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Combination therapy overcomes BET inhibitor resistance, shows study

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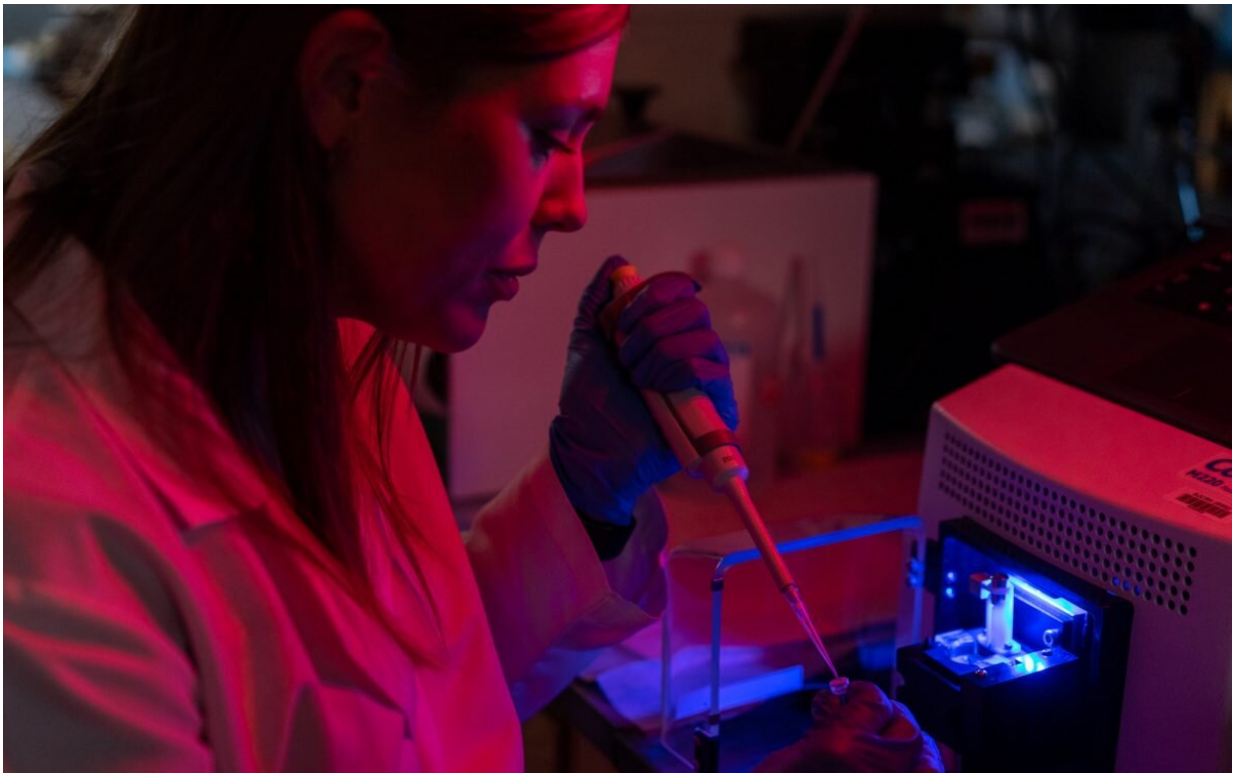

Study first author Shaela Fields (Wright), from the lab of Chunliang, Li, PhD, St. Jude Department of Tumor Cell Biology, led research to understand BET inhibitor resistance. Credit: St. Jude Children's Research Hospital

Scientists at St. Jude Children's Research Hospital developed a novel combination therapy approach for a leukemia subtype harboring

rearrangements in the KMT2A gene. The approach overcomes the cancer's drug resistance, without adding toxicity. The study was published today in *Proceedings of the National Academy of Sciences*.

Bromodomain and extra-terminal domain (BET) inhibitors have been shown to provide therapeutic benefits against many different cancers. However, the mechanisms governing response and resistance to this class of therapies are poorly understood.

Scientists at St. Jude conducted CRISPR screens, performing a genome-wide loss of function analysis in leukemia harboring KMT2A rearrangements. These rearrangements are often found in infants and can occur in acute lymphoblastic or myelogenous leukemia (ALL or AML).

"KMT2A rearrangements are enriched in infant leukemias which generally have a poor prognosis," said co-corresponding author Jun J. Yang, Ph.D., St. Jude Departments of Pharmacy and Pharmaceutical Sciences and Oncology. "Over the past several decades, there has been very little progress in improving cure rates of infants with KMT2A-rearranged leukemias, so there is a clear need to develop new therapies for those patients."

"This is one of the very few genetic abnormalities that can affect ALL and AML, which makes it very interesting from a tumor biology perspective," Yang added.

CRISPR reveals a combination strategy

The researchers found that loss of the SPOP gene causes significant BET inhibitor resistance, which they confirmed in cell lines and xenograft mouse models. Additional CRISPR screens revealed that cells treated with BET inhibitors are sensitive to disruptions in the gene GSK3B.

Armed with this information, the researchers developed a combination therapy approach that uses both BET and GSK3 inhibitors against KMT2A mutated leukemia. The work demonstrated that the combination could impede the growth of leukemia cells.

"Our expertise in combinatorial CRISPR screens allowed us to identify resistance mechanisms, but by also doing reverse screens, we also identified the targetable options that will allow us to overcome resistance," said co-corresponding author Chunliang Li, Ph.D., St. Jude Department of Tumor Cell Biology. "Our findings led us to a combination regimen that can reverse resistance to BET inhibition. The BET and GSK3 inhibitor combination shows remarkable efficacy but also no increase in toxicity because the GSK3 and BET inhibitors synergize, but on its own, the GSK3 inhibitor doesn't seem to have an effect."

The findings suggest that the combination of BET and GSK3 inhibition holds promise for further development in KMT2A-rearranged leukemias.

More information: Shaela Wright et al, Interrogating bromodomain inhibitor resistance in KMT2A-rearranged leukemia through combinatorial CRISPR screens, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2220134120

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