

# Lkit Therapeutics

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*Exploiting synthetic lethality to target p53 mutant cancers using **first-in-class potent and selective small molecule inhibitors** of lipid kinases PI5P4K $\alpha/\beta$ .*

# Project Team

## Ya Ha, Ph.D.

*Associate Professor of Pharmacology  
Yale University*

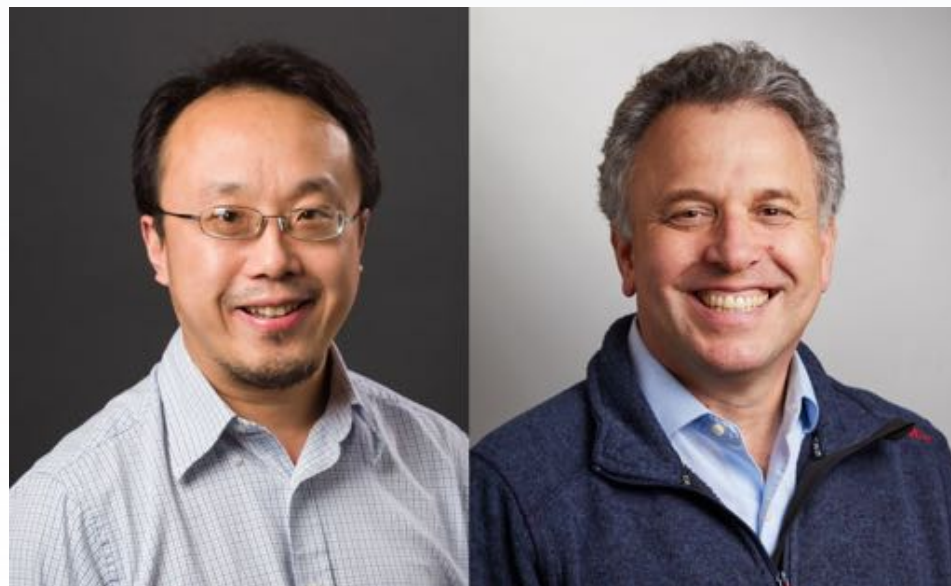
Extensive experience in structural biology and membrane protein biochemistry. Leader in the field of lipid kinase mechanism and function.

## Jonathan Ellman, Ph.D.

*Eugene Higgins Professor of Chemistry  
Yale University*

Extensive experience in organic synthesis and chemical biology.

Co-founded Sunesis Pharmaceuticals; served on founding SABs for Versicor/ Vicuron (purchased by Pfizer for >2 billion \$), Ardelyx, and Lycera; consultant at many pharma companies, including AbbVie and Ono Pharmaceuticals.



**Jointly unraveled the molecular mechanism underlying the synthetic lethality between p53 and lipid kinases PI5P4K $\alpha$  and PI5P4K $\beta$**

# Clinical Need – p53 mutation and human cancer

- *TP53* germline mutation predisposes an individual to tumorigenesis (Li-Fraumeni Syndrome; breast cancer is the most common among LFS patients)
- Somatic mutations in p53 is highly frequent in a wide range of cancers

