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Discovery of RMC-5127, an Oral, RAS(ON) G12V-Selective, Noncovalent, Tri-Complex Inhibitor

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Disclosure Information

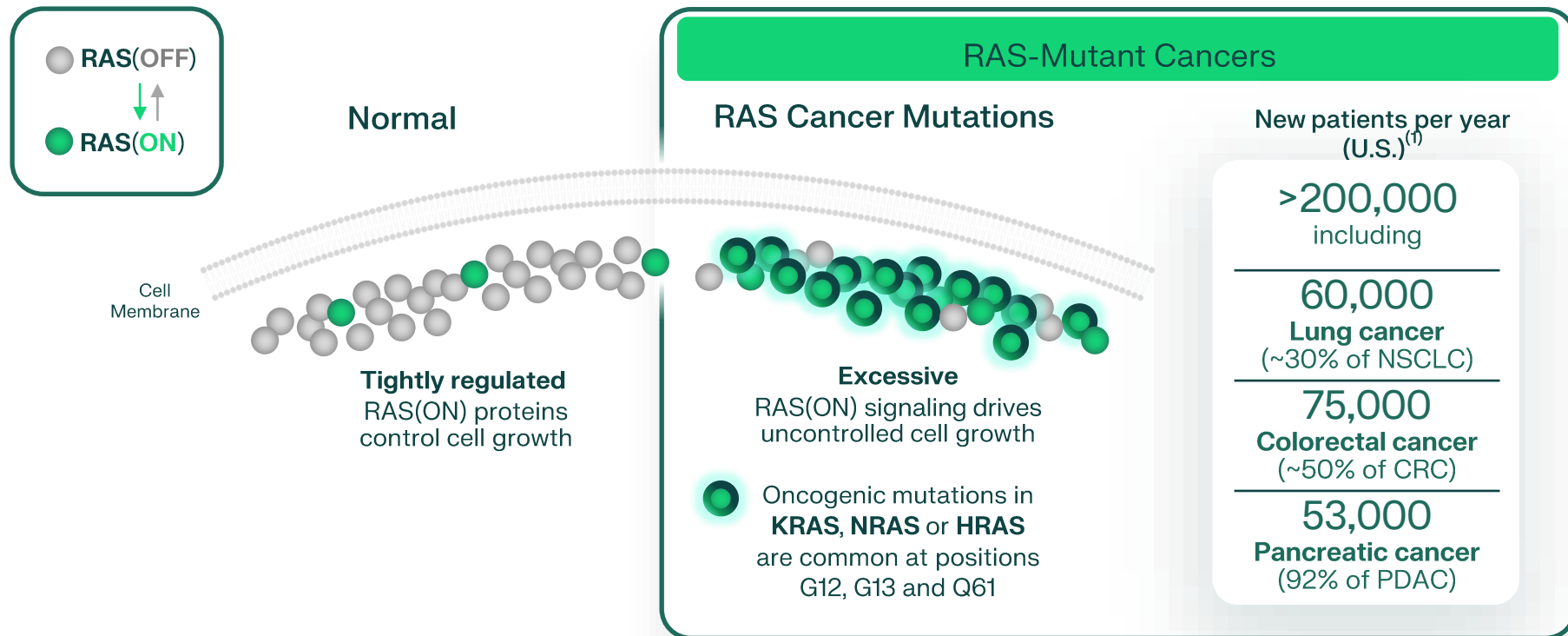
Anne V. Edwards

I have the following relevant financial relationships to disclose:

Employee of: Revolution Medicines

Stockholder in: Revolution Medicines

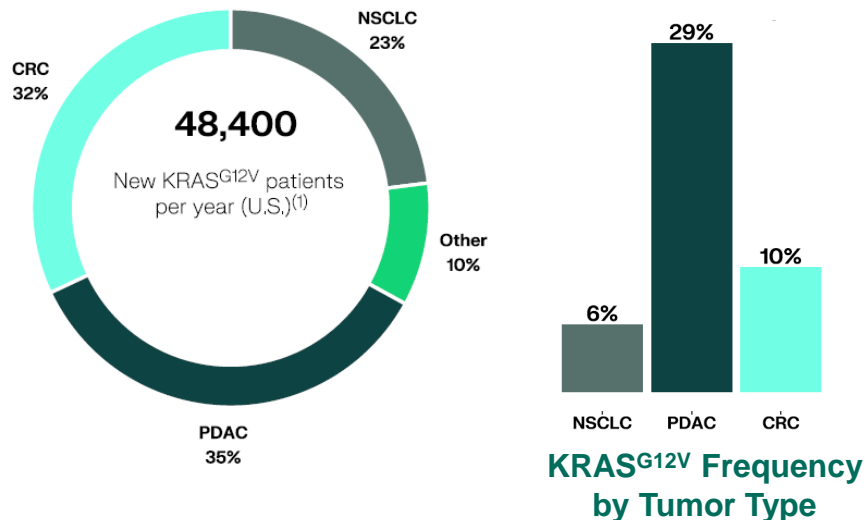
RAS(ON) Proteins are Key Therapeutic Targets in RAS-Addicted Cancers



(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; PDAC = pancreatic ductal adenocarcinoma

