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Title of project: Improving Fatty Acid Flux to Restore HDL's Protective Function with Obesity and Diabetes

ABSTRACT

Obesity and low cholesterol levels in high-density lipoprotein (HDL) significantly increase the risk for coronary heart disease (CHD). Unfortunately, drugs that increase HDL cholesterol have failed to reduce CHD risk. Despite the focus on HDL cholesterol, proteins are 50% of the mass of HDL, and contribute to the main functions of HDL: **1)** to reduce inflammatory signals and, **2)** to promote cholesterol delivery to the liver for secretion as bile, a process known as reverse cholesterol transport (RCT). An emerging paradigm is that obesity influences HDL protein composition, and the HDL can become inflammatory and atherogenic. We are missing the critical link between metabolism changes in obesity and the pathways that control HDL's function. The goal of this application is to combine the expertise of Dr. Stafford's lab from Vanderbilt and Dr. Nielsen's lab at Aarhus University Hospital to discover the pathways by which obesity and fatty liver disease impair HDL's protective functions.

Using animal models Dr. Stafford's lab has developed quantitative proteomics of HDL and functional assays of HDL's anti-inflammatory and RCT capacity to define the pathways that impact HDL function with obesity. They've shown that with obesity, increased delivery of free fatty acids (FFA) to the liver results in non-alcoholic fatty liver disease (NAFLD) and re-programming of the hepatic pathways that regulate expression of HDL-associated proteins that impact HDL function. In humans, Dr. Nielsen's lab has developed state-of-the art stable isotope and PET tracer approaches to understand the kinetics of FFA metabolism with obesity. With this approach they've demonstrated that upper body obesity and type 2 diabetes (DM2) increase FFA flux to the liver and drive NAFLD and atherogenic dyslipidemia.

Our overarching hypothesis is that excess delivery of FFA to the liver with obesity leads to fatty liver and impairments in HDL's anti-inflammatory and cholesterol efflux capacity. We will define the therapeutic significance of this pathway by assessing HDL function in humans with obesity and NAFLD using two strategies to reduce FFA flux to the liver, exercise and treatment with an SGLT2 inhibitor. A major goal of this project and collaboration is to foster trans-institutional collaboration, teaching and training opportunities.