Mechanism of action behind novel cancer agents targeting tumor cell metabolism discovered

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(Medical Xpress) -- The discovery of the mechanism of action behind a novel class of anticancer drugs designed to disrupt cancer cell mitochondrial metabolism may be a major step toward furthering clinical trials of the agents. An analysis of CPI-613, the lead compound in this first-in-class group of anticancer drugs developed by Paul M. Bingham, Ph.D., Associate Professor, and Zuzana Zachar, Ph.D., Research Assistant Professor, both in the Department of Biochemistry and Cell Biology, Stony Brook University School of Medicine, is published in the *Journal of Molecular Medicine*.

In 2008, the Food and Drug Administration (FDA) approved human clinical trials of the lipoate derivative anti-cancer drugs. The clinical trials are sponsored by Cornerstone Pharmaceuticals, Inc., the exclusive licensee and developer of the discoveries made by Drs. Bingham and Zachar. Cornerstone has licensed the technology from The Research Foundation of the State University of New York, on behalf of Stony Brook University. Results of the early stage safety and efficacy clinical trials are pending.

“By analyzing the mechanism of action of CPI-613, which shows multiple pathways of action, we are gaining a significant understanding into the way in which the compounds shut down cancer cell metabolism,” says Dr. Bingham. “Furthermore, this new knowledge will help to refine the class of agents regarding treatment strategies for

specific cancers, as well as strategies for treating cancers resistant to traditional chemotherapy."

Dr. Bingham explains that CPI-613, in all tested in vitro cancer cell line studies, is efficient in causing cancer cell death by multiple and redundant pathways, including apoptosis. Specifically, CPI-613 induces cancer specific regulatory hyper-phosphorylation of the E1 subunits of the centrally important mitochondrial enzyme complex, pyruvate dehydrogenase (PDH) of cancer cells, resulting in the inhibition of PDH function. These effects and related cancer-specific consequences of the drug lead to catastrophic disruption of tumor mitochondrial metabolism. Tumor cells are thereby starved of energy and biosynthetic intermediates, resulting in cell death.

In the JMM article, "Non-redox-active lipoate derivatives disrupt cancer cell mitochondrial metabolism and are potent anti-cancer agents in vivo," Drs. Bingham and Zachar also indicate that CPI-613 is a potent inhibitor of human tumor growth in pre-clinical animal models, producing apparent tumor clearance in some animals. Additionally, CPI-613 strongly inhibits tumor growth in non-small cell human lung cancer and a human pancreatic cancer pre-clinical mouse tumor model.

"Metabolism of cancer cells has recently gained wide attention as a possible source of novel drug targets," adds Dr. Bingham. "The unprecedented mechanism of action of lipoate derivatives and their potency in pre-clinical models is a crucial finding in the process of developing these anticancer drugs, a group we hope will show significant efficacy in treating cancer in humans."

Robert Shorr, Ph.D., CEO of Cornerstone, concurs with Dr. Bingham, and adds: "The research demonstrates that our active analogs of lipoic acid act as potent and selective anti-cancer agents in cell culture and animal models. It will be of great interest to assess their efficacy in

human clinical trials and be able to predict which patients will be most likely to benefit."

CPI-613 is the lead drug candidate in Cornerstone's Altered Energy Metabolism Directed (AEMD) platform. AEMD's attack cancer cells by disrupting biochemical alterations in the conversion of glucose to energy that occur in many types of cancer cells.

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