Considerations for heterobifunctional degraders and translation to clinic

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Disclosure Information

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Danette L. Daniels

I have the following relevant financial relationships to disclose:

Employee of: Foghorn Therapeutics

I have no other financial relationships to disclose.

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Exciting days for degraders as potential therapeutics

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Delivering on the promise of protein degraders
Nature Reviews Drug Discovery | February 2023

Table 1 | Degraders in clinical development

Drug	Company	Target	Lead indication	Clinical stage and trial ID	Route of administration
Bavdegalutamide (ARV-110)	Arvinas	AR	Prostate cancer	Phase II, NCT03888612	Oral
ARV-471	Arvinas / Pfizer	ER	Breast cancer	Phase II, NCT04072952	Oral
ARV-766	Arvinas	AR	Prostate cancer	Phase I/phase II, NCT05067140	Oral
CFT8634	C4 Therapeutics	BRD9	Synovial sarcoma	Phase I/phase II, NCT05355753	Oral
RNK05047	Ranok	BRD4	Solid tumours and lymphoma	Phase I/phase II, NCT05487170	Intravenous infusion
AC176	Accutar Biotech	AR	Prostate cancer	Phase I, NCT05241613	Oral
AC682	Accutar Biotech	ER	Breast cancer	Phase I, NCT05080842	Oral
ARD-LDD/CC-94676	Bristol Myers Squibb	AR	Prostate cancer	Phase I, NCT04428788	Oral
BGB-16673	BeiGene	BTK	B cell malignancies	Phase I, NCT05006716	Oral
DT-2216	Dialectic	Bcl-xL	Solid tumours and haematologic malignancies	Phase I, NCT04886622	Intravenous infusion
FHD-609	Foghorn	BRD9	Synovial carcinoma	Phase I, NCT04965753	Intravenous infusion
HSK29116	Haisco	BTK	B cell malignancies	Phase I, NCT04861779	Oral
HP518	Hinova	AR	Prostate cancer	Phase I, NCT05252364	Oral
GT20029	Kintor	AR	Acne and alopecia	Phase I, NCT05428449	Topical
KT-474	Kymera/Sanofi	IRAK4	Atopic dermatitis or hidradenitis suppurativa	Phase I, NCT04772885	Oral
KT-413	Kymera	IRAK4-IMiD	MYD88 tumours	Phase I, NCT05233033	Intravenous infusion
KT-333	Kymera	STAT3	Liquid and solid tumours	Phase I, NCT05225584	Intravenous infusion
NX-2127	Nurix	BTK-IMiD	B cell malignancies	Phase I, NCT04830137	Oral
NX-5948	Nurix	BTK	B cell malignancies	Phase I, NCT05131022	Oral
CFT1946	C4 Therapeutics	BRAF-V600X	Solid tumours	IND approved, NCT05668585	Oral

AR, androgen receptor; Bcl-xL, B cell lymphoma-extra large; BRD4, bromodomain-containing protein 4; BRD9, bromodomain-containing protein 9; BTK, Bruton's tyrosine kinase; ER, oestrogen receptor; IMiD, immunomodulatory imide drug; IND, investigational new drug application; IRAK4, interleukin-1 receptor-associated kinase 4; STAT3, signal transducer and activator of transcription 3.

doi.org/101.1038/s41573-023-00652-2

- Twenty heterobifunctional/PROTAC degraders in clinic
- Multiple routes of administration utilized
- Majority are for oncology indications, but additional therapeutic areas of degraders are for immunology and skin
- Foghorn FHD-609, a heterobifunctional degrader of BRD9 continues advancement in Phase I
  - Significant degradation of BRD9 in patient metastatic synovial sarcoma tumor biopsies at low dose
  - More Ph I data expected mid-2023

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When do you develop a degrader?

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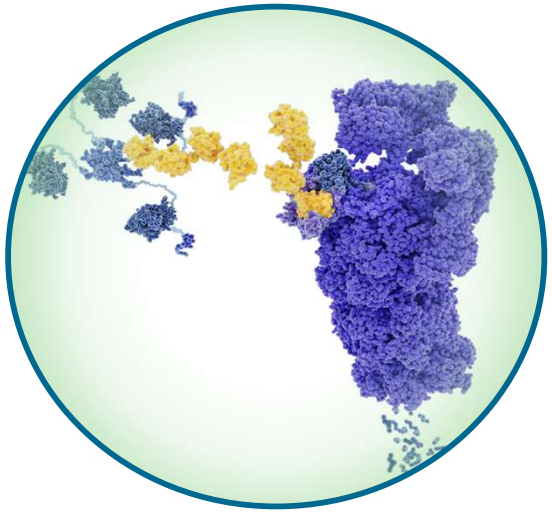
Targeted Protein Degraders



It's all about the Biology!

- Evidence that removal of core disease drivers will halt cell growth and potential progression of the disease as shown by:
  - *siRNA*
  - *CRISPR KO screens*
  - *Temporal degradation via tag fusion PROTACs*
- Understanding that for some targets, inhibition alone is not sufficient or shows toxicity at concentrations used
- Want to target proteins with no enzymatic activity or defined domains
- Disruption of a larger complex activity or scaffold is important
- Target is suitable for a degradation strategy (localization, half-life, etc.)

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Shifting perspective to develop degraders

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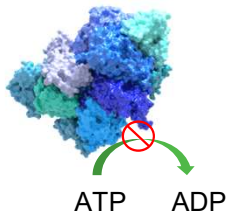
The rules of small molecule inhibitor development and how to achieve success do not apply to degraders!!!

Researchers in degradation: “There are no rules!”

