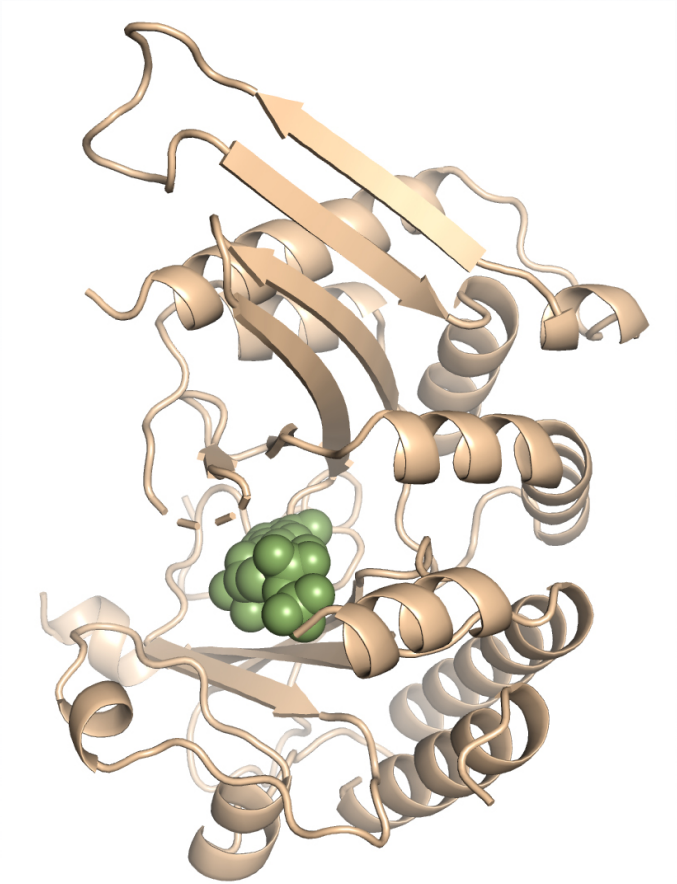
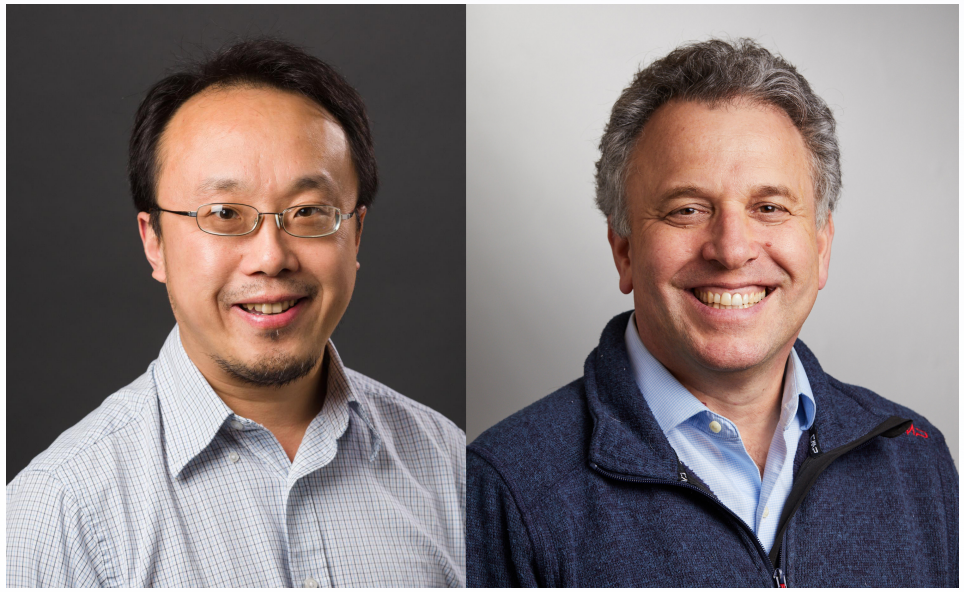


Lkit Therapeutics

Exploiting synthetic lethality to target p53 mutant cancers using first-in-class potent and selective small molecule inhibitors of lipid kinases PI5P4Kα/β.

