

DEPARTMENT OF CANCER BIOLOGY
COLLEGE OF MEDICINE

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE WOMEN

APPLICATION DEADLINE: 03/01/2020

PROJECT TITLE: Regulation of mitochondrial metabolic pathways in pancreatic cancer

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Project Description

Pancreatic ductal adenocarcinoma (PDA) is one of the untreatable cancers with 5-year survival rate after diagnosis is less than 8%. While KRAS is universally mutated in pancreatic cancer, it co-exists with varieties of other genetic mutations. A subset of KRAS mutant PDA exhibit frequent activating GNAS mutations (GNAS-R201C/H). GNAS encodes the G-protein G α s, which induces cyclic-AMP (cAMP) signaling. Overall, GNAS is mutationally activated in 4-11% of PDA and in >50% of a specific subtype of pancreatic precursor lesion. By developing genetically engineered mouse models, we find that GNAS-R201C cooperates with KRAS-G12D to drive pancreatic cancer. Notably, we demonstrate that GNAS-R201C is critical for PDA tumor maintenance, which is mediated by cAMP-dependent activation of protein kinase A (PKA) and resulting inhibition of salt-inducible kinases (SIK1-3). We find that this network prominently reprograms cell metabolism, promoting fatty acid oxidation (FAO) and lipid remodeling. Importantly, GNAS-mutant PDAs are specifically sensitive to the inhibition of these pathways. Building on these findings, our current research seeks to elucidate critical substrates of the SIK kinases, involving mitochondrial metabolism that mediates GNAS-R201C driven tumorigenesis program. SIKs are emerging tumor suppressors in various oncogenic settings. Our overarching hypothesis is that SIKs are important regulators of mitochondrial function in GNAS mutant pancreatic cancer. The WISE student will be generating SIK knockout pancreatic cancer cells by CRISPR-Cas9 constructs. After the characterization of cells through western blotting, the student will verify mitochondrial structure and function by seahorse respirometry, confocal microscopy and perform biochemical assays for mitochondrial lipid metabolism. Using three-dimensional organoid culture, the student will study the impact of perturbation of the SIK mediated metabolic pathways in tumor growth. During this project the student will learn advanced gene deletion techniques, cell culture including organoid culture,

biochemical assays to study metabolism in cancer. The student is expected to participate in lab meetings to present own research data.