Dr. Henry Ginsberg

Summary:
The prevalence of cardiometabolic disorders characterized by an atherogenic dyslipidemia (increased plasma triglyceride (TG) levels hypertriglyceridemia), low levels of high density lipoprotein (HDL) cholesterol (C), and small cholesteryl ester depleted-TG enriched low density lipoproteins (LDL)), insulin resistance (IR) and type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD) or its downstream complication, nonalcoholic steatohepatitis (NASH), have increased over the past 25 years. Dr. Ginsberg, has led an NHLBI funded laboratory for more than 40 years, progressing from *in vivo* studies on the regulation of plasma lipoprotein levels in humans, including the role of IR, to studies of the assembly and secretion of very low density lipoproteins (VLDL) in cultured liver cells, to mouse models of NAFLD, including some with IR. Dr. Ginsberg and his collaborators are uniquely positioned to conduct fully integrated studies of the pathophysiology of dyslipidemia and NAFLD at the genetic, molecular, and whole body levels in cultured cells, mice, and humans. The proposed program is tripartite, with clear opportunities for merging of each major area of investigation. They include: ***Regulation of the assembly and secretion of VLDL assembly and secretion.*** During the past 25 years, the Ginsberg laboratory produced a body of work demonstrating the novel biology of apoB and provided insights needed to identify potential targets for modulating the secretion of atherogenic lipoproteins from the liver. Based on recent exciting data, we will focus experiments in hepatoma cells on ways to maximize the secretion of spare apoB and or the loading of TG onto apoB targeted to secretion. ***Mechanisms for the maintenance of hepatic lipid homeostasis.*** We plan a series of experiments to determine **(a)** the mechanism for lipid induced ER stress and **(b)** the signaling pathway between ER stress and ER autophagy. ***Detailed phenotyping of human mutations affecting plasma lipoprotein metabolism with or without effects on hepatic lipid homeostasis.*** The studies proposed in this section will combine an area in which Dr. Ginsberg has been a leader for several decades, tracer kinetic studies of lipoprotein metabolism, with an area completely new to the Ginsberg laboratory, iPSC-derived hepatocytes. This component of our future work will be carried out in collaboration with a recent arrival at Columbia, Dr. Kam Leong, Samuel Y Sheng Professor of Biomedical Engineering and a member of the National Academy of Engineering, a leader in the field of regenerative medicine and biomaterials. We will study individuals with single gene defects the are associated with NAFLD and hypolipidemia; hypolipidemia without NAFLD, dyslipidemia with NAFLD. **No laboratory has, in the same individual, defined the pathophysiologic effects of mutations in genes affecting lipid and lipoprotein metabolism at both the level of the hepatocyte and the whole body.**