Characterizing the impact of mitochondrial DNA mutations on colorectal cancer

Principal Investigator:

- Agnel Sfeir, PhD - Memorial Sloan Kettering Cancer Center

Co-Principal Investigator:

- Vamsi Mootha, MD - The Broad Institute of MIT and Harvard

Abstract: Except for the nucleus, mitochondria are the only organelles in our cells that contain their own genome – a small and circular DNA (mtDNA) that is wholly dedicated to encoding 13 core components of the electron transport chain and the ATP synthase complex. Inherited mtDNA mutations can lead to devastating neurological diseases impacting multiple organ systems. Somatic mutations in mtDNA have been observed in many human cancers, but recent pan-cancer analyses have demonstrated that colon cancer is one of the few common cancers that harbor truncating mutations in mtDNA. However, at present, a causal link between mtDNA mutations and cancer initiation and/or progression is lacking. Moreover, how these debilitating mutations accumulate is not known. In this proposal, we will leverage breakthrough technology to engineer mtDNA mutations in colonic cells and investigate their causal contribution to colorectal tumor progression. In addition, we will capitalize on our recent discovery of a buffering interaction between electron transport chain defects and hypoxia to test the specific hypothesis that hypoxia generates a permissive environment for mtDNA mutations to accumulate in intestinal tumors. The study draws on the unique strengths of our labs and is expected to provide a unique insight into the interplay between mtDNA mutations, hypoxia, and colon cancer.