Multiple Approaches to Targeting KRAS G12V Mutant Cancers

Clinical Unmet Need for KRAS G12V



Revolution Medicines Planned Clinical Approaches to G12V

Daraxonrasib RAS(ON) multi-selective*

- Noncovalent, selective inhibitor of mutant and wild-type RAS(ON) proteins
- Targeted agent for SOC combinations, including immunotherapies
- RAS(ON) inhibitor doublet combination with RMC-5127

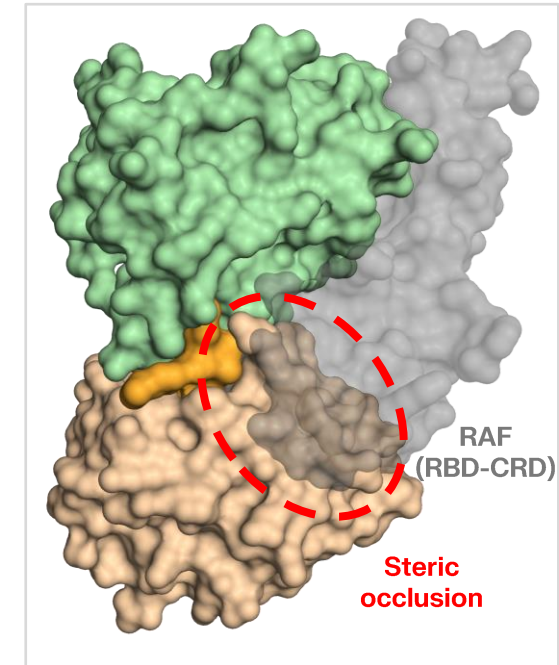
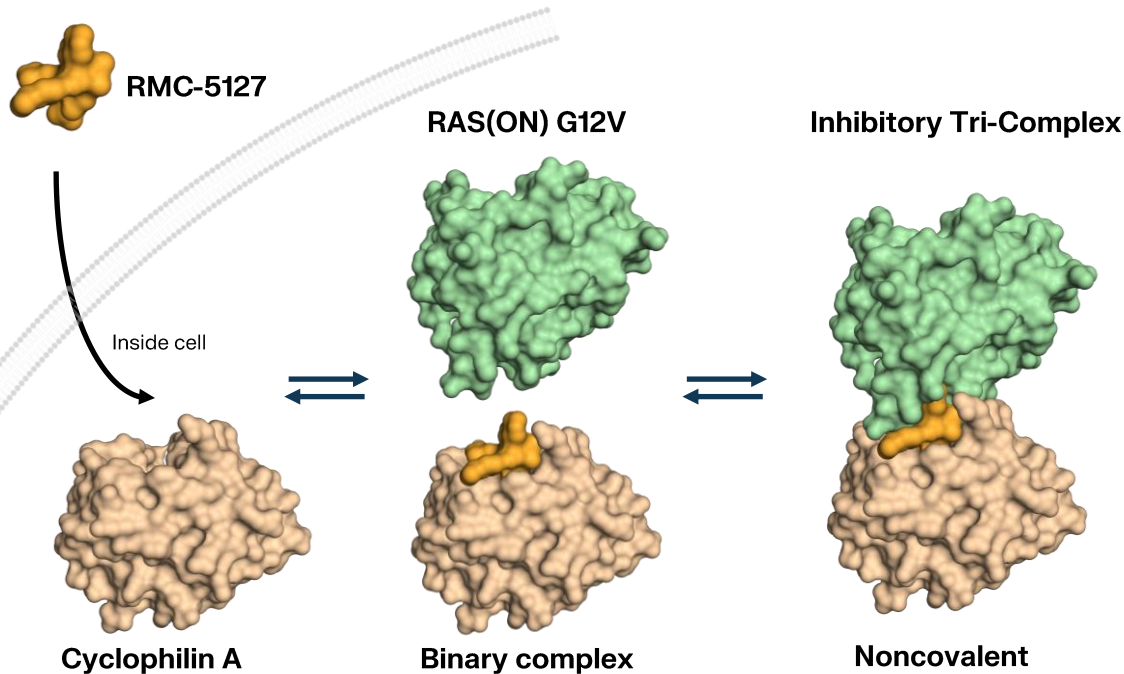
RMC-5127 RAS(ON) G12V-selective

- Alternate monotherapy approach
- Differentiated targeted agent for SOC combinations, including immunotherapies

(1) Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022 and scaled to estimated patient numbers using cancer incidence from ACS Cancer Facts and Figures 2023

