

**Project Title: Overcoming microenvironment-mediated drug resistance in pancreatic cancer**

**Abstract**

The overarching goal of these studies is to uncover mechanisms by which secreted stromal proteins promote drug resistance in pancreatic cancer and to develop strategies to inhibit these mechanisms. Pancreatic ductal adenocarcinoma is one of the most lethal and drug resistant of all cancers. The average survival time is only six months, and in most cases curative surgery is not feasible. Our previous data show that stromal cells and the tumor microenvironment promote drug and stress resistance, and our preliminary data show that pancreatic stellate cells, which are the main secretory cell type in pancreatic cancer, induce drug resistance through protein secretion. Pancreatic stellate cells become activated in pancreatic cancer and obtain a secretory phenotype, which could be used to target these cells. Our current efforts are aimed at identifying the molecules responsible for inducing drug resistance, and this proposal aims at identifying ways to selectively inhibit secretion by the activated stellate cells in order to improve therapy outcomes in pancreatic cancer. With the help of this grant and Ipsen's platform we will develop treatment strategies to block secretion by the pancreatic stellate cells and test their efficacy in our co-culture model systems.