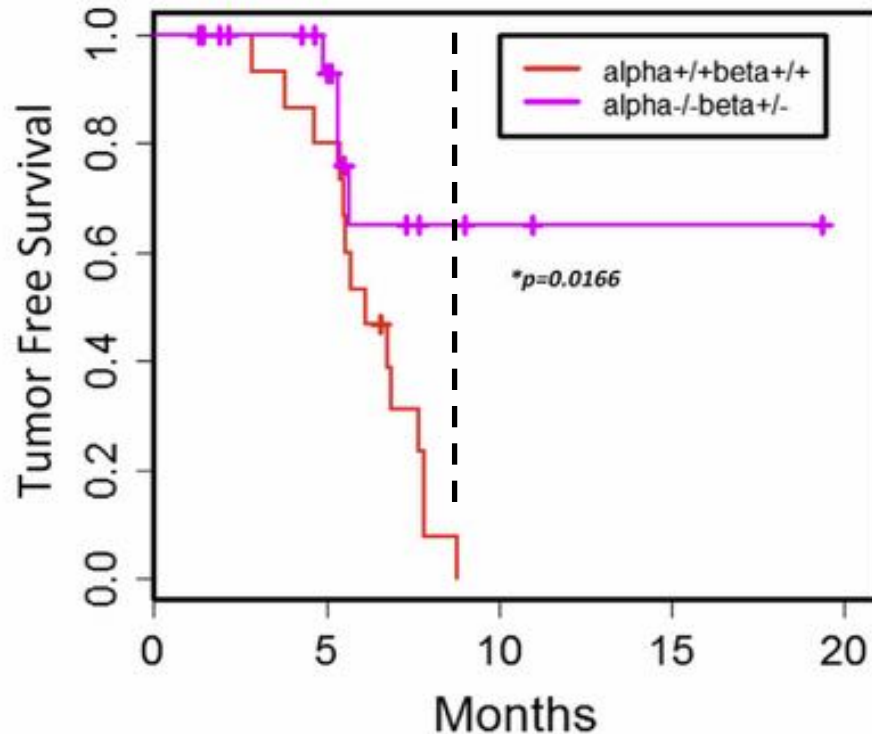
Cancer Location	Deaths Per Year	p53 Mutation Rate
LUNG	160,000	68%
COLORECTAL	50,000	55%
BREAST	40,000	36%
PANCREATIC	40,000	66%
PROSTATE	30,000	21%
LIVER	20,000	32%
OVARIAN	10,000	64%
ESOPHAGEAL	10,000	87%

**No treatment is yet available to specifically target this common genetic abnormality**

# Ground-breaking discovery of PI5P4K function

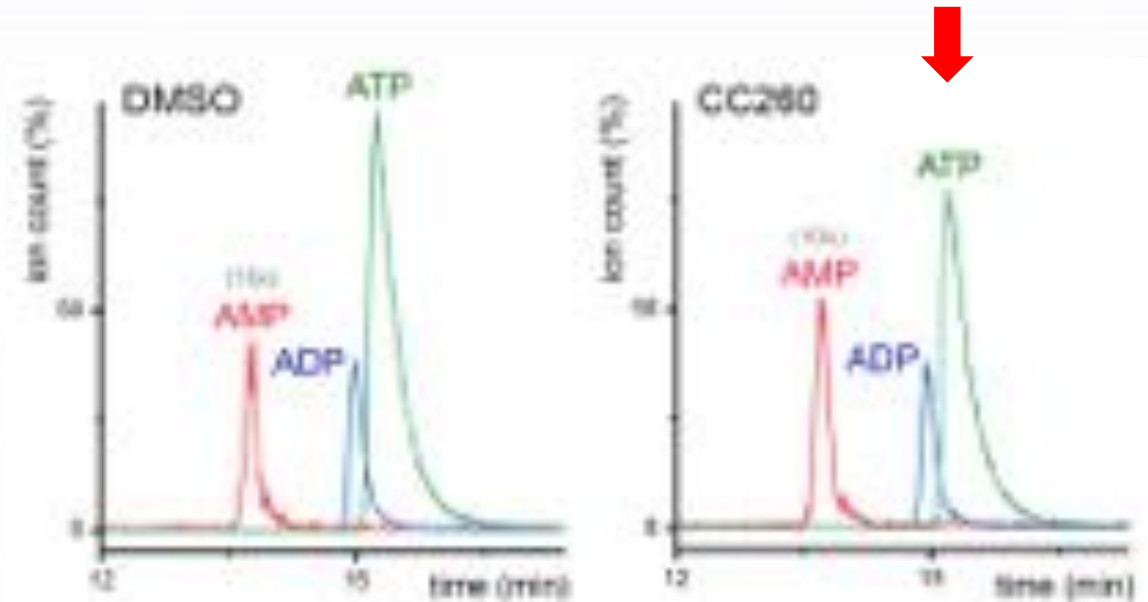
- PI5P4Ks (type 2 PIP kinases) play important roles in cell metabolism and autophagy.
- PI5P4K $\alpha/\beta$  are essential for the growth of p53-mutant breast cancer cells.

