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Discovery and characterization of selective, FGFR1 sparing, inhibitors of FGFR2/3 oncogenic mutations for the treatment of cancers

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Expanding the Reach of Precision Medicine Through the Development of Novel MasterKey Therapies

Addressing significant unmet need for novel precision oncology therapies for patients

Uniquely de-orphaning oncogenic mutations to develop single therapies designed to inhibit specific mutation families

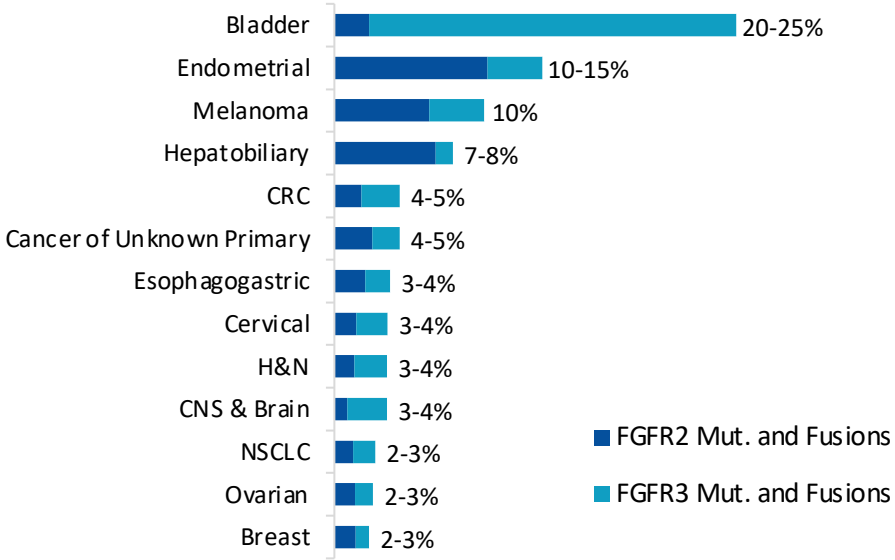
Our proprietary computational Mutation Allostery Pharmacology (MAP) drug discovery engine is designed to develop a spectrum-selective (MasterKey) small molecule therapy

Robust pipeline of oral, potent and selective small molecule kinase inhibitors across a range of indications and target groups including EGFR, HER2, BRAF and FGFR

FGFR2 and FGFR3: Important Oncogenic Drivers in Solid Tumors, Poorly Served by Available Therapies

FGFR2/3: potent oncogenic drivers across human tumors

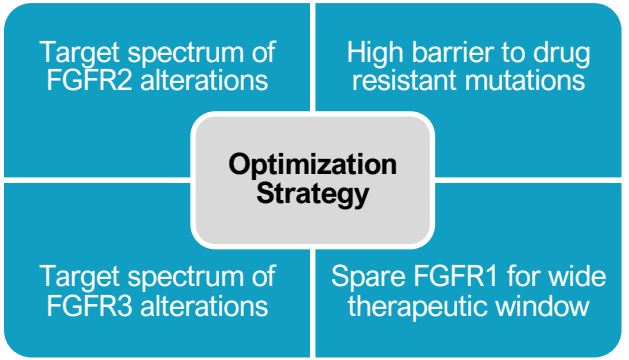
Prevalence of FGFR2/3 mutations and fusions in Solid Tumors



Current drugs limited by lack of selectivity & poor resistance profile

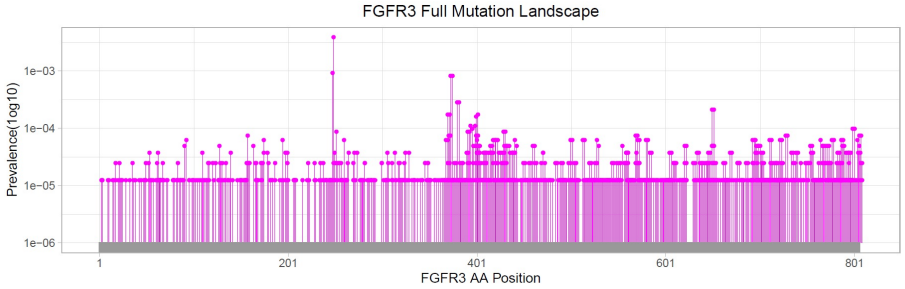
1. Approved pan-FGFR inhibitors suffer from FGFR1-mediated hyperphosphatemia leading to frequent dose interruptions or reductions and limited efficacy.
2. Secondary resistance mutations, at key residues within the kinase domain, emerge following treatment.

