Ruth White, MD, PhD.

Pancreatic ductal adenocarcinoma (PDAC) is a common cause of cancer deaths, and even with aggressive chemotherapy the median overall survival with metastatic disease is less than 1 year. The tumor microenvironment (TME) plays a significant role in promoting tumor growth and metastasis. Nerves are emerging as important regulatory features of the pancreatic tumor microenvironment. Perineural invasion is seen in approximately 80% of PDAC and is thought to play an important role in tumor metastasis and recurrence. We have shown that cholinergic signaling though the vagus nerve inhibits PDAC growth, in part due to regulation of the cancer stem cell pool. However, the effect of muscarinic signaling on the microenvironment is unknown. Recent studies have shown that the muscarinic 1 receptor (M1R) regulates neuron density and neurite outgrowth in response to muscarinic signaling suggesting a role for this receptor in regulating the neural TME in pancreatic cancer. I will expand on our prior studies to further examine the role of cholinergic signaling on the neural component of the TME with a focus on neural proliferation and perineural invasion. I hypothesize that muscarinic agonism inhibits sensory neuron outgrowth and perineural invasion through regulation of the muscarinic 1 receptor. To investigate this I am proposing two aims to answer the following questions: (1) Does muscarinic agonism inhibit sensory neural outgrowth and perineural invasion in the PDAC microenvironment and (2) Does muscarinic signaling promote neural outgrowth and perineural invasion through regulation of the M1R receptor on sensory neurons.