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# Progressing degraders towards and through the clinic

Hanson Wade's 5th Annual
Targeted Protein Degradation Summit, Oct 25-28, 2022

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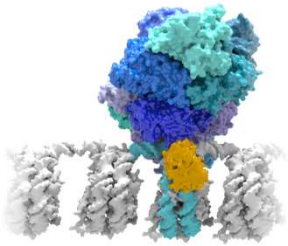
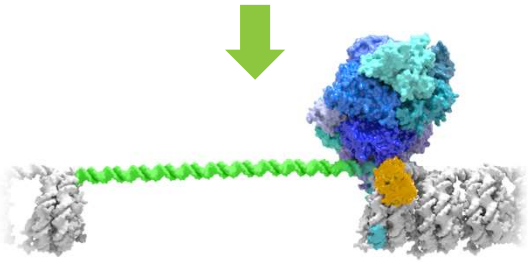
# Targeted Protein Degradation to Regulate Chromatin and Gene Expression in Disease

**Healthy Cells**

**Work together to orchestrate gene expression at the right locations**



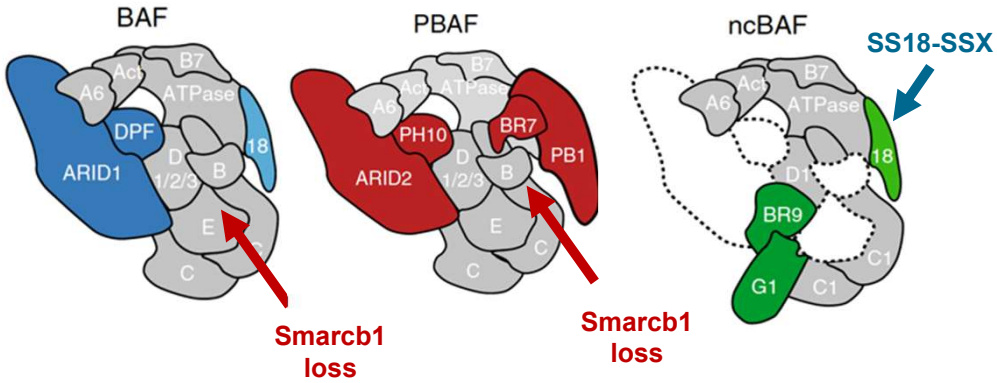
**Chromatin remodeling complex + Transcription Factor**



**Normal gene expression**

**Cancer Cells**

**Aberrations in remodeling complexes (BAF) 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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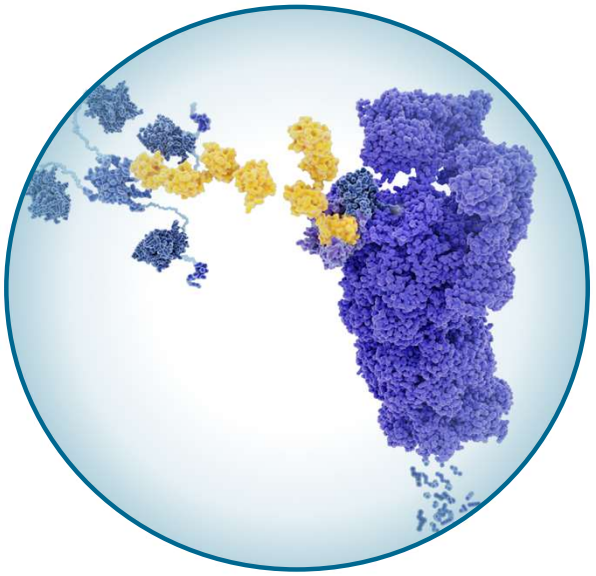
# Development of Degraders Dependent Upon Target Biology

**Targeted Protein Degraders**



## Inhibition versus Degradation - 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

# Outline

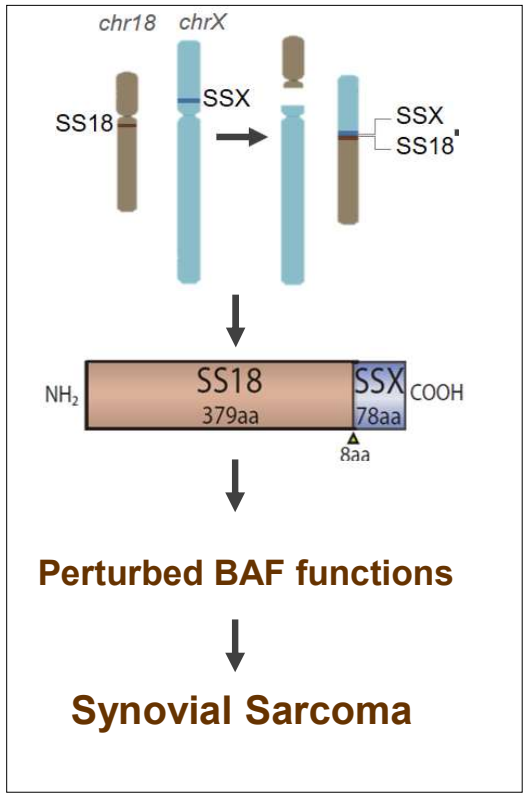
- Advancement of FHD-609, a selective BRD9 PROTAC
  - Pre-clinical validation of selectivity and degradation activity
  - Counter-screening against CRBN off-target IMiD neosubstrate panel
  - Initial Ph I pharmacodynamics (PD) data in patients with metastatic synovial sarcoma

- Expansion of Foghorn degradation platform
  - Orally bioavailable degrader chemistry capabilities
  - Degradation of other key chromatin regulators important in disease
    - Dual BRD7/9
    - Dual CBP/E300
    - Selective CBP and cell proliferation studies

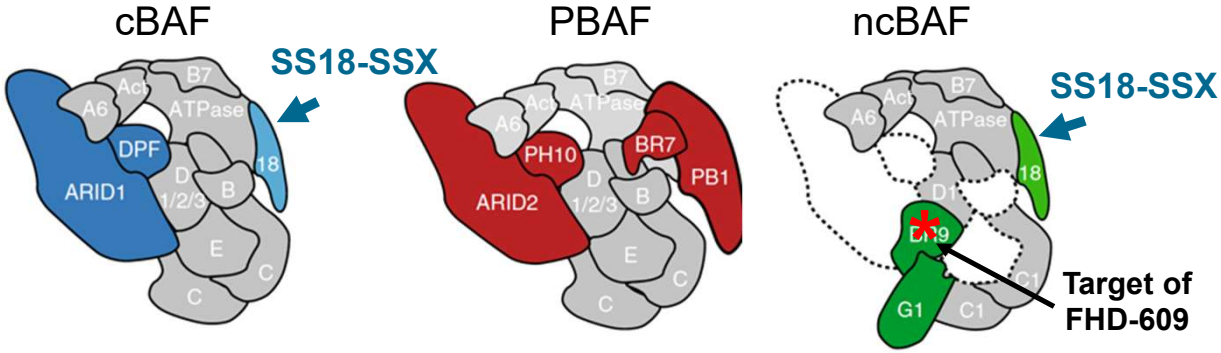
# BRD9 Subunit of the Non-canonical BAF Complex is Required for Survival of Synovial Sarcoma Cells

