

Hunter College of the City University of New York  
Department of Biological Sciences  
Spring 2025 Inga Richter Seminar Series

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**MSKCC**



**Targeting mutant RAS: elucidating mechanisms that reverse the detrimental effect of RAS mutations in cancer**

Approximately 3.4 million patients worldwide are diagnosed each year with cancers harboring pathogenic mutations in one of the three RAS proto-oncogenes: KRAS, NRAS, and HRAS. These mutations impair the GTPase activity of RAS, leading to the activation of downstream signaling pathways that drive tumor growth. As a postdoctoral fellow in Dr. Piro Lito's lab, my work focuses on elucidating the mechanisms of RAS-targeted therapies. In collaboration with colleagues at Revolution Medicines, our lab recently reported the discovery of tri-complex inhibitors (TCIs)—molecular glues that recruit cyclophilin A (CYPA) to the active, GTP-bound conformation of RAS. My research has revealed that some TCIs have a dual mechanism of action: they not only prevent activated RAS from binding to its effectors but also stimulate GTP hydrolysis. We employed biochemical and structural biology techniques to demonstrate that drug-bound CYPA complexes modulate residues in RAS to facilitate GTP hydrolysis in a mutation-specific manner. Importantly, RAS mutants most sensitive to GTPase activity stimulation were more susceptible to treatment than those in which hydrolysis could not be enhanced, suggesting that pharmacological stimulation of hydrolysis enhances the therapeutic effects of TCIs for specific RAS mutants. This work challenges the longstanding belief that the GTPase activity of mutant RAS proteins cannot be restored, demonstrating that pharmacological stimulation of GTP hydrolysis is possible and laying the foundation for a new class of therapeutics that can inhibit cancer growth by stimulating mutant GTPase activity.

Ref: Cuevas-Navarro, A., et al. *Pharmacological restoration of GTP hydrolysis by mutant RAS*. *Nature* 637, 224–229 (2025). <https://doi.org/10.1038/s41586-024-08283-2>

**12:30pm, Monday, Feb. 24, 2025**  
**Hunter College 926HN**  
**Host: Andy Wolfe**