other than replacement therapy has galvanized efforts to discover novel drug targets and develop therapeutics to treat opioid addiction. The critical need for such therapeutics culminated in the launch of the NIH HEAL initiative. The goals of this NIH-wide initiative include identification of novel druggable targets and the development of small molecule therapeutics to treat opioid addiction, with several active RFAs focused on these goals.

Fatty acid binding protein 5 (FABP5) is an intracellular lipid chaperone that delivers bioactive lipids to nuclear peroxisome proliferator-activated receptors (PPARs) including PPARβ/δ. Recent work demonstrates that FABP5 inhibition in the brain attenuates drug self-administration, positioning FABP5 as a promising target for the development of small molecular inhibitors to treat drug addiction. In this application, we leverage our combined expertise in drug discovery and addiction biology to identify novel brain penetrant FABP5 inhibitors bearing distinct scaffolds. Iterative chemical synthesis will be employed to develop more potent and selective analogs with improved membrane penetration profiles. Promising compounds will be advanced to efficacy assessments using an opioid self-administration paradigm in rats. The funding provided by this seed grant will provide us with the opportunity to obtain key preliminary results to submit a large multi-PI R01 proposal to NIDA and/or the HEAL initiative in FY25-26.