Contact | ya.ha@yale.edu -or- jonathan.ellman@yale.edu

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 PI5P4Kα and PI5P4Kβ

Contact | ya.ha@yale.edu -or- jonathan.ellman@yale.edu

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%

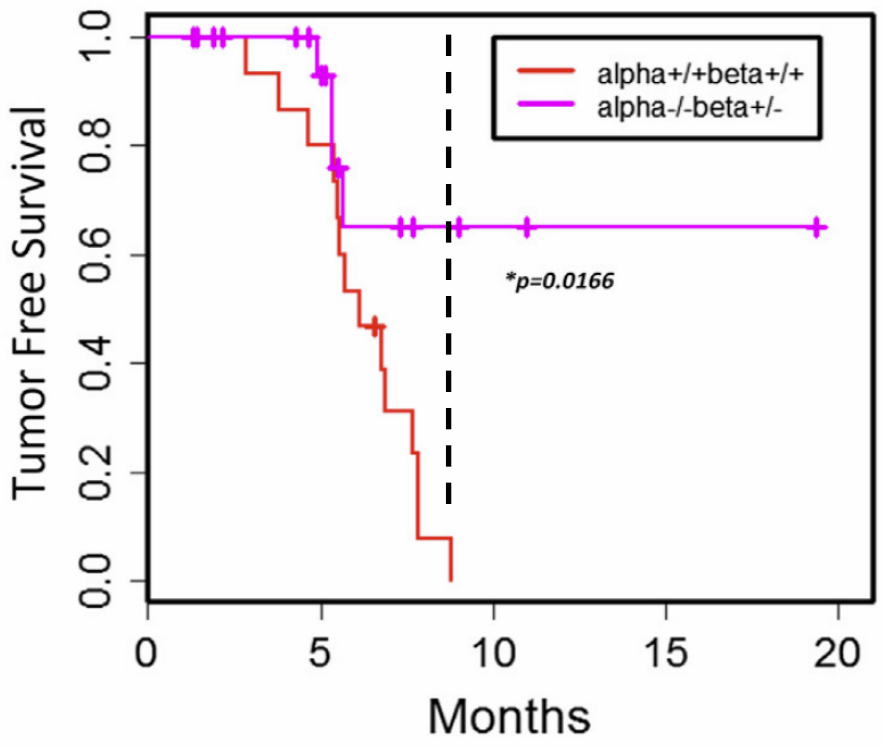
No treatment is yet available to specifically target this common genetic abnormality

