Co-Inhibition of xCT and MEK Presents a New Therapeutic Methodology for Pancreatic Cancer

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Category: Basic/Translational

Hypothesis: ACXT-3102 (ACXT), a targeted xCT inhibitor, compliments inhibitors of KRAS signaling to treat pancreatic ductal adenocarcinoma (PDAC).

Background: Ferroptosis is a recently-described form of programmed cell death that is characterized by impaired cystine import, rapid glutathione depletion, and generation of toxic lipid peroxides. Cancers expressing oncogenic KRAS mutations (including >95% of PDAC) are particularly vulnerable to ferroptosis. ACXT synthetically links a cancer-specific targeting molecule with erastin, which is a canonical ferroptosis inducer that blocks the cystine importer xCT. Combined in a single molecule, ACXT induces brisk cytotoxicity in pancreatic cancer models, and has *in vitro* potency that is ten times greater than either of its component molecules alone (dnot shown). Downstream effectors of KRAS, especially MEK (MAP/Erk Kinase) have been identified as survival mechanisms, and are potential targets to improve ACXT's antitumor effects. Taking a mechanism-based approach, trametinib (MEK1/2 inhibitor) was selected as a potential drug partner for ACXT.

Methods & Results: AsPC-1 cells (human pancreatic cancer) were treated in culture with increasing concentrations of ACXT and trametinib for 24 hours. After treatment, viability was determined with CellTiter-Glo assay. Results were analyzed using Python software. AsPC-1 cells were implanted subcutaneously into the flank of athymic nude mice. Once the tumors reached 100mm^3, they were randomized to receive ACXT (60mg/kg/day PO), trametinib (1mg/kg/day IP), combination treatment, or vehicle control.

In vitro (**Fig. 1A**) and *in vivo* (**Fig. 1B**) effects of ACXT and trametinib co-treatment are displayed. **Fig. 1A** shows the net cytotoxic effect of ACXT (Y axis) and trametinib (X axis) using a heatmap. Combination conditions have better cytotoxicity. **Fig. 1B** shows tumor volume plots over 14 days of treatment with monotherapy, combination therapy, or control. Combination treatment was significantly more effective than either monotherapy alone (p = 0.0085).

Conclusions: Pancreatic cancer is a disease with poor outcomes, which necessitates new approaches for management. In preclinical models, ACXT and trametinib present a novel option for targeted treatment of pancreatic cancers.

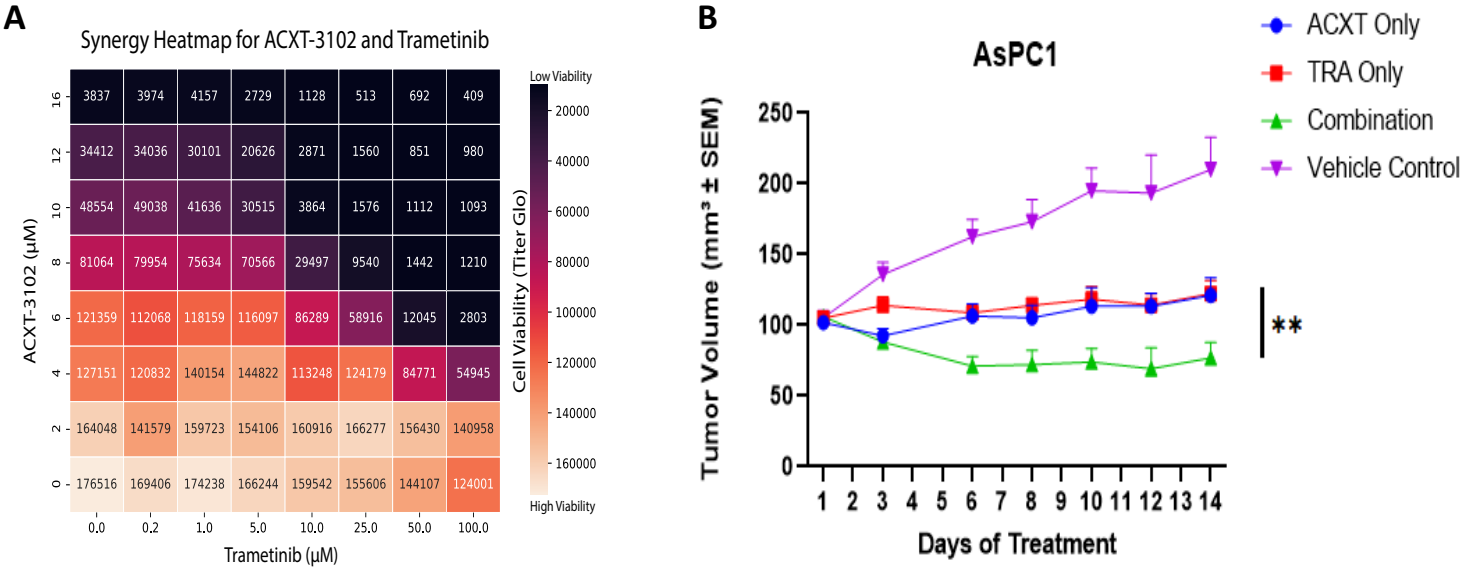

Figure 1: **Combined xCT (ACXT-3102) and MEK inhibition (trametinib) have the potential for synergistic drug interactions. (1A)** 24h treatment of pancreatic cancer cell lines with ACXT (Y axis) and Trametinib (X axis) causes synergistic cell death. Darker colors indicate increased cell death. **(1B)** Mouse xenograft model of pancreatic cancer shows greater responses to co-treatment than to either monotherapy alone.