A Novel Combination of Two Repurposed Drugs for Pancreatic Cancer

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Abstract

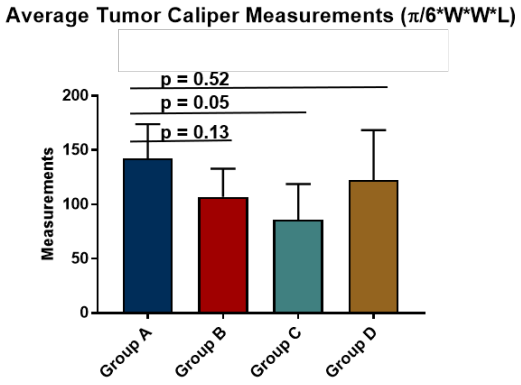
Pancreatic adenocarcinoma (PDA) is among the most deadly cancers. Our research, and recent work by others, suggests that the transcription factor E47 (from the E2A gene) has tumor suppressor activity in PDA. We showed that E2A is inhibited by high expression of its repressor ID3 in PDA. Further, a study from the Tuveson lab has shown that the most common non-coding mutations in human PDA are in binding sites for E47 and its paralog HEB. In preliminary data we showed that loss of the E2A gene in the murine model of pre-cancer that expresses Kras in the pancreas, resulted in larger lesions, classifying E2A as a bona fide tumor suppressor. Moreover, when we restored E47/E2A activity in human PDA cells, cell growth was halted *in vitro* as well as in tumor cells transplanted in mice. Thus, PDA cells remain addicted to dysregulation of E2A suggesting that restoring its activity could be a viable therapeutic avenue. To translate these findings to the clinic we developed a high throughput screen to identify potential inducers of E2A activity. From a library of known (safe) drugs, we identified Pitavastatin and Vorinostat. Each drug alone slowed the growth of PDA cells *in vitro*. Together however, Pitavastatin and Vorinostat worked synergistically to induce endoplasmic reticulum stress, growth arrest, and cell death in PDA cells *in vitro*.

Our goal is to determine whether the drug combination is effective in reducing PDA tumor burden *in vivo*.

<u>Progress</u>

Here we have performed *in vivo* pilot experiment using 4 mice per group listed below. Mice were injected with PANC1 tumor cells on Day 1 and drug was administered daily from Day 5 until Day 30. Plasma samples were analyzed to ensure that there were circulating drug levels in the mice.

A. DMSO
B. Vorinostat
C. Vorinostat +Pitavastatin
D. Pitavastatin



We observed a significant reduction in tumor volume in animals treated with the drug combination (p=0.05, see figure). Therefore, additional in vivo studies will be conducted.