Targeted Protein Degradation and The Chromatin Regulatory System

October 31, 2023

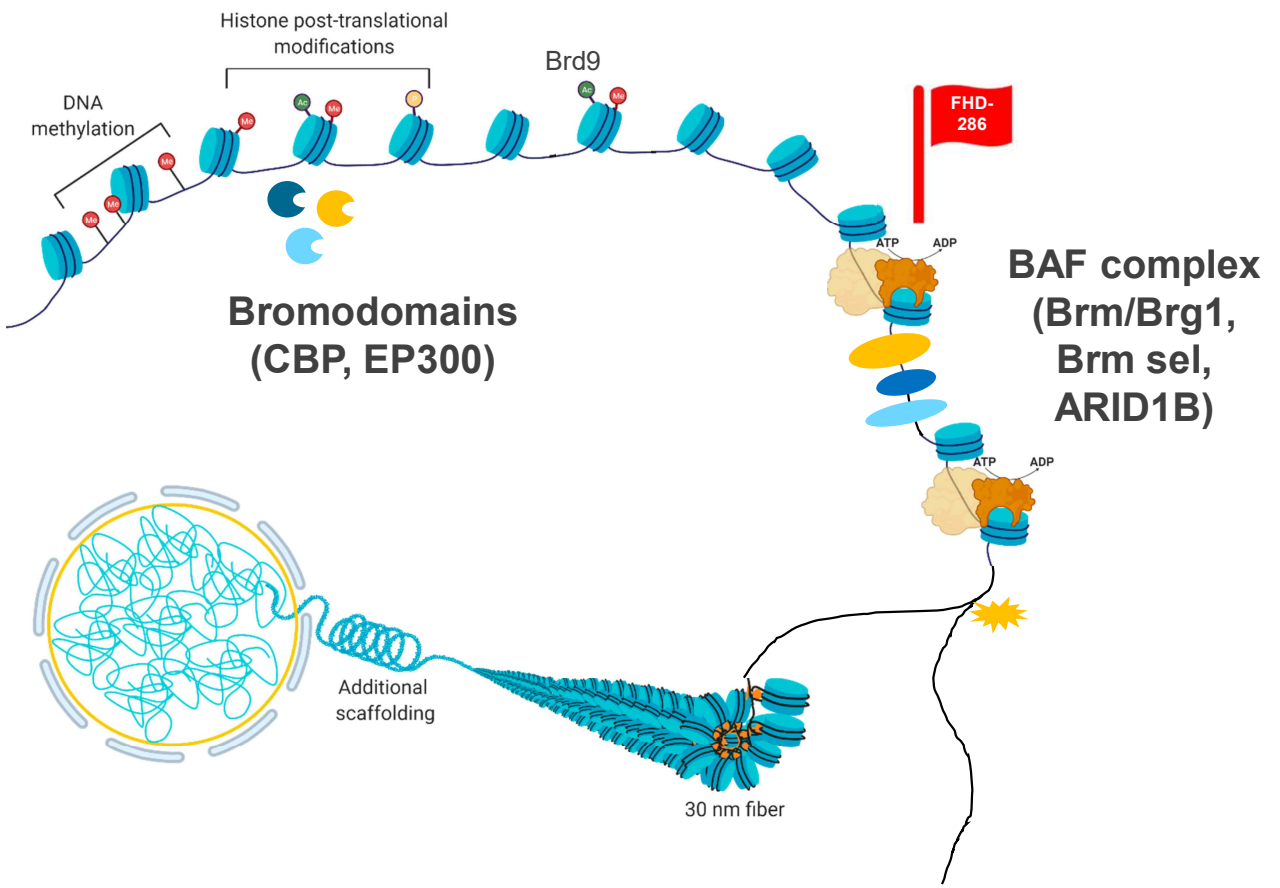
Steve Bellon, CSO

FOGHORN® THERAPEUTICS

Foghorn Research Focused on Chromatin Biology

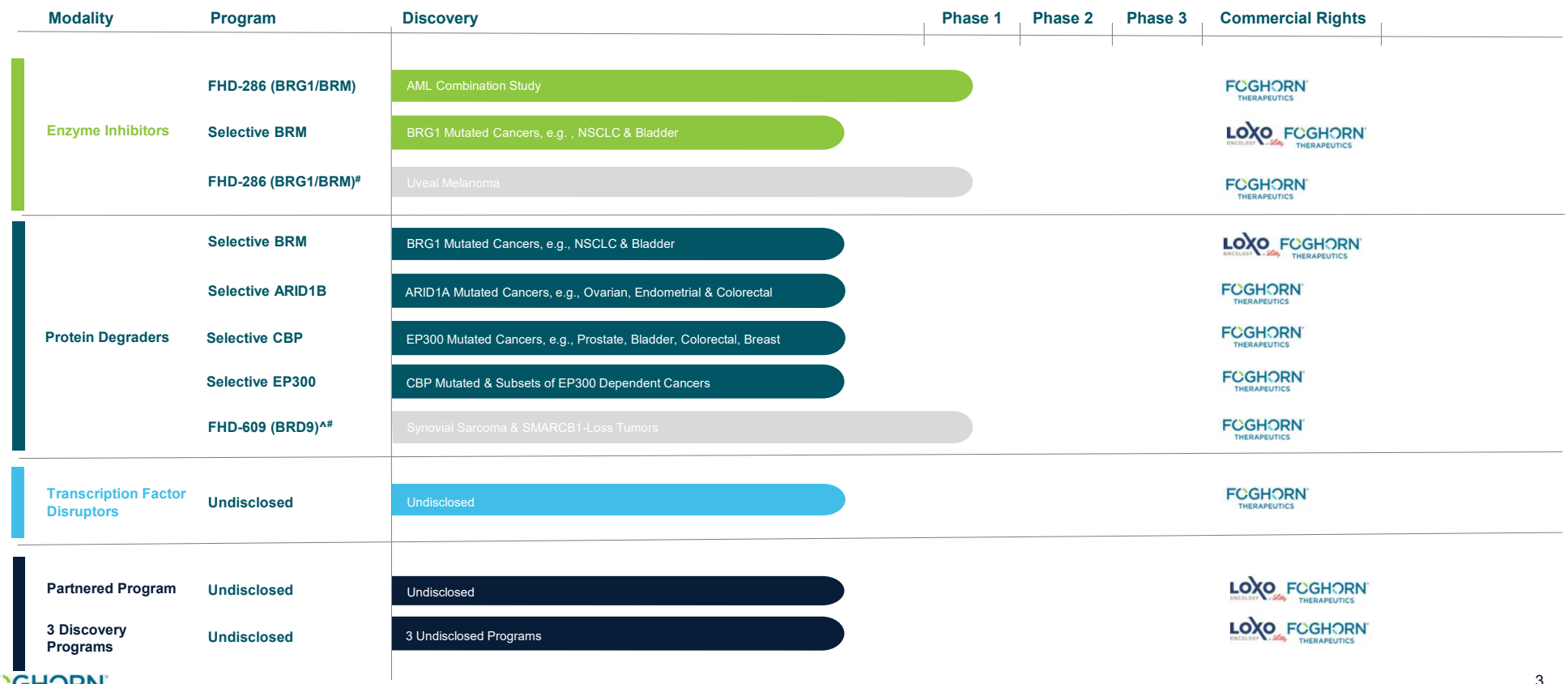
Dysregulated chromatin underlies oncogenesis

Gene expression in the right cells at the right time is critical for normal growth, development, and homeostasis



BROAD PIPELINE ACROSS A RANGE OF TARGETS AND MODALITIES

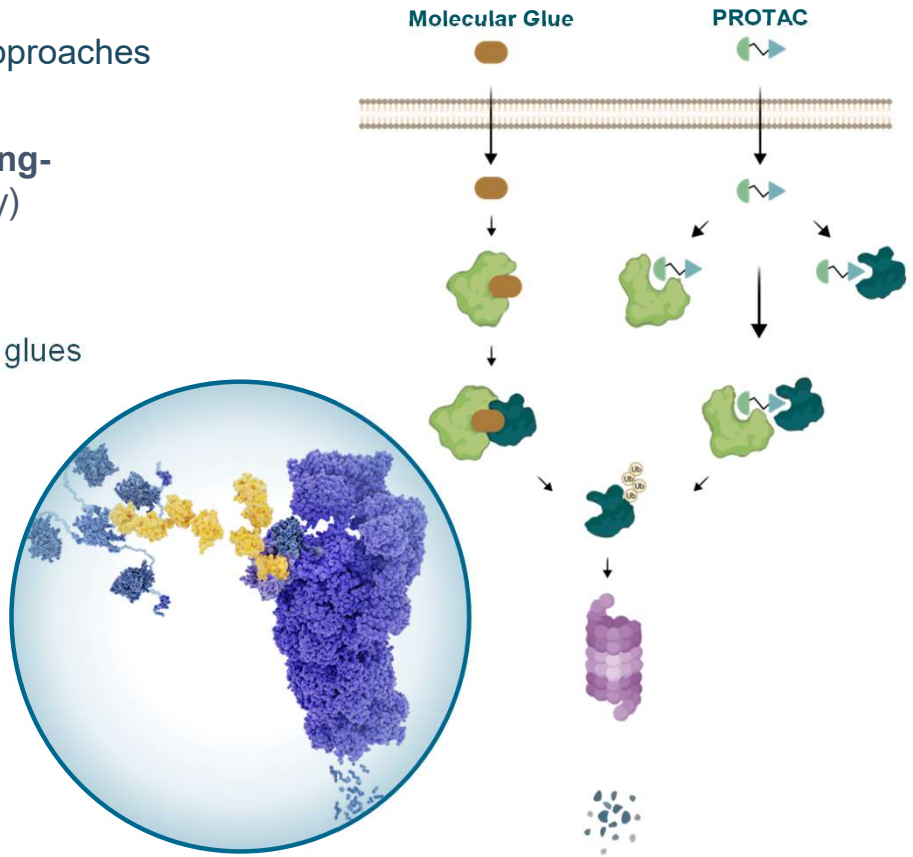
Precision Oncology / Breadth and Depth / Over 15 Programs



