#7076 Discovery of highly potent and selective KAT6A degraders that demonstrates robust anti-tumor activities in preclinical studies

Hanyu Wang, Lei Jiang, Youxi Chen, Baoying Cheng, Yuyao Zhang, Nianfeng Huang, Fan Yang, Feng Zhou
Atheron Therapeutics (Shanghai), Ltd

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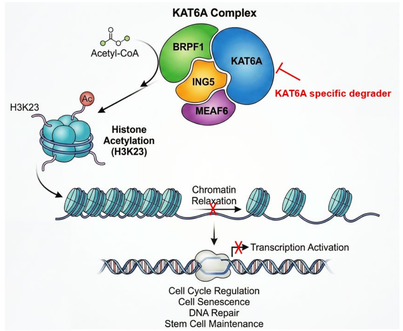
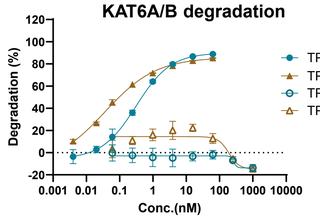
Introduction

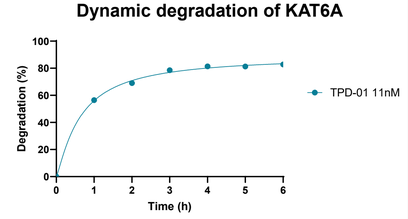
- KAT6A, a member of the MYST family of histone acetyltransferases, regulates gene transcription through acetylating histone H3K23 and thereby participates in multiple cellular processes. Amplification or overexpression of KAT6A have been observed in various cancers.
- KAT6A/6B inhibitor PF-07248144 demonstrated anti-tumor activity in phase 1 clinical studies, but also exhibited hematologic dose-limiting toxicities, potentially due to the simultaneous inhibition of KAT6A/6B.
- Here, we identified highly potent and selective KAT6A degraders that block downstream signaling by specific degradation of KAT6A, resulting in robust anti-tumor activities. Compared with KAT6A/6B inhibitor PF-07248144, KAT6A degraders exhibited reduced activity in preclinical hematotoxicity assays, suggesting a lower risk of hematotoxicity.

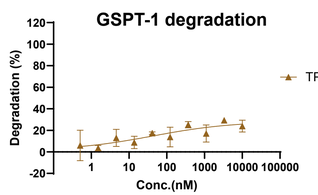


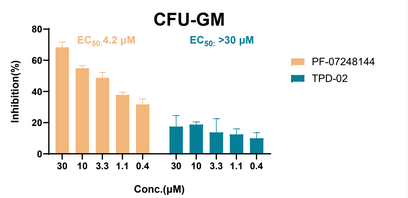
In vitro potency of KAT6A degraders

KAT6A degrader	HeLa KAT6A HiBiT DC_{50}(nM)	HeLa KAT6B HiBiT DC_{50}(nM)	Ternary complex formation EC_{50}(nM)
TPD-01	0.5	>1000	0.6
TPD-02	0.1	>1000	0.1



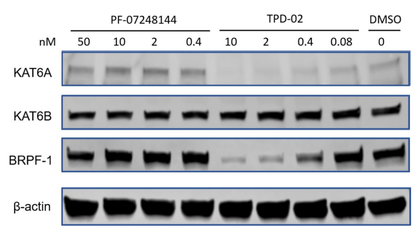


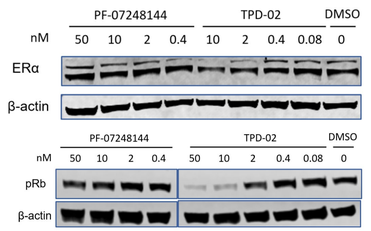




- KAT6A degraders TPD-01 and TPD-02 potently and rapidly induced the degradation of KAT6A, but not KAT6B, suggesting a potential reduction in hematologic toxicity risk.

