Highly Soluble Pyrimido-Dione-Quinoline Compounds: Small Molecules That Stabilize and Activate p53 in Transformed Cells

Description of Technology: The tumor-suppressor p53 protein plays a major role in tumor development. Most human cancers ail to normally activate 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.

This invention reports the composition and function of a pyrimido-dione-quinoline that was found to inhibit HDM2's ubiquitin ligase (E3) activity without the accompanying genotoxicity of current therapeutic drugs. Like the HLI98 family of compounds reported previously (see reference below), the subject of the current invention stabilizes p53 in cells, inhibiting its ubiquitin-mediated proteasomal degradation. Unlike the HLI98 compound, the pyrimido-dione-quinoline reported here induces a robust p53 response, and is highly water-soluble. Thus, these pyrimido-dione-quinoline compounds have the potential to stabilize p53 and activate a p53 response in tumors.

Applications and Modality: Water-soluble with improved potency in stabilizing p53 and activating a p53 response; Inhibits unregulated growth of cancer cells; Reduced genotoxicity compared to many chemotherapeutics.

Market: Small molecule-based cancer therapeutics for tumors expressing wild type p53, which comprises approximately 50% of cancers.

Development Status: The technology is currently in the pre-clinical stage of development.

Inventors: Allan M. Weissman and Yili Yang (NCI).

Related Publication: Y Yang et al. Small molecule inhibitors of HDM2 ubiquitin ligase activity stabilize and activate p53 in cells. Cancer Cell 2005 Jun;7(6):547–559.

Patent Status: U.S. Provisional Application No. 60/813,946 filed 14 Jun 2006 (HHS Reference No. E–138–2006/0–US–01).

Availability: Available for exclusive and non-exclusive licensing.

Licensing Contact: Thomas P. Clouse, J.D.; 301/435–4076; clousetp@*mail.nih.gov.*

Collaborative Research Opportunity: The Laboratory of Protein Dynamics and Signaling (LPDS) at the National Cancer Institute, NIH, is seeking a collaborative partner under a Cooperative Research and Development Agreement (CRADA) to develop therapeutics approaches utilizing inhibitors of the ubiquitin system such as described in this invention. Please contact John D. Hewes, Ph.D. at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Human Cancer Therapy Using Engineered Anthrax Lethal Toxin

Description of Technology: Anthrax lethal toxin (LeTx) consists of two components: The protective antigen (PrAg) and the lethal factor (LF). PrAg binds to the cell surface where it is activated by furin protease, followed by the formation of a PrAg heptamer. LF is then translocated into the cytosol of a cell via this heptamer, where it acts as a metalloprotease on all but one mitogen-activated protein kinase kinase (MAPKK). Approximately 70% of human melanomas contain a mutation (B–RAF V600E) that constitutively activates a MAPKK pathway, and LeTx has been shown to have significant toxicity towards cells which have this mutation. This suggested a potential use for LeTx in cancer therapy. Unfortunately, native LeTx is toxic to normal cells, detracting from its *in vivo* applicability.

PrAg has been engineered to be activated by a matrix metalloprotease (MMP), instead of by furin protease. Because MMPs are highly expressed in tumor cells, this modification increases selectivity towards cancer cells. Surprisingly, mouse data shows that the modified LeTx (denoted PrAg–L1/LF) is less cytotoxic to ''normal'' cells in vivo, when compared to wild-type LeTx. Significantly, PrAg–L1/LF maintained its high toxicity toward human tumors in mouse xenograft models of human tumors, including melanomas. However, this toxicity applied not only to tumors having mutations that constitutively activate MAPKKs, but also to other tumor types such as lung and colon carcinomas. The absence of toxicity to ''normal'' cells coupled to its effectiveness on a wide range of cancer cell types suggests that PrAg–L1/LF may represent a novel cancer therapeutic.

Applications: PrAg–L1/LF has applications as a human cancer therapeutic; Applicability extends beyond melanomas, including lung and colon carcinomas.

Market: The worldwide market for melanoma therapeutics is approximately $437M, and is predicted to reach $680M by the year 2009. Approximately 2.4 million people are afflicted with melanoma, with around 150,000 new cases each year. Demonstration of effectiveness *in vivo* for lung and colon carcinomas will increase the market for this technology.

Development Status: The technology is at the preclinical stage.

Inventors: Stephen H. Leppla (NIAID), Shi-hui Liu (NIAID), Thomas H. Bugge (NIDCR), John R. Basile (NIDCR), Brooke Currie (NIDCR).

Related Publications:

1. S Liu *et al.* Intermolecular complementation achieves high-specificity tumor targeting by anthrax toxin. Nat Biotechnol. 2005 Jun;23(6):725–730.

2. RJ Abi-Habib *et al.* A urokinase-activated recombinant anthrax toxin is selectively cytotoxic to many human tumor cell types. Mol Cancer Ther. 2006 Oct;5(10):2556–2562.

Patent Status: U.S. Provisional Application No. 60/870,050 filed 14 Dec 2006 (HHS Reference E–070–2007/0–US–01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: David A. Lambertson, Ph.D.; 301/435–4632; *lambertsond@od.nih.gov.*

Collaborative Research Opportunity: The NIAID Laboratory of Bacterial Diseases is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize PrAg–L1/LF as a novel cancer therapeutic. Please contact Stephen H. Leppla, Ph.D. at 301/594–2865 and/or *sleppla@niaid.nih.gov* for more information.