>95% of synovial sarcoma tumors contain SS18-SSX fusions

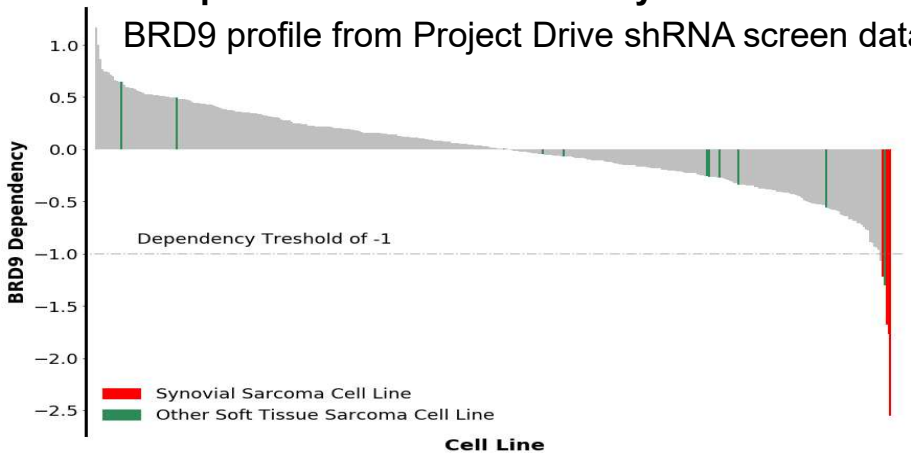
**Synovial Sarcoma is characterized by SS18-SSX fusion oncoproteins**




**Compositions of cBAF, PBAF and ncBAF. Incorporation of SS18-SSX into BAF complexes in Synovial Sarcoma cells**




**BRD9 is required for the survival of Synovial Sarcoma cells**

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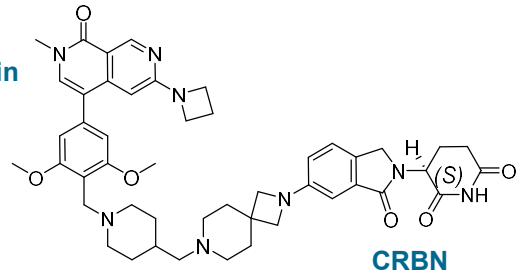
# FHD-609 is a Rapid, Highly Potent BRD9 Degrader which Utilizes CRBN Recruitment

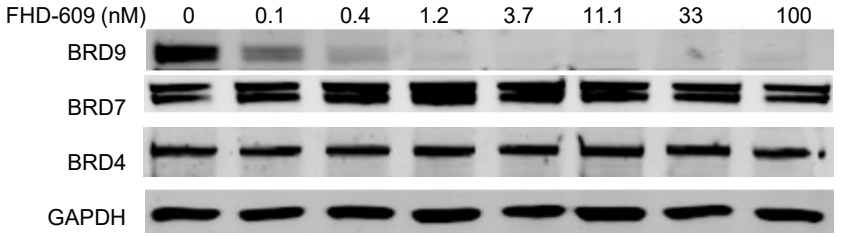
## Structure of FHD-609

BRD7/9 Bromodomain Binder

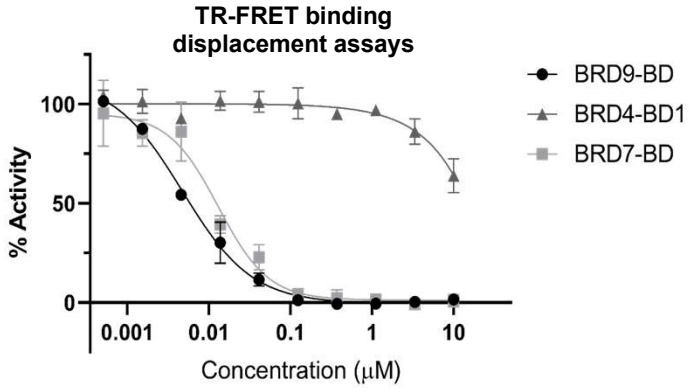


CRBN Binder

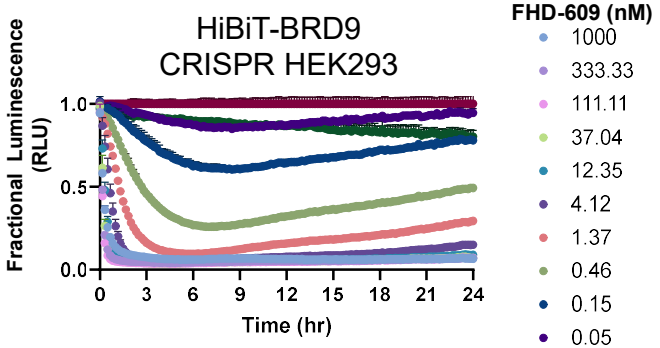
## Selectivity of BRD9 degradation




## Binding to both BRD7 and BRD9




## Live cell kinetic BRD9 degradation




$D_{max}$: 97%
$D_{max50}$: 190pM
Rate ƛ: 5.5 $hr^{-1}$

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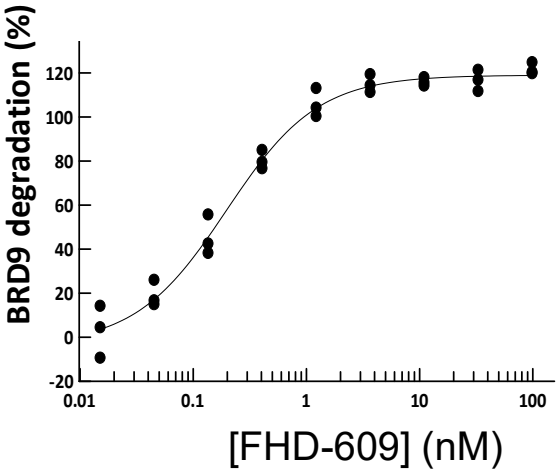
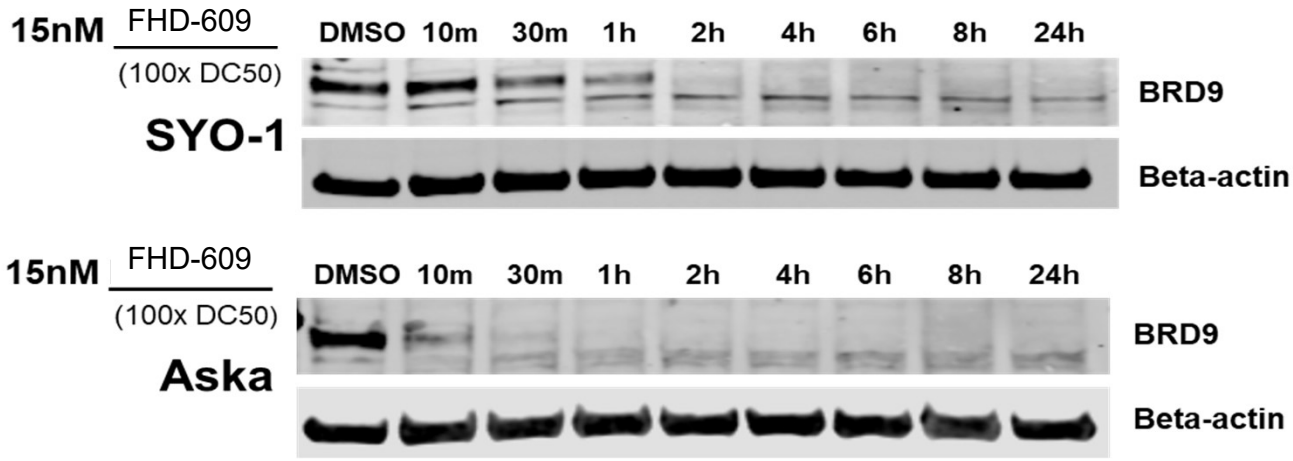
# FHD-609 shows Potent and Rapid BRD9 Degradation in Relevant Synovial Sarcoma Lines

