Advances in understanding and drug development for ALK2/*ACVR1* gain of function mutations in Diffuse Intrinsic Pontine Glioma (DIPG)

Drug Development for DIPG through International Collaborative Open Science

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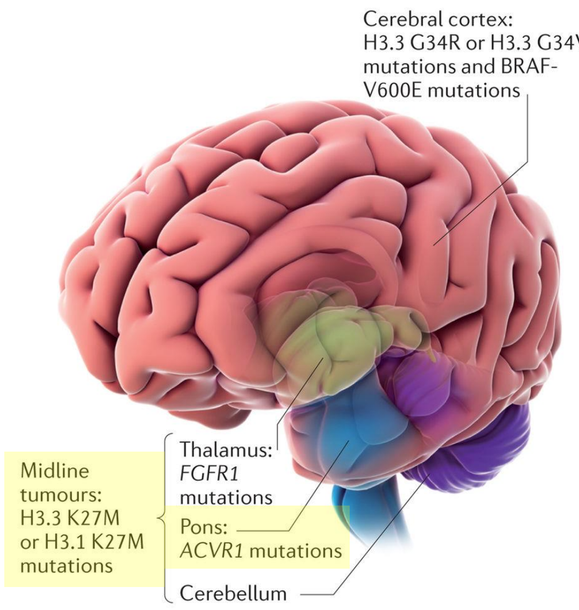
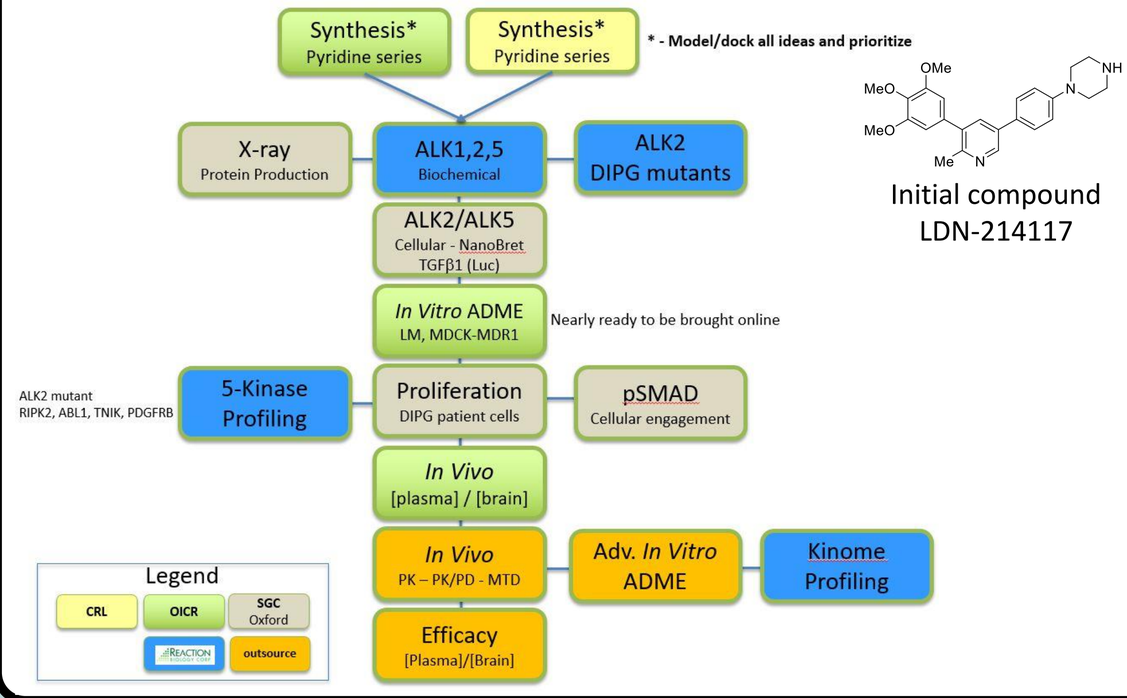
ALK2/*ACVR1* mutations are prevalent in DIPG



