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RAS is among the most potent oncogenes in the human genome and is mutated in over one in four of all human cancers [1]. In pancreatic cancer specifically, KRAS is mutated at an alarmingly high rate, activated in over 95% of all cases [2]. While extinguishing both RAS signaling and mutant RAS protein expression in a transgenic mouse model of pancreatic cancer completely ablates tumors [3], developing specific RAS-inhibitors or other useful therapies for pancreatic cancer patients has proven near impossible. In keeping with this lack of progress, pancreatic ductal adenocarcinoma (PDA) remains one of the most lethal cancers, with a 5-year survival rate of just 5%. It is clear that there is a critical ned to develop novel therapeutic approaches in the field of pancreatic cancer in order to identify more effective and less toxic treatments. Current efforts have been made to identify pathways whose manipulation could prove lethal specifically in the context of cells containing RAS mutations. Such "synthetic lethal" combinations could provide great utility in a clinical setting, limiting the toxicities commonly associated with both radiation and chemotherapeutic approaches, and targeting RAS-driven tumors in a specific, effective way. In 2003, a synthetic lethal chemical screen carried out by Dr. Stockwell identified a specific killer of Ras-mutant cells [4]. This compound, called "erastin," causes an iron-dependent form of oxidative cell death, termed "ferroptosis," through the inhibition of a cystine-glutamate antiporter named system xc- [5]. However, the utility of this approach *in vivo* and the precise role of system xc- in Ras-driven tumors remains unknown. Given the role of mutant RAS in the development and maintenance of PDA, the overall goal of the proposed research is to test the hypothesis that system xc- function is required for the development and maintenance of KRAS mutant pancreatic cancers. Specifically, we aim to interrogate the consequences of genetic and pharmacological manipulation of system xc- on the proliferation and survival of pancreatic cancer cells. Leveraging expertise in molecular genetics, mouse modeling, and preclinical therapeutics, we will interrogate the role of system xc- in the growth and maintenance of PDA and evaluate the clinical viability of targeting this pathway as a means of therapeutic intervention for pancreatic cancer patients. Specifically, we will use shRNA and viral technologies to modulate system xc- *in vitro*. To study the effects of genetic ablation of system xc- *in vivo*, we will cross mice deficient for system xc- function to our preclinical model of PDA, the KPC mouse. Finally, we will use a compound, derived from erastin, to evaluate the effect of pharmacological inhibition of system xc- on pancreatic tumor cells both in vitro and in the KPC model. In summary, the experiments proposed herein will aid our understanding of the precise role of redox state maintenance in cancer growth and survival as well as validate the use of system xc- inhibitors in the effective treatment of pancreatic cancer.