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802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

A Novel and Potent EZH1/2 Dual Inhibitor, HM97662 Demonstrated a Wide Spectrum of Therapeutic Potential for Hematological Malignancies

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Chromatin remodeling is a crucial process for transcriptional regulation, of which dysregulation is often observed in various human cancers. The enhancer of zeste homolog 2 (EZH2) and its homolog EZH1 are catalytic components of polycomb repressive complex 2 (PRC2), which tri-methylate histone H3 at lysine 27 (H3K27me3) to repress transcription of their target genes. Hyperinduction of H3K27me3 mediated by EZH2 overexpression or EZH2 gain-of-function (GOF) mutation (e.g. Y641, A677, and A687) has been associated with the progression of hematological malignancies including B-cell lymphoma, T-cell lymphoma, and multiple myeloma. Hence, it has been suggested that suppressing PRC2 activity by EZH2 inhibition is a potential therapeutic target for hematological malignancies.

Although the methyltransferase activity of PRC2 is mainly contributed by EZH2, EZH1 also conducts a compensatory role to maintain tri-methylation of H3K27. Moreover, EZH1 directly binds to chromatin and modulates its condensation. Therefore, dual inhibition of EZH1 and EZH2 can give better effect than EZH2 inhibition alone in blocking PRC2 function as an anti-cancer therapy.

Herein, we presented a novel EZH1/2 dual inhibitor, HM97662, which simultaneously inhibited the methyltransferase activity of wild-type EZH1 as well as wild-type and GOF mutant EZH2 at nanomolar concentrations. SPR analysis of HM97662 on trimeric complexes (EZH1/EZH2, SUZ12, and EED) demonstrated that HM97662 binds both EZH1- and EZH2-PRC2 complexes. HM97662 potently repressed tri-methylation of H3K27 in KARPAS 422 DLBCL, HH PTCL, and MM.1S MM cell lines. Furthermore, HM97662 showed broader and stronger activities than EZH2 selective inhibitors in long-term proliferation assay against a variety of hematological cancer cell lines. HM97662 induced the differentiation of DLBCL to plasma cells with the increment of cell lineage specific markers (e.g. PRDM1 and CD38), and caused cell cycle G0/G1 arrest and apoptosis in KARPAS 422 DLBCL cells harboring EZH2 Y641N GOF mutation. Additionally, HM97662 increased mRNA expression of several target genes inducing cell cycle arrest and apoptosis in gene panel assay performed in HH PTCL cell line. Two cell cycle repressors, CDKN2A (p16) and CDKN1C (p57), and a pro-apoptotic marker, BTG-2, were significantly increased by HM97662. We further conducted a chromatin accessibility assay and identified that the chromatin structures of that genes were loosened and highly transcribed after the treatment of HM97662.

As a result, HM97662 showed potent antitumor activity in various hematological cell lines xenograft mouse models including B-cell lymphoma, T-cell lymphoma, and multiple myeloma (e.g. KARPAS 422, HuT-102, and MM.1S). Once daily oral dosing of HM97662 greatly inhibited tumor growth in a dose-dependent manner without significant clinical signs compared to the known EZH2 selective or EZH1/2 dual inhibitor.

In conclusion, the present preclinical studies demonstrated that HM97662, an EZH1/2 dual inhibitor, had a promising and wide spectrum of therapeutic potential for hematological malignancies. It is urgent to assess the effectiveness of HM97662 in further clinical trials.

Disclosures Jung: *Hanmi Pharm. Co., Ltd.:* Current Employment. **Byun:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Kim:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Han:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Lee:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Lee:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Park:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Ahn:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Kim:** *Hanmi Pharm. Co., Ltd.:* Current Employment. **Suh:** *Hanmi*

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