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Discovery of FHD-609, a Potent and Selective Heterobifunctional Degrader of BRD9

Cambridge Health Institute 18th Annual Drug Discovery Chemistry Meeting

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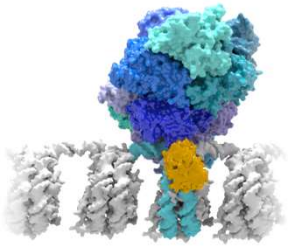
Outline

- Biological rationale
- Degrader identification and strategy
- Identification of FHD-609
- Special considerations for selectivity and stability
- In vivo efficacy
- Degrader kinetics
- Early Phase I patient data

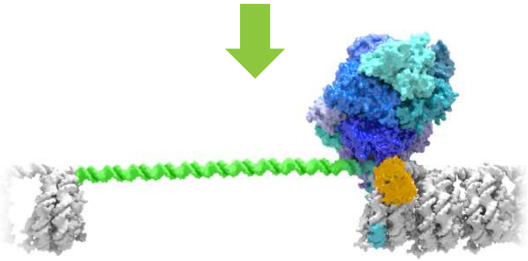
TPD to Regulate Chromatin and Gene Expression

Healthy Cells

Work together to orchestrate gene expression at the right locations



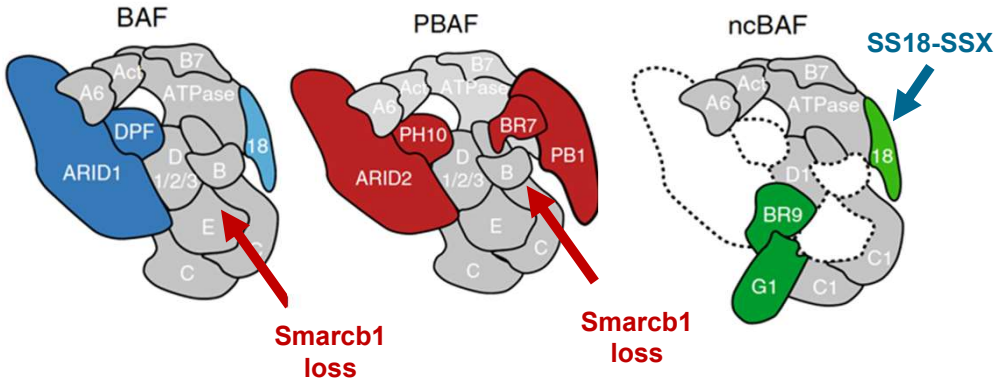
Chromatin remodeling complex + Transcription Factor



Normal gene expression

Cancer Cells

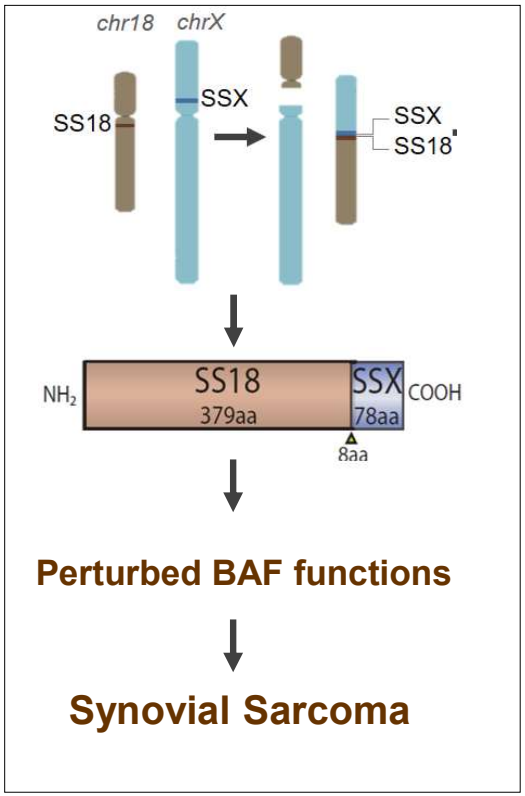
Aberrations in remodeling complexes (BAF) orchestrate gene expression at the wrong locations



