**Background**  Pancreatic ductal adenocarcinoma is responsible for 35,000 deaths per year in the United States and is among the most lethal of cancers, with a median survival of less than 6 months. Approximately 10% of pancreatic cancer patients have an hereditary cancer predisposition, the most common of which is inherited mutations in BRCA1 or BRCA2. These genes are necessary components of the homology directed repair (HDR) pathway. Ovarian and breast tumors arising in hereditary BRCA patients have proven to be particularly sensitive to targeted inhibitors of PARP, an enzyme necessary for efficient repair of single-strand breaks. PARP inhibitors have demonstrated significant clinical potential in treating BRCA deficient breast and ovarian tumors, but have not yet been fully evaluated in pancreatic tumors. Furthermore, it is possible that some spontaneous pancreatic tumors have acquired deficiencies in the HDR pathway which might also render them sensitive to treatment with PARP inhibitors.

**Objective**  The goal of this work is to perform a preclinical intervention trial in genetically engineered mouse models of pancreatic ductal adenocarcinoma. Using novel BRCA2 deficient and wild-type models of pancreatic cancer, we will evaluate the pharmacokinetic behavior and pharmacodynamic responses of a novel PARP inhibitor, MK-4827. This agent is a potent and selective inhibitor of PARP 1 and PARP 2, and is orally available with a long half-life in vivo.

**Specific Aims**
1) to evaluate the efficacy, pharmacokinetics, pharmacodynamics, and mechanisms of response of BRCA deficient pancreatic tumors to PARP inhibition, alone or in combination with cisplatin.
2) to evaluate the efficacy of PARP inhibition in BRCA wild-type pancreatic tumors, and identify genomic signatures of PARP sensitivity in the broader population of spontaneous pancreatic cancers.