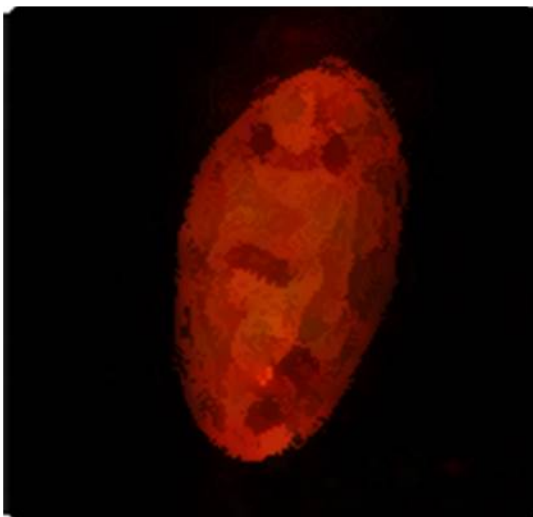


# Novel mechanism in drug combination shows potential for treating leukemia, other cancers

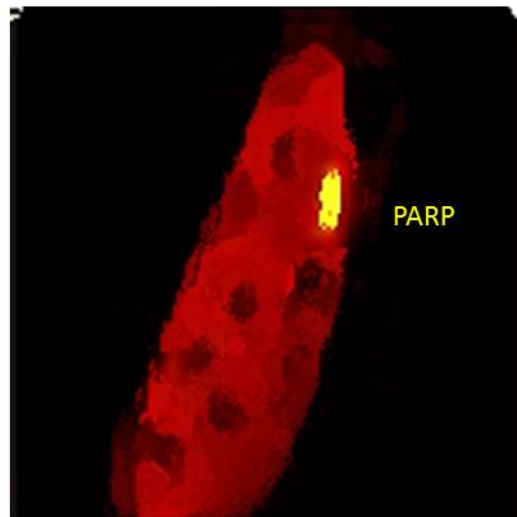
October 10 2016

---

6 hours – one drug



6 hours – both drugs



The goal of the therapy is to cause the protein PARP to be trapped longer at the site of DNA damage within a cancer cell. Microscopic images show a damaged breast cancer cell treated with either a PARP inhibitor or a DNMT inhibitor (left) and one treated with both agents (right). PARP (in yellow) at the damage site prevents the cell from repairing itself, causing it to die. Credit: Johns Hopkins Kimmel Cancer Center

Researchers have discovered a novel mechanism in a combination drug therapy that shows potential as a new approach for treating acute myeloid leukemia (AML) and many other cancers. When combined, these agents cause interactions that significantly disrupt cancer cells' ability to survive DNA damage, according to a preclinical study published today in the journal *Cancer Cell*.

The study looked at a combination of two drugs, both of which significantly reduce some cancer cells' ability to survive and propagate. One was a DNA methyltransferase (DNMT) inhibitor, while the other was a poly-ADP-ribose polymerase (PARP) inhibitor, talazoparib. PARP inhibitors target and block proteins which cancer cells depend on to repair DNA for their survival. DNMT inhibitors, such as 5-azacytidine and decitabine, boost the interactions of PARP inhibitors to block these proteins even further, causing cancer cell death, the researchers found.

"Our preclinical data suggest that combining low doses of these inhibitors will enhance the clinical effects of both drugs as a potential treatment for patients with AML," says the senior author, Feyruz V. Rassool, PhD, associate professor of radiation oncology at the University of Maryland School of Medicine (UM SOM) and a researcher at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCCC).

"Moreover, our initial data suggest that subtypes of AML with a poor prognosis are likely to be sensitive to this new therapeutic approach," she says, adding that less than 10 percent of patients with certain forms of AML achieve long-term survival.

A blood cancer characterized by the rapid growth of abnormal white

blood cells, AML is typically treated with chemotherapy, in some cases followed by a stem cell transplant. DNMT inhibitors are frequently used to treat patients unlikely to respond to chemotherapy or who have not responded to chemotherapy.

