First-in-class potent and selective oral KAT6A degrader development candidate, PRT13722, drives complete tumor regressions as a monotherapy with an improved preclinical hematological safety profile

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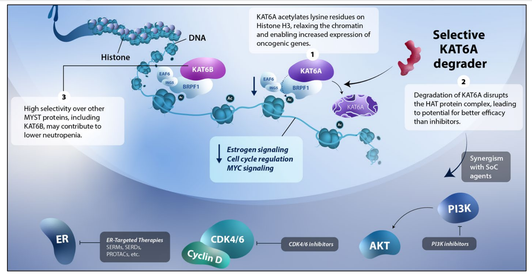
Prelude THERAPEUTICS

#5793

KAT6A Degradation As a Novel Therapeutic Modality for Cancer



- MYST proteins like KAT6A, its paralog KAT6B, and KAT7 are histone acetyltransferases (HAT) that epigenetically regulate chromatin accessibility.[1-2]
- KAT6A is highly expressed in breast cancer and is associated with cancer growth[1-2] via catalytic and non-catalytic functions.[4-5]
- Dual KAT6A/B inhibition is a clinically-validated approach, achieving promising efficacy in ER+/HER2- breast cancer patients and currently under Phase 3 clinical evaluation, albeit with on-target safety considerations like neutropenia.[3,8]
- KAT6A is the dominant cancer-driving paralog, while MYST proteins co-regulate normal hematopoiesis, which may have safety implications for inhibitors co-targeting KAT6B/KAT7.[6]
- KAT6A, mutually exclusive from KAT6B, interacts with a HAT complex to enhance and define its gene regulation, and expression of complex proteins correlate with KAT6A cancer dependency.[1,7]
- Unlike the expanding field of dual KAT6A/B and triple KAT6/7 inhibitors, targeted protein degradation is a highly differentiated approach to improve KAT6A selectivity while disrupting the KAT6A protein complex to drive deeper pathway suppression and efficacy.[7]
- PRT13722, a KAT6A-selective degrader development candidate, is shown herein and demonstrates differentiated preclinical efficacy and safety when compared to a dual KAT6A/B inhibitor, prifetrastat.

**When denoted with an asterisk, PRT13722* indicates data shown is with the racemic mixture of PRT13722.*

Results – *In Vitro*

Table 1. Profile of KAT6A-Selective Degrader Candidate PRT13722

Assay	PRT13722	prifetrastat
KAT6A HiBiT nM DC_{50}	0.3	-
KAT6B HiBiT nM DC_{50} (D_{max})	>999 (<18%)	-
KAT5, KAT7, KAT8 degradation nM DC_{50} (D_{max})	>999 (<22%)	-
T47-D CTG nM EC_{50} (E_{max})*	0.3 (95%)	0.7 (61%)
T47-D *in vivo* efficacy (TGI at 1 mg/kg, PO, QD; Day 42)	102%	76%
Mouse plasma C_{ave} µM at similar TGI*	0.09	5.5
Mouse, rat, dog, cyno F%*	69, 23, 38, 32	-
CYP inhibition panel, hERG inhibition (µM)	All >30, >30	-