## Knockout of PI5P4K $\alpha/\beta$ in *TP53*<sup>-/-</sup> Mice



“survival curves” adapted from Emerling et al., *Cell* 2013

## PI5P4K $\alpha/\beta$ Inhibition Disrupts Cell Energy Metabolism



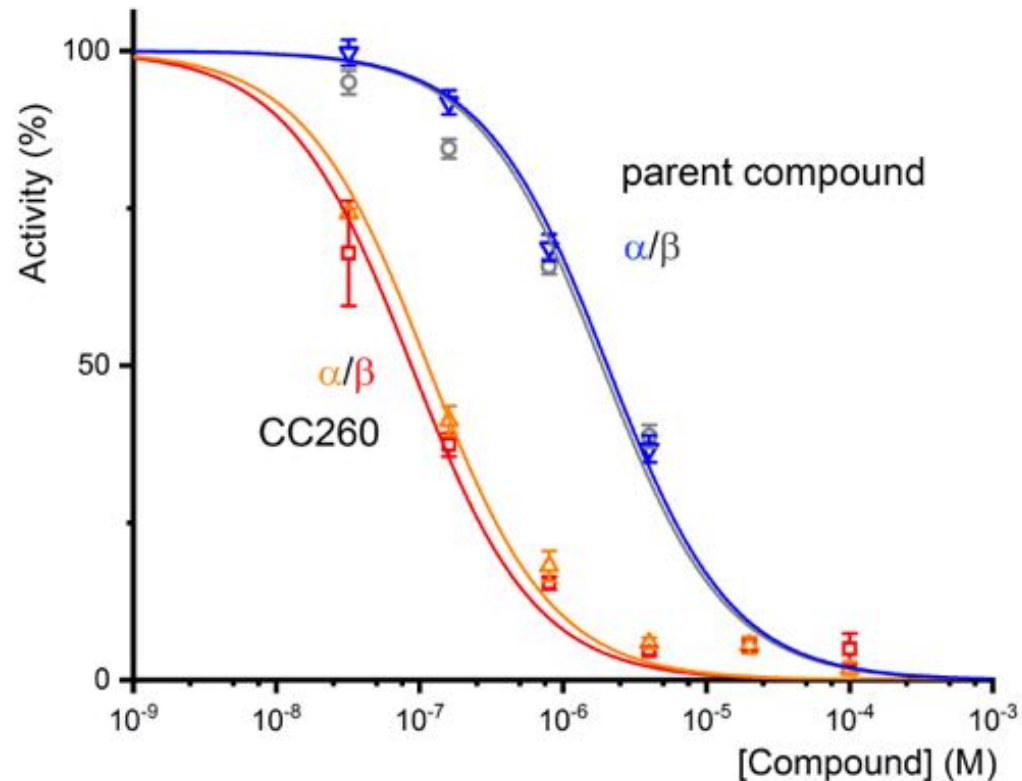
**NO PREVIOUSLY REPORTED DUAL INHIBITORS OF  $\alpha/\beta$  ISOFORMS**

# Therapy Landscape of Targeting p53 Pathway

APPROACH	COMPETITORS	TARGET	DEVELOPMENT STAGE	KEY LIMITATION
Synthetic Lethality	<b>Lkit Therapeutics</b>	PI5P4K $\alpha$ / $\beta$	Discovery	Limited experience in human patients
Boosting Levels of Wildtype p53	Numerous Big Pharma Roche (nutlins), Novartis (HDM201), Daiichi-Sakyo (DS3032), Aileron (ALRN-6924), Innovation Pharmaceuticals (Kevetrin)	MDM2 Degradation Pathway	Phase I, II	Requires some level of functional p53
	Merck (SCH-58500)	Gene Therapy Restoration	Phase III	Selectivity and efficiency
Chaperone/Protein Rescue Approach	Apres Bioscience (APR-246) Cotinga Pharma (COTI-2)	Stabilizing p53 Structure Using Allostery	Phase I	Mutant specific
Metabolism / Synthetic Lethality	Metformin	Unknown	Phase I, II, III	Unknown molecular target
Autophagy	Petra Pharma (Petra-01)	PI5P4K $\alpha$	Preclinical	Does not inhibit PI5P4K $\beta$