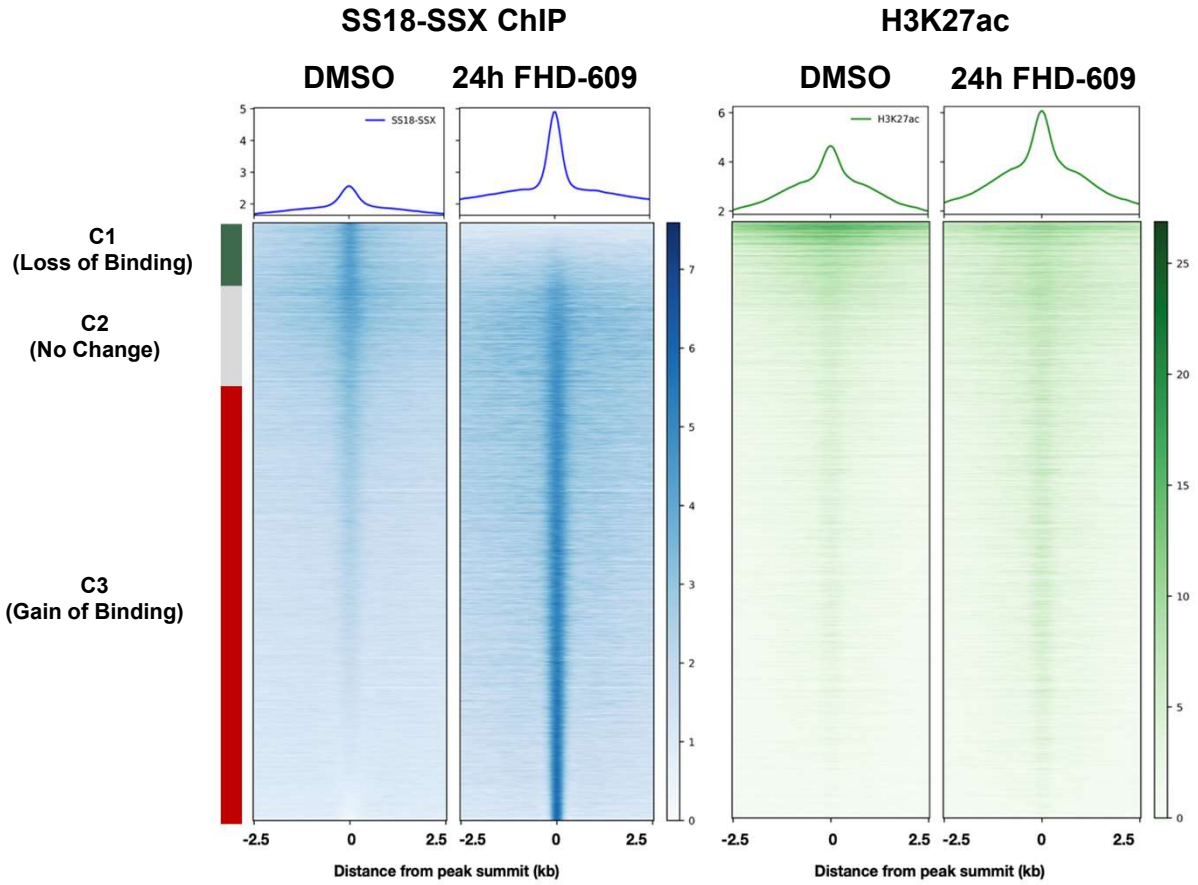
## BRD9 MSD assay (endogenous)

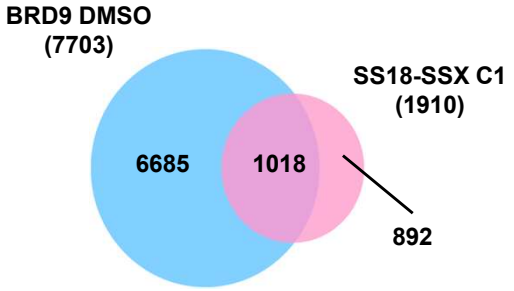



| $DC_{50}$ (pM) | SYO-1 | ASKA | HSSY-II |
|---|---|---|---|
| FHD-609 | 200 | 50 | 140 |



# FHD-609 Treatment results in Global Genomic Redistribution of Synovial Sarcoma Hallmark Fusion Gene SS18-SSX in SYO-1

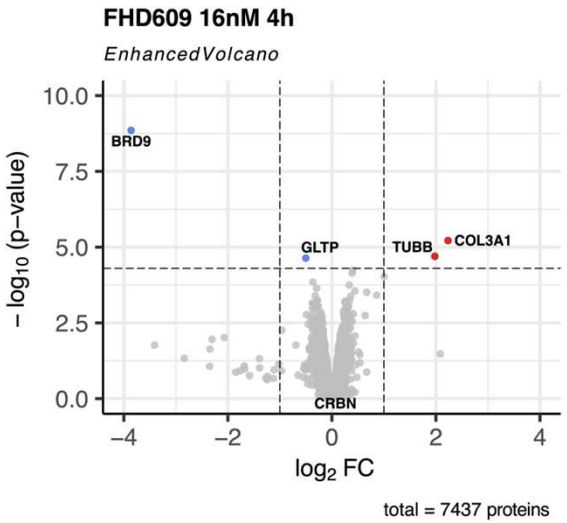


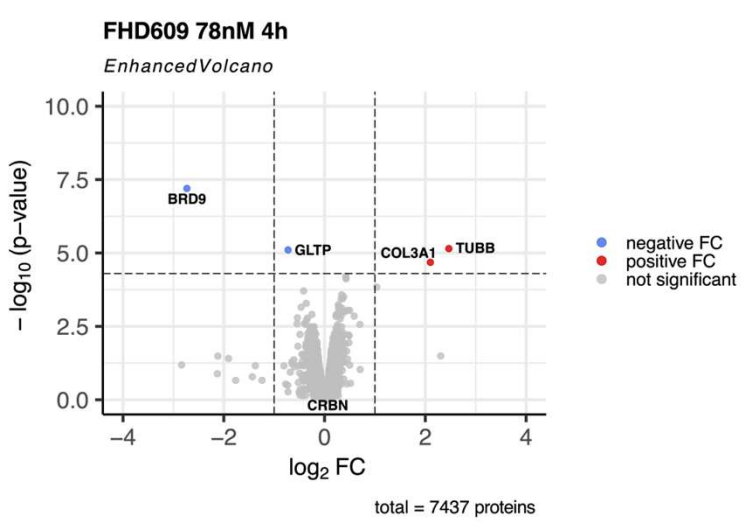

- Genomic regions that lose SS18-SSX peaks with FHD-609 treatment are enriched with active transcription mark H3K27ac and BRD9
- How SS18-SSX redistribution contributes to anti-proliferative activity of FHD-609 in SYO-1 is currently under-investigation