Source: NCI, cBioPortal

Ground-breaking discovery of PI5P4K function

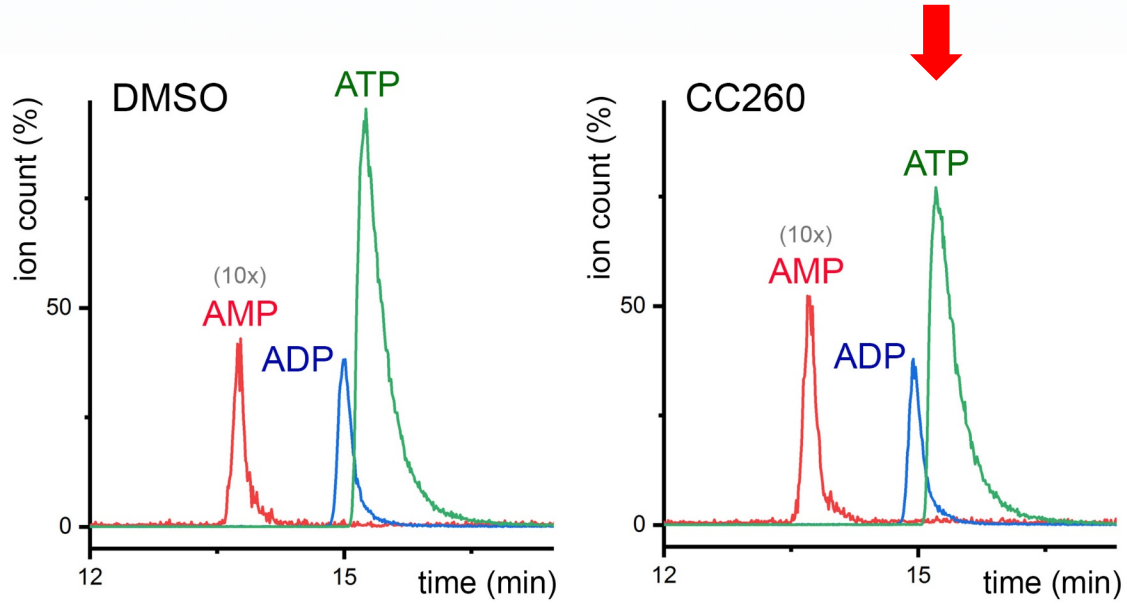
- PI5P4Ks (type 2 PIP kinases) play important roles in cell metabolism and autophagy.
- PI5P4Kα/β are essential for the growth of p53-mutant breast cancer cells.

Knockout of PI5P4Kα/β in *TP53*$^{-/-}$ Mice



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

PI5P4Kα/β Inhibition Disrupts Cell Energy Metabolism



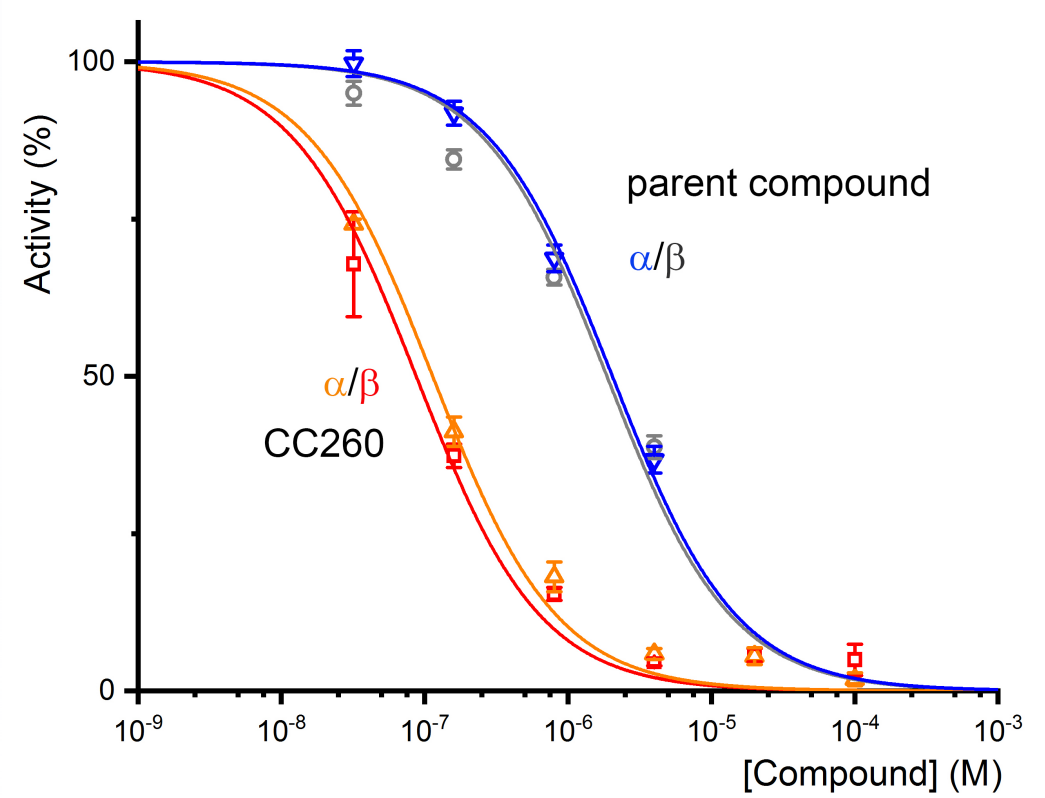
NO PREVIOUSLY REPORTED DUAL INHIBITORS OF α/β ISOFORMS