Figure 1. PRT13722 is a Potent and Highly Selective KAT6A Degrader

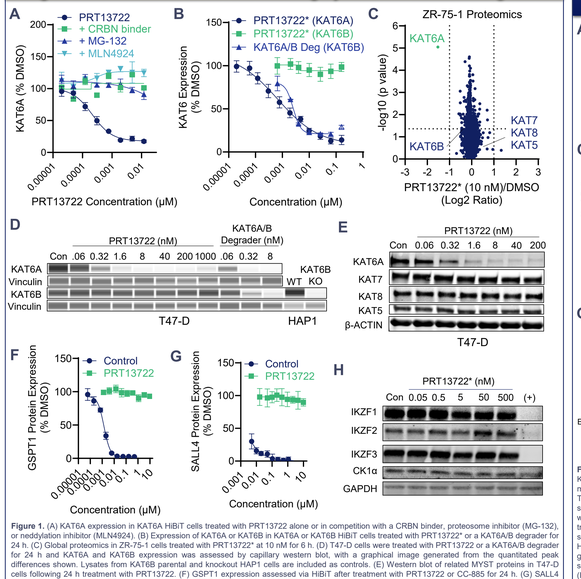


Figure 1. (A) KAT6A expression in KAT6A HiBiT cells treated with PRT13722 alone or in competition with a CRBN binder, proteosome inhibitor (MG-132), or neddylation inhibitor (MLN4924). (B) Expression of KAT6A or KAT6B in KAT6A or KAT6B HiBiT cells treated with PRT13722* or a KAT6A/B degrader for 24 h. (C) Global proteomics in ZR-75-1 cells treated with PRT13722* at 10 nM for 6 h. (D) T47-D cells were treated with PRT13722 or a KAT6A/B degrader for 24 h and KAT6A and KAT6B expression was assessed by capillary western blot, with a graphical image generated from the quantitated peak differences shown. Lysates from KAT6B parental and knockout HAP1 cells are included as controls. (E) Western blot of related MYST proteins in T47-D cells following 24 h treatment with PRT13722. (F) GSPT1 expression assessed via HiBiT after treatment with PRT13722 or CC-885 for 24 h. (G) SALL4 expression assessed via HTRF after treatment with PRT13722 or CC-885 for 24 h. (H) Expression of additional CRBN neosubstrates after treatment with PRT13722* for 24 h, compared to a positive control (+) (CC-885, Pomalidomide).

Figure 2. PRT13722 Drives Superior Depth and Breath of Anti-Cancer Activity in HR+/HER2- Breast Cancer Compared to prifetrastat

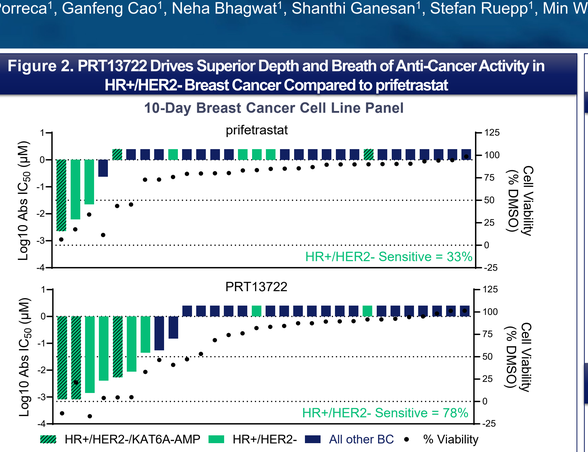


Figure 2. A panel of 29 breast cancer cell lines were assessed for anti-proliferative activity of prifetrastat and PRT13722 head-to-head in 10-day CTG assays up to 2.5 µM. Bars represent potency and black dots represent cell viability reduction.

Figure 3. PRT13722 Has Potent Anti-Cancer Activity and Synergy with Endocrine and CDK4/6-Targeted Therapies in Breast Cancer Cells

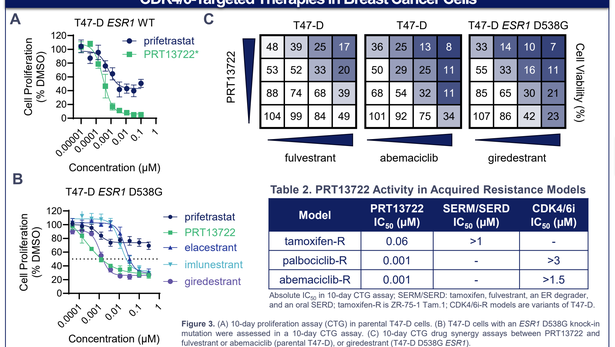


Figure 3. (A) 10-day proliferation assay (CTG) in parental T47-D cells. (B) T47-D cells with an *ESR1* D538G knock-in mutation were assessed in a 10-day CTG assay. (C) 10-day CTG drug synergy assays between PRT13722 and fulvestrant or abemaciclib (parental T47-D), or giredestrant (T47-D D538G *ESR1*).

Table 2. PRT13722 Activity in Acquired Resistance Models

Model	PRT13722 IC_{50} (µM)	SERM/SERD IC_{50} (µM)	CDK4/6i IC_{50} (µM)
tamoxifen-R	0.06	>1	-
palbociclib-R	0.001	-	>3
abemaciclib-R	0.001	-	>1.5

Absolute IC_{50} in 10-day CTG assay; SERM/SERD: tamoxifen, fulvestrant, an ER degrader, and an oral SERD; tamoxifen-R is ZR-75-1 Tam.1; CDK4/6i-R models are variants of T47-D.

