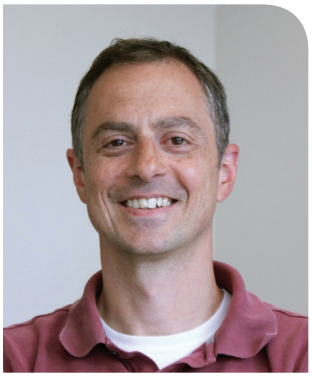
Nabeel Bardeesy, PhD



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 and patient-derived models to define the role of key gene mutations that drive these cancer types. Current projects focus on understanding the function of cancer genes in controlling the way cells modulate their growth and utilize energy in response to available nutrients. Additional studies are exploring how some therapies targeting key mutations initially cause tumor to stop growth and why resistance eventually develops. Each of these studies is being used to inform improved therapeutic approaches.

Bardeesy Laboratory

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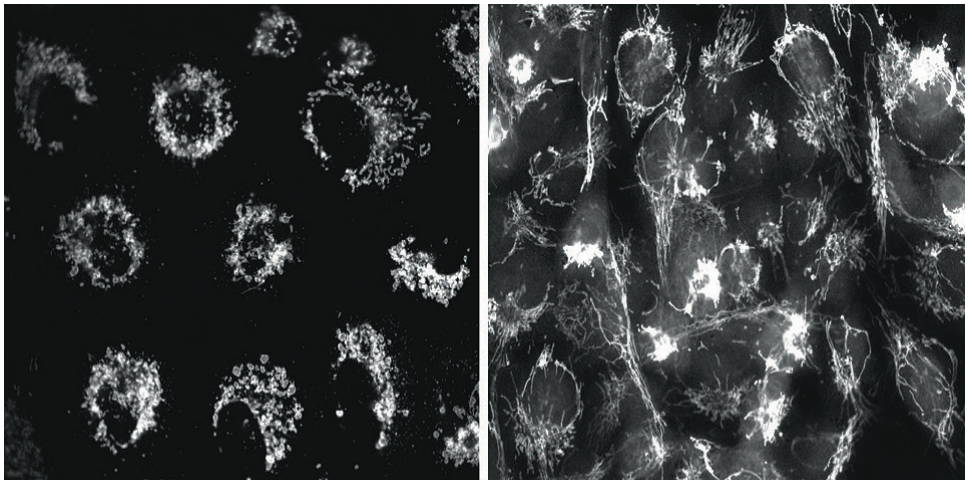
The Bardeesy lab studies the pathways driving the pathogenesis of pancreatic and biliary cancers. The lab has developed a series of genetically engineered mouse models that has elucidated the functional interactions of major gene mutations associated with these diseases in humans. Studies have focused on the roles of key cancer genes in regulation of cell metabolism, the discovery of mechanisms of resistance to targeted therapies.

Interplay between metabolism and chromatin regulation

An important area of current focus in our lab is to elucidate the metabolic regulators of pancreatic cancer and biliary cancers, with particular attention paid to factors that reprogram cancer cell metabolism. We have linked mutations in the LKB1/STK11 and IDH1 genes to changes in metabolism that ultimately alter epigenetic states. Identifying these pathways has provided insights in mechanisms of cell transformation arising from these mutations and predict novel therapeutic vulnerabilities. Mutant IDH proteins acquire a novel enzymatic activity allowing them to convert alpha-ketoglutarate (αKG) to 2-hydroxyglutarate (2HG), which inhibits the activity of multiple αKG-dependent dioxygenases, including the TET family DNA demethylases. We are focusing on how epigenetic defects caused by IDH-mediated inhibition of TET affects cross-talk between tumor and immune cells to support cancer growth.

Genetic regulation of metabolic reprogramming in pancreatic cancer

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 pancreatic cancer, 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. Our recent studies demonstrate that distinct metabolic programs are activated in pancreatic cancer depending on which gene mutations are present. 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.



Genetic control of expression of the Mitochondrial Fission Factor (MFF) dictates mitochondrial architecture and metabolic phenotypes of cancer cells. The image shows mitochondrial staining (Mitotracker) of cancer cells which express high levels of MFF (left panel) or low levels of MFF (right panel). The MFF-high cancer cells show hyper-fragmented mitochondria compared to the fused mitochondrial network of MFF-low cancers. This differential control of mitochondrial dynamics results in distinct metabolic programs and vulnerabilities.

Understanding and targeting FGFR2-driven biliary cancer

Genetic alterations that activate Fibroblast Growth Factor 2 (FGFR2) signaling are common in biliary cancer and predict response to pharmacological inhibition of the FGFR in patients. However, tumor shrinkage is often modest and acquired resistance invariably arises. We are investigating oncogenic mechanisms controlled by FGFR2 in biliary cancer, including direct targets of FGFR2 signaling as well as downstream impact on cellular metabolism and differentiation. Additionally, we are investigating resistance mechanisms and approaches to prevent and overcome resistance.

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 and the use of this system in large-scale genetic and small-molecule screens to systematically define targetable vulnerabilities in molecularly defined subtypes of this cancer.

Selected Publications:

Wu MJ, Shi L, Dubrot J, Merritt J, Vijay V, Wei TY,... Manguso RT, **Bardeesy N**. Mutant IDH Inhibits IFNγ-TET2 Signaling to Promote Immunoevasion and Tumor Maintenance in Cholangiocarcinoma. *Cancer Discov*. 2022 Mar 1; 12(3):812-835.

Wu, Q, Zhen, Y, Shi, L. and **Bardeesy N**. EGFR inhibition potentiates FGFR inhibitor therapy and overcomes resistance in FGFR2 fusion-positive cholangiocarcinoma *Cancer Discov*. 2022 *in press*.

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Goyal L, Shi L, Liu LY, Fece de la Cruz F,... Corcoran RB, **Bardeesy N**. TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma. *Cancer Discov*. 2019 Aug 9; (8):1064-1079.

Patra KC, Kato Y, Mizukami Y,... **Bardeesy N**. Mutant GNAS drives pancreatic tumourigenesis by inducing PKA-mediated SIK suppression and reprogramming lipid metabolism. *Nat Cell Biol*. 2018 Jul 20; (7):811-822.

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Saha SK, Gordan JD, Kleinstiver BP, Vu P,... Benes CH, **Bardeesy N**. Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma. *Cancer Discov*. 2016 Jul 6; (7):727-39.

Perera RM, Stoykova S, Nicolay BN,... **Bardeesy N**. Transcriptional control of the autophagy-lysosome system drives amino acid metabolism in pancreatic cancer. *Nature* 2015 July 13.

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