

Experimental drug shows promise for treatment-resistant leukemias

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Research in mice and human cell lines has identified an experimental compound dubbed TTT-3002 as potentially one of the most potent drugs available to block genetic mutations in cancer cells blamed for some forms of treatment-resistant leukemia.

Results of the research by Johns Hopkins Kimmel Cancer Center investigators, described March 6 in the journal *Blood*, show that two doses a day of TTT-3002 eliminated [leukemia](#) cells in a group of mice within 10 days. The treatment performed as well as or better than similar drugs in head-to-head comparisons.

More than 35 percent of [acute myeloid leukemia](#) (AML) patients harbor a mutation in the gene FMS-like tyrosine kinase-3 (FLT3). Normal FLT3 genes produce an enzyme that signals [bone marrow](#) stem cells to divide and replenish. But when FLT3 is mutated in some AML patients, the enzyme stays on permanently, causing rapid growth of leukemia cells and making the condition likely to relapse after treatment.

Many investigators are developing and testing drugs designed to block the FLT3 enzyme's proliferation, several of which are now in clinical trials. So far, their effectiveness has been limited, according to Donald Small, M.D., Ph.D., the Kyle Haydock Professor of Oncology and director of pediatric oncology at Johns Hopkins. Small led a team of researchers who originally cloned the FLT3 gene and linked it to leukemia a decade ago.

"We're very excited about TTT-3002, because it appears in our tests so far to be the most potent FLT3 inhibitor to date," says Small. "It showed activity against FLT3-mutated cells taken from patients and with minimal toxicity to normal [bone marrow cells](#), making it a promising new candidate for the treatment of AML."

In a series of experiments with the drug, Small,

postdoctoral fellow Hayley Ma, Ph.D., and others found that the amount of TTT-3002 needed to block FLT3 activity in human [leukemia cell](#) lines was six- to sevenfold lower than for the most potent inhibitor currently in clinical trials. TTT-3002 also inhibited proteins made by genes further down the FLT3 signaling pathway, including STAT5, AKT and MAPK, and showed activity against the most frequently occurring FLT3 mutations, FLT3/ITD and FLT3/D835Y. Many cancer drugs are currently ineffective against FLT3/D835Y mutations.

When the Johns Hopkins team tested the drug in a mouse model of leukemia, they found that it not only eliminated the presence of leukemic cells within 10 days of treatment but also that the mice lived an average of more than 100 days following treatment, to study completion, and resumed normal bone marrow activity. By contrast, mice treated with a placebo died an average of 18 days following treatment.

Additional studies found that TTT-3002 performed as well as sorafenib, another FLT3 inhibitor, in treating leukemic mice, and that the drug was toxic to leukemia cell samples taken from newly diagnosed and relapsed patients with AML but did not affect normal bone marrow [cells](#) taken from healthy donors.

A single dose of the medication caused more than 90 percent inhibition against FLT3 signaling that lasted for 12 hours, Small says.

Provided by Johns Hopkins University School of Medicine

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