Discovery and characterization of potent, selective CBP degraders

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INTRODUCTION

- CREB binding protein (CREBBP/CBP) and E1A binding protein (EP300) are paralog histone acetyltransferases involved in many cellular processes via their chromatin regulatory activity.
- 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 CBP has proven challenging.
- Herein we describe a potent, highly selective CBP heterobifunctional degrader with selective biological activity and improved antiproliferative potency compared to CBP/EP300 dual inhibitors.

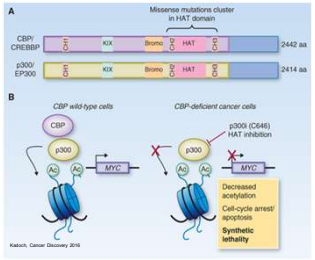


Figure 1. A CBP selective therapy has the potential to address over 100,000 patients per year across many indications

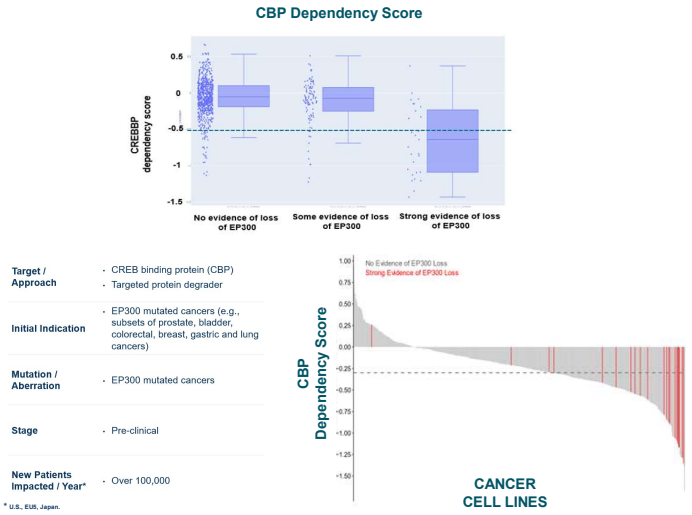


Figure 1: In order to exploit the bi-directional synthetic lethal relationship targeting rationale we explored the DepMap Portal to identify CBP dependent lines based on EP300mut status. This criteria for cell line selection was then applied to patient tumor databases and used to extrapolate potential treatable patient populations.

RESULTS

Figure 2. Identification of potent, selective CBP Degraders

In Vitro Properties	Compound 1
Cellular Potency DC_{50} (KI HiBiT)	>30 µM (EP300) 0.032 µM (CBP)
Dmax (KI HiBiT)	8% (EP300) 78% (CBP)
LogD	3.8
FaSSIF	15µM

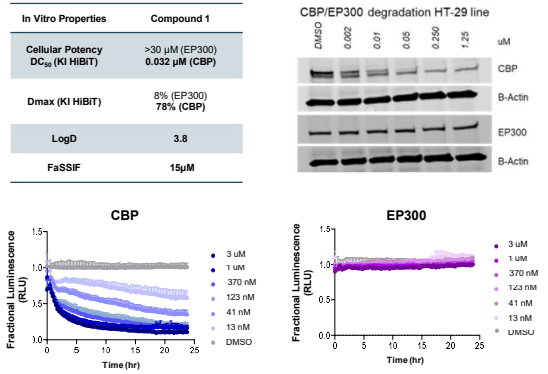
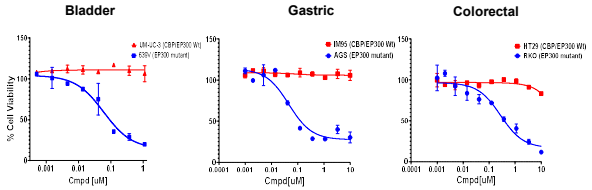


Figure 2: We have identified potent and selective degraders of CBP. Dose response kinetic data confirm CBP selectivity, with minimal effects on EP300, and do not exhibit a hook effect.

Figure 3. CBP selective degraders show an antiproliferative effect in EP300mut cell lines, but not wild type



	Bladder		Gastric		Colorectal	
Cell line	639V	UM-UC-3	AGS	IM95	RKO	HT29
dCBP GI50 (µM)	0.6	>10	0.04	>10	0.2	>10

Figure 3: CBP degraders exhibit potent antiproliferative effects in cell lines, from multiple cancer indications identified through DepMap, that are EP300 mut while sparing those that are CBP/EP300 wt.

Figure 4. CBP selective degraders show improved potency relative to bromodomain and HAT dual inhibitors

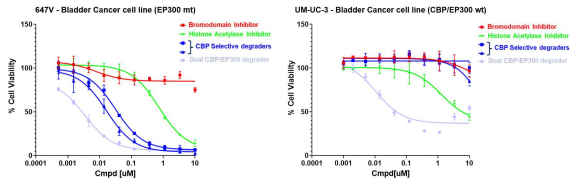


Figure 4: CBP degraders show increased potency relative to inhibitors of the bromodomain and histone acetyltansferase domains in EP300 mut cancer cell lines

Figure 5. CBP selective degraders demonstrate robust, selective degradation in vivo

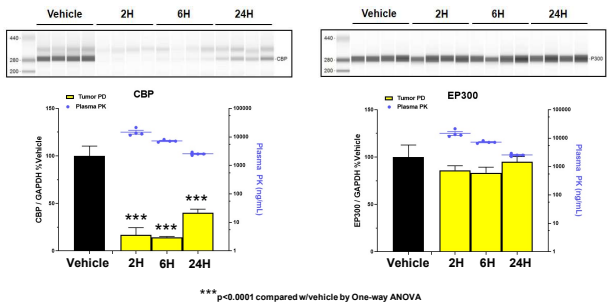


Figure 5: CBP selective degraders show robust, selective and sustained CBP degradation in vivo

CONCLUSIONS

- Based on the synthetic lethal relationship between CBP and EP300, we have used our "some/strong loss of EP300" criteria to identify dependent cancer cell lines and have successfully demonstrated in vitro dependency.
- If successful, the identification and development of a selective CBP degrader may address an unmet medical need for a significant patient population.
- We have identified potent, selective CBP degraders that show anti-proliferative effects across various EP300mut cell lines while sparing paired wild type cell lines.
- Additionally, our selective CBP degraders are in vivo enabled, and demonstrate robust, selective degradation of CBP 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