# FHD-609 Selectively Degrades BRD9 in Synovial Sarcoma Global Proteomics Analyses

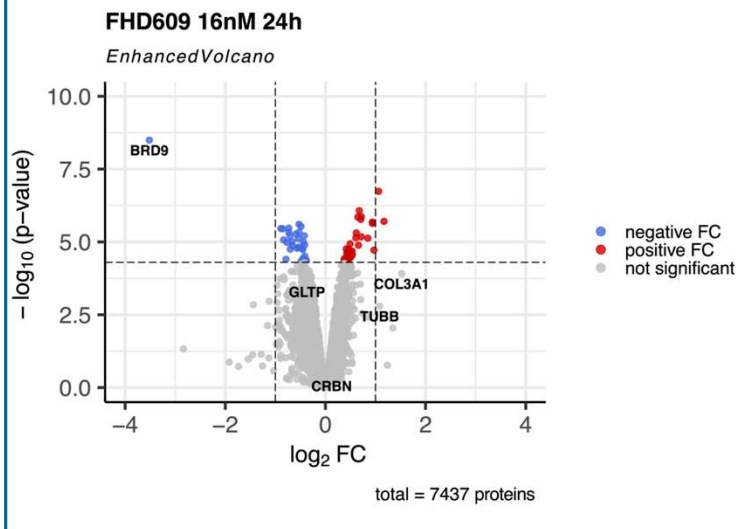
16nM (200x $DC_{50}$)
4hrs in SYO1




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



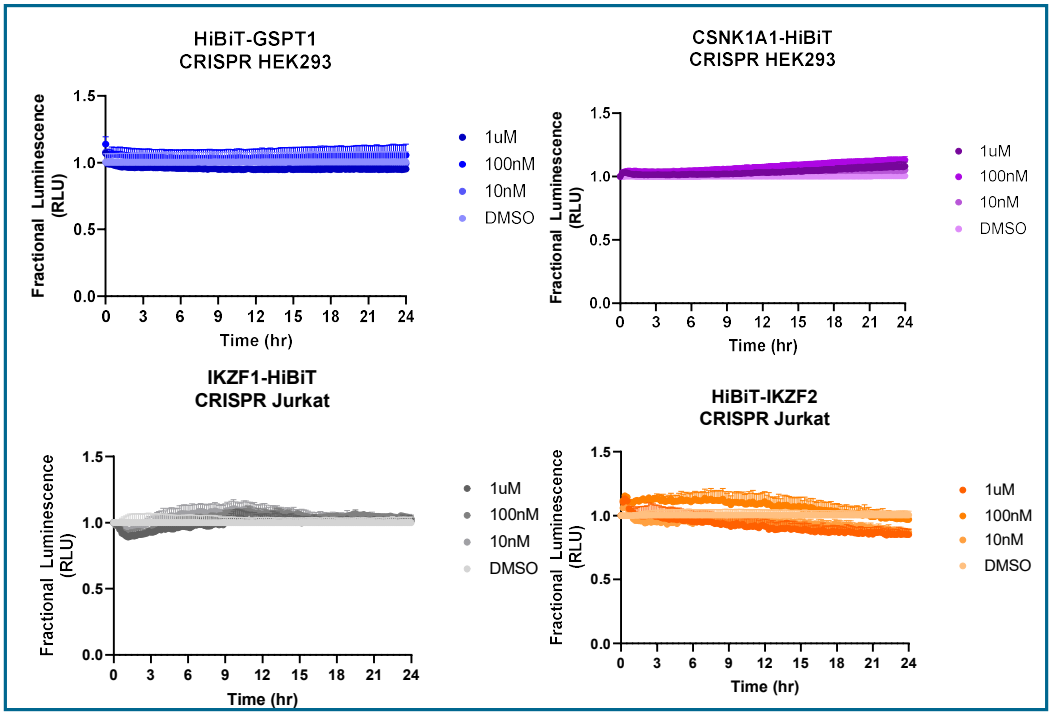

16nM (200x $DC_{50}$)
24hrs in SYO1



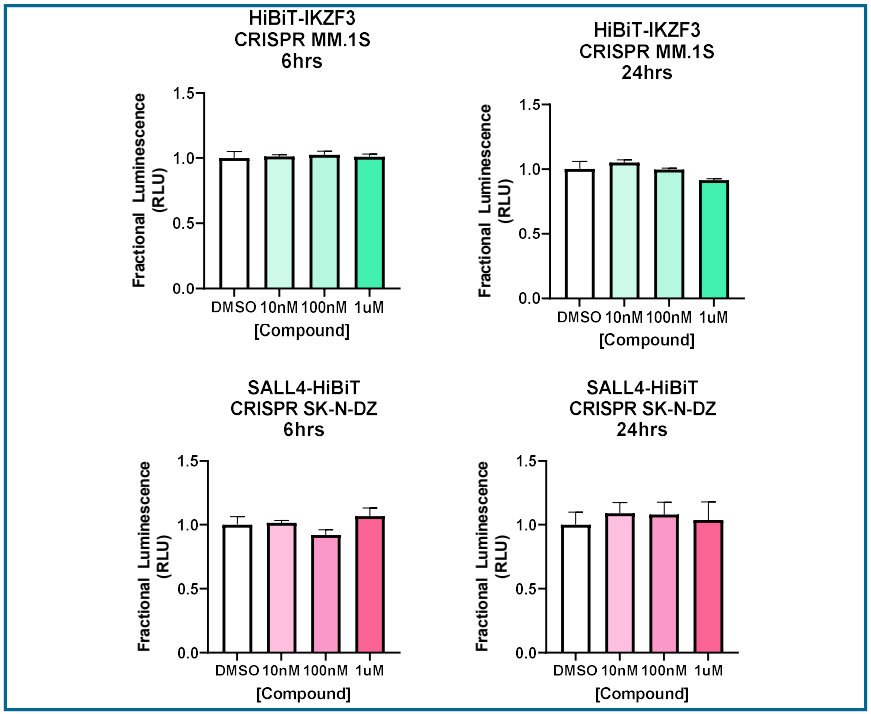

- BRD9 is the only protein significantly degraded at multiple concentrations and time points
- BRD9 shows a 16-fold reduction by quantitative MS analysis.

