



Pharmaceutical Sciences Seminar

Wednesday, March 31, 2021

Join Zoom Meeting

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4:00-5:00 pm

“Optimization of HDL Mimetic Micelle Composition for the Treatment of Atherosclerosis”

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. Atherosclerosis is a serious health complications underlying heart attack and stroke, the fatal diseases causing over 80% of these deaths. Atherosclerosis is a chronic inflammatory disease characterized by the build-up of lipids, inflammatory cells and other substances on the arterial wall, known as plaque, obstructing the arterial lumen. Although synthetic high-density lipoproteins (sHDL) have been shown to possess anti-atherosclerotic activities, the purification of apolipoprotein A-I (ApoA-I) from human plasma, and synthesized recombinant ApoA-1 is costly and difficult. Due to this fact, lipid nanoparticles, such as micelles, have been proposed as an ApoA-I-free alternative to sHDL. Our preliminary studies show that the phospholipid composition of sHDL can affect its physiochemical activity and stability, therefore, we have synthesized a library of micelles composed of PEGylated 2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG) and varying phosphatidylcholine (PC) lipids in order to study this phenomenon in micelles. Of these PC lipids, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1,2-dimyristoyl-sn-glycero-3-phosphorylcholine (DMPC) exist in the liquid crystalline phase and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) lipids exist in the gel ordered phase at physiological temperature, which can affect the accessibility of the lipids in the particle to interact with proteins, receptors and other endogenous molecules in the body. The micelles range from 14-16 nm in diameter in size. We found that POPC and DMPC micelles reduce levels of pro-inflammatory cytokines, TNF- α and IL-6, and reduce nuclear factor- κ B (NF- κ B) to a larger extent in macrophage cells than micelles composed of DPPC and DSPC. We also found that more cholesterol crystals were dissolved in the presence of POPC and DMPC micelles. On the contrary, our *in vivo* endotoxemia study shows that DPPC and DSPC micelles reduces TNF- α levels to a greater degree. Further pharmacokinetic studies show that micelles composed of DPPC and DSPC mobilize more cholesterol than POPC and DMPC micelles and have a larger AUC. On the basis of these findings, more studies need to be completed in order to determine an optimal micelle composition that is therapeutically efficacious for the treatment of atherosclerosis.

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