Sulabha BioPharma

- Since the conception of this idea (2.5 years), the project is funded by the **Arnold O. Beckman Foundation**

Kumar Ashtekar

- Scientist, Biotech (2014-2016)
- Postdoc fellow (2016-2018)
- Consultant for Seattle Genetics
- Co-founder of DOT Pharmaceuticals, LLC

Mark A. Lemmon

- David A. Sackler Professor of Pharmacology
- Co-chair, Cancer Biology Institute

Yale *Cancer Biology Institute*

Advisory Board:

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

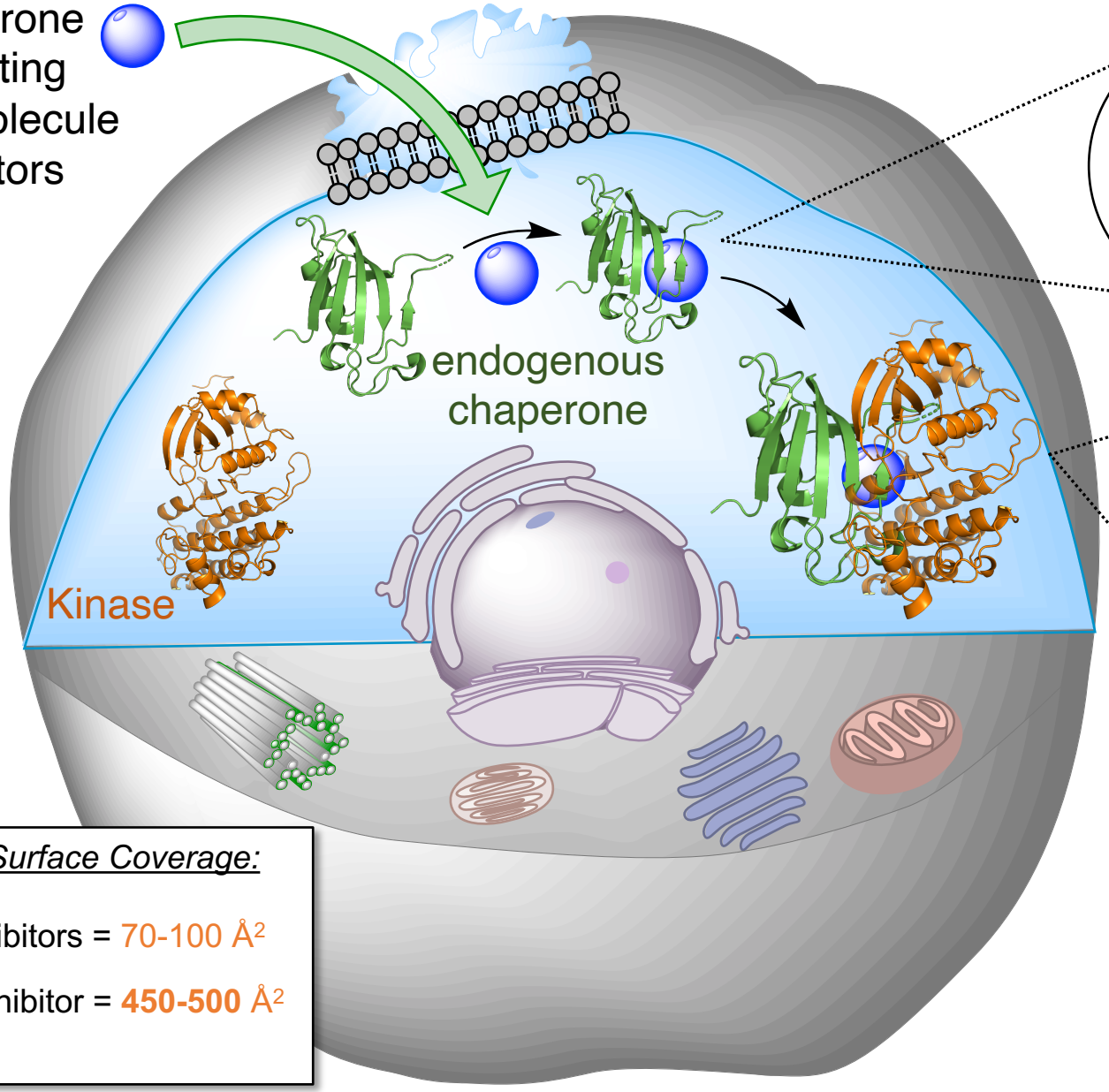
(Director of Research Development & Partnerships, IFOPA)

