Scientific Abstract

SU2C–Lustgarten Foundation Pancreatic Cancer Interception Dream Team:

"Intercepting Pancreatic Cancer in High-Risk Cohorts"

[This abstract was provided by the scientists when their application was accepted.]

Cancer interception has great potential to improve outcomes for patients destined to develop pancreatic ductal adenocarcinoma (PDAC). Currently, there is no universal screening test to apply to the general population, although seminal studies by Dream Team members have helped delineate cohorts that are at significantly higher risk for developing PDAC based on their familial predisposition, and presence of deleterious germline mutations that confer increased cancer susceptibility.

The overall goal of our SU2C Dream Team is to formulate the clinical framework to enable cancer interception in individuals at high risk for PDAC. We will leverage our DT's unparalleled expertise in identifying and screening high-risk cohorts, innovative immune prevention strategies, and cancer biomarker discovery. Our activities will be facilitated by the substantial number of genetically predisposed families that are currently undergoing screening at five DT sites, and by access to hundreds of pre-diagnostic plasma samples from PDAC patients.

Our specific aims are:

Aim 1: *To enhance access to germline testing and screening protocols for cancer interception in highrisk cohorts and combine this with novel imaging algorithms to diagnose early PDAC lesions that are currently undetectable.* In collaboration with Color Genomics, we will develop the evidence base needed to facilitate broader use of genetic counseling and germline testing for newly diagnosed PDAC patients and their family members. Asymptomatic mutation positive first-degree relatives will then be enrolled into an imaging protocol that utilizes "deep learning" algorithms for enhanced detection of early cancer.

Aim 2: *To intercept pancreatic cancer in high-risk cohorts using targeted immune prevention.* We are proposing a first-in-human vaccine trial for PDAC interception in ~50 individuals with an inherited predisposition, who have evidence of precancerous changes in their pancreas and mutant *KRAS* in endoscopic pancreatic juice samples. In conjunction, co-clinical studies of cancer interception will be performed in newly developed CRISPR/*Cas*9-based inducible PDAC models that will inform the ongoing clinical trial on appropriate immunological correlatives, and a "Precancer Atlas" of expressed antigens in high-grade PDAC precursors will be generated for future peptide vaccine targets.

Aim 3: *A blood test for identifying individuals at risk for PDAC who would be candidates for early detection using imaging.* We will perform a "biomarker bakeoff" (protein, autoantibody, and metabolites) to identify an optimal panel that will enrich for individuals at high risk of developing PDAC within 5 years. These studies will be facilitated by our unique access to ~500 pre-diagnostic blood samples from individuals who subsequently developed PDAC within 1-5 years. We will also validate an ultrasensitive circulating tumor DNA (ctDNA) assay for early detection in high risk cohorts likely to harbor an asymptomatic PDAC. In addition to standard imaging, individuals at highest risk for PDAC will also undergo dynamic contrast-enhanced MRI (DCE-MRI).