

C3 / Padres Pedal the Cause 2017

“An over-expressed GPCR in pancreatic cancer associated fibroblasts as a novel therapeutic target”

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SCIENTIFIC ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC), predicted to be the 2nd leading cause of death from cancer by 2020, needs new effective therapeutics. A key feature of PDAC is its dense fibrosis (desmoplasia) formed by cancer-associated fibroblasts (PDAFs), derived from pancreatic fibroblasts (PDs) and/or stellate cells (PSCs). We have identified a G protein-coupled receptor (GPCR), whose agonist is H⁺ and that has increased expression in PCAFs compared to PFS and PSCs. Low pH activation of this GPCR increases PCAF production of fibrotic markers and IL-6. Transfection of the GPCR into PSCs increases pro-fibrotic marker formation; siRNA knockdown blunts fibrotic marker expression and ability of PCAF-conditioned media to promote PDAC cell proliferation. This project will: 1) evaluate the impact of GPCR activation on PCAF gene expression and activities and 2) develop a drug discovery assay and validate in a pilot screen of a SBP library of small molecule inhibitors of this GPCR. Studies will be conducted using PDAC-patient derived PCAF primary cultures with signaling and activity assays (by the Insel lab) and library screening (by SBP) using cAMP as a readout: low pH increases [cAMP] in this GPCR and the identification of "hit" compounds as antagonists of it. Further studies will evaluate the impact of the antagonists on low pH-promoted responses of PCAF cells and will set the stage for in vivo studies of efficacy in blunting the growth of PDAC.

LAY ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is the most common and deadly form of pancreatic cancer with >93% of PDAC patients dying less than 5 years after their diagnosis. Part of the difficulty in treating PDAC is its characteristic dense scarring (“fibrosis”). This scarring is generated by pancreatic cancer-associated fibroblasts (PCAFs). This project seeks to build on our recent discovery that PCAFs have high expression of a novel protein on their cell surface. This protein, known as a GPCR, is activated by the acidic (low pH) environment that exists in pancreatic cancers. When activated by this low pH, the PCAFs communicate with the PDAC cells to enhance their growth. In this project, UCSD investigators will conduct studies to define additional responses produced by exposure of CAFs to low pH and with Sanford-Burnham-Prebys Cancer Center/Medical Discovery Institute (SBP), will assess “libraries” (collections) of chemical compounds, certain of which are predicted to antagonize the GPCR we identified and which, as a result, should block the production of scarring and stimulation of PDAC growth by the PCAFs. These studies that combine efforts at UCSD with those at SBP thus focus on the “tumor microenvironment” in which PDAC cells and PCAFs interact and will test the idea that a drug that blocks a special type of GPCR present in PCAG cells can provide a novel way to assist in the treatment PDAC tumors and thus may be a new way to improve the outcome of this very deadly type of cancer.