



The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY**801.GENE THERAPIES****Repressing HIF-1 α -Induced HDAC9 Contributes to the Synergistic Effect of Venetoclax and Menin Inhibitor in KMT2Ar AML**Qing Ling¹¹Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang, PR China., Hangzhou, China

Background: MLL-rearranged acute myeloid leukemia (MLLr-AML) is one aggressive subtype of AML, and is conferred one extremely poor prognosis under the current therapeutic strategy. Up to now, it still lacked one effective treatment to maintain the long-term survival for patients with MLLr-AML, while the developments of targeted therapy brought hopes. At present, the star drug BCL-2 inhibitor Venetoclax combined with Azacitidine (AZA) or low-dose Cytarabine (LDAC) has become the first-line scheme for elderly AML, which is not beneficial for MLLr-AML patients. So we are committed to finding a more suitable partner for VEN because MLLr-AML is very sensitive to VEN in vitro studies. The MLL-menin complex is crucial for maintaining MLLr-AML, and the research and application of MLL-menin inhibitors (MEN1i) is currently one of the hotspots in the AML field. Therefore in this study, we aimed to uncover the synergistic effect and mechanism of MEN1i combined with Venetoclax in treating MLLr-AML.

Methods: Cell culture and transfection, Cell proliferation, apoptosis and Cell cycle assay, Quantitative RT-PCR, and Western blotting analysis were used to explore biological phenotypes. RNA-seq profiling was performed for DMSO, VEN, MEN1i, and combination of VEN and MEN1i groups in three MLLr-AML cell lines MV4-11, MOLM13, THP-1. Bioinformatic tools were used for differential analysis.

Results: MLLr-AML cells were sensitive to VEN or MEN1i monotherapy, and the combination of two drugs had a strong synergistic effect in vitro and in vivo. Furthermore, we found that combination of VEN and MEN1i significantly enhanced apoptotic induction to influence the MLLr-AML survival. To uncover the synergetic mechanism of VEN and MEN1i, we displayed RNA-Sequencing for DMSO, VEN, MEN1i, and combination of VEN and MEN1i groups in three MLLr-AML cell lines MV4-11, MOLM13, THP-1. Finally we found that repressing HIF-1 α -induced HDAC9 contributes to the synergistic effect of Venetoclax and MEN1i in MLLr-AML.

Conclusion: VEN combined with MEN1i had a strong synergistic effect in the treatment of MLLr-AML. Repressing HIF-1 α -induced HDAC9 contributes to the synergistic effect of Venetoclax and MEN1i in MLLr-AML.

Disclosures No relevant conflicts of interest to declare.

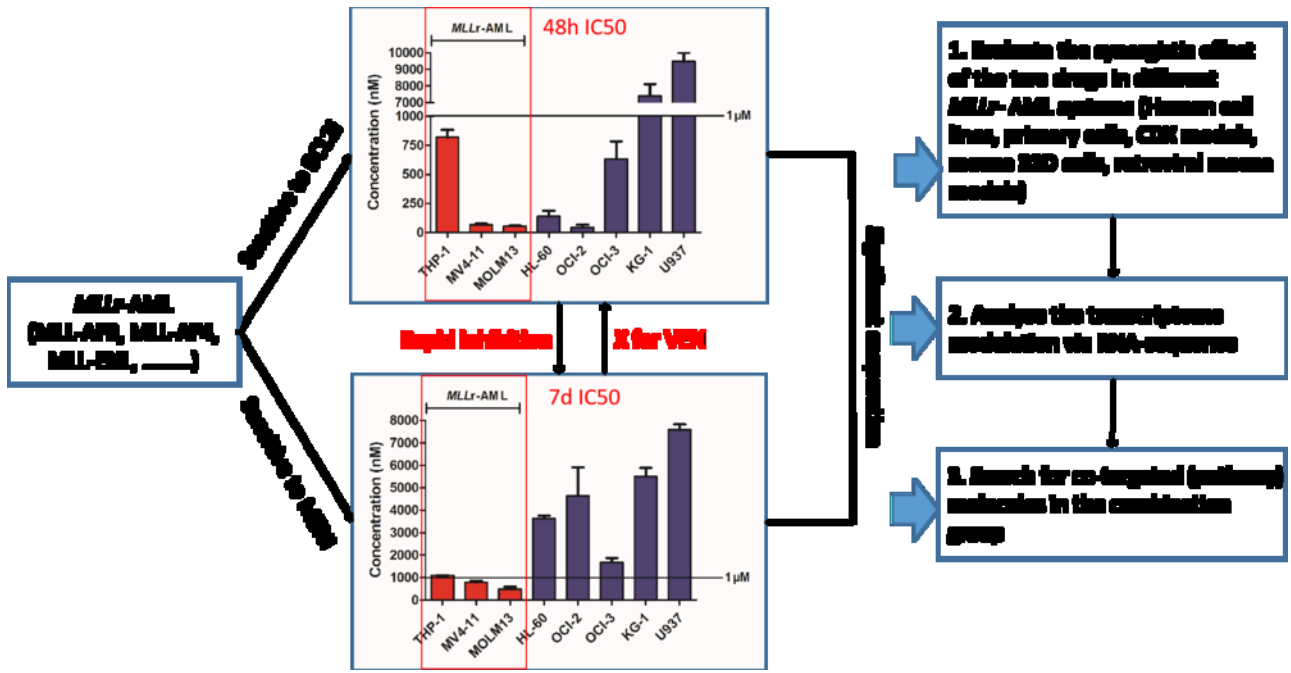


Figure 1

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