Nanoparticle Approach to Inhibiting Endothelial Glycocalyx Dysfunction Related to Atherosclerosis

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Introduction: Cardiovascular diseases (CVD) are the number one cause of death in the world, with more deaths than all forms of cancer combined[1, 5]. Of the numerous CVD, many are caused by atherosclerosis, the buildup of plaque in the arteries which leads to complications such as hypertension and stenosis. The treatments for atherosclerosis include adding a stent and physically bypassing the affected area as well as using statin type drugs to lower cholesterol levels in the blood. Few approaches target the protective glycocalyx component of the blood vessel. Glycocalyx is a thin layer that lines the inner blood vessel wall, forming a barrier between the lumen and endothelial cells. It is composed of glycoproteins and glycosaminoglycans, and responds to flow conditions[1]. Glycocalyx is in a degraded or damaged state for patients with cardiovascular disease. The rapid development of nanotechnology in the last few decades has brought on countless new approaches including biomaterials, nanoparticle drug carriers, and bio-imaging. Furthermore, there is substantial research being conducted on modifications and functionalization of said nanoparticles, allowing for simultaneous specific targeting and knock-out or knock-in capability. My research goal is to use state-of-the art nanotechnology to promote proper glycocalyx function that can deter atherosclerosis and CVD development.

Aims: To achieve my goal, I will explore the following three points:

- Effects of selenium nanoparticles on glycocalyx
- Conjugation of drugs and antibodies onto nanoparticles
- Dose dependency and toxicity of nanoparticles

Methods: Endothelial cells that express robust glycocalyx will be cultured under flow conditions then stained with osmium tetroxide to assess glycocalyx characteristics under electron and confocal microscopy. Damaged glycocalyx will be modeled through degradation using enzymes such as hyaluronidase. Selenium nanoparticles of various sizes will be synthesized to show size and concentration dependency of uptake and transport through the glycocalyx, as well as effects on the glycocalyx conditions. Addition of sulodexide to the nanoparticles should promote glycocalyx growth, and specific targeting of atherosclerotic plaque can be achieved by conjugation of CREKA peptides to target clotted plasma proteins[6]. Experiments will focus on promotion of glycocalyx recovery through the use of nanoparticles.

Significance: The research addresses a significant concern when developing nanoparticle drug delivery systems for cardiovascular applications. The drug carrier must show potential in *in vitro* testing before money and effort are spent on animal models – however, the *in vitro* results may not be of significance due to the incorrect modeling of the glycocalyx.

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