Targeted Protein Degradation and The Chromatin Regulatory System

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Foghorn Research is Focused on Chromatin Biology

Dysregulated chromatin underlies oncogenesis

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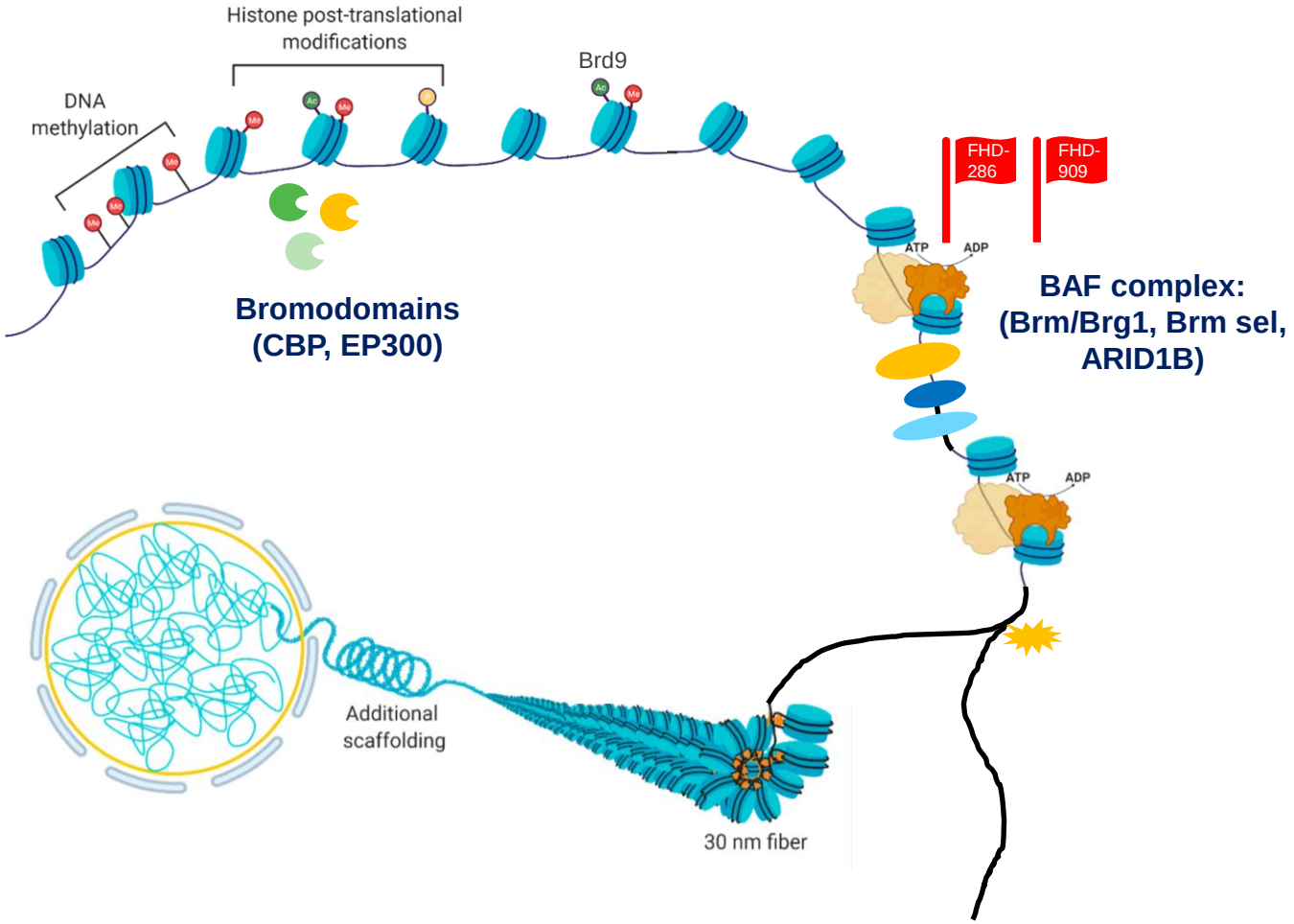
Gene expression in the right cells at the right time is critical for normal growth, development, and homeostasis



Broad Pipeline Across a Range of Targets and Modalities

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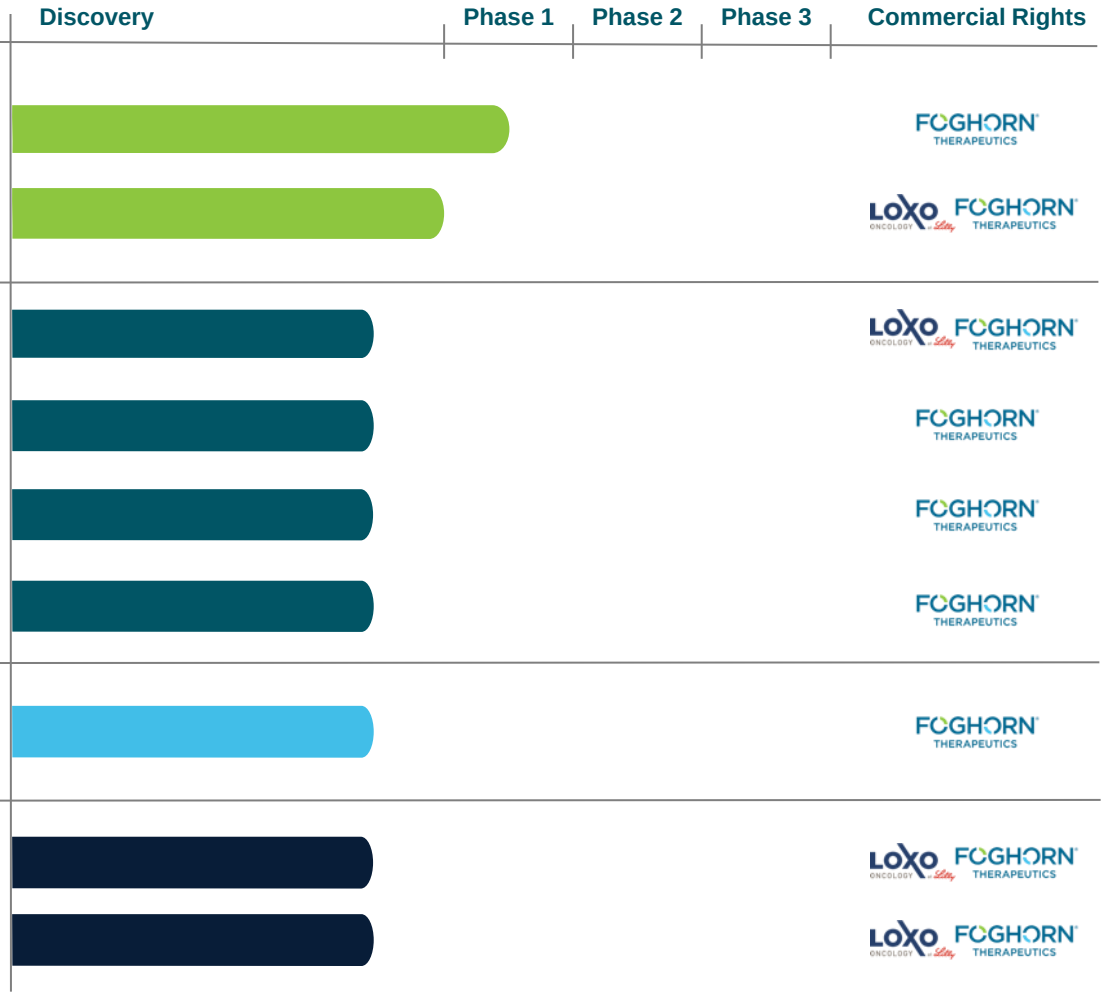
Modality	Program	Disease	Commercial Rights
Enzyme Inhibitors	FHD-286 (BRG1/BRM)	Relapsed/Refractory AML	FOGHORN THERAPEUTICS
	FHD-909 (Selective BRM)	BRG1 mutant cancers (e.g., ~8-10% of NSCLC, bladder, endometrial, colorectal)	LOXO ONCOLOGY at Lilly / FOGHORN THERAPEUTICS
Protein Degraders	Selective BRM	BRG1 mutant cancers (e.g., ~8-10% of NSCLC, bladder, endometrial, colorectal)	LOXO ONCOLOGY at Lilly / FOGHORN THERAPEUTICS
	Selective CBP	EP300 mutant cancers (e.g., ~5-10% of bladder, gastric, breast, NSCLC, colorectal)	FOGHORN THERAPEUTICS
	Selective EP300	EP300 dependent cancers (e.g., prostate, DLBCL), CBP mutant cancers (e.g., ~9-10% of NSCLC, bladder, melanoma)	FOGHORN THERAPEUTICS
	Selective ARID1B	ARID1A mutant cancers (~5% of all solid tumors)	FOGHORN THERAPEUTICS
Transcription Factor Disruptors	Undisclosed	Undisclosed	FOGHORN THERAPEUTICS
Partnered Program	Undisclosed	Undisclosed	LOXO ONCOLOGY at Lilly / FOGHORN THERAPEUTICS
3 Discovery Programs	Undisclosed	Undisclosed	LOXO ONCOLOGY at Lilly / FOGHORN THERAPEUTICS



