# Pre-clinical Characterization of a Novel Series of FGFR2 Selective Inhibitors with Potency Against Clinically Relevant Mutations

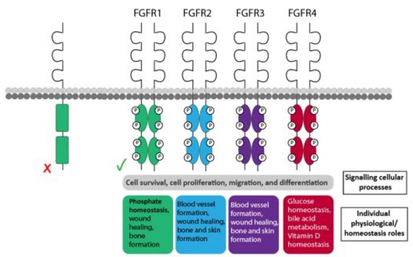
John Fischer, Karyn Bouhana, Mark J Chicarelli, Josh Dahlke, Brad Fell, Jennifer Fulton, Anna Guarnieri, Leyla Haygood, Ravi Jalluri, Amber Johnson, Brent Mclean, Macedonio Mejia, Rob Rieger, John Robinson, Mareli Rodriguez, Francis Sullivan, Yang Wang, Shannon Winski, Yeyun Zhou

Cogent Biosciences, Inc., Boulder, Colorado and Cambridge, Massachusetts USA

**Abstract Number: 167**

## Background

### Figure 1. FGFR2 and FGFR3 are Well-Established Oncogenic Drivers in Multiple Indications




- Fibroblast growth factor receptors (FGFRs) are a family of transmembrane receptors consisting of isoforms FGFR1-FGFR4
- Binding of a ligand to the inactive FGFR monomer leads to receptor dimerization, phosphorylation, and downstream signaling
- Receptor mutations, amplifications, and fusions can result in activation of FGFRs and are recognized as well-established oncogenic drivers in multiple indications[1,2]
- Inhibition of FGFR3 mutations in urothelial cancer and FGFR2 fusions in cholangiocarcinoma has led to improved clinical outcomes in defined patient populations[3,4]

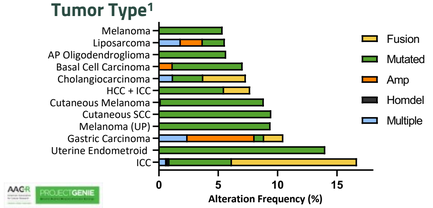
### Table 1. First Generation Pan-FGFR Inhibitors Have Dose Limiting Toxicities (DLT) and Poorly Serve the Landscape of FGFR2/FGFR3-Altered Cancers

| Clinical Compound | Clinical Features | | | | | Approved Clinical Coverage | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IC50 enzyme (nM) (FGFR1,2,3,4) | Dose Schedule | ORR | Hyperphos | Diarrhea | Adv/met ICC | Adv/met UC | FGFR2 fusions | FGFR3 fusions | FGFR2 Activating mutations | FGFR3 mutations (KD) | FGFR2/3 resistance mutations |
| **Pemigatinib**[3,5] | 0.4, 0.5, 1, 30 | 2 wk on/ 1 wk off | 36% (ICC) | 92% | 47% | ■ | | ■ | | | | |
| **Infigratinib**[6,7] | 0.9, 1.4, 1, 60 | 3 wk on/ 1 wk off | 23% (ICC) | 82% | 24% | ■ | | ■ | | | | |
| **Erdafitinib**[8] | 1, 2.5, 3, 6 | Daily (schedule based on phosphate levels) | 32% (UC) | 76% | 47% | | ■ | ■ | ■ | | | |

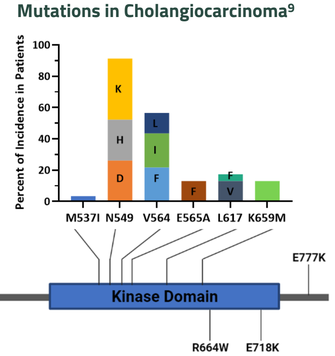
UC, Urothelial Carcinoma; ICC, Intrahepatic Cholangiocarcinoma; KD, Kinase Domain

- FGFR1 mediated hyperphosphatemia was the most common DLT observed in patients taking pan-FGFR inhibitors
- Diarrhea is observed in up to 47% of patients taking pan-FGFR inhibitors
- Approved pan-FGFR inhibitors fail to capture the full landscape of FGFR2 and FGFR3 altered tumor types