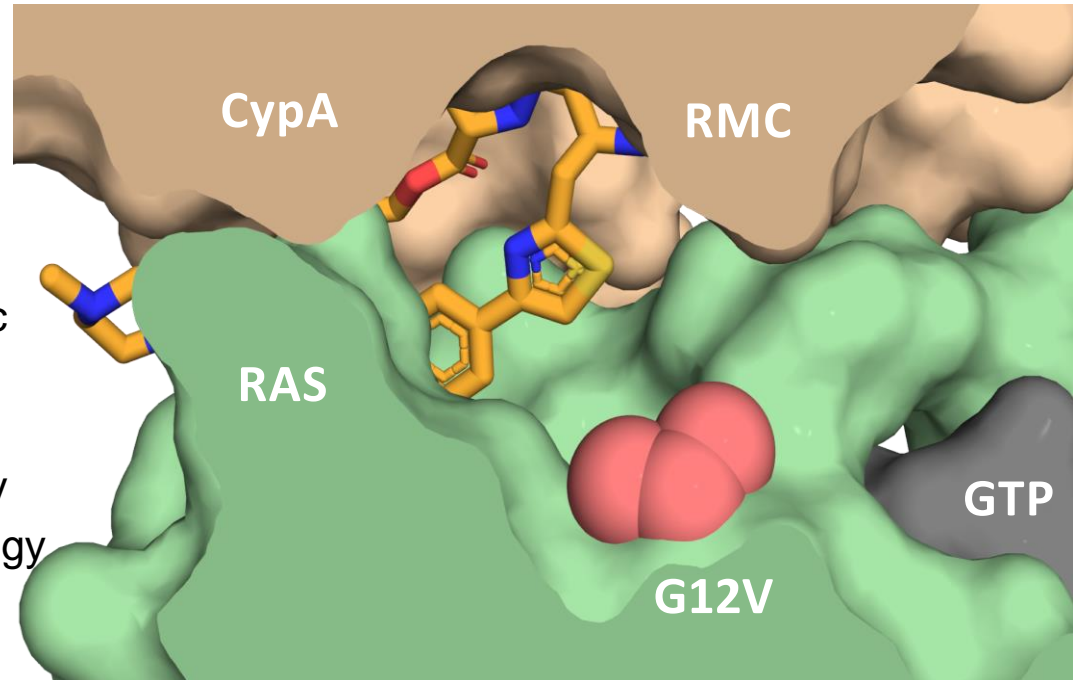
* Cregg, et al. J. Med. Chem. 2025, 68, 6, 6064-6083

Tri-Complex Platform Enables Selective Targeting of Oncogenic RAS(ON) Proteins



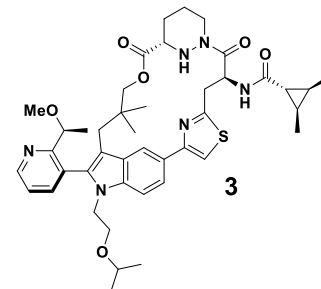
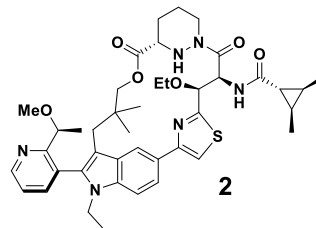
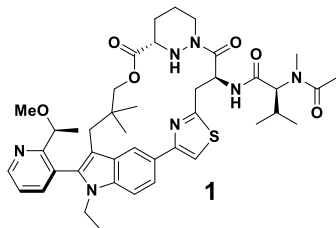
Selective Targeting of RAS(ON) G12V vs RAS(ON) WT is Challenging

- Valine is a larger amino acid than glycine (WT), which minimizes the possibilities of driving the selectivity through steric clash
- V amino acid contains a hydrophobic sidechain with no specific polar interaction to leverage for selectivity
- There is no reactive functionality in V that would allow for a covalent strategy similar to C or D mutants



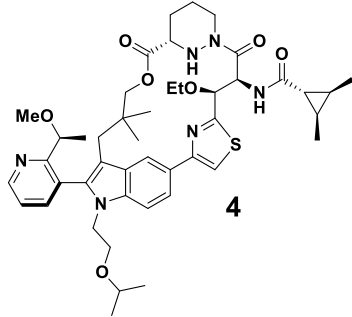
SAR Areas for RAS(ON) G12V Selectivity

Compounds **1**, **2**, and **3** were selected from our internal collection as chemical starting points to introduce noncovalent selectivity

