

Key leukemia defense mechanism discovered

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Virginia Commonwealth University Massey Cancer Center researcher Steven Grant, M.D., and a team of VCU Massey researchers have uncovered the mechanism by which leukemia cells trigger a protective response when exposed to a class of cancer-killing agents known as histone deacetylase inhibitors (HDACIs). The findings, published in the *Journal of Biological Chemistry*, could lead to more effective treatments in patients with leukemia and other cancers of the blood.

"Our findings provide new insights into the ways such [cancer cells](#) develop resistance to and survive treatment," says Grant, associate director for translational research and professor of medicine. "This knowledge will now allow us to focus our efforts on strategies designed to prevent these self-protective responses, potentially rendering the cancer cell incapable of defense and increasing the effectiveness of therapy."

The discovery centers on modification of a protein known as NEMO. Researchers have known for some time that HDACIs trigger a protective response in [leukemia](#) cells by activating a survival signaling pathway known as NF- κ B, which limits the ability of HDACIs to initiate a cancer cell suicide program known as apoptosis. However, it was previously thought this process occurred through activation of receptors residing on the cancer cell surface. What VCU Massey researchers discovered was that HDACIs initially induce DNA damage within the cell nucleus, leading to modification of the NEMO protein, which then triggers the cytoprotective NF- κ B pathway. By disrupting modifications of the NEMO [protein](#), NF- κ B activation can be prevented, and as a

consequence, the cancer-killing capacity of HDACIs increases dramatically.

HDACIs represent an approved form of treatment for certain forms of lymphoma, and VCU Massey Cancer Center has been working for over seven years to develop strategies designed to improve their effectiveness in leukemia and other blood cancers. Grant's team is now focusing on ways to capitalize on this discovery by designing strategies that interrupt NEMO modifications through the use of pharmacologic agents and other means.

"Our goal is to move these findings from the laboratory to the bedside as quickly as we possibly can. There are currently several drugs in early stages of development that hold promise in disrupting the NEMO-related NF- κ B pathway, but further research defining their safety and effectiveness will be required before we can incorporate them into new therapies," says Grant.

Provided by Virginia Commonwealth University

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