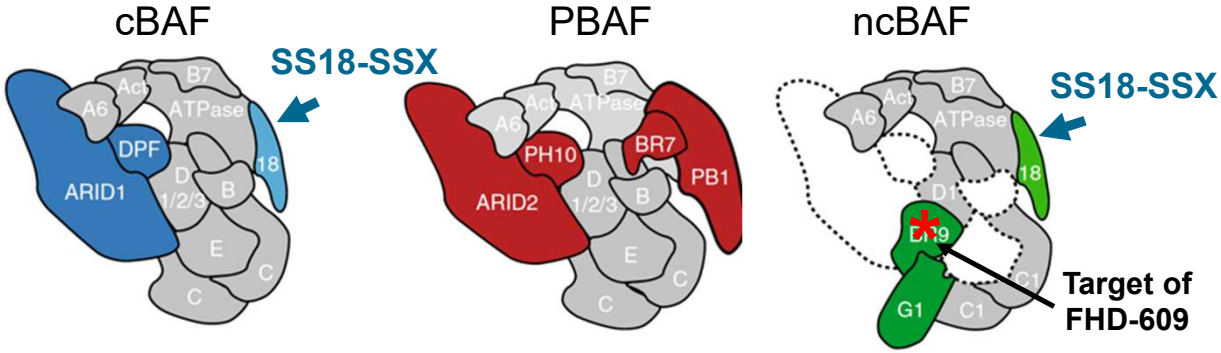
- Component loss and/or improper translocation fusion incorporation
- Cancer driver mutations associated with BAF subunits often results in paralogs or alternative BAF complex dependency
- Results in chromatin dysregulation and improper gene expression

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

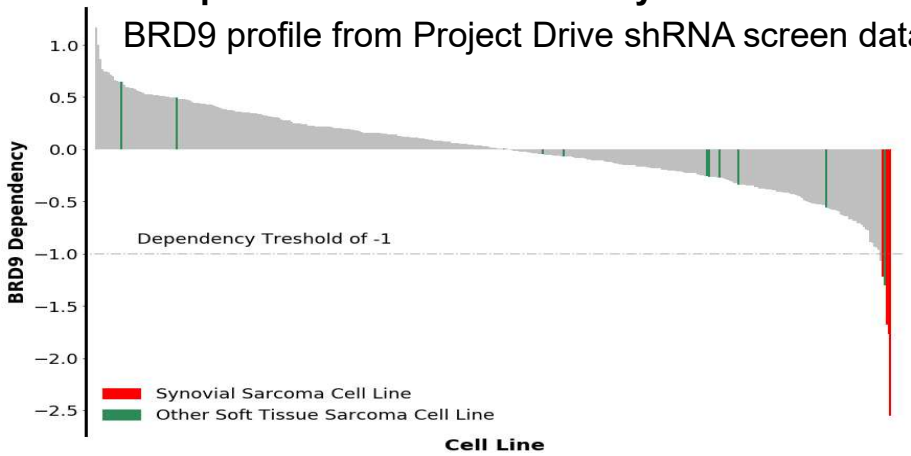
Synovial Sarcoma is characterized by SS18-SSX fusion oncoproteins



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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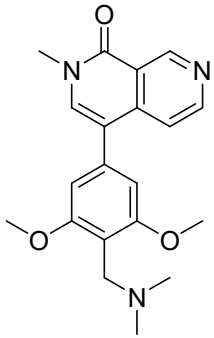
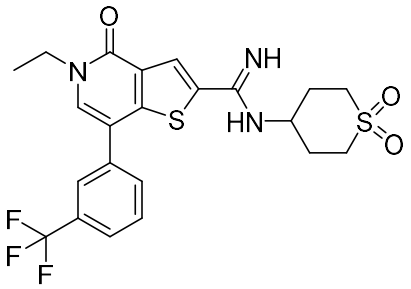
BRD9 Binder Starting Points

