Discovery and Characterization of Novel, Selective EP300 Degraders

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INTRODUCTION

- CREB binding protein (CBP) and E1A binding protein (EP300) are paralog histone acetyltransferases involved in many cellular processes via their activity as transcription factor co-activators
- Dysregulation has been implicated across a variety of cancer indications
- Due to the high homology between EP300 and CBP, identification of selective chemical matter that specifically and directly targets EP300 has proven challenging.
- Herein we describe a potent, highly selective EP300 heterobifunctional degrader with selective biological activity in EP300 dependent cancer cell lines.

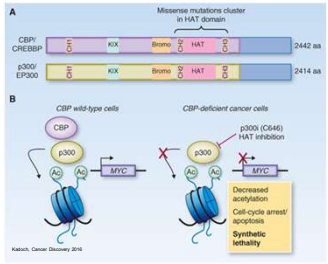
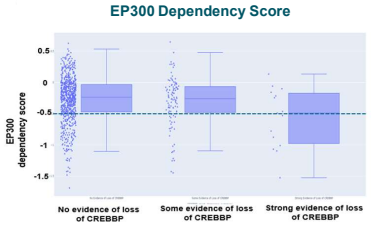


Figure 1. An EP300 selective therapy has the potential to address over 100,000 patients per year across many indications



Target / Approach	E1A binding protein p300 (EP300) Targeted protein degrader
Initial Indication	CBP mutated and subsets of EP300 dependent hematologic malignancies (e.g., Bladder, Prostate, Lymphoma, Myeloma, T-ALL, DLBCL, AML, CML)
Mutation / Aberration	CBP mutated cancers EP300 dependent cancers
Stage	Pre-clinical
New Patients Impacted / Year*	Over 100,000

* U.S., EUR, Japan.

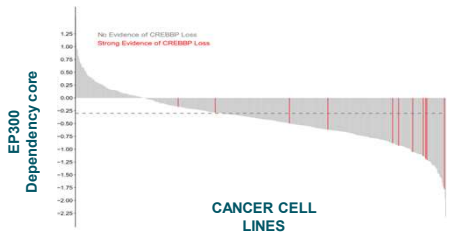
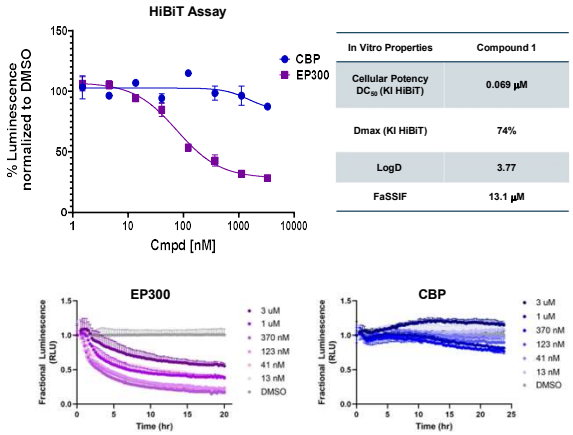


Figure 1: The DepMap Portal was used to identify cell lines with strong dependency on EP300 either based on the bi-directional synthetic lethal relationship with CBP or based on general dependency on EP300. This criteria for cell line selection was then applied to patient tumor databases to extrapolate treatable patient populations

RESULTS

Figure 2. Identification of potent, selective EP300 Degraders



In Vitro Properties	Compound 1
Cellular Potency DC_{50} (KI HiBiT)	0.069 µM
Dmax (KI HiBiT)	74%
LogD	3.77
FaSSIF	13.1 µM

Figure 2: We have identified potent and selective degraders of EP300. Dose response kinetic data confirm EP300 selectivity.

Figure 3a. EP300 selective degraders show an antiproliferative effect in CBPmut and EP300 dependent cell lines, but not wild type

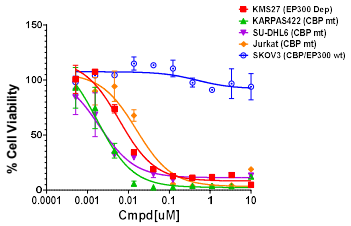


Figure 3b. EP300 selective degraders demonstrate antiproliferative effects in AR+ prostate cell lines

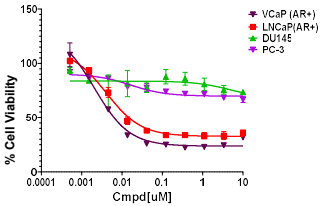
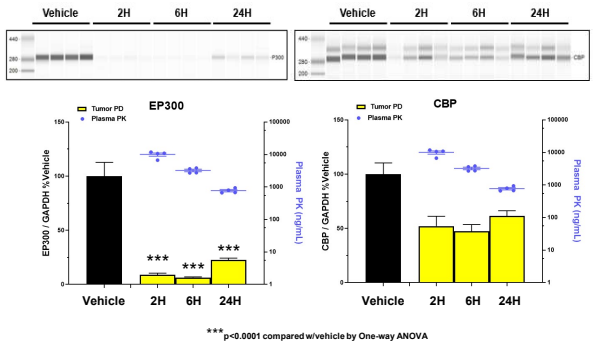


Figure 3a, 3b: EP300 degraders exhibit potent antiproliferative effects in EP300 dependent cell lines (including CBP mt lines) (Fig3a). In particular, we observe greater sensitivity in AR+ vs. AR- prostate cancer cell lines (Fig 3b).

Figure 4. EP300 selective degraders demonstrate robust degradation in vivo



***p<0.0001 compared w/vehicle by One-way ANOVA

Figure 4: EP300 selective degraders show robust, sustained EP300 degradation in vivo

CONCLUSIONS

- EP300 and its paralog CBP are transcriptional co-activators that have been associated with several oncogenic signaling pathways.
- If successful, the identification and development of a selective EP300 degrader may address an unmet medical need for a significant patient population.
- Here, we describe potent, selective EP300 degraders that show anti-proliferative effects in CBP mutant and EP300 dependent cell lines while sparing wild type cell lines
- Our EP300 degraders show increased sensitivity in AR+ vs. AR- Prostate Cancer cell lines.
- Additionally, our selective EP300 degraders are in vivo enabled, and demonstrate robust, selective degradation of EP300 in vivo.
- CBP and EP300 share many overlapping but also non-overlapping functions. Our selective tool degraders will also help us understand and identify cancer indications where the dependency on one of the targets might be agnostic of the paralog's mutational status.

ACKNOWLEDGEMENTS: Thank you to Janice Lee, Matt Netherton and Ricardo Medina for their consulting role in the program

REFERENCES: Kadoch C. Lifting up the HAT: Synthetic lethal screening reveals a novel vulnerability at the CBP-EP300 axis. Cancer Discov. 2016

Sources for incidence numbers: US - SEER Database, EU - ECIS Database, JP - WHO Globocan, Foghorn TCGA and GENIE Analysis, DRG Reports