



## Scientific Abstract

### Pancreatic Cancer Collective Research Team:

#### “Targeting stem cell signals in Pancreatic Cancer New Therapies Challenge”



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

Despite some recent advances in systemic therapy, pancreatic cancer survival rates remain dismal in large part due to the cancer's profound drug resistance, and propensity for early metastasis. Thus, there is a critical need to develop more effective approaches to therapy. In prior work supported by SU2C, the Team has focused on systematically mapping the molecular dependencies of pancreatic cancer stem cells, highly drug resistant cells that are also enriched in the capacity to drive progression.

They utilized a combination of RNA-Seq, ChIP Seq and genome-wide CRISPR screening to develop a network map of core programs regulating pancreatic cancer; this revealed an unexpected role for immunoregulatory genes in stem cell function and pancreatic cancer growth.

A nuclear hormone receptor (NHR) known for its role in T cell differentiation has emerged as a key regulator of pancreatic cancer stem cells. A knockdown of this NHR reduced sphere formation of pancreatic cancer cells *in vitro*, and dramatically suppressed growth of tumor cells *in vivo*. Consistent with this, delivery of an inhibitor specific to this NHR (SR2211) resulted in a dose dependent reduction in the number of pancreatic cancer spheroids *in vitro*.

Their specific aims are as follows:

- Aim 1: Test inhibition of a specific nuclear hormone receptor in combination with chemotherapy in preclinical models.
- Aim 2: Identify biomarkers predictive of response and define a molecular signature reflective of response to nuclear hormone receptor inhibition.