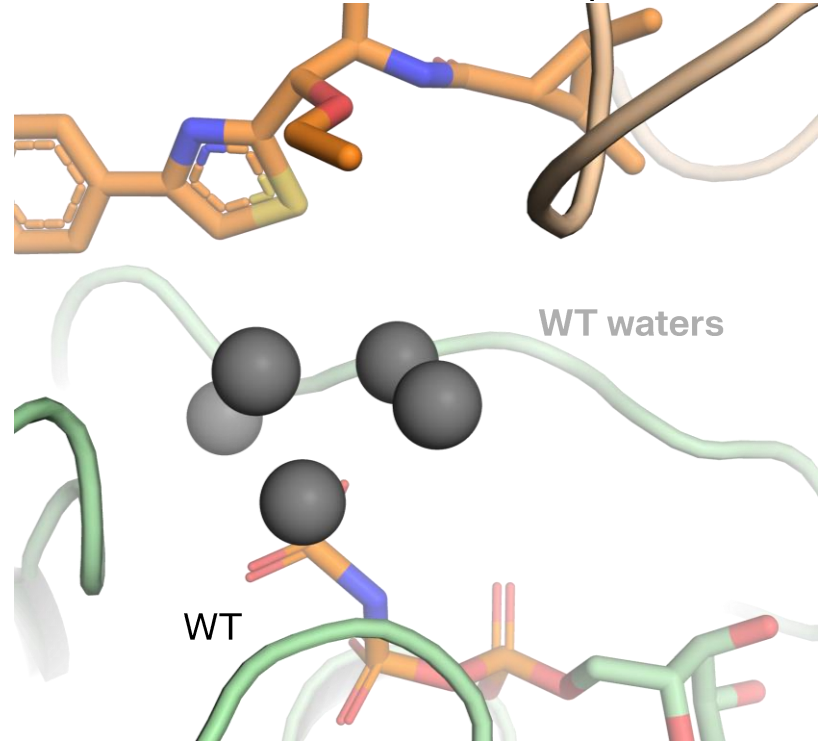


	1	2	3
G12V RAS (ON) RAS-RAF Disruption (nM)	3,547	73	387
WT RAS (ON) RAS-RAF Disruption (nM)	4,920	443	1,226
G12V Selectivity	1.4	6.0	3.2
Capan-1 CTG EC ₅₀ (nM)	149	201	50

RAS(ON) G12V Selectivity is Additive

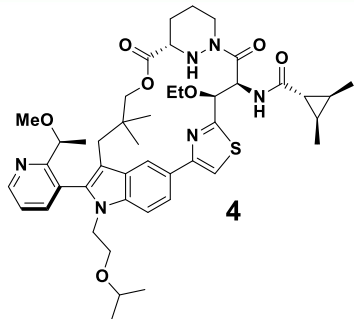


Benzylic ether interacts with the differential water network of G12V versus WT RAS tri-complexes

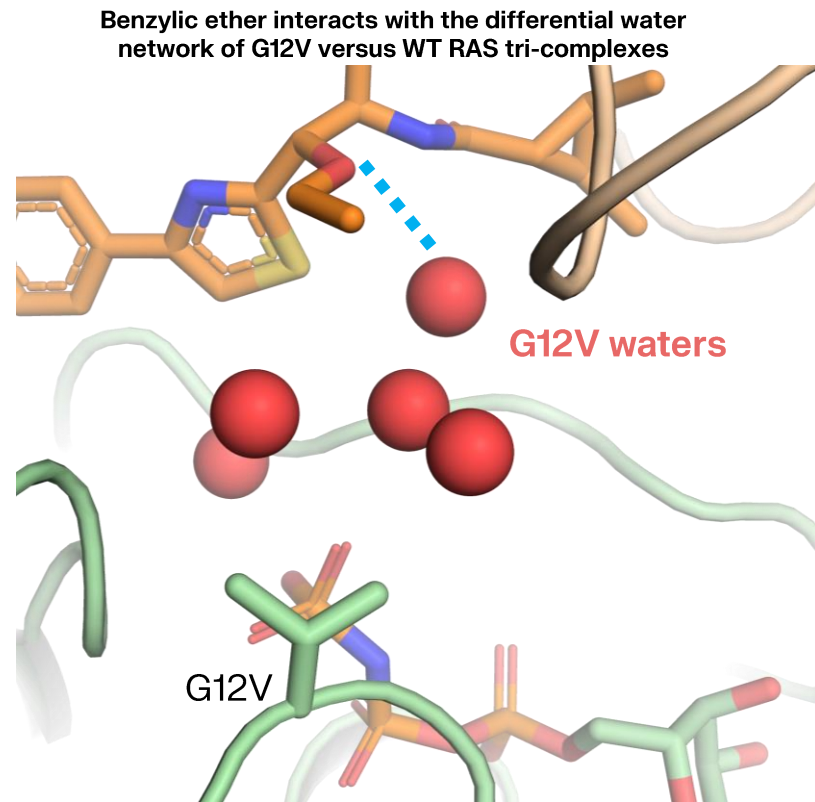


	4
G12V RAS (ON) RAS-RAF Disruption (nM)	90
WT RAS (ON) RAS-RAF Disruption (nM)	1,041
G12V Selectivity	12
Capan-1 CTG EC₅₀ (nM)	513

