Researchers revisit potent drug as promising treatment for acute leukemia

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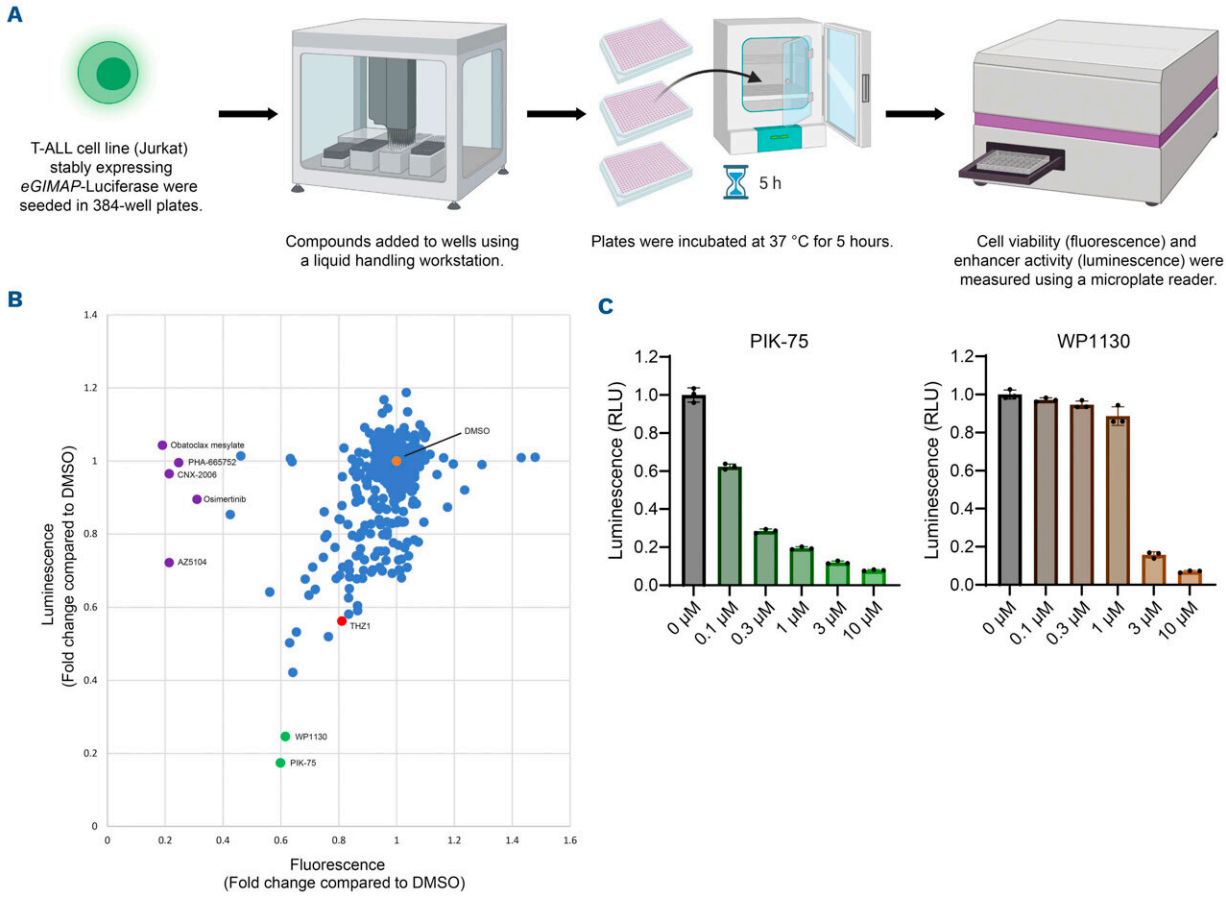

Chemical screening using the GIMAP enhancer reporter system. (A) Overview of the chemical screening strategy. Using a liquid handling workstation, 2,961 compounds from 3 chemical libraries, a negative control (dimethyl sulfoxide [DMSO]) and a positive control (THZ1), were added to Jurkat cells that stably expressed the GIMAP enhancer reporter construct. Cell viability and luciferase activity were measured after 5 hours using a microplate reader. Images were

created by BioRender. (B) Scatterplot showing luminescence (representing the GIMAP enhancer activity) and fluorescence (representing cell viability) of the cells treated with each of the compounds from the anticancer library. The values shown are the means of technical triplicates, presented as fold change compared to THZ1. (C) Jurkat cells stably expressing the GIMAP enhancer construct were treated with PIK-75 and WP1130 at various concentrations. Cell viability and luciferase activity were measured after 5 hours. Relative luminescence was determined by normalizing luciferase activity to cell viability and is presented as the fold change compared to untreated cells. The values are shown as individual dots and the mean ± standard deviation of technical triplicates. Representative results from multiple independent experiments were shown (C). Credit: *Haematologica* (2022). DOI: 10.3324/haematol.2022.280761