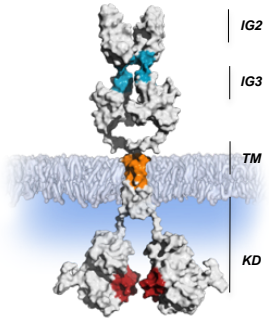
Black Diamond Approach



MAP platform reveals FGFR2/3 oncogenic mutations and resolves structural differences vs FGFR1 to support drug discovery

MAP platform identifies novel, clinically relevant and actionable FGFR2/3 allosteric mutations

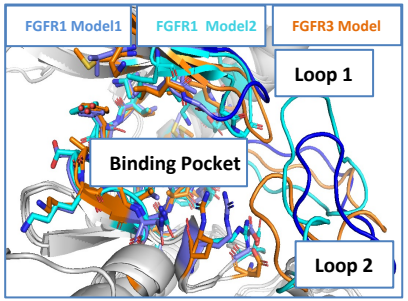




Mutation-Allostery-Pharmacology (MAP) platform is a genomic and proteomic ruled-based algorithm that reveals allosteric oncogenes:

- Revealing the topography of oncogenic mutation hotpots
- Increasing oncogenicity prediction
- Aggregating spectrum of mutations to be drugged by a single compound

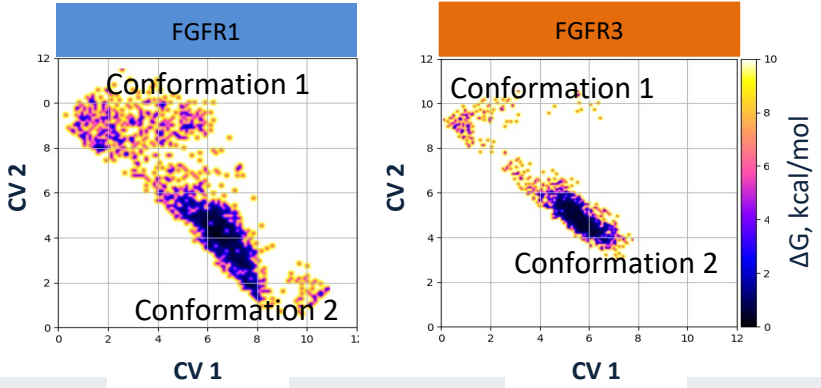
MAP platform coupled with proprietary X-Ray crystal structure and MD simulation reveal actionable differences between FGFR1 and FGFR2/3



Goals: Reveal the structural differences in the active site between FGFR1 and FGFR2/3.

Approach: All-atom MD simulations and study of proprietary the x-ray crystal structure.

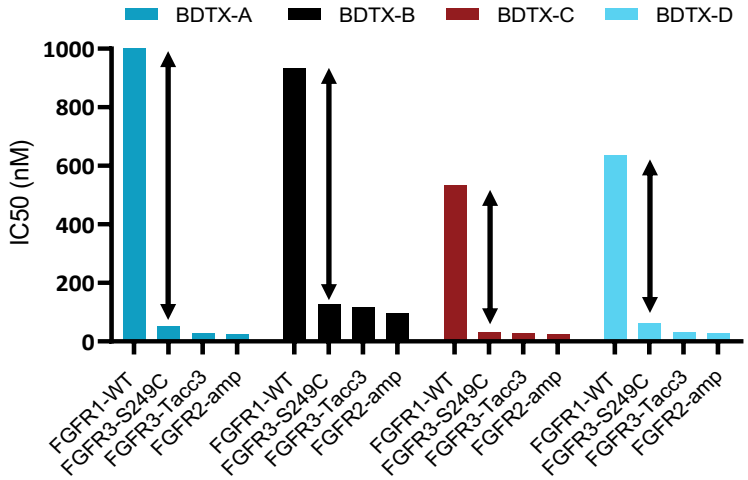
Results: Structural differences in FGFR3 vs FGFR1 active sites revealed



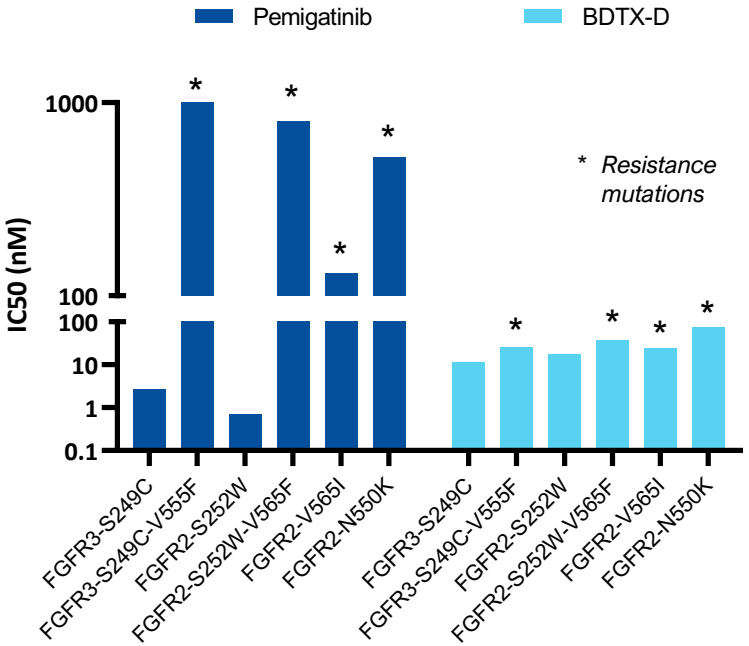
BDTX FGFR2/3 Leads Differentiated by Broad Selectivity Profile While Sparing Wild Type FGFR1 and Potency Against Key Resistance Mutations

