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This combination targeted therapy may offer hope to infants diagnosed with a deadly type of leukemia

City of Hope researchers found that "turning off" the BCL6 protein and using the small molecule ABT-199 eliminated drug resistance in mouse models that had a subtype of B cell acute lymphoblastic leukemia.

DUARTE, Calif. — City of Hope researchers have identified a potential combination targeted therapy for a deadly type of leukemia found in some infants, a population too young to receive full-blown chemotherapy.

Called "mixed lineage leukemia (MLL)-rearranged B cell acute lymphoblastic leukemia (B-ALL)," this blood cancer subtype comes with bleak health outcomes (overall survival rate is less than 50%), disease recurrence and development of resistance to existing therapies.

"Our proof-of-concept animal experiments revealed a promising combination targeted therapy that may one day provide lifesaving treatment to babies, young children, teenagers and adults who do not have many options currently," said Markus Müschen, M.D., Ph.D., chair of the Department of Systems Biology at City of Hope and corresponding author of the new study. "The next step is to test our theory in clinical trials."

Published in the journal Genes & Development on Aug. 8, the study highlighted the transcription factor BCL6 (a protein that promotes tumor formation and drug resistance) as a new target for the treatment of MLL-rearranged B-ALL.

About 10% of B-ALL involve abnormal separation and then relocation of chromosome parts in the MLL gene on chromosome 11.

"Treatment options for infants with leukemia are limited, and patients with MLL-rearranged leukemia are in a group with particularly poor outcomes," Müschen said. "The vast majority of infants and newborns with leukemia actually carry an MLL-rearrangement, so we are very pleased that this combination treatment concept may eventually help this group of patients."

The science that led to the discovery

Müschen and his colleagues analyzed gene expression data from a clinical trial that involved 207 pediatric patients who were at high-risk for B-ALL. They noticed higher-than-normal amounts of BCL6 proteins at disease diagnosis, quicker cancer recurrence and reduced overall survival.

Pulling the data of 49 patients from that pediatric clinical trial, City of Hope researchers noticed BCL6 messenger RNA levels were significantly higher in patients whose cancer relapsed. They observed that patients lacking MLL gene rearrangements had low BCL6 protein levels. Some 85% of them were alive and relapse-free four years after diagnosis. In contrast, only 37% of patients with MLL-rearranged B-ALL experienced relapse-free survival four years after diagnosis. This group tended to have high levels of the BCL6 protein.

The untangling of this data prompted Müschen and his colleagues to conduct experiments involving patient samples and mouse models. They found that most mice with MLL-rearranged B-ALL have abnormal BCL6 protein levels and that BCL6 was rarely found in other kinds of B-ALL.

When the MLL gene was introduced to mouse models, the result was a 10- to 25-fold increase in BCL6 protein levels. In fact, the researchers observed that the BCL6 protein and MLL gene have a symbiotic relationship where each helps the other exist and multiply.

Through other experiments, the researchers discovered that BCL6 blocks the function of a protein commonly known as BIM (BCL2L11), which is responsible for killing tumors and preventing cancer progression. They found that the peptide RI-BPI and the small molecule FX1 could unblock this pathway so that BIM could function normally and kill tumors. Further testing showed that RI-BPI and FX1 work synergistically with ABT-199, a small molecule targeted therapy that has been approved by the U.S. Food and Drug Administration to treat chronic lymphocytic leukemia and small lymphocytic lymphoma.

“Our experiments showed that turning off BCL6 in combination with using ABT-199 could be a simple and nontoxic way to overcome drug resistance,” Müschen said. “We’ve proven the method works in mouse models. Now we’re passing this knowledge on to scientists worldwide so that our proposed combination targeted therapy can be tested in clinical trials.”

Researchers from University of California San Francisco, University of Oxford and Weill Cornell Medical College also contributed to this study, which was supported by the National Cancer Institute, Howard Hughes Medical Institute, The Norman and Sadie Lee Foundation, Falk Medical Research Trust, Pediatric Cancer Research Foundation, Cancer Research Institute, California Institute for Regenerative Medicine, Chemotherapy Foundation, and National Institutes of Health.

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About City of Hope

City of Hope is an independent biomedical research and treatment center for cancer, diabetes and other life-threatening diseases. Founded in 1913, City of Hope is a leader in bone marrow transplantation and immunotherapy such as CAR T cell therapy. City of Hope's translational research and personalized treatment protocols advance care throughout the world. Human synthetic insulin and numerous breakthrough cancer drugs are based on technology developed at the institution. A National Cancer Institute-designated comprehensive cancer center and a founding member of the National Comprehensive Cancer Network, City of Hope is ranked one of America's "Best Hospitals" in cancer by U.S. News & World Report. Its main campus is located near Los Angeles, with additional locations throughout Southern California. For more information about City of Hope, follow us on Facebook, Twitter, YouTube or Instagram.