Pancreatic cancer and biliary cancer are among the most lethal types of human cancers. The Bardeesy laboratory has developed a series of genetically engineered mouse models to define the role of key gene mutations that drive these cancer types. Current projects focus on defining roles for cancer genes in controlling the way cells modulate their growth and utilize energy in response to available nutrients, and on identifying epigenetic regulators responsible for changes in cellular differentiation state that lead to cancer initiation and maintenance.

The Bardeesy lab focuses on defining the pathways driving the pathogenesis of pancreatic and biliary cancers. Our lab has developed a series of genetically engineered mouse models that has elucidated the functional interactions of major gene mutations associated with these diseases in humans. Specifically, we have characterized the roles of key cancer genes in the control of cellular differentiation states and in metabolic regulation.

**Interplay between metabolism and chromatin regulation in pancreatic and biliary cancer**

An important area of current focus in our lab is to elucidate the epigenetic regulators of pancreatic cancer and biliary cancers, with particular attention paid to factors that subvert normal differentiation pathways and reprogram cancer cell metabolism. In pancreatic cancer, we have linked mutations in LKB1/STK11 and other important genetic alterations to changes in metabolism that ultimately alter epigenetic states. Identifying these pathways have provided insights in mechanisms of cell transformation arising from these mutations and predict novel therapeutic vulnerabilities. In biliary cancer, there are recurrent mutations in the IDH1 and IDH2 genes. Mutant IDH proteins acquire a novel enzymatic activity allowing them to convert alpha-ketoglutarate ($\alpha$KG) to 2-hydroxyglutarate (2HG), which inhibits the activity of multiple $\alpha$KG-dependent dioxygenases, including the JmjC family histone demethylases. We are focusing on how IDH mutations affect epigenetic programs and regulation of cellular identity in the liver.

**Targeting master regulators of metabolic reprogramming in PDAC**

In order to couple rapid growth with available nutrients, cancers employ profoundly altered networks of biosynthetic and catabolic pathways. This requirement for metabolic reprogramming is particularly acute in PDAC, which is characterized by hypoxia and limited nutrient availability, and activates anti-oxidant gene expression and autophagy (cellular self-catabolism) as necessary adaptive metabolic changes. While these pathways offer attractive new therapeutic targets, the underlying mechanisms driving altered PDAC metabolism are unclear. We have focused on identifying master transcriptional regulators that broadly orchestrate metabolic reprogramming in PDAC.
Mutant IDH causes expansion and impaired differentiation of liver progenitor cells leading to biliary cancer. Immunohistochemistry (top) and immunofluorescence (bottom) of livers from wild type (WT) and transgenic mice expressing mutant IDH2R172K. Sox9 (top, brown stain; bottom, green) normally marks bile duct cells adjacent to the portal vein (PV), whereas there is aberrant accumulation of Sox9-expressing cells progenitor/stem cells in IDH mutant livers. These cells are highly prone to progression to biliary cancer (cholangiocarcinoma). Image from Saha, Parachoniak et al., Nature 2014.

Mouse models of biliary cancer

Recent genetic studies have identified multiple recurrent mutations in biliary cancers and have indicated considerable genetic heterogeneity between individual tumors. A key limitation in the field includes a paucity of experimental systems with which to define the contributions of the lesions to biliary cancer progression. We have established a series of genetically engineered mouse models that incorporate combinations of the major mutations found in the human disease. In addition, our ongoing efforts include the development of a human biliary cancer cell line bank for the use of genetic and small-molecule, screening in genetically defined subtypes of this cancer.

Control of liver progenitor cells and biliary cancer development

The Hippo pathway is a conserved regulator of organ size. Our lab has shown that this pathway is central for controlling the quiescence of liver progenitor cells, and that its loss leads to massive liver overgrowth and development of both major types of liver cancer (hepatocellular carcinoma and cholangiocarcinoma). The lab is studying the circuitry of the Hippo pathway in liver progenitor cells and the key mediators of tumorigenesis found downstream of this pathway.