Team members:
Dr. Anatoly Kiyatkin

Christopher Unsworth (OCR)
Megan Woods (OCR)

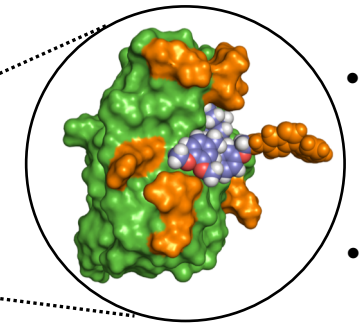
Augmenting Arm for Kinase Inhibitors

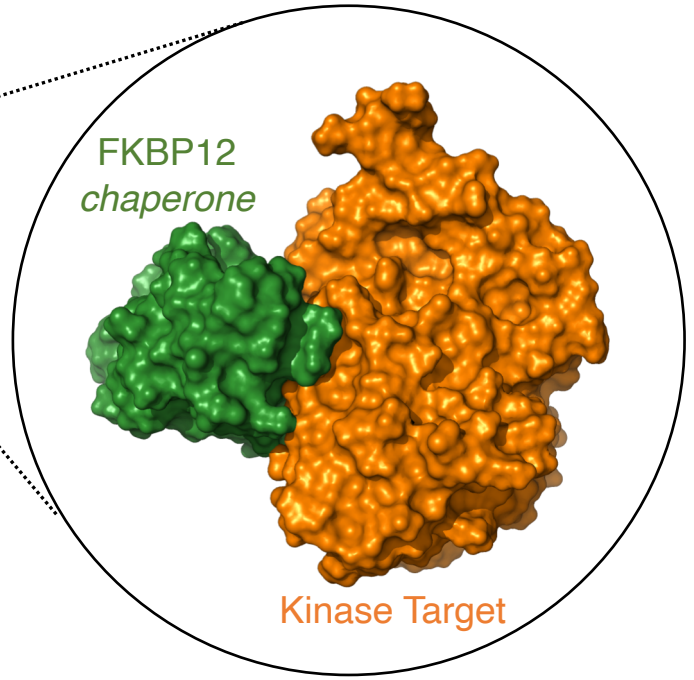
Chaperone recruiting small molecule inhibitors