* Per year incidence in the U.S., EU5, Japan | ^ On partial clinical hold | # Not advancing independently

Fully Capable Degrader Platform
Evolved from Initial Focus on Drugging BAF Complex

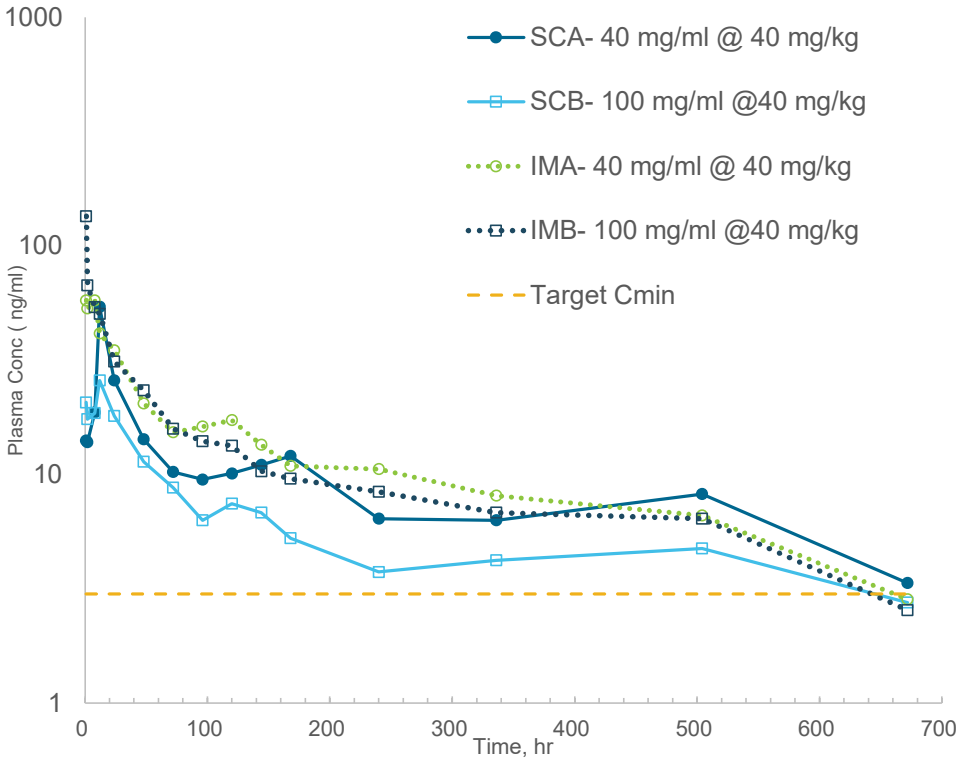
- **PROTAC and non-CRBN based molecular glue** degradation approaches
- Current capabilities allow for **either oral bioavailability**, or for **long-acting formulation** (weekly, to every two weeks, to once monthly)
- **Degrader Chemical Toolbox**
  - Proprietary library of drug-like linkers, E3 ligase binders and potential glues
  - Chemistry to rapidly identify and optimize degraders
- **Advanced Mechanistic Characterization**
  - Native target turnover understanding
  - Cellular degradation kinetics and rates
  - Structural, biochemical, and cellular ternary complex characterization
  - Global proteomics and ubiquitination studies
  - Computational modeling of degraders
  - Degradation efficacy across multiple cell types



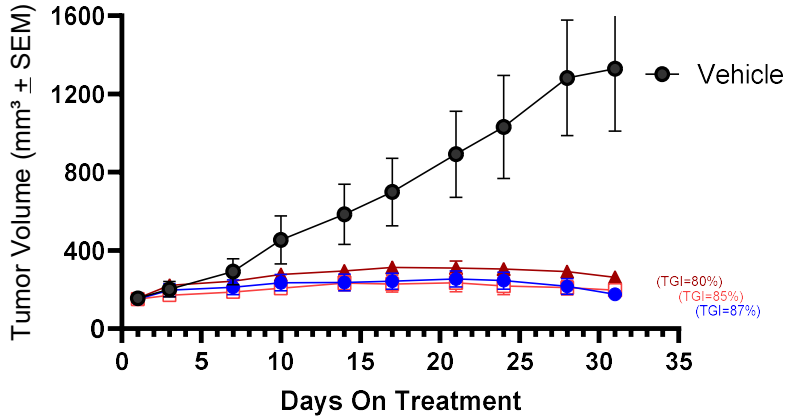
Long-acting Formulation Platform Demonstrates Monthly Delivery of Protein Degrader

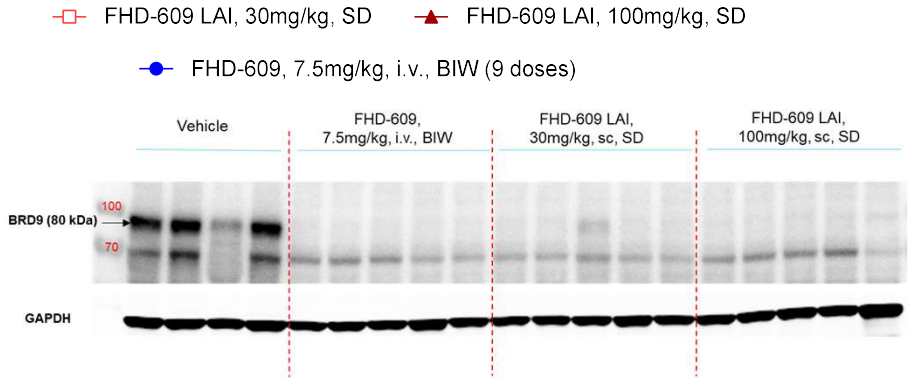
Example: BRD9 Degrader

Single Dose SubQ and IM Delivery of BRD9 degrader



SA10162 SS (SS18-SSX2) PDX TV





BROAD PIPELINE ACROSS A RANGE OF TARGETS AND MODALITIES

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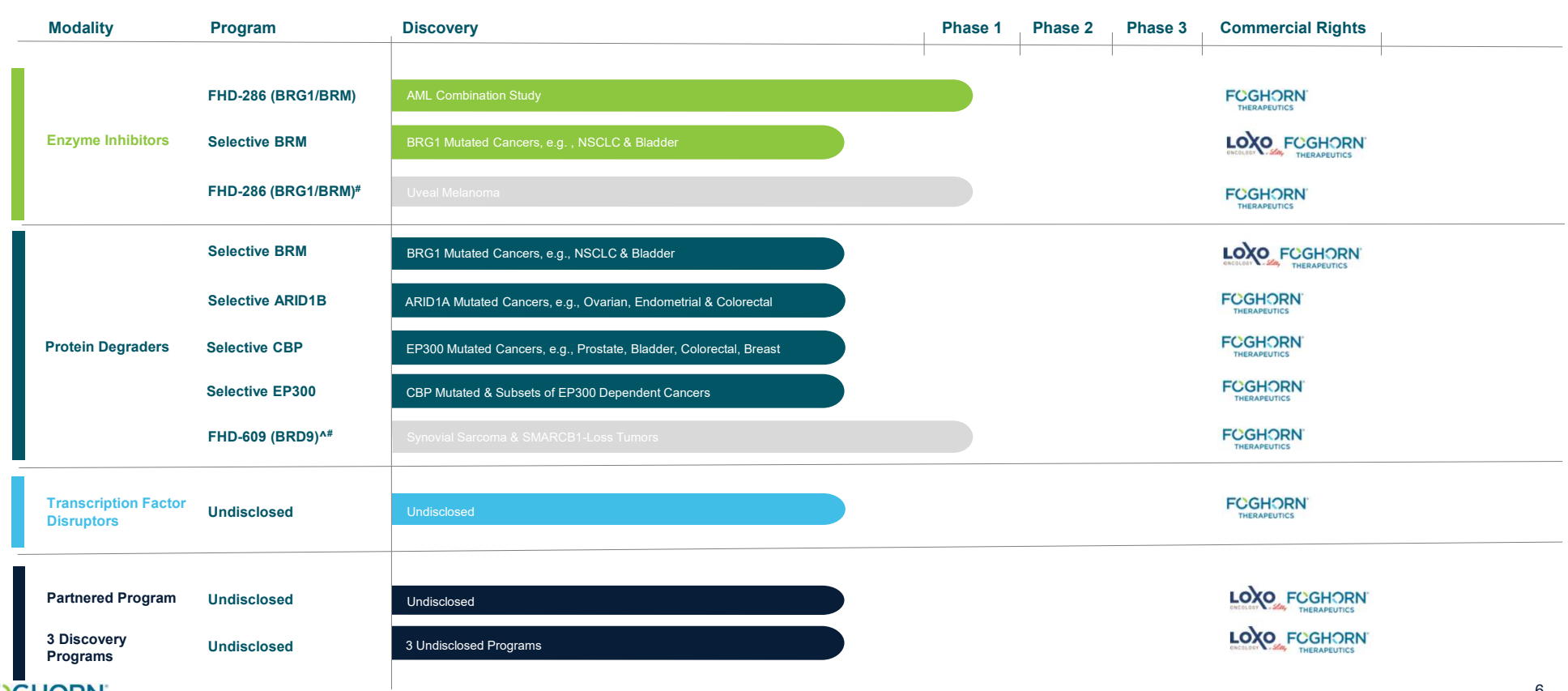
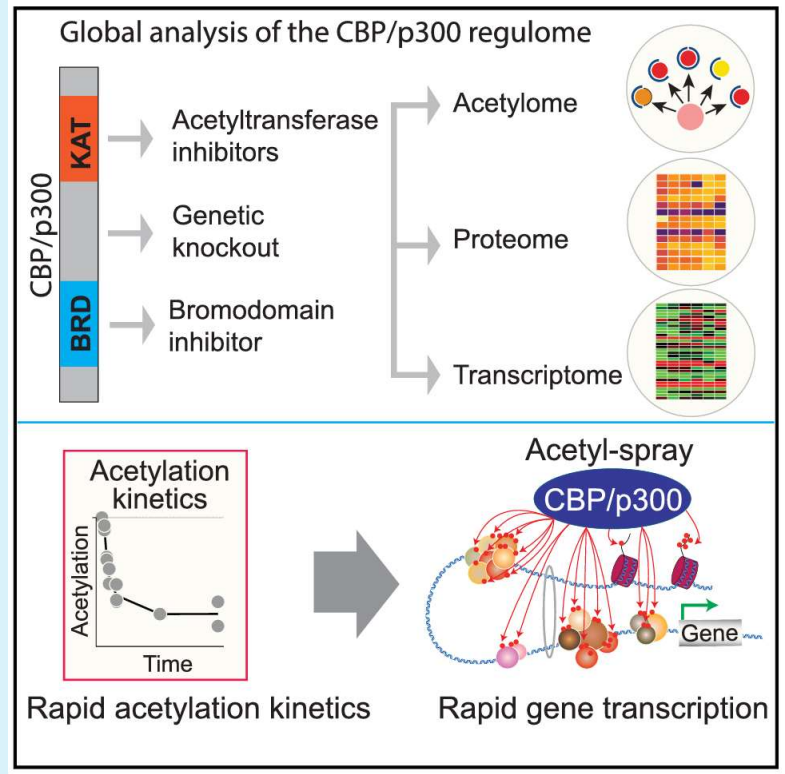