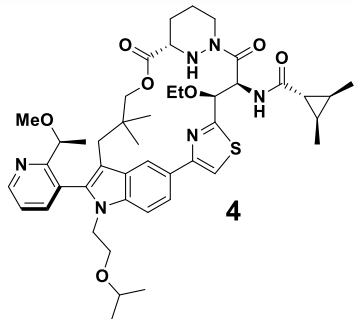
RAS(ON) G12V Selectivity is Additive



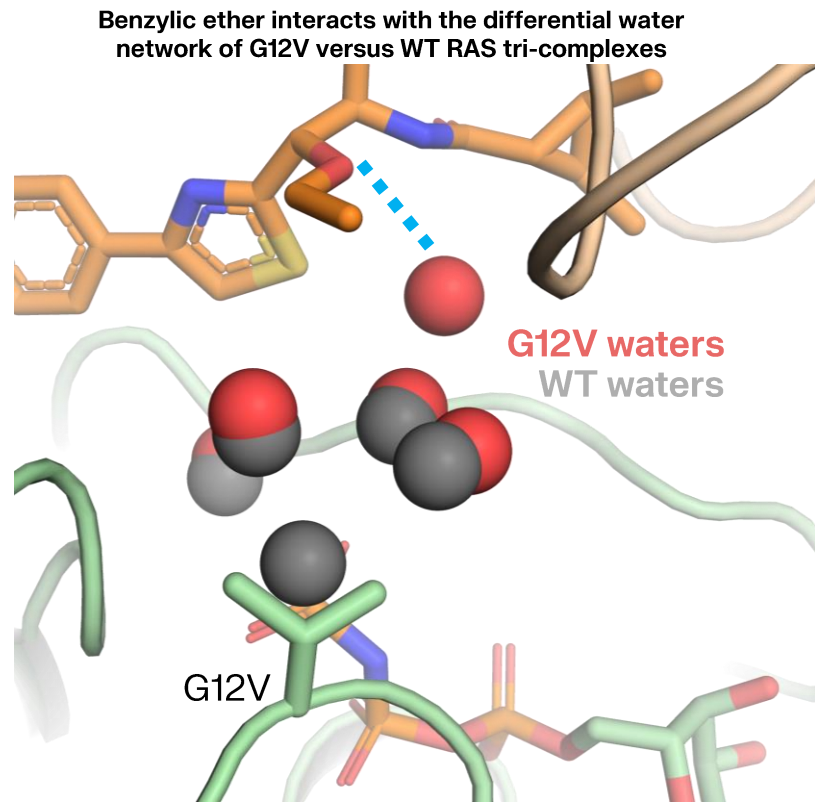
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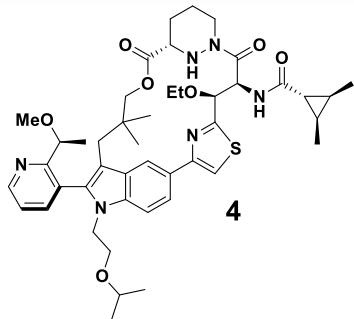
RAS(ON) G12V Selectivity is Additive



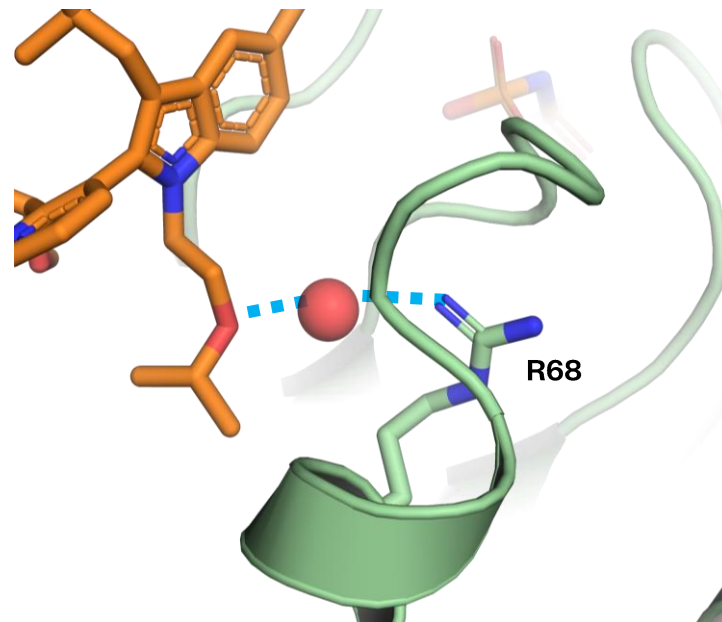
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RAS(ON) G12V Selectivity is Additive

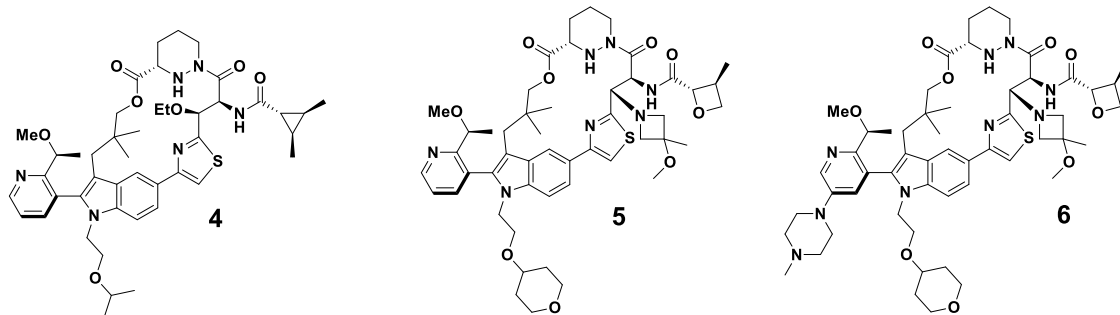


Isopropyl ether forms a through-water interaction with R68, stabilizing SWII preferentially for G12V mutant tri-complexes

