Discovery and proteomic characterization of a novel KAT6A inhibitor

A potential best-in-class KAT6A-selective inhibitor with improved therapeutic window

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Introduction

KAT6A and KAT6B are closely related MYST-family histone acetyl-transferases (HATs) that share high sequence homology, regulating gene expression by acetylating lysine residues on both histone and non-histone substrates.

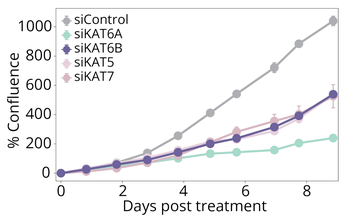
KAT6 has emerged as a promising cancer drug target[1], specifically in estrogen receptor-positive (ER+) breast cancer (BC), with several drugs currently advancing in clinical development. Despite encouraging clinical outcomes, current drugs show several liabilities, such as neutropenia and dysgeusia, representing a need for better, cleaner, and safer drugs for this target.

By integrating computational modeling, structure-based design and medicinal chemistry optimization, Protai's AIMS™ platform identified PAI-CPD14 - a novel, highly potent KAT6A-selective inhibitor.

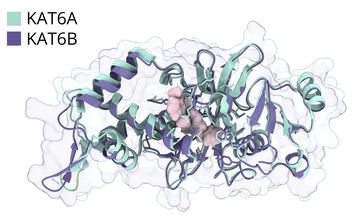
PAI-CPD14 exhibits strong anti-tumor activity both *in vitro* and in xenograft models, as well as reduced hematotoxicity and an overall improved therapeutic window compared to the benchmark compound PF-07248144.

AIMS™ platform designs potent KAT6A-selective inhibitor

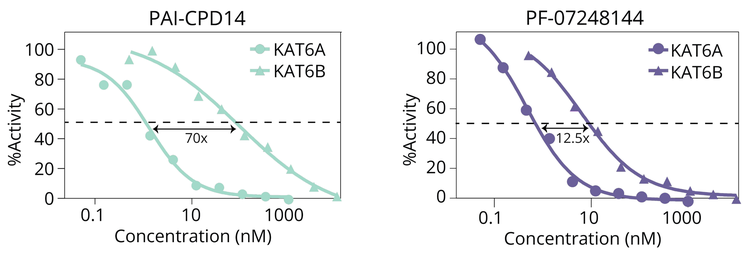
A siRNA of HAT members in ZR-75-1 (ER+ breast cancer)



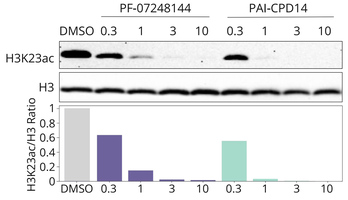
B KAT6A and KAT6B docking models



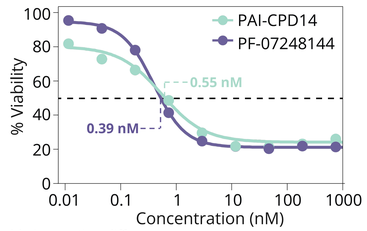
C KAT6A over KAT6B selectivity



D Cell-based H3K23 acetylation



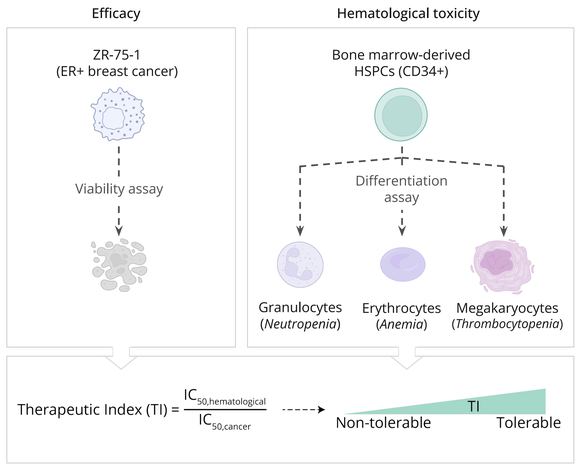
E *In vitro* viability (ZR-75-1)



