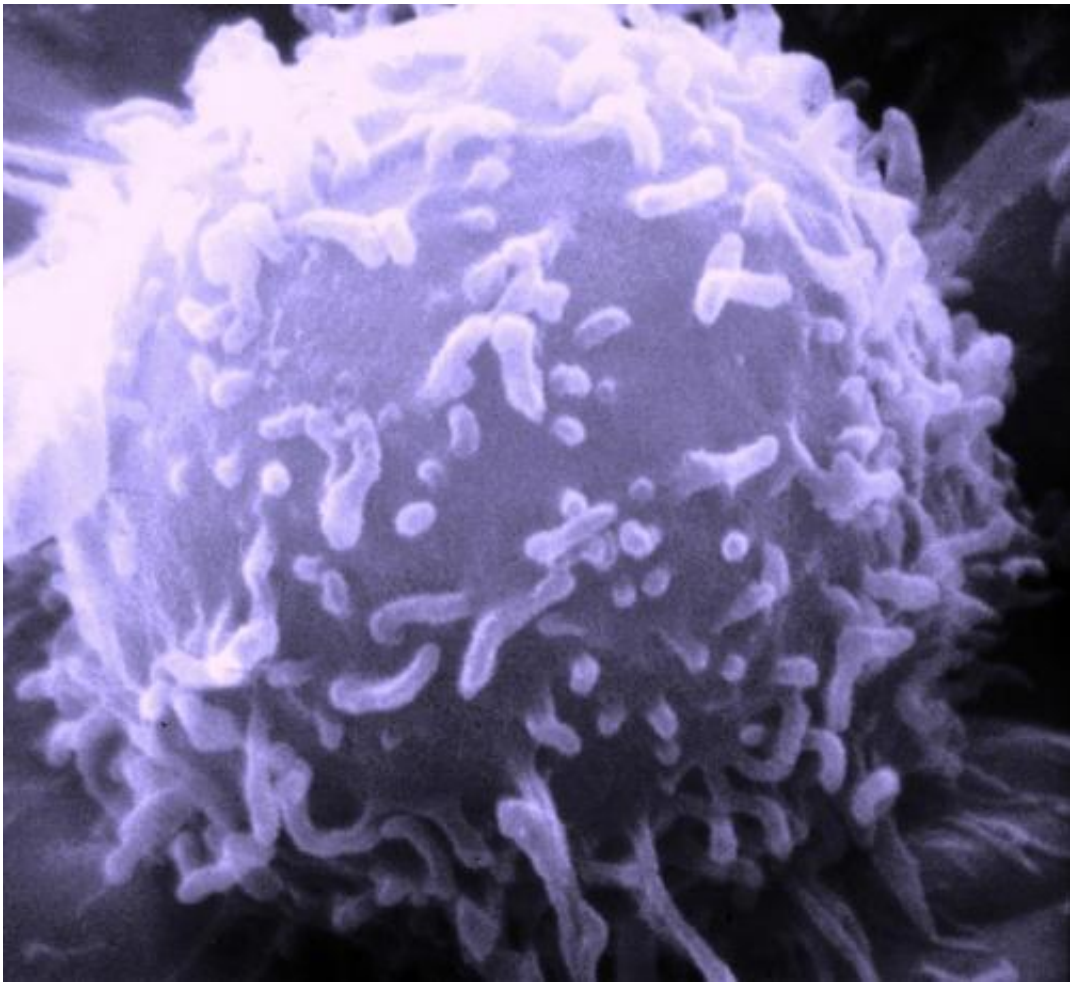
New type of cancer treatment targets cancer cell proteins

November 6 2015, by Geri Clark



Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

A new therapeutic approach that targets an aggressive form of lymphoma may greatly increase the efficacy of treatment and result in better outcomes for patients, according to new research by scientists at Weill Cornell Medicine.

Diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer of the B-cells, a type of white blood cell. It is the most common form of non-Hodgkin lymphoma, affecting approximately 20,000 Americans each year. Current therapies are ineffective for at least 40 percent of patients with DLBCL and come with severe side effects ranging from fever and nausea to heart and nerve damage. But in their study, published Nov. 3 in the *Journal of Clinical Investigation*, scientists from Weill Cornell Medicine, Memorial Sloan Kettering Cancer Center and the University of Michigan Medical School found that a combination therapy that targets proteins in cancer cells was more effective than either of the drugs alone.

"Targeted therapies have drastically advanced the field of cancer therapy, but even they have limitations," said first author Dr. Rebecca Goldstein, a postdoctoral fellow in medicine at Weill Cornell Medicine. "If you use a drug to block one mutant protein, eventually the cancer cell will become resistant to the targeted agent by finding another protein or pathway to use for survival.

"One way to avoid this resistance, and perhaps more powerfully stop tumor growth, is to treat patients with a combination of targeted agents," she added. "However, the number of targeted therapies that exist is enormous and empirically testing all these combinations is impossible. Our goal was to find a way to identify combination therapies specific to a type of cancer and then test them in those cancers."

Conventional thinking about cancer treatment focuses on finding mutations in cancer cells and targeting those mutations. But this is not

always effective, said Dr. Ari Melnick, the Gebroe Family Professor of Hematology/Oncology and a professor of medicine at Weill Cornell Medicine.

"Many mutations occur in only a subset of tumor cells," he said. "Even when you have a drug against those mutations, it will not work in all tumor cells. We need to identify vulnerabilities that exist in in all cancer cells."

Goldstein and Melnick and their team focused on proteins that exist in all cells. In particular, they looked at one protein called Hsp90, which acts like a scaffolding for other proteins in the cells. Cancer cells hijack this scaffolding function to stabilize the mutant proteins they require for survival.

"If we could identify the proteins that Hsp90 is stabilizing in these cells," Goldstein said, "then we might be able to therapeutically target them in combination with Hsp90 inhibition."

The researchers used an experimental drug developed at Memorial Sloan Kettering called PU-H71, which binds to Hsp90 to trap it in a complex with the other proteins it stabilizes, known as client proteins. With this method, they identified client proteins that are critical to lymphoma survival and can be targeted therapeutically. They then treated lymphoma cells in petri dishes, mice and human tumor samples with PU-H71 and ibrutinib, a drug that is used to treat lymphoma that targets one of the major lymphoma survival pathways identified. Every time, the drug combination proved to be more effective at killing lymphoma cells than ibrutinib or PU-H71 alone.

"PU-H71 acts like a stone thrown at a window," Goldstein said. "It hits the window – the cancer cell – and makes all these cracks. It weakens it. And then ibrutinib comes in and just taps it, and it falls apart."

The investigators expect this new combination therapy to soon move into a phase II clinical trial. If successful there, cancer treatment could move in a whole new direction.

"The pharmacoproteomics approach has the potential for truly personalizing lymphoma treatment because, when applied to individual lymphomas, it can identify the group of proteins a particular cancer cell relies on for survival," said co-senior author Dr. Leandro Cerchietti, an assistant professor of medicine and a member of the Meyer Cancer Center at Weill Cornell Medicine. "Thus, it pinpoints to functional nodes in survival pathways that should be targeted to kill that particular lymphoma and a more biologically informed treatment decision could be made."

"This approach offers the possibility of combination treatments that may increase efficacy of standard drugs and also may allow lower doses, which could also reduce side effects in patients," said Dr. John Leonard, the Richard T. Silver Distinguished Professor of Hematology and Medical Oncology and a professor of medicine at the Joan and Sanford I. Weill Department of Medicine and associate dean for clinical research at Weill Cornell Medicine.

Provided by Cornell University