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Novel compound demonstrates anti-leukemic effect in zebrafish, shows promise for human treatment

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A novel anti-leukemia compound with little toxicity successfully treated zebrafish with T-cell acute lymphoblastic leukemia (T-ALL), suggesting its potential to become a new highly targeted therapy for humans – even those resistant to conventional therapies – according to results from a study published online today in *Blood*, the Journal of the American Society of Hematology (ASH).

T-ALL is a cancer of the white blood cells in which genetic mutations cause normal immature T-cells to develop into leukemic cells, or "blasts." These blasts then quickly build up and crowd out normal cells, spreading into the bloodstream and other areas of the body and creating life-threatening symptoms, including excessive bleeding and frequent infections.

Despite major advances made in leukemia treatment – particularly multi-agent chemotherapy – over the last 50 years, chemotherapy remains highly toxic because it attacks both cancerous and normal cells. In addition, patients with T-ALL who relapse typically have a very poor prognosis, underscoring the need for more targeted therapies to combat the high toxicity and mortality associated with current T-ALL treatment.

Because normal immature T-cells and T-ALL blasts share common development and cell activation pathways, Nikolaus Trede, MD, PhD, Associate Professor of Pediatrics and investigator at the Huntsman

Cancer Institute at the University of Utah, and colleagues hypothesized that T-ALL treatments that specifically eliminate one may also target the other. To test their hypothesis, Dr. Trede's team turned to an entirely different species – zebrafish – to identify a compound that could pack an anti-leukemic punch.

"Zebrafish serve as an excellent model for many cancers, including leukemia, because the zebrafish and human genomes and immune systems share many similarities, making them easy targets for genetic modification to mimic human cancers," said Dr. Trede, the study's senior author.

Dr. Trede's team used a line of zebrafish they had previously created, in which immature T-cells were fluorescently labeled so they effectively "glowed" when present, to help identify whether any test compound eliminated those cells while ensuring that they did not affect any other cell types or compromise the overall health of the fish. They screened 26,400 molecules and identified the novel molecular compound Lenaldekar (LDK) as effective in eliminating immature zebrafish T-cells and targeting human T-ALL cell lines without causing major toxicity to other cell types.

After confirming LDK's effectiveness *in vitro*, the investigators then tested its efficacy in zebrafish and mouse models of human T-ALL. After a 14-day treatment period, researchers found that more than 60 percent of all zebrafish treated with LDK maintained long-term remission (more than nine months), while 100 percent of zebrafish treated with the control died by day 40. Similarly, in the mouse model, treatment with LDK significantly slowed disease progression without toxicity.

The team then examined LDK's effectiveness in treating cells taken directly from patients with other leukemias, namely chronic myeloid

leukemia (CML) and B-cell ALL (B-ALL), including those resistant to current therapies. After testing a number of patient samples, researchers found that LDK was active against the vast majority of primary leukemia samples, demonstrating its effectiveness beyond T-ALL.

In addition to demonstrating LDK's efficacy, investigators also discovered that the compound works differently from current leukemia treatments because it inhibits both an important signaling pathway that promotes the survival of leukemia cells and a pathway that controls the cell division process, disrupting the proliferation of leukemic cells and, in essence, leading to their self-induced death. Because of this unusual combination of effects, this study positions LDK as a more selective, less-toxic option than current therapies.

"This is the first successful approach using zebrafish larvae to identify molecules with potency against leukemia from a small molecular library containing compounds with unknown activity," said Dr. Trede. "We are encouraged by LDK's path from a virtual unknown to a potential powerhouse against leukemia, and we are working on discovery of LDK's cellular target, which may ultimately help convert the compound into a drug that can be used in patients with leukemia."

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