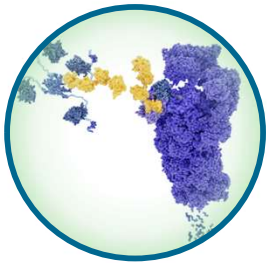
“Occupancy-Driven”

Enzymatic Inhibitors



“Event-Driven”

Targeted Protein Degraders



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A deeper look into the mechanisms of degraders

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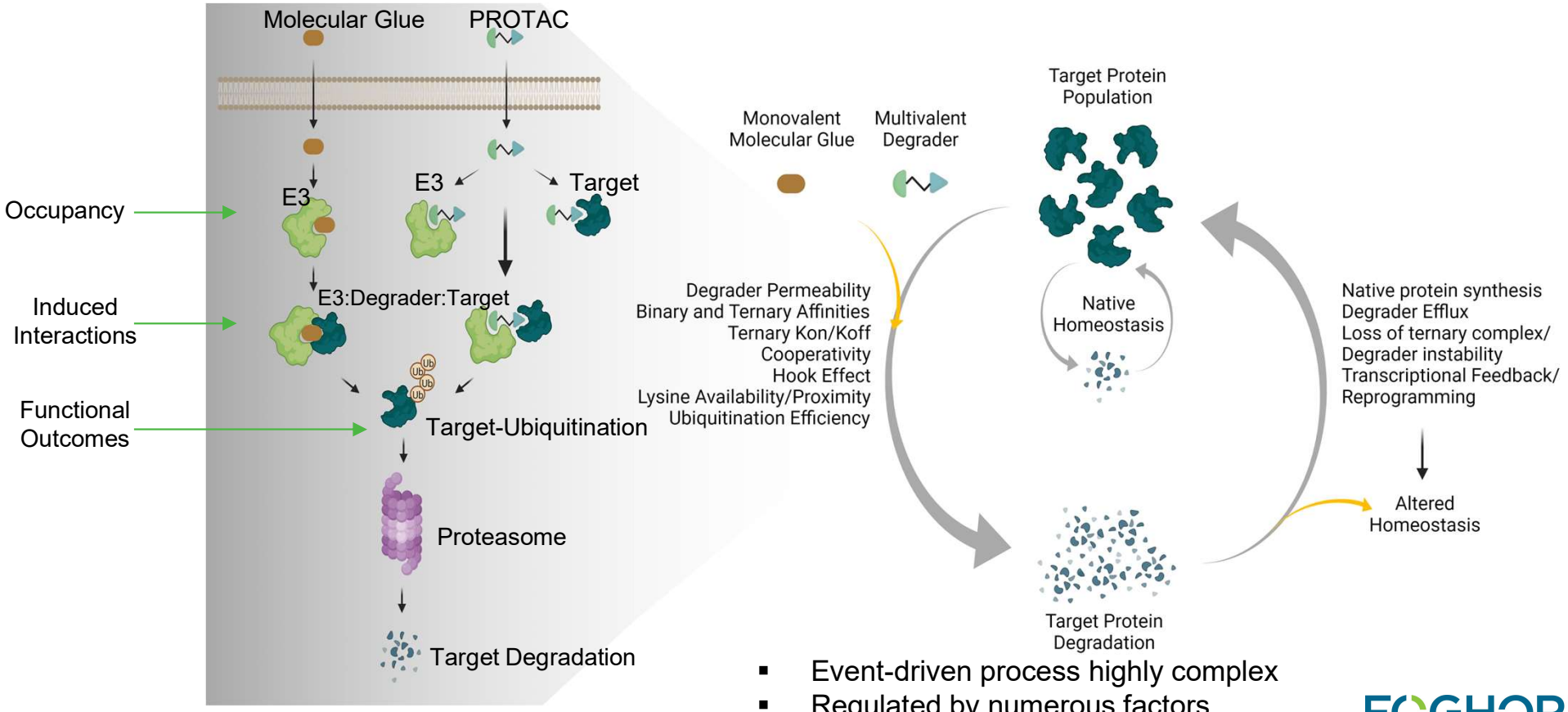

Chem Soc Rev, **2022** 51, 6210-21
Riching, Caine, Urh, and Daniels

- Event-driven process highly complex
- Regulated by numerous factors
- Target, E3 ligase, and cell type dependent

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Degradation is a dynamic process

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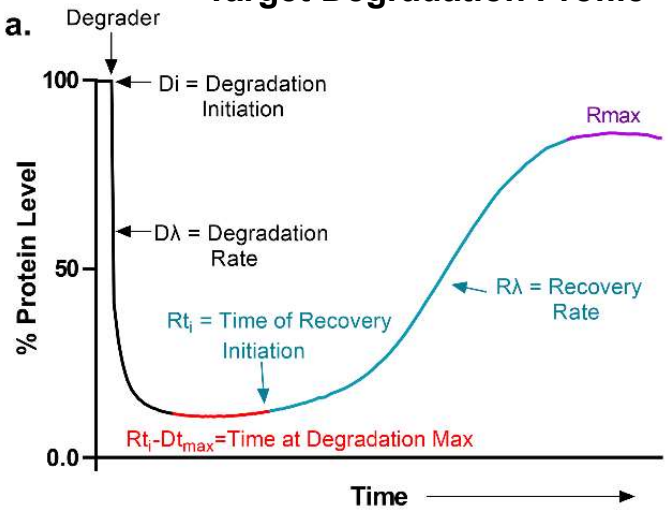
Wherein the journey is as important as the process

Target Degradation Profile



Possible Calculated Degradation Parameters

Time of degradation initiation (Dt_i)
Rate of degradation ($D\lambda$)
Degradation maximum (Dmax)
Half maximal degradation at a specific timepoint (DC_{50})
Half maximal degradation ($Dmax_{50}$)
Time of degradation maximum (Dt_{max})
Time of recovery initiation (Rt_i)
Time at degradation maximum (Rt_i-Dt_{max})
Rate of recovery ($R\lambda$)
Recovery maximum (Rmax)

