Dr. Ira Tabas

The marked increase in cardiovascular disease in patients with type 2 diabetes (T2D) demands an **integrated** cardiometabolic approach. Using this approach, the PPG team has had a highly interactive and productive collaboration for the last 10 years and plans to move forward **to explore common transcriptional and signaling mechanisms in distinct cell types that contribute to cardiometabolic disease**. This goal will be achieved through continued **synergistic interactions** among the 3 projects and Core A. **Project 1** (Tabas) will explore how a common upstream CaMKII/MK2 pathway in hepatocytes (HCs) and macrophages (Mfs) promotes insulin resistance and plaque progression, respectively—and how the HC pathway amplifies the Mf pathway through systemic insulin resistance. The project has a mechanism-based therapeutic/translational component and involves key collaborations with Drs. Tall and Accili. For example, Drs. Tabas & Tall will explore the novel finding that the Mf CaMKII/MK2 pathway downregulates LXR, thereby impairing a key atheroprotective process, efferocytosis. **Project 2** (Tall) will explore the role of T39 in HCs, lesional Mfs, and adipocytes. In HCs and Mfs, T39 alters LXR activation to promote hepatosteatosis and block the suppressive effect of Mf LXR on atherosclerosis. Thus, blocking T39 suppresses both atherosclerosis and fatty liver. Drs. Tall & Tabas with study the role of Mf LXR in suppressing atherosclerosis in T39-deficient mice (above). In adipocytes T39 suppresses beiging, which may promote insulin resistance and atherosclerosis. The mechanism involves down-regulation of PPARg1, which will be explored with Dr. Accili. **Project 3** (Accili) addresses a key problem in T2D therapeutics, namely, thiazolidinedione (TZD) use is markedly limited by cardiogenic fluid retention and bone loss. Dr. Accili discovered that PPARg, the target of TZDs, can be deacetylated, which alters it function and response to TZDs. When TZDs are used in insulin-resistant mice expressing deacetylated mutant PPARg ("2KR"), the insulin-sensitizing benefits remain but fluid retention and bone loss are prevented. With Drs. Tabas & Tall., Dr. Accili will investigate the relevance of these findings to atherosclerosis and will explore mechanism. For example, Drs. Accili & Tabas found that Mfs from 2KR mice have markedly enhanced efferocytosis, which predicts decreased plaque progression. 2KR mice also display adipose beiging, and Drs. Accili & Tall will assess the impact of this on atherogenesis. Core A (Drs. Wang and Wei) will provide essential support and integration for all of the atherosclerosis studies of the PPG and will also provide statistical and bioinformatic support to ensure rigor and reproducibility for all projects. **In summary, through synergistic interactions among the PPG PIs, these new studies will reveal important new concepts and therapeutic targets related to the integrated pathophysiology of cardiometabolic disease.**