Discovery and characterization of a selective p300 degrader reveals deep anti-tumor activity in CBP mutant cancers

Harshil Dhruv, Andrew Fedoriw, Xuqing Zhang, Mike Russell, Jeremy Roach, Nathan Kendsersky, Nelisa Bechtel, Kelsey Annen, Brian Vidal, Timothy Dougherty, Clemente Aguilar-Bonavides, Elham Behshad, Sudeep Banjade, Corey Strickland, Wenxue Wu, Larry J. Jolivette, Helai P Mohammad, Ryan Kruger

SK Life Science Labs, King of Prussia, PA; contact: hdhruv@sklslabs.com

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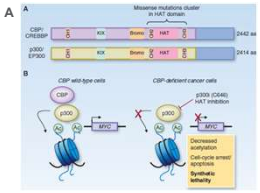
Background

- p300 and CBP are paralogous lysine acetyltransferases that exert both overlapping and nonredundant functions in cancer.
- Paralogous protein pairs serve as compelling targets in cancer due to a clear mechanistic basis for synthetic lethality - highlighted by recent work targeting the histone acetylase transferase p300 in the context of CBP-deficient cancers.[1]
- 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.[2]
- We hypothesize that selective degradation of p300 in tumors harboring CBP loss-of-function (LoF) mutation 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.**
- **Selective p300 degradation induces robust growth inhibition in CBP loss-of-function (LoF) models of BLCA, SCLC, DLBCL, and CRC *in vitro*, accompanied by downregulation of c-Myc signaling.**
- **Once-daily oral administration of the p300 degrader demonstrates marked *in vivo* efficacy in CBP LoF tumor models, including complete tumor regression in multiple models.**

Introduction



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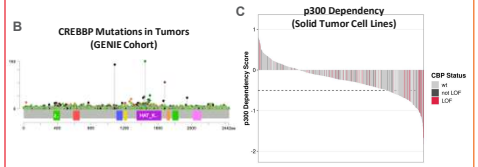
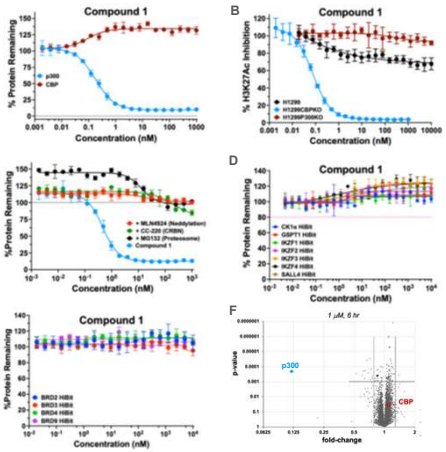


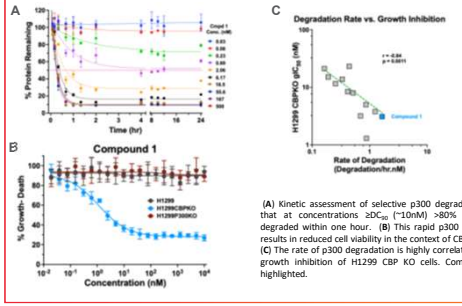
(A) Schematic illustrating the high sequence and structural homology between CBP and p300 (top) and their synthetic lethal relationship (bottom). **(B)** Lollipop plot depicting the distribution of CBP mutations across patient tumors in the GENIE cohort (n = 250,018). **(C)** A proprietary CBP loss-of-function classification enriches for p300 dependency in functional genomics datasets (DepMap), supporting its potential utility as a patient stratification biomarker.

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



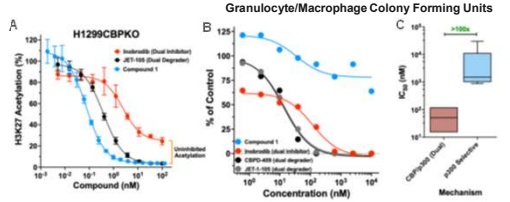
(A) Selectivity of degradation measured by HiBit knock-in of either p300 or CBP in A549 cells using a highly selective p300 degrader (Compound 1). **(B)** Selectivity of functional p300 inhibition measured by H3K27Ac in-cell western (ICW) assay in H1299 Parental, CBP KO, and p300 KO cell lines. **(C)** Degradation of p300 is dependent on the UPS system as evidenced by pretreatment with inhibitors of neddylation (MLN-4924, 1μM), cereblon (CC-220, 1μM) or the proteasome (MG-132, 1μM). **(D)** & **(E)** p300 degrader selectivity is demonstrated by the absence of off-target CRBN neosubstrate degradation and no detectable degradation of BRD proteins in HiBit assays. **(F)** Global proteomics conducted in H1299 cells at a concentration 100-fold higher than the DC_{90} further validates the selectivity and potency of p300 degrader.

