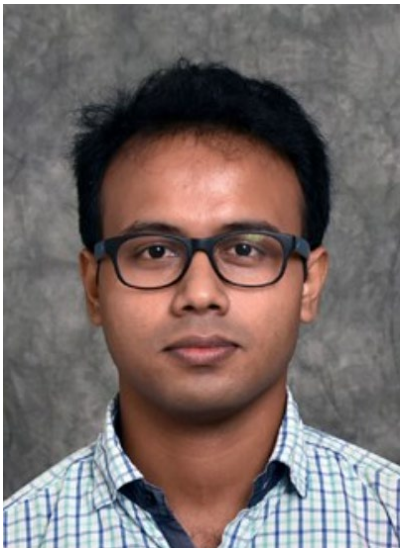
ORGANIC SEMINAR

Tuesday, November 28, 2023

4:30 PM, WTHR 104



"Small Molecule Degraders of Cell Surface and Intracellular Membrane Proteins for Immunomodulation: Cancer and Neurodegeneration Case Studies"

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Abstract: Targeted protein degradation (TPD) has gained considerable attention in recent years due to several advantages over small molecule inhibitors. Proteolysis targeting chimeras using ubiquitin-proteasomal system is one of the most popular TPD strategies that complements lysosomal degradation strategies to degrade intracellular proteins, typically using bifunctional small molecule degraders. Recently, large biomolecular and antibody conjugates have been developed for degrading membrane and extracellular proteins in cells, such as lysosomal targeting chimeras (LYTACs) and genetically encoded LYTACS, among several others. However, larger molecules have limitations to penetrate solid tumors. We have designed and synthesized bifunctional small molecule degraders for programmed death-ligand 1 (PD-L1), a transmembrane protein ligand for the immune checkpoint programmed cell death 1 (PD-1). PD-L1 is highly expressed on several tumors, such as triple negative breast cancer (TNBC), non-small cell lung carcinoma, renal cancer and known to suppress cancer killing immune cells via interaction with PD-1 on T-cells. In addition, PD-L1 is also present on macrophages in the tumor microenvironments leading to further immune suppression and acquired resistance to anti-PD-1 therapy is associated with upregulation of alternative immune checkpoints, thereby reducing anti-tumor efficacy. We have designed and synthesized bifunctional small molecules as PD-L1 degraders with different recruiters and linkers guided by computational studies with known PD-1/PD-L1 structures to show both cell surface and total protein degradation in human TNBC cells. In a separate project, we also developed small molecule conjugates to degrade an intracellular integral membrane protein of the endoplasmic reticulum with unknown 3D structure, namely Diglyceride acyltransferase 2 (DGAT2). Recently, our lab identified DGAT2 as a new target for combating Alzheimer's disease. Specifically, DGAT2 catalyzes triacylglycerol (TAG) synthesis using diacylglycerol and fatty acyl CoA as substrates. The accumulation of TAGs, mechanistically linked to DGAT2, results in "fat" or lipid droplets (LDs) inside the cells. Our lab showed that microglial cells (resident immune cells in the brain) accumulate LDs in the postmortem brains of human patients and in mouse model (5xFAD) of Alzheimer's disease and that the LD accumulation is driven by amyloid-beta (Aβ) – hallmark of Alzheimer's disease – via DGAT2 pathway. Further, these LD-laden microglia have phagocytic defect and spared Aβ thereby affecting plaque accumulation and clearance. Inhibiting DGAT2 reduces the amount of TAG in the brain, which in turn reduces LDs and restores microglial ability to phagocytose Aβ. However, commercially available DGAT2 inhibitors were unable to reduce LD load in older 5xFAD mice. Using AlphaFold's models of DGAT2, we designed and identified sites to synthesize bifunctional DGAT2 degraders that resulted in reduced LDs in mouse primary microglial cells and enhance phagocytosis of Aβ plaques *in vivo* in aged 5xFAD mice. Our approach shows a framework to develop bifunctional small molecule degraders for membrane proteins to potentially combat immune dysregulation in chronic diseases.

PURDUE UNIVERSITY

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