Scientific Abstract

Pancreatic Cancer Collective Research Team:
"Combined Targeting of MEK1/MEK2 and Autophagy for Pancreatic Cancer"

[This abstract was provided by the scientists when their application was accepted.]

Although KRAS sends signals for pancreatic carcinogenesis through the RAF protein kinases and the PI3'-lipid kinases, it is the RAF/MEK/ERK MAP kinase pathway that plays a central role in pancreatic carcinogenesis. Disappointingly, neither pharmacologic inhibition of RAF or PI3'-kinase signaling has offered PDAC patients any clinical benefit. Alternatively, autophagy has been targeted for PDA therapy. However, despite promising preclinical data, this strategy has also proven unsuccessful in the clinic.

The Team has observed that under conditions in which single agent blockade of either RAF/MEK/ERK signaling or autophagy had only modest effects, combined inhibition of both processes resulted in synergistic cytotoxicity *in vitro*, and striking regression of established tumors in mice.

The Team proposes to pursue three specific aims:

1. Test if there is a pancreatic cancer cell genotype -Trametinib (T)/hydroxychloroquine (HCQ) drug response phenotype in PDA cell lines and PDX models with an initial emphasis on *TP53* mutation status.

2. Explore novel targets and agents to inhibit trametinib-induced autophagy in pancreatic cancer cells *in vitro* and PDX models in mice that might become candidates for a PDA clinical trial.

3. Initiate a clinical trial of the combination of trametinib plus HCQ in PDA patients.

If the results of this clinical trial are encouraging, the Research Team will propose to expand our efforts into a large, multi-institutional Phase III clinical trial of the T/HCQ combination therapy to be supported by Round 2 of the Pancreatic Cancer Collective New Therapies Challenge.