10. PROJECT ABSTRACT *(Do not exceed space provided)*

Pancreatic cancer is the tenth most common cancer and the fourth leading cause of cancer-related death in the US. Despite major efforts the prognosis of pancreatic cancer patients remains dismal. Recent advances in understanding the biology of pancreatic cancer have not translated into novel therapeutic strategies. Pancreatic ductal adenocarcinoma is defined through a strong stromal reaction termed desmoplasia. It is now widely accepted that this stromal reaction plays an important part in the intrinsic resistance against standard radio- or chemotherapy seen in pancreatic cancer. Abundant neural structures are part of this desmoplastic reaction and perineural/neural invasion is an almost uniform feature of pancreatic cancer. While it has been demonstrated that there is an active crosstalk between neurons and pancreatic cancer cells and vice versa this phenomenon has largely been studied to understand its role in pain and cachexia. We have shown that targeting neurons in genetically engineered mouse models is sufficient to prevent and treat gastric cancer. Furthermore, we have demonstrated a significant effect of chemical denervation of established pancreatic tumors in mice. Importantly, clinical data trials in pancreatic cancer patients suggest similar effects in humans. Finally, preliminary results from our group show that transgenic mouse models of pancreatic disease faithfully recapitulate all hallmarks of neural remodeling seen in humans. We believe that neural remodeling and cancer/neuron interactions are fundamental components of pancreatic carcinogenesis and valuable therapeutic targets. Therefore we propose to investigate the process of neural remodeling *in vivo* and *in vitro* to better define causal mechanisms. Furthermore, we are going to conduct preventive and interventional studies in clinically relevant mouse models of pancreatic cancer using novel surgical and pharmacological approaches. Successful targeting of the interaction between neurons and pancreatic cancer cells will not only improve pain management and cachexia but could also provide an important route to improve pancreatic cancer therapy.

11. BRIEF 'LAY' DESCRIPTION *(Not to exceed this space)*

Pancreatic cancer is one of the deadliest cancers known to man and standard therapies usually fail. An important feature of pancreatic cancer is a strong inflammatory reaction that can make up the majority of the bulk tumor. Within this stromal reaction large numbers of nerves can be found and cancer cells and neurons communicate with each other. We have shown that disruption of the interaction between nerves and cancer cells can be used to treat gastric cancer and pancreatic cancer in mice. Furthermore, we have demonstrated that mice show the same communication between cancer cells and neurons. We believe that the interaction between cancer cells and the nervous system is important for the survival of pancreatic tumors. Therefore, we would like to investigate the processes underlying this interaction. Additionally, we plan to treat pancreatic cancer by inhibiting the communication between the tumor cells and the neuronal structures. We believe that this will not only lead to less pain and higher quality of life but could also prolong the survival in pancreatic cancer.