# FHD-609 Does Not Show Off-target IMiD Neosubstrate Degradation Activity

## Kinetic degradation (24hr) profiling of GSPT1, CK1a, IKZF1, and IKZF2 with FHD-609



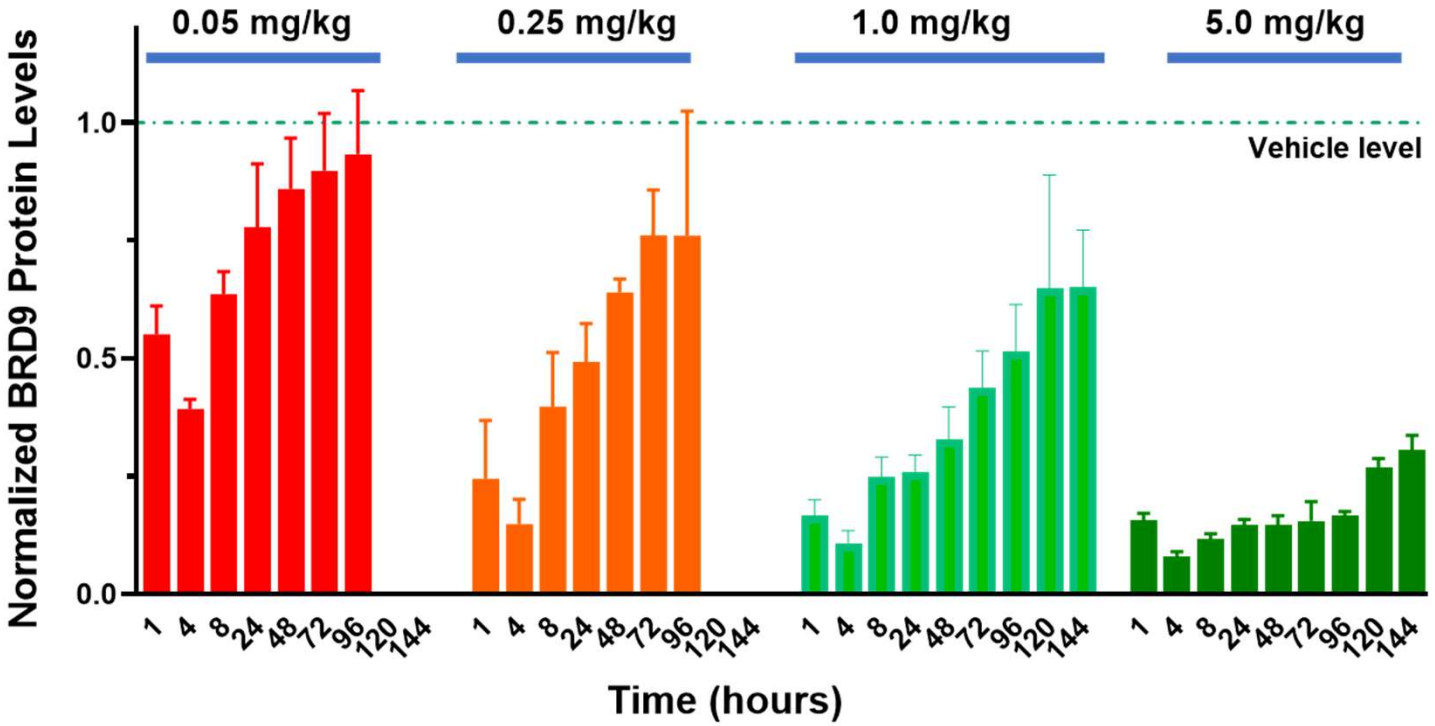

## Endpoint degradation (6hr and 24hr) profiling of IKZF3 and SALL4 with FHD-609




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

# FHD-609 Demonstrates Dose- and Time-dependent *in vivo* BRD9 Degradation

SYO-1 Synovial Sarcoma CDX PKPD with racemic FHD-609
(Single dose IV administration)

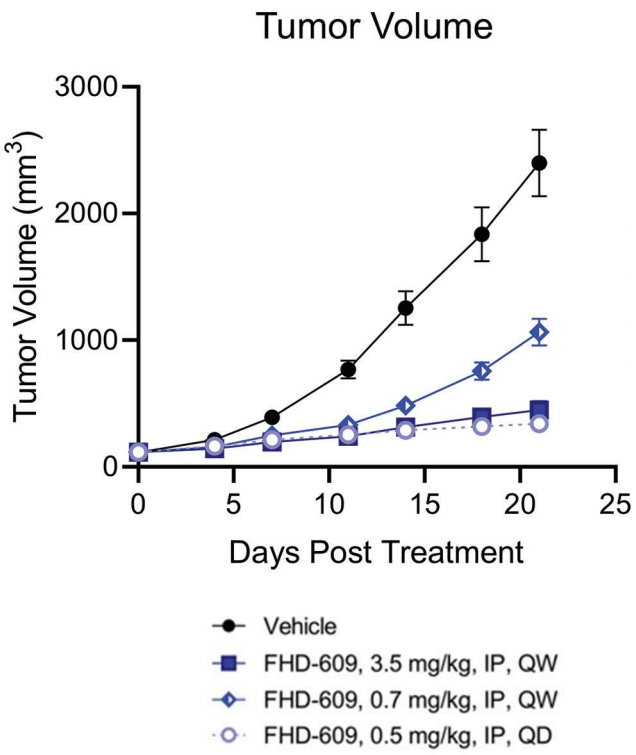


# Robust *in vivo* Activity Observed in Synovial Sarcoma Model and BRD9 Degradation Associated with FHD-609* Treatment

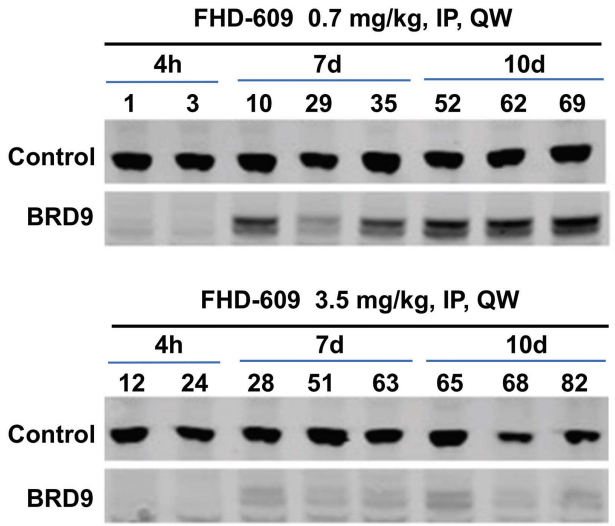
Weekly dosing of racemic FHD-609* achieved sustained BRD9 degradation

## SYO1 Synovial Sarcoma CDX Model

- Mutation: **SS18-SSX2**
- Inhibited tumor growth
- Dose dependent BRD9 degradation correlated with anti-tumor activity

