

Dr. Gisette Reyes Soffer

Lipoprotein (a) [Lp(a)] was identified by Kare Berg in 1963, but much remains to be learned about this unique lipoprotein, which is an independent risk factor for cardiovascular disease (CVD). Hoff et al demonstrated Lp(a) within atherosclerotic lesions 30 years ago, and in the JUPITER trial (a high dose statin trial), Lp(a) was a significant determinant of residual CVD risk in subjects receiving rosuvastatin. Lp(a) levels have been difficult to alter, but newly approved and developing drugs lower Lp(a) plasma concentrations significantly. Lp(a) is comprised of apolipoprotein (a) [apo(a)] covalently bound to apolipoprotein B [apoB], and both components Lp(a)-apo(a) and Lp(a)-apoB, are implicated in the development of CVD. Although it is closely related to LDL biochemically, Lp(a) has been found in varying density fractions of apoB isolated via ultracentrifugation. Many studies have highlighted the importance of Lp(a) in disease, however, *key questions remain about the assembly of Lp(a) (where and how the apo(a) and apoB100 particle bind) within the liver and/or plasma and how it is removed from the circulation.* **Our laboratory uses stable isotopes to examine the clearance and production of lipoproteins in humans.** Recent advances in mass spectrometry has allowed us to use Lp(a) isolated from plasma by immunoprecipitation directed against apo(a) to examine clearance and production of the whole Lp(a) particle, its apo(a) and apoB components, and isoforms of apo(a). Lp(a) levels are largely determined by variation in KIV-type 2 repeats (Isoforms). The current application addresses existing gaps in Lp(a) metabolism and examines relationships between Lp(a) metabolism and isoform size. *We have two aims:*

Aim 1: We will isolate Lp(a) from plasma by immunoprecipitation (IP) and determine the fractional clearance rates and secretion rates of Lp(a)-apo(a) and Lp(a)-apoB using primed constant infusion of stable isotopes and newly established mass spectrometry (MS) methods. We will also determine the number of KIV-2 repeats in all subjects. We will enroll individuals with low and high Lp(a) concentrations (N=20, Lp(a) 15 -30nmol/L and N=20, Lp(a) 75-350nmol/L). We have developed comprehensive models to allow characterization of pathways of Lp(a) metabolism.

Aim 2: We will examine 15 subjects from Aim 1 with two detectable apo(a) isoforms. After IP of Lp(a), we will isolate two apo(a) isoforms (each will be linked to apoB100) via non-denaturing electrophoresis and determine the FCRs of Lp(a)-apo(a) and Lp(a)-apoB within the isolated complexes via MS. As improved therapeutic approaches to Lp(a) move forward, it is imperative that we have a detailed and precise understanding of the factors that regulate Lp(a) levels and if the KIVtype 2 repeats have an effect on metabolism of this cardiovascular risk factor.