



**[Billing Code 4140-01-P]**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**National Institutes of Health**

Notice of Availability of License; Mutant IDH1 Inhibitors Useful for Treating Cancer

**AGENCY:** National Institutes of Health.

**ACTION:** Notice.

**SUMMARY:** The invention Mutant IDH1 Inhibitors Useful for Treating Cancer is owned by an agency of the U.S. Government and is available for licensing and/or co-development in the U.S.

**FOR FUTURE INFORMATION CONTACT:** Information on licensing and co-development research collaborations, and copies of the U.S. patent applications listed below may be obtained by contacting: Attn: Sury Vepa, Ph.D., J.D., Senior Licensing and Patenting Manager, National Center for Advancing Translational Sciences, NIH, 9800 Medical Center Drive, Rockville, MD 20850, Phone: 301-217-9197, Fax: 301-217-5736, or email [NCATSPartnerships@mail.nih.gov](mailto:NCATSPartnerships@mail.nih.gov). A signed Confidential Disclosure Agreement may be required to receive copies of the patent applications.

**SUPPLEMENTARY INFORMATION:** This notice is made in accordance with 35 U.S.C. 209 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development.

**Intellectual Property**

Description of Technology: Isocitrate dehydrogenase 1 (IDH1) is an enzyme whose normal function is to convert isocitrate to  $\alpha$ -ketoglutarate. Mutated forms of this enzyme (mIDH1) are common in a variety of cancers including acute myeloid leukemia (AML),

glioma, cholangiocarcinoma, chondrosarcoma and melanoma. The IDH1 mutation at position 132 and similar IDH1 mutations result in the enzyme gaining the ability to catalyze the NADPH-dependent reduction of the wild type enzyme's product,  $\alpha$ -ketoglutarate to R-2-hydroxyglutarate (2-HG). 2-HG is an oncometabolite, and its elevated levels have been shown to lead to de-differentiation of cells. Mutant IDH1 is an attractive target for anti-cancer therapeutics as inhibition reduces levels of 2-HG. It is expected that lower 2-HG levels will result in fewer undifferentiated cancer cells. Furthermore, inhibition of mutant IDH1 is expected to have little effect on non-cancerous cells, as these cells do not express the IDH1 mutation resulting in lower toxicity than typical cytotoxic anticancer agents.

In collaboration with the University of North Carolina, the National Center for Advancing Translational Sciences (NCATS) investigators have discovered a series of novel compounds that potently and selectively inhibit mIDH1. These compounds reduce 2-HG levels in cell lines in vitro as well as in human cancer cells grown in mouse xenografts in vivo. These compounds show greater than 250-fold selectivity for the mutant enzyme over the wild-type, show favorable in vitro stability (in mouse, rat, dog and human hepatocyte exposure studies), are AMES negative, and exhibit no significant metabolic CYP liabilities. These compounds possess very favorable in vivo rodent pharmacokinetics and bioavailability and are well tolerated in rodents, even when dosed at high levels.

### **Potential Commercial Applications**

- Potential treatment of cancer (AML or other solid tumors listed above)
- Potential treatment of rare diseases including Maffucci Syndrome and Ollier Disease.

## Value Proposition

- Novel mutant IDH1 inhibitors are effective at lowering the oncometabolite, 2-HG in in vivo mouse proof-of-concept studies and are well suited for IND enabling studies.

Development Stage: Pre-clinical (in vivo validation).

Inventor(s): Matt Boxer, Kyle Brimacombe, Mindy Davis, Rajan Pragani, Jason Rohde, Li Liu, Surendra Karavadhi, Daniel Urban, Min Shen, Anton Simeonov, Ajit Jadhav (NCATS) Xiaodong Wang and Andrew McIver (Univ. of North Carolina at Chapel Hill)

Intellectual Property:

1. International Application No. PCT/US15/067406 filed on 12/22/2015 which is entitled “Mutant IDH1 Inhibitors Useful for Treating Cancer” (HHS Ref. No: E-243-2014/0-PCT-02), and
2. U.S. Provisional Application No. 62/353298 filed on 06/22/2016 which is entitled “Mutant IDH1 Inhibitors Useful for Treating Cancer” (HHS Ref. No. E-189-2016/0-US-01)

October 5, 2016

Dated

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Pamela McInnes, D.D.S.

Deputy Director

Office of the Director

National Center for Advancing Translational Sciences

[FR Doc. 2016-25468 Filed: 10/20/2016 8:45 am; Publication Date: 10/21/2016]