Dr. Rassool says that a clinical trial is planned to test whether low doses of a DNMT inhibitor, decitabine, and an investigational PARP inhibitor, talazoparib, can be safely combined and whether this therapy shows efficacy for AML patients, especially those who cannot receive intensive chemotherapy, whose leukemia is resistant to treatment, or who have experienced a relapse after treatment. The trial, which will be led by Maria R. Baer, MD, professor of medicine at UM SOM and director of hematologic malignancies at UMGCCC, will enroll patients at the Greenebaum Comprehensive Cancer Center and several other sites.

"This is really a new paradigm mechanism that is being translated into a clinical trial," Dr. Rassool says. "It's not just putting two drugs together. We have shown in the laboratory that the proteins that these inhibitors target actually interact, so the effects of these inhibitors are enhanced through this interaction. Therein lies the novelty of this new approach."

The research, conducted in cell lines and mouse models, explored enhancing the cancer-killing effects of PARP inhibitors not only in regard to AML but also triple-negative breast cancer. PARP inhibitors have shown efficacy for a small group of patients with breast cancer with inherited mutations in BRCA genes, but have failed in the more aggressive triple-negative disease. "Our findings suggest that this new drug combination would also help patients with this type of aggressive breast cancer as well as other cancers, such as lung, prostate and ovarian cancers," Dr. Rassool says.

Dr. Rassool and colleagues at UMGCCC and UMSOM collaborated with scientists at the Sidney Kimmel Comprehensive Cancer Center at Johns

Hopkins and the National Institute on Aging. Stephen B. Baylin, MD, the Virginia and DK Ludwig Professor of Oncology and Medicine and associate director for research programs at the Johns Hopkins Kimmel Cancer Center, is the study's co-senior author.

The research, which builds on previous work by Dr. Rassool and Dr. Baylin, was funded by a number of grants, including Stand Up To Cancer's inaugural Laura Ziskin Prize in Translational Research - a \$250,000 grant awarded to the two researchers in 2012. Ziskin, a Hollywood film producer who died of metastatic [breast cancer](#), was a co-founder of Stand Up To Cancer, an initiative founded in 2008 by nine women in the entertainment industry to accelerate groundbreaking research and bring new treatments to patients as quickly as possible.

PARP inhibitors are used primarily to treat tumors linked to defects in BRCA genes, but may show promise in other cancers when combined with other drugs. Certain kinds of cancer cells depend heavily on PARP to repair DNA damage. If PARP is blocked, these cells die. PARP inhibitors also cause PARP to become trapped in the cancer cells' DNA, a process that is greatly enhanced when a DNMT inhibitor is added, Dr. Rassool says. This leads to massive DNA damage that cannot be repaired, and the [cancer cells](#) self-destruct.

DNMT inhibitors suppress DNA methylation, resulting in gene expression that significantly interferes with cancer cell growth. They are not usually combined with PARP inhibitors.

"Dr. Rassool and her colleagues have identified an exciting new mechanism for attacking cancer that may ultimately provide a new option for treating patients with leukemia and other cancers," says E. Albert Reece, MD, PhD, MBA, vice president for medical affairs at the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of UMSOM. "We are committed to

translational research, and this is excellent example of how we are able to move an important scientific discovery in the laboratory into the clinic where it may potentially benefit patients."

**More information:** *Cancer Cell*,  
[dx.doi.org/10.1016/j.ccell.2016.09.002](https://doi.org/10.1016/j.ccell.2016.09.002)

Provided by University of Maryland School of Medicine

Citation: Novel mechanism in drug combination shows potential for treating leukemia, other cancers (2016, October 10) retrieved 8 May 2024 from  
<https://medicalxpress.com/news/2016-10-mechanism-drug-combination-potential-leukemia.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.