Preclinical In Vitro and In Vivo Characterization of Novel Wild-Type-Sparing PI3Kα H1047R Mutant-Selective Inhibitors

Aaron C. Smith, Ben Arwood-Levine, Abiezer Blandon, Alexandra Born, Richard Brizendine, Payal Chatterjee, Mark J Chicarelli, Michael L. Conner, Brad Fell, Jennifer Fulton, Anna Guarnieri, Ravi Jalluri, Hailey J. Knox, Keith Koch, Daniel Krischlunas, Vijay Kumar, Colin Mchugh, Brent Mclean, Kelsey Nassar, Brad Newhouse, Rob Rieger, John Robinson, Marelí Rodriguez, Leah Salituro, Lee Stunkard, Francis Sullivan, Roy Turton, Shannon Winski, and Yeyun Zhou; Cogent Biosciences, Inc., Boulder, CO and Waltham, MA

San Antonio Breast Cancer Symposium®
December 5-9, 2023
Presentation Number: PO3-26-01

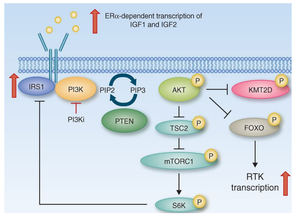
Cogent PI3Kα H1047R Inhibitor Opportunity

Target Product Profile

PI3Kα Wild-Type Sparing	Avoids dose modifications related to inhibition of PI3Kα WT
Potent on Mutation	Highly potent against the major PI3Kα H1047R oncogenic mutation
Oral Dosing	High oral bioavailability, low clearance Low peak-to-trough avoids C_{max}-driven AEs
Selective	Selective for PI3Kα H1047R across the kinome, receptors, hERG, and channel panel
Combinable	Low potential for CYP-mediated DDI based on in vitro data

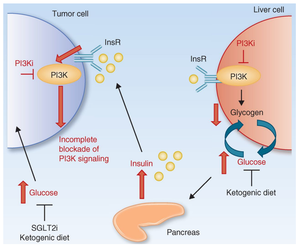
Background

Figure 1. PI3Kα Receptor Signaling Pathway[1]



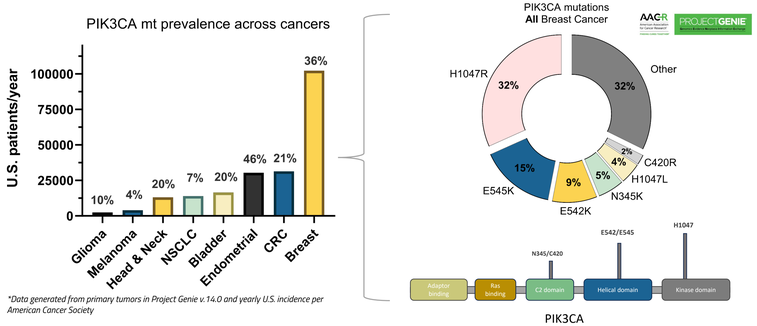
- The phosphoinositide 3-kinases (PI3K) pathway is a key cell cycle regulating pathway that has an established role in tumor growth and development
- The H1047R mutation of the p110α subunit of PI3K is a known activating mutation that is targeted by inhibitors under clinical investigation as well as by the approved drug alpelisib

Figure 2. Effect of Insulin on Healthy and Tumor Cells[1]



- On-target inhibition of PI3Kα WT by approved inhibitors has led to tolerability issues including hyperglycemia, gastrointestinal issues, and skin reactions
- Inhibition of PI3Kα WT in healthy cells leads to glucose dysregulation with increases in insulin which cause activation of PI3Kα in tumor cells leading to diminished efficacy from clinical inhibitors[1]

Figure 3. PI3Kα Mutational Frequency in Solid Tumors, and Distribution in Breast Cancer