Promoter Complex

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





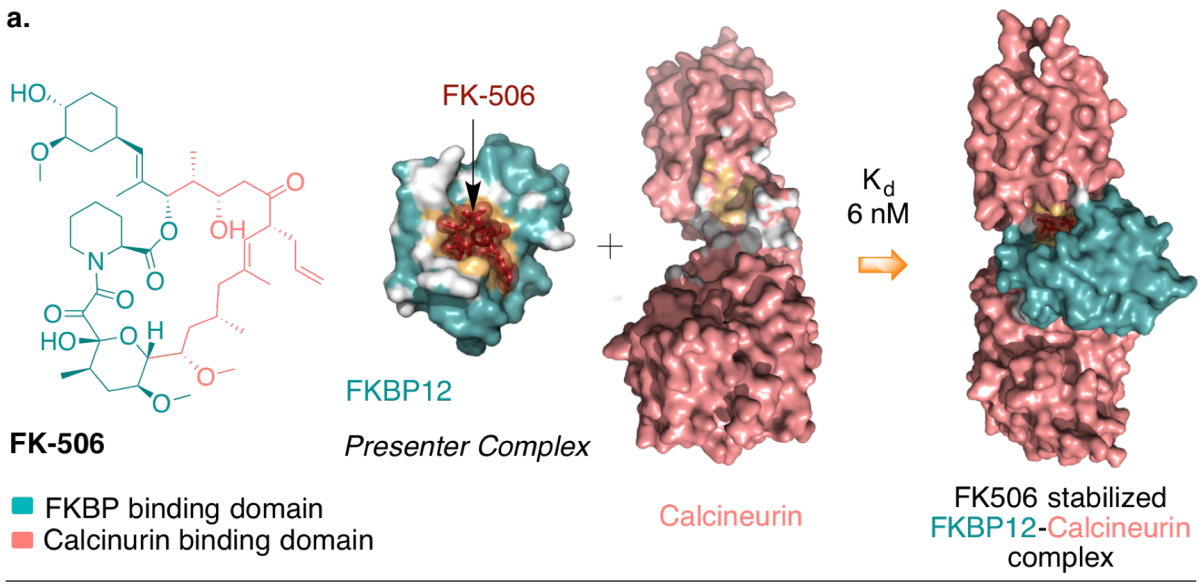
Multiple Contact-Inhibition Complex

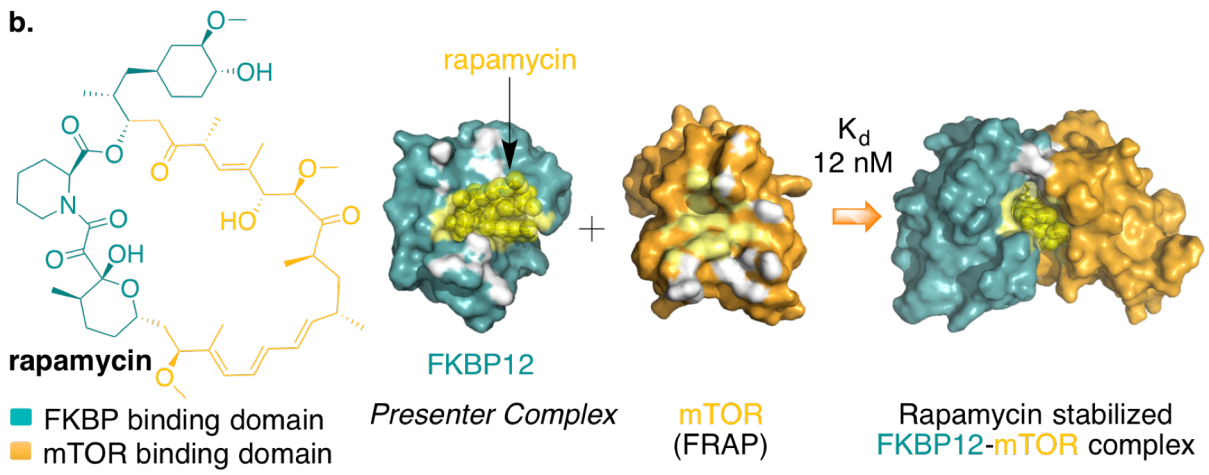
On Target Surface Coverage:

Generic Inhibitors = 70-100 Å^2

