Target Mutant KRAS with Molecular Glue

**Significance:** KRAS is considered undruggable due to the lack of binding sites on the protein surface. The authors use a natural product-derived small molecule that binds to cellular chaperone cytochrome A (CYP A) to form a CYP A:drug:KRASG12C tricomplex, which deactivates oncogenic signaling and leads to tumor regression in multiple human cancer models.

**Comment:** The authors based their structural design on sanglifehrin A, a natural product that binds CYP A with high affinity. A SAR study conducted with various Cys-reactive warheads yields RMC-4998 as the lead compound with high potency and selectivity in inhibiting GTP-bound KRASG12C, blocking its downstream signaling activity.