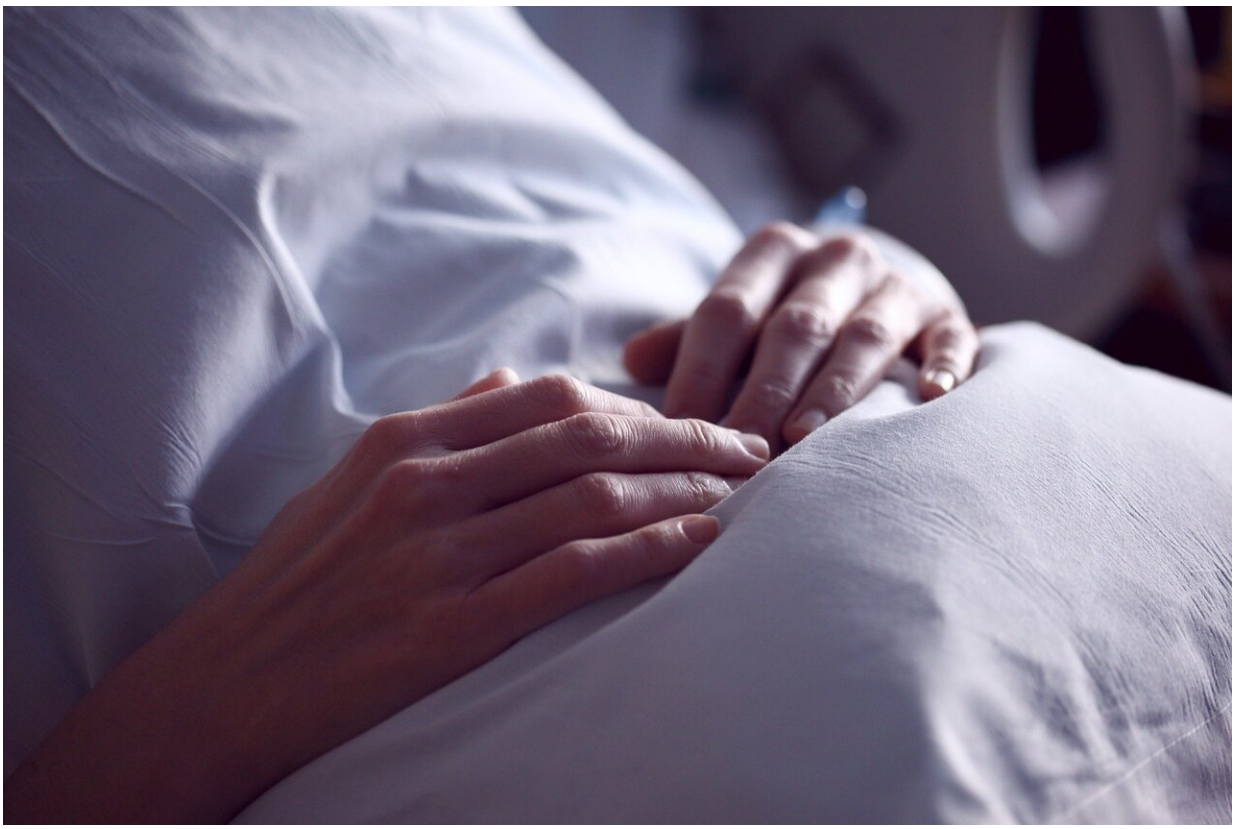
New cancer study provides insight into underlying gene mutations in myelodysplastic syndromes

December 9 2023



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A new study from researchers with Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine and

collaborating organizations provides insight into the underlying mechanisms of gene mutations commonly seen in patients with myelodysplastic syndromes (MDS) and other myeloid neoplasms.

Their findings, to be presented at ASH 2023, the American Society of Hematology's annual meeting in Santa Diego, Dec. 9-12, could lead to development of more effective drug combinations and targeted therapies for MDS patients carrying these mutations.

About half of MDS patients carry genetic alterations, also known as somatic mutations, in the spliceosome genes, with SF3B1 being the most common one. However, no successful therapy exists to target this pathway.

Previous findings from a phase 2 clinical trial of selinexor, an Exportin-1 (XPO1) inhibitor for relapsed or refractory MDS, showed increased effectiveness in patients with SF3B1-mutated MDS. Exportin-1 is the nuclear export receptor responsible for exporting more than 200 proteins, but also plays a role in transporting multiple small nuclear RNAs and select messenger RNAs.

Sylvester researchers and collaborators hypothesized that 1) inhibiting XPO1 may preferentially affect SF3B1-mutant cells via altered splicing and 2) high-risk MDS patients with this mutation would have a better response to dose-controlled, targeted drug combinations with next-generation XPO1 inhibitors.

For this study, the researchers deployed a combination of scientific techniques in their analysis, including:

- **RNA sequencing** to evaluate the underlying mechanism for the SF3B1 mutation's sensitivity to XPO1 inhibitors.
- **Whole genome CRISPR screens** in two myeloid leukemia cell

lines with eltanexor, a next-generation XPO1 inhibitor with lower toxicity than the drug selinexor. The analyses identified several novel targets that were tested for synergy in combination with eltanexor for the specific SF3B1 mutation. Two drugs were identified for strong synergy with eltanexor: venetoclax and navitoclax.

- **In vitro studies** to test combinations identified from the CRISPR screen using cell viability tests and western blots.
- **In vivo studies** to further validate these combinations through use of transplant tests in laboratory mice.

"This is the first study to examine the effects of XPO1 inhibition on RNA export to better understand the underlying mechanisms involved with the most common mutation seen in MDS patients," explained Sana Chaudhry, Sylvester researcher and lead presenter at the ASH conference.

"Our study's findings may contribute to development of synergistic therapeutic combinations to better treat SF3B1-mutant MDS," said Justin Taylor, M.D., senior author and a member of the Translational and Clinical Oncology Program at Sylvester.

Additionally, Taylor noted, recent data from human studies has shown that venetoclax can overcome the poor prognosis often associated with acute myeloid leukemia patients with mutations. "As a result, combining eltanexor with venetoclax could represent a potentially effective SF3B1-specific therapy," he concluded.

More information: Presentation Title: 44 "Altered RNA Export in SF3B1 Mutants Increases Sensitivity to Nuclear Export Inhibition"