COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

## Pharmaceutical Sciences Seminar Series

Wednesday, November 15, 2023
4:00pm
NCRC Building 10 Research Auditorium
Zoom

**"Evaluation of synthetic high-density lipoprotein and mimetic micelle composition for the treatment of cardiovascular disease"**

Presented by:

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Abstract: Nearly 17.9 million people die every year from cardiovascular-related diseases, which accounts for 31% of all deaths worldwide. Endogenous high-density lipoproteins (HDL) are natural cardioprotective particles that have been shown to reduce cardiovascular related risks. Therefore, synthetic high-density lipoproteins (sHDL) and HDL mimetic nanoparticles have been synthesized to mimic the structure and function of endogenous HDL. In these projects, we aim to investigate the therapeutic potential of both sHDL and HDL-mimicking micelles for protecting endothelial function and treating atherosclerosis, respectively, and understand how the lipid composition affects the therapeutic activity and stability of the particles in vitro and in vivo.

In project 1, we synthesized a library of micelles composed of different phosphatylcholine lipids and ratios of phosphatylcholine to PEGylated lipids. We tested these micelles in vitro and in vivo to better understand how lipid properties influence the physiochemical activity and therapeutic potential of the particles. Overall, we found that the composition of micelles affects the particle's in vitro anti-atherosclerotic properties, including reduction of pro-inflammatory cytokine release, cholesterol crystal dissolution and cholesterol efflux capacity, as well as it's pharmacokinetic parameters and cholesterol mobilization in vivo. Micelles composed of lipids in the liquid crystalline phase at physiological temperature, as well as micelles containing less PEGylated lipid, had more potent effects on cytokine levels in vitro, while more PEGylated micelles had a longer circulation half-life and mobilized more cholesterol in vivo. Therefore, a fine balance in lipid composition must be achieved to obtain an optimized micelle that shows promising therapeutic activity with favorable pharmacokinetics.

In project 2, we wanted to test the therapeutic potential of sHDL in protecting endothelial function. sHDLs were prepared using 22A, an ApoA-1 mimetic peptide, and different phospholipids. In lipopolysaccharide (LPS) activated human umbilical vein endothelial cells (HUVECs), addition of sHDLs decreased the expression of adhesion molecules, including VCAM-1, ICAM-1, and E-selectin. Addition of DMPC-sHDLs to HUVECs lead to an increase in nitric oxide (NO) levels measured in cell media. Furthermore, DMPC-sHDL treatment reduced Evans blue dye leakage through the blood brain barrier in a traumatic brain injury murine model, suggesting positive effects of sHDLs on endothelial integrity. On the basis of these findings, further studies will need to be completed in order to elucidate the mechanisms of sHDL protection on the endothelium and to determine the optimal composition of sHDL that can improve endothelial function.