Figure 4. PRT13722, But Not KAT6A/B Inhibitors, Disrupt KAT6A Complexes, Inducing Deeper Molecular Perturbations in Breast Cancer Cells

Figure 4. (A) Graphical representation of proposed KAT6A degrader, but not KAT6A/B inhibitor, effect on the KAT6A multiprotein complex. (B) T47-D cells were treated with PRT13722 or prifetrastat for 72 h and probed for markers of degradation and inhibition target engagement by western blot. (C) Cell cycle analysis performed in T47-D cells after treatment with indicated compounds. (D) Induction of senescence was assed by β-galactosidase staining in CAMA-1 cells treated (100 nM prifetrastat, 10 nM PRT13722) for 12 days. (E) Induction of apoptosis was kinetically assessed at 40 nM in ZR-75-1 cells by Incucyte® Annexin V Red assay. (F) ZR-75-1 cells were treated for 72 h with PRT13722, and protein expression was measured by western blot. (G-I) Using T47-D samples collected in parallel from the study shown in panel B, bulk RNA-seq and ATAC-seq was performed. (G) Hallmark GSEA from RNA-seq data was then performed on the 5 nM PRT13722 samples versus DMSO using genes ranked by sign(log2FC) × -log10(p value). Pathways shown met p value ≤ 0.05. (H) Integrated RNA+ATAC-seq analysis (PRT13722 5 nM vs prifetrastat 50 nM) showing genes significant in both RNA-seq and ATAC-seq (FDR < 0.05 in both assays) and classified as concordant if RNA and ATAC changed in the same direction and discordant if they changed in opposite directions. (I) Curated integrated heatmap showing RNA log2FC and ATAC log2FC versus DMSO for selected canonical genes. Darker colors represent deeper molecular changes.

Results – *In Vivo*

Figure 5. PRT13722* Achieves Selective KAT6A Degradation and Target Engagement *In Vivo*

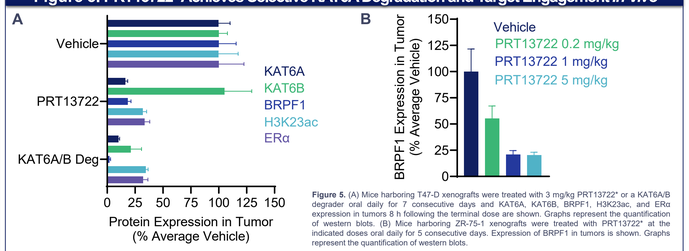


Figure 5. (A) Mice harboring T47-D xenografts were treated with 3 mg/kg PRT13722* or a KAT6A/B degrader oral daily for 7 consecutive days and KAT6A, KAT6B, BRPF1, H3K23ac, and ERα expression in tumors 8 h following the terminal dose are shown. Graphs represent the quantification of western blots. (B) Mice harboring ZR-75-1 xenografts were treated with PRT13722* at the indicated doses oral daily for 5 consecutive days. Expression of BRPF1 in tumors is shown. Graphs represent the quantification of western blots.

Figure 6. PRT13722* Monotherapy Drives Deep and Complete *In Vivo* Tumor Regressions in Multiple KAT6A-Amplified Breast Cancer Xenografts

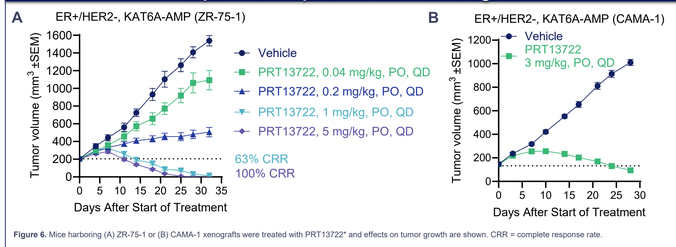


Figure 6. Mice harboring (A) ZR-75-1 or (B) CAMA-1 xenografts were treated with PRT13722* and effects on tumor growth are shown. CRR = complete response rate.