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



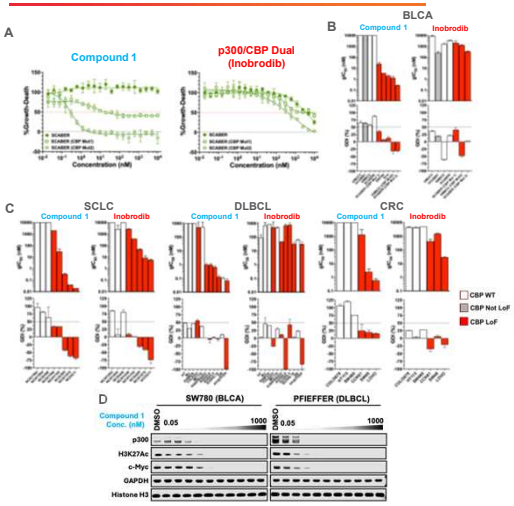
(A) Kinetic assessment of selective p300 degrader indicates that at concentrations ≥DC_{90} (~10nM) >80% of p300 is degraded within one hour. **(B)** This rapid p300 degradation results in reduced cell viability in the context of CBP knockout. **(C)** The rate of p300 degradation is highly correlated with the growth inhibition of H1299 CBP KO cells. Compound 1 is highlighted.

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



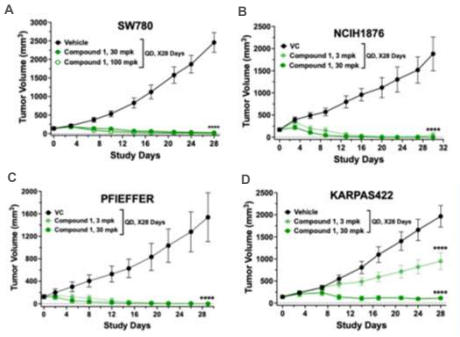
(A) p300 selective degrader achieves near complete suppression of H3K27Ac in H1299 CBPKO cell lines exceeding activity of p300/CBP dual inhibitor (inobrodib). **(B)** & **(C)** p300 selective degrades demonstrate significantly lower activity in an *in vitro* bone marrow toxicity assay relative to p300/cbp dual inhibitor & degraders.

Figure 4. Degradation of p300 results in selective cell growth inhibition in predicted LoF cell lines across indications



(A) A p300-selective degrader shows superior potency and selectivity in isogenic bladder cancer clones with engineered CBP LoF mutations compared with a clinical-stage dual p300/CBP inhibitor. **(B)** & **(C)** Selected cancer cell lines harboring putative CBP LoF mutations are preferentially sensitive to p300-selective degradation, whereas a BLCA line with a non-LoF CBP mutation remains largely insensitive. The dual p300/CBP inhibitor does not clearly discriminate between CBP-mutant and CBP-wild-type cell lines. **(D)** In SW780 (BLCA) and PFIEFFER (DLBCL) cells, p300-selective degradation drives dose-dependent reduction of H3K27ac with concomitant suppression of c-MYC.

Figure 5. Selective p300 Degradation Show Antitumor Activity Against CBP LoF Tumor Models



Once-daily oral administration of the p300-selective degrader induces near-complete tumor regression in the **(A)** SW780 BLCA, **(B)** NCI-H1876 SCLC, and **(C)** Pfeiffer DLBCL xenograft models. **(D)** In the KARPAS422 DLBCL model, once-daily oral dosing of the p300-selective degrader produces 20% tumor regression.

Conclusions

- A selective, orally bioavailable p300 degrader was identified with potent activity (DC_{90} < 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 CBP LoF cancer models, selective p300 degradation suppresses H3K27ac, leading to downregulation of c-MYC and robust antiproliferative activity, while sparing CBP wild-type and CBP-altered non-LoF models.
- Once-daily oral administration of the p300 degrader induces near-complete tumor regression in CBP LoF xenograft models at clinically relevant exposures.

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2. Rebel VI, 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.

3. Kadoch C. Lifting Up the HAT: Synthetic Lethal Screening Reveals a Novel Vulnerability at the CBP-p300 Axis. *Cancer Discovery* **2016** Apr;6(4):350-2.