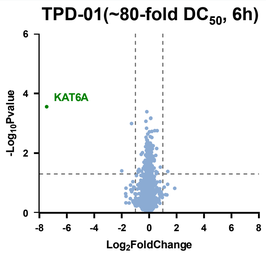
The effect of KAT6A degraders on downstream signaling

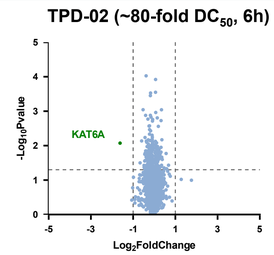




- Compared with PF-07248144, degraders specifically induced the degradation of KAT6A and the complex scaffold protein BRPF1 in ZR-751 (24h), further down-regulated the expression of ER and downstream signaling pRb (72h).

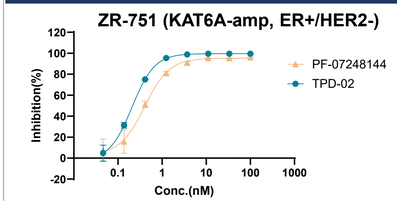
Selectivity of KAT6A degraders

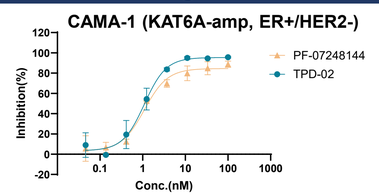


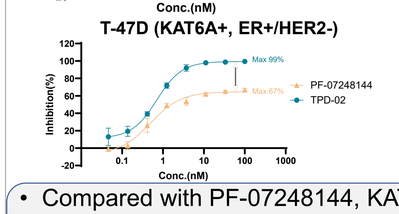


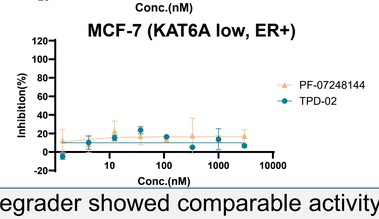
- Both of KAT6A degraders demonstrated good selectivity in ZR-751 cells in proteomic studies.

Anti-proliferation activity of KAT6A degraders



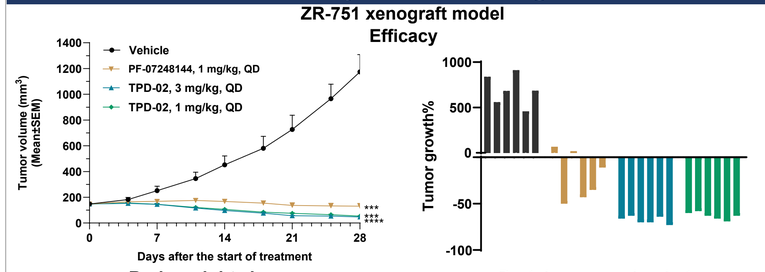


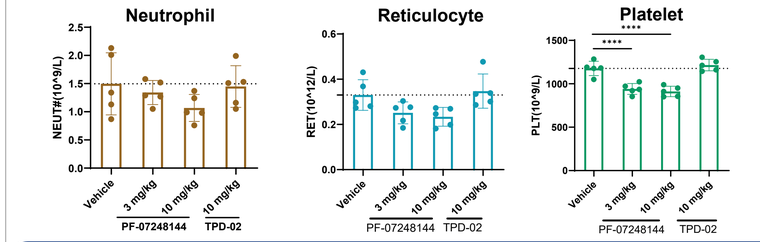




- Compared with PF-07248144, KAT6A degrader showed comparable activity in KAT6A-amplified cell lines. Moreover, it exerted a more profound inhibitory effect in KAT6A-expressing T-47D cells, potentially due to the degradation-mediated blockade of the non-enzymatic functions of KAT6A.

In vivo efficacy of KAT6A degraders





- KAT6A degrader was well tolerated and exhibited robust anti-tumor efficacy in the ZR-751 model, with reduced protein levels of KAT6A and ER observed in a satellite group for PD study.
- KAT6A degrader showed potential for lower bone marrow toxicity *in vivo* compared to PF-07248144.

Summary

- Highly potent and specific KAT6A degraders are identified and demonstrate robust anti-tumor efficacy *in vitro* and *in vivo*.
- Compared with KAT6A/B inhibitor PF-07248144, KAT6A degraders drive deeper anti-tumor response and decrease the risk of hematotoxicity via a distinct mechanism, supporting their potential as single agents or in combination with SOC therapy.
- IND filling is expected to be achieved in 2026 H2.

Contact: BD@atheronmed.com