### Figure 2a. FGFR2 is Highly Altered Across Tumor Type[1]

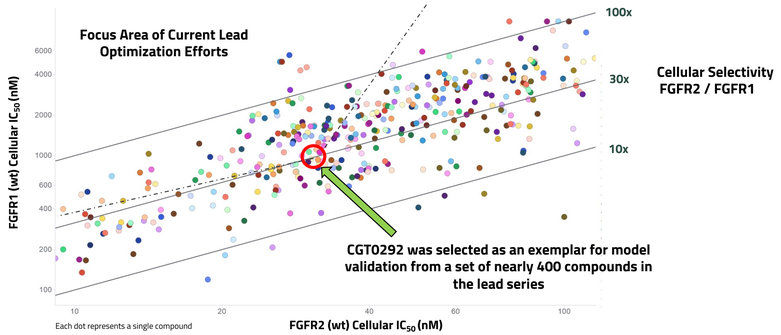



### Figure 2b. FGFR2 Resistance Mutations in Cholangiocarcinoma[9]




## Results

### Figure 3. Majority of Lead Series Compounds are >30-Fold Selective for FGFR2 vs. FGFR1




### Table 2. Drug-Like In Vitro Properties

| Assay | CGT0292 |
|---|---|
| **tPSA / clogP / MW** | ~80 / ~2.0 / <400 |
| **Solubility (pH 1.2 / 6.5 / 7.4)** | 3250 / 454 / 335 |
| **Permeability A-B Efflux Ratio** | 16 ($10^{-6}$ cm/sec) 9 |
| **Microsomal CL (% ER) M / R / H** | 20 / 13 / 11 |
| **Hepatocyte CL (% ER) M / R / H** | 61 / 14 / 21 |
| **Protein Binding (%) M / R / H** | 70.6 / 72.9 / 64.6 |
| **Reversibility Assay Enzyme $IC_{50}$ with Preincubation** | 0 min = 2.1 nM<br>30 min = 2.1 nM<br>60 min = 2.2 nM |

**CGT0292:**

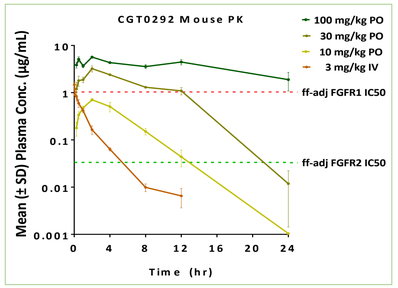
- Has drug-like calculated physiochemical properties
- Exhibits BCS Class 1 properties with high thermodynamic solubility and high MDR1-MDCKII permeability
- Shows low CL across species in microsomes and hepatocytes
- Displays low plasma protein binding across species tested: favorable free fraction-adjusted target coverage observed
- Is a reversible inhibitor, $IC_{50}$ does not change with preincubation
  - Avoids potential for time-dependent inhibition of FGFR1
  - Potential proteome selectivity advantage
  - Avoids non-traditional glutathione metabolism
- Provides a robust scaffold for further compound optimization

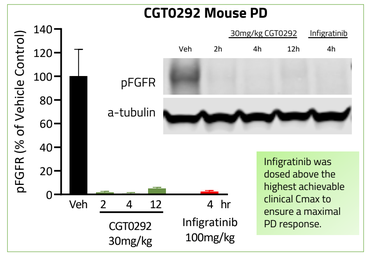
### Table 3. CGT0292 Demonstrates Progress Toward Superior FGFR1 Selectivity and Mutant Target Coverage Compared to Late Stage / Approved Pan-FGFRi

| Compound | Cell $IC_{50}$ (nM) | | Enzyme $IC_{50}$ (nM) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | FGFR1-WT | FGFR2-WT | FGFR1-WT | FGFR2-WT | FGFR2 N549H | FGFR2 V564I | FGFR2 V564F | FGFR3-WT | FGFR4-WT |
| CGT0292 | 949 | 30 | 27 | 2.1 | 0.93 | 5.6 | 3.0 | 5.8 | 213 |
| Infigratinib | 10.8 | 4.2 | 0.37 | 0.45 | 0.93 | 63 | 879 | 4.6 | 65 |
| Pemigatinib | 10.1 | 1.6 | 0.49 | 0.18 | 1.7 | 5.2 | 244 | 1.1 | 13 |
| Erdafitinib | 5.3 | 1.4 | 0.24 | 0.11 | 0.32 | 0.16 | 173 | 0.14 | 1.0 |
| Futibatinib | 4.2 | 2.1 | 0.55 | 0.20 | 0.59 | 0.70 | 54 | 0.32 | 1.0 |

