**Dr. Elena Koltun, Revolution Medicines**

**February 25th, 2025, 5PM (Berlin time, CET)**

**Registration link:**

<https://us06web.zoom.us/webinar/register/WN_WpxydDhRSs-tgcoXQjoSww>

**Targeting the Oncogenic State of RAS with Tri-Complex Inhibitors**

In this talk, Elena Koltun will highlight how Revolution Medicines has designed a series of tri-complex inhibitors that specifically target the GTP-bound, active state of RAS (RAS(ON)). These macrocyclic, small molecule inhibitors bind non-covalently to an abundant intracellular protein, cyclophilin A (CypA). The resulting binary complex selectively engages RAS(ON), forming a tri-complex that sterically inhibits RAS interaction with its downstream effectors. We have generated mutant-selective inhibitors that covalently engage RAS(ON) G12C (elironrasib, RMC-6291), RAS(ON) G13C (RMC-8839), and RAS(ON) G12D (zoldonrasib, RMC-9805). Both RMC-6291 and RMC-9805 have shown encouraging initial antitumor activity and manageable safety in patients with advanced solid tumors harboring KRAS G12C and KRAS G12D mutations, respectively.

In addition, clinical candidate daraxonrasib (RMC-6236) and our *in vivo* tool, RMC-7977, are RAS(ON) multi-selective inhibitors that noncovalently inhibit the active, GTP-bound state of mutant and wild-type variants of the canonical RAS isoforms (KRAS, NRAS, and HRAS). RMC-6236 has shown both antitumor activity and manageable safety in patients with advanced solid tumors harboring various KRAS G12X or other RAS mutations.