

# Nabeel Bardeesy, PhD



## Bardeesy Laboratory

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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.

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, and the discovery of mechanisms of resistance to targeted therapies.

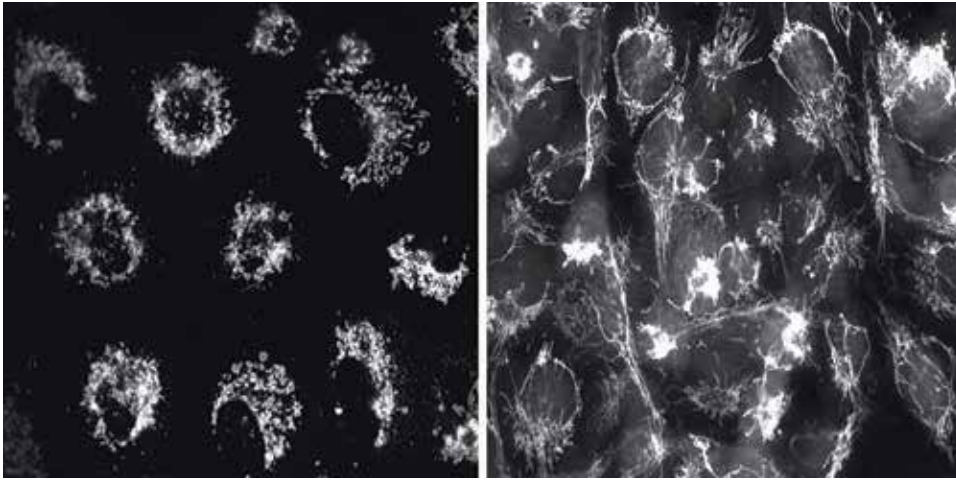
### Interplay between metabolism and chromatin regulation

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 IDH1 gene 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 ( $\alpha$ KG) to 2-hydroxyglutarate (2HG), which inhibits the activity of multiple  $\alpha$ KG-

dependent dioxygenases, including the TET family DNA demethylases. We are focusing on how epigenetic defects caused by IDH-mediated inhibition of TET affect cross-talk between tumor and immune cells to support cancer growth.

### Oncogenic functions of protein kinase A signaling in pancreatic and liver cancers

The protein kinase A (PKA) signaling pathway is activated by mutations in a number of tumor types. These include the subset of pancreatic and biliary tumors harboring mutations in GNAS, an upstream regulator of PKA, and a type of liver tumor (fibrolamellar carcinoma) harboring activating gene fusions of PKA. Although PKA is an important driver of the growth of these tumor types, the specific oncogenic mechanisms have not been as widely studied as for many other cancer gene mutations. We have focused on elucidating the primary mechanisms of PKA-driven growth. Our work has identified the Salt-inducible kinases (SIK1-3) as the critical targets of cancer-causing PKA alterations. In addition, we have linked this pathway to a downstream epigenetic mechanism controlling proliferation and reprogramming mitochondrial function and tumor cell metabolism.



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:

Shi L, Shen W, Davis MI, Kong K, Vu P, Saha SK, Adil R, Kreuzer J, Egan R, Lee TD, Greninger P, Shrimp JH, Zhao W, Wei TY, Zhou M, Eccleston J, Sussman J, Manocha U, Weerasekara V, Kondo H, Vijay V, Wu MJ, Kearney SE, Ho J, McClanaghan J, Murchie E, Crowther GS, Patnaik S, Boxer MB, Shen M, Ting DT, Kim WY, Stanger BZ, Deshpande V, Ferrone CR, Benes CH, Haas W, Hall MD, **Bardeesy N**. SUL1A1-dependent sulfonation of alkylators is a lineage-dependent vulnerability of liver cancers. *Nat Cancer*. 2023 Mar;4(3):365-381.

Wu MJ, Shi L, Dubrot J, Merritt J, Vijay V, Wei TY, Kessler E, Olander KE, Adil R, Pankaj A, Tummala KS, Weerasekara V, Zhen Y, Wu Q, Luo M, Shen W, García-Beccaria M, Fernández-Vaquero M, Hudson C, Ronseaux S, Sun Y, Saad-Berreta R, Jenkins RW, Wang T, Heikenwälder M, Ferrone CR, Goyal L, Nicolay B, Deshpande V, Kohli RM, Zheng H, Manguso RT, **Bardeesy N**. Mutant IDH Inhibits IFN $\gamma$ -TET2 Signaling to Promote Immuno-evasion 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 Apr 14:OF1-OF18.

Cleary JM, Raghavan S, Wu Q, Li YY,...(**Bardeesy N\***, Wolpin BM\*). FGFR2 Extracellular Domain In-Frame Deletions are Therapeutically Targetable Genomic Alterations that Function as Oncogenic Drivers in Cholangiocarcinoma. *Cancer Discov*. 2021 Apr 29.

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 tumorigenesis by inducing PKA-mediated SIK suppression and reprogramming lipid metabolism. *Nat Cell Biol*. 2018 Jul 20; (7):811-822.

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