* Per year incidence in the U.S., EU5, Japan | ^ On partial clinical hold | # Not advancing independently

CBP and EP300 Regulate Enhancer-Mediated Transcription and Protein Stability Making them Important Targets in Cancer

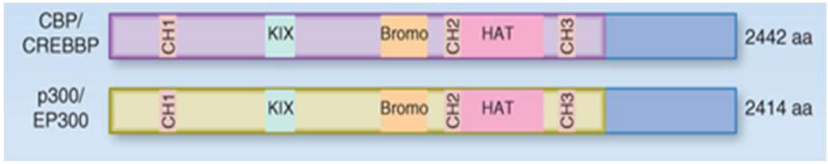
- CBP and EP300 are chromatin regulators and histone acetyltransferases
- Inhibition or knockout of EP300/CBP results in downregulation of a subset of expressed genes (~10-12%)
- Additionally, EP300/CBP regulate protein abundance through acetylation-dependent protein stability
- RNAi and CRISPR screens point to a synthetic lethal relationship that can be exploited in a variety of cancer indications

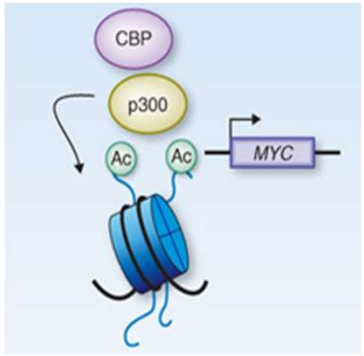


Weinert et al., Cell, 2018

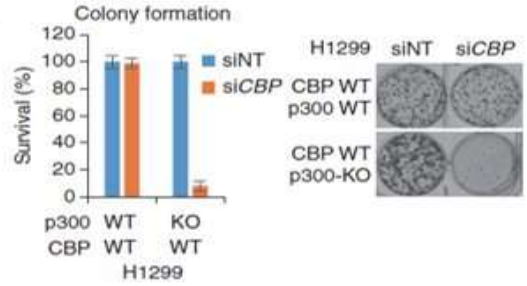
CBP and EP300 Proteins…A Decades Long Challenge in Selectivity

CBP and EP300 have multiple conserved domains, thus achieving selectivity with a small molecule is a significant challenge





(Kadoch, Cancer Discovery 2016)



(Ogiwara et al, Cancer Discovery, 2016)

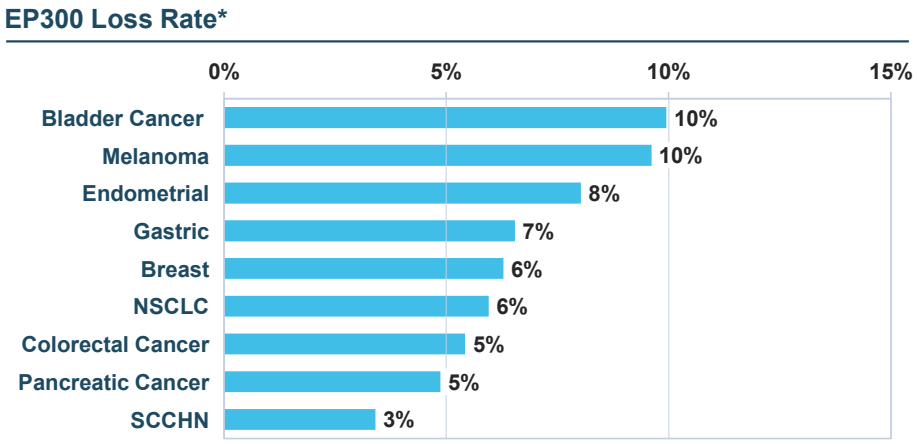
➢ Drug targeting

- They have a synthetic lethal relationship and together are pan essential
- CBP and EP300 are enzymes
- Several domains within CBP/EP300 with known binders and inhibitors
  - HAT enzymatic inhibitors
  - Bromodomain inhibitors
- Current small molecules in development do not have selectivity
- Dual targeting has revealed tolerability and safety issues

Selective Degradation of CBP to Address Mutant EP300 Cancers

A CBP Selective Degrader Could Address Up To 100K+ Patients Annually Across Multiple Tumor Types

EP300 Mutant Cancers



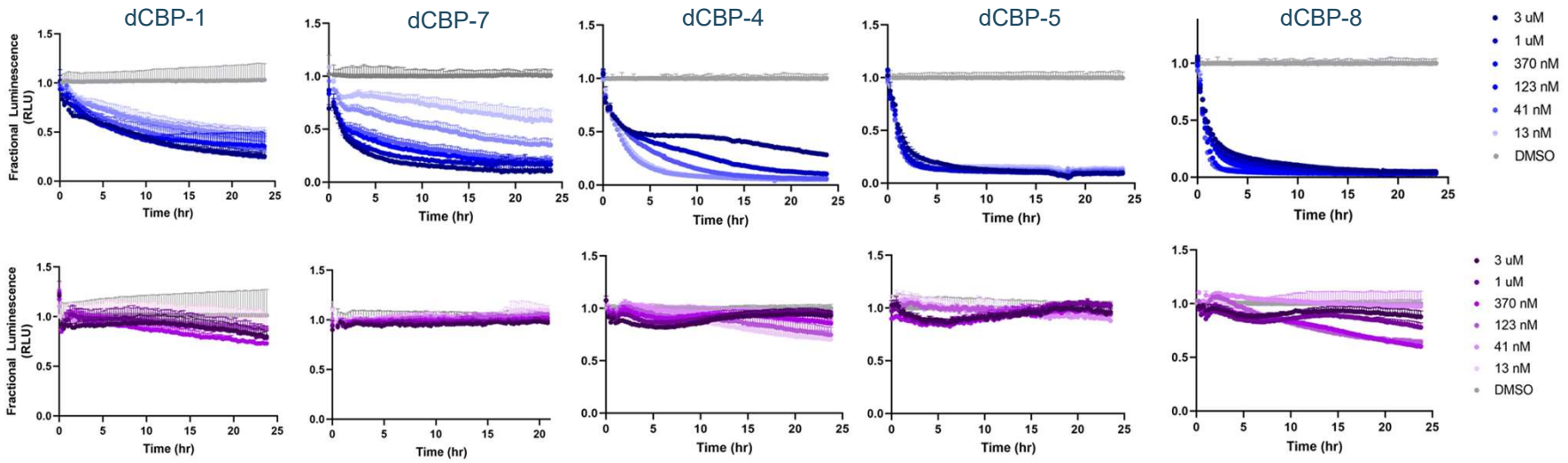
Additional opportunities include other malignancies with EP300 loss such as cervical and ovarian cancer, esophageal cancer, liver and DLBCL

Large Addressable Population (G7)

