C3 / Padres Pedal the Cause 2020

"Protein Kinase C as a Novel Biomarker and Target in Pancreatic Cancer"

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SCIENTIFIC ABSTRACT

The goal of this proposal is to determine whether restoring protein kinase C (PKC) signaling, via targeting of its negative regulator the phosphatase PH domain leucine rich repeat protein phosphatase (PHLPP1), is a viable potential strategy to improve survival in pancreatic ductal adenocarcinoma (PDAC). The premise of this proposal is our recent analysis of 105 PDAC tumors revealing that patients with relatively high levels of PKC and low levels of PHLPP1 had significantly improved survival rates compared with patients with low levels of PKC and high levels of PHLPP1: whereas no patient with low PKC survived past 5 years, a striking 50% of patients with high PKC expression survived 5 years (1). The proposal draws on the extensive expertise of Dr. Newton in PKC signaling and of Drs. Tiriac and Lowy in pancreatic cancer. To achieve our aims, we will use a library of >80 patient-derived pancreatic cancer organoids established and characterized by Drs. Tiriac and Lowy. These will be treated with PHLPP1 inhibitors developed by the Newton lab and proliferation and survival measured in culture and in orthotopic transplants in mice. Additionally, the mechanism by which PKC confers a survival advantage will be addressed, focusing on determining whether PKC suppresses K-Ras.

LAY ABSTRACT

Pancreatic cancer remains one of the deadliest and most aggressive types of cancer, with a five-year survival rate of 9%. We recently discovered that the levels of two proteins predict survival outcome. One protein, PKC, is a tumor suppressor and the other protein, PHLPP1, is its negative regulator that controls how much PKC is present. We found that in pancreatic cancer, high PHLPP1/low PKC correlated with poor prognosis: in a cohort of 105 patients, none survived longer than five years. But 50% of patients with low PHLPP1/high PKC survived longer than 5 years. This proposal Aims to set the stage for clinicians to one day use a pancreatic cancer patient's PHLPP1/PKC levels as a predictor for prognosis, and for researchers to develop new therapeutic drugs