

OP-3136, a selective KAT6 inhibitor, demonstrates anti-tumor activity in prostate, ovarian, and non-small cell lung cancer preclinical models

Abstract
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Background

- Histone lysine (K) acetyltransferases KAT6A and KAT6B are frequently dysregulated in cancer and are mechanistically linked to key oncogenic processes.¹
- Small-molecule inhibitors of KAT6 have shown promising clinical efficacy, particularly in advanced estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer.²
- KAT6 inhibitors remain largely unexplored in other solid tumors despite strong biological and mechanistic rationale for KAT6 as a potential target.^{3,4}

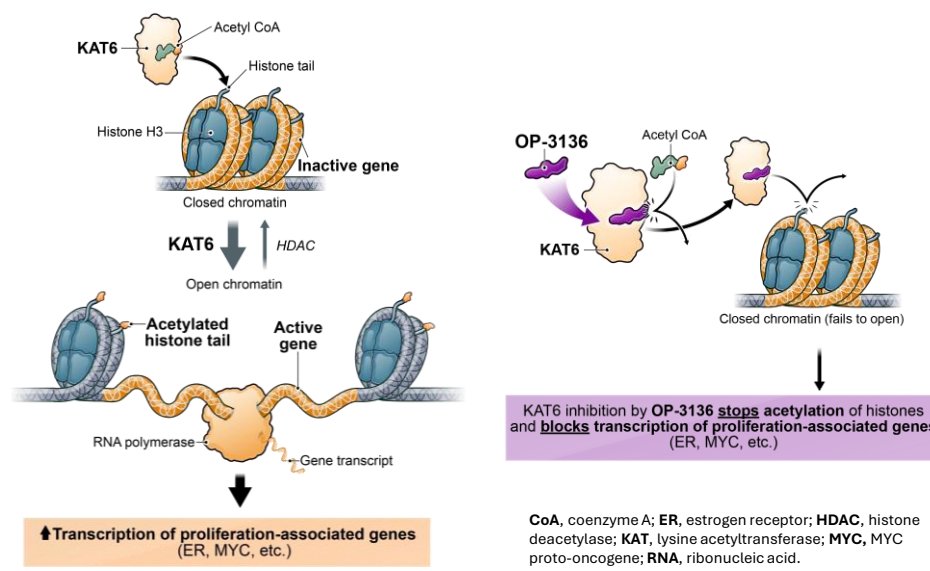


Figure 1: Inhibition of KAT6 enzymes blocks histone acetylation and downregulates transcription of proliferation-associated genes

- Here, for the first time, we report robust anti-tumor activity of OP-3136—a highly selective KAT6 inhibitor currently in Phase 1 clinical trials—in preclinical models of prostate cancer, ovarian cancer and non-small cell lung cancer (NSCLC), both in vitro and in vivo.

Methods

Cell proliferation assays: Optimized densities of named cell lines were plated in 96-well plates in a complete medium and incubated overnight. Cells were treated with serial dilutions of OP-3136 for between 7-21 days. Cell number was assessed using CellTiter-Glo 2.0 and normalized to T=0.

Xenograft studies: BALBc nude or severe combined immunodeficient (SCID) Beige mice (immune deficient) were implanted subcutaneously with 22Rv1 (prostate; male), OVCAR3 (ovarian; female) or LCLC-97TM1 (NSCLC; female) in the right flank. Mice were randomized into groups when the tumor volume reached ~150 mm³ and were treated for at least 28 days with either vehicle or the indicated regimens.

Comparator compound: PF compound E from the published patent⁵ was used as a positive control comparator.