# Inhibitors with dual specificity against $\alpha$ and $\beta$ isoforms

- Leveraged our extensive structural insights to identify key features required to develop dual inhibitors



**Dual Specific Inhibitors with  $K_i \sim 30$  nM**

## Drug-like Properties of CC260

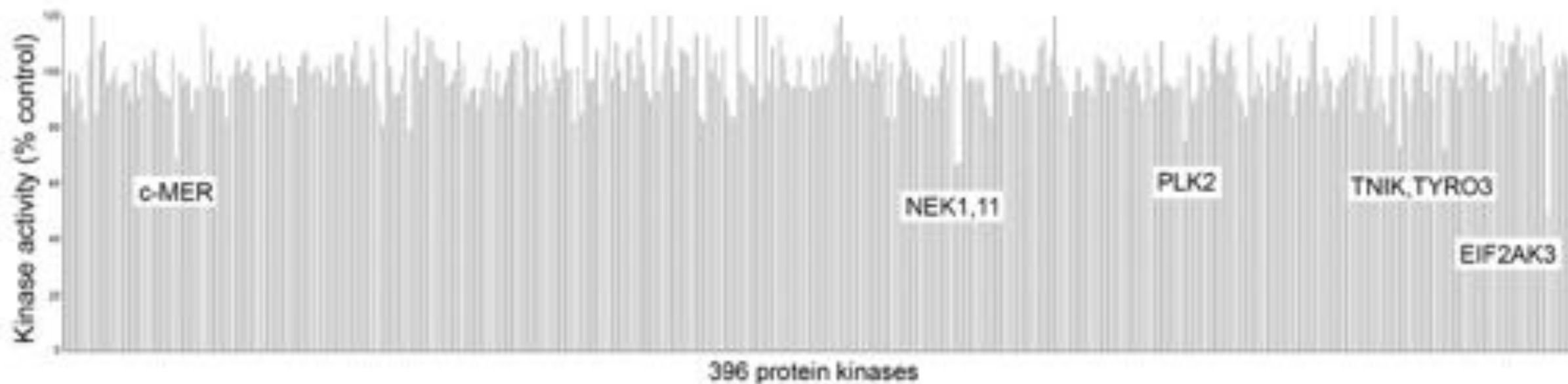
PI5P4K $\alpha$ Activity	40 nM
PI5P4K $\beta$ Activity	30 nM
Mol. Wt.	490 Da
cLogP	6
TPSA	82 Å <sup>2</sup>

## Intellectual Property Positioning

Yale has filed a patent covering composition of matter for the lead dual PI5P4K inhibitors (Aug. 8, 2019)  
- Further Med. Chem. will enhance patent portfolio

