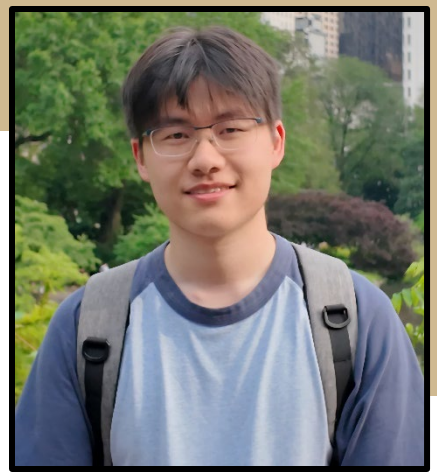
ORGANIC SEMINAR



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"Receptor-Mediated Delivery of DGAT2 Modulators to Lipid Droplet–Laden Microglia in Alzheimer's Disease"

Lipid droplet (LD) accumulation in plaque-associated microglia is an emerging hallmark of dysfunction in Alzheimer's disease (AD). We identified elevated triacylglycerol (TAG) levels and upregulation of diacylglycerol O-acyltransferase 2 (DGAT2) in LD-laden microglia proximal to amyloid β (Aβ) plaques. Ex vivo DGAT2 inhibition reduced LD burden and restored Aβ phagocytosis in young 5xFAD microglia; however, systemic administration to the brain failed to achieve comparable in vivo efficacy, revealing a delivery–target engagement disconnect at plaque-associated microglia. With aging, DGAT2 protein levels further increase, rendering enzymatic inhibition insufficient. To overcome this target-expression barrier, we developed a DGAT2-targeting PROTAC that degrades DGAT2, reduces LD accumulation, improves microglial function, and decreases plaque burden and neuritic dystrophy in aged 5xFAD mice. To address both exposure limitations and systemic liability, we engineered receptor-mediated, microglia-directed DGAT2 modulators. Bifunctional and trifunctional small molecules couple a microglial-enriched receptor ligand to either a DGAT2 inhibitor or degrader, enabling preferential uptake in plaque-associated microglia. These targeted constructs reduce Aβ-induced LD accumulation in vitro and restore microglial phagocytosis and plaque pathology in vivo. Together, this work establishes a modular chemical platform for selective DGAT2 modulation to rejuvenate lipid-dysregulated microglia and therapeutically counteract neurodegeneration in AD.