Scientific Abstract

SU2C–National Science Foundation–Lustgarten Foundation Pancreatic Cancer Convergence Research Team:

"Liberating T-Cell Mediated Immunity to Pancreatic Cancer"

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

Pancreas ductal adenocarcinoma (PDAC) is a frequent cause of cancer death in the United States; it currently is the third most common cause of cancer death and is expected to become the second most common cause of cancer death within the next five years. Clearly novel approaches to this disease are needed.

Activation of cellular immunety using checkpoint inhibitors, vaccine strategies and transfer of genetically modified T cells has not been shown to be effective in pancreas cancer. Barriers to successful immunotherapy of pancreas cancer include a relative paucity of effector T cells and the presence of immunosuppressive T cells in the tumor microenvironment, as well as the elaboration of immunosuppressive cytokines by cancer associated fibroblasts, termed stellate cells, in the tumor stroma.

Studies of human pancreatic stellate cells in culture have demonstrated that the elaboration of immunosuppressive cytokines can be inhibited by activation of the Vitamin D receptor. Vitamin D agonists inhibit the ability of pancreatic stellate cells to protect pancreatic cancer cells from the cytotoxic activity of the chemotherapeutic agent gemcitabine *in vitro* and enhance the antitumor effects of gemcitabine in the KPC transgenic mouse model of pancreas cancer. These findings led to the initiation of a Phase 1 neoadjuvant clinical trial utilizing conventional chemotherapy (gemcitabine plus nab-paclitaxel) administered with the Vitamin D analogue paricalcitol. This study demonstrated anti-tumor efficacy and minimal incremental toxicity related to paricalcitol. Intriguingly, histologic examination demonstrated that patients who received this treatment had a substantial infiltration of CD3+CD8+ T lymphocytes into their tumors. Preliminary analysis suggests a five to ten-fold increase in the frequency of these T cells in tumors of treated patients. However, the relative contributions of the neoadjuvant chemotherapy and the paricalcitol treatment to this process is unclear.

The proposed studies will build on these findings to further explore potential immunotherapeutic approaches to pancreas cancers. A neoadjuvant clinical trial of chemotherapy with or without paricalcitol in concert with the administration of the checkpoint inhibitor nivolumab will be performed. A recently opened second trial will evaluate a short course of oral vs intravenous paricalcitol vs no treatment prior to surgery in resectable patients. Exomic sequencing and prediction of tumor neoantigens will be performed in all patients, and the T cell repertoire of tumor

infiltrating T cells will be assessed. Peripheral blood T cells from patients in the nivolumab trial will be studied for reactivity against tumor neoantigens *in vitro* before and after treatment. A team of biophysicists will mathematically model T cell responses in tumors and link this to clinical responses in patients.