Researchers develop first-in-class inhibitors against key leukemia protein

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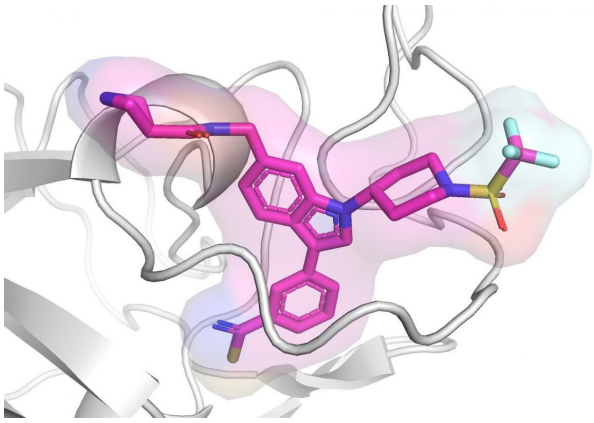

An X-ray crystallography image showing an ASH1L inhibitor developed at U-M in complex with the protein. Credit: Grembecka/Cierpicki Labs

The protein made by the ASH1L gene plays a key role in the development of acute leukemia, along with other diseases. The ASH1L protein, however, has been challenging to target therapeutically.

Now a team of researchers led by Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D., from the University of Michigan has developed first-in-class small molecules to inhibit ASH1L's SET domain—preventing critical molecular interactions in the development and progression of leukemia.

The team's findings, which used fragment-based screening, followed by medicinal chemistry and a structure-based design, appear in *Nature Communications*.

In mouse models of mixed lineage leukemia, the lead compound, known as AS-99, successfully reduced leukemia progression.

"This work points to a new, exiting avenue to develop new therapeutic agents against acute leukemia, as well as providing a new approach to further study the biological functions of ASH1L and its role in the development of the disease," says Grembecka, associate professor of pathology at Michigan Medicine and co-director of the developmental therapeutics program at the U-M Rogel Cancer Center.

The study was a close collaboration between her lab and the lab of co-senior author Cierpicki, an associate professor of biophysics and pathology.

More information: David S. Rogawski et al, Discovery of first-in-class inhibitors of ASH1L histone methyltransferase with anti-leukemic activity, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23152-6

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