CBP and EP300 Proteins… A Decades Long Challenge in Selectivity

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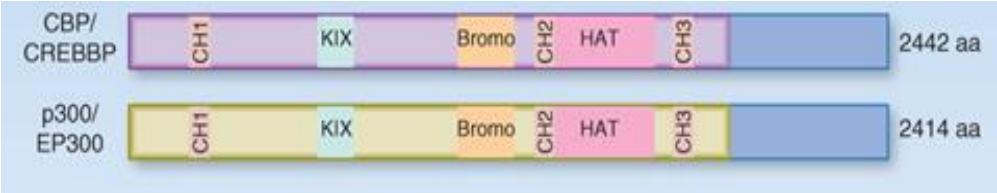
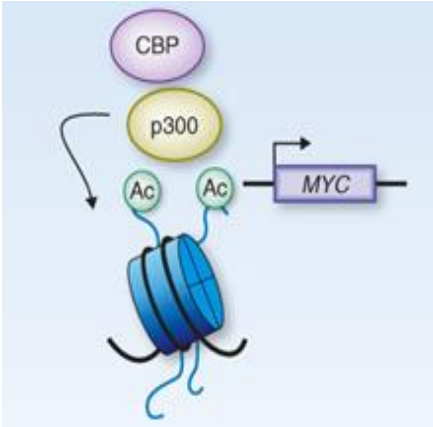
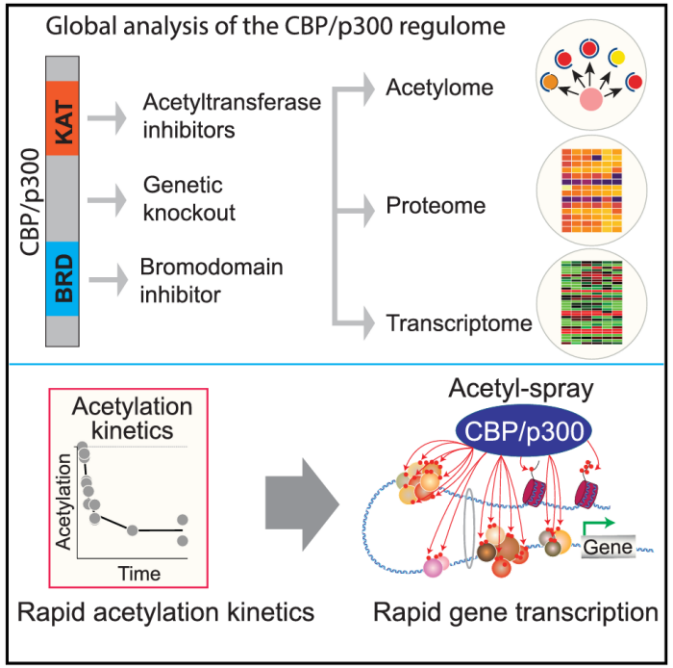
CBP and EP300 have multiple conserved domains, thus achieving selectivity with a small molecule is a significant challenge



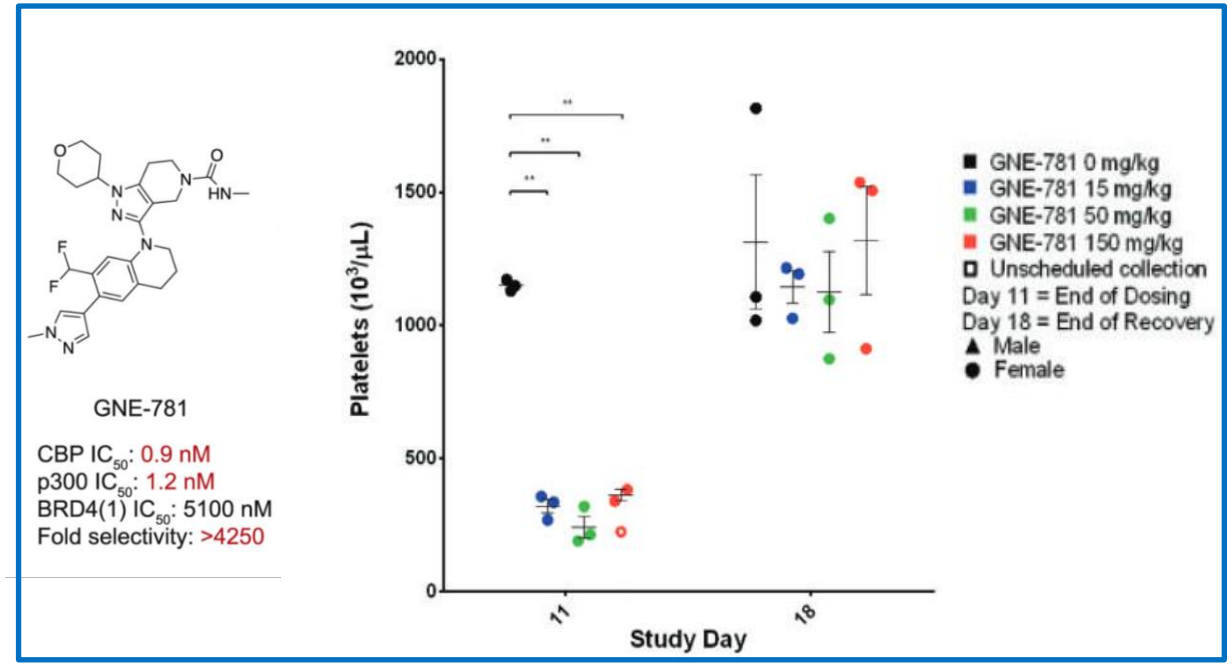


(Kadoch, Cancer Discovery 2016)

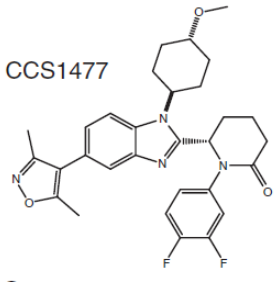


- CBP and EP300 are chromatin regulators and histone acetyltransferases
- EP300/CBP regulate protein abundance through acetylation-dependent protein stability
- RNAi and CRISPR screens point to a synthetic lethal relationship that can be exploited in a variety of cancer indications
- Several domains within CBP/EP300 with known binders and inhibitors
  - HAT enzymatic inhibitors
  - Bromodomain inhibitors
- Dual targeting has revealed tolerability and safety issues

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



Genentech



	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

Katavolos et al., Toxicol Pathol, 2020

Selective Degradation of CBP to Address Mutant EP300 Cancers

- CBP Selective Degrader Poster (D. Sappal):
  Session: Tuesday, April 9, 1:30pm–5pm; 6067 / 26
- Long-Acting Injectable Platform Poster (M. Lin):
  Session: Wednesday, April 10, 9am–12:30pm; 7185 / 26

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

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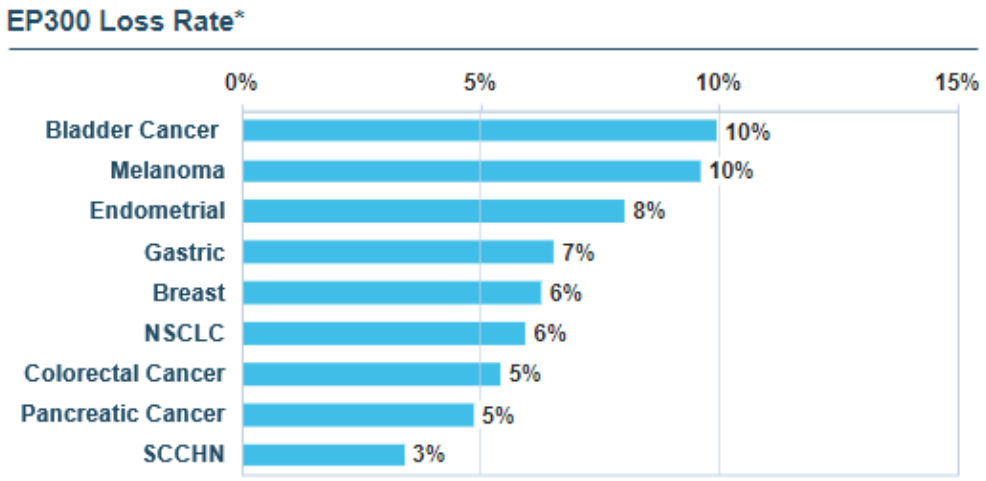
EP300 Mutant Cancers