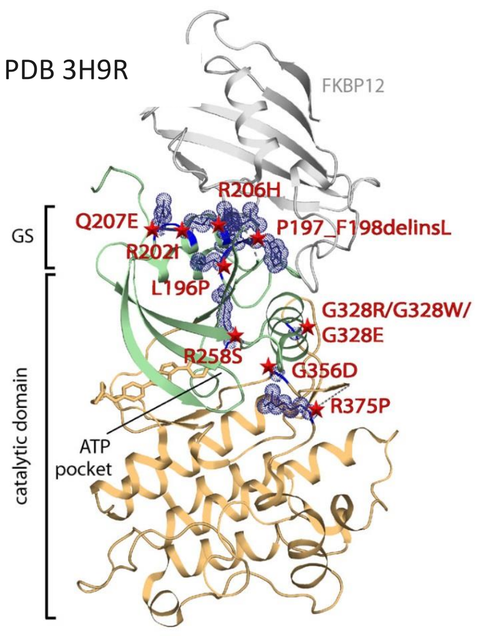
- DIPG tumours harbor histone H3K27M mutations
- 25% also carry missense mutations in the BMP receptor serine/threonine kinase ALK2/*ACVR1*
- ALK2/*ACVR1* mutations are not prevalent in any other cancer suggesting a specific role in DIPG.

Jones and Baker, NatRevCancer 14, 651–661

Workflow for ALK2 inhibitor development through M4K Pharma



Crystal structure of the ALK2-FKBP12 complex



Chaikuad et al J Biol Chem 287(44):36990-8 2014

- ALK2 mutations in DIPG are identical to those in FOP, a monogenic disease of extraskeletal bone formation.

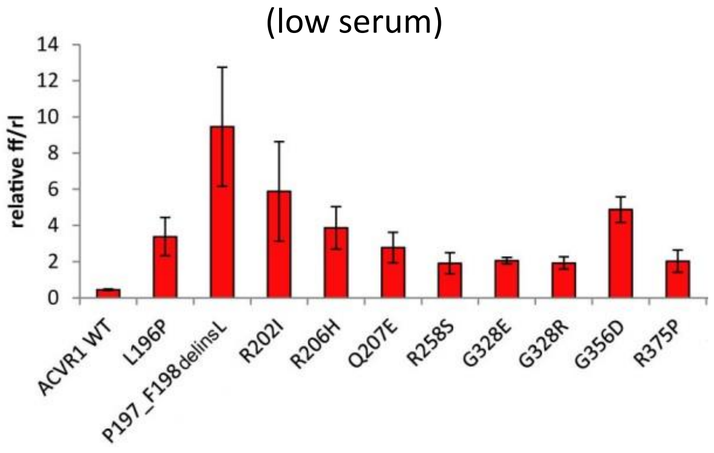
- We solved the crystal structure of ALK2 bound to antagonist FKBP12
- All mutations cluster at sites that will unlock the kinase activity

M4K Pharma: Towards Affordable "Meds 4 Kids"

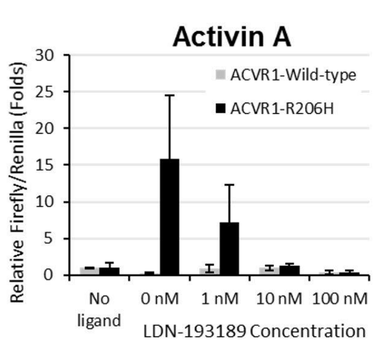
- First open science drug discovery company
- Beneficiaries are 'open science and the public good'
- Aim to align diffuse academic, foundation and industry research into a traditional drug development programme

ALK2 mutants show increased BMP pathway activity

BRE-Luciferase reporter (low serum)



Activin Neofunction



- ALK2 mutations are activating (i.e. a gain of function).
- Mutant ALK2 also signals via SMAD1/5 in response to Activin revealing a neofunction.

Summary

- Astrocytic DIPG tumours carry recurrent mutations in the BMP receptor kinase ALK2/*ACVR1* in addition to H3K27M mutations. Identical germline ALK2/*ACVR1* mutations are also the cause of fibrodysplasia ossificans progressiva (FOP), in which damaged soft tissue regrows as bone.
- Our biochemical analyses show that ALK2 mutations destabilize the inactive conformation of the kinase domain causing a weak shift towards active BMP-SMAD signalling.
- M4K Pharma was established to foster an open science collaborative effort to develop ALK2 inhibitors for DIPG
- Early stage ALK2 inhibitors with low nanomolar potency for ALK2 show promising initial efficacy in DIPG xenograft models.

Acknowledgements

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