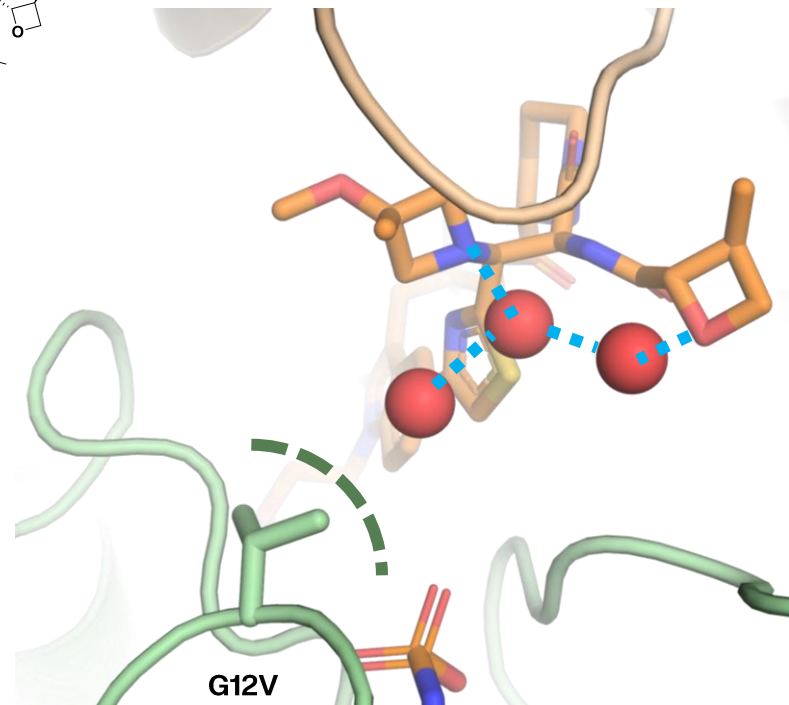


	4
G12V RAS (ON) RAS-RAF Disruption (nM)	90
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G12V Selectivity	12
Capan-1 CTG EC₅₀ (nM)	513

Improved RAS(ON) G12V Potency and Selectivity



Oxetane engages additional structural water, further stabilizing shielded water network

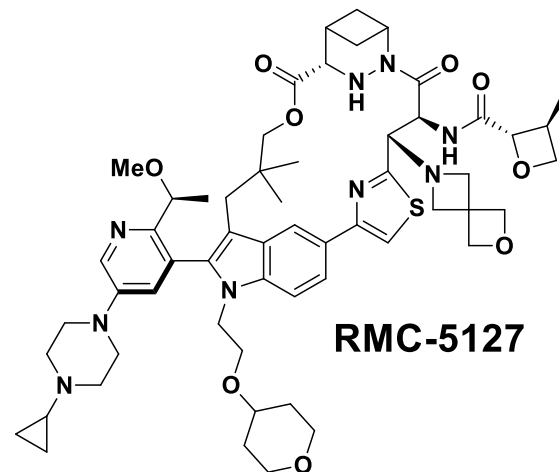


	4	5	6
G12V RAS (ON) RAS-RAF Disruption (nM)	90	90	72
WT RAS (ON) RAS-RAF Disruption (nM)	1,041	3,320	2,132
G12V Selectivity	12	37	30
Capan-1 CTG EC₅₀ (nM)	513	126	4.0

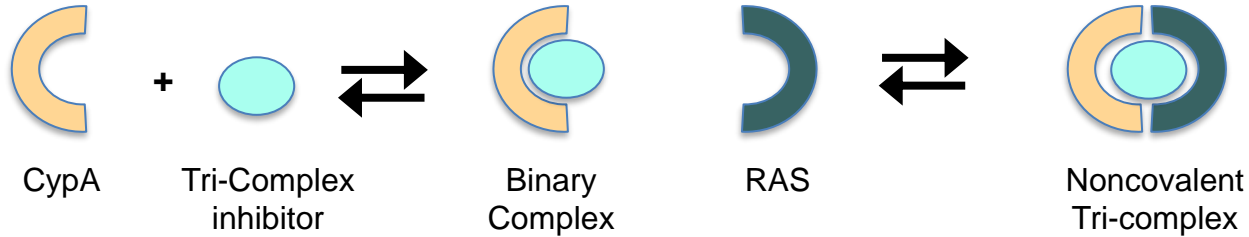
Compound 6 is RMC-8449 and is a preclinical tool compound

RMC-5127 is a Potent and Selective RAS(ON) G12V Inhibitor with a High-Quality Drug-Like Profile

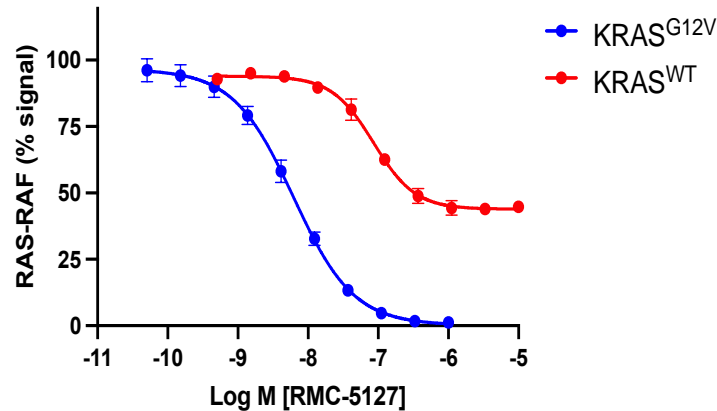
ID	RMC-5127
G12V RAS-RAF Disruption (EC₅₀, nM)	73
WT RAS-RAF Disruption (EC₅₀, nM)	2285
RAS-RAF Disruption Selectivity	30
pERK, (Capan-1, EC₅₀, nM)	0.6
CTG, (Capan-1, EC₅₀, nM)	2.1
Selectivity over WT RAS cell lines (CTG, EC₅₀ fold difference)	26
% oral bioavailability Avg (x-species)	35
Clearance (x-species)	Moderate
Safety Panels	Low Risk