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

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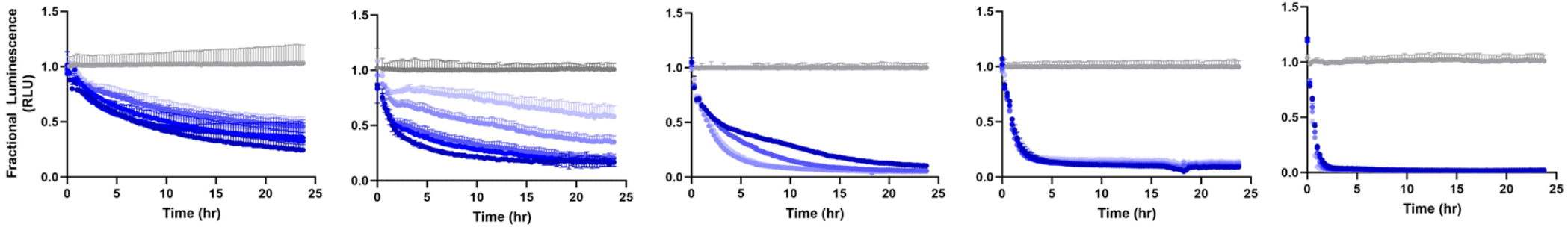
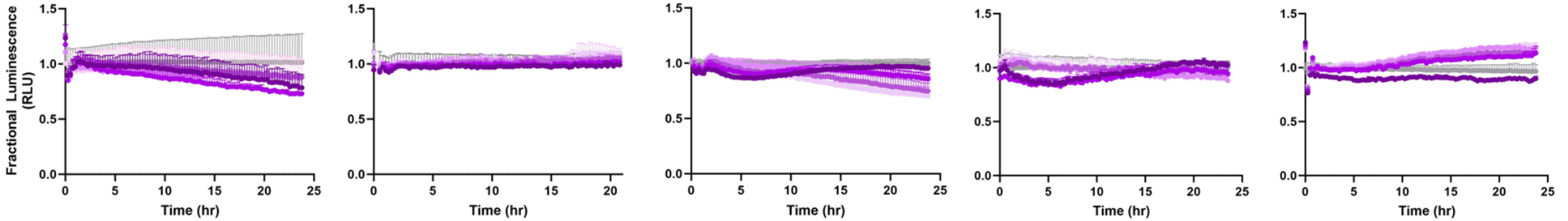
	dCBP-1	dCBP-7	dCBP-4	dCBP-5	dCBP-10
CBP					
EP300					
Max Rate	0.4	0.6	0.7	1.1	2.2
Dmax	75%	90%	95%	90%	98%

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

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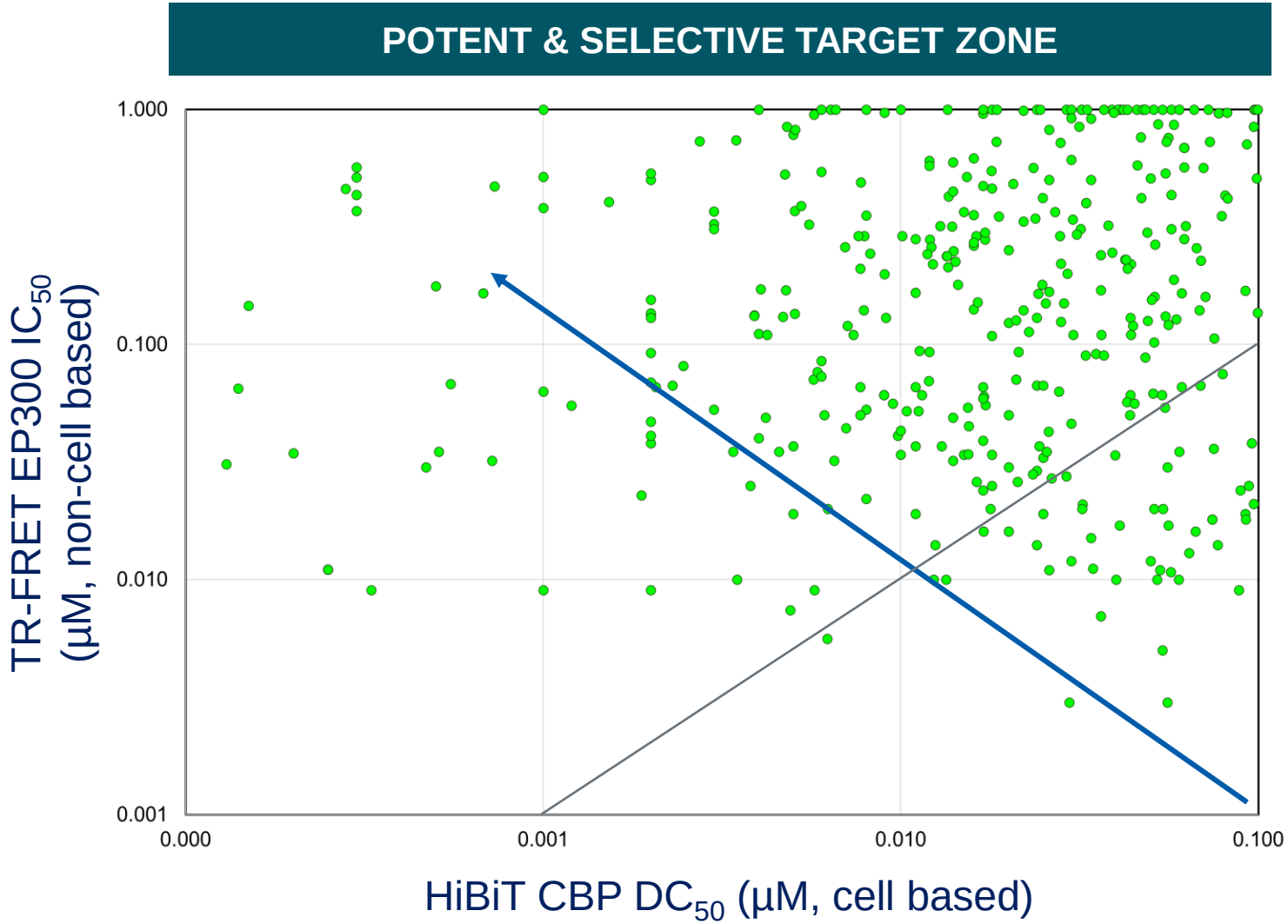
- Established robust SAR to significantly reduce CBP & EP300 bromodomain binding affinities while enhancing selective CBP degradation potency.
- The majority of our potent CBP selective degraders have > 10µM binding affinity (TR-FRET IC_{50}) for BRD4 with no observed degradation of BRD4.



Advanced CBP Selective Degraders Validate Synthetic Lethal Hypothesis Across EP300$_{mut}$ Cell Lines

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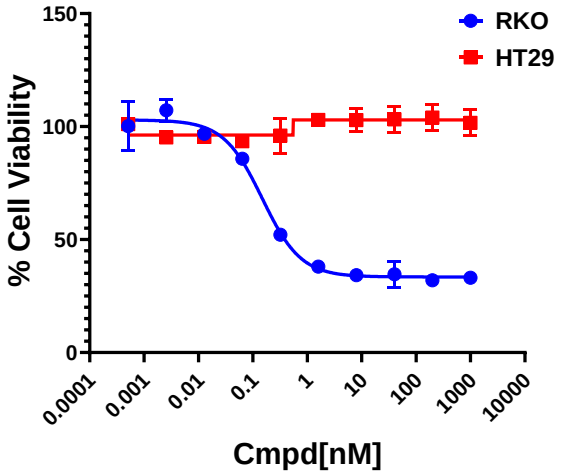
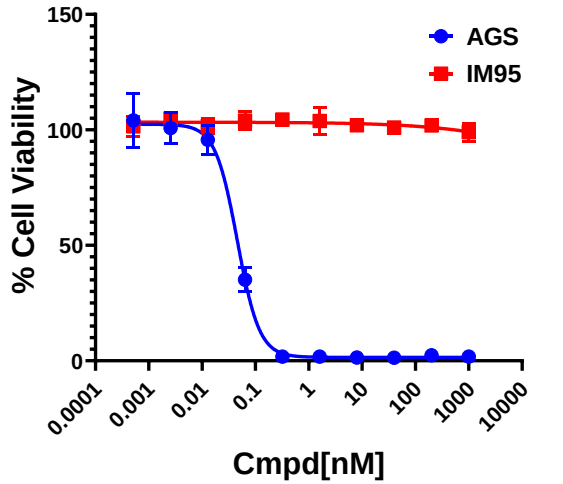
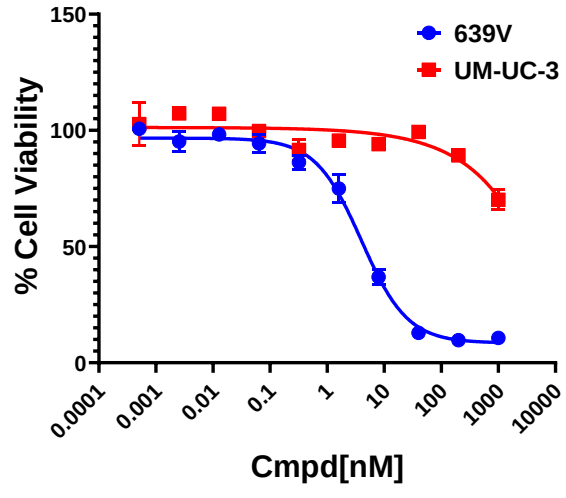
Colorectal



