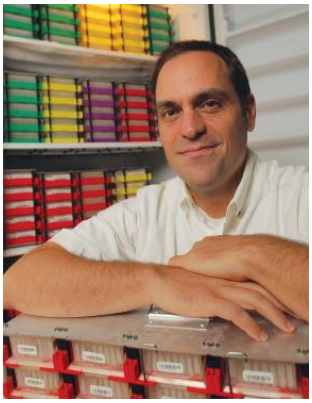

Jonathan Z. Sexton, Ph.D.

Title: Discovery and Development of Novel Activators of AMP-Activated Protein Kinase as Potential Therapeutics for Fatty Liver Disease and NASH.

Western diet and lifestyle has led to an epidemic in obesity related disorders including metabolic syndrome and type 2 diabetes that causes a progression of chronic liver disease that starts as non-alcoholic fatty liver disease with progression to nonalcoholic steatohepatitis (NASH) and cancer. Maintaining cellular energy is a basic biological need mediated in part through AMP-activated protein kinase (AMPK), therefore controlling cellular energy metabolism can play a role in treating metabolic disorders including chronic liver disease. Indeed, AMPK regulation has been a widely accepted pharmacological target with a tremendous amount of discovery research that has produced no major clinical successes to date. To identify drugs that modulate AMPK activity independent of the canonical ATP-binding pocket found throughout the kinome, we designed a robust fluorescence-polarization high-throughput screening assay biased t owards the identification of molecules that bind the gamma regulatory subunit of AMPK. High throughput screening of 56,000 compounds (average Z'-prime=0.7) yielded 76 dose-responsive hits that were counter-screened in a cell-based AMPK activation assay and a novel high-content multivariate hepatic steatosis model. 12 dose-responsive actives were demonstrated to bind AMPK, increase phospho-AMPK, regulate downstream effectors (ACC, Raptor) and clear excess lipid accumulation in the hepatic steatosis model. Two exemplars from different chemotype clades were selected for *in vivo* proof of concept studies in the C57-high fat (60%) diet-induced obesity model. Both tested compounds significantly increased glucose disposal during oral glucose tolerance testing and were found to dramatically reverse hepatic steatosis in H&E stained liver sections. Thus, this AMPK discovery platform has demonstrated its utility to discover compounds that allosterically activate AMPK via the gamma regulatory subunit with high clinical translational potential. Current efforts are focused on medicinal chemistry optimization of three main scaffolds with 46 current active compounds.

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