

# Discovery and characterization of a selective p300 degrader reveals broad anti-tumor activity in p300-dependent cancers



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## Background

- p300 and CBP are paralogous lysine acetyltransferases that exert both overlapping and nonredundant functions in cancer.
- p300 functions as a critical transcriptional co-activator in malignancies driven by lineage- or tumor-specific gene-expression programs, including AR-positive prostate cancer and hematologic cancers.<sup>1</sup>
- Efforts to develop p300-selective inhibitors have been constrained by the high degree of sequence homology between p300 and CBP, whereas dual p300/CBP inhibitors have shown limited clinical progress due to on-target hematologic toxicity arising from concomitant inhibition of both paralogs.<sup>2</sup>
- We hypothesize that selective degradation of p300 in p300-dependent tumor contexts will preserve antitumor activity while improving the therapeutic index relative to dual p300/CBP-targeting approaches.

## Key Findings

- Identification of novel orally bioavailable p300-selective degrader.
- p300 degradation produces robust growth inhibition in AR<sup>+</sup> prostate cancer models, with downregulation of c-Myc and AR signaling.
- p300 degraders outperform dual p300/CBP inhibition and pomalidomide in multiple myeloma models in vitro and drive strong tumor growth inhibition in vivo.

## Introduction

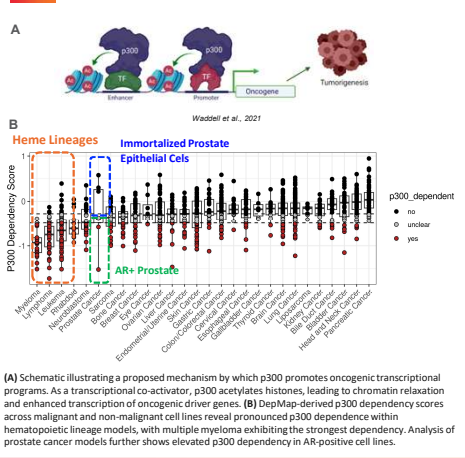


Figure 1. p300 Degrader Show Superb Selectivity & Potency In Vitro

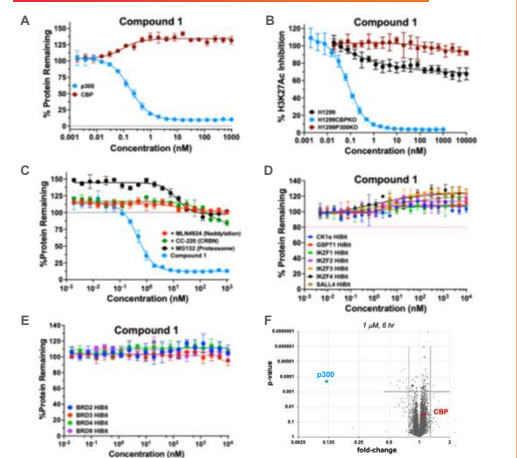


Figure 2. Rapid Degradation of p300 Results in Potent Growth Inhibition

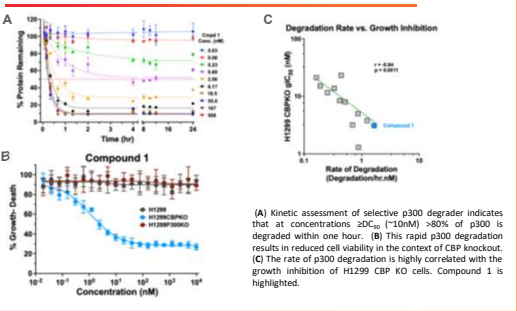


Figure 3. p300 Selective Degrader Show Potential to Achieve Greater Efficacy & Tolerability

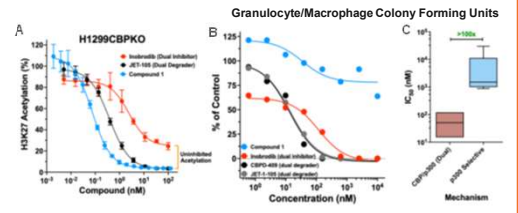


Figure 4. Selective p300 Degradation Drives Antitumor Responses in AR<sup>+</sup> Prostate Cancer Models

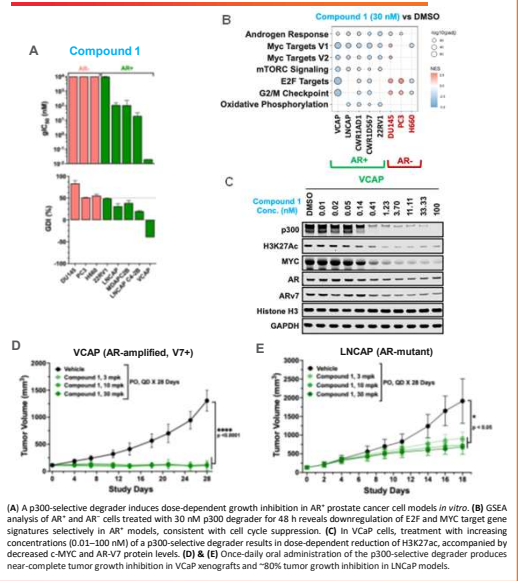
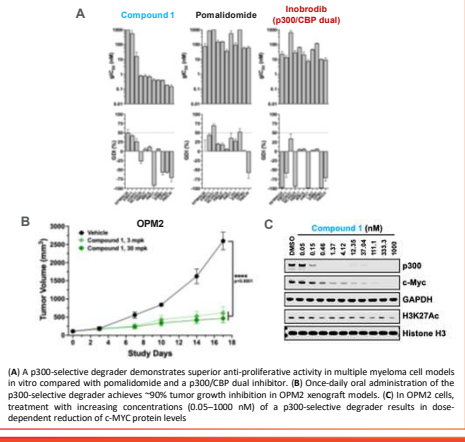


Figure 5. Selective p300 Degradation Show Antitumor Activity Against Multiple Myeloma Models



## Conclusions

- A selective, orally bioavailable p300 degrader was identified with potent activity ( $DC_{50} < 10$  nM;  $D_{max} > 90\%$ ). Mechanistic studies confirm on-target activity with high functional selectivity for p300 over its paralog CBP.
- Studies in CBP knockout models demonstrate that selective p300 degradation is sufficient to drive growth inhibition, supporting a direct mechanistic link between target engagement and antiproliferative effects.
- The p300-selective degrader exhibits an improved safety margin in in vitro bone marrow colony formation assays relative to dual p300/CBP targeting approaches.
- In AR<sup>+</sup> prostate cancer models, p300 degradation leads to suppression of H3K27ac, with consequent downregulation of AR-V7 and c-MYC, and drives robust antitumor activity in vivo (VCAP and LNCAP xenografts).
- In multiple myeloma models, selective p300 degradation demonstrates superior antitumor activity compared with p300/CBP dual inhibition in vitro, and induces significant tumor growth inhibition in vivo.

1. Waddell AR, Huang H and Liao D. CBP/300: Critical Co-Activators for Nuclear Steroid Hormone Receptors and Emerging Therapeutic Targets in Prostate and Breast Cancers. *Cancers* 2021 13(12) 2872.  
2. Rebel VJ, Kung AL, Tanner EA, Yang H et al. Distinct roles for CREB-binding protein and p300 in hematopoietic stem cell self-renewal. *PNAS* 2002 99(23): 14789-14794.