Chem Soc Rev, **2022** 51, 6210-21

- Degraders will initiate a kinetic target degradation profile that is dependent upon degrader concentration
- Target recovery will occur when target synthesis outcompetes induced degradation
- If cellular kinetic profiles are determined, numerous parameters can be calculated

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Using targeted protein degradation to regulate chromatin and gene expression in oncology

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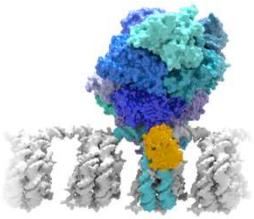
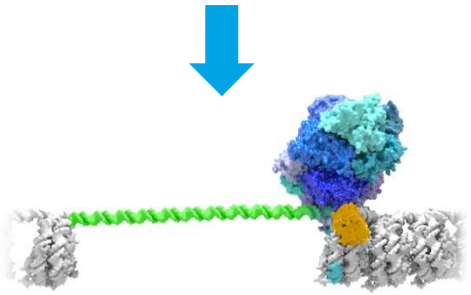
Healthy Cells

Work together to orchestrate gene expression at the right locations



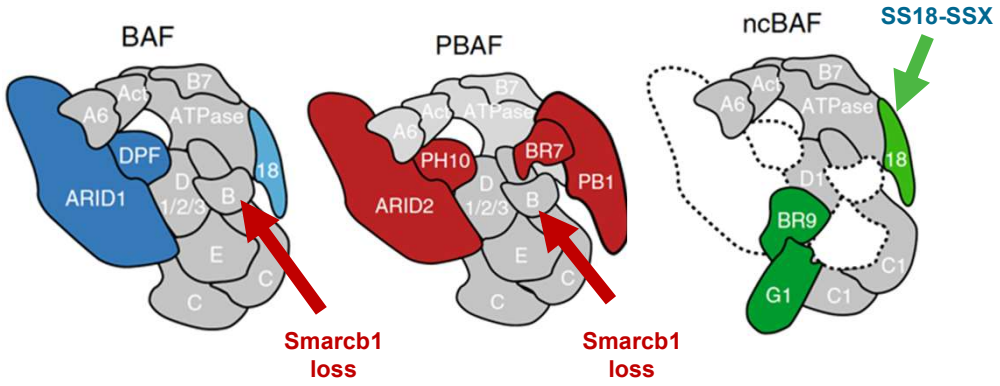
Chromatin remodeling complex + Transcription Factor



Normal gene expression

Cancer Cells

Aberrations in remodeling complexes (BAF) to orchestrate gene expression at the wrong locations



- Component loss and/or improper translocation fusion incorporation
- Cancer driver mutations associated with BAF subunits often results in paralogs or alternative BAF complex dependency
- Results in chromatin dysregulation and improper gene expression

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When do you develop a degrader?
FHD-609 an excellent example

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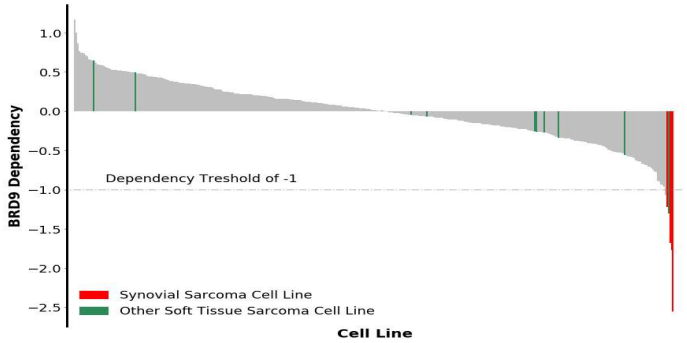
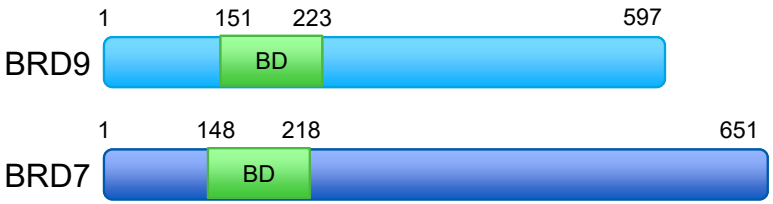
It's all about the Biology!

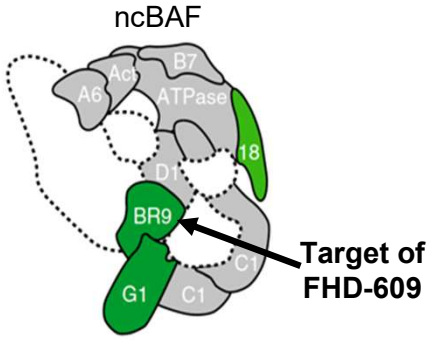
- BRD9 is required for the survival of synovial sarcoma cells



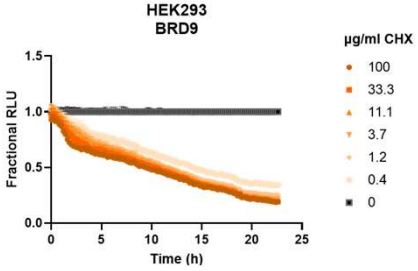
- BRD9 is not an enzyme. It is a bromodomain (BD) containing protein with a closely related family member, BRD7



- BRD9 is part of the larger BAF complex and scaffold implicated in synovial sarcoma



- BRD9 has an excellent half-life and is natively degraded via the ubiquitin-proteasome pathway



Native degradation rate: 0.03hr^{-1}
BRD9 half-life: 9hrs

Curr. Chem. Biol., **2021,** 1, 100009

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Leveraging degradation to introduce selectivity