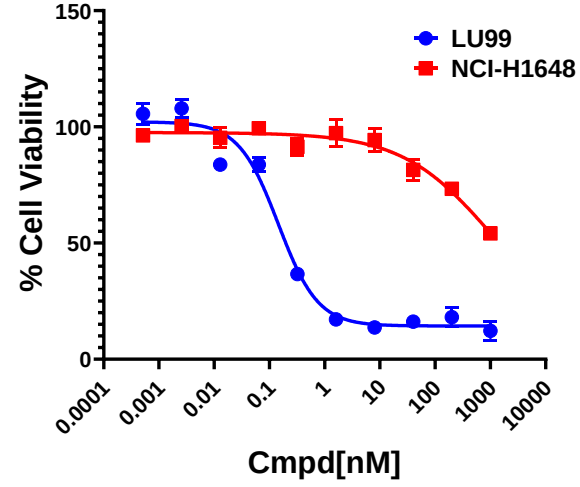
Gastric



Bladder



Lung



	COLORECTAL		GASTRIC		BLADDER		LUNG	
Cell line	RKO	HT29	AGS	IM95	639V	UM-UC-3	LU99	NCI-H1648
GI50 (nM)	0.15	>1000	0.045	>1000	3.9	>1000	0.14	972.8

Selective CBP Protein Degradation Results in Significant Tumor Growth Inhibition in Colorectal and Bladder EP300 Null Models

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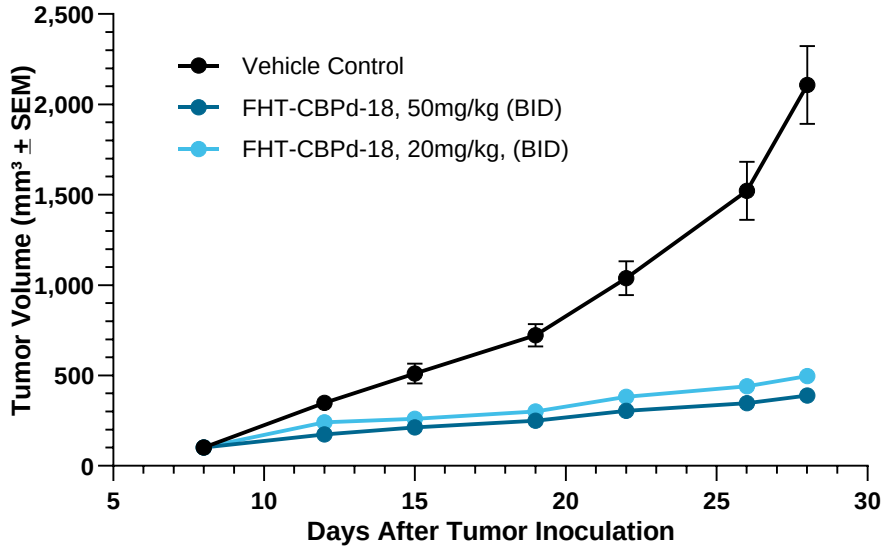
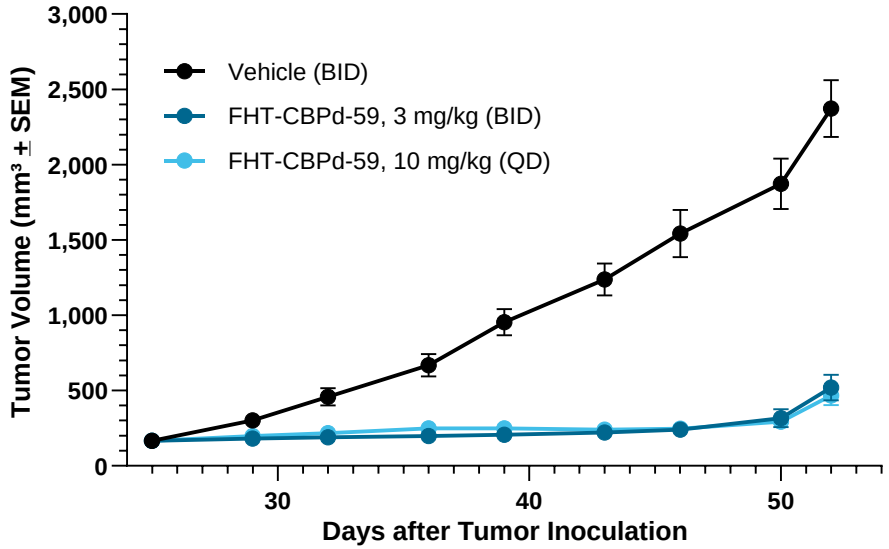
COLORECTAL

RKO (EP300 Null) Model



BLADDER

639V (EP300 Null) Model



Selective CBP Protein Degradation Results in Tumor Regression in Gastric EP300 Null Model

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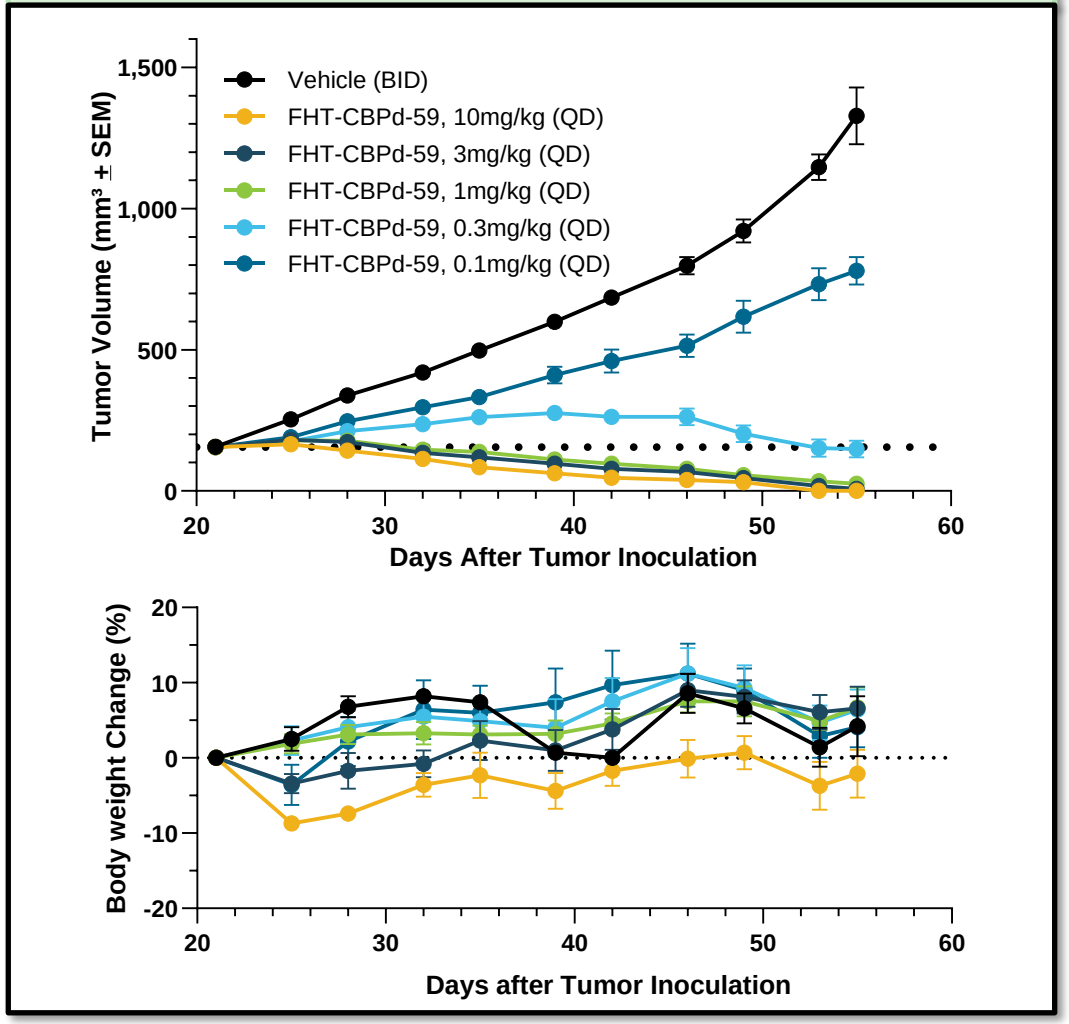
GASTRIC

