

Novel drug therapy targets aggressive form of non-Hodgkin's lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma and the seventh most frequently diagnosed cancer. The most chemotherapy resistant form of DLBCL, called activated B-cell – DLBCL (ABC-DLBCL), remains a major therapeutic challenge. An international research team, led by two laboratories from Weill Cornell Medical College, has developed a new experimental drug therapy to target this aggressive form of lymphoma.

In the journal *Cancer Cell*, researchers report the discovery of an experimental small molecule agent, MI-2, that irreversibly inactivates MALT1—a key protein responsible for driving the growth and survival of ABC-DLBCL cells.

"In our study we show the drug MI-2 we developed inactivates any MALT1 protein it touches, and without any apparent toxicity in animal models," says the study's lead investigator, Dr. Ari Melnick, associate professor of medicine and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College.

The research team, which includes investigators from Spain, Canada and several other U.S. institutions, are now working to optimize the drug while testing MI-2 with other drug therapies that could be less toxic than current [chemotherapy regimens](#).

"No single drug can cure [lymphoma](#). This is why we need to combine

agents that can strike-out the different [cellular pathways](#) that [lymphoma cells](#) use to survive," says Dr. Melnick, who is also a hematologist-oncologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. "We want to eliminate the use of toxic chemotherapy in the treatment of [lymphoma patients](#), and these new study findings take us one-step closer to our goal of creating effective combinational molecular targeted therapy regimens to reduce treatment toxicity and improve lymphoma patient outcomes."

"A Bona Fide Therapeutic Target"

MALT1 is highly active in ABC-DLBCL and plays an important role in lymphoma [cancer cell growth](#) and survival. The unique protein is the only paracaspase produced in humans —and is a particular type of protease protein that cuts apart other proteins. But when MALT1 slices proteins in ABC-DLBCLs, it activates growth-promoting molecules and stops the work of other proteins that inhibit that growth.

"In essence, MALT1 turns off the brakes and presses the gas pedal to accelerate cell growth and survival in this aggressive cancer," Dr. Melnick says.

In this study, the researchers developed an activated form of MALT1 in the test tube that allowed them to study the structure of the molecule, and search for small molecule agents to shut it down. The key insights enabling this technical feat were achieved by co-lead investigator Dr. Hao Wu, an expert in biochemistry and structural biology and a former faculty member at Weill Cornell who is now at Harvard Medical School.

The researchers screened libraries of chemicals until they found one that tightly bonded to MALT1, preventing it from cutting other proteins. The agent, MI-2, also inactivated MALT1 in human samples of ABC-DLBCL, according to researchers.

When they tested the agent in mice, the research team found it stopped cancer growth without toxicity in normal tissues—a trait Dr. Melnick says is due to the fact that MALT1 is not required for biological processes essential for life.

If tested successfully in human clinical trials, MI-2 could have benefits for other diseases, including MALT1 lymphoma, a lower-grade type of lymphoma. It could also possibly play a role in a variety of inflammatory and autoimmune disorders.

"MALT1 is a bona fide [therapeutic target](#), and with the discovery of MI-2 we have provided a lead compound that forms the basis of a new class of therapeutic agents," says Dr. Melnick.

The Cornell Center for Technology Enterprise and Commercialization, on behalf of Cornell University, has filed a patent application on this research work.

Provided by New York- Presbyterian Hospital

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