Identification of an FGFR1 Sparing, Reversible, FGFR2 Clinical Development Candidate with Potency Against Gatekeeper and Molecular Brake Mutations

John Fischer[1], Karyn Bouhana[1], Richard Brizendine[1], Mark Chicarelli[1], Brad Fell[1], Jennifer Fulton[1], Anna Guarnieri[1], Leyla Haygood[1], Ravi Jalluri[1], Amber Johnson[1], Keith Koch[1], Erika Koslov-Davino[1], Macedonio J. Mejia[1], Rob Rieger[1], John Robinson[1], Mareli Rodriguez[1], Francis Sullivan[1], Yang Wang[1], Shannon Winski[1], Silas Wood[1], YeYun Zhou[1]

[1]Cogent Biosciences, Inc., Boulder, CO and Waltham, MA

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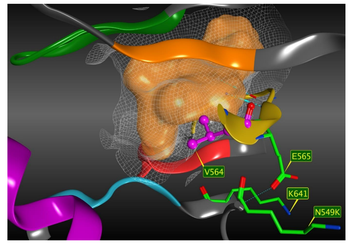
Cogent FGFR2 Inhibitor Opportunity

Target Product Profile

FGFR1 Sparing	Improved target engagement over time by avoiding hyperphos-related dose mods
Potent on Mutations	Retains high potency against prevalent gatekeeper and molecular brake mutations
Reversible Non-Covalent	Possibility for improved tolerability Active against potential C491S mutation
Selective	Selective for FGFR across the kinome, receptors, hERG, and channel panel
Combinable	Low potential for CYP-mediated DDI based on in vitro data, BCS Class 1 or 2

Figure 1. Crystal Structure of CGT4859 Bound to FGFR2-N549K



- 1.9 Å Crystal structure of CGT4859 (shown as an orange surface) bound to FGFR2-N549K
- CGT4859 does not clash with prevalent FGFR2 mutations which are common modes of resistance to current drugs (Fig 1)

Background

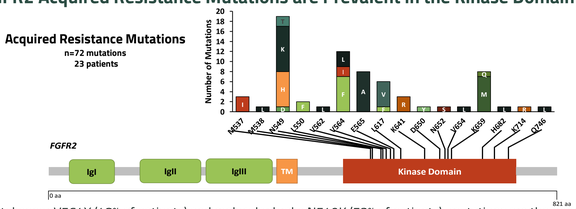
Table 1. Clinical Features and Clinical Coverage of Pan-FGFR Inhibitors

Clinical Compound	Dose Schedule	ORR	Hyperphos	Stomatitis	Indication	Approved FGFR Alteration
Pemigatinib[1,2]	2 wk on/ 1 wk off	36% ICC	92%	35%	Adv/met ICC	FGFR2 fusion
Infigratinib[3,4]	3 wk on/ 1 wk off	23% ICC	82%	56%	Adv/met ICC	FGFR2 fusion
Erdafitinib[5]	Daily, monitor tolerability	32% UC	76%	56%	Adv/met UC	FGFR2/3 fusion, select 1° FGFR3 mt
Futibatinib[6]	Daily, monitor tolerability	42% ICC	85%	30%	Adv/met ICC	FGFR2 fusion

UC, Urothelial Carcinoma; ICC, Intrahepatic Cholangiocarcinoma

- Fibroblast growth factor receptors (FGFRs) consist of four transmembrane receptor tyrosine kinases, FGFR1-4[7]
- Receptor mutations, amplifications, and fusions result in activation of the FGFRs and are well-established oncogenic drivers in multiple indications[7,8]
- Approved pan-FGFR inhibitors show on target toxicities. The most common DLT for these inhibitors, FGFR1 mediated hyperphosphatemia, was observed in >75% of patients regardless of the clinical compound (Table 1)
- These drugs are not approved outside of ICC/UC or for patients with FGFR2 primary and acquired mutations

Figure 2. FGFR2 Acquired Resistance Mutations are Prevalent in the Kinase Domain

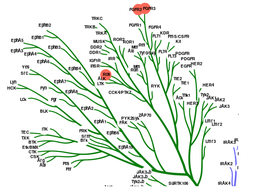


- The FGFR2 gatekeeper V564X (48% of patients) and molecular brake N549K (52% of patients) mutations are the most common emerging resistance mutations[9-11]
- Selective FGFR2 inhibitors in development have shown substantially reduced potency against gatekeeper and molecular brake mutations vs. wild-type FGFR2
- **There is an unmet medical need for a selective FGFR2 inhibitor, with coverage of activating and resistance mutations, which avoids FGFR1 mediated hyperphosphatemia**

Results

Figure 3. CGT4859 Is Potent on FGFR2 Mutants and Highly Selective

Selective Across the Kinome

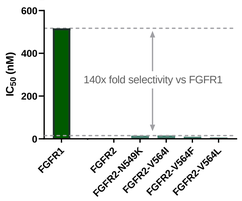


p-FGFR Inhibition Cell IC_{50} and Selectivity Heat Map

Assay	CGT4859	Futibatinib	RLY-4008
FGFR2 WT	2 *	1*	4*
Fold shift vs. FGFR2 Cellular IC_{50}			
FGFR1 WT	140X	2X	250x
FGFR2 N549K	4x	3x	7x
FGFR2-V564I	4x	1x	11x
FGFR2-V564F	3X	64X	<1X
FGFR2-V564L	1.5X	15X	<1X