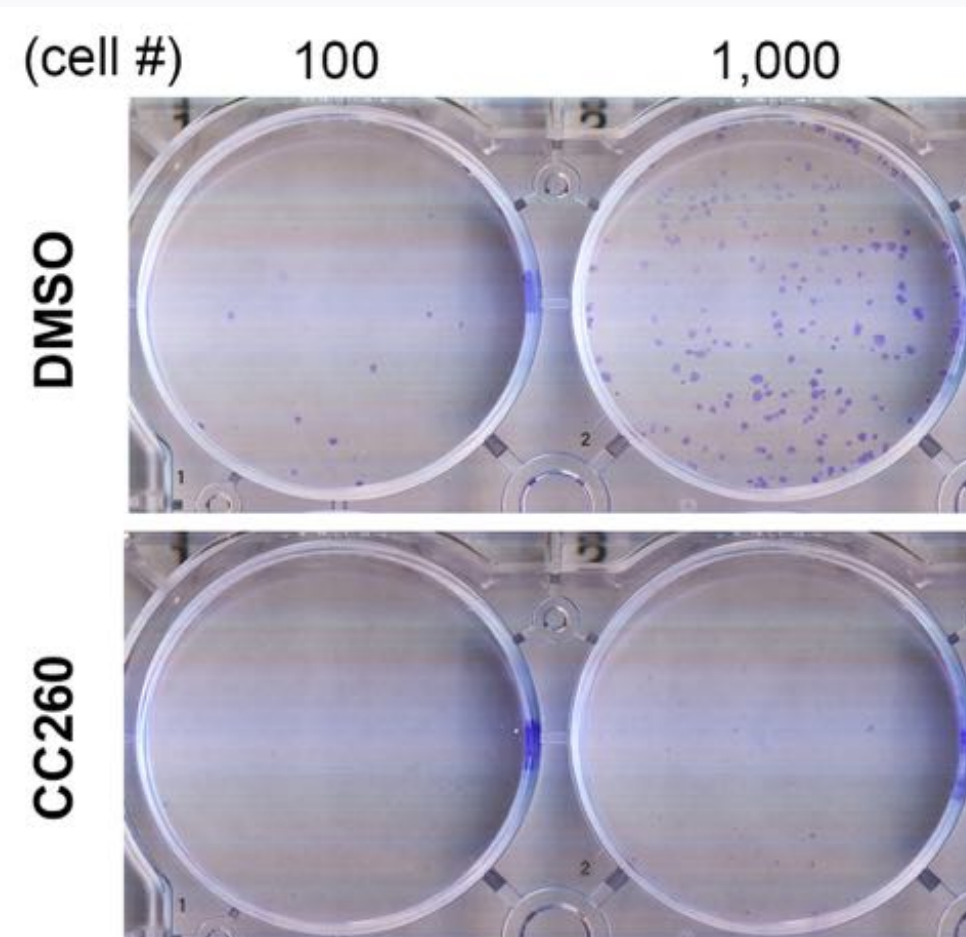


# Lead compound has exquisite selectivity



Highly Selective with Mild Inhibition of Only 7/396 Protein Kinases

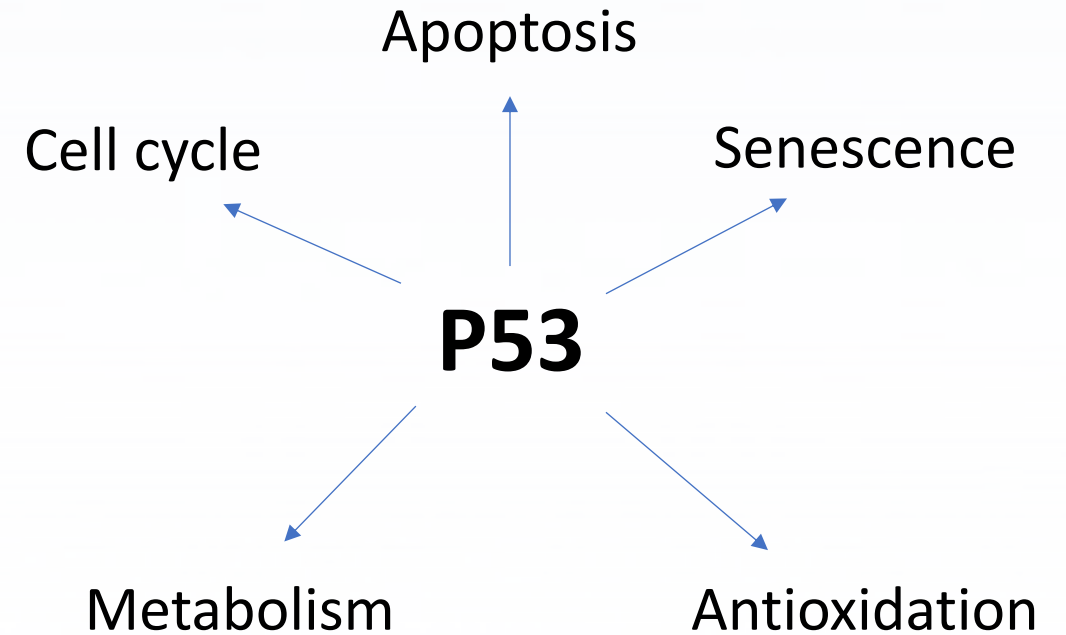
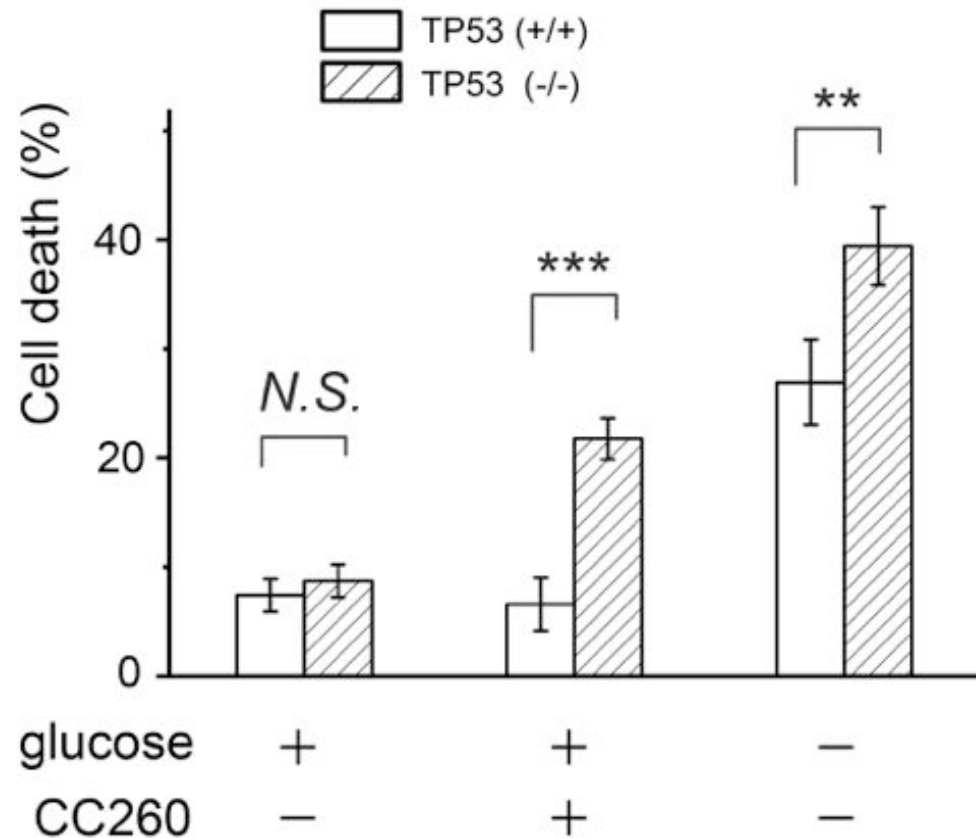
# Validation of lead compound's cellular activity



Inhibition of Cancer Cell Colony Formation



# Cytotoxicity correlates with cancer cell's p53 status



We are now ready to progress our compounds into *in vivo* efficacy studies

## Project Summary

- First-in-class potent and selective dual PI5P4K $\alpha/\beta$  inhibitors
- Potential broad application in cancer treatment

## Intellectual Property Positioning

- Yale University has filed a patent covering composition of matter for the lead dual PI5P4K inhibitors (Aug. 8, 2019)
  - Further medicinal chemistry will enhance patent portfolio

# Goals for Utilizing Blavatnik Award Funding

**Value Inflection Point to be Achieved with Blavatnik:** Held meetings with venture capital firms on their interest who request proof-of-concept efficacy in mouse models.