Therapy Landscape of Targeting p53 Pathway

APPROACH	*COMPETITORS*	*TARGET*	*DEVELOPMENT STAGE*	*KEY LIMITATION*
Synthetic Lethality	**Lkit Therapeutics**	PI5P4Kα/β	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)	PI5P4Kα	Preclinical	Does not inhibit PI5P4Kβ

Inhibitors with dual specificity against α and β isoforms

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



Dual Specific Inhibitors with K_i ~ 30 nM

Drug-like Properties of CC260

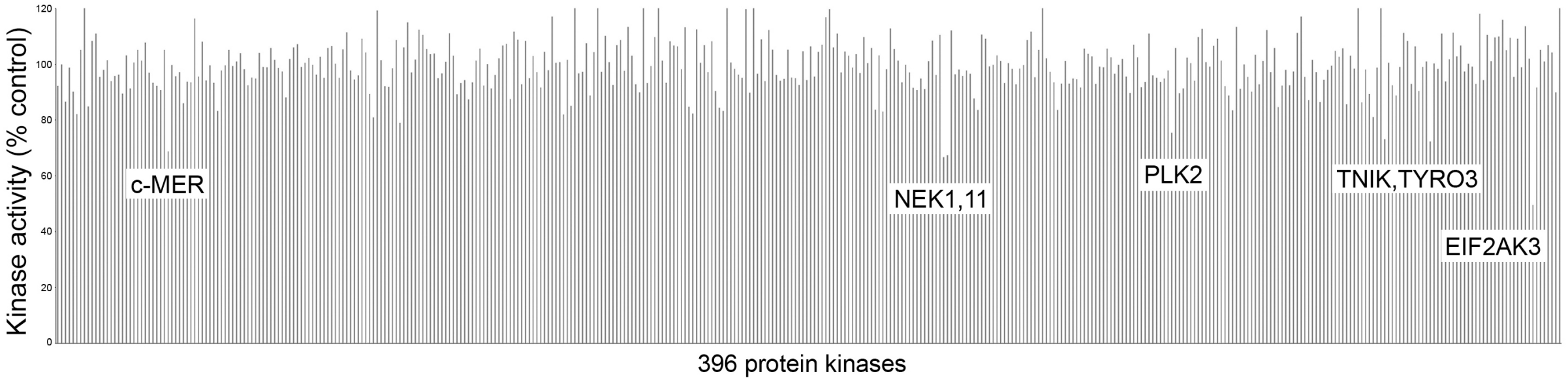
PI5P4Kα Activity	40 nM
PI5P4Kβ Activity	30 nM
Mol. Wt.	490 Da
cLogP	6
TPSA	82 Å^2

Intellectual Property Positioning

Yale has filed a patent covering composition of matter for the lead dual PI5P4K inhibitors (Aug. 8, 2019)

