Dr. Nir Uriel

Project summary: This proposal details a comprehensive 5-year training program for my career development in academic Cardiovascular Medicine. I have completed advanced training in Heart Failure (HF) and Transplant at Columbia University Medical Center. I now plan to embark on a mentored research program to obtain additional scientific training necessary for an independent academic career focused on translational research in congestive HF. Accordingly, throughout the period of this award, I will receive formal training in the design and conduct of medical research and gain in-depth experience in exercise physiology and fuel metabolism in patient with chronic HF. Drs. Ulrich Jorde and Henry Ginsberg will mentor my scientific career development. Dr. Ulrich Jorde has a strong NIH track-record with emphasis on cardiovascular pharmacology and physiology in patients with congestive HF. His particular expertise is in conducting mechanistic studies centered on exercise physiology and neurohormonal activation, and his laboratory's most recent focus is fuel metabolism in HF. Dr. Jorde is also a renowned expert in the medical aspects of left ventricular assist device therapy. Dr. Henry Ginsberg, the co-mentor, is an internationally recognized expert in lipoprotein metabolism. Dr. Ginsberg has a particular interest in the pathophysiology of dyslipidemia associated with insulin resistance and diabetes mellitus. In addition, an advisory committee of established basic and clinical scientists in cardiovascular and endocrine medicine (Drs. Ira Goldberg, Jeanine Albu, Domenico Accili, Dympna Gallagher, and Yoshifumi Naka) statistician (Dr. Rajasekhar Radakrishnan) and administrators (Dr Jaime Rubin) will provide scientific and career advice to complement a comprehensive didactic program.

The main hypothesis of this proposal is that increased adrenergic activation causes increased basal FFA release from adipose tissue and that this increased basal FFA secretion contributes (via storage depletion akin to what is seen with NE in HF) **to an inadequate FFA response to exercise and thus exercise intolerance.** We propose to test this hypothesis by performing a nested case control study of HF patients with and without IR (Aim 1). Additionally, we will use long term mechanical circulatory support with a LVAD to formally test whether reversing HF reverses IR and normalizes circulating FFA availability (Aim 2).

Aim 1: To investigate mechanisms underlying reduced exercise-induced FFA availability in HF patients with IR. In aim 1a, we hypothesize that the decreased FFA availability we observed during exercise in HF-IR is due to decreased exercise-induced FFA release from adipose tissue rather than increased clearance of FFA from the circulation. We will identify 15 HF subjects with IR (HF-IR), 15 subjects with matched HF without IR (HF-No-IR), and a group of healthy controls. Total body fat, organ specific fat, and muscle mass will be measured in HF subjects to control for body composition. We will then evaluate exercise-induced changes in circulating FFA using cardiopulmonary exercise testing (CPET) and stable isotope techniques to measure FFA appearance and fractional clearance from plasma (FFA turnover). In aim 1b, we hypothesize that the mechanism for decreased FFA release is blunted catecholamine-induced adipocyte lipolysis. Basal and catecholamine-induced rates of FFA release will be measured in fat tissue obtained by biopsies of all subjects to test whether adipocytes chronically subjected to elevated plasma NE levels (measured simultaneously) fail to increase release of FFA during an acute catecholamine challenge. We will also measure post heparin plasma lipoprotein lipase (LPL) activity to assess the availability of circulating lipoprotein-derived FFA in each group of subjects.

Aim 2: To determine whether and how LVAD therapy reverses IR and the defect in exercise-induced increase in FFA. In aim 2, we hypothesize that LVAD therapy reverses IR in HF and also restores exercise induced FFA availability. We will study 20 HF patients undergoing LVAD implantation. We will comprehensively
assess body composition, IR, adipocyte FFA release, LPL activity, adrenergic activation and exercise-induced FFA availability as well as FFA turnover as described in aim 1. The severity of HF will be serially assessed using CPET and hemodynamic studies. Tests will be done before as well as 1, 3 and 6 months after LVAD.

Significance: HF is a disease of endemic proportions, and the development of IR in HF heralds a decline in functional capacity and worsening prognosis. We will determine the mechanistic underpinnings of HF-IR with

particular emphasis on altered FFA metabolism and its reversibility and provide direction for future studies: If our flux studies demonstrate that impaired FFA release underlies impaired availability, they will identify fat tissue and lipid breakdown as potential therapeutic targets. For example, adrenergic blockade using high lipophilicity agents directed at the adipose tissue may normalize basal FFA secretion and thus restore FFA response to exercise in HF. In contrast, if increased fractional FFA removal underlies the low stress-induced FFA levels in HF-IR, cardiac and/or skeletal muscle FFA metabolism should be studied. Our approach using LVAD therapy as a non-pharmacological means to reverse and study late stage HF-IR is entirely novel and, if successful, will lay the foundation for treatment and possibly prevention of HF-IR in earlier phases of HF.