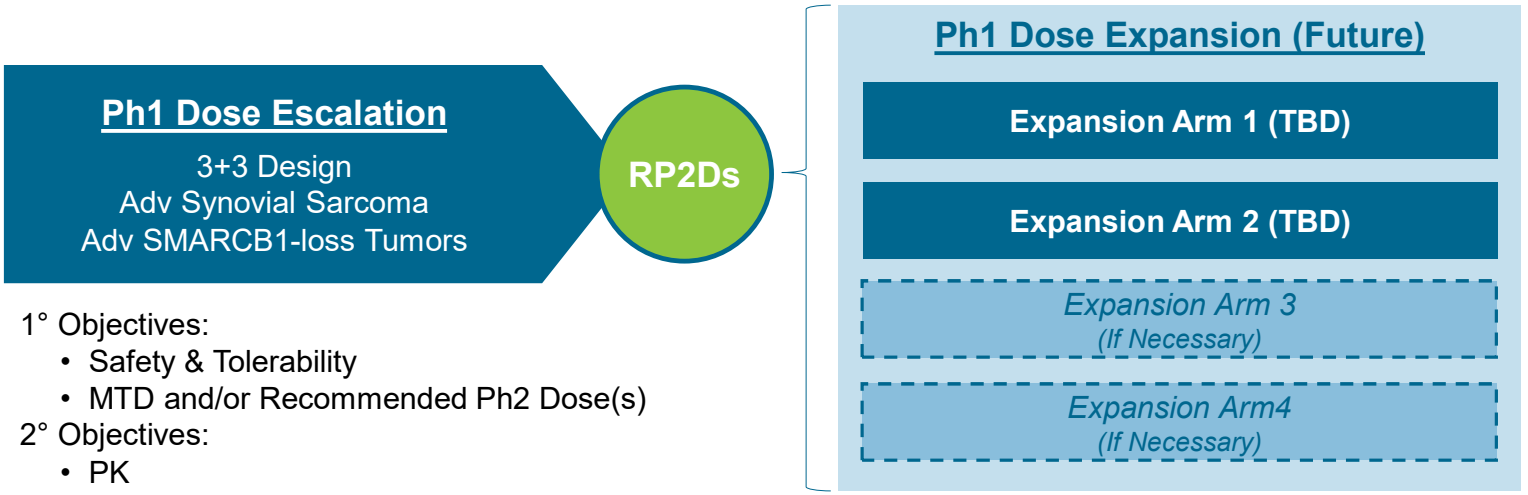



## Sustained BRD9 Degradation




*Racemic FHD-609 utilized in this study

# FHD-609 Phase 1 Study Overview and Progress



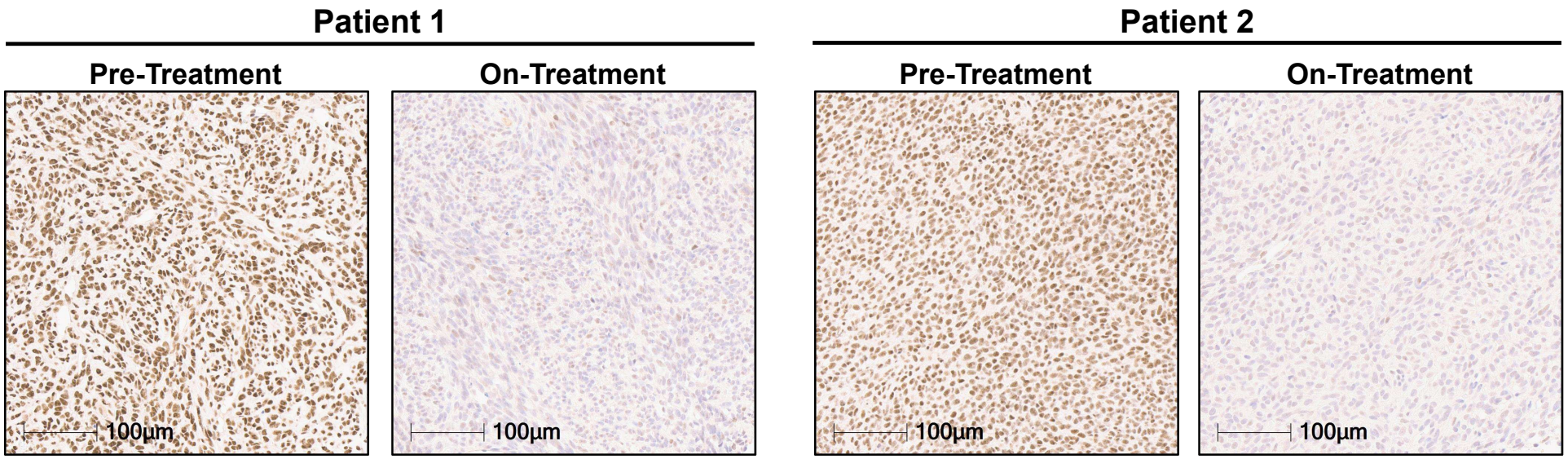

1° Objectives:
- Safety & Tolerability
- MTD and/or Recommended Ph2 Dose(s)

2° Objectives:
- PK
- Preliminary Clinical Activity

Exploratory Objectives:
- PD

**Ph1 study continues to progress through dose escalation cohorts**
**– MTD and RP2D(s) not yet established –**

# Early Analyses of On-Treatment Tumor Biopsies Shows BRD9 Degradation




- Tumor biopsies from two patients with metastatic synovial sarcoma treated with same low dose of FHD-609
- Biopsies taken either 1 day (Patient 1) or 2 days (Patient 2) following FHD-609 administration
- Uniform loss of BRD9 staining observed in both patient tumors while receiving FHD-609 treatment
- Phase 1 dose escalation study is on-going to determine Maximum Tolerated Dose (MTD) and/or appropriate dose(s) to evaluate in dose expansion phase

# Outline

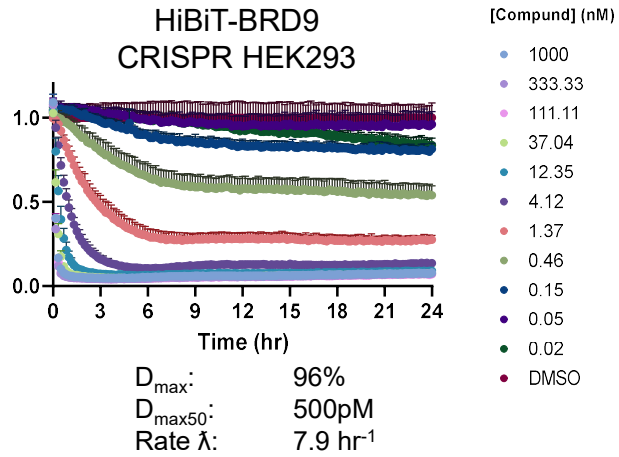
- Advancement of FHD-609, a selective BRD9 PROTAC
  - Pre-clinical validation of selectivity and degradation activity
  - Counter-screening against CRBN off-target IMiD neosubstrate panel
  - Initial Ph I pharmacodynamics (PD) data in patients with metastatic synovial sarcoma

- Expansion of Foghorn degradation platform
  - Orally bioavailable chemistry degrader capabilities
  - Degradation of other key chromatin regulators important in disease
    - Dual BRD7/9
    - Dual CBP/E300
    - Selective CBP and cell proliferation studies

# Development of Orally Bioavailable Selective Degraders

- FHD-609 first to clinic to address unmet needs of synovial sarcoma patients and actively progressing in Ph I
- Oral BRD9 program followed as potential back-up and expansion of degrader chemistry portfolio