- 100K+ patients annually*
- Identification via existing diagnostic tests

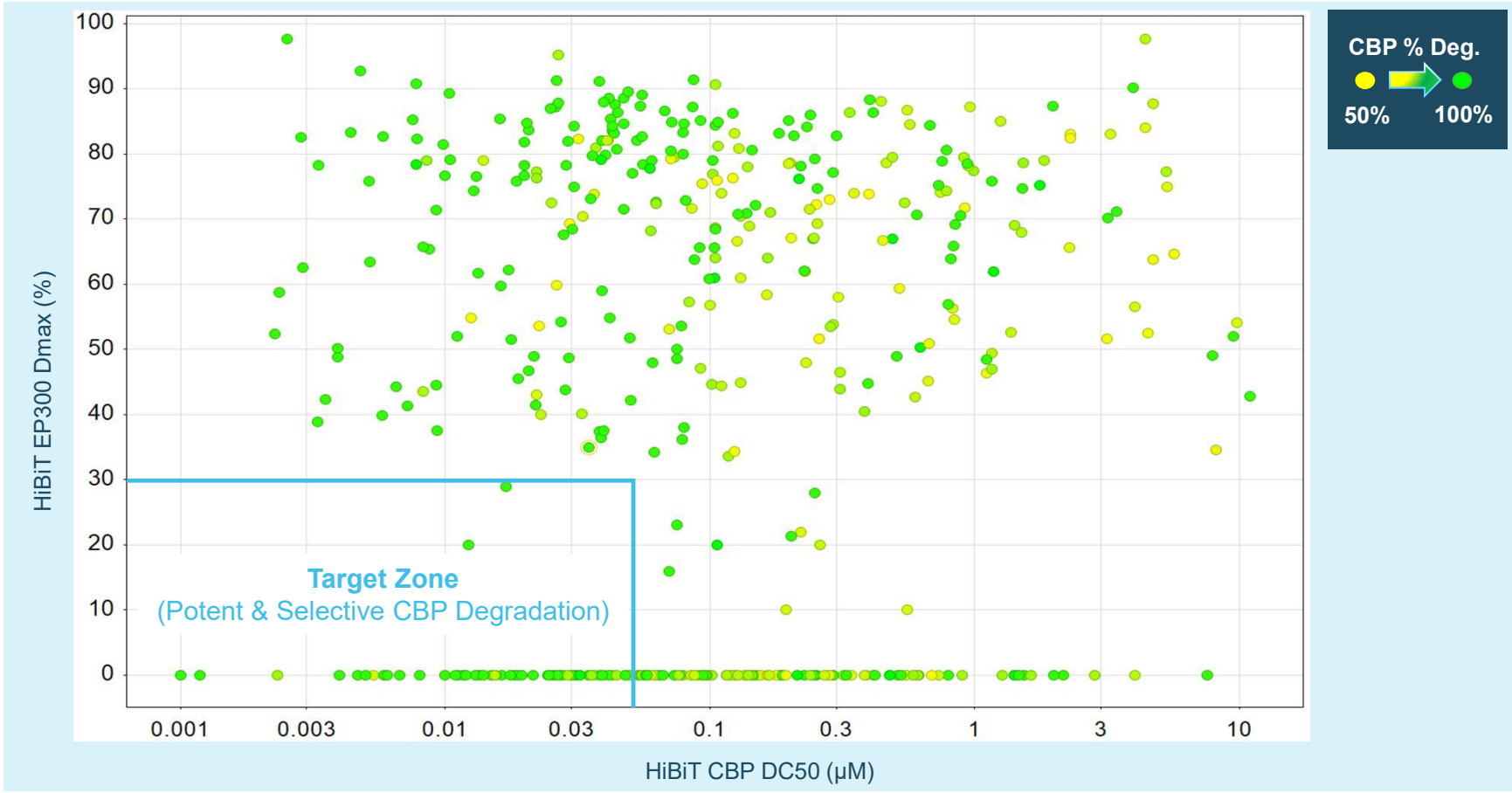
Notes: *EP300 loss can be imparted by any of the following genetic alterations: deep deletion, high impact mutation with loss of heterozygosity, multiple high impact mutations, one moderate impact mutation and one or more moderate or high impact mutations, moderate impact mutation with loss of heterozygosity, or low gene expression. **Sources**: DRG Epidemiology Data, TCGA Analysis

CBP Selective Degrader Evolution Has Yielded Fast Kinetics, and Complete Target Degradation with Selectivity Over EP300



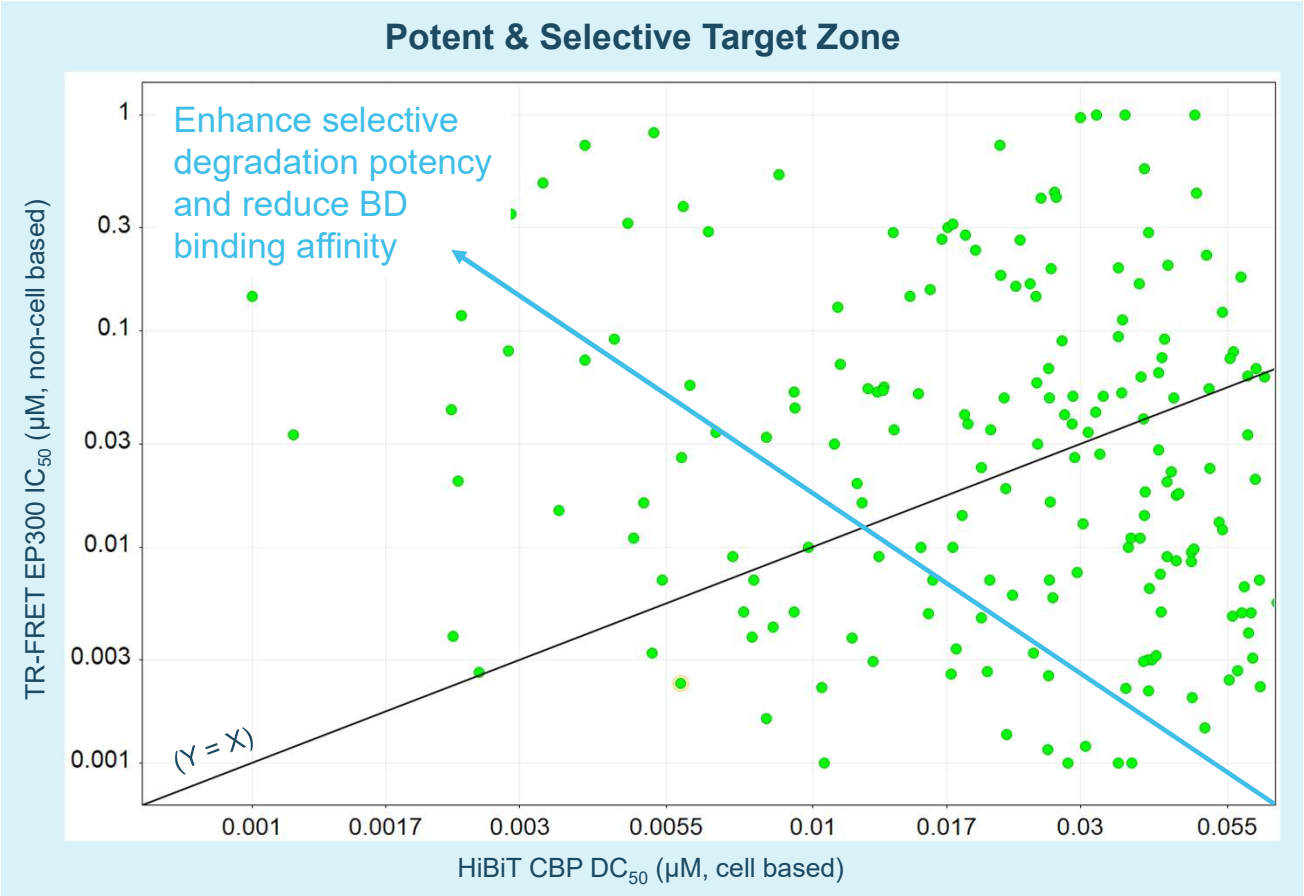
	dCBP-1	dCBP-7	dCBP-4	dCBP-5	dCBP-8
Rate	0.7	0.6	0.7	1.1	1.8
Dmax	75%	90%	95%	90%	95%
Dmax50	5 nM	14 nM	0.4 nM	0.04 nM	0.09 nM

Enriching Pool of CBP Degraders with Desired Potency and Selectivity



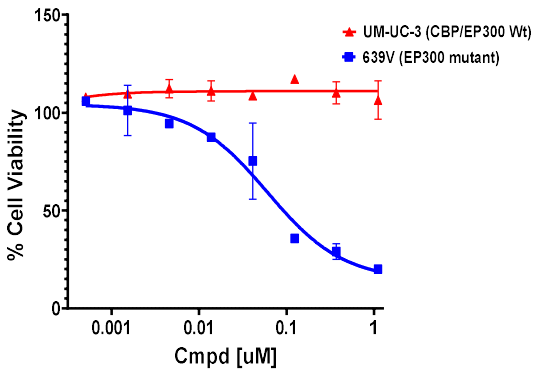
Enhancing Selective CBP Degradation While Significantly Reducing CBP/EP300 Bromodomain Binding

- Established robust SAR to significantly reduce CBP & EP300 bromodomain binding affinities while enhancing selective CBP degradation potency
- The majority of our potent CBP selective degraders have > 10μM binding affinity (TR-FRET IC_{50}) for BRD4 with no observed degradation of BRD4

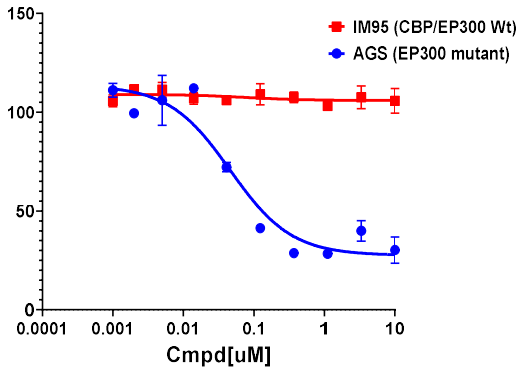


Advanced CBP Selective Degraders Validate Synthetic Lethal Hypothesis Across EP300mut Cell Lines

