

# CPI-613 attack on tumor mitochondrial metabolism synergizes with mechanistically diverse chemotherapeutics in vitro and in the clinic



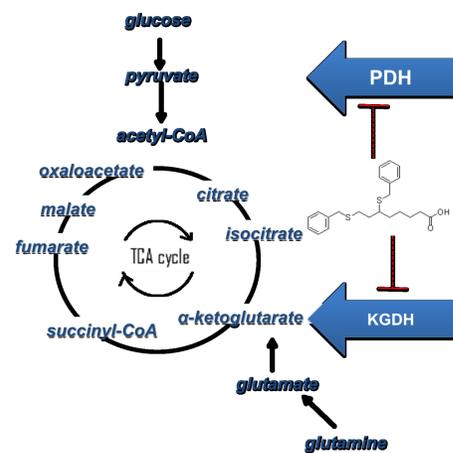
<sup>1</sup>Department of Biochemistry and Cell Biology, <sup>2</sup>Genetics PhD Program, Stony Brook University, Stony Brook, New York

<sup>3</sup>Rafael Pharmaceuticals, Cranbury, New Jersey



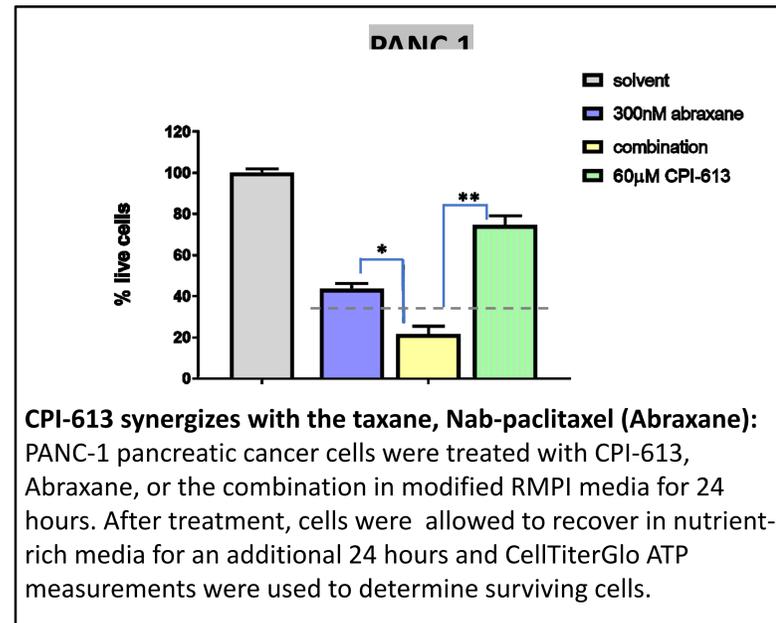
Moises Guardado Rivas<sup>1,2</sup>, Shawn Stuart<sup>3</sup>, Michael Dahan<sup>3</sup>, Ke Hu<sup>3</sup>, Paul M. Bingham<sup>1,3</sup>, Zuzana Zachar<sup>1,3</sup>

**INTRODUCTION: CPI-613 simultaneously inhibits PDH and KGDH selectively in tumor cells, exploiting lipoate-sensitive regulatory systems altered in cancer and opening novel clinical opportunities**

