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Targeting fibroblast heterogeneity to improve surgical outcomes in pancreatic cancer

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Scientific Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and the third leading cause of cancer-related deaths in the United States. Currently, the only curative treatment for PDAC is surgical resection. However, 5-year survival rates remain alarmingly low even for patients with operable disease (around 25%), highlighting the difficulty of achieving the tumor-free margins necessary for curative resection. Fluorescence guided surgery (FGS) and photoimmunotherapy (PIT) are new approaches that utilize fluorophore-conjugated tumor-specific antibodies to provide high fidelity real-time tumor visualization during surgery, increasing the success of obtaining tumor-free margins. However, the implementation of these approaches in PDAC is limited by the presence of an extensive desmoplastic stroma that inhibits vascularization and drug delivery to the tumors. Pioneering work from our team has demonstrated an unparalleled ability for VDR agonists to remodel the tumor microenvironment and sensitize PDAC to drugs typically excluded from the tumor by driving activated cancer associated fibroblast (CAF) populations back towards a quiescent state. The goals of this proposal are 1) to determine if VDR agonist therapies can increase surgical success rates for FGS and PIT by promoting delivery of fluorophore-conjugated antibodies and 2) to define how recently discovered heterogeneity in CAF populations contributes to PDAC desmoplasia and VDRdriven therapeutic responses. Importantly, as VDR agonist therapies are already FDA approved, this work has significant potential to rapidly inform ongoing clinical efforts to test the efficacy of FGS and PIT in improving surgical outcomes.

Lay Abstract:

Currently, the only curative treatment for pancreatic cancer is surgical resection. However, for the majority of patients that undergo surgery, some cancer cells are inadvertently left behind and tumors regrow. The recent development of fluorescence-guided surgery and photoimmunotherapy techniques have tremendous potential to capture these remaining tumor cells and allow surgeons to achieve truly curative resections where patients remain disease free. Importantly, these revolutionary new approaches rely on the delivery of labeled drugs to tumors. One major roadblock for their successful application in pancreatic cancer comes from the presence of a cellular support network (or “stroma”) that surrounds the tumor, forming a physical barrier that hides tumor cells and prevents drugs from reaching them. This stromal response is largely driven by a collection of cells known as cancer associated fibroblasts (CAFs). In breakthrough studies, we have found that therapeutically targeting the Vitamin D Receptor (VDR) in CAFs can destabilize this stromal barrier. Here, we will use mouse models that accurately mimic human disease to test if VDR-targeted therapies can aid fluorescence-guided surgery and photoimmunotherapy to improve surgical success rates. In addition, we will use recent advances in single cell genomic analyses to understand precisely how VDR-targeted therapies impact the different types of CAFs that establish stromal barriers for drug delivery. In summary, by combining VDR-targeted therapies with fluorescence-guided surgery and photoimmunotherapy, we believe we are poised to dramatically enhance the success of surgical resection, paving the way for increased patient survival of this deadly disease.