BDTX FGFR2/3 leads demonstrate 15-40 fold selectivity vs WT-FGFR1

IC50 (nM)	Erdafitinib	Infigratinib	Pemigatinib
FGFR1	1.2	0.9	0.4
FGFR2	2.5	1.4	0.5
FGFR3	3	1	1.2
FGFR4	5.7	60	30

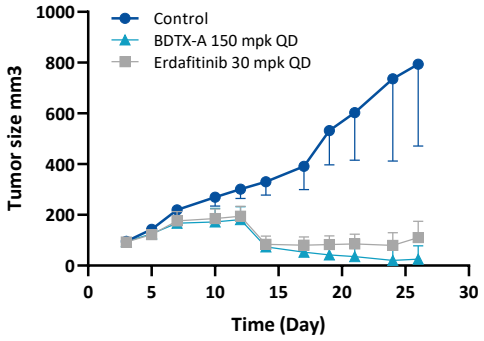


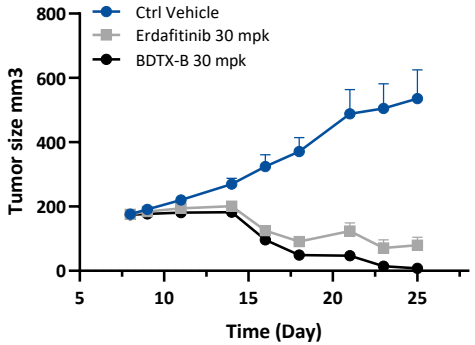
BDTX FGFR2/3 leads demonstrate improved potency against resistance mutations



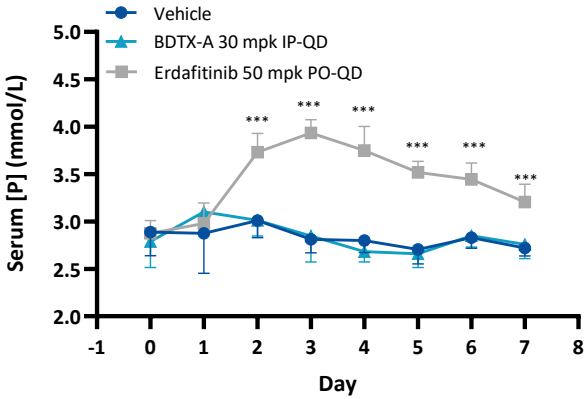
BDTX FGFR2/3 Leads Demonstrate In-vivo Efficacy While Limiting FGFR1-related Toxicity

UM-UC-14 (FGFR3-S249C) tumor model in mice





Repeat dosing in Rats at efficacious exposures



Erdafitinib			
Source	**Species**	**Dose**	**Unbound AUC_{last} (h·μM) (M/F)**
BDTX	Mouse	30 mpk PO-QD	0.252
	Rat	50 mpk PO- QD	0.344
NDA [NME] 212018	*Human*	*8 mg/day*	*0.394*

BDTX-A			
Source	**Species**	**Dose**	**Unbound AUC_{last} (h·μM)**
BDTX	Mouse	150 mpk PO-QD	4.29
	Rat	30 mpk IP-QD	4.44

- In mouse and rat models, while Erdafitinib promote hyperphosphatemia, BDTX compounds, dosed at efficacious exposure, don't promote hyperphosphatemia.

Black Diamond to Deliver the Next Generation of Oncogenic FGFR Inhibitors

AACR American Association for Cancer Research FINDING CURES TOGETHER | NIH NATIONAL CANCER INSTITUTE | EORTC European Organisation for Research and Treatment of Cancer — The future of cancer therapy

Approved Drugs

Target FGFR2	Drug resistant mutations
Target FGFR3	Target FGFR1

Black Diamond Approach

Target Spectrum of FGFR2 Alterations	High Barrier to Drug Resistant Mutations
Optimization Strategy	
Target Spectrum of FGFR3 Alterations	Spare FGFR1 for Wide Therapeutic Window

Differentiated Activity Profile

- Designed for potent inhibition of a spectrum of allosteric FGFR2/3 mutations

Designed to Capture Efficacy

- FGFR1-sparing
- Activity against gatekeeper mutations

Strong Pre-Clinical Data

- Tumor regression observed in pre-clinical FGFR3 mutant PDX tumors

Rapid Pre-Clinical Advancement

- Lead optimization ongoing with IND anticipated in 2022