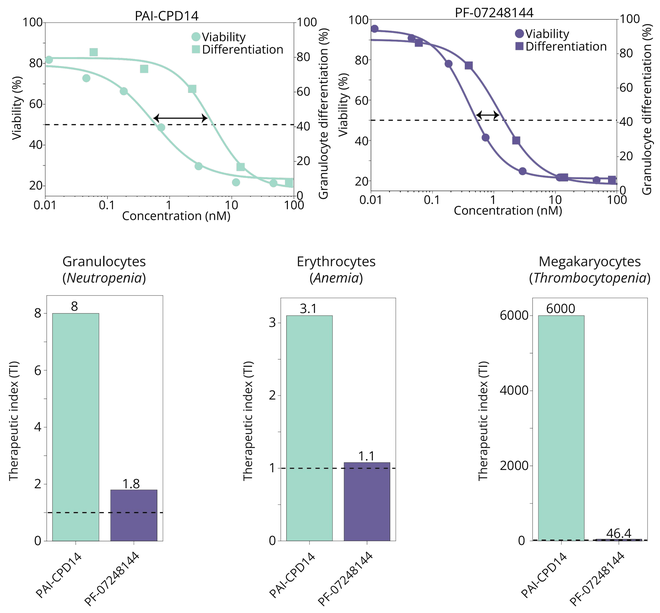
(A) KAT6A and KAT6B docking models exhibit subtle yet actionable interaction differences
(B) KAT6A KD substantially suppresses ZR-75-1 growth compared to KD of KAT6B and other HATs
(C) PAI-CPD14 shows greater KAT6A/B selectivity compared to PF-07248144 in enzymatic assays
(D) Dose-dependent reduction of H3K23 acetylation in ER+ BC cells (T47D) following treatment (nM) with PAI-CPD14
(E) PAI-CPD14 inhibits the growth of ZR-75-1 ER+ BC cell line, with similar efficacy to PF-07248144

PAI-CPD14 shows improved therapeutic window *in vitro*

A Lineage-specific hematotoxicity evaluated by hematopoietic differentiation assay



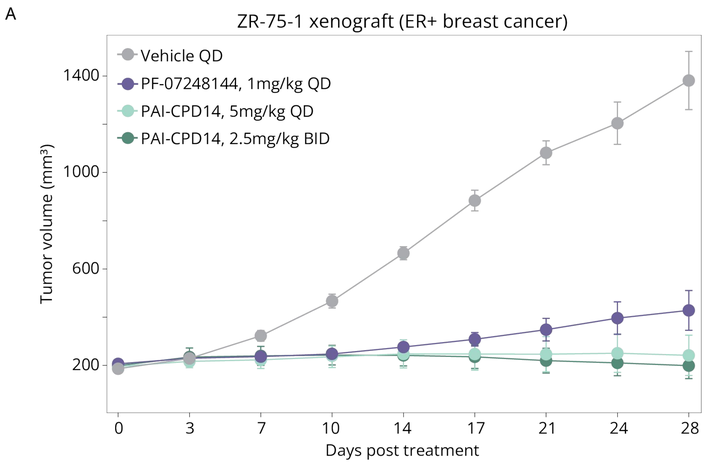
B Therapeutic index: comparison of hematological toxicity and anticancer efficacy



(A) Therapeutic window analysis using the IC_{50} ratio of hematopoietic stem cell differentiation assay (14 days, CD13+ and CD15+ markers were used for quantifying granulocytes, CD71+ for erythrocytes, and CD41+ and CD61+ for megakaryocytes), and efficacy assay of ZR-75-1 (10 days).
(B) PAI-CPD14 reduces the hematological toxicity of PF-07248188, while maintaining anticancer efficacy across all tested hematological lineages (granulocytes, erythrocytes, megakaryocytes)

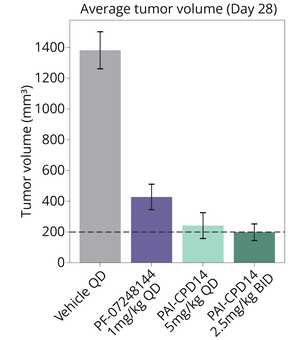
PAI-CPD14 shows *in vivo* efficacy

A



- Female BALB/c nude mice were xenografted with the ZR-75-1 cell line. When tumor size reached 200 mm^3, mice were treated with KAT6 inhibitors for 4 weeks
- PAI-CPD14 shows substantial tumor growth inhibition compared to PF-07248144 (A, n=5 per group), as also observed by average tumor volume on day 28 for each group (B)
- PF-07248144 dosage was derived from clinical trials. PAI-CPD14 dosage was selected based on TI ratios, hypothesizing it would be as efficacious while sparing safety

B



Summary

- Leveraging AIMS™ platform we performed structural analysis of KAT6A vs. KAT6B and designed PAI-CPD14, a novel KAT6A-selective inhibitor
- KAT6A-selective inhibition demonstrated equivalent anticancer efficacy with improved hematological safety *in vitro*, showing improved tolerability and suggesting potential best-in-class therapy for ER+ breast cancer patients and beyond
- Further *in vivo* toxicology studies are planned to evaluate hematotoxicity and dysgeusia
- The program is advancing toward IND enabling studies and clinical trials

References

1. Mukohara et al. "Inhibition of lysine acetyltransferase KAT6 in ER+ HER2− metastatic breast cancer: a phase 1 trial." Nature medicine (2024)
2. Bergamasco et al. "The histone acetyltransferase KAT6B is required for hematopoietic stem cell development and function." Stem Cell Reports (2024)