- CGT0292 displays >30X selectivity between FGFR1 and FGFR2 in cellular assays
- Is potent against all tested FGFR2 mutations, enzyme $IC_{50}$ < 10 nM
- Exhibits > 100x selectivity for FGFR2 over FGFR4 in the enzyme assay

### Figure 4. CGT0292 Shows Promising In Vivo Performance and Complete Suppression of pFGFR

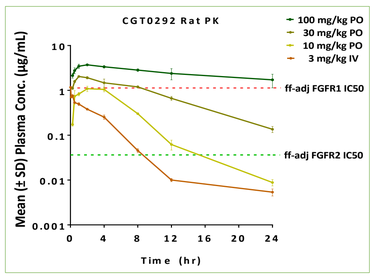


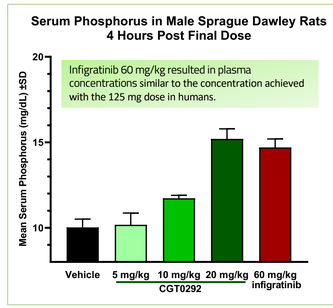




Snu-16 xenograft tumors were harvested at the indicated timepoints after a single oral dose and analyzed via Western blot normalized to tubulin.

- CGT0292 showed increased exposure with increased dose in mice
- IV CL: 35.9 mL/min/kg, F: 87.9% (10 mg/kg PO dose)
- Comparable to Infigratinib, CGT0292 showed complete inhibition of pFGFR2 in the SNU-16 PK/PD model

### Figure 5. CGT0292 Does Not Show Serum Phosphorus Increase at a 5 mg/kg Dose in the SD Rat Model of Hyperphosphatemia




- Exposures above free cellular $IC_{50}$ of FGFR1 leads to increase in serum phosphorus preclinically

Male Sprague Dawley rats (n= 4/group) were dosed with 5, 10, or 20mg/kg CGT0292 (PO, BID) or 60mg/kg infigratinib (PO, QD) for a total of 3 days followed by serum collections 4 hours after the last dose for serum phosphorus levels.

## Conclusions

- FGFR1 mediated hyperphosphatemia is the most common dose limiting toxicity with pan-FGFR inhibitors
- Approved inhibitors fail to capture the full landscape of FGFR2 and FGFR3 altered tumor types
- PK/PD and hyperphosphatemia models have been established to interrogate and enlarge the therapeutic window during further optimization of CGT0292 and related compounds in the series

**•CGT0292:**

- Provides >30X selectivity window for FGFR2 vs. FGFR1 in wt p-FGFR cell assay
- Shows potency against a panel of FGFR2 gatekeeper and molecular brake mutations
- Has drug-like physiochemical properties with desirable solubility, permeability and plasma protein binding
- Displays dose ascending PK with low to moderate IV clearance and high oral bioavailability in mice
- Has equivalent inhibition of pFGFR2 compared to Infigratinib in the SNU-16 tumor PK/PD model
- Exhibits dose related increases in serum phosphorus levels

**References :** 1. AACR Project GENIE Consortium. *Cancer Discov.* 2017;7(8):818-831; 2. Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259-267; 3. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21(5):671-684. 4. Siefker-Radtke et al. *Lancet Oncol.* 2022;23(2):248-258; 5. PEMAZYRE (pemigatinib; prescribing information). Wilmington, DE: Inctye Corporation; 2021;
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*All animal studies were conducted in accordance with The Guide for the Care & Use of Laboratory Animals and IACUC approved policies and procedures at the facilities where they were performed.

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