FKBP12 + Inhibitor = **450-500** Å^2

Evolving on the Modality of Nature

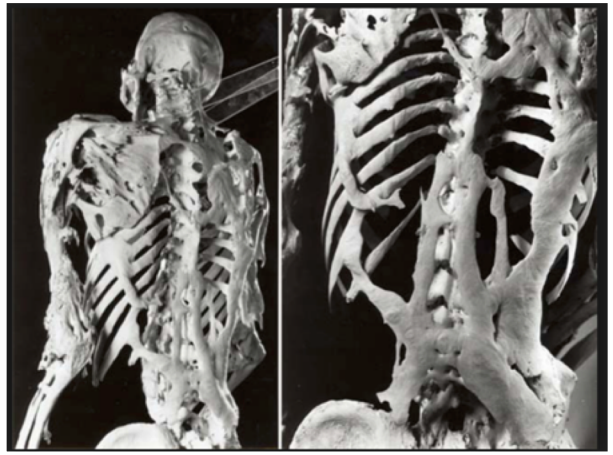




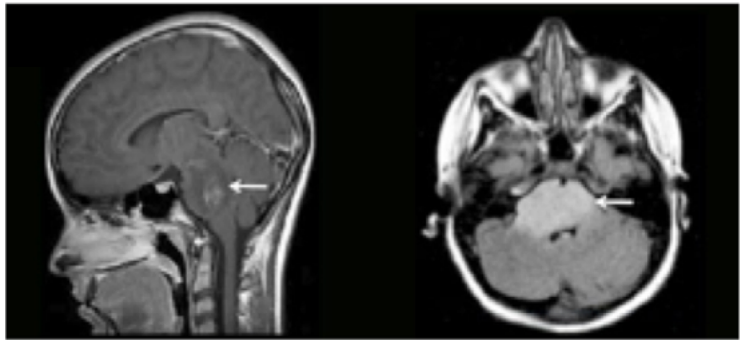
Advantages:

- 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!

