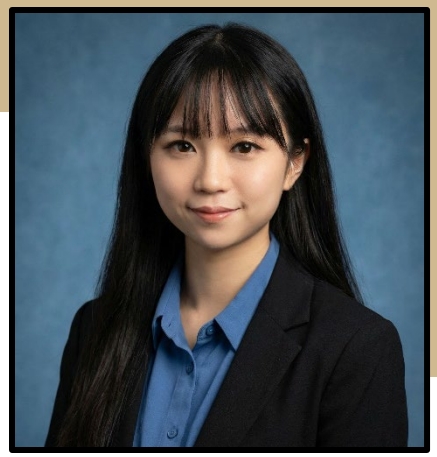
BIOCHEMISTRY SEMINAR



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"Development of a folate targeted all-in-one trivalent cancer vaccine"

Therapeutic cancer vaccines represent a promising strategy to generate tumor-specific T-cell immunity in solid tumors. Genetically mutated tumors can generate neoantigens that serve as potential T-cell targets; however, effective immune responses depend on productive antigen presentation and dendritic cell–mediated T-cell priming. Current cancer vaccine platforms face key limitations. Peptide-based vaccines often fail to reliably deliver antigen and activation signals to the same dendritic cell in vivo, resulting in inefficient T-cell priming. In contrast, autologous dendritic cell vaccines enforce correct priming biology but require complex, patient-specific ex vivo manufacturing, limiting scalability and rapid deployment. In this work, we develop a dendritic cell–targeted trivalent vaccine that co-delivers targeting, antigen, and activation signals within a single construct. By directing vaccine uptake to dendritic cells and promoting coordinated delivery of priming signals in vivo, this approach is designed to improve the efficiency of neoantigen-specific T-cell priming without the need for ex vivo cell manipulation. We show that folate receptor-β is expressed on both murine and human dendritic cells, supporting a conserved targeting strategy. Vaccination induces antigen-specific T-cell expansion and leads to significant tumor growth suppression in vivo. Together, these results demonstrate a scalable, DC-targeted vaccine strategy that addresses key biological and practical limitations of existing cancer vaccine platforms.

BIOCHEMISTRY SEMINAR

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"Targeted DGAT2-Degradation as a Strategy to Reverse Lipid Droplet-Driven Microglial dysfunction in Alzheimer's disease"

Alzheimer's disease (AD) features amyloid-β (Aβ) plaques and profound microglial dysfunction, including impaired phagocytosis. We previously showed that Aβ drives lipid droplet (LD) formation in microglia; LD-laden microglia accumulate near plaques in human AD brain and 5xFAD mice and exhibit compromised phagocytic activity, accompanied by depleted free fatty acids and elevated triacylglycerols (TGs). We identified diacylglycerol acyltransferase 2 (DGAT2), which converts fatty acids into TGs, as a key regulator of pathological LD accumulation. Although DGAT2 enzymatic inhibition improves phagocytosis and reduces LD burden ex vivo in early-stage models, DGAT2 protein progressively accumulates with aging and disease progression in vivo, and catalytic inhibition fails to resolve LDs in late-stage contexts, suggesting a stabilizing role for DGAT2 on LDs. To address this, we developed a DGAT2-targeted PROTAC to degrade accumulated DGAT2 protein. Across primary microglia, aged wild-type mice, and aged 5xFAD mice, DGAT2 degradation reduces LD burden, restores microglial morphology toward ramified states, enhances Aβ phagocytosis, and attenuates plaque-associated pathology and dystrophic neurites. These findings define stage-specific DGAT2 biology and support targeted DGAT2 degradation as a therapeutic strategy for late-stage AD and aging, where biomarkers may enable patient stratification.