Identification of a Novel KAT6A/B Inhibitor with Enhanced Antitumor Activity and Reduced Hematologic Toxicity

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Background:

KAT6A/B are promising therapeutic targets in breast cancer. However, Phase I data of PF-07248144 revealed significant treatment-related neutropenia (≥ Grade 3 in 38.3% of patients), including Grade 4 events, which emerged as the primary dose-limiting toxicity. To address this challenge, this project focuses on developing highly selective KAT6A/B inhibitors with a "fast-on, fast-off" pharmacokinetic profile to maximize antitumor activity while mitigating hematopoietic toxicity.

Methods:

Compound cytotoxicity was evaluated in ZR-75-1 cells using the CellTiter-Glo assay. *In vitro* inhibitory activity against KAT family acetyltransferase was assessed via a radiolabeled acetyl-CoA-based assay. *In vivo* efficacy was tested in three models: the ZR-75-1 xenograft model, a fulvestrant and cyclin-dependent kinase 4 and 6 inhibitors resistant (CDK4/6i-resistant) breast cancer patient-derived xenograft (PDX) model and the T47D model. H3K23 acetylation inhibition was analyzed via Western blot.

Results:

HLX97 demonstrated more potent KAT6A/B inhibition and improved selectivity over KAT5/7/8, with cytotoxicity mechanistically linked to H3K23 acetylation suppression. *In vivo*, HLX97 displayed dose-dependent antitumor efficacy in the ZR-75-1 xenograft model and the PDX breast cancer model. In T47D model, HLX97 demonstrated statistically significant synergistic effects with fulvestrant, palbociclib, and their combination. Notably, HLX97 showed markedly reduced hematologic toxicity in three independent efficacy studies, likely attributable to its relatively rapid *in vivo* clearance—a property intentionally prioritized during candidate screening to differentiate it from other candidates. HLX97 displayed no off-target effects in WuXi Mini 44 safety panel at 10 μM.

Conclusions:

HLX97 represents a best-in-class KAT6A/B inhibitor with optimized efficacy and safety profiles. An Investigational New Drug (IND) application is anticipated to be submitted by the end of 2025.

HLX97 Demonstrated Superior Enzymatic Inhibition and Enhanced Selectivity Profile Versus Benchmark

KAT member	Benchmark	Folds relative to KAT6A/KAT6B	HLX97	Folds relative to KAT6A/KAT6B
KAT6A	5.4	1.0x/0.5x	2.6	1.0x/0.6x
KAT6B	11.0	2.0x/1.0x	4.6	1.8x/1.0x
KAT5	625.6	115.9x/56.9x	5578.5	2145.6x/1212.7x
KAT7	71.5	13.2x/6.5x	140.8	54.2x/30.6x
KAT8	103.2	19.1x/9.4x	593.0	228.1x/128.9x

Table 1. IC_{50} (nM) of HLX97 and benchmark in KAT5/KAT6A/KAT6B/KAT7/KAT8 enzymatic assays, with corresponding selectivity ratios relative to KAT6A and KAT6B.

HLX97 Exhibited Enhanced Cellular Activity in H3K23 Acetylation-Inhibition and Cytotoxicity Assays

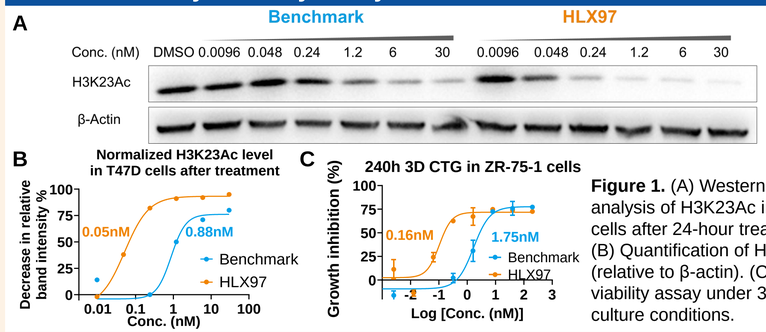


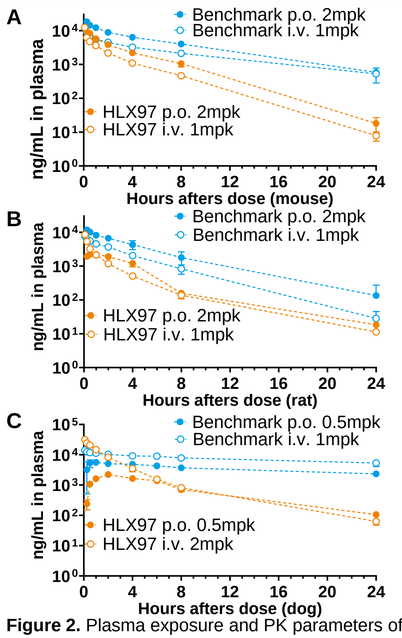
Figure 1. (A) Western blot analysis of H3K23Ac in T47D cells after 24-hour treatment. (B) Quantification of H3K23Ac (relative to β-actin). (C) Cell viability assay under 3D cell culture conditions.

HLX97 Demonstrated Promising ADMET Profiles

Kinetic solubility (pH 7.4)	>90 μg/mL	Caco-2 Permeability	>8 ×10^{-6} cm/s
hERG	>30 μM	CYPs (1A2, 2C9, 2C19, 2D6, 3A-M) IC_{50}	All >30 μM
Mini-Ames	Negative	WuXi Mini 44 safety panel	0 hit @ 10 μM

Table 2. Summary of key ADMET properties of HLX97.

