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Novel drug shuts down master protein key to lymphoma

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Researchers have discovered how an experimental drug is capable of completely eradicating human lymphoma in mice after just five doses. The study, led by researchers at Weill Cornell Medical College, sets the stage for testing the drug in clinical trials of diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma, itself the seventh most frequently diagnosed cancer in the U.S.

In the journal *Cell Reports*, published today online, the scientists describe how the powerful master regulatory transcription factor Bcl6 regulates the genome, ensuring that aggressive lymphomas survive and thrive. They also show how the Bcl6 inhibitor, developed at Weill Cornell, effectively gums up the protein, stopping it from working.

While Bcl6 is active in a number of cancers, including leukemia and breast cancer, work testing a Bcl6 inhibitor is most advanced in DLBCL. "That's because we desperately need a new strategy to treat this lymphoma—many patients are resistant to currently available treatments," says the study's senior investigator, Dr. Ari Melnick, Gebroe Family Professor of Hematology/Oncology and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell.

Dr. Melnick developed the first BCL6 inhibitors nine years ago, and has continued to improve upon the design of these drugs so they could be used to treat cancer patients. He has since collaborated with colleagues at

many institutions in a systemic effort to understand how both Bcl6 and its inhibitor drugs function.

In a study published in March in Nature Immunology, Dr. Melnick and his team reported that it is possible to shut down Bcl6 in DLBCL without affecting its vital role in the T cells and macrophages needed to support a healthy immune system. The protein has long been considered too complex to target with a drug as it also is crucial to proper function of many immune system cells, not just B cells gone bad.

That finding suggested Bcl6 inhibiting drugs may have few side effects, says Dr. Melnick, who is also a hematologist-oncologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

The latest study was designed to understand exactly how Bcl6 promotes DLBCL.

Transcription factors are responsible for either inhibiting or promoting the expression of genes, and master regulatory transcription factors are like transcription factors on steroids: their actions regulate thousands of genes in different kinds of cells. Bcl6 can control the type of immune cell that develops in the bone marrow—pushing them to become B cells, T cells, or macrophages—and it has a primary role in the developmental phase of B cells, during which they generate specific antibodies against pathogens.

The researchers found that in order to help B cells produce antibodies against an infection, Bcl6 "builds a huge shopping mall-style complex" that sits on top of a stretch of the genome. By binding onto these genes, Bcl6 deactivates the DNA, stopping genes from producing RNA and proteins. "Bcl6 acts like a barcode reader. When it sees that barcode—the DNA sequence—it attaches there," Dr. Melnick.

Normally, the protein complex goes away after an immune reaction has been successfully mounted against the pathogen. But when it doesn't, and remains stuck to the genes, DLBCL can result. That's because Bcl6 is inhibiting genes that stop cells from dividing and that sense damage to the genome, Dr. Melnick says. "We now know the genes that Bcl6 is repressing and how that helps lymphoma develop and survive."

Bcl6 also has a second, independent function that Dr. Melnick says acts like a switch on railroad track that routes a train in one direction or another. One track is needed when antibodies are required for an immune response, while the other keeps B cells in a constant state of division.

The researchers found that in order for DLBCL to survive, Bcl6 needs to maintain both its shopping mall protein complex and keep the train tracks on the path toward B cell division.

To their surprise, they also found that both the complex and the train switch attach to the Bcl6 protein at the same site. "They fit into the same keyholes on Bcl6," Dr. Melnick says. "There are two identical binding sites on the protein surface."

Even better, the Bcl6 inhibitor they developed was designed to fit into that same keyhole.

"This is wonderfully serendipitous—our drug just happens to be able to overcome both of the biological mechanisms that are key to survival of aggressive lymphoma," Dr. Melnick says, adding that the inhibitor completely eradicated DLBCL in mice in a short time, with no detectable side effects.

The team is conducting additional research toward an investigational new drug application from the federal Food and Drug Admission.

Provided by Weill Cornell Medical College