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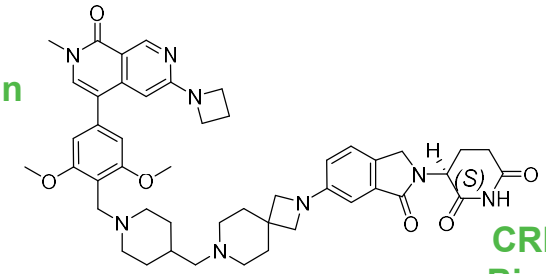
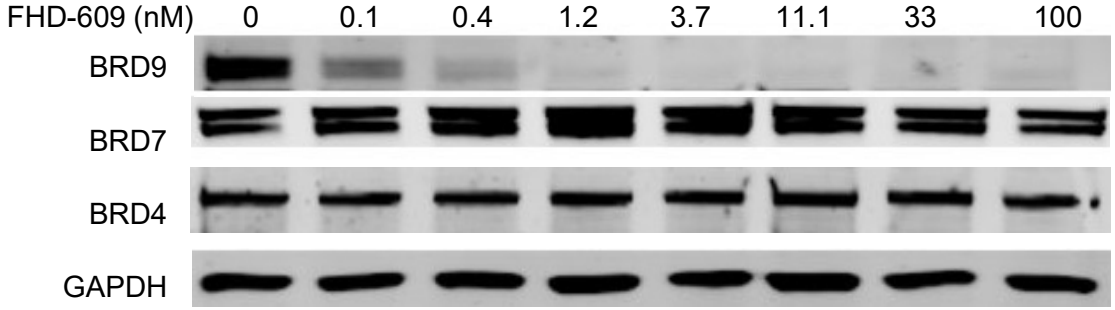
Structure of FHD-609

BRD7/9 Bromodomain Binder

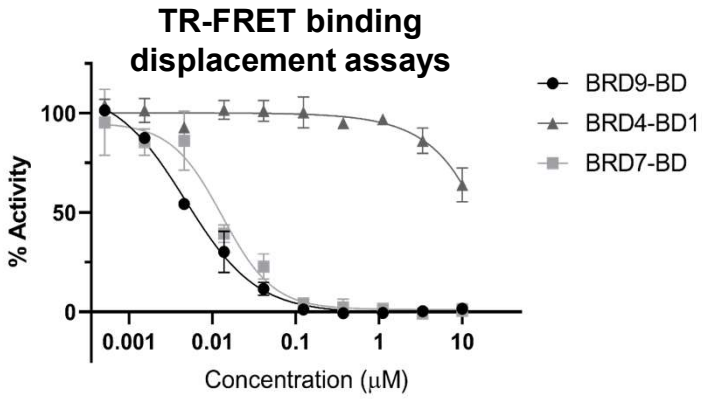


CRBN Binder

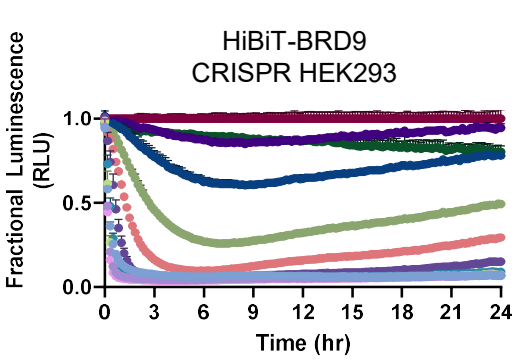
Selectivity of BRD9 degradation



Binding to both BRD7 and BRD9



Live cell kinetic BRD9 degradation



FHD-609 (nM)

- 1000
- 333.33
- 111.11
- 37.04
- 12.35
- 4.12
- 1.37
- 0.46
- 0.15
- 0.05
- 0.02
- DMSO

D_{max}: 97%
D_{max50}:190pM
$Rate_{\lambda}$: 5.5 hr^{-1}

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CBP/EP300 – a decades long challenge for selectivity

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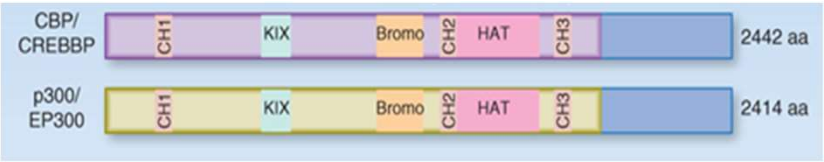
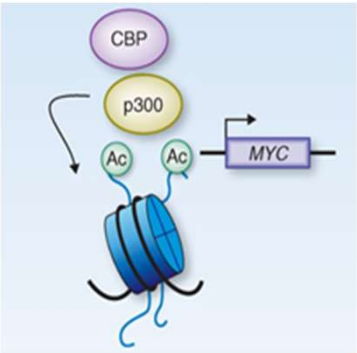
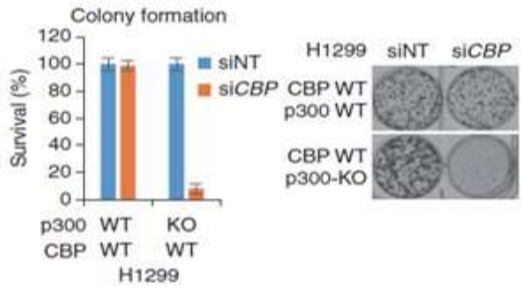




(Kadoch, Cancer Discovery 2016)



(Ogiwara et al, Cancer Discovery, 2016)

CBP and EP300

- Chromatin regulators and histone acetyltransferases
- Highly homologous with similar domain structure

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
- Current small molecules in development do not have selectivity
- If you target one, you must maintain the activity of the other

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Assessment of CBP and EP300 for a degradation strategy