Submaximal Inhibition of RAS WT by RMC-5127



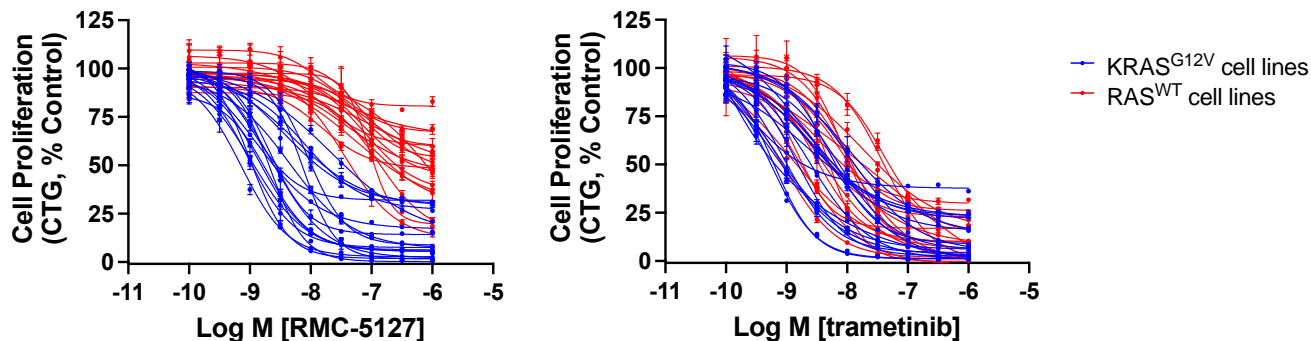
NanoBRET RAS-RAF disruption (Cellular)



Cellular CypA levels limit binary complex concentration and potential for maximal inhibition of WT RAS

Submaximal Inhibition of RAS WT by RMC-5127

Human Cancer Cell Panel (KRAS^{G12V} vs. K/N/HRAS^{WT})

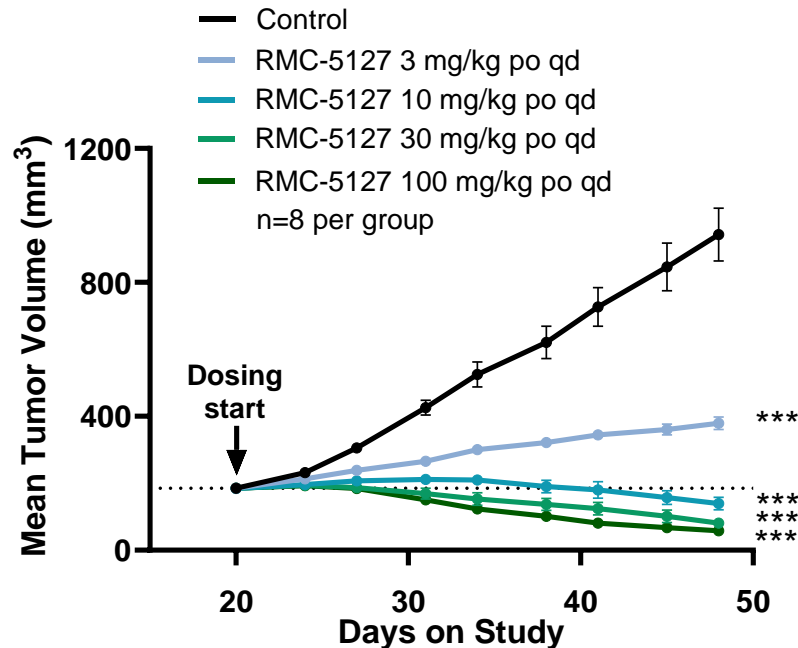
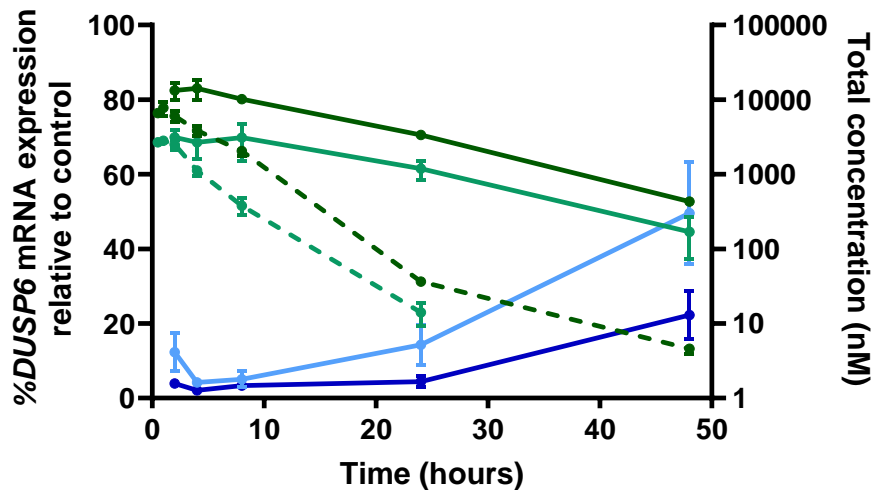


