







Advisory Board:

- Prof. Craig Crews
- Prof. Suk-Won Jin
- Adam Sherman, iFOPA

(Director of Research Development & Partnerships, IFOPA)

### Kumar Ashtekar

- Scientist, Biotech (2014-2016)
- Postdoc fellow (2016-current)
- Consultant for Seattle Genetics

### Mark A. Lemmon

- David A. Sackler Professor of Pharmacology
- Assoc. Dir. Basic Science, Yale Cancer Ctr
- Co-chair, Cancer Biology Institute

Team member: Anatoly Kiyatkin

#### Yale Cancer Biology Institute

OCR contact: Christopher Unsworth

## **Conventional Kinase Inhibitors**

### **Off-targets:**

#### **RSK** inhibitor fmk:



Tauton and co-workers. Science, 2005, 308, 1318

#### EGFR inhibitor core:



#### Shokat and co-workers. Nat. Chem. Bio, 2007, 3, 229

### Acquired resistance:

#### Translational Cancer Mechanisms and Therapy

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



Clinical

Cancer Research

Anna Truini<sup>1</sup>, Jacqueline H. Starrett<sup>2</sup>, Tyler Stewart<sup>3</sup>, Kumar Ashtekar<sup>4,5</sup>, Zenta Walther<sup>2</sup>, Anna Wurtz<sup>1</sup>, David Lu<sup>4</sup>, Jin H. Park<sup>4,5</sup>, Michelle DeVeaux<sup>6</sup>, Xiaoling Song<sup>1</sup>, Scott Gettinger<sup>1,3</sup>, Daniel Zelterman<sup>1,6</sup>, Mark A. Lemmon<sup>1,4,5</sup>, Sarah B. Goldberg<sup>1,3</sup>, and Katerina Politi<sup>1,2,3</sup>

**CANCER RESEARCH |** TRANSLATIONAL SCIENCE

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

Jacqueline H. Starrett<sup>1</sup>, Alexis A. Guernet<sup>2</sup>, Maria Emanuela Cuomo<sup>2</sup>, Kamrine E. Poels<sup>3</sup>, Iris K. van Alderwerelt van Rosenburgh<sup>4,5</sup>, Amy Nagelberg<sup>6</sup>, Dylan Farnsworth<sup>6</sup>, Kristin S. Price<sup>7</sup>, Hina Khan<sup>8</sup>, Kumar Dilip Ashtekar<sup>4,5</sup>, Mmaserame Gaefele<sup>9</sup>, Deborah Ayeni<sup>1</sup>, Tyler F. Stewart<sup>10</sup>, Alexandra Kuhlmann<sup>11</sup>, Susan Kaech<sup>12</sup>, Arun M. Unni<sup>13</sup>, Robert Homer<sup>1,14</sup>, William W. Lockwood<sup>6</sup>, Franziska Michor<sup>3,15</sup>, Sarah B. Goldberg<sup>9,10</sup>, Mark A. Lemmon<sup>4,5,9</sup>, Paul D. Smith<sup>16</sup>, Darren A.E. Cross<sup>17</sup>, and Katerina Politi<sup>1,9,10</sup>

#### **Osimertinib**



# First in line inhibitor for FOP and DIPG



Germline origin Alk2<sup>(R206H)</sup>



Somatic origin Alk2<sup>(R206H)</sup>

### 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

M. Pacifici, E.M. Shore / Cytokine & Growth Factor Reviews 27 (**2016**) 93–104. Cancer Res. 2014 Sep 1; 74(17): 4565–4570, http://www.erdekesvilag.hu/kepek/szobor-emberek/fop-1.jpg

### **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)



# **Exceptional Structural Identity**

Overlay of Alk1, 2, 5 and 6 structures



Alk1-7 (TKD): 69% identity

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



### **Competition Landscape**



## Augmenting Arm for Kinase Inhibitors



# Gaining Selectivity in Alk2 Inhibition



### Selectivity within the sub-family of ALKs



#### Control Inhibitor 2

## Timeline



<sup>\*</sup>Amounts based on quotes from CROs (Jubilant and NEDP)