AGS (EP300 Null) Model



Long-Acting Injectable Formulations Provide 2 Weeks of Sustained PK and CBP Degradation From a Single Dose (sc or im)

2-week PK/PD study in RKO tumor-bearing mice

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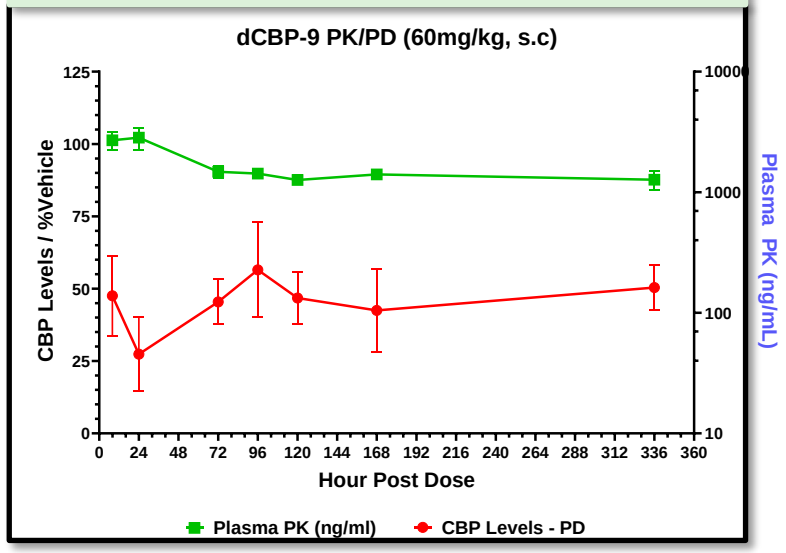
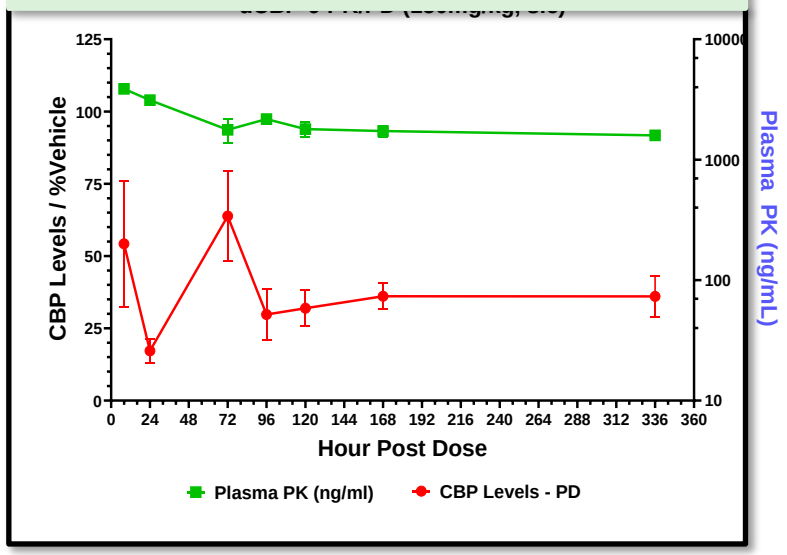
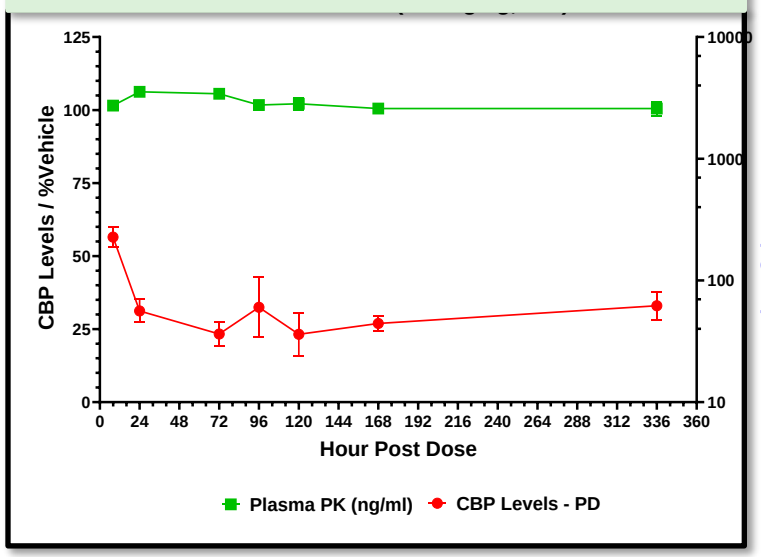
dCBP-59 PK/PD (60mg/kg, sc)



dCBP-59 PK/PD (150mg/kg, sc)



dCBP-59 PK/PD (150mg/kg, im)



In Contrast to Competitor Compounds, Selective CBP Degraders Do Not Show Thrombocytopenia at Efficacious Doses

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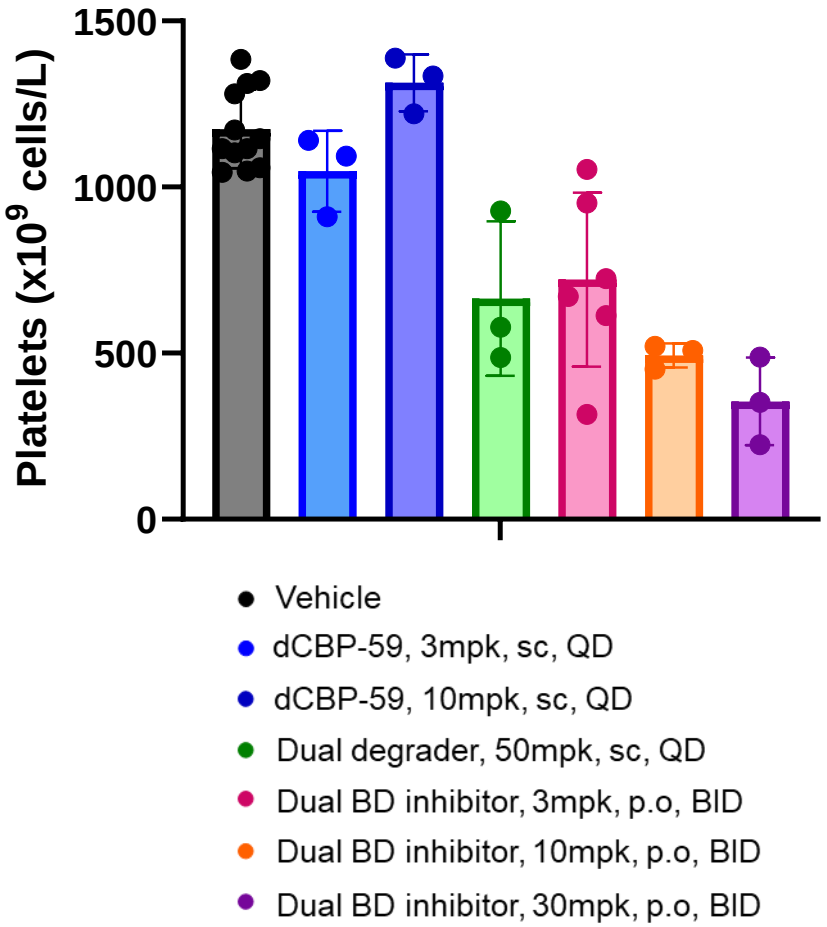
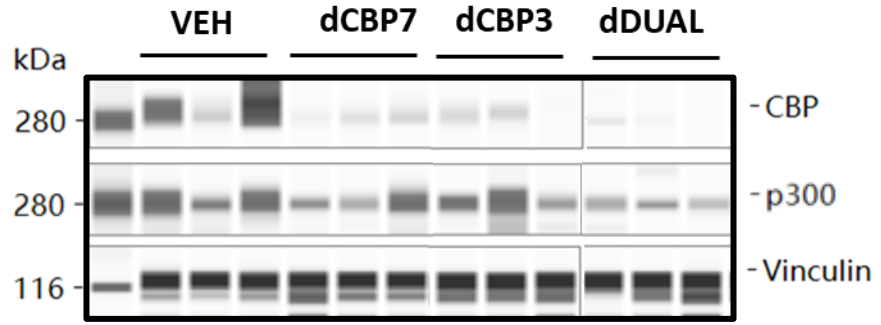


- Selective CBP degradation has no impact on platelet count following 14-days of dosing in an investigational safety study in mice
- Dual CBP/EP300 inhibition or degradation results in a significant decrease in platelets
- Confirmed degradation of CBP in mouse liver and spleen (shown below) tissues taken at the end of an earlier investigational safety study