Figure 7. PRT13722 Monotherapy Safely Drives Deep and Durable *In Vivo* Tumor Regressions in Breast Cancer Xenografts with Superior Efficacy and Pharmacology Than prifetrastat

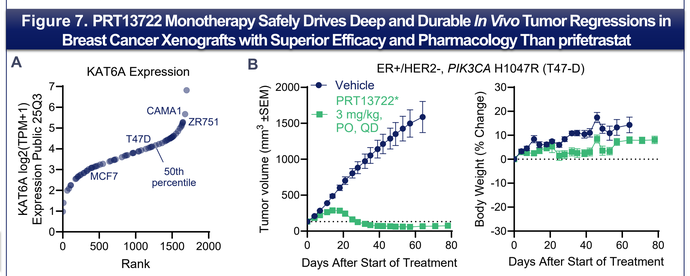


Figure 7. (A) Representation of KAT6A mRNA expression across breast cancer cell lines in the DepMap database annotated with amplified, moderate, and low KAT6A-expressing models. (B) Mice harboring T47-D tumors were treated with PRT13722* continuously for 2.5 months and the effects on tumor growth and mouse body weight are shown. (C) Mice harboring T47-D tumors were treated with PRT13722 or prifetrastat at an equivalent dose and effects on tumor growth are shown. (D) Mouse plasma concentrations of prifetrastat or PRT13722 at concentrations used in efficacy studies are shown. Average of PK from replicate studies shown where available. **p < 0.05, t-test.

Figure 8. PRT13722 Monotherapy Durably Eradicates Post Endocrine Therapy Patient-Derived Tumors

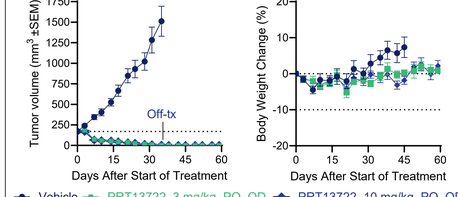


Table 3. PRT13722 Percent CRR in PDX Model

Treatment	Mouse % CRR
PRT13722 3 mg/kg, PO, QD	100% (8/8)
PRT13722 10 mg/kg, PO, QD	100% (8/8)

Tumors at endpoint; CRR = complete response rate (no detectable tumor)

Figure 8. Mice harboring ER+/HER2- patient-derived xenografts, originating from a patient with recurrent disease post chemotherapy and tamoxifen therapy, were treated with PRT13722 at the indicated doses and effects on tumor growth are shown. Off-tx indicates treatment cessation.

Figure 9. PRT13722 Demonstrates Robust *In Vivo* Combinability with Current and Advanced Next-Generation Clinical Endocrine-, CDK4/6-, and PI3Kα-Targeted Therapies

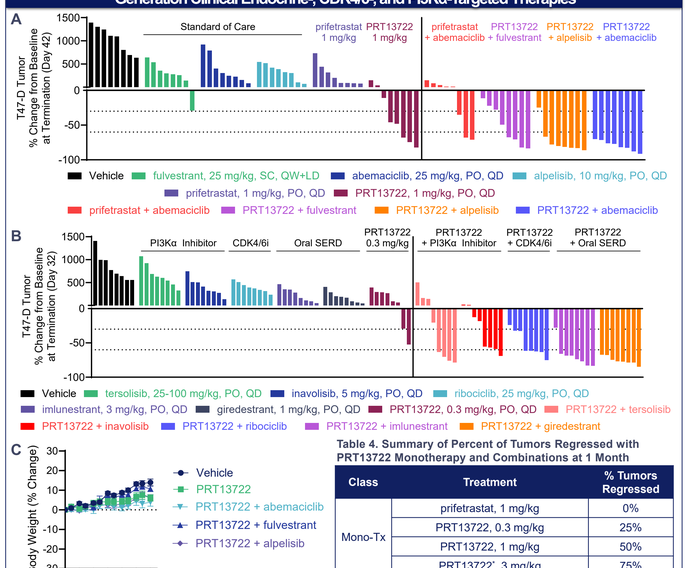


Table 4. Summary of Percent of Tumors Regressed with PRT13722 Monotherapy and Combinations at 1 Month

