Pancreatic ductal adenocarcinoma (PDAC) is on track to become the second leading cause of cancer-related death this year. Yet, advances in the treatment of PDAC, including the application of immunotherapies, have been hindered by the presence of highly fibrotic and immunosuppressive desmoplastic stroma that limits drug delivery, promotes tumor survival, and establishes the tumor as a site of immune privilege. Recently developed epigenetic therapies, such as bromodomain inhibitors, have the potential to broadly rewire the PDAC stroma, overturning therapeutic resistance and sensitizing pancreatic tumors to immunotherapies. Indeed, we find that bromodomain inhibition dismantles immunosuppressive gene expression programs within multiple stromal cell populations and synergize with otherwise ineffective immune checkpoint therapies in mouse models of PDAC. However, the utility of bromodomain inhibitors in achieving durable anti-tumor immune responses is limited by a high systemic toxicity that precludes long-term treatment. In this proposal, we will use a cutting-edge peptide-targeting technology to promote tumor selective uptake of bromodomain inhibitors, reduce systemic toxicity, and enhance synergy with anti-PD-L1 checkpoint blockade. We will test established tumor-targeting peptides that have been validated in PDAC as well as develop novel fibroblast-specific targeting peptides that allow for cancer-associated fibroblasts to be selectively targeted for the first time. Collectively, this work will provide a viable approach for realizing the therapeutic potential of both bromodomain inhibitors and immune checkpoint therapy in pancreatic cancer. Importantly, this strategy is poised for rapid translation to the clinic, as both bromodomain inhibitors and tumor-targeting peptides are currently being tested in patient trials.
simultaneously reducing the adverse effects of existing therapies, as well as to sensitize pancreatic cancer to immunotherapies, could profoundly increase patient survival.