Sulabha biopharmaceuticals

Mark A. Lemmon
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Advisory Board:
• Prof. Craig Crews
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• Adam Sherman, iFOPA
  (Director of Research Development & Partnerships, iFOPA)

Team member:
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Conventional Kinase Inhibitors

**Off-targets:**

RSK inhibitor fmk:

**Acquired resistance:**

The EGFR Exon 19 Mutant L747-A750→P Exhibits Distinct Sensitivity to Tyrosine Kinase Inhibitors in Lung Adenocarcinoma

Anna Truini¹, Jacqueline H. Starrett², Tyler Stewart³, Kumar Ashtekar⁴,⁵, Zenta Walther², Anna Wurtz¹, David Lu⁴, Jin H. Park⁴,⁵, Michelle DeVeaux⁴, Xiaoiling Song¹, Scott Gettinger⁶,⁷, Daniel Zelterman⁸,⁹, Mark A. Lemmon¹,⁴,⁵, Sarah B. Goldberg¹,³, and Katerina Politi¹,²,³

CANCER RESEARCH | TRANSLATIONAL SCIENCE

Drug Sensitivity and Allele Specificity of First-Line Osimertinib Resistance EGFR Mutations

Jacqueline H. Starrett¹, Alexis A. Guernet², Maria Emanuelu Cuomo³, Kamrine E. Poels⁴, Iris K. van Alderwerelt van Rosemburgh³,⁴, Amy Nagelberg⁵, Dylan Farnsworth⁶, Kristin S. Price⁷, Hina Khan⁶, Kumar Dilip Ashtekar⁴,⁵, Mmaserame Gaeefe⁷, Deborah Ayeni¹, Tyler F. Stewart¹, Alexandra Kuhlmann¹, Susan Kaech³, Arun M. Unni¹,¹¹, Robert Homer¹⁵, William W. Lockwood⁴, Franziska Michor³,⁴, Sarah B. Goldberg¹,³, Mark A. Lemmon⁴,⁵,³, Paul D. Smith¹,¹, Darren A.E. Cross⁷, and Katerina Politi¹,²,³

First in line inhibitor for FOP and DIPG

**Fibrodysplasia Ossificans Progressiva (FOP)**

- Rare disease in children
- 5,000 patients worldwide (ifopa.org)
- Estimated cost per patient >$350,000/year
- No FDA approved drugs on market

**Diffuse Intrinsic Pontine Glioma (DIPG)**

- DIPG accounts for approximately 25% of all childhood cancers (5-7 years old)
- Constitutes to 75-80% of all pediatric brainstem tumors
- 150-300 patients diagnosed every year in US alone (dipgregistry.org and dipg.org) with median survival of 8-11 months
- No FDA approved drugs on market
Activin Like receptor Kinase family (Alks1-7)

Need exquisite selectivity among subfamily members to evade toxicity!
Exceptional Structural Identity

Overlay of Alk1, 2, 5 and 6 structures

Side chain residues comprising ATP-binding pocket (Alk1, 2, 5 and 6)

Alk1-7 (TKD): 69% identity
Competition Landscape

Clinical trials (repurposing)
- Palovarotene (RAR agonist)

Antibodies against ligand (Activin-A)
- Garetosmab (Phase I)
- BLU782

Conventional ATP competitive inhibition
- Alk2, Alk4, Alk5, Alk6
Augmenting Arm for Kinase Inhibitors

Chaperone recruiting small molecule inhibitors

 FKBP12 chaperone

On Target Surface Coverage:

Generic Inhibitors = 70-100 Å²
chaperone + Inhibitor = 450-500 Å²

Promoter Complex
- antibody-like enhanced surface area
- exclusive target specificity
- evade off-target effects

Multiple Contact-Inhibition Complex
Gaining Selectivity in Alk2 Inhibition
Selectivity within the sub-family of ALKs

Toxicity studies

Stimulation by Activin A in presence of 10 μM inhibitors (5 days)

Stimulation with Activin A (Alk2 pathway)

Stimulation with BMP4 (Alk5 pathway)
Timeline

2021
- May thru Nov: Synthesis of 13 hit compounds
- Dec: Cell assays
- $185K*

2022
- May thru Jun: Synthesis of lead compounds for POC
- Jun: Go/no go!
- 2 of 13 compounds
- $315K*
- Jun: Animal model POC
- ~$140K

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*Amounts based on quotes from CROs (Jubilant and NEDP)