Dr. Kenneth Olive

“Pancreatic Ductal Adenocarcinoma (PDA) is the only major cancer with a 5-year survival rate below 10%. PDA is unusually resistant to both genotoxic and targeted chemotherapies. This may be related to the particularly insidious combination of alterations in K-ras, p53, cdkn2a, and smad4 that are found in the majority of ductal pancreatic tumors. Unfortunately, none of these alterations can currently be therapeutically targeted in a direct manner. In this proposal, we take the alternative approach of targeting epigenetic alterations that are found in pancreatic cancer, using a novel inhibitor of th Bmi1 protein. Bmi1 is a member of the Polycomb Group (PcG) of proteins that participate in the modification of chromatin complexes. It is strongly overexpressed in PDA and its expression correlates with increased metastasis and reduced overall survival. Bmi1 plays a key role in the enzymatic function of the PRC1 complex, which causes mono-ubiquitylation of Histone H3, a chromatin modification that causes gene silencing. Among the genes targeted for transcriptional silencing by Bmi1 are p16Ink4a and PTEN, two tumor suppressors that are known to play critical roles in PDA that are frequently downregulated through non-genetic mechanisms. Finally, pancreas-specific deletion of Bmi1 prevents KrasG12D-driven formation of PanIN precursor lesions. Together these data argue that Bmi1 may be an effective therapeutic target for pancreatic cancer. Working in collaboration with PTC Therapeutics, we propose to perform a pilot evaluation of PTC596, a first-in-class small molecule inhibitor of Bmi1. We propose to carry out pharmacokinetic and pharmacodynamic studies of the agent using KPC mice and an innovative abdominal tumor biopsy surgery developed by our group. In addition, we will carry out an initial efficacy evaluation of the agent, alone or in combination with the genotoxic chemotherapeutic gemcitabine, using high resolution ultrasound to longitudinally monitor tumor volume. Using tissues from these two studies, we will study the effect of PTC596 treatment on Bmi1 phosphorylation, PRC1 function, target gene methylation (which correlates with chromatin state), and target gene expression. We will also evaluate the cellular responses to treatment using histopathology and immunohistochemistry. Together these experiments will provide pilot data necessary to support (or refute) future large-scale preclinical studies. These studies have the potential to identify a promising new therapeutic approach to a particularly deadly cancer for which there are few current treatment options.”