Pan-IDH Mutant Inhibitor AG-881

National Cancer Institute

Source

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An orally available inhibitor of mutated forms of both isocitrate dehydrogenase type 1 (IDH1, IDH1 [NADP+] soluble) in the cytoplasm and type 2 (IDH2, isocitrate dehydrogenase [NADP+], mitochondrial) in the mitochondria, with potential antineoplastic activity. Upon administration, pan-IDH mutant inhibitor AG-881 specifically inhibits mutant forms of IDH1 and IDH2, thereby inhibiting the formation of the oncometabolite 2-hydroxyglutarate (2HG) from alpha-ketoglutarate (a-KG). This prevents 2HG-mediated signaling and leads to both an induction of cellular differentiation and an inhibition of cellular proliferation in tumor cells expressing IDH mutations. In addition, AG-881 is able to penetrate the blood-brain barrier (BBB). IDH1 and 2, metabolic enzymes that catalyze the conversion of isocitrate into a-KG, play key roles in energy production and are mutated in a variety of cancer cell types. In addition, mutant forms of IDH1 and 2 catalyze the formation of 2HG and drive cancer growth by blocking cellular differentiation and inducing cellular proliferation.