First in line inhibitor for FOP and DIPG



Germline origin
Alk2$^{(R206H)}$



Somatic origin
Alk2$^{(R206H)}$

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)

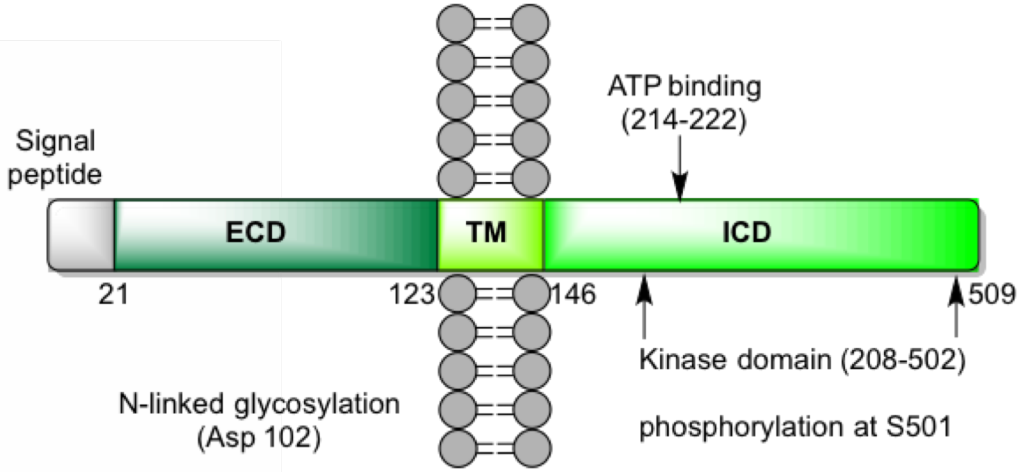
- DIPG accounts for approximately 25% of all childhood cancers (5-7 years old)
- Constitutes to 75-80% of all pediatric brainstem tumors
- 150-300 patients diagnosed every year in US alone (dipgregistry.org and dipg.org) with median survival of 8-11 months
- No FDA approved drugs on market

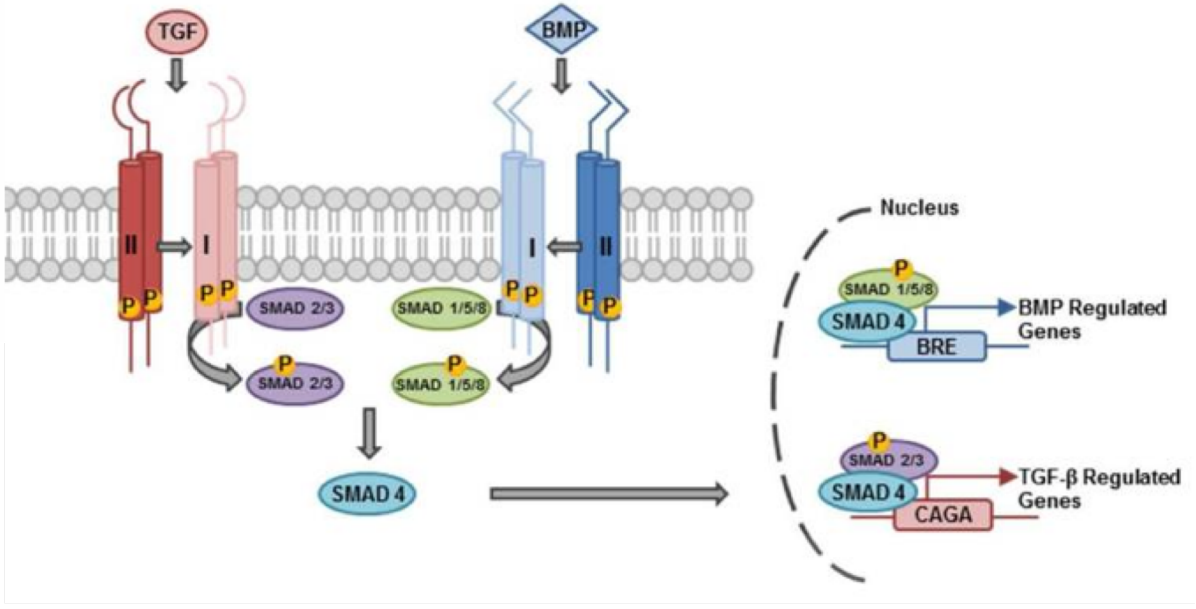
M. Pacifici, E.M. Shore / Cytokine & Growth Factor Reviews 27 (**2016**) 93–104.
Cancer Res. 2014 Sep 1; 74(17): 4565–4570,
http://www.erdekesvilag.hu/kepek/szobor-emberek/fop-1.jpg

