Discovery of potent and selective EP300 degraders with anti-cancer activity

Mark Zimmerman[1], Darshan Sappal[1], Ammar Adam[1], Benjamin Adams[1], Ketaki Adhikari[1], Wesley Austin[1], Breanna Bullock[1], Julie Di Bernardo[1], Thomas Dixon[1], GiNell Elliot[1], Brian Ethell[1], Anais Gervais[1], Md Imran Hossain[1], David Huang[1], Dave Lahr[1], Mei Yun Lin[1], David Mayhew[1], Karolina Mizeracka[1], Solymar Negretti[1], Tyler Nguyen[1], Olga Prifti[1], Shawn Schiller[1], Brenna Sherbanee[1], David Terry[1], Nihan Ucisik[1], Elizabeth Wittenborn[1], Laura La Bonte[1], Danette Daniels[1]

[1]*Foghorn Therapeutics, Cambridge, MA 02143*

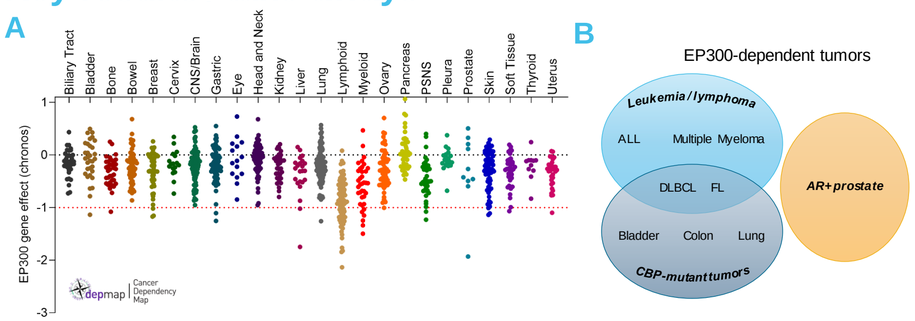
FOGHORN® THERAPEUTICS

www.foghorntx.com

Abstract

E1A binding protein (EP300) and CREB binding protein (CBP) are paralog histone acetyltransferases involved in many cellular processes via their activity as transcriptional co-activators. Dysregulation of one or both proteins has been implicated in various cancers, and functional genomic screens have demonstrated a bidirectional synthetic lethal relationship between the two genes in tumor cells. Due to the high homology between EP300 and CBP, identifying chemical matter that selectively targets EP300 or CBP has proven challenging. Here, we describe a potent, highly selective heterobifunctional degrader of EP300 with biological activity in CBP-deficient and EP300-dependent tumor cells. This compound achieves robust degradation of EP300 *in vivo* at doses that sustain EP300 degradation with minimal effects on CBP protein level. Targeted degradation of EP300 protein resulted in a stronger suppression of cell growth and survival than targeting the bromodomain or HAT activity of EP300/CBP with small molecule inhibitors. Strong anti-proliferative effects have been demonstrated in multiple cancer cell lines, including lymphomas and prostate tumors, highlighting the essential role of EP300 in the malignant phenotype of these tumors.

Key results / take-aways



A) EP300 is a selective dependency across tumor cell lines, and is required for the growth and survival of lymphocytes, AR+ prostate and CBP-mutant cell lines B) Indications and cell types potentially sensitive to an EP300-selective targeted therapy