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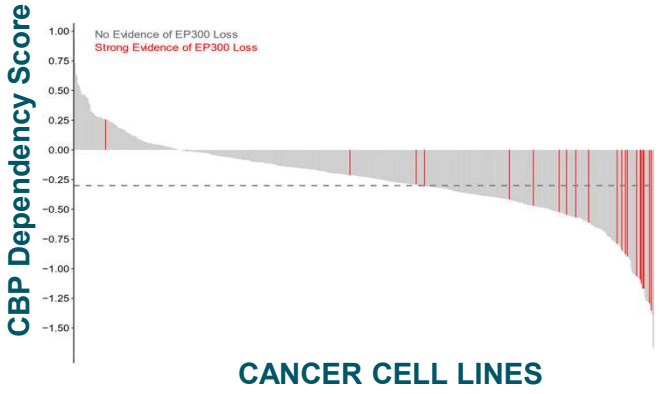
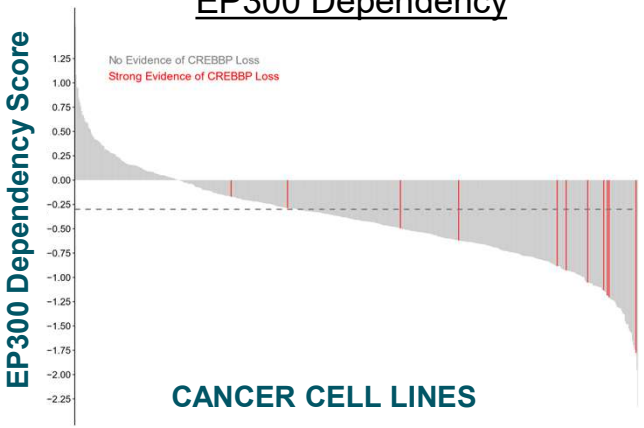
It's all about the Biology!

- CBP dependency observed in a significant number of EP300 mutated or EP300 loss cancers: Prostrate, Bladder, Colorectal, Breast, Gastric, and Lung
- EP300 dependency observed in a significant number of CBP mutated or CBP loss cancers: Bladder, NSCLC, and various lymphomas and leukemias
- CBP and EP300 have excellent half-lives and are natively degraded via the ubiquitin-proteasome pathway

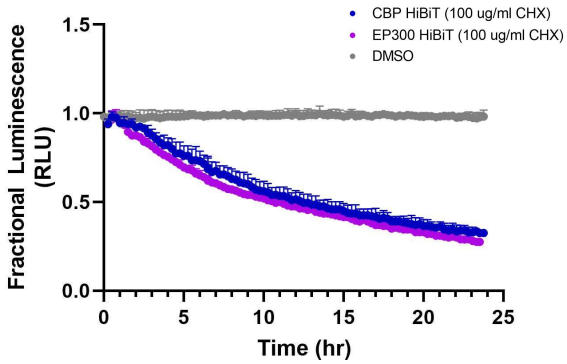
CBP Dependency



EP300 Dependency



CBP and EP300 U2OS



CBP and EP300 Native degradation rate: 0.1hr^{-1}
CBP and EP300 half-life: 10.5hrs

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Initial development of a dual CBP and EP300 degrader

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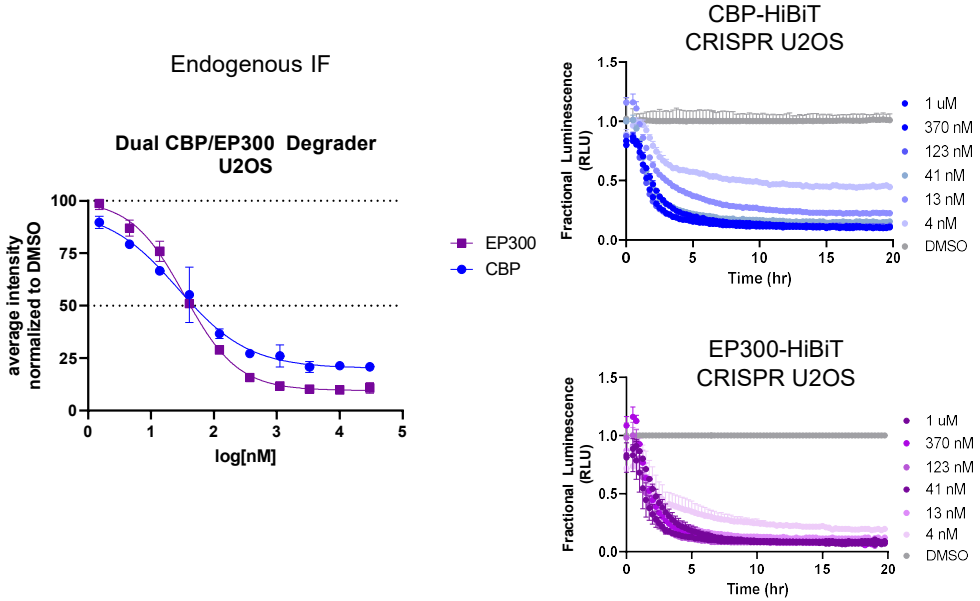
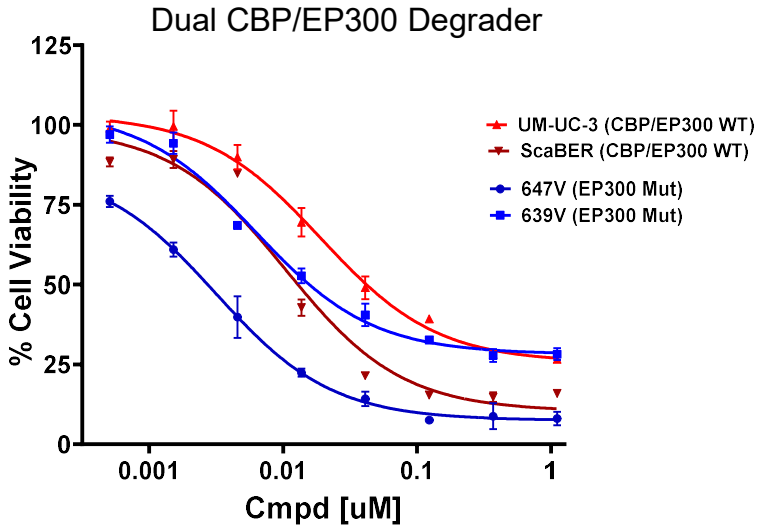
Dual CBP and EP300 degradation



