Novel inhibitor discovered for B-cell lymphoma treatment

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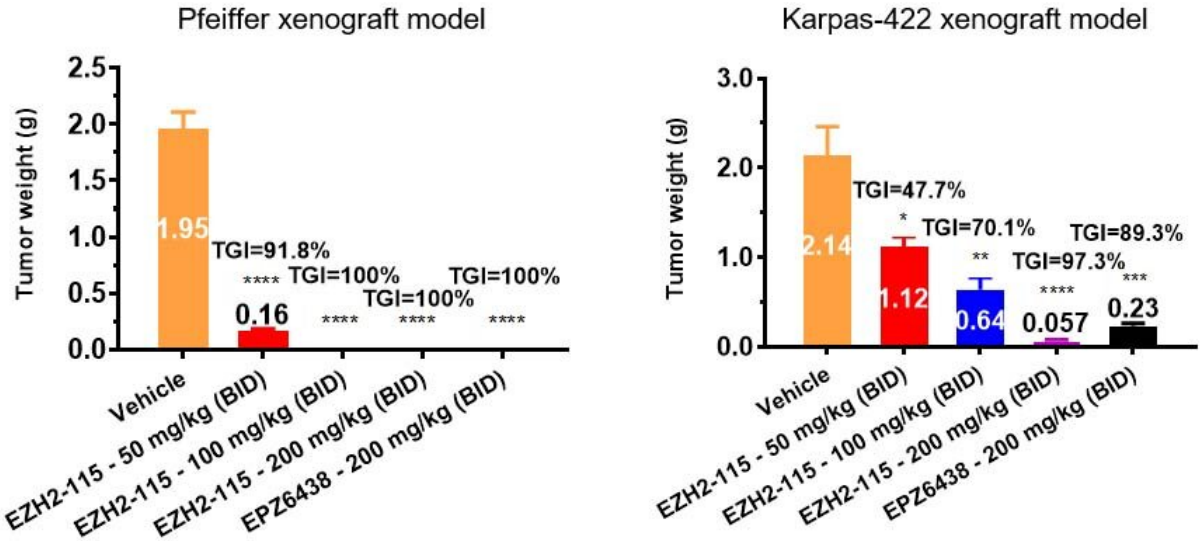

Anti-tumor efficacy evaluation of IHMT-EZH2-115 in xenograft mouse models. Credit: ZHOU Bin

A potent and selective enhancer of zeste homolog 2 (EZH_2) inhibitor IHMT-EZH_2-115 was recently discovered by researchers led by Prof. Liu Qingsong from the Hefei Institutes of Physical Science of the Chinese Academy of Sciences for the treatment of B-cell lymphomas.

EZH_2 is the enzymatic subunit of polycomb repressive complex 2. As a therapeutic target for the treatment of cancer, it has been extensively

studied. Overexpression or mutation of EZH_2 has been identified in hematologic malignancies and solid tumors. EPZ6438 (Tazemetostat) is the first selective inhibitor of EZH_2 wild-type and mutants approved by the Food and Drug Administration (FDA). Despite the clinical success, the diversity of EZH_2 inhibitors is still highly demanded for both the preclinical mechanistic and clinical pathological studies.

In this study, starting from EPZ6438 which exhibited anti-B-cell lymphoma efficacies in the preclinical models, the researchers obtained IHMT-EZH_2-115 using a focused medicinal chemistry approach guided by computer-aided drug design.

According to the biochemical assay, IHMT-EZH_2-115 was highly potent to both EZH_2 wild-type and mutants. Meanwhile, it showed high selectivity over a broad range of histone methyltransferases. Furthermore, the inhibitor exhibited excellent antiproliferative activities against cells carrying the heterozygous EZH_2 A677G, Y641F, Y641N, and Y641S mutations.

In vivo, IHMT-EZH_2-115 exhibited favorable pharmacokinetic characteristics for oral administration and demonstrated dose-dependent antitumor efficacies in two xenograft mouse models of diffuse large B-cell lymphoma cell lines harboring EZH_2 mutations, Pfeiffer (EZH_2 A677G) and Karpas-422 (EZH_2 Y641N).

These results indicate that IHMT-EZH_2-115 may be a potential clinical development candidate for the EZH_2 mutant driven tumors.

More information: Bin Zhou et al, Discovery of IHMT-EZH2-115 as a Potent and Selective Enhancer of Zeste Homolog 2 (EZH2) Inhibitor for the Treatment of B-Cell Lymphomas, *Journal of Medicinal Chemistry* (2021). DOI: 10.1021/acs.jmedchem.1c01154

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