

# Drug compound could be next-generation treatment for aggressive form of leukemia

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Herman Sintim, the Drug Discovery Professor of Chemistry in Purdue University's Department of Chemistry, is leading a team of researchers developing a series of drug compounds that have shown promise in treating acute myeloid leukemia, most notably in cases where patients have a recurrence of the fairly rare but aggressive blood cancer that is one of the most lethal cancers. Here, Sintim looks at a model of a molecule. Credit: (Purdue Research Foundation image/Hope Sale)

Researchers have been struggling for years to find a treatment for patients who have a recurrence of acute myeloid leukemia (AML), an aggressive blood cancer that is one of the most lethal cancers. About 19,520 new cases are diagnosed a year, and about 10,670 people a year die from it, according to the American Cancer Society.

Purdue University researchers are developing a series of drug [compounds](#) that have shown promise in treating such cases. About 30 percent of AML [patients](#) have a mutation caused by a kinase called FLT3, which makes the [leukemia](#) more aggressive. Inhibitors of FLT3, such as Radapt, approved last year by the U.S. Food and Drug Administration, have shown good initial response to treating leukemia. Gilteritinib, another FLT3 inhibitor, was recently approved toward the end of 2018. But AML patients on FLT3 inhibitor therapy often relapse because of secondary mutations in the FLT3 and existing treatments have not been fully successful in treating those cases.

Researchers on a team led by Herman O. Sintim, the Drug Discovery Professor of Chemistry in Purdue's Department of Chemistry, say they have developed a series of compounds that work not only on AML with common FLT3 mutation, but also drug-resistant AML harboring problematic mutations, such as the gatekeeper F691L mutation, which some leukemia patients who relapse harbor.

"These compounds have a great potential to be the next-generation AML therapeutics for relapsed patients who no longer respond to first- or second-generation FLT3 inhibitors," Sintim said.

The results of the study were published Friday in the journal *EBioMedicine*.

Results of the study are encouraging because, while advancements have been made in many other forms of cancer over the past three decades,

advancement for AML has been slow.

AML, which accounts for only about 1 percent of all cancers, occurs when blood cells fail to mature or differentiate and multiply unchecked, causing a lack of adequate oxygen-carrying red blood cells. AML is uncommon before the age of 45, but it does occur in children. The five-year survival rate is about 30 percent, and for patients over the age of 65, the five-year survival rate is less than 10 percent.

The compounds the Purdue researchers are studying, alkynyl aminoisoquinoline and alkynyl naphthyridine, have been successful in preclinical studies, Sintim said. "In mouse studies, almost no leukemia burden was visible after compound treatment for only a few weeks. Crucially this new class of FLT3 inhibitor also works against drug-resistant secondary mutations, such as the problematic F691L mutatio," Sintim said.

In the clinic, the goal is to reduce leukemia levels enough so that a patient can undergo a bone marrow transplant. Most often if the leukemia burden is not drastically reduced before [bone marrow transplant](#), there is a high likelihood that the AML will return.

Sintim said the compounds the researchers are developing have shown no signs of toxicity. Observations in clinical testing show that high doses of the compounds result in no weight loss, irritability or essential organs dysfunction. Another advantage of the compounds the Purdue researchers are developing is they can be taken orally, which makes it easier for patients to take at home compared with an injection.

Sintim said there's much still to be learned about AML.

"Acute myeloid leukemia is not caused by only one mutation. It's caused by many [mutations](#). What that means is that you might have an acute

myeloid leukemia patient who would have one type of a mutation and you could have another one with another type of mutation and you cannot give them the same drug. Even when a patient initially presents with one type of mutation, during treatment a new mutation could emerge" he said. "So to effectively treat a cancer you need to know what the aligning mutation is, this is what is called precision medicine; tailoring a drug to a particular disease driver."

**More information:** Amino alkynylisoquinoline and alkynyl naphthyridine compounds potently inhibit acute myeloid leukemia proliferation in mice, *EBioMedicine* (2019).

Provided by Purdue University

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