PanCAN abstract:

Over the past 15 years, it has become canon that activation of angiogenesis is a necessary component to tumor progression. However, pancreatic ductal adenocarcinoma presents an intriguing counterexample. These tumors are poorly vascularized and perfused, yet they are among the most aggressive of human malignancies. Beginning early in tumorigenesis, pancreatic tumors develop a profuse desmoplastic stroma that appears to contribute to the maintenance of a hypovascular state. Depletion of the stroma from established tumors using an inhibitor of the Hedgehog pathway results in increased vascularity in as few as ten days. However, this increased angiogenesis does not promote tumor growth or progression as might be expected. The unusual hypoperfusion of pancreatic tumors presents a biological paradox: how do these aggressive tumors acquire the necessary nutrients for growth and discard resulting waste products? Cancer is an evolutionary process, so what is the selective advantage that hypoperfusion provides to pancreatic tumor cells?

Here we investigate the role of hypoxia on pancreatic tumor development and progression. In most tissues, hypoxia induces a potent signalling program that promotes angiogenesis as a means to reverse the hypoxic state. This program is mediated by Hypoxia Inducible Factors (HIFs), transcription factors that are sensitive to low oxygen tension. In particular, HIF1α accumulates to high levels in cells under hypoxic conditions and transactivates pro-angiogenic target genes such as vegf.

Using a genetically engineered mouse model of pancreatic ductal adenocarcinoma, we will examine the development and response of pancreatic tumor cells to hypoxia. Using a combination of advanced small animal imaging, physiological and pharmaceutical interventions, ex vivo microscopy, and molecular biology techniques, we will explore the responses of different cellular compartments to acute hypoxia and hyperoxia. We will examine HIF-1α target gene expression in hypoxic and normoxic regions of tumors, and at different stages of tumorigenesis. Finally, we will also investigate a proposed Sonic Hedgehog-dependent positive feedback loop promoting desmoplasia and hypoxia in PDA. These experiments will further our understanding of the basic mechanisms of tumor development in pancreatic cancer, the fourth-leading cause of cancer mortality in the United States.