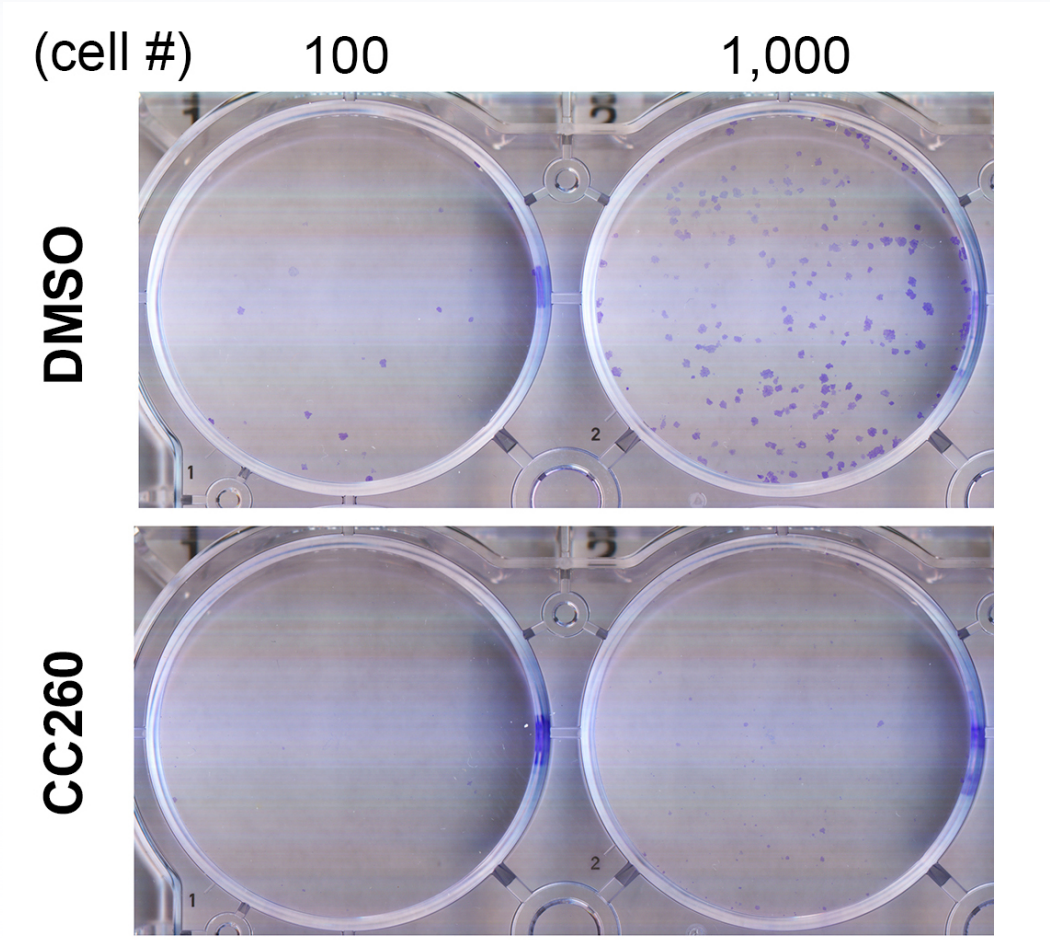
- Further Med. Chem. will enhance patent portfolio