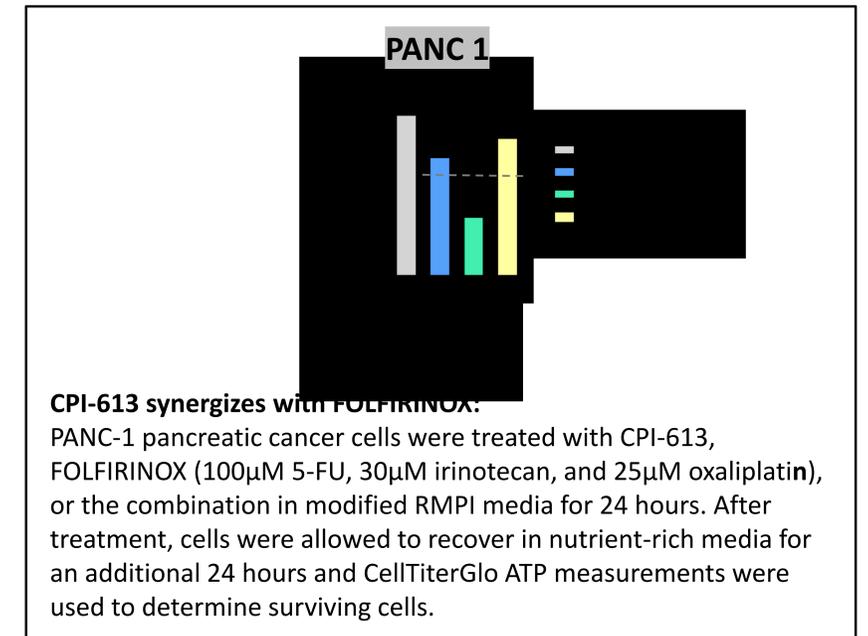


CPI-613 powerfully inhibits the two main entry points for carbon into mitochondria (PDH and KGDH), selectively in tumor cells. This effect dramatically reduces tumor cell production of ATP (catabolism) and TCA cycle metabolites (anabolism)(1,2). These two sets of products of mitochondrial metabolism are expected to be essential to support most or all cell stress responses, including resistance to chemotherapeutic standards of care (SOC). Consistent with this expectation, we find highly significant synergy between CPI-613 and various SOC agents (see in vitro cell survival figures). Moreover, the high CPI-613 tumor selectivity allows the drug to be combined with diverse SOCs in clinical trials with very low side effect toxicity. Resulting clinical studies to date show strong CPI-613/SOC synergy with FOLFIRINOX (3). We report in new vitro synergies with other important SOCs here, laying the groundwork for future new clinical trials.

## CPI-613 synergizes with paclitaxel in vitro



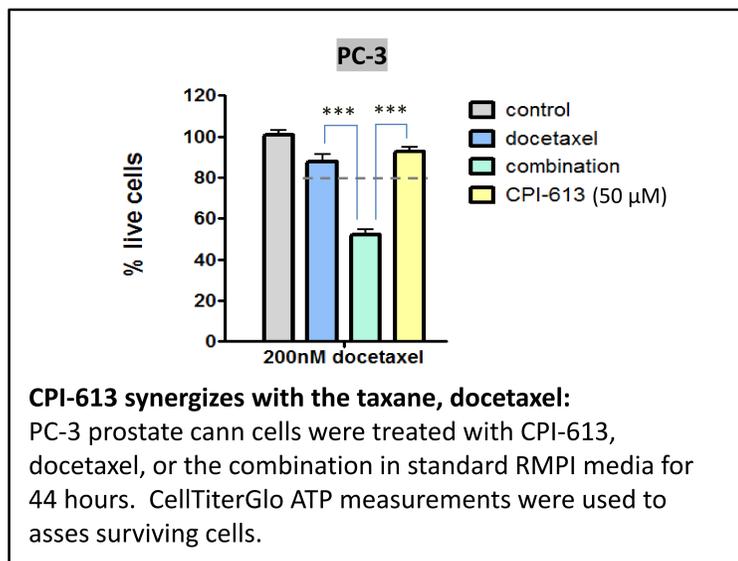
## CPI-613 synergizes with FOLFIRINOX in vitro



## CPI-613 Synergizes with FOLFIRINOX in the clinic

	Gemcitabine	Gemcitabine + Abraxane	FOLFIRINOX	mFORFIRINOX + CPI-613
N	171	431	171	18
CR	0%	<1%	<1%	17%
ORR	9.4%	24%	31.6%	61%
Median PFS (months)	3.3	5.5	6.4	11.5
Median age	61	62	61	64
Reference	4	5	4	3

## CPI-613 synergizes with docetaxel in vitro



## Conclusions

- **CPI-613's mechanisms of action (MOA; 1,2) synergize with diverse chemotherapeutics in vitro, including the PDAC standard of care (SOC), FOLFIRINOX.**
- **Correspondingly, CPI-613 synergizes in the clinic with FOLFIRINOX in PDAC patients.**
- **CPI-613 synergizes with other SOC chemotherapeutics with different MOA's (including the taxanes shown here) in vitro.**
- **We are currently exploring whether this taxane synergy will translate into the clinic and to diverse other cancers.**

## References

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