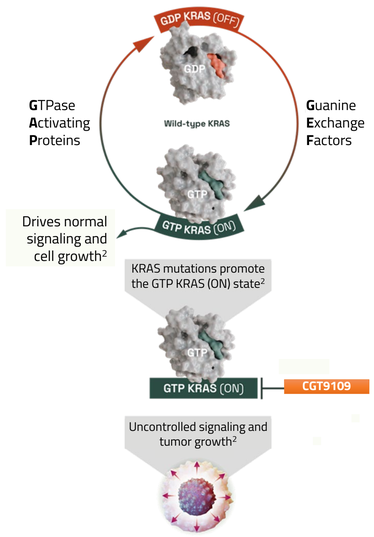
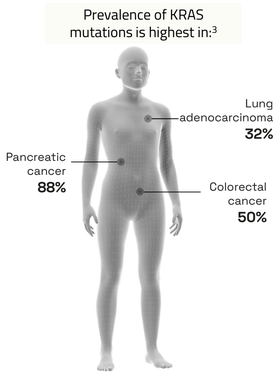
Identification of a Potent KRAS(ON) Inhibitor with Selectivity for Mutant KRAS over HRAS and NRAS

Keith Koch, Yeyun Zhou, Kim Alley, Karyn Bouhana, Richard Brizendine, Paul Carlson, Mark J Chicarelli, Michelle Crow, Brad Fell, John Fischer, Jennifer Fulton, Anna Guarnieri, Jackie Harrison, Madison Hillman, Ravi Jalluri, Amber Johnson, Cori Malinky, Matthew G. McDonald, Macedonio J. Mejia, Brad Newhouse, Scott Niman, Rob Rieger, John Robinson, Mareli Rodriguez, Leah Salituro, Vinny Scarato, Aaron Smith, Francis Sullivan, Yang Wang, Shannon Winski, Silas Wood; Cogent Biosciences, Inc., Boulder, CO and Waltham, MA

Poster #3
Abstract #6974

11% of All Carcinomas have KRAS Mutations[1]

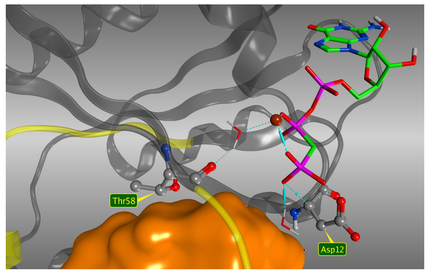




CGT9109, A SELECTIVE PAN-KRAS INHIBITOR

- Potently inhibits KRAS across prevalent KRAS mutations
- Shows >1000x selectivity for KRAS over HRAS and NRAS isoforms, which may confer tolerability advantages over RAS multi-selective inhibitors

CGT9109 Binds In the Switch II Pocket of KRAS(ON)



- 1.9Å resolution crystal structure of CGT9109 co-crystallized with GMPPCP loaded $KRAS^{G12D}$ protein was solved
- GMPPCP is clearly visible in the upper right of the image with a chelated Mg
- **CGT9109 is an active GTP-KRAS(ON) Switch II binder**

CGT9109 is a Potent KRAS(ON) Binder with Selectivity over HRAS/NRAS

RAS(ON) SPR Binding Assay K_D							
KRAS						HRAS	NRAS
WT	G12V	G12D	G12C	G13D	Q61H	WT	WT
1.1 nM	3.3 nM	0.7 nM	0.9 nM	0.7 nM	1.2 nM	>5000 nM	>5000 nM

- Kinetic SPR binding of CGT9109 bound to WT and mutant KRAS proteins as well as WT HRAS and NRAS each loaded with the GTP stable analog GMPPCP was determined
- nM/pM binding to KRAS WT and mutants with > 1000x selectivity over HRAS or NRAS was observed for CGT9109
- RMC-6236 showed no selectivity with equal potency across Ras isoforms: KRAS, NRAS and HRAS[4]

CGT9109 Key Findings

- **pM Inhibitor of mutant KRAS**: CGT9109, more potent second generation lead to previously reported CGT6137[5], showed pM inhibitory activity in a panel of mechanistic cell assays from diverse tumor types with KRAS mutations measuring inhibition of pERK
- **Binds in the Switch II pocket**: An X-Ray structure of CGT9109 bound to $KRAS^{G12D}$ loaded with GTP analog GMPPCP shows CGT9109 bound in the switch II pocket with the gamma phosphate of GMPPCP clearly visible
- **Selective for KRAS over HRAS/NRAS**: nM-pM Binding was observed by SPR to wild type and mutant KRAS loaded with GMPPCP with >1000x selectivity for WT HRAS and NRAS
- **Potent inhibitor of active GTP KRAS(ON)**: A minimal shift in potency was observed with CGT9109 in a (+/-) EGF challenge cellular assay using AsPC-1 $KRAS^{G12D}$ and SW480 $KRAS^{G12V}$ cell lines
- **Robust PD at 30 mg/kg oral dose**: Potent inhibition of pERK observed with CGT9109 dosed PO at 30 mg/kg in an AsPC-1 $KRAS^{G12D}$ mouse model
- **Regressions in a $KRAS^{G12D}$ TGI model**: CGT9109 demonstrated tumor regression when dosed PO BID at 30 mg/kg in 14-day AsPC-1 $KRAS^{G12D}$ tumor bearing mouse TGI model
- **Lead optimization of this series is ongoing**

