Investigational drug may prevent life-threatening muscle loss in advanced cancers

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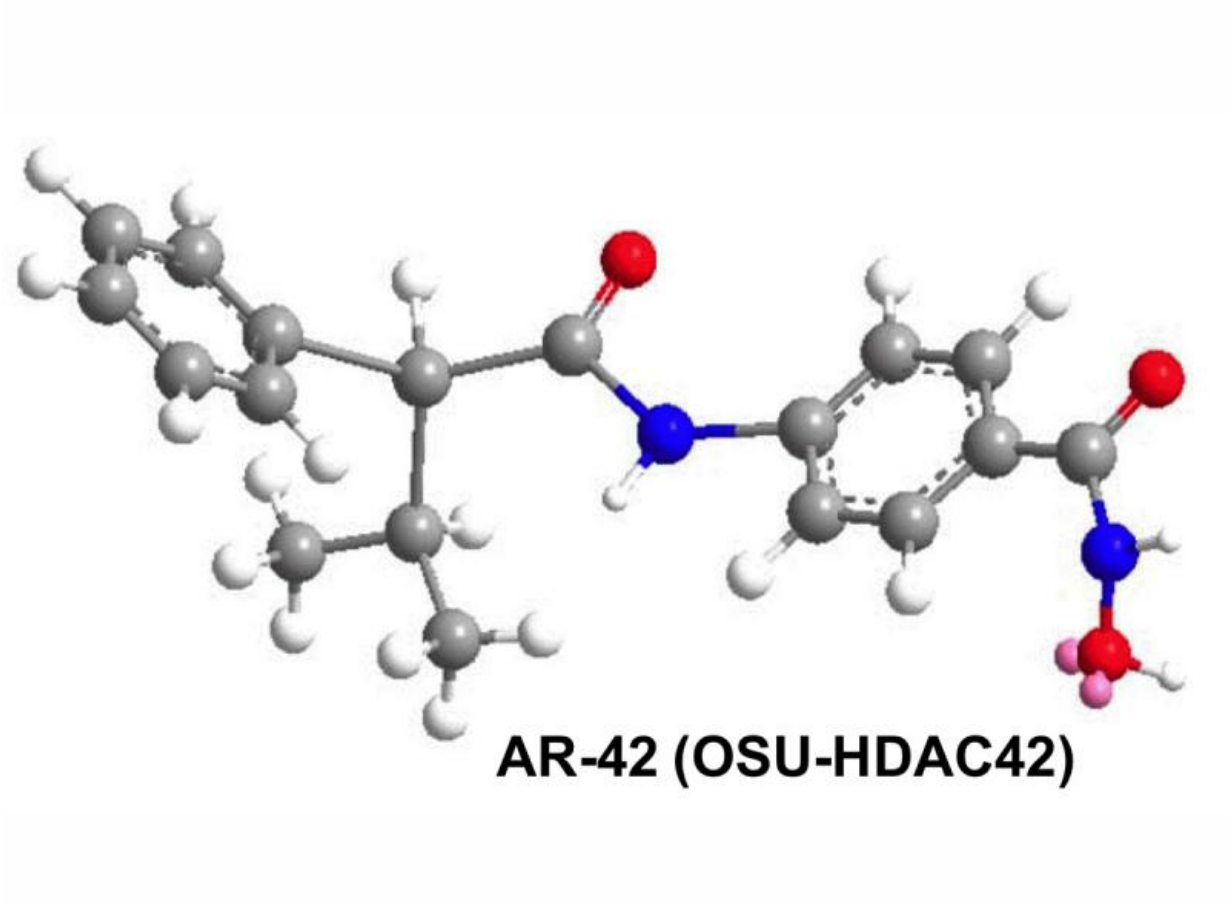

New data describes how an experimental drug can stop life-threatening

muscle wasting (cachexia) associated with advanced cancers and restore muscle health. The experimental agent, known as AR-42 while in testing, was developed and tested in preclinical studies at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James).

AR-42 is part of a class of drugs known as HDAC (histone deacetylase) inhibitors, which are designed to block proteins that play a key role in mediating skeletal muscle breakdown. In cancer, HDAC proteins also tend to drive the pathways in cancer cells that lead to aggressive cancers. AR-42 is unique among HDAC inhibitors because it appears to have beneficial effects on muscle health and function, according to this new OSUCCC - James research.

In this new preclinical study, Tanios Bekaii-Saab, MD, and colleagues report data illustrating that orally administered AR-42 can significantly preserve body weight and prolong survival while simultaneously preventing the loss of muscle and fat tissue mass and preserving the health/strength of muscle.

Findings were reported online ahead of print in the *Journal of the National Cancer Institute*. The study will appear in the December 2015 issue of the journal.

According to Bekaii-Saab, most advanced cancer patients will experience significant loss of muscle mass as the result of their cancer at some point during their treatment, a condition clinically known as "cachexia." The condition is most common in pancreas and gastrointestinal cancers, with up to 70 to 80 percent of patients experiencing severe loss of muscle mass that impacts their ability to tolerate necessary treatments. The molecular mechanisms behind why this occurs are not well understood, so there are currently no good intervention strategies to reverse the effects of cachexia.

"Roughly a third of pancreatic cancer patients die from the impact of cachexia - not their cancer. Finding better intervention strategies for the condition is critical so we can keep our patients strong enough to tolerate the cancer treatments necessary to give them the best chances of eradicating their cancer," says Bekaii-Saab, gastrointestinal oncology section chief and corresponding author of the current study.

Study Design and Methods

AR-42 was developed in the lab of Ching-Shih Chen, PhD, a professor and scientist with the OSUCCC - James Molecular Carcinogenesis and Chemoprevention research program.

For this study, researchers evaluated AR-42 against two other HDAC inhibitors called vorinostat and romidepsin to determine each agent's ability to prevent cachexia. This was done using metabolomic profiling to evaluate the pathways involved in muscle changes that lead to cachexia as well as other advanced molecular testing. AR-42 was the only agent shown to have a strong protective effect against tumor-associated muscle wasting. These findings were confirmed in a second preclinical model.

"These new findings show that AR-42 can preserve muscle and every aspect of its functionality, which is an important step in refining potential methods of stopping cancer cachexia," says Chen.

Researchers expect to begin evaluating AR-42 in human pancreatic cancer clinical trials within a year. Funding support for this work comes from the Lucius A. Wing Endowed Chair Fund, Cure for Pancreatic Cancer Philanthropic Fund and a pancreatic cancer research grant from The Ohio State University Wexner Medical Center and OSUCCC - James.

More information: Yu-Chou Tseng et al. Preclinical Investigation of the Novel Histone Deacetylase Inhibitor AR-42 in the Treatment of Cancer-Induced Cachexia, *Journal of the National Cancer Institute* (2015). DOI: 10.1093/jnci/djv274