



## Scientific Abstract

### SU2C Pancreatic Dream Team:

#### “Cutting Off the Fuel Supply: A New Approach in the Treatment of Pancreatic Cancer”



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

Pancreatic cancer is the 4<sup>th</sup> leading cause of death from cancer in the U.S. Unfortunately, current treatments have had little impact on the disease. At present, over 91% of patients with pancreatic cancer die of their disease, most within the first year after diagnosis. Clearly, a new approach to therapy is required if we are to defeat this devastating illness.

Recent evidence has demonstrated that most cancer cells acquire mutations that result in rendering them addicted to a continual supply of nutrients to maintain their survival. This addiction results from the fact that the mutations that arise in cancer commit the cell to dependence on specific nutrients to both maintain their survival and produce the energy needed to support their continual proliferation.

In most cancers, the major nutrient the cancer cells use is glucose. Modern tumor imaging can measure the excess glucose utilization by a tumor and such tests are in routine use in clinical practice. In many types of cancers, the amount of glucose a tumor uses correlates with its stage of malignancy and predicts the likelihood that the tumor will spread. The ability of chemotherapy to reverse the excess glucose uptake of a tumor has been shown to be a good predictor of whether a patient's therapy will be effective.

Pancreatic cancer is a notable exception to the above observations. At the time of diagnosis, most pancreatic cancers are aggressive and highly invasive. Despite this, many pancreatic cancers do not appear to fuel their growth and survival through glucose. Instead, pancreatic cancers are often addicted to the use of the amino acid glutamine to produce the energy they need to grow.

Cancers that use glutamine as their energy source are frequently resistant to standard chemotherapy. The excess metabolism of glutamine by a cancer can lead to extreme weight loss, also known as cancer cachexia. It results from the body's attempt to compensate for the glutamine consumption of the tumor through the breakdown of muscle proteins.

This syndrome is frequently observed in pancreatic cancer patients. In addition, the waste generated by inefficient combustion of glucose and glutamine also induces an intense reaction from surrounding normal cells which then secrete growth factors that help the tumor cell grow. Therefore, interfering with tumor cell nutrient supply by targeting the tumor cells and/or supporting stromal cells has the potential to substantially improve the survival of patients with pancreatic cancer.





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This Dream Team has been assembled to develop new clinical tests to determine what nutrients pancreatic cancer cells use to fuel their growth and survival. These tests will allow a patient's doctor to tailor their therapies to more effectively attack the tumor cell's fuel supply. Such tests will aid in designing more individualized treatment.

With the funds from this proposal, we will immediately initiate clinical trials of drugs designed to inhibit pancreatic cancer cells from effectively using either stromal cell-derived cytokines or glucose and/or glutamine to maintain their survival. These drugs will be tested in combination with existing standard of care chemotherapy. Since most cells in the body do not depend solely on either stromal cell-derived cytokines or specific nutrients to maintain their survival, this approach has the potential to avoid many of the toxic side effects of traditional combinational cancer therapy.