Class	Treatment	% Tumors Regressed
Mono-Tx	prifetrastat, 1 mg/kg	0%
	PRT13722, 0.3 mg/kg	25%
	PRT13722, 1 mg/kg	50%
	PRT13722', 3 mg/kg	75%
+ ET	prifetrastat, 1 mg/kg + fulvestrant	13%
	PRT13722, 1 mg/kg + fulvestrant	88%
	PRT13722, 0.3 mg/kg + imlunestrant	100%
	PRT13722, 0.3 mg/kg + giredestrant	100%
+ CDK4/6i	prifetrastat, 1 mg/kg + abemaciclib	38%
	PRT13722, 1 mg/kg + abemaciclib	100%
	PRT13722, 0.3 mg/kg + ribociclib	100%
+ PI3Kαi	PRT13722, 1 mg/kg + alpelisib	88%
	PRT13722, 0.3 mg/kg + tersolisib	63%
	PRT13722, 0.3 mg/kg + inavolisib	75%

% T47-D tumors regressed below baseline by Day 31-32; Combination agents given at doses with 0% regression. All agents besides fulvestrant are PO QD: giredestrant 1 mg/kg; imlunestrant 3 mg/kg; abemaciclib 25 mg/kg; ribociclib 25 mg/kg; alpelisib 10 mg/kg; inavolisib 5 mg/kg; tersolisib 25-100 mg/kg; fulvestrant 25 mg/kg, SC, QW + LD

Figure 9. (A-B) T47-D xenografts were treated with PRT13722 or prifetrastat ± endocrine therapies, CDK4/6i, or PI3Kαi and change in tumor volume from baseline is shown. (C-D) Mouse body weight change from the study in (C) panel A and (D) panel B.

Figure 10. PRT13722 Has Potential for an Improved Hematological Safety Profile vs prifetrastat

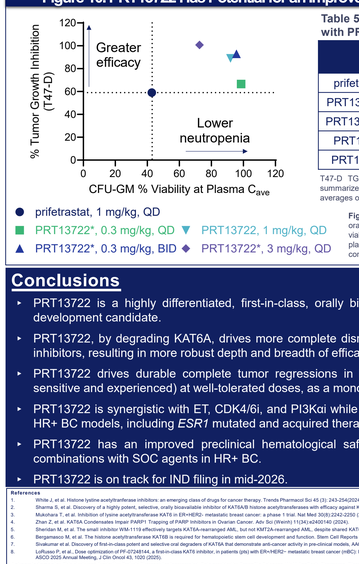


Table 5. Summary of Efficacy, Exposure, and CFU-GM Viability with PRT13722 Compared to prifetrastat

Treatment	Day 28 TGI	Plasma C_{ave} (µM)	CFU-GM % Viability
prifetrastat, 1 mg/kg, QD	59% (n=16)	5.50	43
PRT13722*, 0.3 mg/kg, QD	67% (n=8)	0.09	99
PRT13722*, 0.3 mg/kg, BID	93% (n=8)	0.19	96
PRT13722, 1 mg/kg, QD	89% (n=16)	0.35	92
PRT13722*, 3 mg/kg, QD	101% (n=8)	1.32	73

T47-D TGI after oral dosing of compounds for 28 days and CFU-GM viability values are summarized, with associated plasma C_{ave} concentrations. Where applicable, data represents averages of replicate studies.

Figure 10. Mice harboring T47-D xenografts were treated with prifetrastat or PRT13722 orally at different doses for four weeks to assess % TGI. Human myeloid progenitor percent viability (CFU-GM; protein binding adjusted) in response to prifetrastat or PRT13722* at plasma Cavg concentrations are shown. CFU-GM was run head-to-head between compounds in the same donor and study.

Conclusions

- PRT13722 is a highly differentiated, first-in-class, orally bioavailable, potent and highly selective KAT6A degrader development candidate.
- PRT13722, by degrading KAT6A, drives more complete disruption of KAT6A regulatory pathways than dual KAT6A/B inhibitors, resulting in more robust depth and breadth of efficacy in HR+/HER2- breast cancer.
- PRT13722 drives durable complete tumor regressions in HR+/HER2- CDX and PDX xenograft models (both ET sensitive and experienced) at well-tolerated doses, as a monotherapy.
- PRT13722 is synergistic with ET, CDK4/6i, and PI3Kαi while maintaining monotherapy and combination activity across HR+ BC models, including *ESR1* mutated and acquired therapy-resistant cancer cells.
- PRT13722 has an improved preclinical hematological safety profile compared to prifetrastat, which may enable combinations with SOC agents in HR+ BC.
- PRT13722 is on track for IND filing in mid-2026.

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