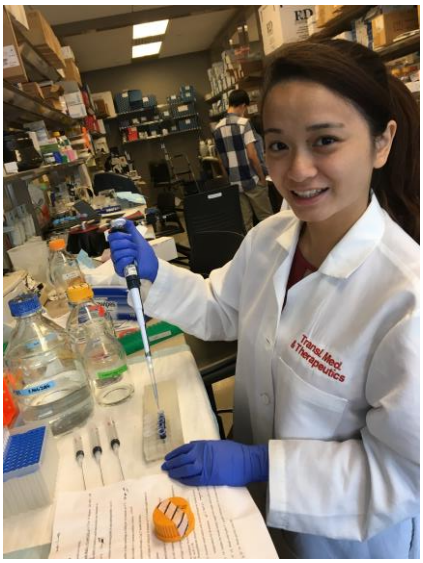

Gold-based Nanoparticles for Accessing HDL-induced Anti-inflammatory Signaling Pathways in Atherosclerosis
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Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality in the US and in the world. ASCVD is promoted by low-density lipoprotein (LDL). LDL particles penetrate through the endothelial layer in the intima-media of the coronary arteries. LDL-cholesterol then activates endothelial cells to begin releasing pro-inflammatory signaling molecules and expressing surface proteins that allow monocytes to attach and enter the arterial wall. Once in the sub-endothelium, monocytes differentiate into macrophages, which engulf LDL and store the LDL-cholesterol as cholesterol ester in lipid droplets and become 'foam cells', a hallmark of atherosclerosis. Unmanaged atherosclerosis may eventually cause occlusion of the artery and ischemic injury to the heart muscle. The role of HDL in atherosclerosis is thought to be two-fold: first, to transport cholesterol from the arterial macrophages to the liver; second, to down-regulate inflammation. However, a recent study from Dr. Rader's lab showed that HDL-cholesterol is pro-inflammatory, just as LDL-cholesterol. My goal was to develop a HDL-inspired ASCVD therapeutic that down-regulates inflammation, but does not take up cholesterol.

The HDL-inspired nanodevice that I created consists of short peptides that mimic apolipoprotein AI (apoAI), the main protein of HDL, and a gold particle on which the peptides are immobilized. HDL consists of several apoAI molecules associated with phospholipid and cholesterol. We hypothesized that the peptides will bind ABCA1, one of the key HDL receptors, and induce anti-inflammatory signaling through the STAT3 and other pathways, but, being attached to a gold particle, will not be able to undergo conformational changes and rearrangements required to take up cell cholesterol and become a cholesterol-rich HDL particle. I synthesized the peptides and then I visited the Cormode Lab to gain experience with producing gold particles and conjugating them with peptides. Electron microscopy was used to confirm the presence of the peptide on the

surface of the gold nanoparticles. Through cellular cholesterol efflux assays, I confirmed that free-peptides are efficient at taking up cell cholesterol and forming cholesterol-rich HDL. But immobilized peptides had severely reduced cholesterol uptake. Next, I cross-linked ABCA1 and the nanodevice to show that immobilized peptides bind ABCA1, but the results were inconclusive. Right now, I am investigating with western blotting whether the STAT3 anti-inflammatory pathway is accessed by the nanodevice. Regardless of the final outcome, my work will contribute to a better understanding of the potential of HDL-inspired therapeutics in treatment of ASCVD. My findings may also form a basis for other projects into the role of HDL in alleviation of inflammation in ASCVD.

Throughout the project, I was able to learn and practice a variety of techniques, such as gold nanoparticle synthesis, sterile cell culture, cholesterol efflux assays, western blotting, and electron microscopy. In addition, I worked with many specialists in different fields, exposing me to interdisciplinary work. I am grateful for the Vagelos Undergraduate Research Grant allowed me this opportunity; the skills I have gained will continue to support my interest in research in the field of bioengineering.