Binder Starting Points



A

BRD9 TR-FRET IC_{50} 15 nM
BRD7 TR-FRET IC_{50} 90 nM

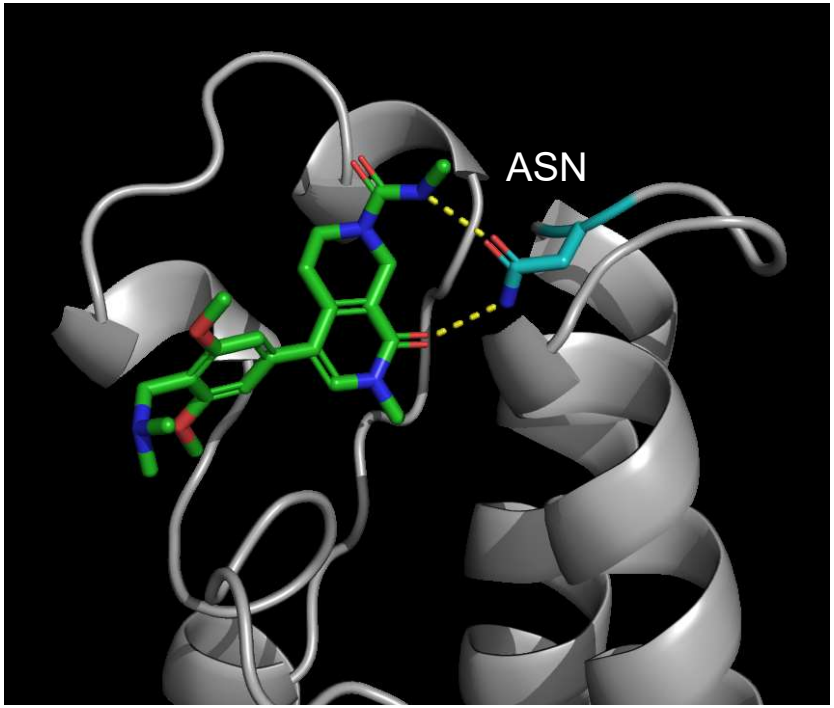


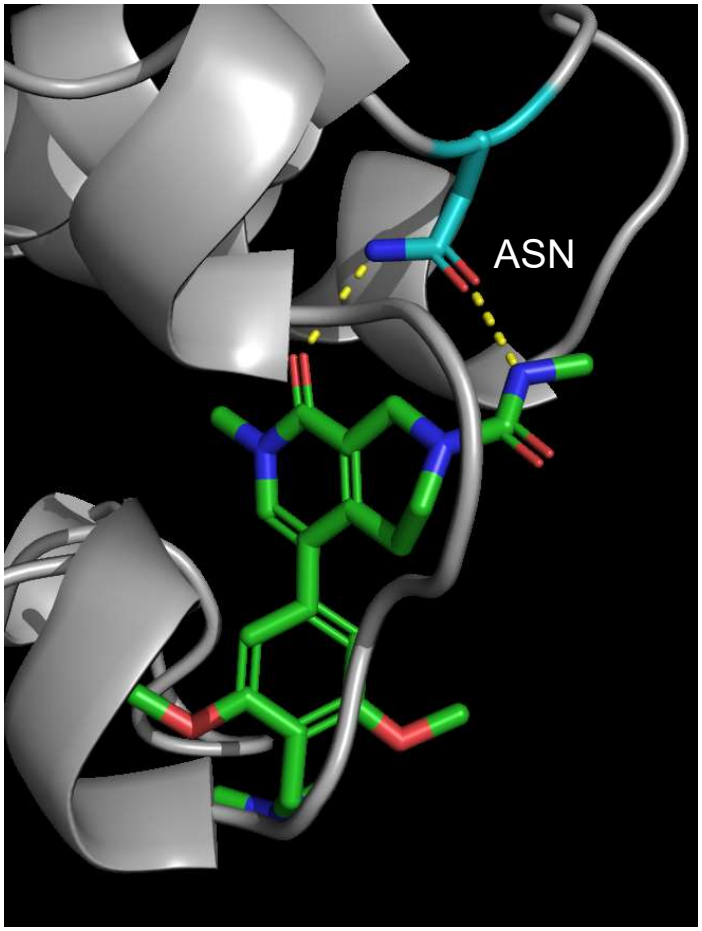
B

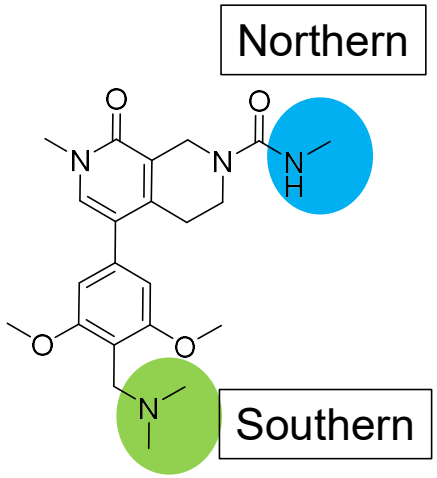
BRD9 TR-FRET IC_{50} 30 nM
BRD7 TR-FRET IC_{50} 40 nM

- Established binding modes
- Good affinity for developing degrader
- Dual BRD 7/9 affinity
- Selective over other bromodomains