## Oral BRD9 degrader




$D_{max}$: 96%
$D_{max50}$: 500pM
Rate λ: 7.9 $hr^{-1}$

## Selective degradation and oral bioavailability

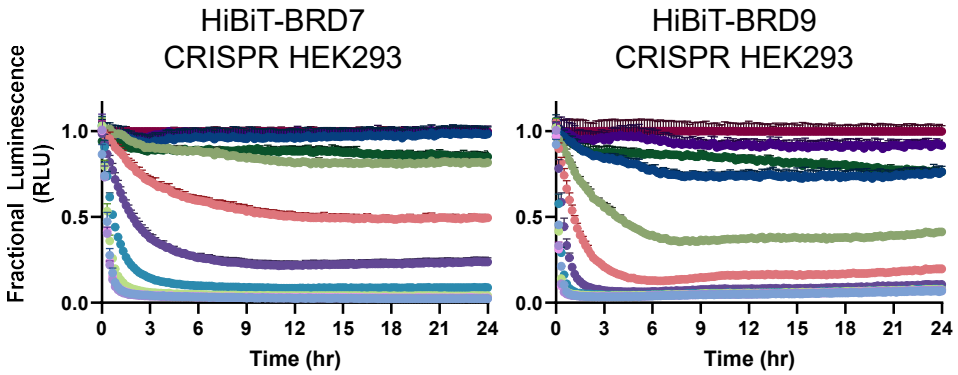
| Proteins assessed by WB | $DC_{50}$ (Dmax) |
|---|---|
| BRD9 | 600pM (100%) |
| BRD7 | --- (0%) |
| BRD4 | --- (0%) |

| Oral Bioavailability | |
|---|---|
| Rat $t_{1/2}$, oral bioavailability | 5.0 h, 35% |
| Monkey $t_{1/2}$, oral bioavailability | 5.9 h, 60% |

- Several oral BRD9 degraders with high potency, selectivity, rapid degradation, and excellent oral bioavailability
- Apply these chemistry learnings and tools to additional degrader programs

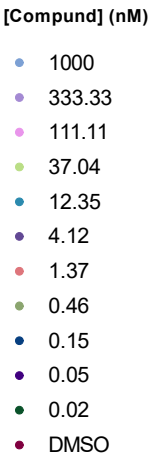
# From Selective BRD9 Degradation to Robust Dual BRD7 and BRD9 Degradation

## Dual BRD7 and BRD9 kinetic degradation

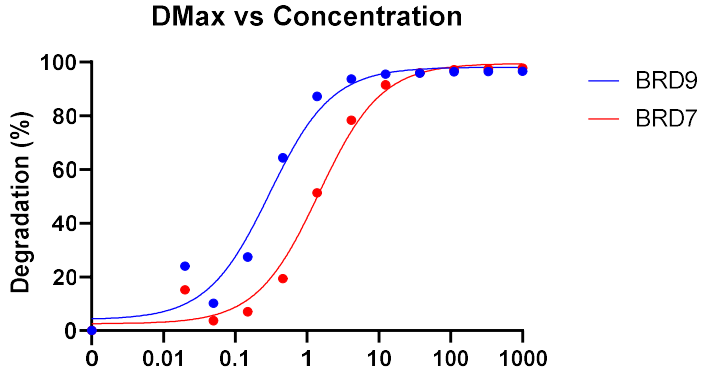



$D_{max}$: 98%
$D_{max50}$: 1.5nM
Rate ƛ: 2.8 $hr^{-1}$

$D_{max}$: 97%
$D_{max50}$: 300pM
Rate ƛ: 7.9 $hr^{-1}$

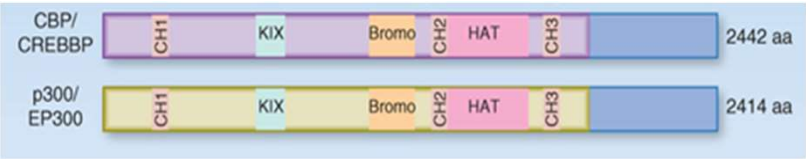


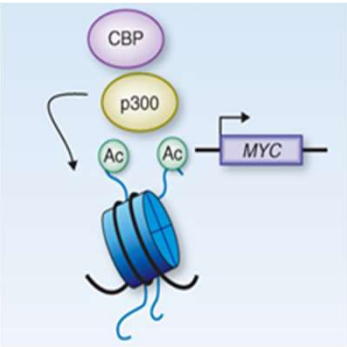

## FHT Dual BRD7/9 PROTAC



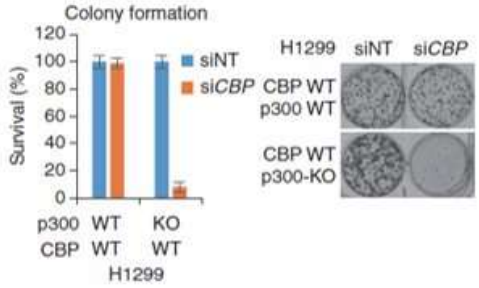

- CRBN-based dual heterobifunctional degrader
- Rapid and potent degradation of both BRD7 and BRD9
- Enables studies of pBAF and ncBAF function

# Targeting CBP (CREB Binding Protein) and EP300 for Degradation




(Kadoch, Cancer Discovery 2016)




(Ogiwara et al, Cancer Discovery, 2016)

## CBP and EP300

- Chromatin regulators and histone acetyltransferases
- Highly homologous with similar domain structure
- Synthetic lethal relationship between CBP and EP300

## Disease implications and indications

- CBP and EP300 frequently mutated in cancers
- Numerous oncology indications showing CBP or EP300 deficiency
  - *Gastric*
  - *Colorectal*
  - *Breast*
  - *Lung*

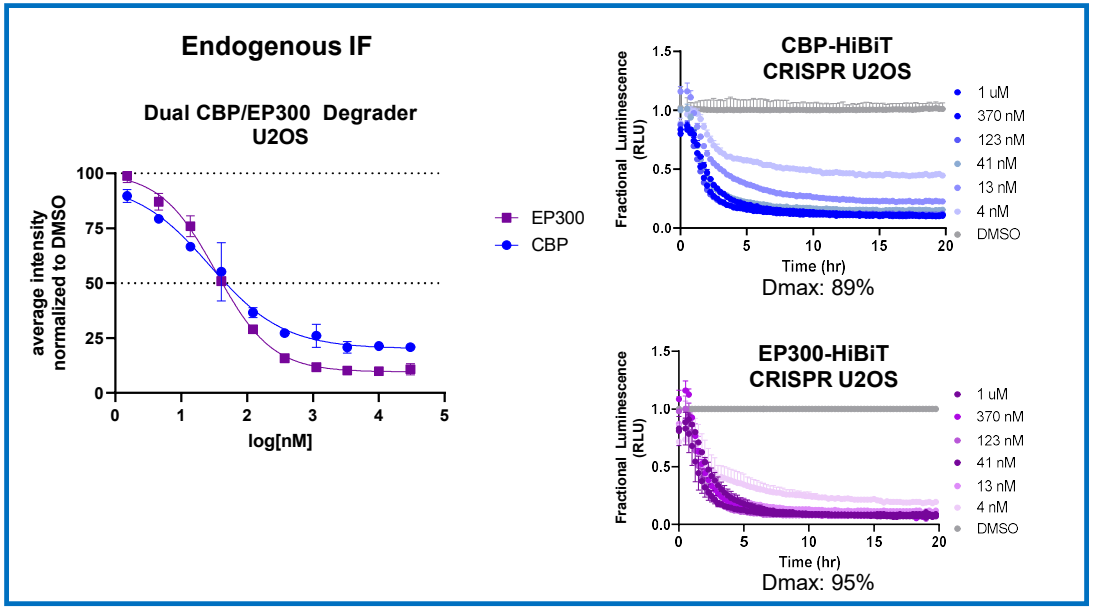
## Drug targeting

- Several domains within CBP/EP300 with known binders
- Binders or inhibitors are not selective for CBP or EP300

