Selective Inhibition of the Active State of KRAS\textsuperscript{G12V} with the Non-Covalent, Tri-Complex Inhibitor RMC-5127


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\textbf{Abstract}

- KRAS\textsuperscript{G12V} mutations are found in multiple cancers, and successful targeting of KRAS\textsuperscript{G12V}-mutant tumors represents an important unmet medical need.
- We previously applied our tri-complex inhibitor platform, which utilizes chemical remodeling of the cellular chaperone cytoplasmic A(CypA) to bind to undruggable surfaces, to design mutant-selective inhibitors targeting KRAS\textsuperscript{G12V}, KRAS\textsuperscript{G12D}, and KRAS\textsuperscript{Q61R}. In addition to the RAS\textsuperscript{G12V} inhibitor RMC-6236,
- RMC-5127 binds to CypA with high affinity, creating a necromorphic interface that forms a selective, non-covalent interaction with KRAS\textsuperscript{G12V}.
- The resulting tri-complex sterically blocks effector binding to KRAS\textsuperscript{G12V}, thereby inhibiting downstream signaling.
- RMC-5127 potently suppresses ERK phosphorylation in KRAS\textsuperscript{G12V}-mutant cancer cells, and is infinitely selective for KRAS\textsuperscript{G12V} over RAS\textsuperscript{G12D}-driven cancer cell lines due to a limiting cellular concentration of CypA.
- In preclinical species, RMC-5127 shows good bioavailability, dose-proportional exposure, and low clearance, allowing for oral dosing.
- In human xenograft tumors harboring KRAS\textsuperscript{G12V} mutations, a single dose of RMC-5127 induces dose-dependent, deep, and durable suppression of RAS pathway signaling in vivo.
- Repeated daily oral administration of RMC-5127 is well tolerated and demonstrates profound anti-tumor activity in these preclinical models.

\textbf{Mechanism of Action}

\textbf{Results}

- Cellular CypA concentration puts an upper bound on the active binary complex concentration.
- Affinity (K\textsubscript{i}) of the RMC-5127:CypA binary complex for KRAS\textsuperscript{G12V} is 2.8 nM, close to the concentration of CypA (~10 µM).
- Therefore, complete saturation of CypA with RMC-5127 is insufficient to fully inhibit KRAS\textsuperscript{G12V}.
- The analog RM-049 exhibits similar G12V selectivity to RMC-5127 but has 10+ greater potency, with a K\textsubscript{i} of the RM-049:CypA binary complex for KRAS\textsuperscript{G12V} of 0.27 µM, and can fully inhibit KRAS\textsuperscript{G12V}.

\textbf{Acknowledgements:} We thank Friends of the Cancer Cause; the Comprehensive Cancer Center at the University of Michigan; the National Institutes of Health; the Cancer Therapy Evaluation Program, Division of Cancer Prevention and Control, National Cancer Institute; and the Department of Health and Human Services for support of this work. We thank Drs. James Moore, Andrew Tenen, and James Boudreau for helpful discussions and suggestions.