Two Potential Bromodomain Exit Vectors Identified







c

BRD9 TR-FRET IC_{50} 8 nM
BRD7 TR-FRET IC_{50} 9 nM

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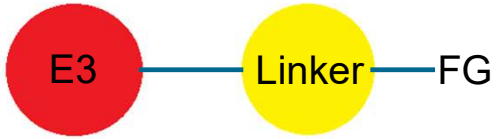
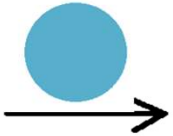
Developing a Chemistry Toolbox

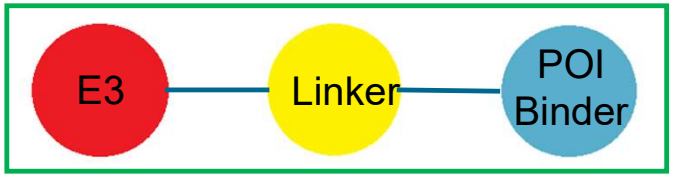
Hit Finding



Library of Ligase-Linker Conjugates
"PRETACS"



Add POI Binder
in one Step



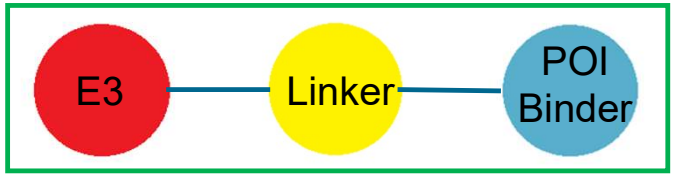
Rapid synthesis of Library of
Degraders to find **Hits**

Hit Expansion

Library of building
blocks
(>1 gram)

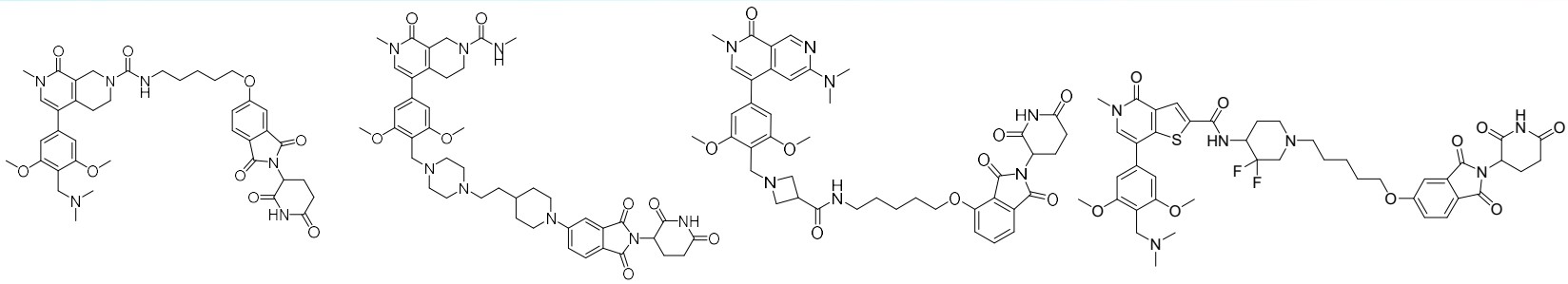
Library of mono-
protected bifunctional
linker BBs
(>500 mg)

2-3 step
Library
Synthesis



Bespoke degrader libraries
for rapid **SAR expansion**

Representative First Generation Compounds



Class	Northern urea	Southern urea	Southern DMAP	Northern thiophene
	D	E	F	G
MW / cLogD / tPSA / Rot Bonds	743 / 2.5 / 169 / 13	823 / 1.9 / 166 / 10	794 / 2.3 / 182 / 15	863 / 2.9 / 167 / 15
BRD9 / BRD7 DC_{50} nM (%D_{max})	4 (100) / NC (29)	0.2 (99) / NC (14)	0.8 (100) / 25 (100)	0.08 (100) / 2 (100)
pH 7.4 PBS kinetic soubility μM	266	108	25	266
Plasma stab. m/h % rem. @ 2 hrs	22 / 57	90 / 90	45 / 93	27 / 19
mouse IV PK (1 mpk) Cl / $T_{1/2}$ (h) / Vd_{ss}	43 / 0.3 / 0.9	11 / 5.4 / 1.3	62 / 0.6 / 2.4	82 / 1.7 / 8.9