Challenge: Engineer selectivity with a degrader

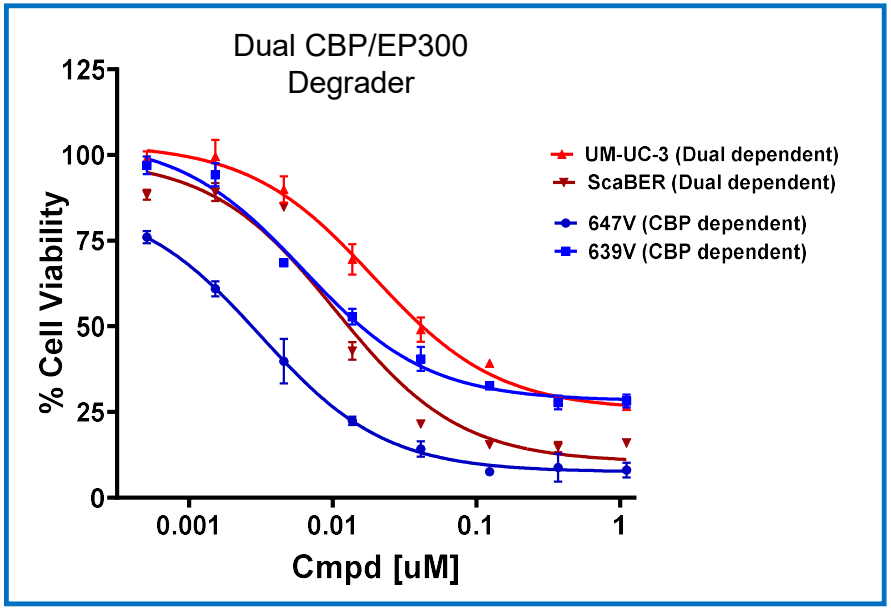
# Initial Development of Dual CBP/EP300 Degraders

## Dual CBP and EP300 degradation




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

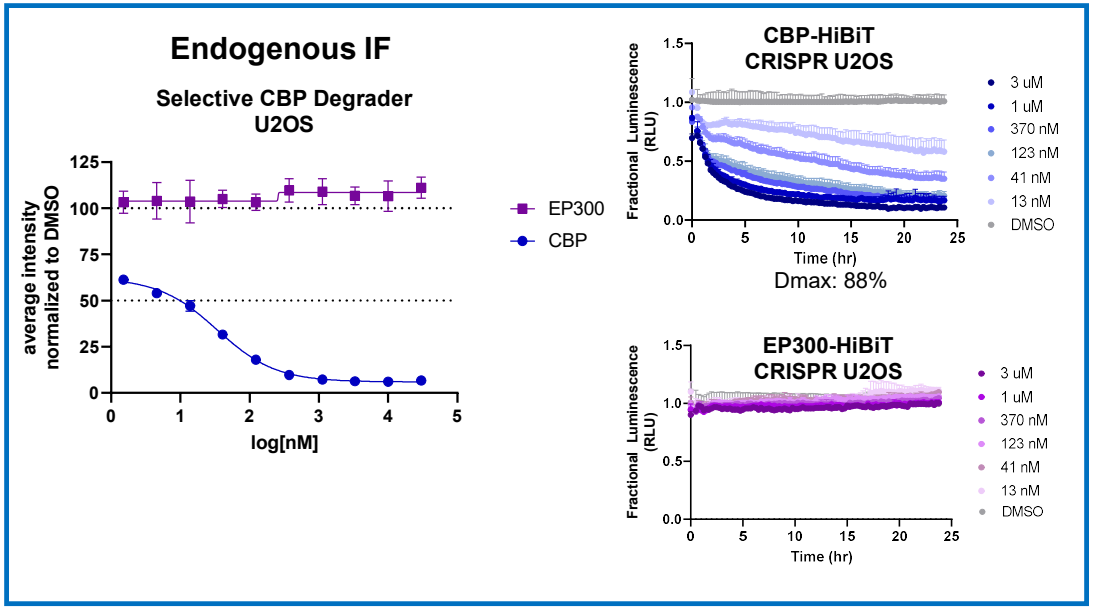
## Cell proliferation assays



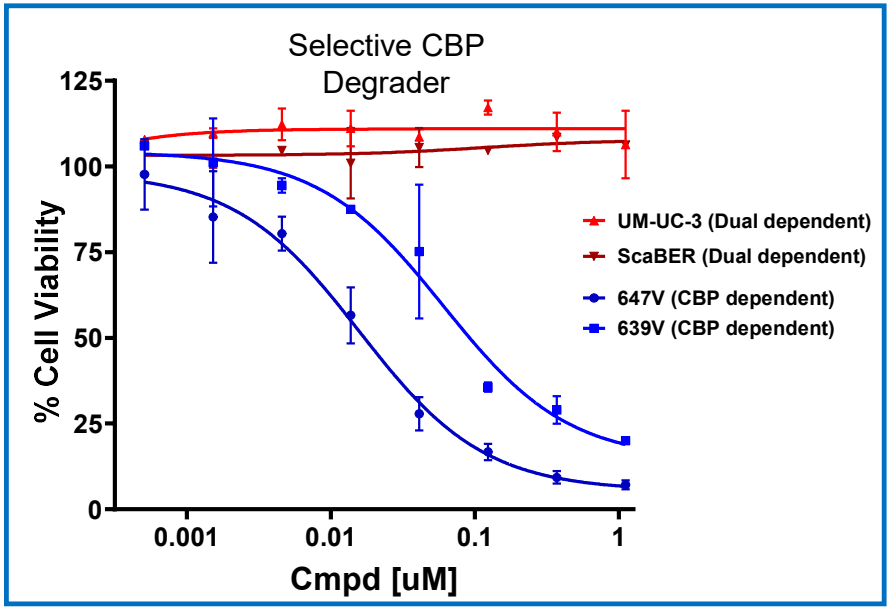

- Robust impact on cell proliferation in both dual (CBP and EP300) dependent or CBP dependent bladder cancer cell lines

# Advancement of Highly Selective Degraders for CBP

## Selective CBP degradation




## Cell proliferation assays




- Robust loss of cell viability only in CBP-dependent cell lines while sparing the dual dependent ones
- Selective CBP degradation translating to selective CBP-dependent cell killing

# Summary

**FHD-609**

- Synovial sarcoma is a rare, often aggressive soft tissue malignancy with limited therapeutic options and most common among adolescents and young adults

- FHD-609 is a CRBN-based PROTAC with pM potency, exquisite selectivity, and does not show off-target CRBN neosubstrate activity

- FHD-609 is in a phase 1 clinical trial for synovial sarcoma

  *Initial PD shows uniform and rapid loss of BRD9 in on-treatment metastatic synovial sarcoma biopsies*

  *FHD-609 is a monotherapy and administered intravenously*

**Foghorn Degradation Platform**

- Chemistry capabilities to develop both parenteral and orally bioavailable heterobifunctional degraders

- Regulate specificity of degradation within our target degrader series to introduce selectivity when required

- Achieving CBP selective degradation is a promising advancement towards treatment of CBP-dependent cancers

# Acknowledgements

## Thank you!

## Questions?