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.
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

<table>
<thead>
<tr>
<th>Cancer Location</th>
<th>Deaths Per Year</th>
<th>p53 Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUNG</td>
<td>160,000</td>
<td>68%</td>
</tr>
<tr>
<td>COLORECTAL</td>
<td>50,000</td>
<td>55%</td>
</tr>
<tr>
<td>BREAST</td>
<td>40,000</td>
<td>36%</td>
</tr>
<tr>
<td>PANCREATIC</td>
<td>40,000</td>
<td>66%</td>
</tr>
<tr>
<td>PROSTATE</td>
<td>30,000</td>
<td>21%</td>
</tr>
<tr>
<td>LIVER</td>
<td>20,000</td>
<td>32%</td>
</tr>
<tr>
<td>OVARIAN</td>
<td>10,000</td>
<td>64%</td>
</tr>
<tr>
<td>ESOPHAGEAL</td>
<td>10,000</td>
<td>87%</td>
</tr>
</tbody>
</table>

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**

![Graph showing tumor free survival](image)

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

**PI5P4Kα/β Inhibition Disrupts Cell Energy Metabolism**

![Graph showing ion counts](image)

NO PREVIOUSLY REPORTED DUAL INHIBITORS OF α/β ISOFORMS
# Therapy Landscape of Targeting p53 Pathway

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>COMPETITORS</th>
<th>TARGET</th>
<th>DEVELOPMENT STAGE</th>
<th>KEY LIMITATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Lethality</td>
<td><strong>Lkit Therapeutics</strong></td>
<td>PI5P4Kα/β</td>
<td>Discovery</td>
<td>Limited experience in human patients</td>
</tr>
<tr>
<td>Boosting Levels of Wildtype p53</td>
<td>Numerous Big Pharma: Roche (nutlins), Novartis (HDM201), Daiichi-Sakyo (DS3032), Aileron (ALRN-6924), Innovation Pharmaceuticals (Kevetrin)</td>
<td>MDM2 Degradation Pathway</td>
<td>Phase I, II</td>
<td>Requires some level of functional p53</td>
</tr>
<tr>
<td></td>
<td>Merck (SCH-58500)</td>
<td>Gene Therapy Restoration</td>
<td>Phase III</td>
<td>Selectivity and efficiency</td>
</tr>
<tr>
<td>Chaperone/Protein Rescue Approach</td>
<td>Apres Bioscience (APR-246)</td>
<td>Stabilizing p53 Structure Using Allostery</td>
<td>Phase I</td>
<td>Mutant specific</td>
</tr>
<tr>
<td></td>
<td>Cotinga Pharma (COTI-2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism / Synthetic Lethality</td>
<td>Metformin</td>
<td>Unknown</td>
<td>Phase I, II, III</td>
<td>Unknown molecular target</td>
</tr>
<tr>
<td>Autophagy</td>
<td>Petra Pharma (Petra-01)</td>
<td>PI5P4Kα</td>
<td>Preclinical</td>
<td>Does not inhibit PI5P4Kβ</td>
</tr>
</tbody>
</table>
Inhibitors with dual specificity against $\alpha$ and $\beta$ isoforms

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

**Drug-like Properties of CC260**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI5P4K$\alpha$ Activity</td>
<td>40 nM</td>
</tr>
<tr>
<td>PI5P4K$\beta$ Activity</td>
<td>30 nM</td>
</tr>
<tr>
<td>Mol. Wt.</td>
<td>490 Da</td>
</tr>
<tr>
<td>cLogP</td>
<td>6</td>
</tr>
<tr>
<td>TPSA</td>
<td>82 Å²</td>
</tr>
</tbody>
</table>

**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.

Stage I: PK/ADME characterization & Med. Chem.
- LogD (pH 7.4)
- Solubility
- CACO2
- Microsomal Stability (RLM)
- CYP inhibition
- PK study (IV in mice)

Stage II: Proof-of-Concept animal experiments
- Scaleup synthesis
- Patient-Derived Xenograft (PDX) mouse models

Quote from Genesis™ Drug Discovery & Development