Strategy overcomes EZH2 inhibitor resistance in SMARCB1-mutated cancer

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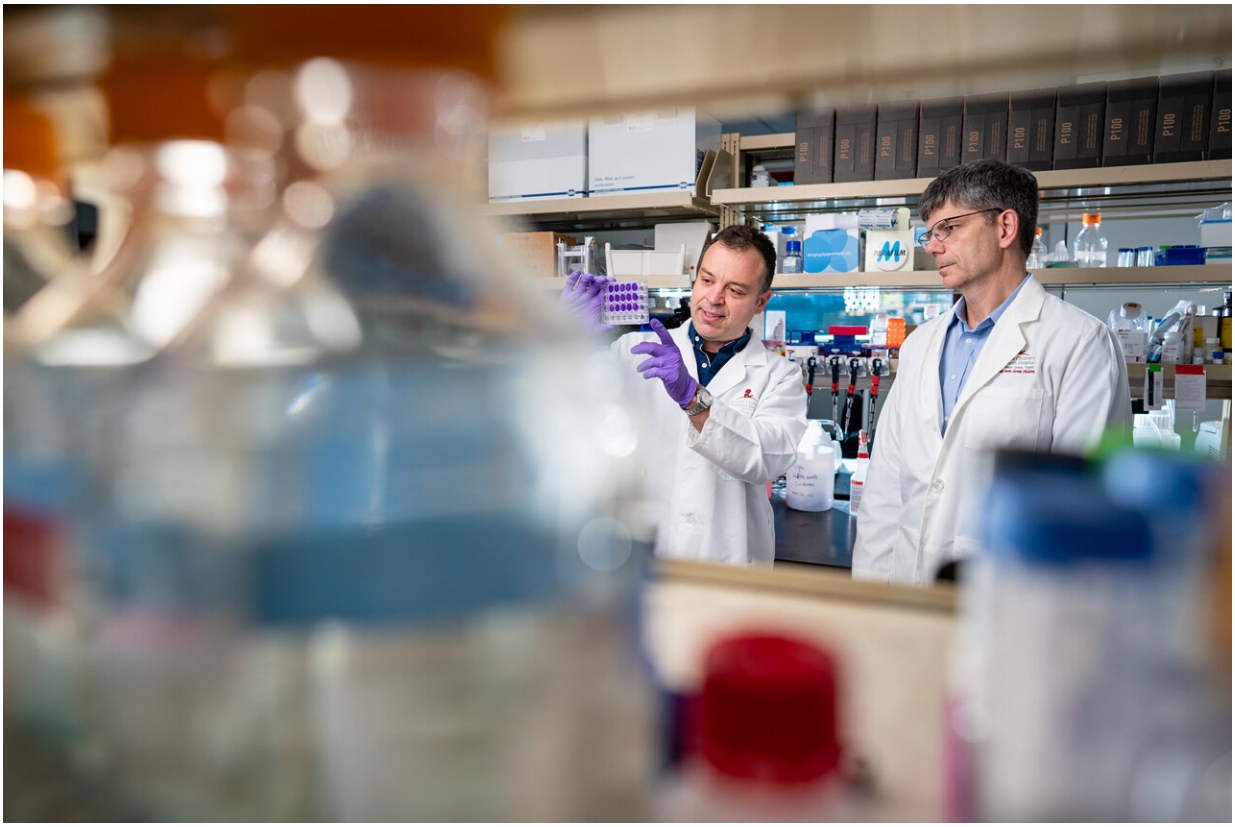

Dr. Yiannis Drosos and Dr. Charles Roberts of St. Jude Children's Research Hospital. Credit: St. Jude Children's Research Hospital

Inhibitors of the protein EZH2 are effective against cancers with SMARCB1 mutations such as rhabdoid tumors in children. However,

these drugs are subject to treatment resistance. Scientists at St. Jude Children's Research Hospital have identified a novel drug target that may help overcome resistance to EZH2 inhibitors. A paper on the work appeared today in *Molecular Cell*.

Rhabdoid tumor is a rare cancer that occurs in children. It can grow in the kidneys and soft tissues (malignant rhabdoid tumor) or in the brain (atypical teratoid rhabdoid tumor). These cancers have a characteristic loss of SMARCB1, a mutation where the gene and the protein it creates are missing.

Previous work by corresponding author of the study Charles W.M. Roberts, M.D., Ph.D., St. Jude Comprehensive Cancer Center director, showed that inhibitors of EZH2 are effective against cancers with SMARCB1 mutations. EZH2 is a component of the Polycomb repressive complex, a multi-protein machine that silences gene expression at specific genes.

The EZH2 inhibitor Tazemetostat is U.S. Food and Drug Administration (FDA) approved for cancers with SMARCB1 mutations. Roberts's work inspired further investigations and then clinical trials of the EZH2 inhibitor Tazemetostat, which ultimately resulted in FDA approval for its use in cancers that carry SMARCB1 mutations.

Resistance, where a cancer cell finds a way to circumvent a drug's effect, is a common problem that can make therapies ineffective. In the current study, Roberts's team investigated the mechanisms cancer uses to resist EZH2 inhibitor treatment. The scientists used CRISPR screens in SMARCB1-mutant rhabdoid tumor cells to identify potential resistance mechanisms.

"This study illuminates how chromatin regulators interact to control transcription," Roberts said. "It not only helps us understand this

aggressive childhood cancer but also offers insight into treating cancers that carry activating mutations in EZH2."

Chromatin regulation holds the key

Chromatin is a complex of DNA and protein tightly compacted inside cells. Chromatin must unwind to turn genes on and off in closely regulated processes. Cancers often carry mutations that affect the SWI/SNF chromatin remodeling complex, of which loss of SMARCB1 is one example.

The study showed that loss of the chromatin regulator NSD1 caused EZH2 inhibitor resistance. The researchers showed how NSD1 coordinates transcriptional control and expanded their understanding of the relationship between SWI/SNF and Polycomb. When cancers have a loss of SMARCB1 and are treated with an EZH2 inhibitor, the genes that cause the cell to differentiate are turned back on.

"We discovered that NSD1 is that critical next step after EZH2 inhibition to focus on in terms of getting this drug to be effective and understanding how the transcriptional network gets activated," said first author Yiannis Drosos, Ph.D., St. Jude Oncology Department. "We know NSD1 is doing that by placing a very specific mark on chromatin, so we started thinking, how can we get around it?"

The researchers found that the cells need NSD1 to turn on the genes that are activated by EZH2 inhibition, such that loss of NSD1 results in resistance to EZH2 inhibition. To circumvent the resistance, the scientists looked to a gene that opposes NSD1 function. The researchers showed that inhibiting this gene, called KDM2A, restored sensitivity of the cancer cells to EZH2 inhibition.

This finding extends beyond rhabdoid tumor to any cancer with a loss of

SMARCB1, such as some lymphomas. Currently there is not an inhibitor of KDM2A ready for clinical use, but the findings may support development by a pharmaceutical company in the future.

The work was part of the St. Jude Collaborative Research Consortium on Chromatin Regulation in Pediatric Cancer. Through the collaborative, investigators at different institutions conduct research that requires the expertise of scientists with different specialties streamlining and speeding up progress.

More information: Yiannis Drosos et al, NSD1 mediates antagonism between SWI/SNF and polycomb complexes and is required for transcriptional activation upon EZH2 inhibition, *Molecular Cell* (2022). DOI: 10.1016/j.molcel.2022.04.015

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