

A Novel Combination of Two Repurposed Drugs for Pancreatic Cancer

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Background

From a library of known (safe) drugs, we identified Pitavastatin and Vorinostat that each 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 was to determine whether the drug combination is effective in reducing PDA tumor burden *in vivo*. As reported in our last update, in a pilot study we observed a significant reduction in tumor volume in animals treated with the drug combination versus controls or either drug alone (p=0.05).

Update

To optimize tumor studies several seeding densities of PDA cells were tested in mice. In the pilot experiment we observed solubility issues with the drugs that could interfere with correct dosing. Therefore, to optimize drug availability *in vivo* we treated mice with drugs solubilized by several methods and administered by IP or orally. Plasma samples collected at multiple time points after drug administration were assayed against a standard curve for each drug by LC-MS. The data revealed that circulating drug levels were maximized by IP administration and preferred diluents were chosen.

Pitavastatin						Vorinostat							
IP 40 mg/kg						IP 100 mg/kg							
Vehicle: 2.5% DMSO in corn oil						Vehicle: 2.5% DMSO in corn oil							
	Plasma concentration (ng/ml)				AUC	Ratio		Plasma concentration (ng/ml)				AUC	Ratio
Time (hr)	AN1#	AN2#	AN3#	Mean (n=2)	(ng/ml*hr)		Time (hr)	AN1#	AN2#	AN3#	Mean (n=3)	(ng/ml*hr)	
0.5	697	1550	39400	1123.5			0.5	279	509	1270	686.0		
2	118	160	5500	139.0			2	5.02	15.2	22	14.1		
6	1.37	2.79	85.8	2.1	1509.9	0.42	6	<LOQ	<LOQ	5.43	1.8	728.3	0.66
													LOQ: 0.98 ng/ml
IP 40 mg/kg						IP 100 mg/kg							
Vehicle: PBS						Vehicle: 10% HP-b-CD							
	Plasma Concentration (ng/ml)				AUC			Plasma Concentration (ng/ml)				AUC	
Time (hr)	AN1#	AN2#	AN3#	Mean (n=3)	(ng/ml*hr)		Time (hr)	AN1#	AN2#	AN3#	Mean (n=3)	(ng/ml*hr)	
0.5	3080	3650	3480	3403.3			0.5	1310	862	966	1046.0		
2	33.8	42.4	99.4	58.5			2	8.42	6.7	36.8	17.3		
6	4.73	3.7	4.55	4.3	3572.9	1.00	6	<LOQ	<LOQ	16	5.3	1104.3	1.00
Oral 40 mg/kg						Oral 100 mg/kg							
Vehicle: PBS						Vehicle: 10% HP-b-CD							
	Plasma Concentration (ng/ml)				AUC			Plasma Concentration (ng/ml)				AUC	
Time (hr)	AN1#	AN2#	AN3#	Mean (n=3)	(ng/ml*hr)		Time (hr)	AN1#	AN2#	AN3#	Mean (n=3)	(ng/ml*hr)	
0.5	1810	591	1080	1160.3			0.5	218	118	102	146.0		
2	91.3	44.5	100	78.6			2	16.4	8.13	24.1	16.2		
6	39.7	163	66.4	101.4	1579.2	0.44	6	23	2.74	4.4	12.9	216.3	0.20

Unfortunately, COVID 19 has interfered with the capacity of our animal facility for preclinical studies. We are slated to begin a large study in January 2021.