	Median EC ₅₀		Selectivity EC ₅₀	Maximum % Inhibition	
	KRAS ^{G12V} (n = 18)	RAS ^{WT} (n = 18)	WT/G12V	KRAS ^{G12V}	RAS ^{WT}
RMC-5127	2.1 nM	53 nM	26x	93%	53%
Trametinib (MEK)	1.7 nM	4.6 nM	3x	94%	92%

Dose-Dependent Exposure, RAS Pathway Inhibition and Antitumor Activity in a KRAS G12V Human Cancer Model

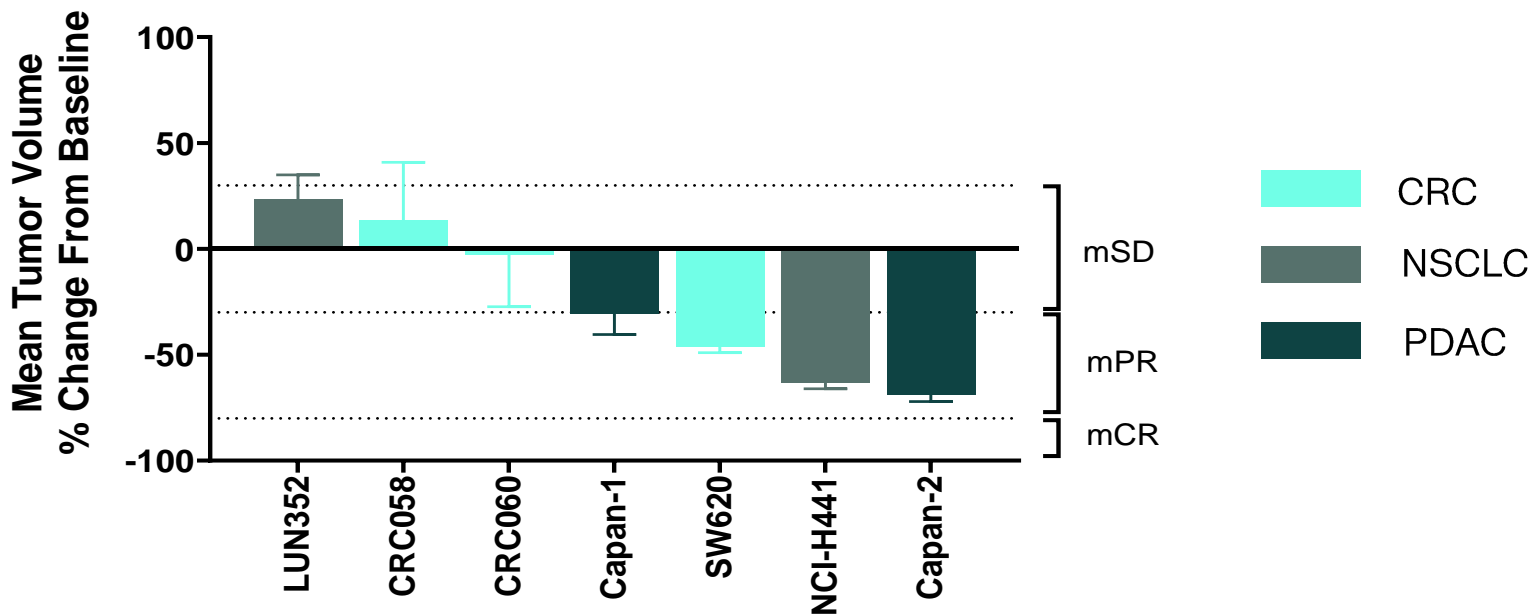
Capan-2 xenograft tumors (KRAS^{G12V/WT}, PDAC)

RMC-5127 30 mg/kg ● blood ● tumor ● PD
 RMC-5127 100 mg/kg ● blood ● tumor ● PD
 n=3 per time point



RM two-way ANOVA ***p<0.001 compared to the control

Robust Antitumor Activity Across KRAS G12V Human Cancer Models



Revolution Medicines preclinical research as of 10/30/24

RMC-5127 dosed at 100 mg/kg po qd; n=3-10/group

Responses after 28 ± 2 days of treatment unless maximal tumor burden reached sooner or control tumor reached 2 doublings (4* initial TV) later

Responses assigned according to mRECIST (modified from Gao et al. Nat Med. 2015)

Progression defined as tumor doubling from baseline

RMC-5127 is a Potent, Orally Bioavailable, and Selective RAS(ON) G12V Inhibitor

- RMC-5127 is a RAS(ON) G12V-selective, noncovalent, tri-complex inhibitor
- Selectivity of RMC-5127 for G12V over WT RAS arises from two properties:
 - Greater affinity of the CypA:RMC-5127 binary complex for RAS G12V, as showcased by the RAS-RAF disruption assay
 - Submaximal engagement of WT RAS in cells, where cellular CypA levels put an upper limit on the achievable binary complex concentration
- RMC-5127 induces deep and durable regressions in preclinical models of KRAS^{G12V} tumors across histotypes
- Activities are underway to advance RMC-5127 to a clinic-ready stage in 2025 to enable an expected Phase 1 initiation in 2026

Acknowledgments

- Revolution Medicines Research and Development Teams