References

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Results

In Vitro Prostate Cancer

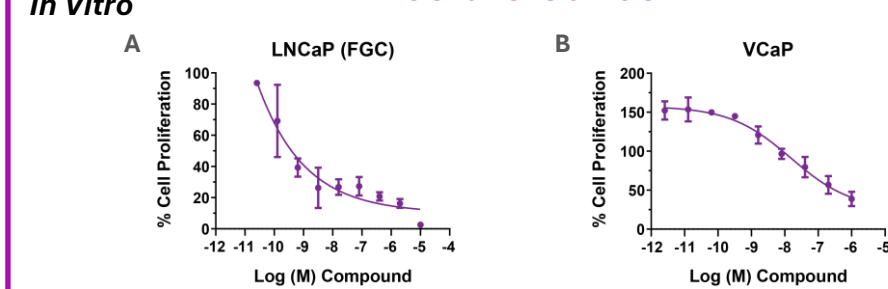


Figure 2: OP-3136 dose-response curves for LNCaP (FGC clone) (A), and VCaP (B) cell lines

- OP-3136 inhibited proliferation of two androgen receptor (AR+)/androgen-sensitive prostate cell lines, LNCaP (FGC) and VCaP with nanomolar potency; LNCaP growth inhibition 50% (GI₅₀) 0.39 nM (Figure 2A), and VCaP GI₅₀ 319 nM (Figure 2B).

In Vivo: 22Rv1 Cell Line-Derived Xenograft (CDX)

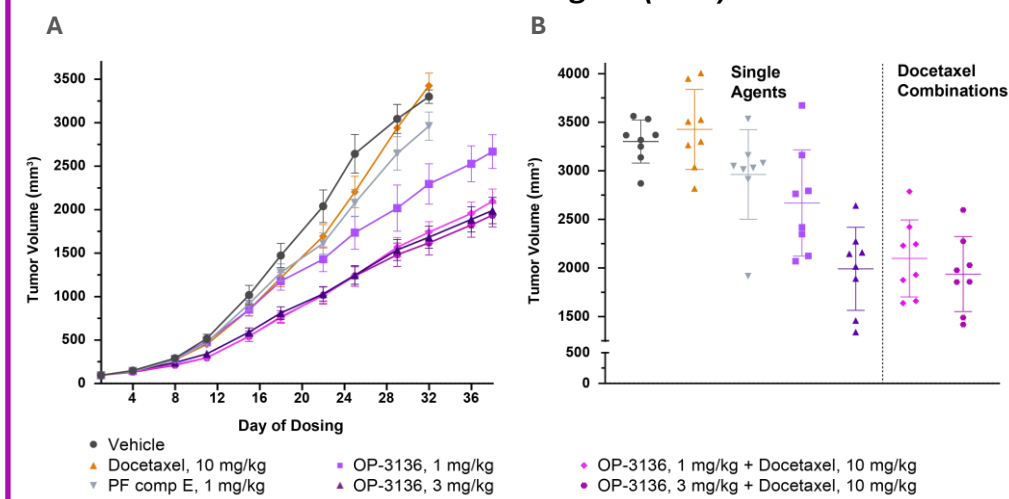


Figure 3: Tumor volume over time (A), scatter plot (B), and waterfall plot (C, below) of a 22Rv1 cell-line derived xenograft (CDX) tumor model (AR+/androgen-sensitive/enzalutamide-resistant)

- OP-3136 inhibited tumor growth in a dose-dependent manner in 22Rv1 CDX, an AR+ prostate cancer model (Figure 3A, B, C).
- Combining OP-3136 (1 mg/kg) with the standard of care agent, docetaxel resulted in enhanced anti-tumor activity.

Waterfall Plot: Percent Change in Tumor Volume on Day 32 From Baseline



In Vitro Ovarian Cancer

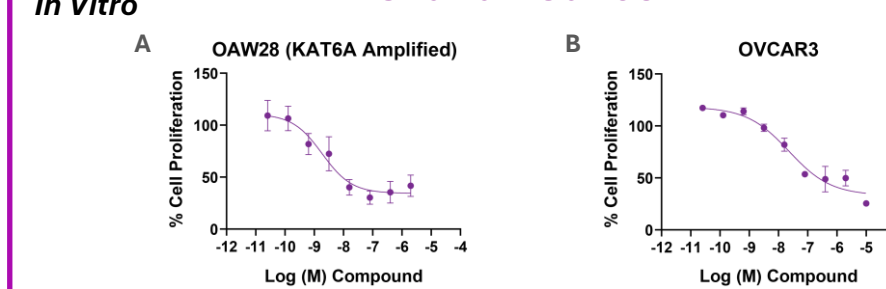


Figure 4: Dose-response curves of OP-3136 treatment of OAW28 (A), and OVCAR3 (B) cell lines

- OP-3136 inhibited proliferation of two high-grade serous ovarian cancer cell lines with GI₅₀ values of 9 and 231 nM calculated for OAW28 and OVCAR3, respectively (Figure 4A, B).