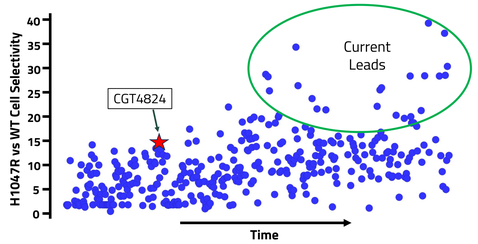


Data generated from primary tumors in Project Genie v.14.0 and yearly U.S. incidence per American Cancer Society

- PI3Kα mutations are highly prevalent in many solid tumors including bladder, endometrial, colorectal, and breast cancer[2,3]
- H1047R is the most common PI3Kα mutation encompassing ~32% of all PI3Kα mutations in breast cancer and up to ~40% in ER+/Her2- breast cancers[2]

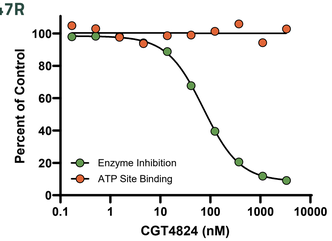
Results

Figure 4. SAR Breakthrough Is Leading to Increased PI3Kα H1047R vs WT Selectivity



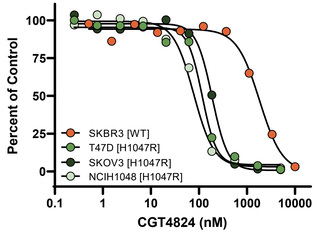
- CGT4824 is an early lead compound that was used to validate our in-house model systems
- SAR breakthroughs are driving increased selectivity of > 35-fold for advanced leads

Figure 6. CGT4824 Is an Allosteric Inhibitor of PI3Kα H1047R



- Enzymatic inhibition was observed with CGT4824
- CGT4824 does not displace an ATP site probe
- CGT4824 inhibits enzyme activity from an allosteric binding site

Figure 8. Robust Inhibition of H1047R Mutant Cell Lines



- CGT4824 was profiled in four cell lines measuring inhibition of pAKT
- Similar potency was observed across H1047R mutant lines
- Early lead shows 15x mutant selectivity compared to PI3Kα WT SKBR3 line

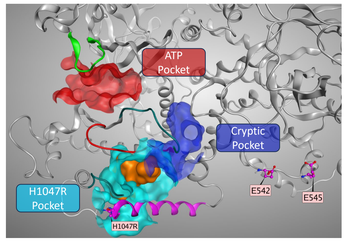
Figure 5. CGT5580 and CGT5450 Demonstrate Progression Toward Highly Selective Compounds

Assay	CGT4824	CGT5450	CGT5580
H1047R Mutant Cell Line IC_{50}*			
T47D	21 nM	14 nM	8 nM
Selectivity	15x	28x	35x
WT Cell Line IC_{50}*			
SKBR3	298 nM	385 nM	288 nM

*Adjusted for FBS-binding

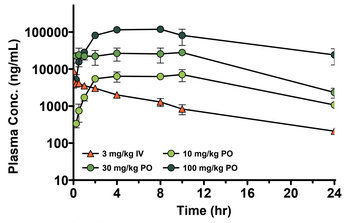
- Related compounds were profiled in PI3Kα H1047R Mutant T47D and PI3Kα WT SKBR3 mechanistic cell assays measuring inhibition of pAKT
- Current lead matter, CGT5450 and CGT5580, has improved potency and increased selectivity over PI3Kα WT versus CGT4824

Figure 7. Allosteric Binding Confirmed by Crystallography



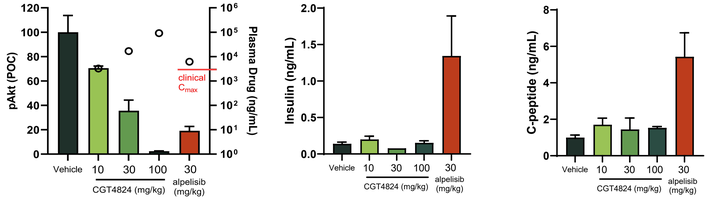
- 2.7A Crystal structure of CGT4824, shown as orange surface, is bound in the H1047R-allosteric pocket, cyan surface, of PI3Kα.
- Rapid generation of ~40 co-crystal structures enabled structure-based approaches to develop selective and potent compounds.