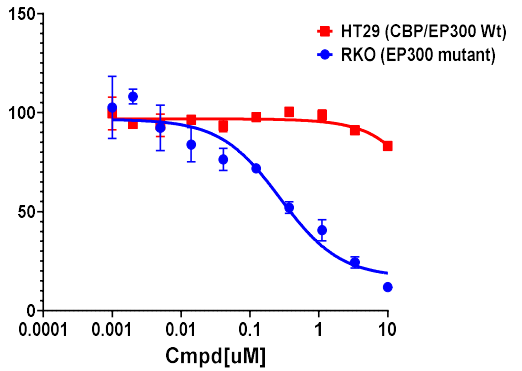
Bladder



Gastric



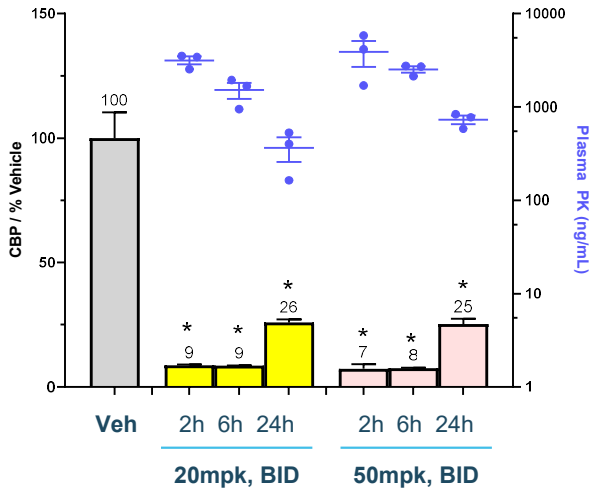
Colorectal

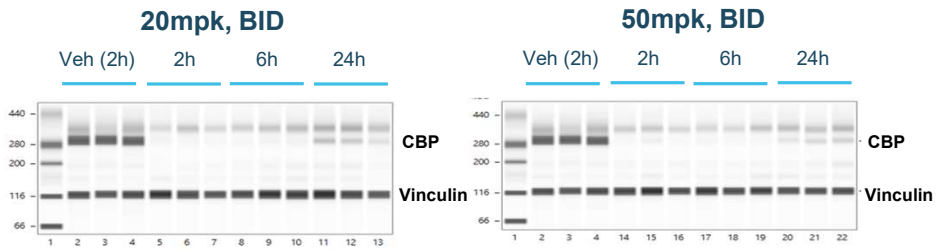


	Bladder		Gastric		Colorectal	
Cell line	639V	UM-UC-3	AGS	IM95	RKO	HT29
GI50 (mM)	0.6	>10	0.04	>10	0.2	>10

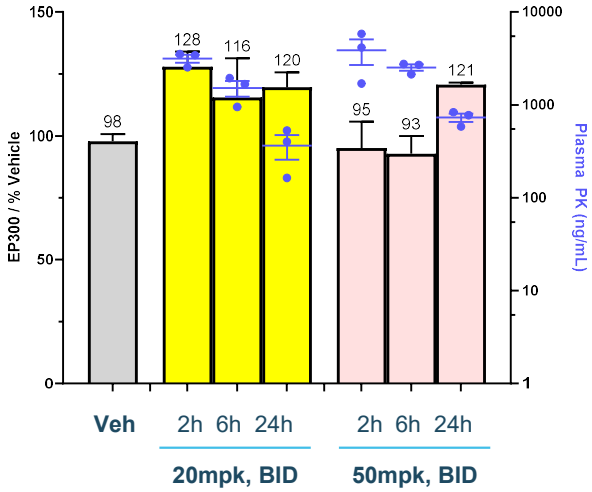
CBP Selective PD in a CBP/EP300 Wild Type Cell Line (MM1S)

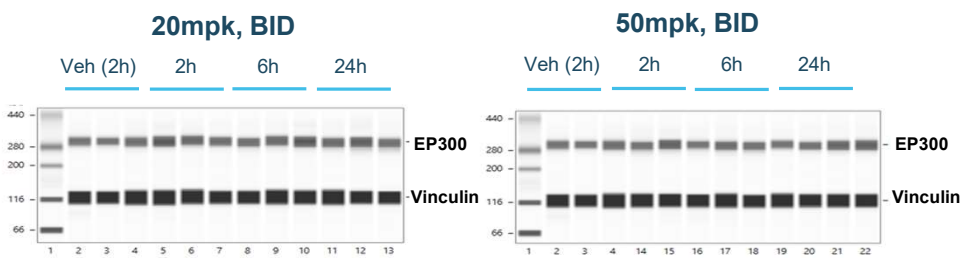
CBP





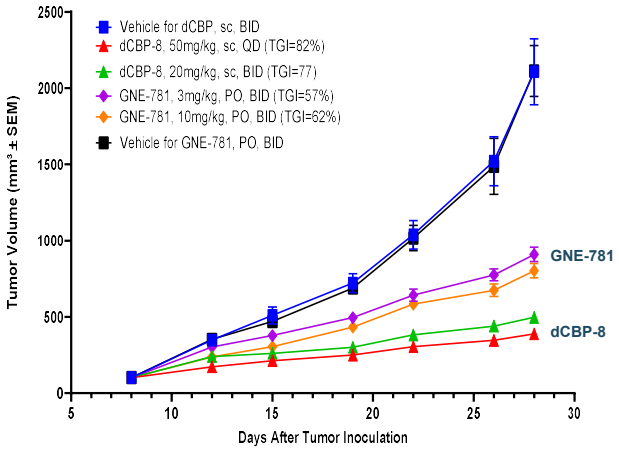
EP300



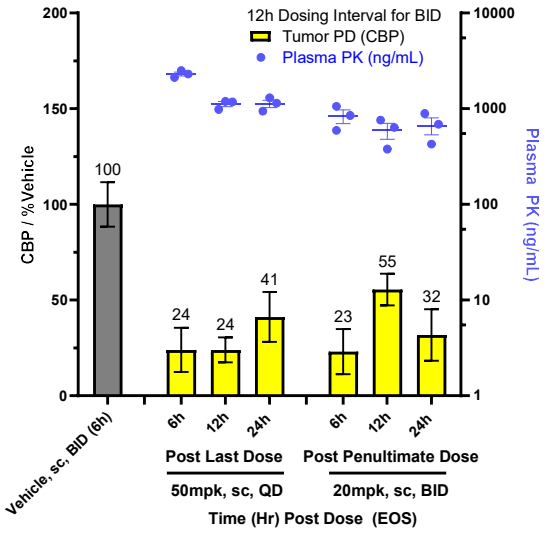


CBP Selective Degraders Demonstrate Durable Degradation and Tumor Growth Inhibition in EP300mut Colorectal Model, Superior to Small Molecule Dual Inhibition

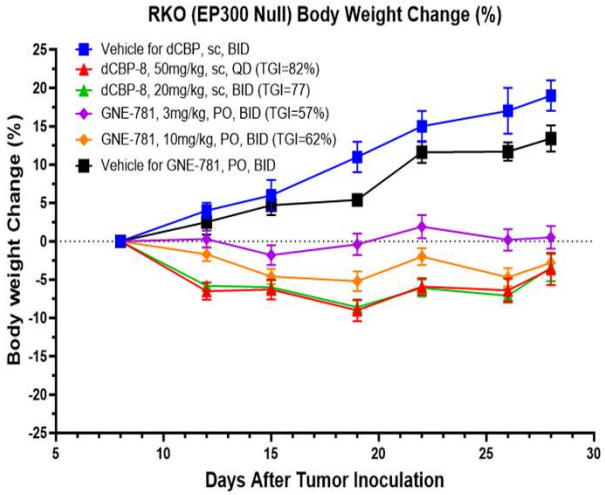
RKO (EP300 Null) TV



dCBP-8 PKPD in RKO (EP300 Null)



RKO (EP300 Null) Body Weight Change (%)



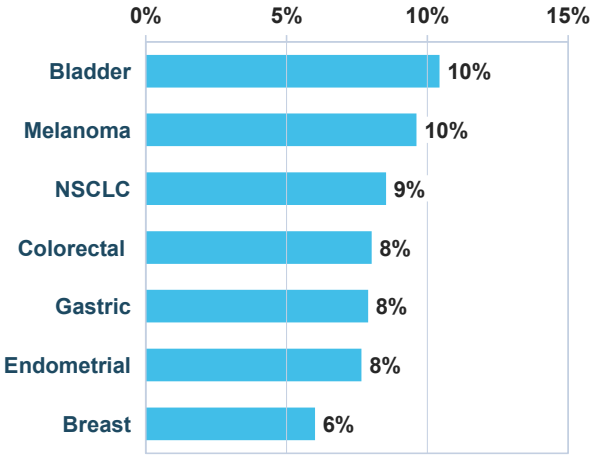
In vivo, selective CBP degraders show improved TGI compared to a dual CBP/EP300 small molecule bromodomain inhibitor at tolerated doses

Selective Degradation of EP300 to Address CBP Mutation and EP300 Dependent Cancers

An EP300 Selective Degrader Would Address 250K+ Patients Annually Across Solid Tumors and Heme Malignancies

CBP Mutant Tumors + **EP300 Dependent Cancers** → **Large Addressable Population (G7)**