- Efficient and complete degradation of EP300 and CBP with dual degrader

Cell Proliferation Assays



- Robust impact on cell proliferation in both dual (CBP and EP300 WT) dependent and CBP dependent (EP300 mutant) bladder cancer cell lines

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Introducing CBP selectivity with a degrader

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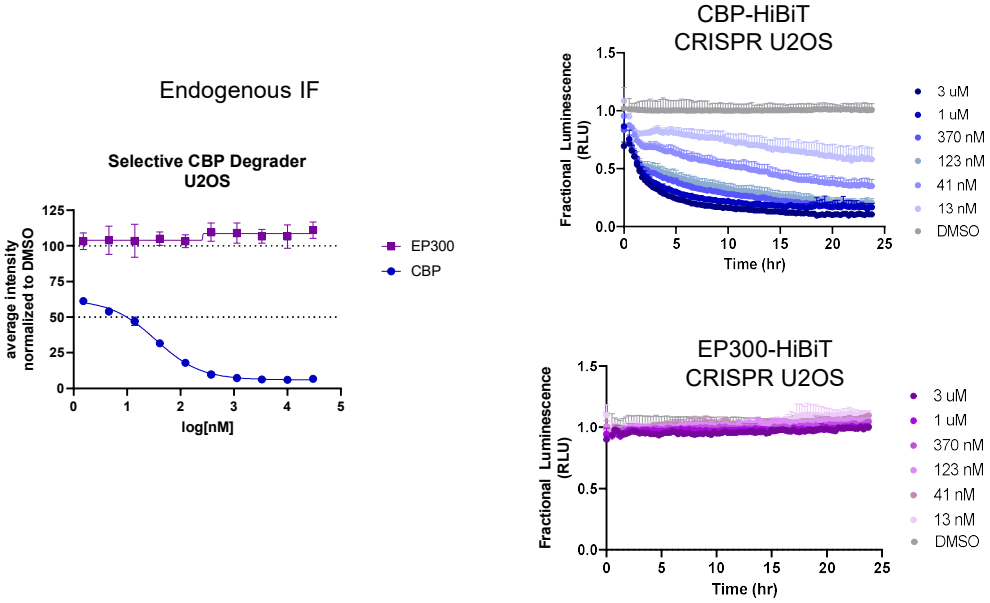
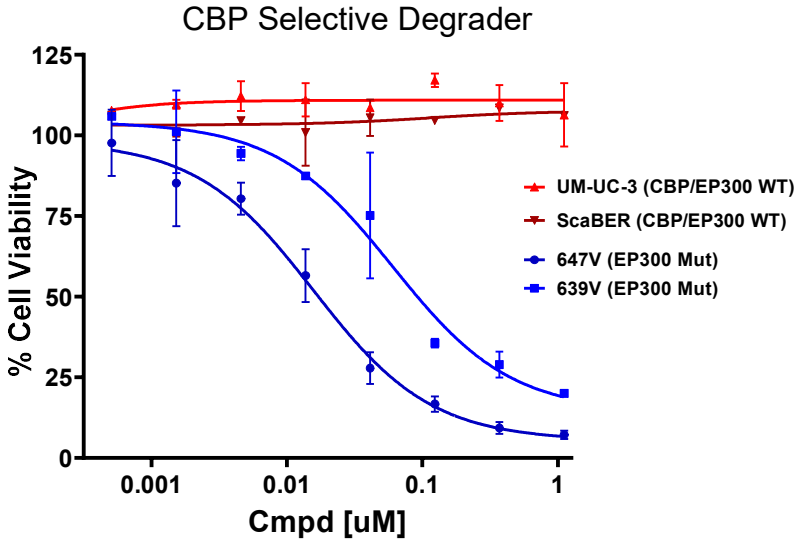
CBP selective degradation



- Efficient and complete degradation of CBP with no degradation of EP300 even at high concentrations

Cell Proliferation Assays



- Selective CBP degradation translating to selective CBP dependent (EP300 mutant) cell line death
- Sparing of EP300 activity allows for CBP/EP300 WT cell lines to not be impacted

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Towards an EP300 selective degrader

