COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar Series

Wednesday, March 1, 2023
4:00pm
NCRC Building 10 Research Auditorium
Zoom

"Synthetic high-density lipoprotein loaded with oxylipin for the treatment of arterial thrombosis"

Presented by:

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Abstract: Cardiovascular disease remains the main cause of death in the world, where platelet activation plays a primary role in the pathophysiology. Thus, inability to regulate platelet function leads to atherothrombotic events resulting in myocardial infarction and stroke. Yet, currently available antiplatelet agents inhibit platelet aggregation at the great risk of bleeding. In efforts to find a better target, our collaborator previously identified the 12-lipoxygenase (12-LOX) derived DGLA lipid product (oxylipin), 12(S)-hydroeicosatetraenoic acid (12(S)-HETrE), to potently inhibit platelet activation in vitro and to significantly prevent occlusive thrombus formation in vivo without compromising hemostasis. High-density lipoproteins (HDL) are well known for its cardioprotective effects which are attributed to its ability to enhance reverse cholesterol transport; however, it also displays antioxidant, antiapoptotic, anti-inflammatory, and antithrombotic effects. Because of the complexity of HDL structure and the variety of bioactive protein and lipid components, HDL possesses a wide range of biological functions. We have previously used synthetic high-density (sHDL), as a carrier of the 12-LOX inhibitor ML355. We found that sHDL alone can modulate platelet activity, be uptaken by platelets, and inhibited platelet aggregation in vitro and thrombus growth in vivo. Therefore, in this present study we exploit the innate antithrombotic properties of sHDL and increase its inhibitory effects by loading the bioactive lipid 12-HETrE. Our optimized 12-HETrE-sHDL formulation consists of apolipoprotein A-I (ApoA-I) mimetic peptide, 22A, and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) at a 1:2 w/w ratio, containing 12-HETrE at 2.3% w/w loading. Studies on sHDL alone determined that nanoparticles made with DMPC phospholipid showed the greatest inhibitory effects on platelet aggregation in vitro and this was dose dependent. Encapsulating 12-HETrE in DMPC based sHDL led to heightened antiplatelet effects, where we showed that 12-HETrE-sHDL potently and dose-dependently inhibited platelet aggregation in vitro after stimulation with both thrombin and collagen. We demonstrated that sHDL prevents platelet activation and alpha granule secretion as measured by flow cytometry using markers PAC1 and CD62P, respectively. Further studies will focus on investigating the pharmacokinetics of 12-HETrE-sHDL, examining the antithrombotic effects of 12-HETrE-sHDL in vivo, and determining the mechanism by which sHDL modulates platelet activity. This study concludes that 12-HETrE-sHDL can serve as a novel therapeutic approach to treat occlusive thrombosis.