CBP Selective Degrader Spares Megakaryocytes In Vivo

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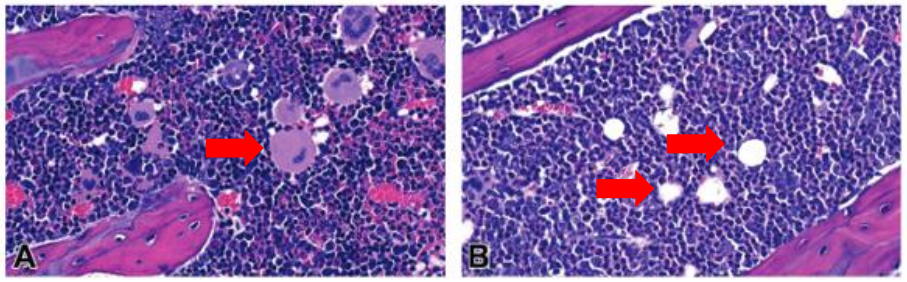
GNE781 (dual BDi)

- Internally validated observation of decreased platelet counts at efficacious doses/exposures
- Dual CBP/EP300 degradation recapitulated the platelet loss seen with dual inhibition
- In addition, Genentech revealed bone marrow hypocellularity in rat (shown) and dog tox studies

Ctrl **GNE-781**

Rat

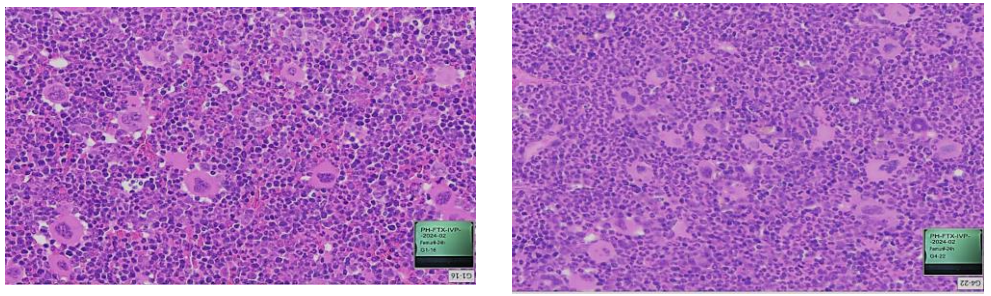


CBP Selective Degraders

- To date, we have not observed thrombocytopenia with any of our CBP degraders
- Selective degraders exhibit reduced effect on megakaryocyte differentiation and platelet production in vitro as compared to dual BD inhibitors
- Bone marrow H&E staining in the mouse shows sparing of megakaryocytes in vivo

Ctrl **dCBP-99 10mg/kg QD**

Mouse



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

- EP300 Selective Degrader Poster (M. Zimmerman): Session: Tuesday, April 9, 1:30pm-5pm; 6064 / 23

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An EP300 Selective Degrader Would Address 100K+ Patients Annually Across Solid Tumors and Heme Malignancies

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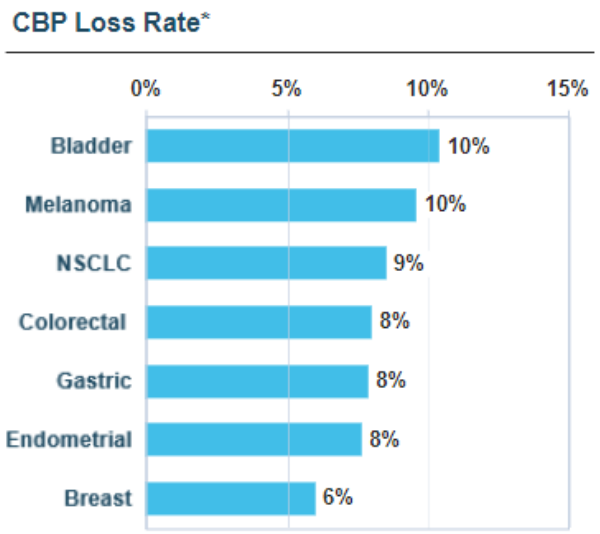
CBP Mutant Tumors + **EP300 Dependent Cancers** → **Large Addressable Population (G7)**



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

- **100K+ 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

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

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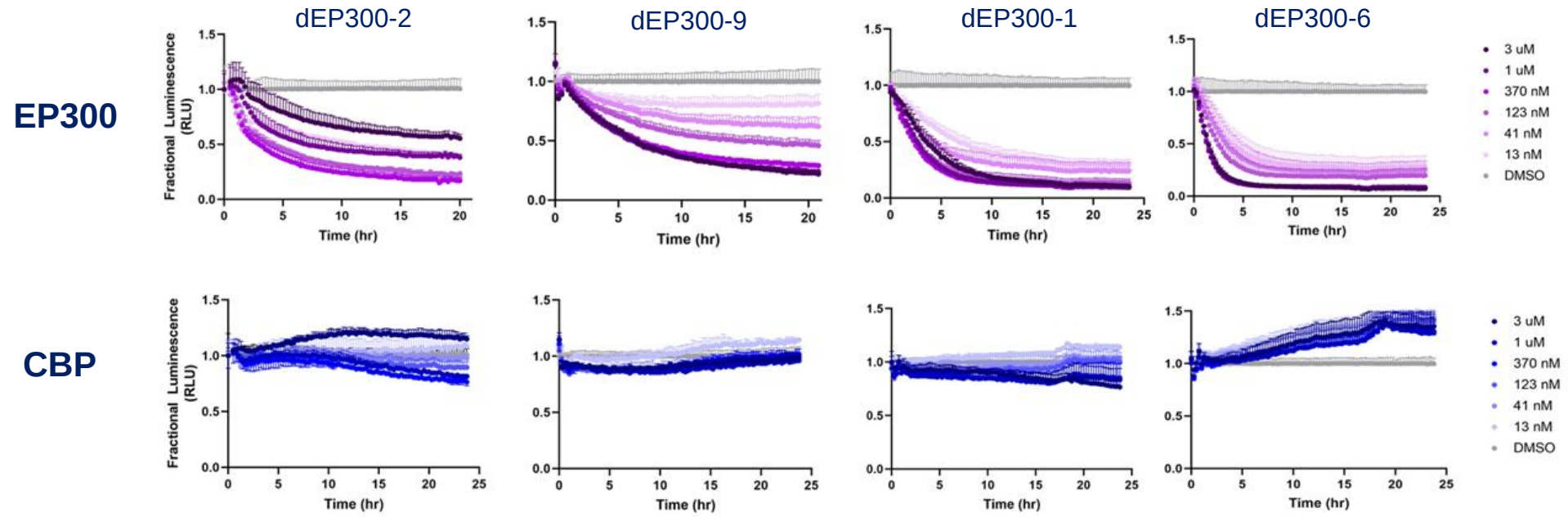

	dEP300-2	dEP300-9	dEP300-1	dEP300-6
Max Rate	0.4	0.3	0.35	0.75
Dmax	80%	80%	92%	94%

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

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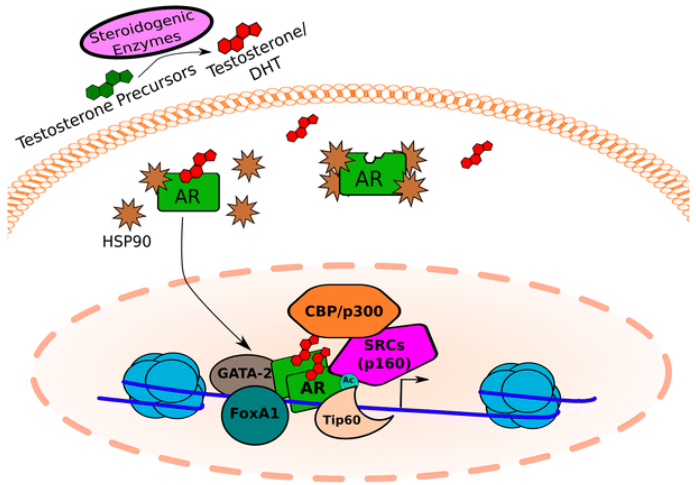
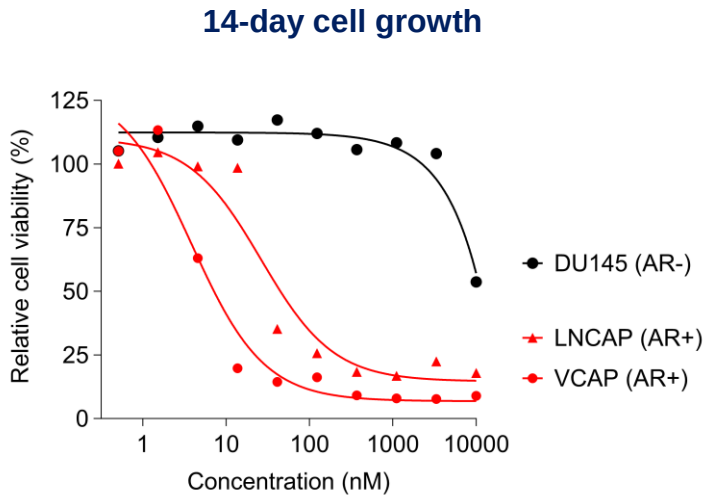
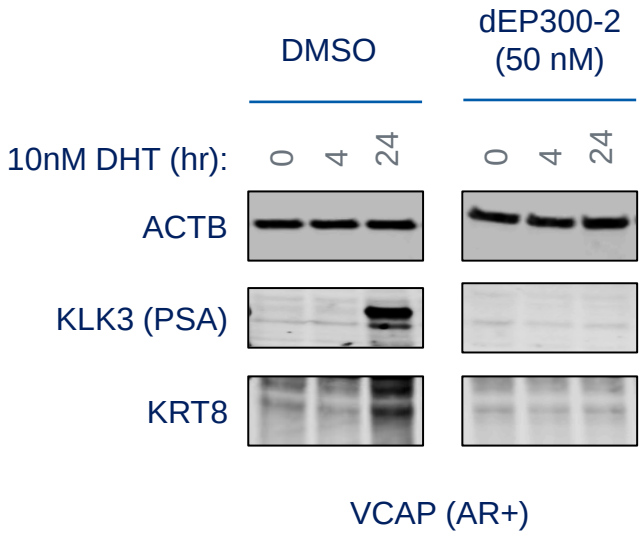




