HIGHLY SOLUBLE PYRIMIDO-DIONE-QUINOLINE COMPOUNDS: SMALL MOLECULES THAT STABILIZE AND ACTIVATE P53 IN TRANSFORMED CELLS

SUMMARY (1024-CHARACTER LIMIT)

Researchers at the National Cancer Institute (NCI) have developed an invention reporting the composition and function of a pyrimido-dione-quinoline that was found to inhibit HDM2's ubiquitin ligase (E3) activity without accompanying genotoxicity. The current invention results in the stabilization of p53 in cells through the inhibition of its ubiquitin-mediated proteasomal degradation resulting in a robust p53 response in tumors. NCI researchers seek licensing and/or co-development partners for this invention.

NIH REFERENCE NUMBER

E-138-2006

PRODUCT TYPE

- Therapeutics

KEYWORDS

- Cancer, p53 Activation, HDM2 Inhibitor, Apoptosis, Weissman

COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

CONTACT

- John D. Hewes
  NCI - National Cancer Institute

  240-276-5515

  John.Hewes@nih.gov

STATUS

Active

DESCRIPTION OF TECHNOLOGY

The tumor-suppressor p53 protein plays a major role in tumor development. Most human cancers fail to normally activate wild-type p53, which is at least partly responsible for the unregulated growth of cancer cells and their failure to undergo apoptosis. While many chemotherapeutics enhance p53 levels, their non-specific DNA damage (genotoxicity) causes unfavorable side effects.

Defects in the pathways that control the stabilization and activation of p53 in response to stress can contribute to cancer development, without the requirement for mutation within the p53 gene itself. Many tumors that retain wild-type p53 show evidence of alterations that prevent efficient activation of p53 in response to stress, linked to a failure to inactivate HDM2. In these tumors, inhibition of HDM2 and reactivation of p53 is an attractive therapeutic strategy. Researchers at the National Cancer Institute (NCI) have developed a water-soluble, small molecule inhibitor of HDM2's E3 activity resulting in activation of p53 in tumors that retain wild-type p53.

This invention does not lead to the genotoxicity commonly observed when using other therapeutics directed at activating p53, making it an attractive option for cancer therapy. The NCI is seeking statements of capability or interest from parties interested in licensing or in collaborative research to co-develop technologies that inhibit HDM2's activity and reactivate p53 activity for the treatment of cancer.

POTENTIAL COMMERCIAL APPLICATIONS

- Targeted therapies for activating wild-type p53 in tumors to induce apoptosis
- Inhibits unregulated growth of cancer cells

COMPETITIVE ADVANTAGES

- Reduced genotoxicity compared to many chemotherapeutics
- Water-soluble with improved potency in stabilizing p53 and activating a p53 response

INVENTOR(S)

Alan M Weissman (NCI), Yili Yang ((formerly NCI))

DEVELOPMENT STAGE

- Discovery (Lead Identification)

PUBLICATIONS

Yang Y et al. Small molecule inhibitors of HDM2 ubiquitin ligase activity stabilize and activate p53 in cells [PMID 15950904]

PATENT STATUS

- **U.S. Provisional:** U.S. Provisional Patent Application Number 60/813,946 , Filed 14 Jun 2006
- **U.S. Patent Filed:** U.S. Patent Application Number PCT/US2007/013952 , Filed 13 Jun 2007
- **U.S. Patent Filed:** U.S. Patent Application Number 8,877,765 , Filed 28 Oct 2009
- **U.S. Patent Issued:** U.S. Patent Number 8,877,765 , Issued 04 Nov 2014

RELATED TECHNOLOGIES

- E-070-2005

THERAPEUTIC AREA

- Cancer/Neoplasm