Activin like receptor kinase 2 (Alk2)–ACVR1

FKBP12
Alk2-WT

PDB code: 3h9r





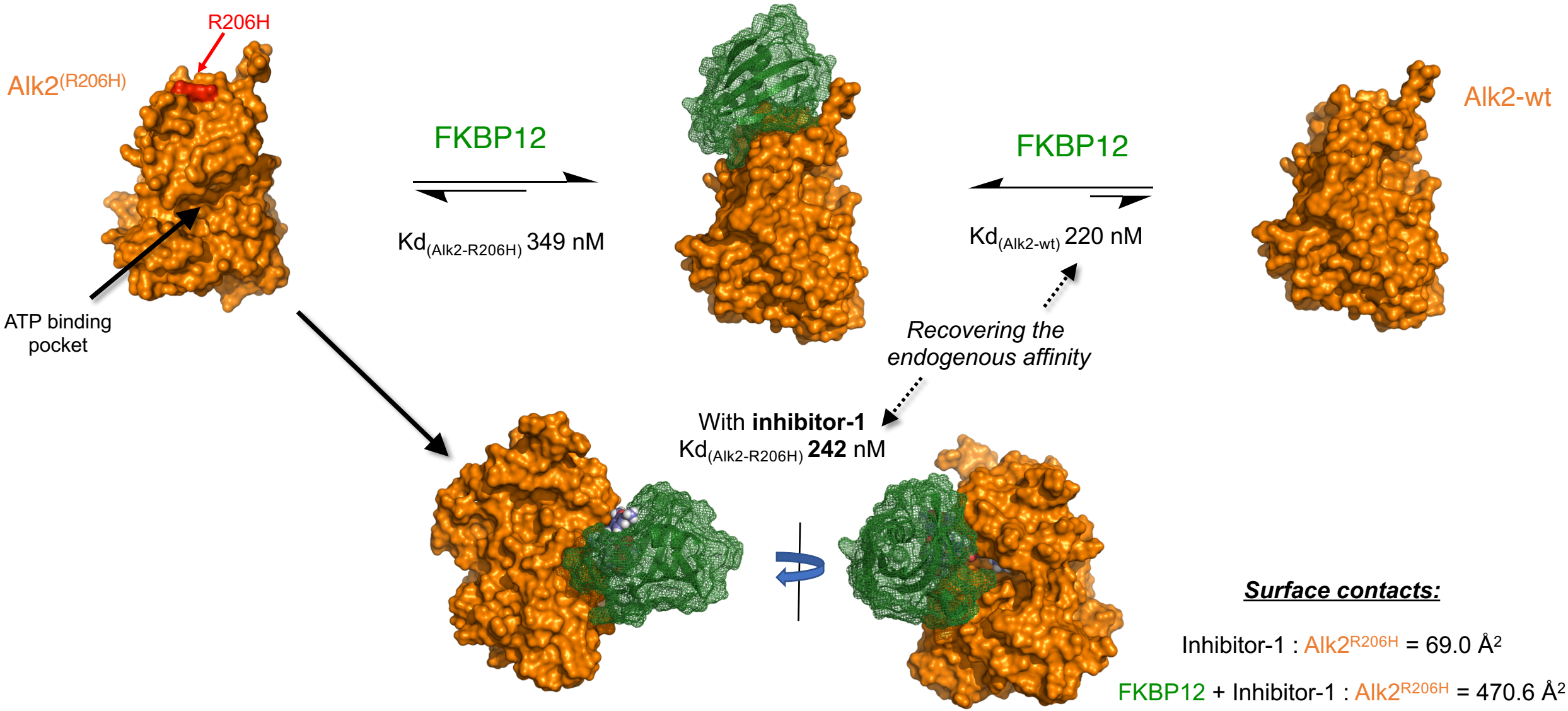
Competition

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

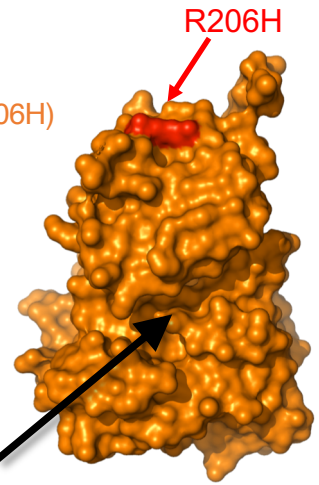
Surface contacts:

Inhibitor-1 : Alk2^{R206H} = 69.0 Å^2

FKBP12 + Inhibitor-1 : Alk2^{R206H} = 470.6 Å^2

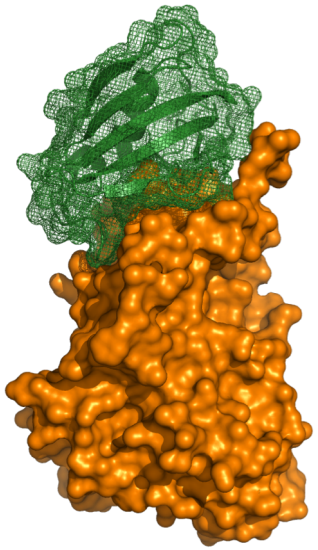
(http://www.ebi.ac.uk)

