War on Cancer: Development of the Covalent Inhibitor on KRASG12D

Jia Wen Wang, Emmanuel Abijoye, Haifan Wu
Department of Chemistry and Biochemistry, Wichita State University

Mutations in the KRAS protein, such as G12C and G12D have been linked to many types of cancers including lung, colorectal, and pancreatic. Small molecules specifically targeting KRASG12C have been found to effectively bind to this protein to disable the protein and cease uncontrolled cell growth. Using this small molecule has led to successful cancer treatments with this cysteine (G12C) mutation. However, no such small molecule has been synthesized that can covalently bind to the aspartate (G12D) mutation to disable this protein, even though KRASG12D is the more common form of the KRAS mutations. Our overall goal is to synthesize a small molecule to target the Asp12 on the KRASG12D mutation using 2H-azirine. We have successfully purified three constructs of the KRAS protein: KRAS wild type, KRASG12C, and KRASG12D as well as incorporated GDP in each construct. GDP-bound KRAS is inactive. Small molecules targeting and maintaining this KRAS state can reduce cell proliferation. We are in the process of synthesizing the inhibitor to covalently label Asp12. If successful, this small molecule inhibitor would create opportunities for treatments of KRASG12D mutations.