This abstract was originally published in the **Federal Register** on Wednesday, February 7, 2007, 72 FR 5726, with an incorrect title of ''Extended Transgene Expression for a Non-Integrating Adenoviral Vector Containing Retroviral Elements.''

Dated: February 20, 2007.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E7–3436 Filed 2–27–07; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Agency Information Collection Activities: Proposed Collection; Comment Request

In compliance with Section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 concerning

opportunity for public comment on proposed collections of information, the Substance Abuse and Mental Health Services Administration (SAMHSA) will publish periodic summaries of proposed projects. To request more information on the proposed projects or to obtain a copy of the information collection plans, call the SAMHSA Reports Clearance Officer on (240) 276–1243.

Comments are invited on: (a) Whether the proposed collections of information are necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) ways to enhance the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology.

Proposed Project: Underage Drinking Prevention: Town Hall Meeting Feedback Form—New

The Substance Abuse and Mental Health Services Administration's (SAMHSA), Center for Substance Abuse Prevention (CSAP) is proposing the project the 2008 Underage Drinking Prevention: Town Hall Meetings (THM) Initiative. In 2006, approximately 1,510 THMs were held in 1,262 community-based organizations (CBO) throughout the Nation. Each of the THMs strived to increase the understanding and awareness of underage alcohol use and its consequences by encouraging individuals, families, and communities to address the problem. The local THMs gave communities the opportunity to come together to learn more about the new research on underage alcohol use and its impact on both the individuals and the community. They also discussed how their communities can best prevent underage alcohol use.

To help guide decision making and planning for future THMs, SAMHSA/CSAP plans to conduct a process assessment of the THMs to be held in 2008. CBOs who agree to participate in this initiative will be asked to provide feedback about the implementation and results of the THMs in their community. This information collection is being implemented under the authority of Section 501(d) (4) of the Public Health Service Act (42 U.S.C. 290aa).

The contractor conducting this information collection will distribute a brief feedback form to all participating organizations. The form includes 14 items about the THM, including where, when, and who conducted the meeting, number of attendees, format of meeting, participants in the presentations, actions planned, media coverage of the meeting, composition of the audience, responses of the attendees, materials provided in the town hall meetings, and indications of increased awareness and increased involvement. In addition to distributing the feedback form, the contractor will be responsible for collecting, compiling, analyzing, and reporting on information requested through this feedback form.

The feedback form will be completed by an estimated 1,200 employees from CBOs. The paper form will take an average of 10 minutes (.167 hours) to review instructions, complete the form, and mail it in a self-addressed, stamped envelope. This burden estimate is based on comments from several potential respondents who reviewed the form and provided comments on how long it would take them to complete it.

Form name	Number of respondents	Responses per respondent	Hours per response	Total hour burden
Feedback Form	1,200	1	.167	120

Send comments to Summer King, SAMHSA Reports Clearance Officer, Room 7–1044, One Choke Cherry Road, Rockville, MD 20857. Written comments should be received within 60 days of this notice.

Dated: February 22, 2007.

Elaine Parry,

Acting Director, Office of Program Services.

[FR Doc. E7–3468 Filed 2–27–07; 8:45 am]

BILLING CODE 4162–20–P

DEPARTMENT OF HOMELAND SECURITY

Bureau of Customs and Border Protection

Notice of Issuance of Final Determination Concerning Digital Color Multifunctional Systems

AGENCY: U.S. Customs and Border Protection, Department of Homeland Security.

ACTION: Notice of final determination.

SUMMARY: This document provides notice that the Bureau of Customs and Border Protection (CBP) has issued a final determination concerning the country of origin of certain digital color multifunctional systems to be offered to the United States Government under an undesignated government procurement contract. Based on the facts presented, the final determination found that Japan is the country of origin of the subject digital color multifunctional systems for purposes of U.S. government procurement.

DATES: The final determination was issued on February 8, 2007. A copy of the final determination is attached. Any party-at-interest as defined in 19 CFR 177.22(d), may seek judicial review of this final determination within 30 days of February 28, 2007.

FOR FURTHER INFORMATION CONTACT: Daniel Cornette, Valuation and Special Programs Branch, Office of International Trade; telephone (202) 572–8731.

SUPPLEMENTARY INFORMATION: Notice is hereby given that on February 8, 2007, pursuant to subpart B of part 177, Customs Regulations (19 CFR part 177, subpart B), CBP issued a final determination concerning the country of origin of certain digital color multifunctional systems to be offered to the United States Government under an undesignated government procurement contract. The CBP ruling number is HQ 563491. This final determination was issued at the request of Sharp Electronics Corporation under procedures set forth at 19 CFR part 177, subpart B, which implements Title III of the Trade Agreements Act of 1979, as amended (19 U.S.C. 2511–18).

The final determination concluded that, based upon the facts presented, the assembly in Japan of Japanese and foreign components to create the subject digital color multifunctional systems substantially transformed the foreign components into a product of Japan.

Section 177.29, CBP Regulations (19 CFR 177.29), provides that notice of final determinations shall be published in the **Federal Register** within 60 days of the date the final determination is