CGT9109 Shows pM Inhibition Across Mutant KRAS Cell Lines

Cell Line	Tumor Type	KRAS Mutation	CGT9109 Cellular IC_{50}	RMC-6236 Cellular IC_{50}
PC-9	Non-small cell lung cancer	(WT)	0.50 nM	2.7 nM
NCI-H2009	Non-small cell lung cancer	G12A	0.18 nM	0.75 nM
NCI-H358	Non-small cell lung cancer	G12C	0.23 nM	0.27 nM
AsPC-1	Pancreatic cancer	G12D	0.26 nM	1.4 nM
A549	Non-small cell lung cancer	G12S	0.17 nM	0.59 nM
SW480	Colorectal cancer	G12V	0.31 nM	0.28 nM
HCT116	Colorectal cancer	G13D	0.29 nM	0.79 nM
NCI-H460	Non-small cell lung cancer	Q61H	0.17 nM	0.50 nM

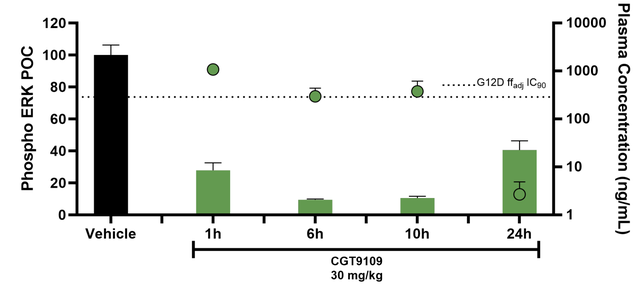
- Inhibition of pERK was determined for CGT9109 and RMC-6236 in a variety of cell lines and tumor types to interrogate inhibition across a range of KRAS mutations
- CGT9109 showed pM pERK inhibition across the spectrum of KRAS cell lines shown

Cellular EGF Challenge Confirms GTP KRAS(ON) Activity for CGT9109

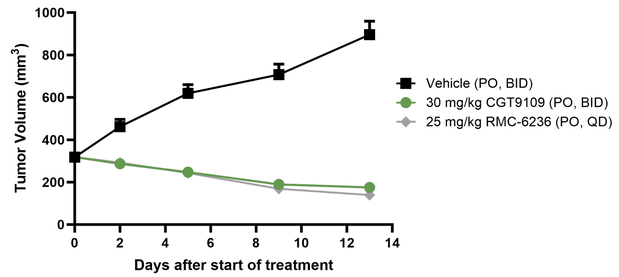
Compound	Cell Line	KRAS Mutation	(-) EGF IC_{50}	(+) EGF IC_{50}
CGT9109	AsPC-1	G12D	1.1 nM	3.4 nM
	SW480	G12V	2.3 nM	7.0 nM
RMC-6236	AsPC-1	G12D	1.3 nM	5.2 nM
	SW480	G12V	0.8 nM	2.6 nM

- Mechanistic cellular assay in the presence of EGF forces KRAS into the active GTP-KRAS(ON) state, similar potency +/- EGF indicates GTP KRAS(ON) mechanism of action[6]
- The minimal shift in IC_{50}s of CGT9109 in the presence/absence of EGF for both AsPC-1(G12D) and SW480(G12V) cell lines supports a KRAS(ON) mechanism of inhibition, data for the RAS(ON) inhibitor RMC-6236 is shown for comparison

CGT9109 has Robust In Vivo Efficacy in AsPC-1(G12D) Tumors



- pERK and drug plasma levels were measured in an AsPC-1 (G12D) PK/PD model following a single oral dose of 30 mg/kg CGT9109
- 10 Hour drug plasma coverage of the free fraction adjusted IC_{90} resulted in 90% inhibition of pERK; supporting a 30 mg/kg BID dosing regimen



- In a subcutaneous AsPC-1 (G12D) TGI model, 30 mg/kg BID (PO) CGT9109 robustly inhibited tumor growth and was equivalent to RMC-6236 administered at clinically matched exposures[7]
- CGT9109 was well tolerated with no body weight loss observed

References: 1. Yang Y et al. J. Clin. Med 2023; 12, 709. doi: 10.3390/jcm12020709. 2. Moore A et al. Nat. Rev. Drug Discov. 2020; 19(8): 533–52. 3. Singhal A et al. Nat Med. 2024; 30: 969–83. 4. Cregg J et al. J. Med. Chem. 2025; 68: 6064-83. 5. Fischer J et al. EORTC/NCI/AACR 2024. 6. Zhang J et al. Cancer Discov. 2024; 14(9):1675-1698. 7. Spira A et al. EORTC/NCI/AACR 2023.

Acknowledgments/Disclosures This study was funded by Cogent Biosciences. All authors are employees of Cogent Biosciences.