HLX97 Showed Faster Metabolic Clearance in Mouse, Rat, and Dog



Route	IV	PO
Dose (mpk)	1	2
CL (L/h/kg)	0.052	-
V_{ss} (L/kg)	0.17	-
$T_{1/2}$ (h)	2.70	2.72
C_{max} (ng/mL)	-	9381
AUC_{last} (h*ng/mL)	19299	32848
AUC_{0-inf} (h*ng/mL)	19330	32925
F (%)	-	85.2

Route	IV	PO
Dose (mpk)	1	2
CL (L/h/kg)	0.101	-
V_{ss} (L/kg)	0.26	-
$T_{1/2}$ (h)	3.80	3.31
C_{max} (ng/mL)	-	2284
AUC_{last} (h*ng/mL)	10187	11184
AUC_{0-inf} (h*ng/mL)	10249	11273
F (%)	-	55.0

Route	IV	PO
Dose (mpk)	2	0.5
CL (L/h/kg)	0.035	-
V_{ss} (L/kg)	0.10	-
$T_{1/2}$ (h)	4.03	5.13
C_{max} (ng/mL)	-	2237
AUC_{last} (h*ng/mL)	59848	18317
AUC_{0-inf} (h*ng/mL)	60221	19109
F (%)	-	127

Figure 2. Plasma exposure and PK parameters of HLX97 in mouse (A), rat (B), and dog (C) after single dose.

HLX97 Demonstrated Potent Antitumor Efficacy in the ZR-75-1 ERα+ and a Fulvestrant and CDK4/6i-resistant PDX Breast Cancer Model

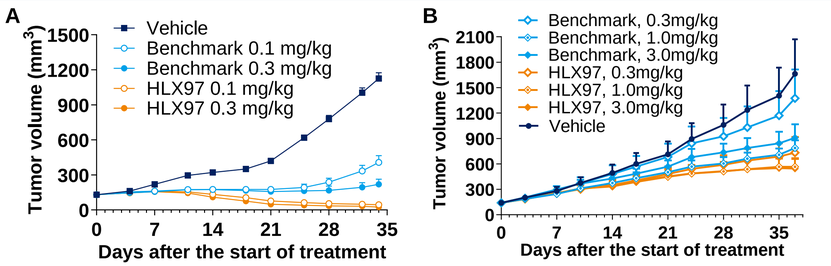


Figure 3. Efficacy of HLX97 compared to benchmark in the ZR-75-1 ERα+ breast cancer model (A: p.o. QD x 34 days), and a fulvestrant/CDK4/6i-resistant breast cancer PDX model (B: p.o. QD x 37 days).

HLX97 Synergized with Fulvestrant/Palbociclib in the T47D Model

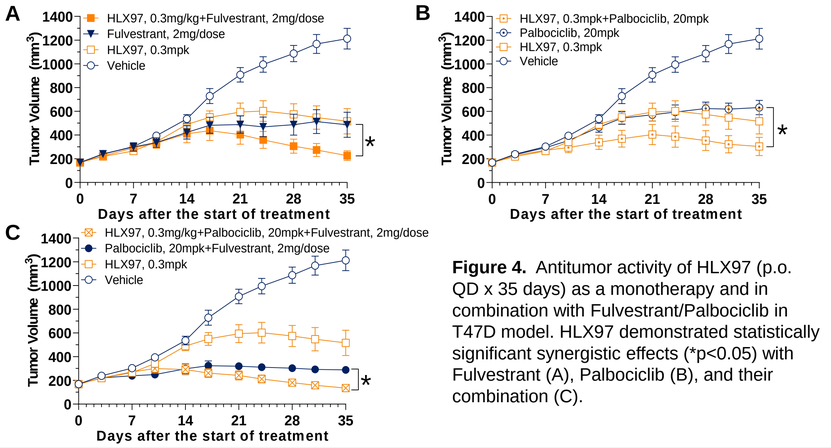


Figure 4. Antitumor activity of HLX97 (p.o. QD x 35 days) as a monotherapy and in combination with Fulvestrant/Palbociclib in T47D model. HLX97 demonstrated statistically significant synergistic effects (*p<0.05) with Fulvestrant (A), Palbociclib (B), and their combination (C).

HLX97-treated Cohorts Exhibited Reduced Hematological Toxicity Relative To Benchmark in All Three Tested Models

Treatment	Model 1: ZR-75-1				Model 2: PDX				Model 3: T47D			
	Dose (mpk)	TGI (%)	↓WBC# (%)	↓Lym# (%)	Dose (mpk)	TGI (%)	↓WBC# (%)	↓Lym# (%)	Dose (mpk)	TGI (%)	↓WBC# (%)	↓Lym# (%)
Benchmark	0.1	72	19	3	0.3	19	29	47	0.3	50	28	43
	0.3	91	31	24	1	58	54	64				
HLX97	0.1	109	15	3	0.3	61	0.4	10	0.3	67	7	13
	0.3	111	23	15	1	72	32	51				

Table 3. Treatment-associated reductions in leukocyte and lymphocyte in three efficacy studies.

After 5 weeks treatment, HLX97 demonstrated superior tumor growth inhibition (TGI%) compared to benchmark. At comparable TGI% levels, HLX97-treated cohorts exhibited reduced hematological toxicity.

Disclosures: LR, CY, ZX, TX, JC, LZ, YH, ZQ, HL, YW, YJ, YX, MZ, ZY and HC are employees of Henlius.

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