Inactivating the “Active” complex



FKBP12

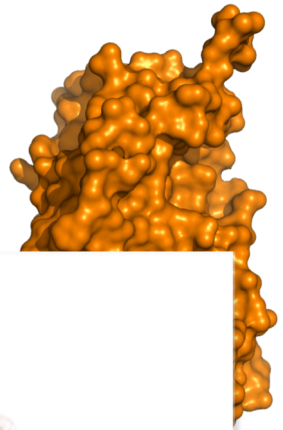
$Kd_{(Alk2\text{-}R206H)}$ 349 nM



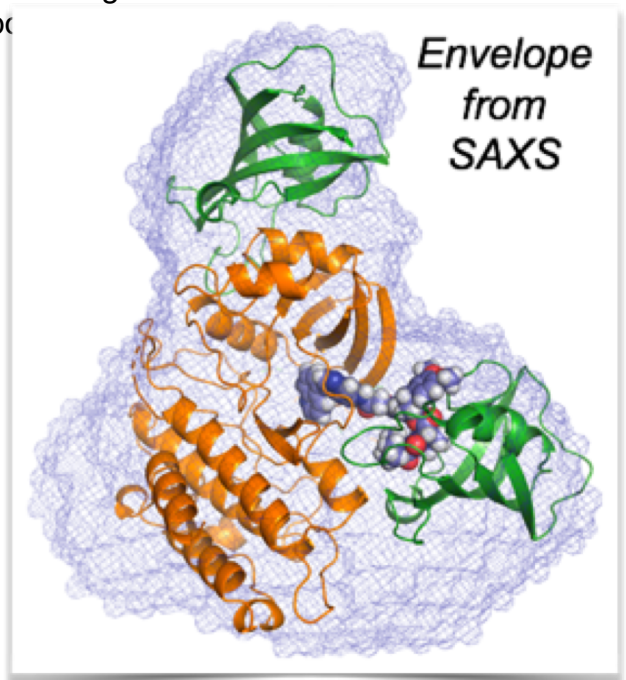
FKBP12

$Kd_{(Alk2}$

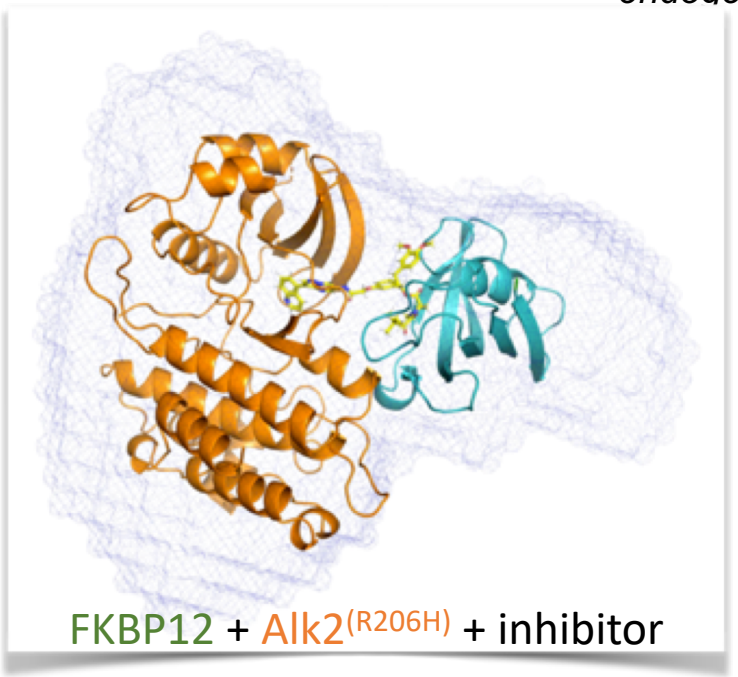
Alk2-wt



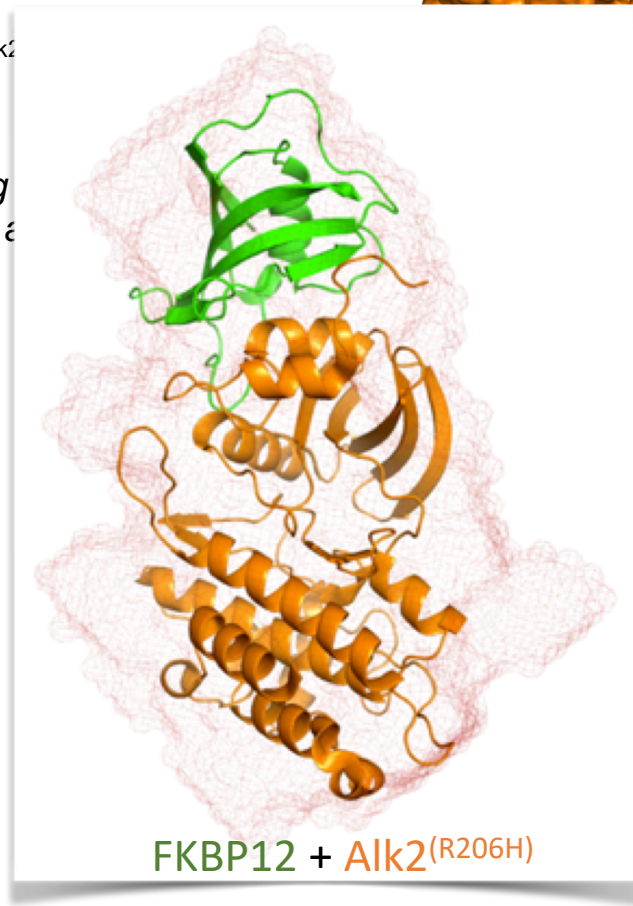
Recovering endogenous a



2x FKBP12 + Alk2(R206H) + inhibitor



FKBP12 + Alk2(R206H) + inhibitor

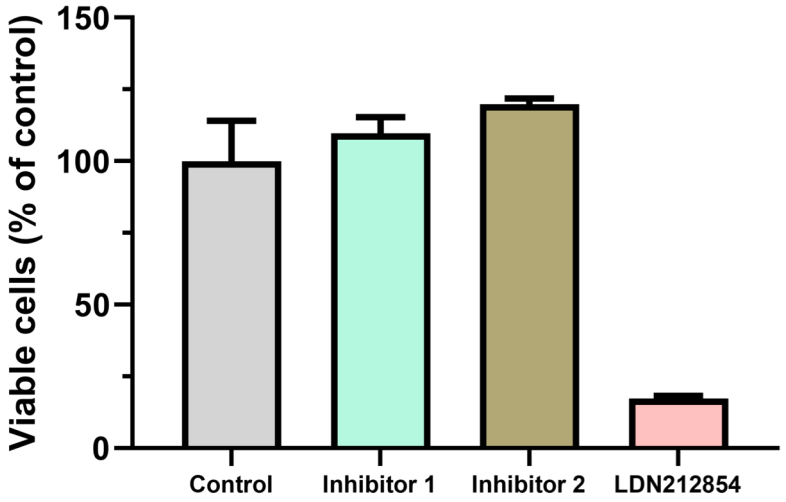


