

**Curebound Discovery Spring 2022**

**Targeting metabolic vulnerabilities unique to pancreatic ductal adenocarcinoma**

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**Scientific Abstract:**

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a 5-year survival rate of 11%. Unique to PDAC is a highly desmoplastic stroma and high propensity for liver metastasis. Targeted PDAC therapy is nonexistent. We found that although the desmoplastic stroma restricts nutrient access, the cancer cells bypass this restriction by using the stroma to stimulate and feed their metabolism. Importantly, we discovered that collagen (Col) remodeling plays a key role in controlling PDAC metabolism; whereas cleaved Col I (cCol I) generated by matrix metalloproteases activates the receptor tyrosine kinase DDR1, intact Col I (iCol I) induces DDR1 degradation, curtailing tumor metabolism and growth. Stimulation of PDAC metabolism by DDR1 depends on transcription factor NRF2 which induces expression of TFAM, the master activator of mitochondrial biogenesis. The cCol I: iCol I ratio and DDR1-NRF2-TFAM signaling pathway output strongly correlate with survival of resected PDAC patients, such that high cCol I: iCol I ratio and DDR1-NRF2-TFAM activation predict poor survival. Correspondingly, inhibitors of DDR1-NRF2-TFAM signaling and mitochondrial biogenesis, especially the FDA approved antibiotic tigecycline, compromise human PDAC growth and survival in mice. We propose to develop new targeted PDAC therapy based on the complementation of tigecycline with inhibitors of ULK1, a protein kinase required for mitophagy, a process that supports recycling of old mitochondria, to completely deplete PDAC mitochondria and block energy production. We will test the efficacy of the innovative tigecycline plus ULKi combination in preclinical models and human PDAC tumor slice cultures.

**Lay Abstract:**

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a 5-year survival rate of 11%. Most patients die within 6 months of diagnosis from metastatic disease, but even patients who qualify for surgical resection eventually succumb to the disease. No targeted therapies are available. Unique to PDAC is a dense tumor stroma that restricts nutrient acquisition by the cancer cells, which bypass this obstacle through upregulation of alternative nutrient procurement and energy generating mechanisms. Key to upregulation of these mechanisms is the ratio of cleaved (cCol) and intact (iCol) collagen in the tumor stroma. Using preclinical models, we found that the cCol:iCol ratio dictates PDAC metabolism and growth by regulating the expression and activity of a specific collagen sensor called DDR1, thereby controlling the generation of mitochondria, the cellular power stations that provide PDAC cells with energy. The tumor cCol:iCol ratio, DDR1 activity and mitochondrial content strongly correlate with patient survival after resection. Importantly, high mitochondrial content predicts poor survival, suggesting that mitochondria reducing treatments may inhibit tumor growth. Indeed, we found that an FDA-approved antibiotic called tigecycline reduces mitochondrial content and curtails PDAC metabolism and growth in preclinical models. Here we propose to potentiate tigecycline's anti-PDAC activity by complementing it with inhibitors of an enzyme, ULK1, needed for the recycling and repair of PDAC mitochondria. This novel approach, which will be tested in several preclinical models and fresh

human PDAC slice cultures, should be highly effective in blunting PDAC growth by cutting off tumor energy supplies.