

# Scientists see potential in novel leukemia treatment

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Scientists at Virginia Commonwealth University Massey Cancer Center may be one step closer to developing a new therapy for acute myeloid leukemia (AML) after discovering that the targeted agents obatoclax and sorafenib kill leukemia cells much more effectively when combined than when the drugs are administered individually.

Recently published in the [journal Blood](#), the results of a study led by Steven Grant, M.D., Shirley Carter Olsson and Sture Gordon Olsson Chair in Oncology Research, associate director for translational research and program co-leader of Developmental Therapeutics at VCU Massey Cancer Center, and Mohamed Rahmani, Ph.D., associate professor in the Department of Internal Medicine at VCU School of Medicine, showed that the combination of obatoclax and [sorafenib](#) synergized to induce a form of [cell suicide](#) known as apoptosis and reduced the growth and survival of several types of AML cells while exerting only limited toxicity toward normal, healthy tissues. The results were first obtained in test-tube experiments and were then confirmed by similar findings and extended survival in animal models of AML.

"Prior research suggested that these two drugs may enhance each other's activity as they inhibit complementary survival pathways in [leukemia cells](#)," says Grant. "The results of our study are promising. We're looking forward to translating these findings into clinical trials, and we are hopeful we can bring a new, potentially more effective treatment to patients suffering from AML."

Sorafenib is currently approved by the [Food and Drug Administration](#) to treat kidney and liver cancers, but recently has been shown to kill a diverse array of [malignant cells](#), including AML cells, particularly those with a specific mutation in a protein known as FLT3. Obatoclax is currently being investigated in clinical trials for various [blood cancers](#).

In AML cells, Grant's team found the [combination therapy](#) caused profound cell death and mitochondrial injury, as well as prolonged survival in animal models. Both drugs inhibit the protein Mcl-1, but do so through different mechanisms. Mcl-1 is a protein that has been shown to prevent apoptosis in various cancer cells, and very recently has been shown to play a critical role in the survival of AML cells.

The combination of the two drugs nearly abolished Mcl-1 expression in AML cells, and in doing so unleashed Bax and Bak proteins. Bax and Bak are usually held in check by Mcl-1, and both help initiate apoptosis in cancer cells. Increased levels of Bim were also observed in treated cells. Bim is another pro-apoptotic protein that is often referred to as a "death trigger." Increased levels or activation of all three of these proteins contributed to the pronounced killing of AML cells.

Grant's team also observed protective mechanisms at play in the AML cells. The combination therapy induced autophagy, a process that diverts energy from less critical cellular constituents to enhance survival. Using chloroquine, a drug that suppresses immune responses and is typically used to treat malaria, the researchers were able to inhibit autophagy and increase AML cell death even further.

"When cancer cells are placed under stress, they seek any possible way to remain alive," says Grant. "The combination of these drugs served to block molecular 'escape routes,' leaving the [cells](#) no option other than suicide. Thus, it is theoretically possible that a third agent such as chloroquine may enhance the effectiveness of this regimen even further

by reducing the cell's ability to induce autophagy."

Moving forward, Grant's team, led by Prithviraj Bose, M.D., assistant professor of internal medicine and hematologist-oncologist at Massey, is proposing a Phase I clinical trial testing this therapy in AML patients. The researchers are working with the involved drug companies, the National Cancer Institute and multiple potential collaborators to initiate the study.

Provided by Virginia Commonwealth University

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