Abstract. Somatic mutations in the small GTPase K-Ras are the most common activating lesions found in human cancer, and are generally associated with poor response to standard therapies. Efforts to directly target this oncogene have faced difficulties due to its picomolar affinity for GTP/GDP and the absence of known allosteric regulatory sites. Oncogenic mutations result in functional activation of Ras family proteins by impairing GTP hydrolysis. With diminished regulation by GTPase activity, the nucleotide state of Ras becomes more dependent upon relative nucleotide affinity and concentration. This gives GTP an advantage over GDP and increases the proportion of active GTP-bound Ras. I will discuss the development of small molecules that irreversibly bind to a common oncogenic mutant, K-RasG12C. These compounds rely on the mutant cysteine for binding and therefore do not affect the wild type protein (WT). Crystallographic studies reveal the formation of a new pocket that is not apparent in previous structures of Ras, beneath the effector binding switch-II region. These data provide structure based validation of a novel allosteric regulatory site on Ras that is targetable in a mutant-specific manner. I will also discuss the development of a new class of mTOR kinase inhibitors that overcomes resistance to existing first- and second-generation inhibitors of this target. The third-generation mTOR inhibitor exploits the unique juxtaposition of two drug-binding pockets to create a bivalent interaction that allows inhibition of these resistant mutants. These two projects highlight non-traditional chemical approaches for tackling highly validated yet difficult to drug targets in oncology.