CBP Loss Rate*



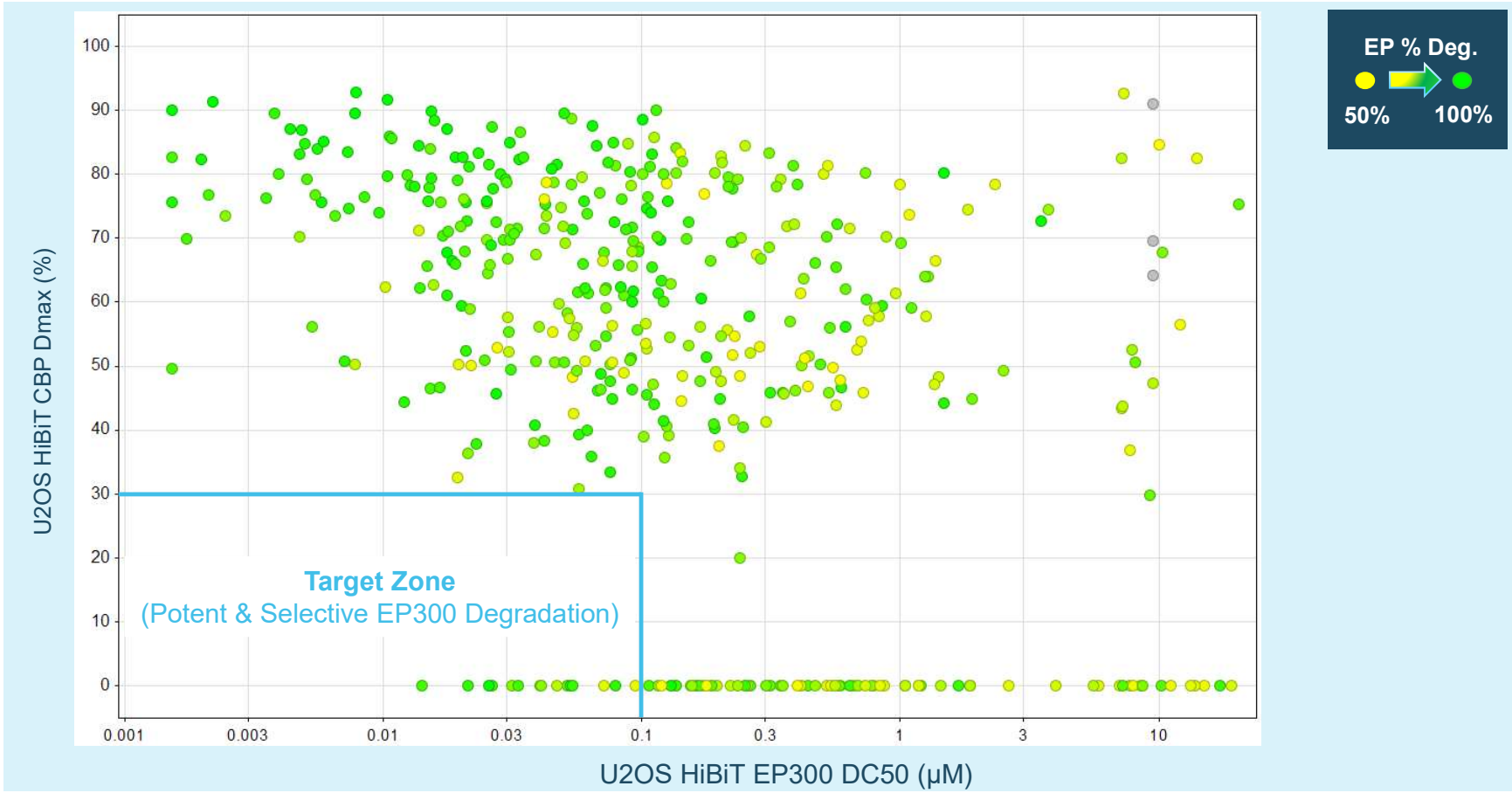
- **Solid tumors**
  - AR+ mCRPC
- **Hematologic malignancies**
  - DLBCL
  - Multiple Myeloma

- **250K+ patients annually***
- **Identification via existing diagnostic tests**

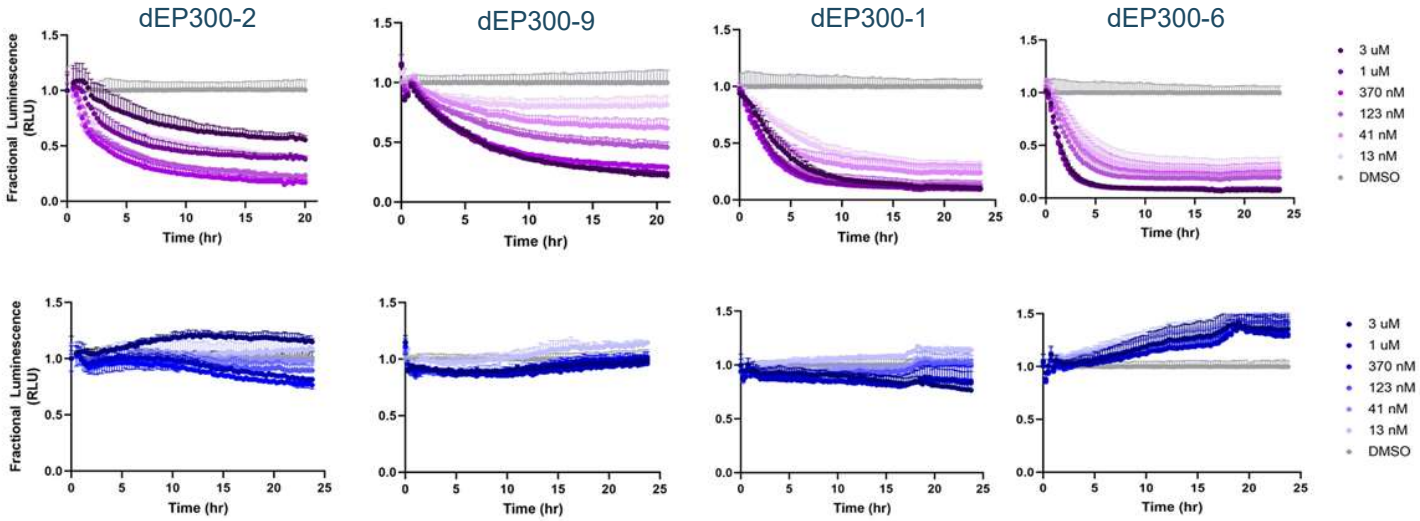
Additional opportunities include EP300-dependent malignancies (e.g., NHL), or CBP loss (e.g., ovarian cancer, SCCHN, cervical cancer)

Notes: *CBP Loss can be imparted by any of the following genetic alterations: deep deletion, high impact mutation with loss of heterozygosity, multiple high impact mutations, one moderate impact mutation and one or more moderate or high impact mutations, moderate impact mutation with loss of heterozygosity, or low gene expression **Sources**: DRG Epidemiology Data, TCGA Analysis; 1. Welti et al. Cancer Discov 2021; Zou et al. Acta Pharmacologica Sinica 2019; Bluemn et al. Cancer Cell 2017 2. Morin et al. Clin Cancer Res; 22(9); 2290–300; Pasqualucci *Nature*. 2011 March 10; 471(7337): 189–195

Continuing to Discover Potent, Selective EP300 Degraders



Improving Rate and Depth of Degradation As We Advance EP300 Selective Chemical Matter

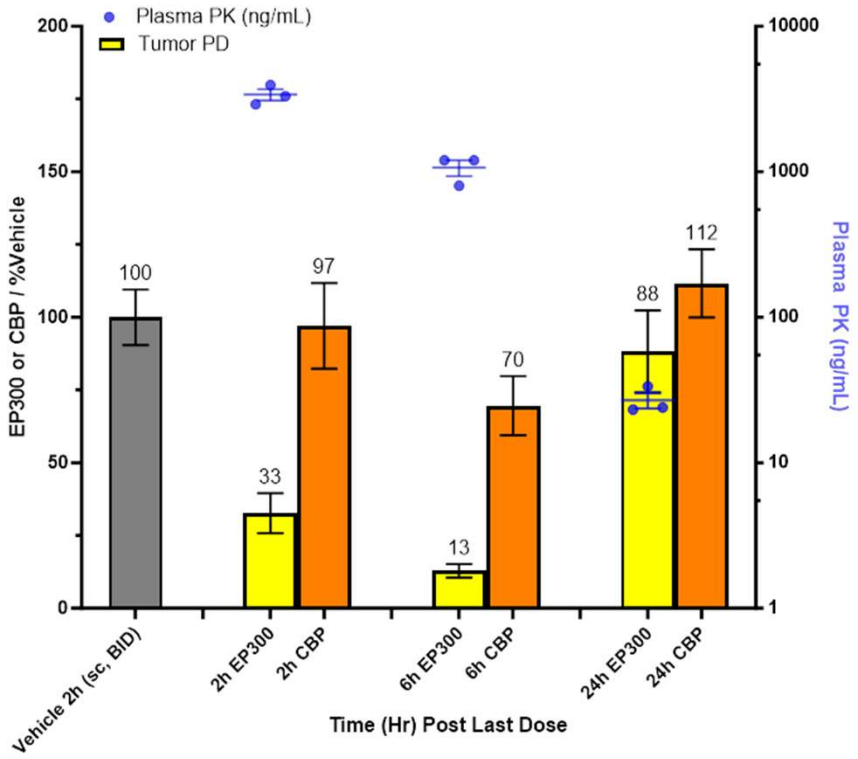


	dEP300-2	dEP300-9	dEP300-1	dEP300-6
Max Rate	0.4	0.3	0.35	0.75
Dmax	80%	80%	92%	94%

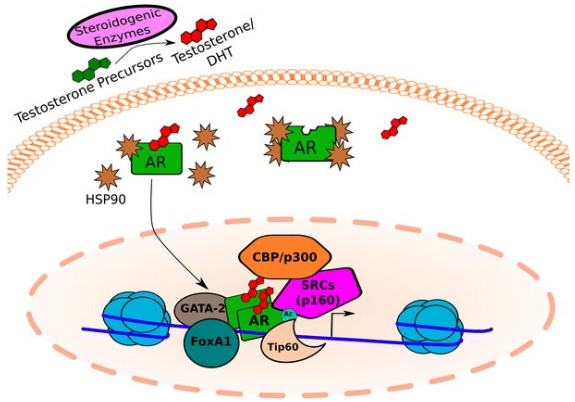
Improvement of both the depth and rate of degradation while maintaining selectivity

