A number of human cancers harbor somatic point mutations in the genes encoding isocitrate dehydrogenases-1 and -2 (IDH1, IDH2)[1]. These mutations alter residues in the enzyme active sites and confer a gain-of-function in cancer cells, resulting in the accumulation and secretion of the oncometabolite R(-)-2-hydroxyglutarate (2HG). 2HG is a potent inhibitor of DNA methylating enzymes such as TET2[2]. This suggests a connection between cancer related IDH mutations and aberrant epigenetics. As such, IDH represents an important new druggable target in the pursuit of novel cancer therapies. We have developed a small molecule, AGI-6780, that potently and selectively inhibits the tumor-associated mutant IDH2/R140Q. A crystal structure of AGI-6780 complexed with IDH2/R140Q revealed that the inhibitor binds in an allosteric manner at the dimer interface[3]. While structures of IDH1 and IDH2 were known, this is the first ever structure of an inhibited IDH protein and shows a novel conformation of IDH2. The results of steady-state enzymology analysis were consistent with allostery and slow-tight binding by AGI-6780. Treatment with AGI-6780 induced differentiation of TF-1 erythroleukemia and primary human acute myelogenous leukemia (AML) cells in vitro. These data provide proof-of-concept that inhibitors targeting mutant IDH2/R140Q could have potential applications as a differentiation therapy for cancer.


Keywords: inhibitor, epigenetics, IDH