FKBP12 + Alk2(R206H)

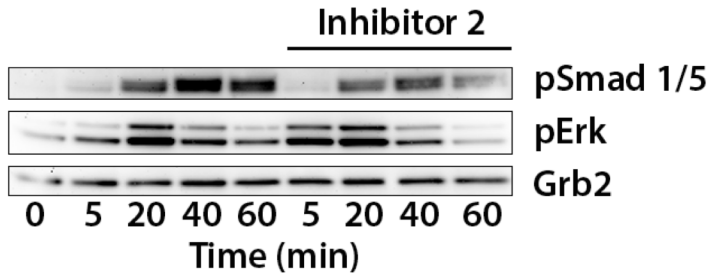
Inhibiting the “leaky” signal in primary cells

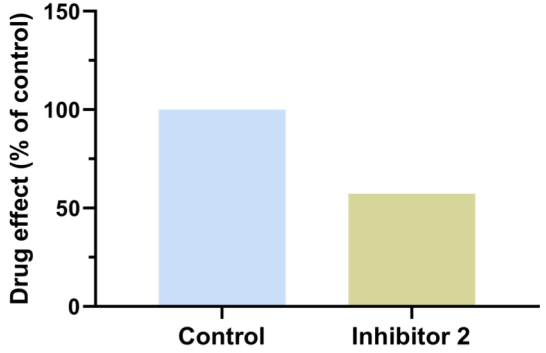
Toxicity studies

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

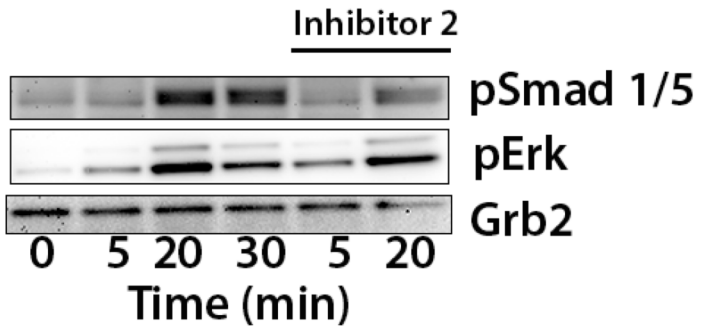


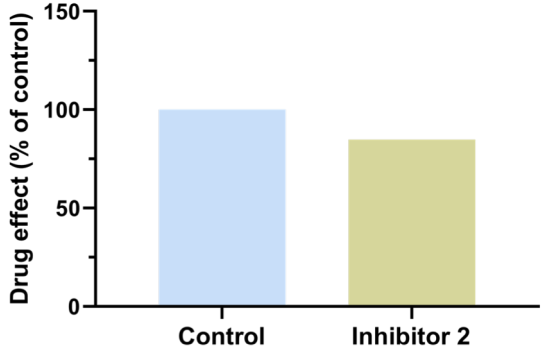
Stimulation with Activin A (Alk2 signaling)





Stimulation with BMP4 (Alk5 signaling)





Projected Pipeline