New Publication in Science Shows That Agios IDH1 Inhibitor Can Reverse Cancer-Causing Effects of Oncometabolite 2HG in Leukemia Model

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Cambridge, Mass. – February 13, 2013 – Agios Pharmaceuticals, Inc., the leading biopharmaceutical company focused on discovering and developing novel drugs in the fields of cancer metabolism and rare metabolic genetic diseases, announced today a recent publication of research from Agios collaborator and scientific advisor William G. Kaelin, Jr., M.D., of the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and the Dana-Farber/Harvard Cancer Center, that demonstrates the cancer-causing effects of the oncometabolite 2-hydroxyglutarate (2-HG) in a leukemia cell model. Notably, these effects were reversible when treated with an isocitrate dehydrogenase 1 (IDH1) inhibitor discovered, developed and provided by Agios, which blocks the production of 2-HG. The article "(R)-2-Hydroxyglutarate Is Sufficient to Promote Leukemogenesis and Its Effects Are Reversible" was published in *Science* online on February 7, 2013.

"Our lead IDH1 and IDH2 programs are making tremendous progress, and this study reveals for the first time the ability of our IDH1 inhibitor to suppress and reverse the main driver of cell growth in an *in vitro* model of leukemia," said David Schenkein, M.D., chief executive officer at Agios. "These findings bring us one step closer to developing highly specific therapeutics that can have a significant positive impact for cancer patients whose tumors carry the IDH1 or IDH2 mutations. This paper also reflects the first in a series of publications that will further elucidate the mechanism of IDH oncogenesis and the potential of IDH inhibitors to effect tumor growth in cancer models."

Tumors carrying IDH mutations are known to produce high levels of 2-HG, as shown originally by Agios scientists in *Nature* in 2009. In this new article, Dr. Kaelin and colleagues from several institutions, with support from Agios, report that the IDH1 mutation and the 2-HG it produces are sufficient to transform growth factor dependent pre-leukemic cells into cells showing uncontrolled proliferation in the absence of growth factors. This finding adds to evidence that IDH1 mutations are potential driver mutations in leukemia. More importantly, those effects were reversible when 2-HG production was blocked by an Agios IDH1 inhibitor. Upon treatment with the inhibitor, the transformed cells lost their ability to rapidly proliferate in the absence of exogenous growth factors and reverted to their previous state.

Background on IDH Mutations & AML

Acute myeloid leukemia (AML) is caused by genetic mutations that deregulate hematopoietic cell proliferation and prevent normal cellular differentiation. Recent genomic sequencing efforts have identified a number of recurrent mutations in AML that might contribute to leukemogenesis, including mutations in the key metabolic enzymes IDH1 and IDH2.

The connection between cancer and metabolism has been the central focus of scientists at Agios, who were the first to identify the neo-activity of IDH1 mutations to produce the oncometabolite 2-HG in research published in *Nature* in 2009. These insights revealed the potential of IDH1 mutations as a novel therapeutic target in cancer. The IDH1 gene mutation was initially discovered in brain cancers in 2008 by researchers at Johns Hopkins. More recently, mutations in both IDH1 and IDH2 have been linked to AML, one of the most common types of leukemia in adults, as well as several other cancers.

About Agios Pharmaceuticals, Inc.

Agios is the leading biopharmaceutical company focused on discovering and developing novel drugs in the fields of cancer metabolism and rare metabolic genetic diseases. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has multiple first-in-class programs in cancer metabolism and inborn errors of metabolism advancing toward the clinic. All Agios programs focus on genetically identified patient populations leveraging our knowledge of metabolism, biology and genomics. For more information, please visit our website at www.agios.com.