Boston University
College of Arts & Sciences
Office of the Dean
725 Commonwealth Avenue
Boston, MA 02215
T 617-353-2401
F 617-353-5374

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CONTACT: Patrick Farrell
Boston University
+1-617-358-1185
pmfarrel@bu.edu

New research advances search for chemical/genetic approach to inhibit tumor cell growth

Rocaglamide A identified as strong inhibitor of HSF1 activation

A new study co-authored by John A. Porco Jr.,Professor of Chemistry and director of the Center for Chemical Methodology and Library Development at Boston University (CMLD-BU) along with collaborators at the Whitehead Institute has identified rocaglamide A, an inhibitor of translation initiation, as a strong inhibitor of Heat Shock Factor 1 (HSF1) activation. HSF1 inhibitors have received significant attention for their potential role in the rapid development of anticancer drugs with completely new modes of action.

HSF1 is the master regulator of the Heat Shock Response (HSR) in cells, which attempts to maintain protein homeostasis during times of proteotoxic cellular stress. This stress results in the accumulation of misfolded proteins and has been identified as a cause of cancerous cells. Experimenting with a number of chemical and genetic approaches to determine how information about a cell's metabolic state is conveyed, the researchers earlier established that HSF1, which is centrally positioned to regulate cellular proliferation, functions as the primary translator (transducer) of this information. The present study, published in the journal *Science*, found that rocaglamide A, a naturally occurring anticancer agent, effectively inhibits HSF1 activation. (See "Tight Coordination of Protein Translation and HSF1 Activation Supports the Anabolic Malignant State," S. Santagata et al., Science 341, 1238303 (2013). DOI: 10.1126/science.1238303; the article is available online at http://dx.doi.org/10.1126/science.1238303).

The study is the latest product of a three-year research grant from the National Institutes of Health awarded to Porco and Dr. Luke Whitesell, senior scientist in the laboratory of Prof. Susan Lindquist at MIT's Whitehead Institute. This combined biology/chemistry team came together specifically to identify highly potent and selective HSF1 inhibitor probes with useful activity *in vivo*.

Whitesell and his colleagues have shown that HSF1 is co-opted by tumor cells to promote their own survival at the expense of their hosts; their ongoing research has focused on explaining how the HSF1 coordinates this activity during malignancy, how it might relate to a classic HSR, and whether it impacts human cancer. Whitesell enlisted the Porco laboratory for its expertise in the synthesis of complex natural products and derivatives. The unique photocycloaddition methodology, developed by the Porco laboratory for the

synthesis of various targets, is the basis of the medicinal chemistry efforts in the NIH award to optimize these compounds as HSF-1 inhibitors.

To identify the transcriptional effects of modulating translational activity in malignant cells in the present study, the researchers used integrated chemical and genetic approaches, including a gene signature–based genetic and chemical screen of more than 600,000 gene expression profiles (LINCS database) and an independent, reporter-based chemical screen of more than 300,000 compounds. A lead compound was tested in several cell lines unified by their increased dependence on HSF1 activation for growth and survival, and in an *in vivo* cancer model. The screens identified rocaglamide A, an inhibitor of translation initiation, as the strongest inhibitor of HSF1 activation. Cell-based cancer models characterized by high dependence on HSF1 activation for growth and survival also were highly sensitive to the rocaglate rohinitib (RHT), an analog of rocaglamide A, as were cells derived from diverse hematopoietic malignancies.

About Boston University—Founded in 1839, Boston University is an internationally recognized private research university with more than 30,000 students participating in undergraduate, graduate, and professional programs. As Boston University's largest academic division, the College and Graduate School of Arts & Sciences is the heart of the BU experience with a global reach that enhances the University's reputation for teaching and research. In 2012, BU joined the Association of American Universities (AAU), a consortium of 62 leading research universities in the United States and Canada.

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Contact information:

Prof. John A. Porco
Department of Chemistry,
Boston University
590 Commonwealth Ave.
Boston, MA 02215
Phone (617) 353-2493
Email porco@bu.edu