

MCC-C3 Padres Pedal the Cause Spring 2020

Peptide Targeted Delivery of Epigenetic Therapies in Pancreatic Cancer



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Scientific Abstract:

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.

Lay Abstract:

Pancreatic cancer is a devastating disease with few effective treatments. Moreover, recent immunotherapy approaches that have been remarkably successful in certain cancers have failed in pancreatic cancer. This poor performance of current therapies is in large part due to the presence of a complex cellular support network or stroma that surrounds the tumor. Importantly, the presence of the stroma compromises the immune response as well as drug delivery to the tumor. Cancer associated fibroblasts (CAFs) are major contributors to this stromal response, and as such, approaches that reduce the activities of CAFs may improve the effectiveness of existing therapies. Towards this end, we have promising findings that the epigenetic drug OTX can reduce the tumor supporting and immune suppressive actions of CAFs, however the adverse side effects of OTX are prohibitive. Here we will explore whether targeting technologies that focus drug delivery to the pancreas are able to reduce the adverse effects of OTX, and whether the therapeutic effects of this combination therapy are sufficient to enable immunotherapies. In addition, we will explore whether the existing targeting approach can be modified to selectively target the critical CAF population. These studies will be undertaken in mouse models that accurately mimic human disease, where the effects of therapy combinations on disease burden and ultimately survival will be measured. The potential of these studies to improve the effectiveness while

simultaneously reducing the adverse effects of existing therapies, as well as to sensitize pancreatic cancer to immunotherapies, could profoundly increase patient survival.