Discovery of Best-in-Class FGFR3 small molecule inhibitors with high isoform selectivity and activity against gatekeeper mutations

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Onco3R Therapeutics

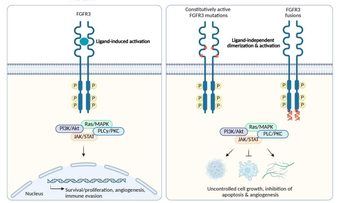
Right team - Right strategy - Right drugs

Abstract

Fibroblast Growth Factor Receptor (FGFR) 3 genomic alterations, with S249C being the most prevalent, are established **oncogenic drivers** in 10-60% of all bladder cancers depending on the disease stage.

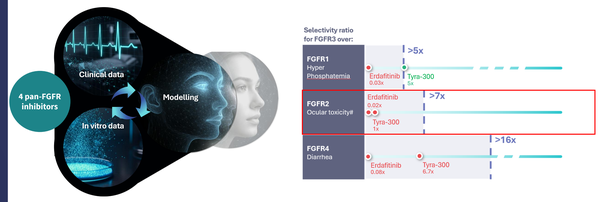
Erdafitinib, a pan-FGFR inhibitor, has been approved for the second line treatment of advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic alterations. However, the emergence of resistance together with **dose-limiting toxicities driven by off-target inhibition of FGFR1/2/4**, limit the overall response rate to approximately 35%. These limitations often lead to **treatment discontinuation** and **prevent** the use of Erdafitinib in **earlier lines** of treatment, less advanced stages of the disease or combination regimens.

There is a **clear need to develop a highly potent and selective FGFR3 small molecule inhibitor** to fully unlock the therapeutic potential of this target.



FGFR3 signaling in healthy individuals *vs.* FGFR3 genomic alterations in bladder cancer.

Unique translational modelling Defined Required FGFR3 Selectivity to Mitigate Toxicity



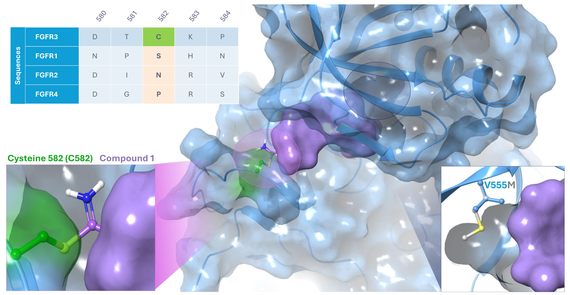
Onco3R Model-Based Meta-Analysis (O3R-MBMA) defined the required FGFR3 selectivity window to mitigate toxicity related to FGFR1, 2 & 4 isoforms (~50% incidence reduction of all grade hyperphosphatemia and diarrhea and 90% incidence reduction of all grade ocular toxicity vs Erdafitinib, with 85% FGFR3 inhibition through 24hr).

Based on internal data, none of the competitors reached the predicted sufficient selectivity (expressed as the IC_{50} ratio of HEK293 overexpressing FGFR3 S249C/V555M over WT FGFR1, 2 & 4).

#Central Serous Retinopathy and Retinal Pigment Epithelial Detachment

Results

1. Onco3R series target FGFR3 C582 covalently to enable best-in-class selectivity

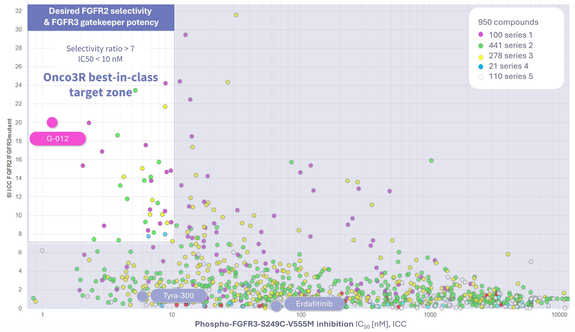


2.9 Å co-crystal structure with compound 1 shows covalent bond with C582 of FGFR3.

Capitalizing on 10 proprietary X-ray co-structures, Structure-Based and AI-augmented Drug Design led to:

- Optimized binding mode in the kinase domain
- Retention of potency on gate keeper mutant V555M
- Improved potency and selectivity against FGFR1/2 and 4, as well as the general kinome

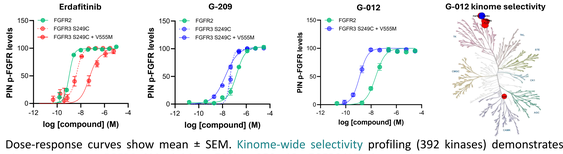
2. Onco3R patient-centric drug discovery approach delivered multiple chemical series with desired *in vitro* profile



$FGFR3\ IC_{50}$ values and FGFR2/FGFR3 selectivity ratios were determined in HEK293 cells overexpressing FGFR3 S249C/V555M or FGFR2, using immunocytochemistry (ICC).