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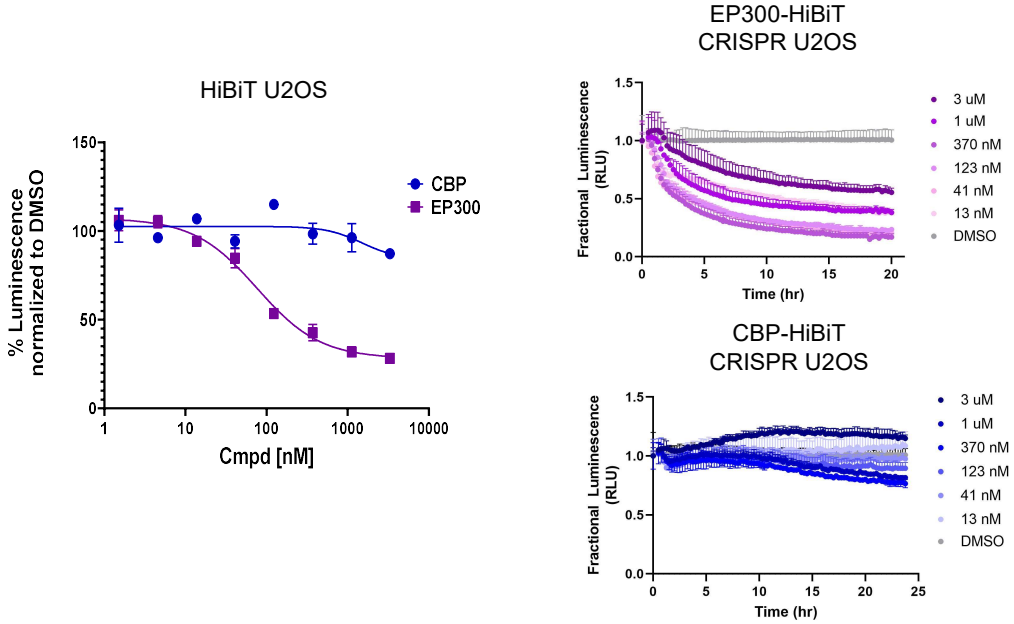
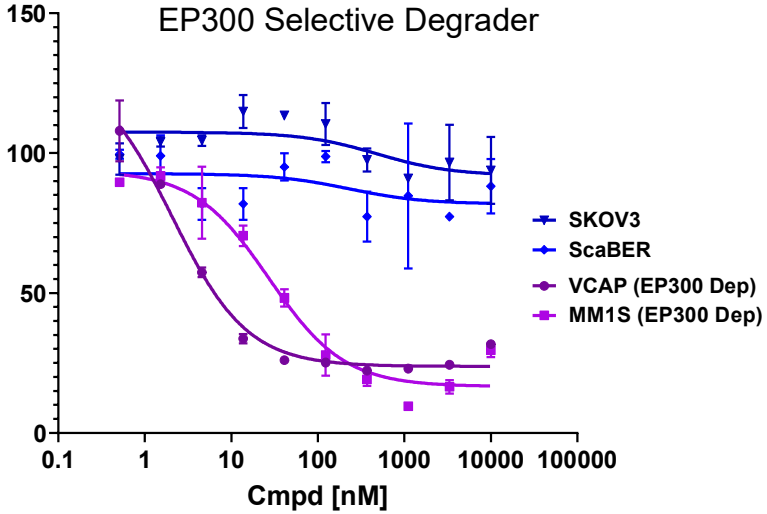
EP300 selective degradation



- Efficient degradation of EP300 with minimal degradation of CBP

Cell Proliferation Assays



- Selective EP300 degradation translating to selective EP300 dependent cell line death
- Small fractional loss of CBP allows for dual dependent cell lines to be minimally impacted

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Monitoring degrader selectivity in unbiased fashion

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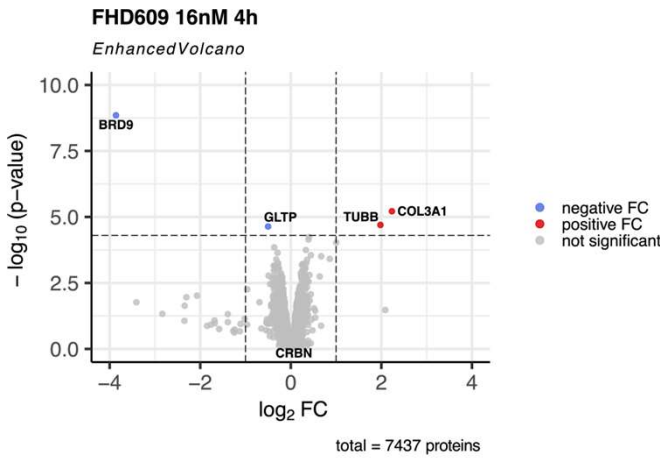
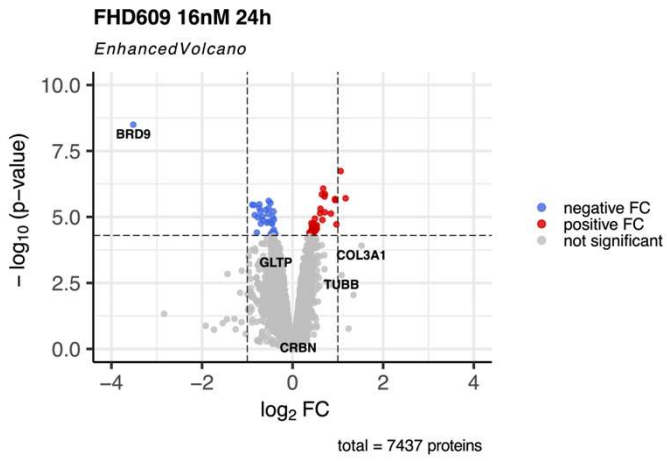
- It is important for all degraders to study selectivity in an unbiased fashion at multiple time points and concentrations
- This can be achieved with mass spectrometry global proteomics analysis
- Results can be indicative if loss of target is direct via degrader mechanism or indirect via other pathways

Clinical BRD9 Degrader FHD-609

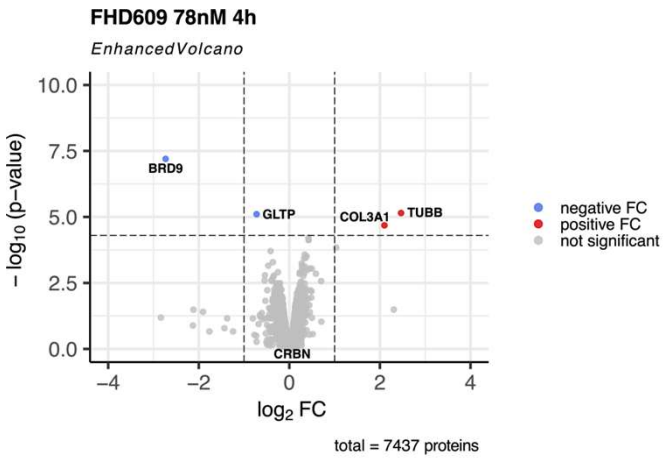
16nM (200x DC_{50})
4hrs in SYO1



16nM (200x DC_{50})
24hrs in SYO1



78nM (1000x DC_{50})
4hrs in SYO1



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Tuning out off-target activity of IMiD handles in PROTACs