In Vivo: OVCAR3 CDX

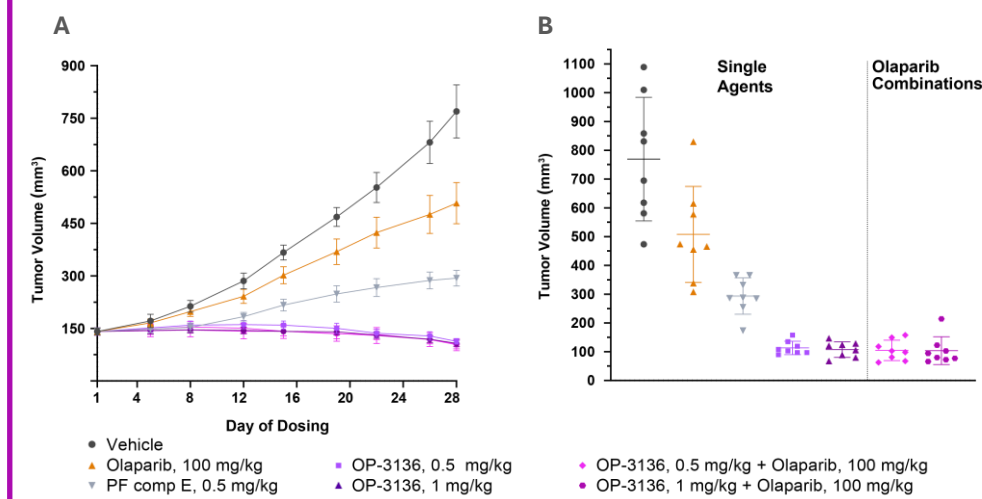


Figure 5: Tumor volume over time (A), scatter plot (B), and waterfall plot (C, below) of a 28-day OVCAR3 xenograft tumor model

- OP-3136 monotherapy demonstrated robust inhibition of tumor growth in the OVCAR3 xenograft ovarian cancer model (Figure 5A, B).
- At both 0.5 and 1 mg/kg, tumor regression was observed, which was sustained across the 28-day study period (Figure 5C).
- In combination with olaparib, no additional benefit was observed (Figure 5B).

Waterfall Plot: Percent Change in Tumor Volume on Day 28 From Baseline



In Vitro Non-Small Cell Lung Cancer

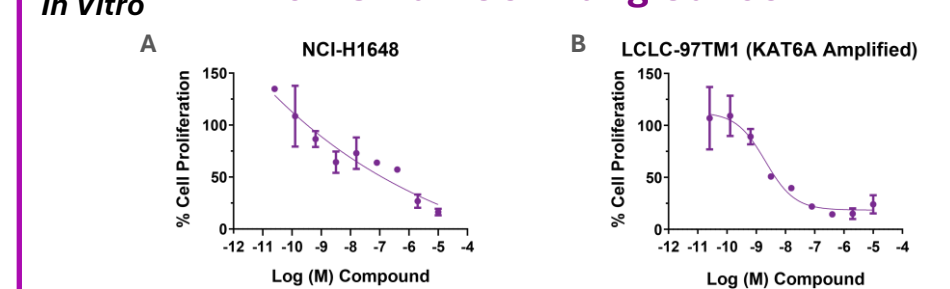


Figure 6: OP-3136 dose-response curves for NCI-H1648 (A), and LCLC-97TM1 (B) cell lines

- OP-3136 inhibited proliferation of NSCLC cell lines NCI-H1648 with a GI₅₀ of 69.5 nM (Figure 6A) and LCLC-97TM1 with a GI₅₀ of 4.6 nM (Figure 6B).