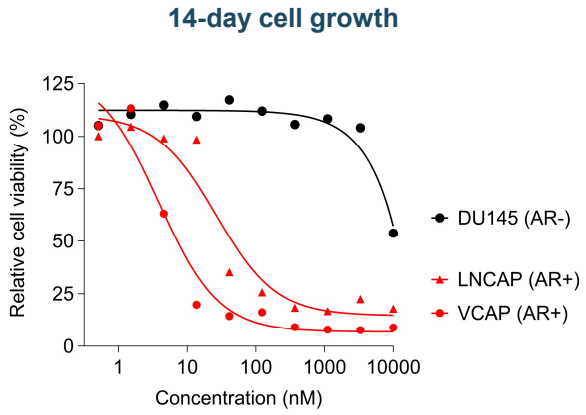
EP300 Biased Degrader dEP300-2: In Vivo Validation of Selectivity in CBP/EP300 Wild Type Line (MM1S)

dEP300-2 PKPD (50mg/kg, sc, BID)

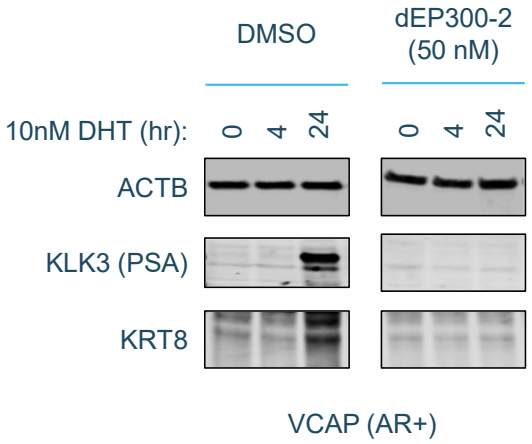


EP300 Biased Degradation Attenuates Proliferation of AR+ Prostate Lines and Blocked DHT Induced PSA Induction in VCAP Prostate Model





dEP300-2



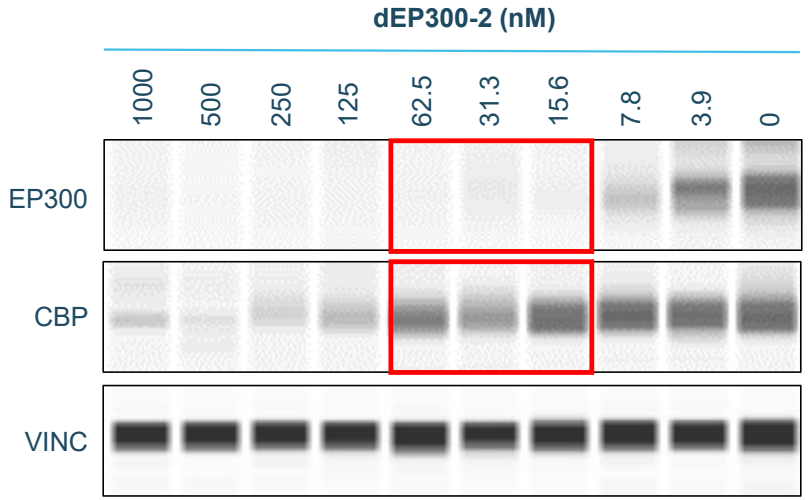
VCAP (AR+)

- EP300 biased degradation by dEP300-2 has a cell killing effect in AR+ prostate cell lines but not in AR- prostate lines
- EP300 degradation by dEP300-2 in VCAP cells blocks DHT-induced PSA/KLK3 expression
- We hypothesize that an EP300 selective degrader would be sufficient to abrogate the activity of AR

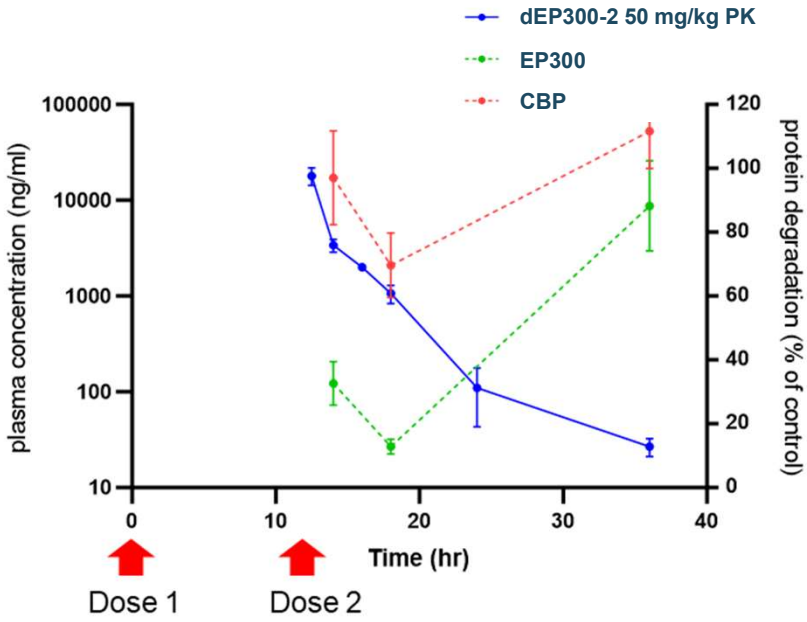
Foley & Mitsiades, 2016

dEP300-2 Can Achieve Biased Degradation of EP300 Over CBP in the VCaP (AR+) Prostate Model In Vitro and In Vivo

dEP300-2 has a Strong Selectivity Window in VCAP (AR+) Prostate Cells

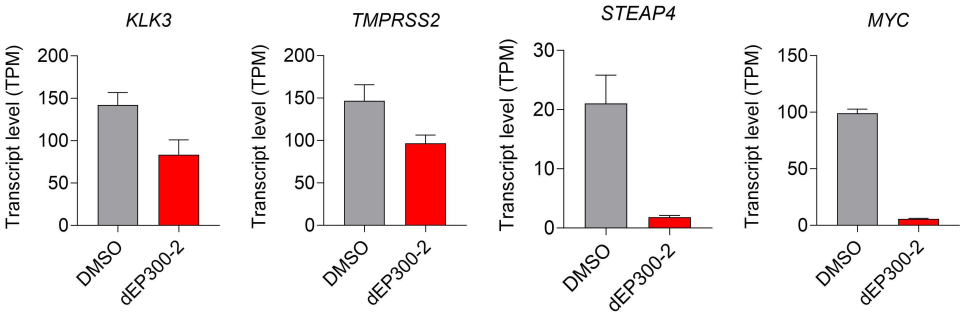


VCAP (AR+) Prostate CDX Model



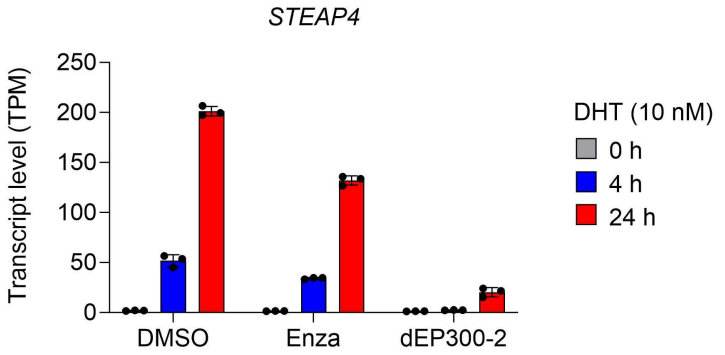
mRNA Sequencing Demonstrates That Dep300-2 Attenuates AR-signaling In VCAP Cells Both *In Vitro* And *In Vivo*

dEP300-2 treatment attenuates AR-driven transcription in VCAP xenograft tumors



- VCAP CDx tumors underwent single-day treatment with either vehicle or dEP300-2 (50 mg/kg, BID) and samples were collected 6 h after the final dose.

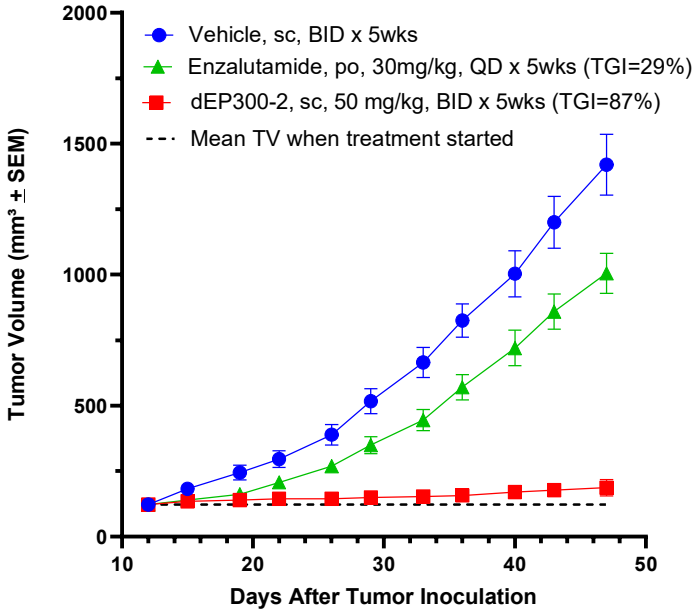
dEP300-2 blocks the upregulation of AR targets in VCAP cells following DHT stimulation

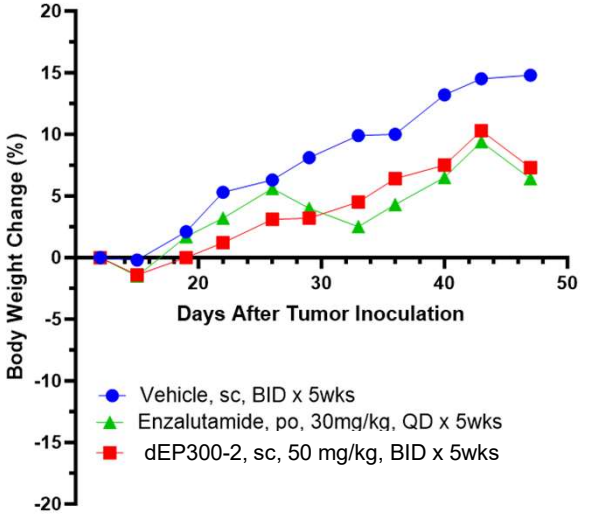


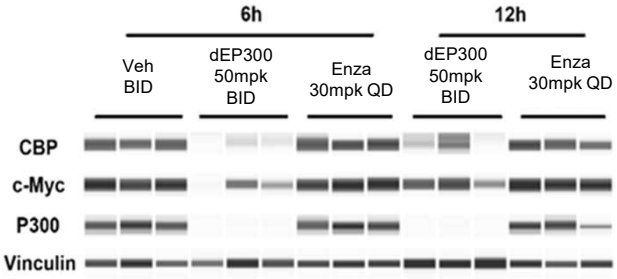
- VCAP cells were incubated in media containing charcoal-stripped serum and either DMSO, Enzalutamide (1 uM) or dEP300-2 (50 nM) for 24 h. Cells were stimulated with for 0, 4 or 24 h.

