Adoptive T cell therapy with chimeric antigen receptor (CAR) T cells has entered the routine practice of oncology with the approval by FDA for leukemia and other tumors derived from B cells. We already have 4 approved checkpoint blockade drugs targeting CTLA-4 and PD-1 that are showing great effectiveness against melanoma and some other solid tumors. Thus the toolbox available for immuno-oncology is expanding and we have entered an exciting new era in cancer immunotherapy as the field begins to learn how to combine CAR T cells with other modalities including checkpoint inhibitors, vaccines, cytokines, radiation and chemotherapy. However, with the exception of melanoma and B cell malignancies, adoptive T cell therapy and checkpoint blockade is urgently in need of research to improve the potency and persistence of the infused T cells and antitumor effects.

We have come together to address this issue in order to identify mechanisms of resistance to CAR T cell therapy and discover approaches to enhance the potency of the infused engineered T cells, checkpoint blockade and combination immunotherapies. Our focus is to use state-of-the-art epigenetic approaches and preclinical models to examine CAR T cells and tumor cells in responding and non-responding patients. We have chosen to initially study patients with metastatic pancreatic cancer. These are cancers with a high unmet medical need and are generally considered incurable with present therapies. When safety is established, we also plan to study resistance mechanisms in the neoadjuvant setting for patients with pancreatic cancer.