COLLEGE OF PHARMACY
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UNIVERSITY OF MICHIGAN

Department of Pharmaceutical Sciences
Ph.D. Dissertation Defense Seminar

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1:00PM
NCRC Building 10 G063/G064
Zoom Meeting: https://umich.zoom.us/j/91718606951
Passcode: 01222024

"Title: Evaluation of Lipid-Based Nanoparticles for the Treatment of Cardiovascular Disease"

Presented by:

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Abstract: Nearly 18 million people die every year from cardiovascular disease, which accounts for 32% 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) have been synthesized to mimic the natural cardioprotective behaviors of endogenous HDL. In this work, we investigated the therapeutic potential of both sHDL and HDL-mimetic micelles for improving endothelial function and treating atherosclerosis, respectively, and sought to understand how the lipid composition affects the activity of particles in vitro and in vivo, and the remodeling of the particle in the presence of other endogenous lipoproteins contained in human serum. In project 1, we examined how the phospholipid composition of HDL-mimicking micelles impacts the atheroprotective properties of the nanoparticle. While all micelles showed similar cholesterol efflux capacities, the lipid composition affected the anti-inflammatory activity and cholesterol crystal dissolution capabilities of the particles in vitro and impacted the pharmacokinetics and cholesterol mobilization in vivo. Therefore, a fine balance must be achieved to determine a micelle composition with optimal therapeutic benefit and favorable pharmacokinetics. In project 2, we evaluated the endothelial protective properties of sHDL. We found that DMPC-sHDL has protective effects on the endothelium and promotes proper endothelial function through reduction of adhesion molecules expression and partial restoration of eNOS expression in human umbilical vein endothelial cells (HUVECs) challenged with LPS and TNF-α, increasing nitric oxide production in HUVECs, and decreasing Evan blue dye leakage into the brain after traumatic brain injury, suggesting potential positive effects on endothelial barrier integrity. In project 3, we evaluated the effect of lipid composition on the stability and remodeling of sHDL in human serum containing other endogenous lipoprotein populations. Due to the dynamic nature of endogenous HDL and the exchange of components with LDL and VLDL through transfer proteins and enzymes, assessing how sHDLs remodel in human serum is vital to understanding the stability and pharmacokinetics of the nanoparticle as a stand-alone therapy or drug delivery carrier. By tracking the movement of sHDL components to different lipoprotein populations using SEC and LC-MS analysis, we found that sHDLs formulated with POPC remodeled to the largest extent, while sHDLs formulated with DSPC stayed the most intact after 24 hours of incubation with human serum. Our studies highlight the importance of considering lipid composition and remodeling kinetics when developing sHDLs as therapeutics. In summary, we found that the lipid composition of HDL-mimicking micelles and sHDLs affects the particle's overall activity, pharmacokinetics, stability, and remodeling, making composition a crucial factor to consider when optimizing lipid-based nanoparticles as therapeutics.