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POSTER ABSTRACTS

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Novel Orally Available Degrader to Target Lck in T-Cell Acute Lymphoblastic Leukemia

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Background
T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive blood cancer that develops from abnormal growth of immature T-cell progenitors and constitutes about 15% of all pediatric ALL cases. Despite an overall survival rate of 80% in pediatric T-ALL patients, 20% of patients eventually experience relapse or succumb to refractory disease. Therefore, novel therapies for refractory/relapsed T-ALL patients are urgently needed, and they are currently being developed in clinical and preclinical studies. Based on recent literature, the over-activation of preTCR-LCK signaling has been revealed as a highly effective therapeutic target in T-ALL, with LCK being identified as a therapeutic vulnerability in ~44% of T-ALL cases. The LCK inhibitor, dasatinib, exhibited an anti-leukemia effect in a subset of T-ALL cases but was transient in most cases. Therefore, the development of new agents capable of sustaining inhibition of LCK signaling is needed.
Method
To validate the effects of the LCK degrader UBX-363, both in vitro and in vivo tests were conducted using dasatinib-sensitive HSB-2 cells (which have higher LCK activity compared to other T-ALL cell lines) and dasatinib-insensitive CCRF-CEM cells. UBX-363 is designed to target LCK through ubiquitin-proteasome system-mediated degradation. Cell proliferation was assessed using detection methods such as the CellTiter-Glo assay, and the degradation activity of the LCK protein in the tested cell lines was evaluated by immunoblotting. To examine the in vivo antitumor effects of UBX-363 or dasatinib, we performed HSB-2 and CCRF-CEM xenograft murine models. CB17/SCID mice were subcutaneously inoculated with $1x10^{7}$ HSB-2 and $5x10^{6}$ CCRF-CEM cells. UBX-363 was orally administered at doses of 0.2, 1, or 5 mg/kg (for HSB-2) and 2.5, 5, or 10 mg/kg (for CCRF-CEM), while dasatinib was orally administered at doses of 5 mg/kg (for HBS-2) and 10 mg/kg (for CCRF-CEM) once daily for 12 days.
Results
UBX-363 showed superior degradation activity against LCK proteins in the subnanomolar or single-digit nanomolar range of half-maximal degradation concentration in HSB-2 and CCRF-CEM cell lines (0.478 nM and 1.502 nM, respectively). In comparison to the LCK inhibitors dasatinib (~0.307 nM) and saracatinib (~17.41 nM), UBX-363 (~0.121 nM) demonstrated slightly superior anti-proliferative efficacy in HSB-2 cells. In CCRF-CEM cells, UBX-363 exhibited prominent anti-proliferative activity at lower treatment concentrations compared to the other LCK inhibitors (UBX-363: 11.12 nM, dasatinib: 3483 nM, saracatinib: 4383 nM). Furthermore, UBX-363 demonstrated faster tumor regression than dasatinib in the HSB-2 xenograft models. In the CCRF-CEM xenograft model, UBX-363 effectively suppressed tumor growth in a dose-dependent manner, whereas dasatinib showed no inhibitory effect on tumor growth. After 12 days of UBX-363 dosing on CCRF-CEM xenograft mice, the levels of LCK protein in tumor tissue significantly reduced. The degradation activity of UBX-363 on LCK showed about 100% reduction at dosages of 5 mg/kg and 10 mg/kg on day 12.
Conclusion
UBX-363 demonstrated strong anti-proliferative and anti-tumor effects, as well as degradation activity of LCK, in both in vitro and in vivo models of T-ALL. These results highlight UBX-363 as a promising therapeutic agent for LCK-activated T-ALL. In the future, we will conduct additional research to explore the advantages of this degrader, such as its ability to disrupt scaffolding of LCK, over LCK small molecule inhibitors.

Disclosures No relevant conflicts of interest to declare.

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