Discovery and characterization of a p300-selective degrader demonstrates potent anti-tumor activity in preclinical models of prostate cancer

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Background

- Although strategies targeting androgen receptor (AR) in the treatment of prostate cancer (PCa) have shown clear clinical benefits, a variety of AR-signaling loops remain ultimately untargeted.
- The androgen receptor-driven pathology p300 and CBP are key co-regulators of AR, and have been implicated in survival of hormone-refractory PCa.
- To date, development of dual CBP/p300 inhibitors have found clinical challenges with clinical toxicity, as heterogeneous progenitors may require distinct strategies to maintain self-renewal capacity.
- We propose that p300 serves as a key regulator of AR signaling and by sparing CBP we should retain anti-tumor activity against AR-driven PCa with an improved safety margin.

Key Findings

- Identified novel orally bioavailable p300-selective degraders.
- p300 degradation inhibits the growth of AR+ prostate cancer.
- Oral administration of p300 degraders demonstrated significant anti-tumor activity of AR+ prostate cancer CDSs in vivo.

Introduction

Figure 1. p300 degraders show superb selectivity and potency in vitro

Figure 2. p300 degraders results in selective pharmacology using engineered model systems

Figure 3. AR+ prostate cancer cells lines exhibit sensitivity to p300-specific degraders

Figure 4. Degradation of p300 results in a suppression of AR-mediated gene signatures

Figure 5. Oral administration of Compound 1 shows favorable pharmacodynamics, efficacy and therapeutic window

Conclusions

- We identified selective orally bioavailable degraders with < 10 nM potency against p300.
- CBP inhibitors confirmed the on-target pharmacology of targeting p300 via selective H3K27 acetylation and growth inhibition.
- p300 degradation inhibits the growth of AR+ prostate cancer cells in vitro and results in potent downregulation of AR-target genes.
- Oral administration of our compound demonstrated >90% degradation of p300 in vivo.
- Dose levels shown led to significant anti-tumor activity in AR+ prostate cancer models in mice.