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- Postdoc fellow (2016-2018)
- Consultant for Seattle Genetics
- Co-founder of DOT Pharmaceuticals, LLC

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- Co-chair, Cancer Biology Institute

Team members:
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- Christopher Unsworth (OCR)
- Megan Woods (OCR)
Augmenting Arm for Kinase Inhibitors

Chaperone recruiting small molecule inhibitors

On Target Surface Coverage:
- Generic Inhibitors = 70-100 Å²
- FKBP12 + Inhibitor = 450-500 Å²

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

Multiple Contact-Inhibition Complex

Kinase

endogenous chaperone

FKBP12 chaperone

Kinase Target

endogenous chaperone
- FKBP12 concentration ranges from 1-10 µM depending on cell type

- Unlike traditional inhibitors, the above inhibition complexes display several protein-small molecule and protein-protein contacts……as a consequence, point mutations in target proteins won’t lead to resistance!
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

Germline origin
Alk2\(^{(R206H)}\)

Somatic origin
Alk2\(^{(R206H)}\)

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

Cancer Res. 2014 Sep 1; 74(17): 4565–4570,
http://www.erdekesvilag.hu/kepek/szobor-emberek/fop-1.jpg
Activin like receptor kinase 2 (Alk2)–ACVR1

- Signal peptide
- ATP binding (214-222)
- N-linked glycosylation (Asp 102)
- Kinase domain (208-502)
- Phosphorylation at S501

- FKBP12
- Alk2-WT
- PDB code: 3h9r
Competition

- Two compounds from BioCryst pharma and one each from Keros Therapeutics, LaJolla pharmaceutical and BLU-782 by Blueprint Medicines/Ipsen in pre-clinical development and phase I.

- Several studies involving repurposing known drugs (Ipsen/Clementia-palovarotene, OTSSP167) for FOP and DIPG with little to no improvement

"Conventional Kinase Inhibitors"
Inactivating the “Active” complex

Inhibition Complex

\((\text{Alk2}^{\text{R206H}} + \text{inhibitor-1} + \text{FKBP12})\)

**ATP binding pocket**

**Surface contacts:**

- Inhibitor-1 : \(\text{Alk2}^{\text{R206H}} = 69.0 \text{ Å}^2\)
- \(\text{FKBP12} + \text{Inhibitor-1} : \text{Alk2}^{\text{R206H}} = 470.6 \text{ Å}^2\)

**Kd values:**

- \(\text{Kd}_{(\text{Alk2-R206H})} = 349 \text{ nM}\)
- \(\text{Kd}_{(\text{Alk2-wt})} = 220 \text{ nM}\)
- \(\text{Kd}_{(\text{Alk2-R206H})} = 242 \text{ nM}\)

Recovering the endogenous affinity

(http://www.ebi.ac.uk)
Inactivating the “Active” complex

ATP binding pocket

R206H

\[ \text{FKBP12} \]

\[ \text{Alk2}^{(R206H)} \]

\[ \text{FKBP12} \]

\[ \text{Kd}_{(\text{Alk2-R206H})} = 349 \text{ nM} \]

2x FKBP12 + Alk2\(^{(R206H)}\) + inhibitor

FKBP12 + Alk2\(^{(R206H)}\) + inhibitor

FKBP12 + Alk2\(^{(R206H)}\)
Inhibiting the “leaky” signal in primary cells

Toxicity studies

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

Stimulation with Activin A (Alk2 signaling)

Stimulation with BMP4 (Alk5 signaling)
Inhibitor optimization
Linear bifunctional molecule → macrocyclic bifunctional
$74,000

PK/PD and Tox studies in mice
CRO studies in collaboration with iFOPA
~$120,000

IND filing

Clinical trials