Lead compound has exquisite selectivity



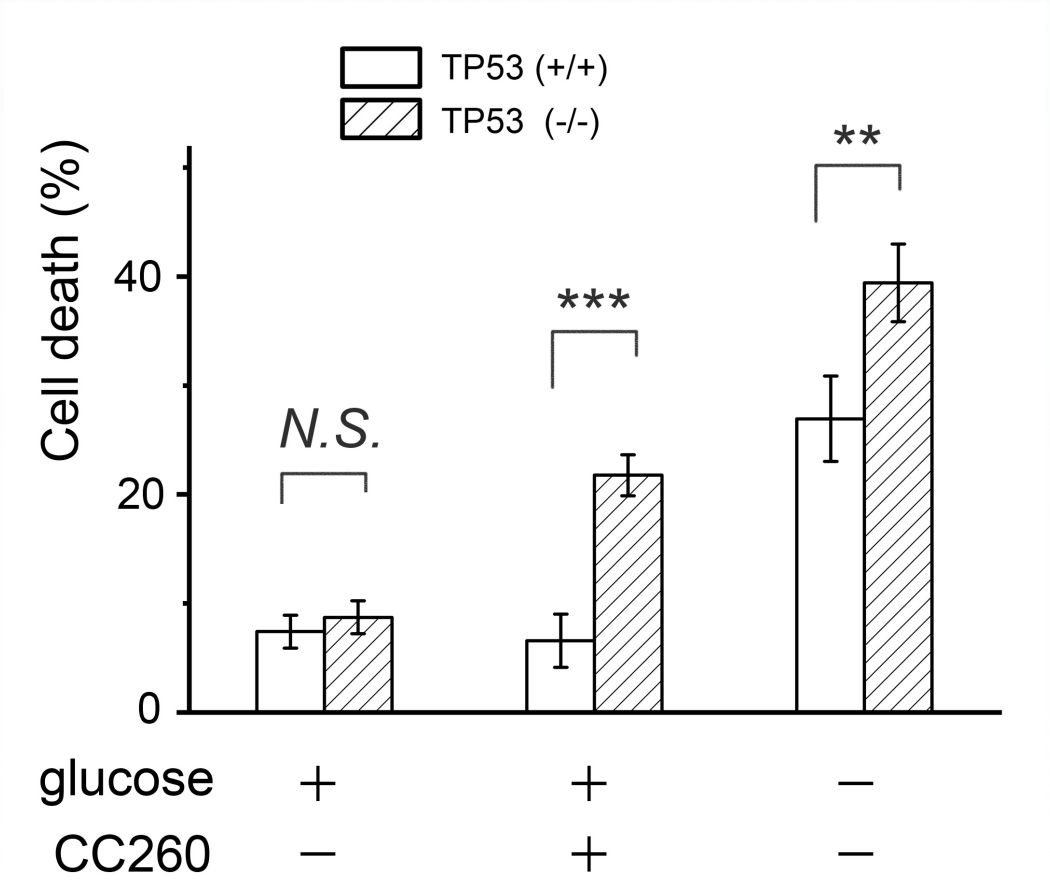
Highly Selective with Mild Inhibition of Only 7/396 Protein Kinases

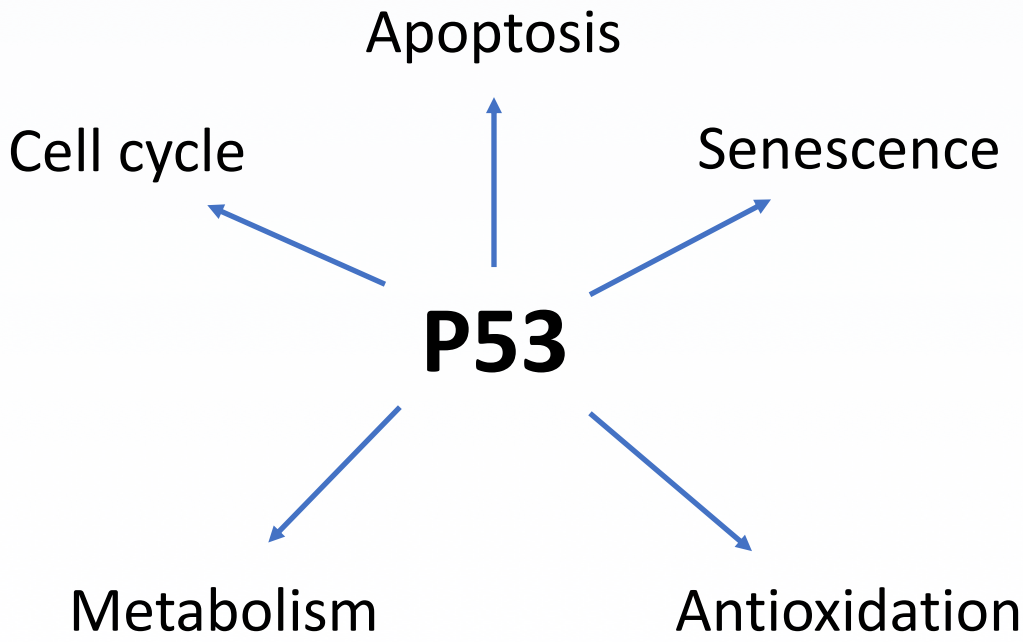
Validation of lead compound's cellular activity



