Study demonstrates effects of mutant IDH1 and IDH2 inhibitors in primary tumor models

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Agios Pharmaceuticals announced today the publication of two articles in the journal *Science* by Agios scientists and their collaborators demonstrating the effects of the company's small molecule isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutant specific inhibitors in primary human tumor models. These data add to a growing body of scientific research demonstrating the significant promise of targeting mutant IDH1 and IDH2 enzymes as novel approaches to treating cancer.

"These papers represent the first publications to show the effects of inhibiting mutant IDH1 and IDH2 enzymes in patient-derived tumor samples, extending Agios' record of scientific leadership in cancer metabolism," said David Schenkein, M.D., chief executive officer at Agios. "While IDH mutations are genetically validated cancer targets, these findings provide further preclinical support that these mutations are driving disease, and appropriately targeted therapeutics can reverse the effects. Our IDH programs continue to produce promising results, and we are excited to advance toward clinical studies that will bring a potentially transformative treatment option to patients."

Tumors carrying IDH mutations are known to produce high levels of 2-HG, as shown originally by Agios scientists in Nature in 2009. In the first *Science* article, titled "Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation," Agios scientists show that cancer-associated IDH mutations may cause a block in cellular differentiation to promote tumorigenesis. To elucidate the relationship between mutant enzyme activity, 2-HG levels and oncogenic state, Agios developed a mutant-selective IDH2 inhibitor. Primary samples of acute myeloid leukemia (AML) cells were derived from four patients with AML carrying the IDH2 mutation. Upon treatment with the inhibitor, differentiation of blast (leukemic) cells was observed. In a separate experiment in TF-1 cells, the inhibitor was able to restore the ability of the cells to differentiate upon stimulation with erythropoeitin. Each of these observations was correlated with dose-dependent reductions in the oncometabolite 2-HG, which is thought to block differentiation in leukemia cells harboring IDH mutations.

In the second article, "An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells," Agios researchers, Ingo K. Mellinghoff, M.D., of Memorial Sloan-Kettering Cancer Center, and colleagues from several institutions report that a selective mutant IDH1 inhibitor discovered at Agios blocked the ability of mutant IDH1 to produce 2-HG in an in vivo primary xenograft model, impairing the growth of patient-derived IDH1-mutant glioma (brain cancer) cells. Furthermore, reduction of 2-HG to near basal levels induced expression of genes involved in both astroctyic and oligodendrocyte differentiation.

These data suggest that targeted therapy with IDH mutant inhibitors could induce tumor cell differentiation and support clinical study of IDH1 and IDH2 mutant targeted agents for the treatment of AML and other cancers. Both articles were published online in the journal *Science* on April 4, 2013.

More information: "Targeted Inhibition of Mutant IDH2 in Leukemia Cells Induces Cellular Differentiation," by F. Wang et al *Science*, 2013. "An Inhibitor of Mutant IDH1 Delays Growth and Promotes Differentiation of Glioma Cells," by D. Rohle et al *Science*, 2013.

Source: Agios Pharmaceuticals