

Microsymposium

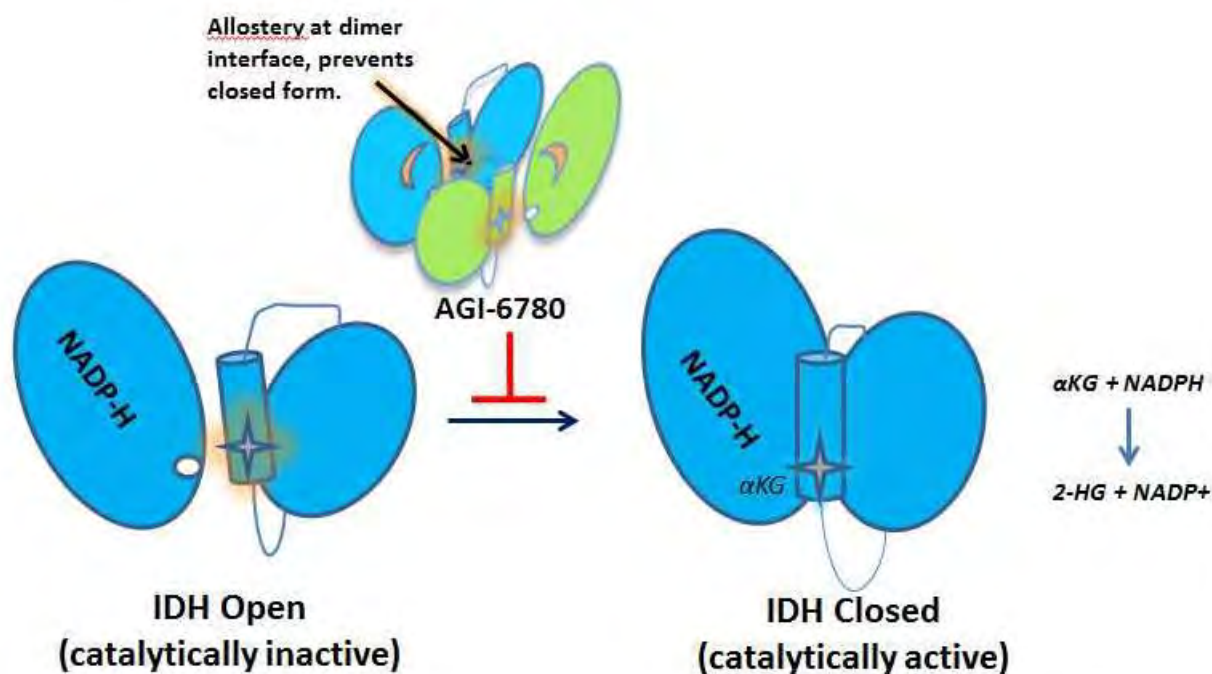
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Structural Biology of Mutant IDH2 Inhibition

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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.

[1] K. E. Yen, M. A. Bittinger, S. M. Su, V. R. Fantin, *Cancer-associated IDH mutations: biomarker and therapeutic opportunities. Oncogene* 29, 6409 (Dec 9, 2010)., [2] W. Xu et al., *Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell* 19, 17 (Jan 18, 2011)., [3] Fang et al., *Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. Science*. 2013 May 3;340(6132):622-6.



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