(PF463) CD71-TARGETED AND ROS-RESPONSIVE MICELLES FOR HOMOHARRINGTONINE DELIVERY TO ENHANCE THERAPEUTIC EFFICIENCY AGAINST FLT3-ITD ACUTE MYELOID LEUKEMIA

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

The FLT3-ITD (FMS-like tyrosine kinase 3- internal tandem duplication) subtype of acute myeloid leukemia (AML) is associated with poor clinical outcomes. Homoharringtonine (HHT), a natural protein inhibitor, has shown strong activity against FLT3-ITD AML. However, its clinical use is limited by rapid clearance and systemic toxicity.

Aims

To address these limitations, a CD71-targeted, ROS-responsive micelle (TDTP/HHT) was developed for precise and efficient HHT delivery.

Methods

CD71 expression was assessed in AML patient samples and cell lines. TDTP/HHT was prepared by self-assembly using a D-peptide ligand (^{D}T7) for CD71 targeting and a ROS-cleavable linker for stimuli-responsive drug release. Cellular uptake, cytotoxicity and signaling pathway inhibition were evaluated in vitro across AML cell lines with distinct FLT3 statuses. The therapeutic efficacy of TDTP/HHT was further validated in a disseminated AML xenograft mouse model.

Results

Cytotoxicity analysis revealed that FLT3-ITD AML is intrinsically sensitive to HHT. Analysis of patient samples and cell lines revealed high CD71 expression and elevated ROS levels in AML, most predominantly in the FLT3-ITD subtype. The designed TDTP/HHT showed prolonged circulation time, ROS-responsive drug release, and stable targeting capacity. It did not compete with endogenous transferrin for binding sites but instead demonstrated transferrin-promoted cellular uptake. Both *in vitro* and *in vivo* studies confirmed that TDTP/HHT significantly inhibited the growth of FLT3-ITD AML cells. Mechanistically, TDTP/HHT suppressed multiple key downstream signaling proteins of FLT3-ITD.

Summary/Conclusion

This study presents a novel targeted nanodrug that exploits the intrinsic HHT sensitivity of FLT3-ITD AML cells and their characteristic high CD71 expression and elevated ROS levels. By enabling specific intracellular accumulation of HHT and multitarget inhibition of FLT3-ITD signaling pathways, this system achieves superior anti-AML efficacy both *in vitro* and *in vivo*, offering strong potential for future clinical translation.