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UNH Researchers Discover New Inhibitor Drug Combination for Rare Form of Cancer

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DURHAM, N.H.— Waldenström macroglobulinemia (WM), a rare form of lymphoma, does not have any known cure and only one FDA-approved treatment making it challenging to treat patients. Researchers at the University of New Hampshire took the novel approach of targeting specific cell proteins that control DNA information using inhibitors, or drugs, that were effective in reducing the growth of the cancer cells and when combined with a third drug were even more successful in killing the WM cancer cells which could lead to more treatment options.

“This is the first study to report the promising results of inhibitors in Waldenström macroglobulinemia which could open the door to new clinical possibilities,” said Sherine Elswa, associate professor of molecular, cellular and biomedical sciences. “We know that targeting these types of proteins with inhibitors can increase high therapeutic results in many other kinds of cancer but desired results in WM cells has been lacking.”

In their study (<https://www.futuremedicine.com/doi/10.2217/epi-2020-0189>), just published in the journal Epigenomics, Elswa and her team focused on the epigenetic regulation of WM cancer cells. Epigenetics is the study of how DNA is opened and closed to allow certain genes to be expressed or encoded. Each protein has a different function—some write the genetic code, some read or interpret it and others can erase the code. The researchers focused on two proteins, bromodomain and extraterminal (BET), which are epigenetic readers. BET proteins have been shown to be involved in pathological conditions including cancer. Drugs that inhibit these proteins can block gene expression that regulate cancer cells by slowing and stopping their growth.

The WM cancer cells were treated with the BET inhibitors JQ-1 and I-BET-762 which reduced the growth of the WM cells in the lab. While the dose dependent effect was significant for both drugs, JQ-1 showed the strongest inhibitory effect with 70% reduction in cell proliferation at the highest dose. However, neither inhibitor was effective in inducing cell death.

Researchers tried adding three different drugs, venetoclax, panabinstat and ibrutinib (the only FDA approved therapy specifically for WM patients), one at a time in combination with the BET inhibitors (JQ-1 and I-BET-762). After studying each separate drug combination, they found that adding venetoclax or panabinstat to the inhibitors was more effective than adding ibrutinib—with panobinstat offering the greatest combination therapy. Although ibrutinib alone has shown efficacy in WM patients, the study suggests epigenetic targeting is likely to provide a better therapeutic outcome and WM patients undergoing ibrutinib therapy may benefit from the addition of JQ1 which may enhance the efficacy of ibrutinib.



The research was supported by a grant from the International Waldenström Macroglobulinemia Foundation and the Leukemia & Lymphoma Society (IWMF-LLS), an award from the National Institutes of Health Centers of Biomedical Research Excellence (COBRE) (CIBBR, P20GM113131), and an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences.

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