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Inhibitors of shuttle molecule show promise in acute leukemia

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A novel family of experimental agents that blocks a molecule from shuttling proteins out of the cell nucleus might offer a new treatment for people with acute leukemia, according to a study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

The agents, called KPT-SINEs (selective inhibitors of nuclear export), target a transport protein called CRM1. Using acute myeloid leukemia (AML) cells and an animal model, the researchers showed that these agents inhibited leukemia-cell proliferation, arrested cell division, and induced cell death and differentiation.

In the animal model of AML, KPT-SINEs – described by the researchers as one of the most advanced agents in pre-clinical development – extended survival by 46 percent compared with controls.

KPT-SINEs were particularly effective when the leukemia cells also had mutations in the tumor-suppressor gene NPM1, which are present in about one-third of all adult AML.

The findings were published online in the journal *Blood*.

"Our study suggests that these agents might be an effective therapy for AML, particularly for patients with NPM1 mutations," says principal investigator Dr. Ramiro Garzon, assistant professor of medicine and a researcher with the OSUCCC – James Molecular Biology and Cancer

Genetics Program.

"We hope to start a phase I trial using one of these agents soon and to pursue further preclinical studies using this drug in combination with other current chemotherapies," Garzon says.

CRM1 normally transports molecules out of the cell nucleus to the surrounding cytoplasm. In acute leukemia cells, the molecule carries tumor-suppressor, apoptotic and other protective proteins out of the nucleus, thereby contributing to leukemia development. Karyopharm Therapeutics, Inc., developed KPT-SINEs. This study also showed that these agents:

- Reduce the amount of CRM1 protein in the nucleus and increase the amount of tumor-suppressor protein such as p53 and NPM1 in AML cells.
- Strongly down-regulate FLT3 and KIT, oncogenes that are commonly overexpressed in AML.
- Increase survival in a leukemia animal model, with treated mice living an average of 39 days versus 27 days for untreated animals.

Provided by Ohio State University Medical Center