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Title of project: Identification and Validation of Non-Invasive Biomarkers for Non-Alcoholic Steatohepatitis (NASH).

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), and the more necro-inflammatory and progressive steatohepatitis (NASH) is an emerging disease, highly associated with features of the metabolic syndrome (obesity, type 2 diabetes/insulin resistance, dyslipidemia). NASH can further progress to cirrhosis and liver failure. In the near future NASH will become the primary reason for a liver transplant in the US. A major challenge for understanding the epidemiology and pathophysiology of NASH, as well as clinical trial enrollment and therapeutic efficacy assessments, is that NASH is currently diagnosed exclusively via a liver biopsy. Identification of a circulating marker, or panel of markers, that highly predict NASH or the progression of NASH relative to disease pathogenesis is paramount. NASH, and are not currently considered gold standards by regulatory agencies. As fibrosis is the strongest predictor of mortality associated with NASH a circulating marker of hepatic fibrosis that correlates with NASH and identifies rapidly progressing liver damage would be of extremely high value. We have a variety of therapeutics that are effective against NAFLD/NASH in terms of decreasing the steatosis and halting fibrosis. However, the mechanism of action (particularly at the molecular level) by which these agents alleviate the diseased state is not well understood. A phosphoproteomics analysis and evaluation of other post-translational modifications of protein relative to the pathogenesis of NAFLD/NASH and reversal by therapeutics, together with validation studies, would gain valuable insight into signaling pathways and protein regulation in hepatocytes key to NAFLD/NASH pathogenesis and treatment. This approach should also be insightful for NAFLD/NASH biomarker identification and analysis.