# Researchers identify new drug target for blood cancer, potentially solid tumors

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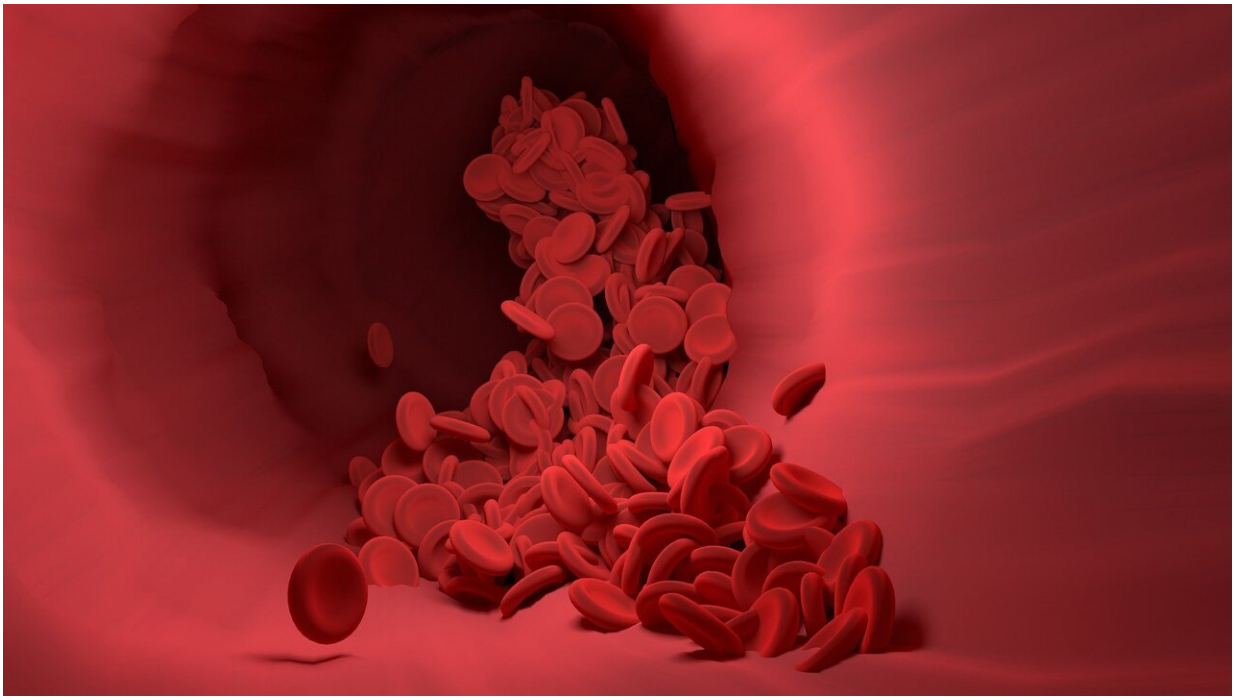

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Mount Sinai and UC San Diego researchers have shown for the first time how mutations affecting a cellular process called RNA splicing alter cells to develop myelodysplastic syndrome (MDS) and other hematologic malignancies and solid tumors, according to a study published in *Cancer Discovery* in October.

Their research found that these mutations produce an alternative version of the protein created by the gene *GNAS.* This protein can be targeted by drugs already approved by the Food and Drug Administration for treating other cancers, and therefore could be a good target in MDS. The researchers are creating a clinical trial to test these drugs, known as MEK inhibitors and named for the proteins they inhibit to stop cancer.

MDS is a rare blood cancer that has no effective treatments and a poor prognosis. The mutations investigated in this study, however, are also found in other cancers, which extends the possible applications of these findings.

"This is the first study to discover that the altered protein created by *GNAS* is increased in cells with these mutations in MDS, and this results in the activation of processes that would render the cancer cells vulnerable to the MEK inhibitors," said co-senior author Eirini Papapetrou, MD, Ph.D., Associate Professor of Oncological Sciences at The Tisch Cancer Institute. "The discovery that we can try to use MEK inhibitors in this cancer is also a first, and our findings also support future drug development to target *GNAS*, identified in this study."

Papapetrou led the study with Gene Yeo, Ph.D., professor at UC San Diego School of Medicine. The researchers generated models of the mutations using stem cells, in order to study them in a physiological genetic context. They then turned the engineered cells into hematopoietic progenitor cells—which are the relevant cell type in blood cancers—and performed splicing and RNA binding analyses.

"This work integrates isogenic models of disease with cutting-edge RNA-omics to converge onto a new target for MDS," Yeo said.

These analyses allowed the team to identify high-confidence targets and to identify the driver of the disease. The team showed that MDS cells

from the model as well as cells from MDS patients with these mutations were sensitive to treatment with MEK inhibitors.

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