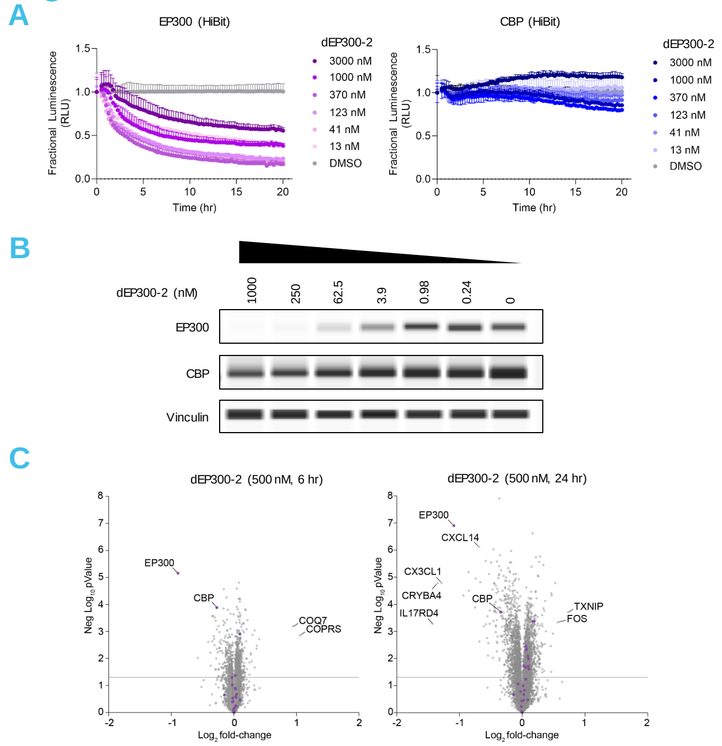
Conclusions

- Selective degradation of EP300 over CBP can be achieved with a targeted protein degradation approach using small molecules
- EP300 disruption can inhibit the growth and survival of multiple tumor cell types (Leukemia/lymphoma, CBP-mutant, AR+ prostate)
- Selective targeting of EP300 is tolerable at therapeutically relevant doses with no signs of overt toxicity in mouse CDx models

References

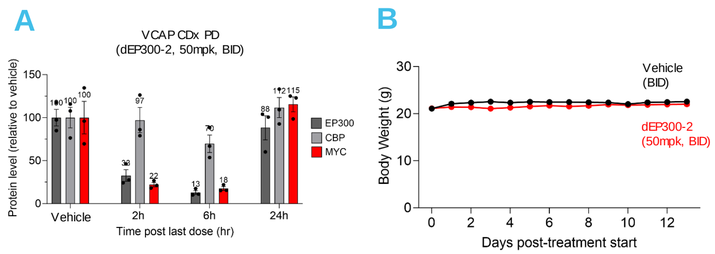
- Ogiwara et al., Cancer Discovery, 2016 (PMID: 26603525)
- Welti et al., Cancer Discovery, 2021 (PMID: 33431496)
- Durbin et al., Cancer Discovery, 2022 (PMID: 34772733)

Figure 1



Selective degradation of EP300 over CBP in tumor cells. A) Kinetic graphs demonstrating rapid and sustained loss of EP300 protein with minimal effects on CBP. B) Western blot demonstrating dose-dependent loss of EP300 after U2OS cells are treated for 24 hours C) Global proteomics from U2OS cells treated for 6 or 24 hr

Figure 2

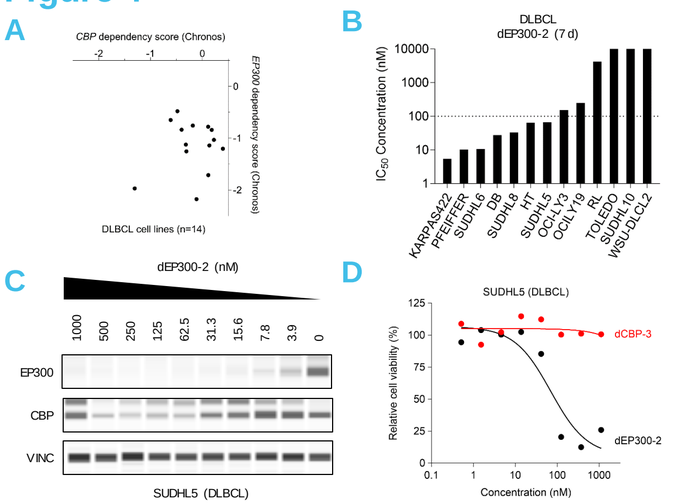


Degradation of EP300 *in vivo* is achievable without significant body weight loss. A) Protein levels for EP300, CBP and MYC in VCAP xenografts following single day treatment with dEP300-2. B) Body weight analysis in BALB/C mice treated with dEP300-2 (50 mpk, BID) for 2 wk.

Figure 3

Selective degradation of EP300 but not CBP attenuates androgen signaling and histone acetylation in AR+ prostate cells. A) 7-day cell titer glo viability assay on n=6 prostate cell lines. B) H3K27ac quantification in VCAP cells following degradation of EP300 for 24 hr.) Western blot of VCAP cells (AR+) pre-treated with EP300/CBP inhibitors and degraders for 24 hr and stimulated with DHT for 0, 4, 24 hr.

Figure 4



Degradation of EP300 suppresses the growth of DLBCL. A) Dependency scores for EP300 and CBP in DLBCL. B) IC_{50} values of DLBCL cell lines treated with dEP300-2 for 7 days. C) Western blot demonstrating dose-dependent loss of EP300 but not CBP after 24 hours. D) Degradation of EP300 but not CBP suppresses the growth of SUDHL5 cells