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**Title:** *Overcoming Undruggable Nature of the Most Common Human Oncogene, K-Ras*

**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. I will discuss the development of small molecules that irreversibly bind to a common oncogenic mutant, K-Ras G12C. These compounds rely on the mutant cysteine for binding and therefore do not affect the wild type protein (WT). I will also discuss ways to leverage immune cell killing of K-Ras G12C cells treated by combining small molecule inhibitors and bi-specific T-Cell engagers.