In Vivo: LCLC-97TM1 CDX

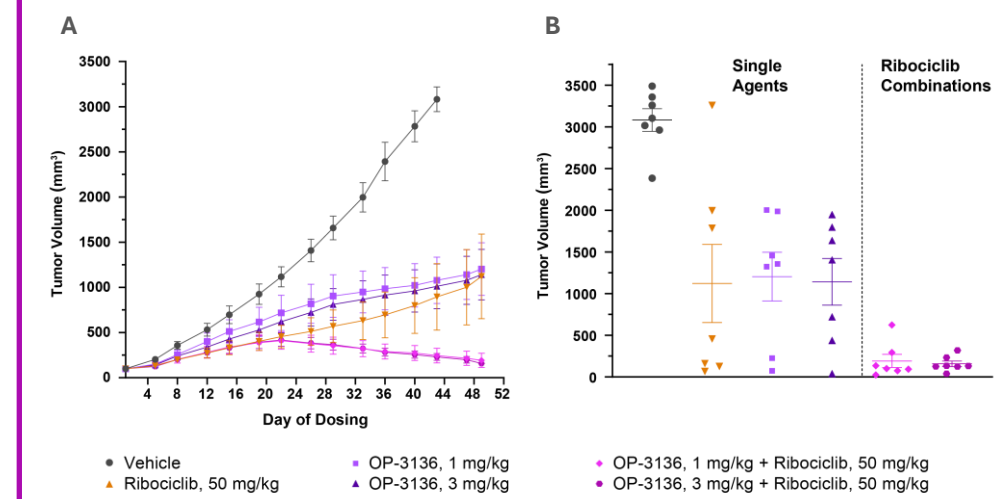
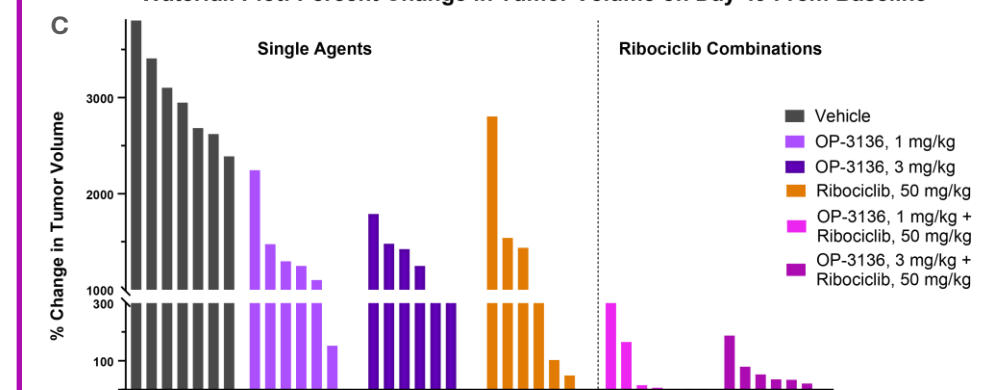


Figure 7: Tumor volume over time (A), scatter plot (B), and waterfall plot (C, below) of a 49-day LCLC-97TM1 xenograft tumor model

- OP-3136 at 1 and 3 mg/kg inhibited tumor growth in the LCLC-97TM1 xenograft lung cancer model (Figure 7A, B).
- As a monotherapy, OP-3136 demonstrated tumor growth inhibition comparable to ribociclib.
- In combination, OP-3136 and ribociclib demonstrated synergy and enhanced anti-tumor activity (Figure 7C).

Waterfall Plot: Percent Change in Tumor Volume on Day 49 From Baseline



Conclusions

- OP-3136 inhibited proliferation of multiple prostate, ovarian, and NSCLC cell lines in vitro, with nanomolar potencies
- OP-3136 monotherapy demonstrated anti-tumor activity in prostate, ovarian and NSCLC xenograft models
- In the OVCAR3 model, OP-3136 monotherapy demonstrated sustained tumor regression
- KAT6A amplification/overexpression was not a significant prerequisite for OP-3136-mediated efficacy
- In combination with standard of care drugs, OP-3136 demonstrated synergy and enhanced tumor growth inhibition in 22Rv1 (prostate) and LCLC-97TM1 (NSCLC) xenografts
- These data indicate OP-3136, currently in Phase I clinical trial, may be effective in treating prostate, lung and ovarian cancer indications in addition to breast cancer

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