dEP300-2



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 & Mitsaiades, 2016

mRNA Sequencing Demonstrates That dEP300-2 Attenuates AR-signaling in VCAP Cells Both *In Vitro* And *In Vivo*

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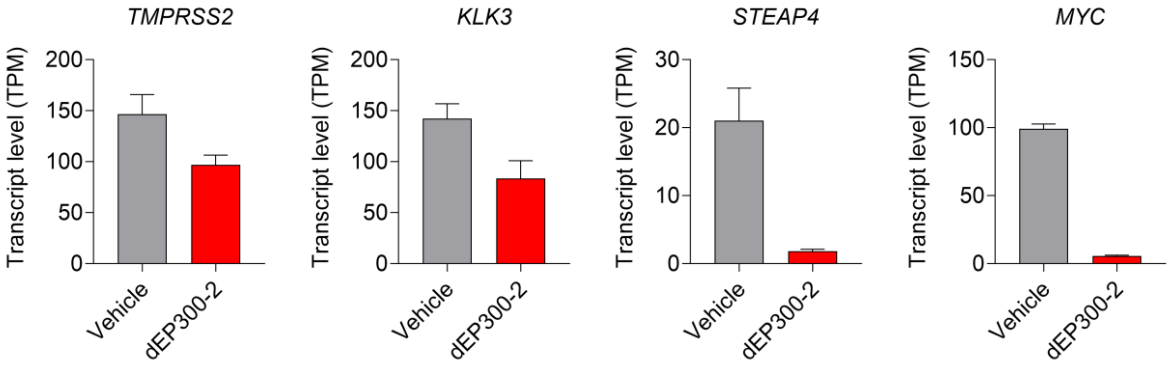
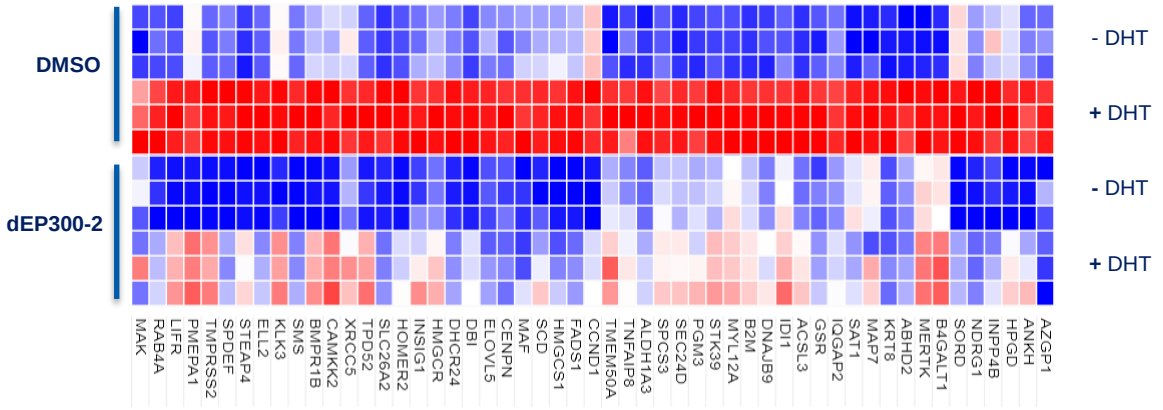
dEP300-2 TREATMENT ATTENUATES AR-DRIVEN TRANSCRIPTION IN VCAP XENOGRAFT TUMORS



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

dEP300-2 BLOCKS THE UPREGULATION OF AR TARGETS IN VCAP CELLS FOLLOWING DHT STIMULATION

VCAP (partially castration-resistant)



- 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 or 24 h

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

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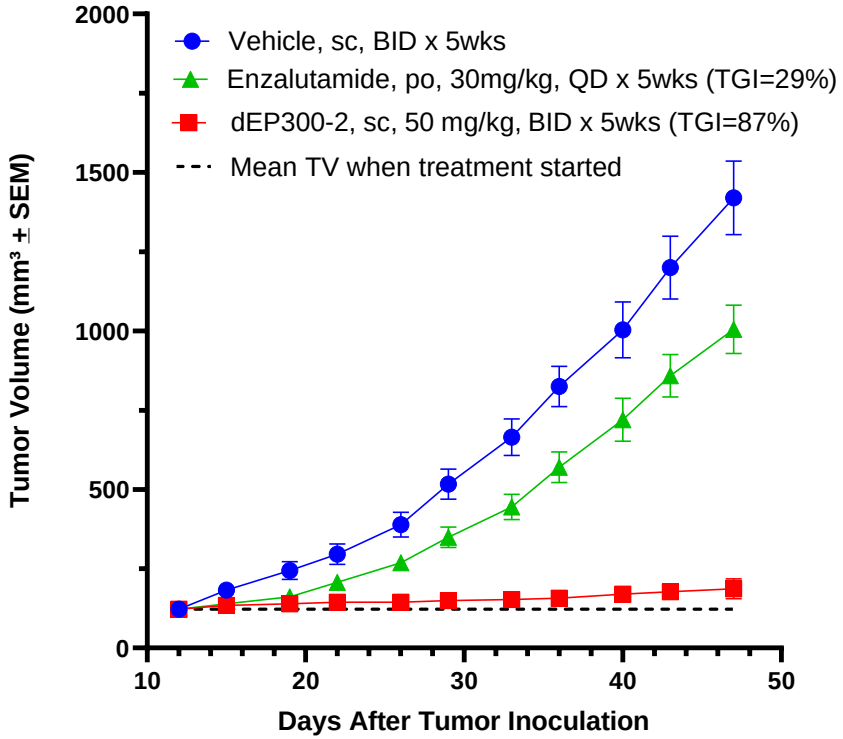
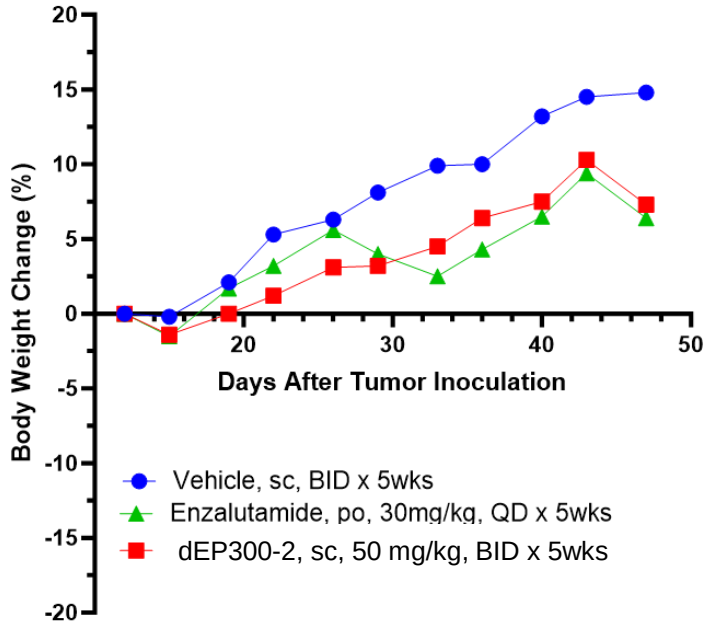
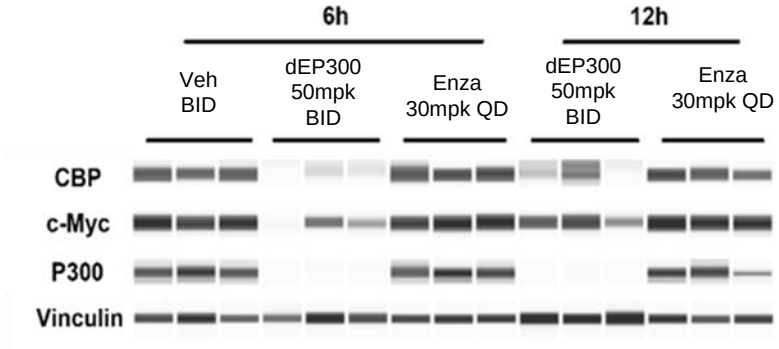
VCAP (AR+) Prostate CDX Model