A team of researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore, led by Associate Professor Takaomi Sanda and Dr. Lim Fang Qi, has breathed new life into an existing drug—combatting a type of blood cancer called T-cell acute lymphoblastic leukemia, or T-ALL.

The drug, called PIK-75, was initially discovered over a decade ago but was dismissed in favor of newer ones. Now, it has made a comeback that deems it unmissable—the researchers established that the drug could block not just one but two crucial cancer-causing pathways of T-ALL, enabling them to develop new treatments that could effectively stem the disease.

Predominantly afflicting children, T-ALL is aggressive and progresses rapidly, affecting stem cells in the bone marrow that produce T-cells, which help maintain an individual's ability to fight off infection. The condition results in the formation of immature, or ill-developed, T-cells that accumulate and overwhelm their normal counterparts, thereby compromising the patient's immunity. Many patients who have

previously recovered from pediatric T-ALL suffer from relapse, and in some cases even fail to respond to first-line therapy.

Killing two birds with one stone

"Current cancer treatment strategies mostly focus on targeting a single molecule specific to the disease, like an oncoprotein," said Assoc Prof Sanda, lead author of the study. "We learned that the ability of cancer cells to survive and proliferate is underpinned and promoted by multiple mechanisms, of which identifying and inhibiting just one is often not sufficient to slow the march of the disease."

With that in mind, the team uncovered the relevant underlying pathways, so that medical interventions can be deployed to destroy all the potential routes the disease can take as it attempts to spread throughout the patient's body.

In T-ALL, the mechanisms that drive the disease progression are differentiated into "type A" and "type B" abnormalities. A prime example of the former is the overexpression of the TAL1 oncogenic transcription factor—powerful proteins that sustain the multiplication of cancer cells and are prevalent in nearly half of all human T-ALL cases.

In contrast, type B is characterized by the activation of an abnormal signaling pathway such as PI3K-AKT-PTEN pathway—a series of reactions in which a group of proteins in a cell team up to control the function of the cell, ultimately promoting the emergence of cancer cells. Together, these two mechanisms work together to support the proliferation of malignant T-ALL cells in patients.

In their study, the researchers performed a drug screening to hunt for potential candidates that could treat T-ALL. Among roughly 3,000 compounds, PIK-75 stood out for exhibiting the ability to block TAL1

transcription factor activity as well as the PI3K-AKT-PTEN signaling pathway, thereby greatly reducing the survivability of T-ALL cells.

To the researchers' surprise, PIK-75 had originally been touted as an inhibitor of the PI3K-AKT-PTEN pathway 15 years ago but has since been left in oblivion as newer drugs come to the fore.

"Focusing on an 'oncogenic collaboration' mechanism, we demonstrated the efficacy of the novel therapeutic compound in inhibiting the core oncogenic machinery—which includes both type A and type B abnormalities—that drives T-ALL progression," explained Assoc Prof Sanda. "PIK-75 produced a strong cytotoxicity against T-ALL cells at low doses compared to previous studies involving other types of drugs that required higher concentrations to inhibit their growth."

The team's efforts are a notable contribution to NUS' pursuit of research breakthroughs in biomedical science and translational medicine. Their findings were published in the scientific journal *Haematologica* on September 8, 2022.

Looking ahead to more effective treatments

As the dual-inhibition mechanism of the novel drug is highly feasible in a clinical setting, the researchers are now looking to develop a soluble analog of the drug, which is currently in an insoluble form, so that it can eventually be administered to patients.

"We are delving deeper into the pathogenesis of cancers to uncover more life-saving insights," said Dr. Lim. "We also plan to unearth more novel drugs that can efficiently inhibit the primary oncogenic mechanisms of T-ALL."

More information: Fang Qi Lim et al, Targeting dual oncogenic

machineries driven by TAL1 and PI3K-AKT pathways in Tcell acute lymphoblastic leukemia, *Haematologica* (2022). DOI: 10.3324/haematol.2022.280761