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

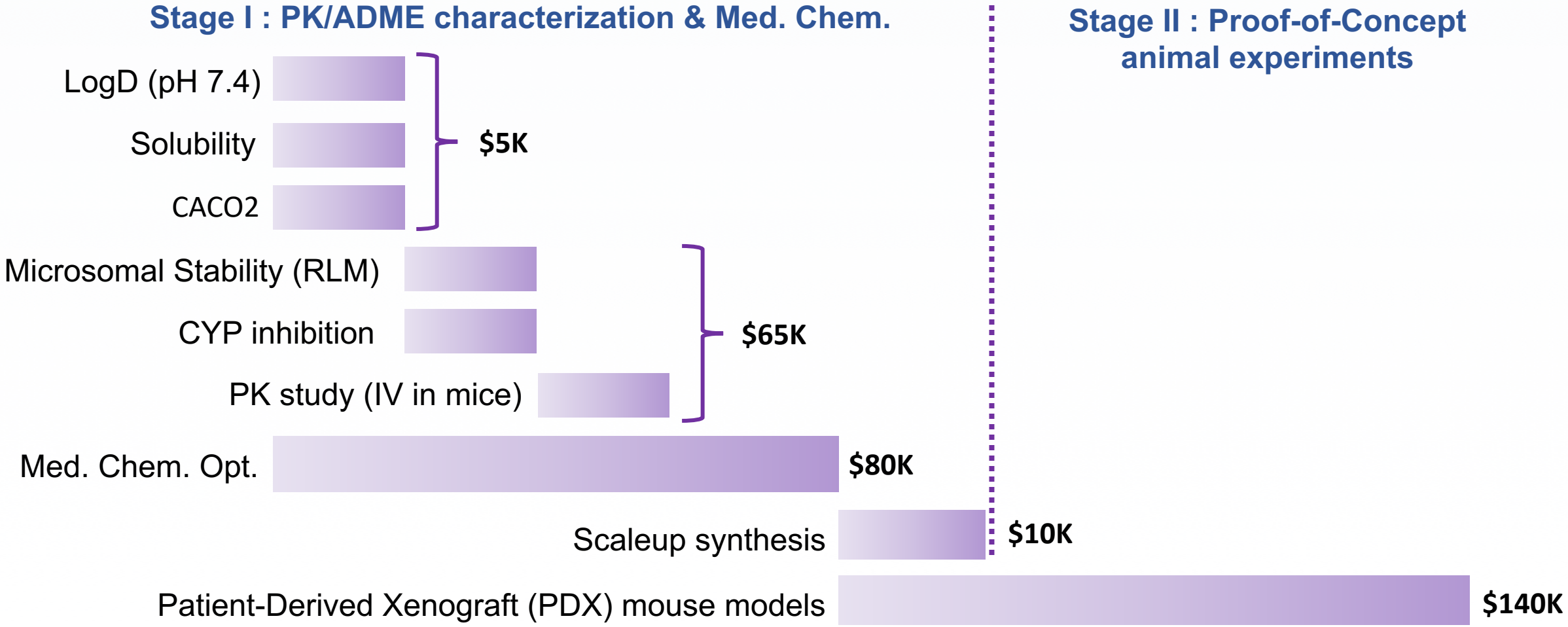
- First-in-class potent and selective dual PI5P4Kα/β inhibitors
- Potential broad application in cancer treatment

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.**



Quote from Genesis™ Drug Discovery & Development