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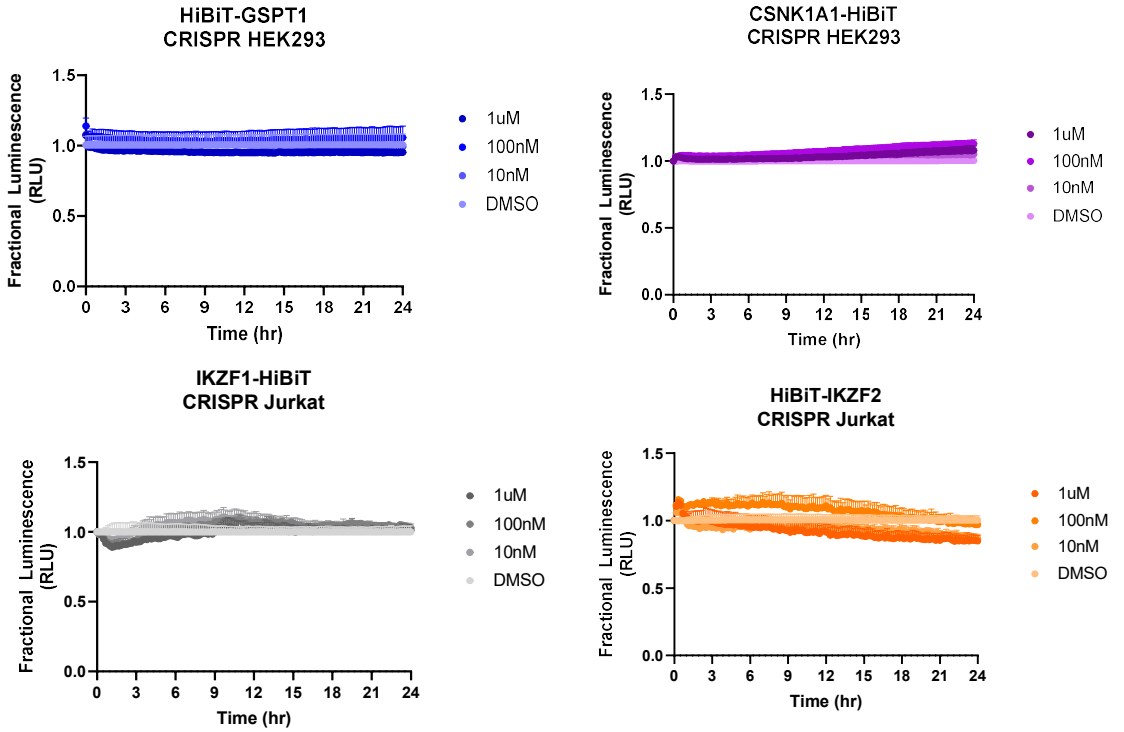
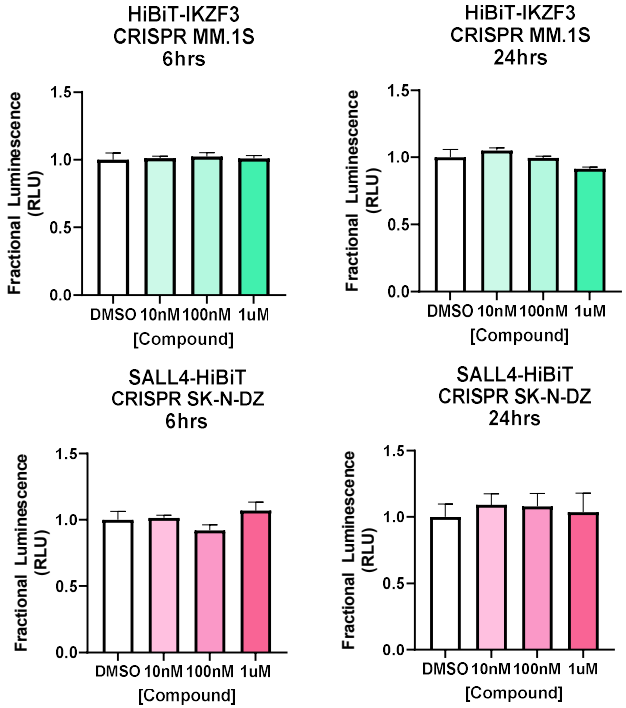
Clinical BRD9 Degrader FHD-609, a CRBN-based heterobifunctional degrader



10nM (50xDC$_{50}$) 100nM (500xDC$_{50}$) 1µM (5000xDC$_{50}$)



- No off-target IMiD molecular glue activity of known CRBN neosubstrates

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Summary

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- Numerous heterobifunctional degraders at various stages in the clinic, mainly for oncology applications but expanding to other disease areas
- Many initial considerations are important when considering a new target for degradation
  - What is the consequence of target loss?
  - Is the target amenable for degradation?
  - Does it play an important scaffolding role?
  - Would degradation yield advantages over inhibition (resistance mutants, etc.)?
- Targeted protein degradation can be an excellent strategy to introduce selectivity for closely related family members, paralogs, or even splice variants
- Assessment of selectivity, not only between related proteins, but proteome-wide and in multiple cell types important for understanding potential off-target liabilities

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Acknowledgements

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The Foghorn Therapeutics Team

Thank you!
Questions?

For more information on Foghorn Therapeutics CBP/EP300 Degrader Programs visit the following posters:

Session PO.ET09.05 – Epigenetics
April 19th, 2023 9:00am-12:30pm
Section 20

- Poster 6287/25 – Discovery and characterization of potent, selective CBP degraders Dr. Laura La Bonte
- Poster 6288 / 26 – Discovery and characterization of potent, selective EP300 degraders Dr. Darshan Sappal

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