Antitumor Activity of Novel Reversible LSD1 Inhibitor in Preclinical Models of AML and SCLC

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Abstract

LSD1 overexpression is associated with poor prognosis in various cancers. LSD1-mediated epigenetic modifications is known to play a key role in the regulation of gene expression by removing the methyl groups from methylated lysine 4 and lysine 9 of histone H3. Alterations in histone modification lead to aberrant silencing of expression of multiple genes involved in tumor survival and in cell cycle. Moreover, epigenetic modifications plays a critical role in pathogenesis of various types of cancers such as acute myeloid leukemia (AML) or small cell lung cancer (SCLC). In this study, we have characterized typical compounds (HM97211, HM97278, HM97293) of HM97XX series as novel reversible LSD1 inhibitors, and assessed its potential as a novel therapy for SCLC and AML patients.

Biochemical and cell proliferation assays, immunoblotting, apoptosis analysis, and in vivo anti-tumor activity were carried out to validate LSD add an antitumor activity of HM97XX derivatives in AML and SCLC. HM97XX derivatives altered expression of various genes and induced differentiation and apoptosis, resulting in growth inhibition of leukemia and SCLC cells. Moreover, HM97XX derivatives significantly induced programmed cell death in AML and SCLC cells. Oral administration of HM97XX derivatives inhibited tumor growth in human AML and SCLC cell xenograft models. Efficacy of HM97XX derivatives was further evaluated as single therapy in SCLC cell model or in combination with FLT3 inhibitor in AML cell model. Collectively, these results suggest that novel LSD1 inhibitors of HM97XX derivatives could serve as effective therapeutic agents for cancer patients such as AML and SCLC.

Histone Modification and LSD1

In vitro Proﬁles of LSD1 Inhibitors

- In vitro Enzyme & Cell Activity

- Effect of HM97211 on Proliferation of SCLC Cell Lines

- Effect of HM97293 on Proliferation of AML Cell Lines

- Histone Methylation and PD Markers

- Histone Methylation and PD Marker Evaluation in SCLC

- Histone Methylation and Differentiation Marker in AML

- PK/PD Proﬁle in SCLC Xenograft Model

- Efficacy Xenograft Model

- Induction of Apoptotic Signaling

- Induction of Apoptosis in AML

- Induction of Apoptosis in SCLC

Conclusions

- HM97XX derivatives are novel reversible LSD1 inhibitors that effectively enhance not only global methylation of H3K4 but also apoptosis induction in SCLC and AML.

- In animal of PD profile, LSD1 inhibition by HM97XX derivatives revealed the important role of LSD1 inhibition in neuroendocrine-association transcription of SCLC.

- Oral administration of HM97293 showed strong antitumor activities in SCLC cell xenograft models without significant body weight loss. Combination treatment of HM97293 and HM43239 (FLT3 inhibitor) enhanced anti-tumor efficacy in MV-4-11 cell xenograft model.

- Clinical candidate of HM97XX derivatives will be selected soon and GLP toxicity study will begin in the second half of 2019.

References

1. Cancer Cell. 2015, 28(1), 57-69
2. Cell Proteomics. 2016, 15, 125H-1259
4. J. Nutr. Pharm. 2015, 18, 1150-1157