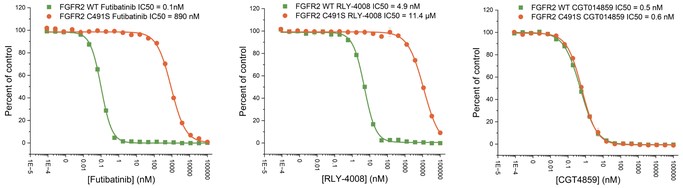
* FBS Adjusted IC_{50}s

Selective Over FGFR1 and Potent Against Prevalent FGFR2 Mutations



- CGT4859 was profiled at 10X the enzyme IC_{50} for FGFR2 against a panel of 371 kinases
- FGFR2, FGFR3, and ROS1 where the only kinases that showed >50% target inhibition
- Additionally, CGT4859 is selective across a panel of ion channels and receptors
- CGT4859 ~140x selective for FGFR2 over FGFR1
- CGT4859 exhibits low nM potency on FGFR2 WT and retains activity across FGFR2 mutations
- CGT4859 outperforms current SOC and second-generation inhibitors vs. key resistance mutations

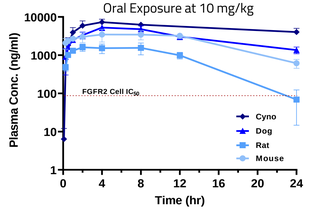
Figure 4. CGT4859 Retains Activity vs. the FGFR2 C491S Cysteine Mutation



- Resistant mutations emerge over time in patients treated with covalent inhibitors such as ibrutinib (BTK)[12] and osimertinib (EGFR)[13]. In many cases, these mutations occur at the cysteine site of covalent modification
- By analogy, FGFR2 C491S was generated as a potential resistance mutation formed by treatment with a covalent FGFR inhibitor
- The covalent inhibitors futibatinib and RLY-4008 showed >1000x shift of IC_{50} values between FGFR2 WT and mutant FGFR2 C491S while reversible non-covalent CGT4859 maintained equal potency in both the WT and C491S mutant enzyme assays

Figure 5. CGT4859 Showed High Bioavailability Across Species, Preclinical Studies Support QD Dosing in Humans

Oral Exposure at 10 mg/kg

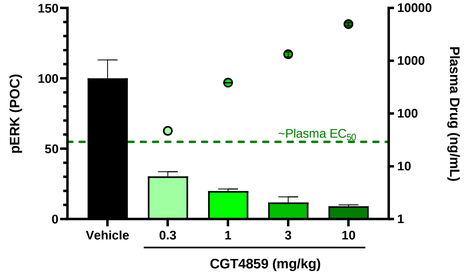


PK Data at 10 mg/kg

PK	Mouse	Rat	Dog	Cyno
Time (h) with $C_{plasma,free}$ > Cell IC_{50}	>24	>24	>24	>24
$t_{1/2}$ (hr)	5.2	3.3	22	21
F (%)	>100	81	>100	94
IV CL (mL/min/kg)	3.6	5.1	5.3	0.8
VD_{ss} (L/kg)	1.2	1.3	2.2	1.0

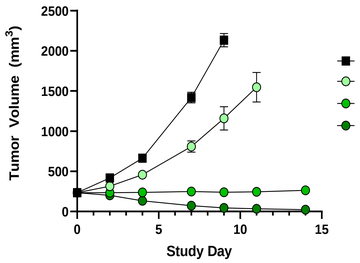
- Exploratory PK studies of CGT4859 dosed in mouse, rat, dog, and cyno at 1 or 3 mg/kg IV and 10 mg/kg PO
- CGT4859 showed 24-hour coverage of the free fraction adjusted WT FGFR2 cellular IC_{50} across species at 10 mg/kg
- High oral bioavailability and low clearance were observed in all species

Figure 6. Mouse AN3 CA (K310R/N549K) Model, CGT4859 Showed Dose Responsive Inhibition of pERK



- CGT4859 was dosed by oral gavage at 0.3, 1, 3, or 10 mg/kg in AN3 CA (K310R/N549K) tumor-bearing mice
- Dose-related effects were observed on the inhibition of ERK phosphorylation (4 hr post dose administration)
- >90% inhibition of pERK was observed at the 10 mg/kg dose, with a plasma EC_{50} <30 ng/mL

Figure 7. CGT4859 Showed Complete Tumor Regressions at 5 mg/kg in the Clinically Relevant AN3 CA (K310R/N549K) Model



- CGT4859 was dosed once daily by oral gavage at 1, 2.5, or 5 mg/kg for 14 days in AN3 CA K310R/N549K tumor-bearing mice
- Dose-related tumor growth inhibition was observed, and complete tumor regression occurred at 5 mg/kg QD
- In rats, no increase in serum phosphate levels were observed at the matched efficacious plasma concentrations of CGT4859

Conclusions

- CGT4859 is a potential best-in-class FGFR2/3 inhibitor, outperforming current SOC and second-generation inhibitors vs. key resistance mutations in pre-clinical studies
- CGT4859 is selective vs the broad kinome, as well as a panel of ion channels and receptors
- PK studies across species showed CGT4859 to be a low clearance compound with high oral bioavailability
- In AN3 CA mouse models, CGT4859 showed:
  - PD: >88% inhibition of pERK was observed when dosed at or above 3mg/kg PO
  - TGI: Dose response with complete regressions at 5 mg/kg PO QD
- CGT4859 had no observed increase in serum phosphorus at efficacious plasma concentrations
- CGT4859 is currently in IND enabling studies with a planned initiation of clinical trials in 2024

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