In Vivo POC: EP300 Degradation Results in Significant Tumor Growth Inhibition in AR+ VCaP Prostate Model and Positively Differentiates from Enzalutamide

VCAP (AR+) Prostate CDX Model







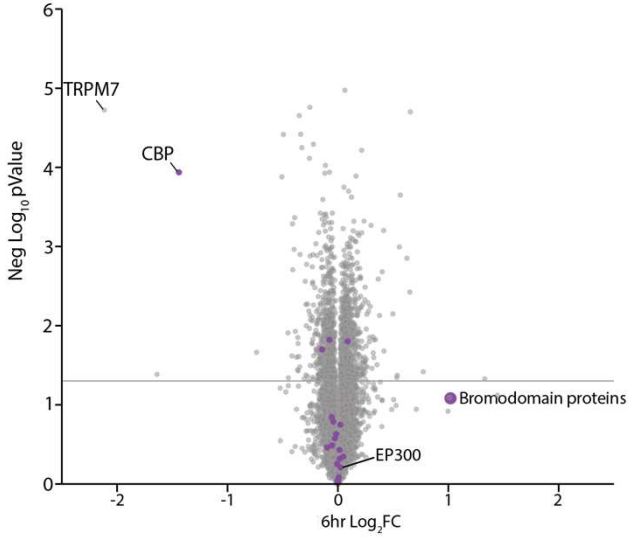
End of study PD

- Accumulation of dEP300-2 in tumor observed at end of study that is consistent with partial degradation of CBP observed in some animals
- Future studies will explore more selective degraders

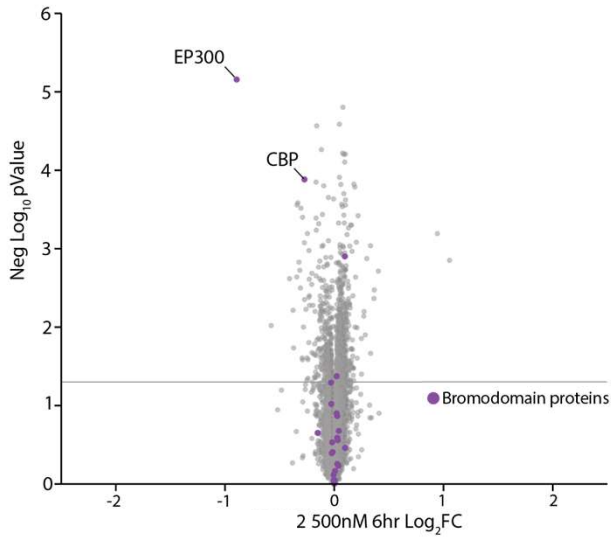
Tolerability of CBP and EP300 Degraders

Global Proteomics to Assess Selectivity in U2OS Cell Lines

CBP Selective Degrader U2OS (Osteosarcoma) Cell Line
6hrs – 100nM

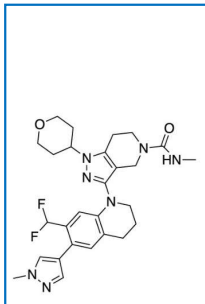


EP300 Biased Degrader U2OS Cell Line
6hrs – 500nM



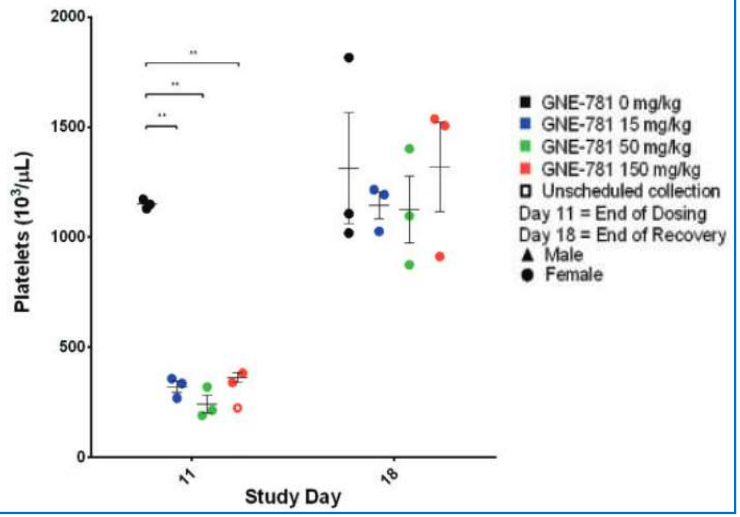
- **CBP selective degrader (dCBP-7) shows depletion of CBP (~70%) without any loss of EP300 or other bromodomain proteins, including BRD4**
- **EP300 biased degrader (dEP300-2) shows EP300 is the most depleted protein (~55%), but there is also partial loss of CBP (~15%)**

Genentech and Cellcentric Have Reported Significant, But Reversible, Thrombocytopenia for Their Dual CBP/EP300 Bromodomain Inhibitors

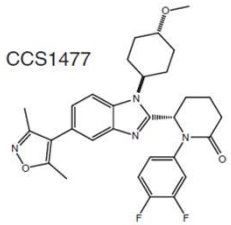


GNE-781

CBP IC_{50}: 0.9 nM
p300 IC_{50}: 1.2 nM
BRD4(1) IC_{50}: 5100 nM
Fold selectivity: >4250



GNE



CCS1477

	K_D (nmol/L)
p300	1.3
CBP	1.7
BRD4	222

Table 3: Treatment-emergent AE

TEAE	Any Grade n=28 (%)	Grade 3/4 n=28 (%)
Thrombocytopenia	16 (57)	11 (39)
Fatigue	15 (54)	1 (4)
Anaemia	12 (43)	9 (32)
Hypercalcaemia	10 (36)	1 (4)
Diarrhoea	9 (32)	0
Blood creatinine increased	9 (32)	0
Decreased appetite	8 (29)	1 (4)
Pneumonia	7 (25)	6 (21)
Acute kidney injury	3 (11)	3 (11)

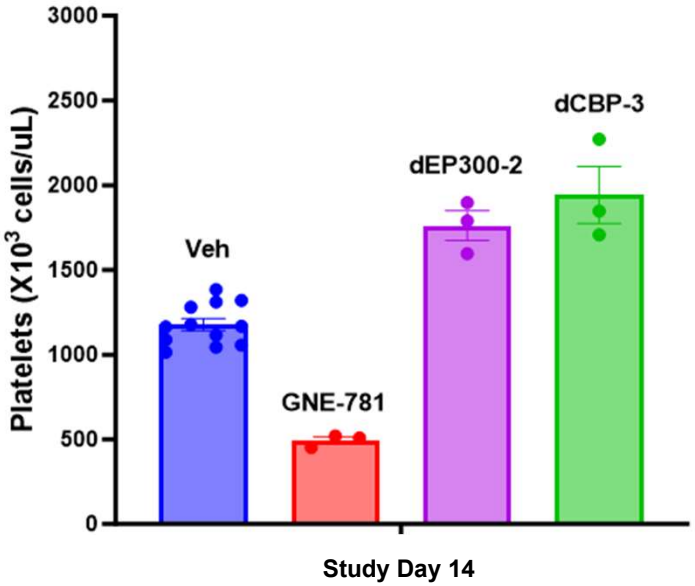
any grade: ≥25% and/or grade 3/4: ≥10%

Cellcentric

A key question for our degrader programs has been whether having a selective degrader would mitigate this risk

Katavolos et al., Toxicol Pathol, 2020

Selective CBP or Selective EP300 Degradation Does Not Show Thrombocytopenia in Mice at Pharmacologically Relevant Doses



- Vehicle, sc, BID
- GNE-781, 10mpk, PO, BID
- dCBP-3, 50mpk, sc, BID ★
- dEP300-2, 50mpk, sc, BID ★

★ Efficacious dose (TGI >75%)

** Reported Historical Platelet Mean (Low-High; 95% Interval): 963 (476-1611)*

- The observation of decreased platelet counts recapitulated in mice with a dual bromodomain inhibitor to a similar degree as reported
- In contrast, CBP and EP300 degraders show a slight increase in platelets at relevant doses

Summary

- *In Vivo* proof of concept obtained for both CBP and EP300 selective degraders
- Both CBP and EP300 selective degraders able to demonstrate efficacy without thrombocytopenia
- Foghorn aggressively advancing both programs in parallel

Acknowledgements

Thank you!