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

EP300 Dependency in Hematological Malignancies

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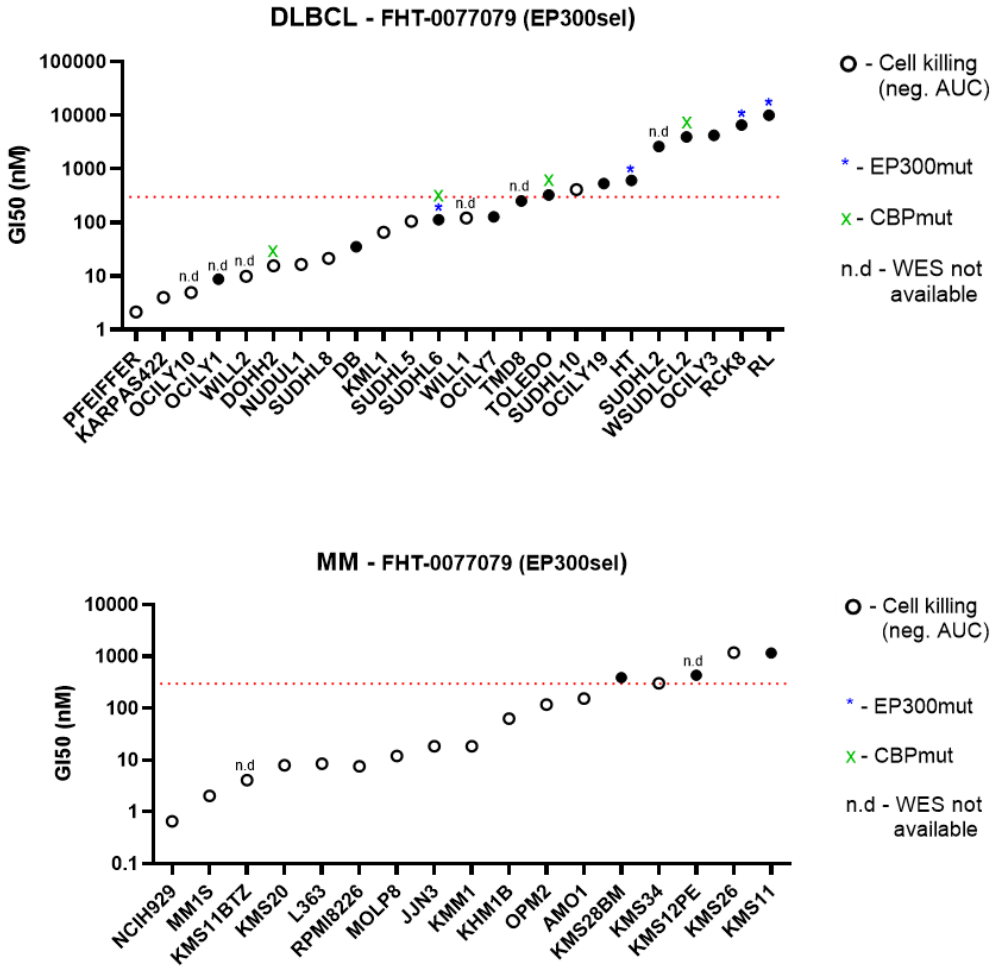

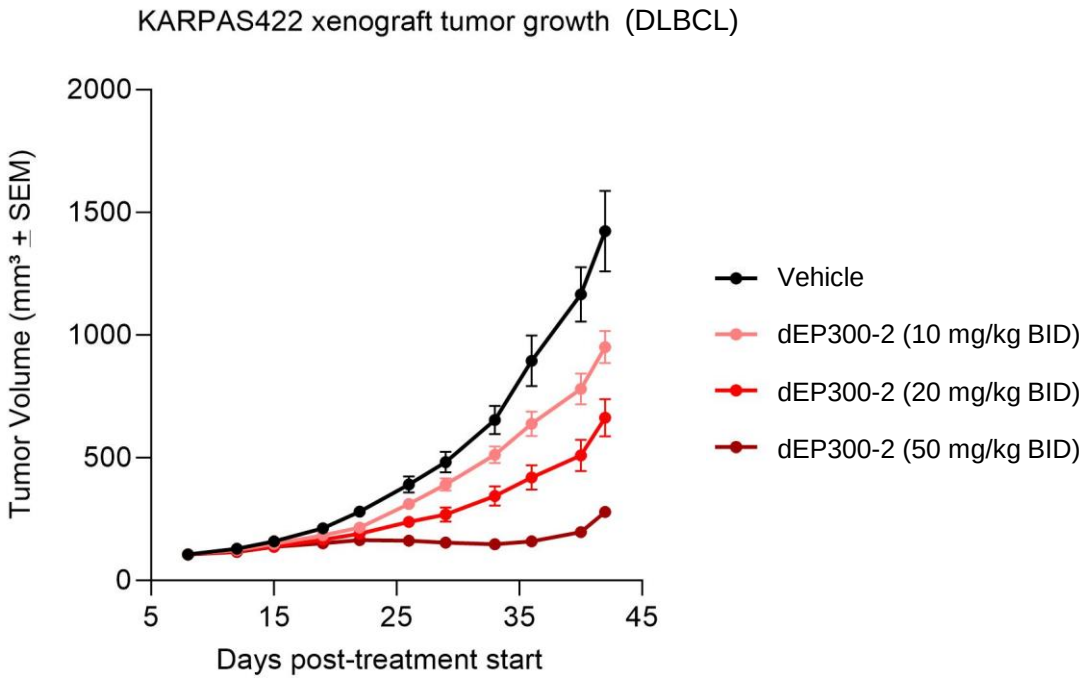

- **Additional in vitro anti-proliferation studies are ongoing in AML and other NHL/B-cell malignancies**
- **Considering an in vitro PDX screen across B-cell heme malignancies**

EP300 Degraders Do Not Show Thrombocytopenia at Efficacious Doses

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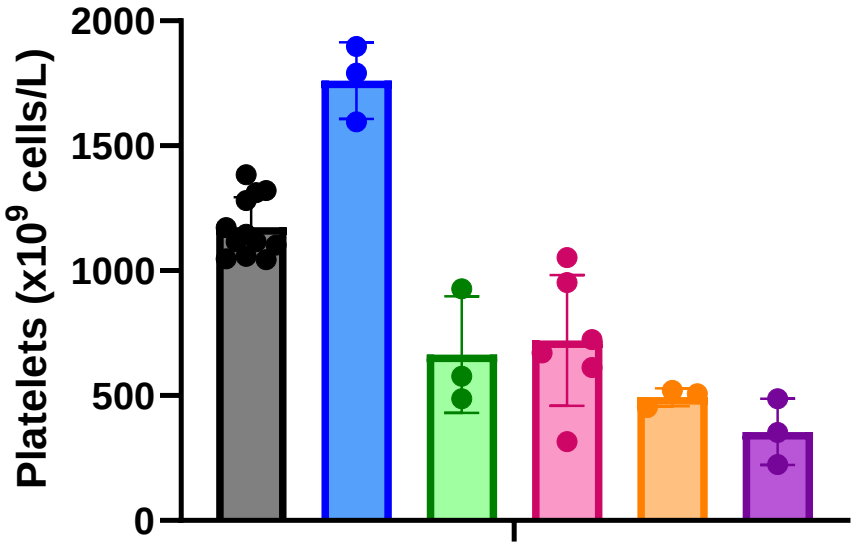

- Vehicle
- dEP300, 50mg/kg, sc, BID
- Dual degrader, 50mg/kg, sc, QD
- Dual BD inhibitor, 3mg/kg, p.o, BID
- Dual BD inhibitor, 10mg/kg, p.o, BID
- Dual BD inhibitor, 30mg/kg, p.o, BID

- At efficacious doses, our EP300 degrader shows no reductions in platelet count following 14-days of dosing in an investigational safety study in mice
- In contrast, dual CBP/EP300 inhibition or degradation results in a significant decrease in platelets

Disclosure Information

Steven Bellon

I have the following relevant financial relationships to disclose:

Employee and stockholder and option holder of Foghorn Therapeutics Inc.