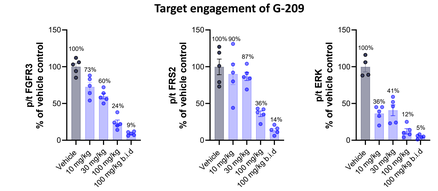
3. G-012 demonstrates best-in-class potency and selectivity *in vitro*

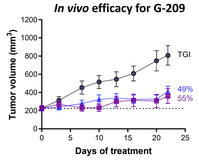
	Erdafitinib	Tyra-300	G-209	G-012
MOA	Not covalent	Not covalent	Covalent	Covalent
Cellular pFGFR ICC (exogenous overexpression in HEK293) IC_{50} [nM]				
pFGFR1	1.8	28	759	162
pFGFR2	1.4	5.7	119	24
pFGFR3 S249C + V555M	60	5.6	23	1.2
pFGFR3 S249C MSD	3.3	8.4	31	NA
pFGFR4	4.8	37	156	201
Selectivity ratio (vs 1/2/4)	0.03/0.02/0.08	5.0/1.0/6.7	32/5.1/6.7	135/20/168
Phenotypic effects IC_{50} [nM]				
DMS-114 (FGFR1)	4.6	140	2580	504
KATO-III (FGFR2)	0.5	10.9	195	157
RT-112 (FGFR3 TACC3)	1.6	7.5	52	3.8
UM-UC-14 (FGFR3 S249C)	1.5	12	45	4.7
Selectivity ratio for RT-112 (vs 1/2)	2.9/0.3	18.7/1.5	49.5/3.8	130/40



Dose-response curves show mean ± SEM. Kinome-wide selectivity profiling (392 kinases) demonstrates high selectivity for FGFR3 (% inhibition >70%, at 250 x IC_{50} FGFR3 WT biochemical assay).

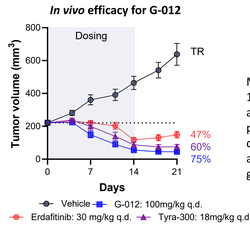
4. Robust target engagement and *in vivo* efficacy demonstrated with early lead G-209





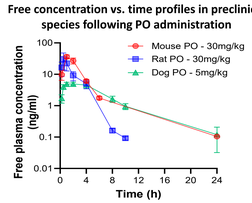
Mice were engrafted with RT-112 cells and treated orally with 100 mg/kg b.i.d. of G-012 and 18mg/kg q.d. of Tyra-300. To determine target engagement, tumors were collected 8h post-dose and pFGFR3, pFRS2 and pERK were measured using MSD and JESS respectively. Tumor volumes were determined twice weekly. Data are mean ± SEM.

5. G-012 shows robust *in vivo* efficacy and favorable drug-like properties



Mice were engrafted with UM-UC-14 cells and treated orally for 14 days with 100 mg/kg q.d. of G-012, 18mg/kg q.d. of Tyra-300 and 30mg/kg q.d. of Erdafitinib. Tumor regrowth was evaluated post-dosing (study still ongoing). Tumor volumes were determined twice weekly. TR = tumor regression at day 14. Data are mean ± SEM. (One mouse sacrificed in Tyra-300 & G-012 group).

	mouse	rat	dog	human
***In vitro* ADME parameters**				
Hep $T_{1/2}$ (min)	40	9	> 60	> 60
PPB (% bound)	97.5	97.99	97.26	99.5
Cl prediction Poulin (% LBF)	17	29	11	**2.5**
***In vivo* PK parameters**				
Cl (% LBF)/Vss (L/kg)	25/1.7	70/2.6	15/1.9	
F (%) (dose mg/kg)	38 (30)	33 (30)	14 (5)	



G-012 shows favorable cross-species PK profile. Human PK and dose projection is ongoing.

Key Properties	Target	Onco3R G-012
FGFR3 cellular potency in S249C/V555M (IC_{50} nM)	<10nM	**1.2nM**
Selectivity vs. FGFR1/2/4	5x / 7x / 16x	**135x / 20x / 168x**
***In vitro* ADME**	Oral bioavailability and limited drug/drug interaction liabilities	Favorable ADME profile No drug/drug interaction liabilities expected at anticipated efficacious concentration
***In vitro* Safety**	Favorable cardiosafety profile and no genotoxicity risk	No relevant hERG, Na, Ca channels inhibition No aneugenicity
DMPK	Oral <300mg daily projected human dose	Favorable PK profile across species ***Human PK and dose projection ongoing***
PK/PD/Efficacy	Similar efficacy in multiple FGFR3-driven models to selective FGFR3 inhibitors	Robust target engagement and tumour regression

Conclusions

- **G-012** is a **highly potent** and **selective** FGFR3 small molecule inhibitor with a **best-in-class profile**
- G-012 indicates **robust tumor regression** in the UM-UC-14 bladder cancer model
- G-012 shows **favorable ADME/safety** and **cross-species PK** properties
- G-012 is currently being advanced **towards DRF studies**
- **IND-enabling studies** are anticipated in mid-2026