Figure 9. CGT4824 – Favorable Differentiated Dose Ascending Oral PK



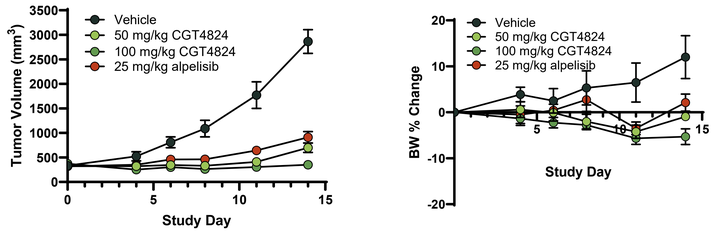
- PK study of CGT4824 dosed in mouse at 3 mg/kg IV, and 10, 30, and 100 mg/kg PO
- CGT4824 showed high oral bioavailability, F>100% at 10 mg/kg
- Low clearance was observed, extraction ratio = 2% provides sustained target coverage

Figure 10. CGT4824 Shows >95% Inhibition of pAKT with No Increases in Insulin or C-Peptide in an H1047R PD Model



- CGT4824 showed dose-responsive inhibition of pAKT in an NCI-H1048R lung cancer (H1047R) PD model, achieving >95% inhibition at 100 mg/kg
- A 30 mg/kg dose of alpelisib showed 80% inhibition of pAKT at plasma concentrations above those achieved clinically
- At maximally efficacious concentrations CGT4824 does not show increases in insulin or C-peptide

Figure 11. CGT4824 Showed Superior Efficacy Compared to Alpelisib in an NCI-H1048 Tumor Model



- CGT4824, dosed PO QD at 50 and 100 mg/kg, was compared to alpelisib, dosed PO QD at 25 mg/kg in a H1047R lung cancer model
- CGT4824, in a dose response fashion, achieved maximal tumor growth inhibition compared to a clinically-relevant alpelisib dose
- Well tolerated with ≤5% body weight loss and no deaths observed at any of the doses

Conclusions

- **CGT4824– Early lead compound with selectivity for PI3Kα H1047R over WT identified**
  - **Allosteric inhibitor with no binding to the ATP binding site of PI3Kα**
  - **Low nM potency in H1047R mutant PI3Kα cell lines**
  - **15-Fold selectivity for PI3Kα H1047R mutant vs WT**
  - **Differentiated dose ascending PK in mice with high bioavailability and low clearance**
- **CGT4824 shows >95% inhibition of pAKT in an H1047R PD model with no increases in insulin and C-peptide**
- **CGT4824 demonstrated superior efficacy compared to a clinically-relevant dose of alpelisib in the NCI H1048 mouse tumor growth inhibition model**
- **CGT4824 was well tolerated in the TGI efficacy models**
- **Next Gen Cogent compounds are continuing to show increased potency (<10 nM) and selectivity (>35 fold) to enable high clinical target engagement without metabolic disfunction caused by inhibition of PI3Kα WT**

REFERENCES: 1. Hanker, A. B.; Kaklamani, V.; Arteaga, C. L. Challenges for the Clinical Development of PI3K Inhibitors: Strategies to Improve Their Impact in Solid Tumors." Cancer Discovery, 2019, 9, 482–491. 2. The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through An International Consortium, Cancer Discov. 2017 Aug;7(8):818-831, 3. American Cancer Society. Cancer Facts & Figures 2023. Atlanta: American Cancer Society; 2023

For questions, please contact aaron.smith@cogentbio.com.

DISCLOSURES: All authors are employees of Cogent Biosciences
ACKNOWLEDGEMENTS: Dr. Anil Patel and their O2H Discovery chemistry team