- Sub-nanomolar selective degraders identified
- Variable plasma stability and protein binding
- Reasonable solubility and IV mouse PK achievable

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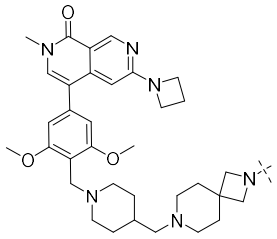
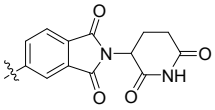
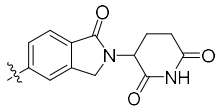
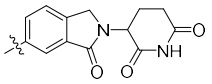
Identification of FHD-609









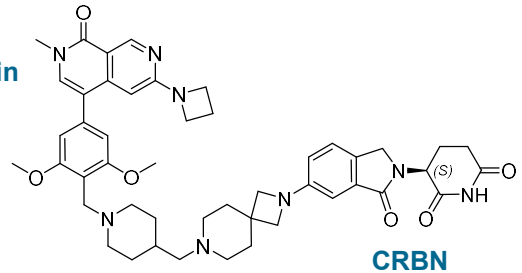
FHT ID	H	I	rac-FHD-609
BRD9 / BRD7 DC_{50} nM ($\%D_{max}$)	0.4 (94) / NC (6)	0.2 (75) / NC (4)	0.1 (100) / NC (6)
BRD4 DC_{50} nM ($\%D_{max}$)	>1000 (<10)	>1000 (<10)	>1000 (<10)
Thermodynamic solubility μM	1	142	155
Plasma stab. m/h % rem. @ 2 hrs	81/87	92/95	100/100
PPB % unbound m/r/d/h/mk			23/34/38/40/38
Cyno IV PK (1 mpk) Cl /T1/2 / Vdss			26/17/33

- Selective picomolar degrader of BRD9
- Long half-life and large volume of distribution across species
- High plasma stability and low-moderate PPB
- Acceptable solubility
- Poor gut permeability → low oral bioavailability across species

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

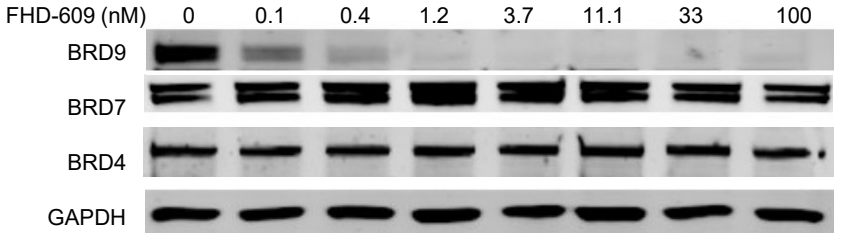
Structure of FHD-609

BRD7/9 Bromodomain Binder

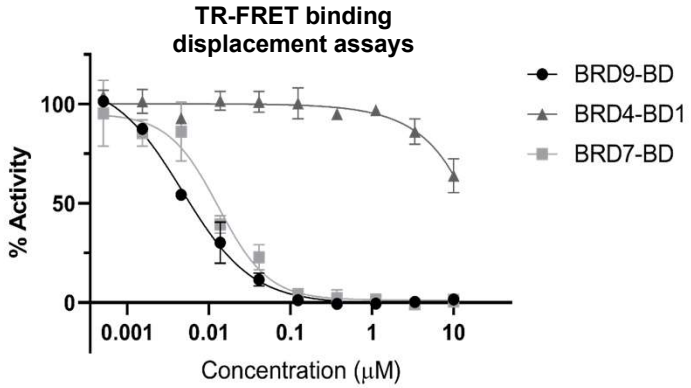


CRBN Binder

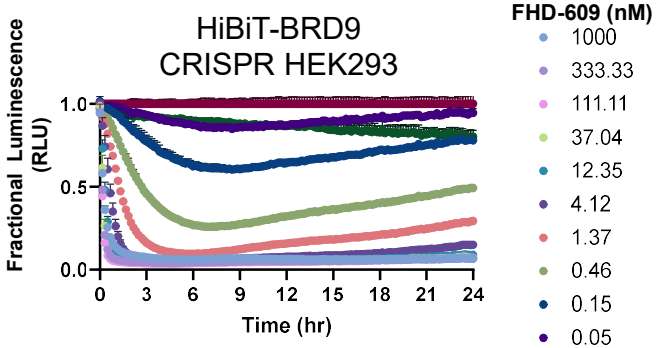
Selectivity of BRD9 degradation



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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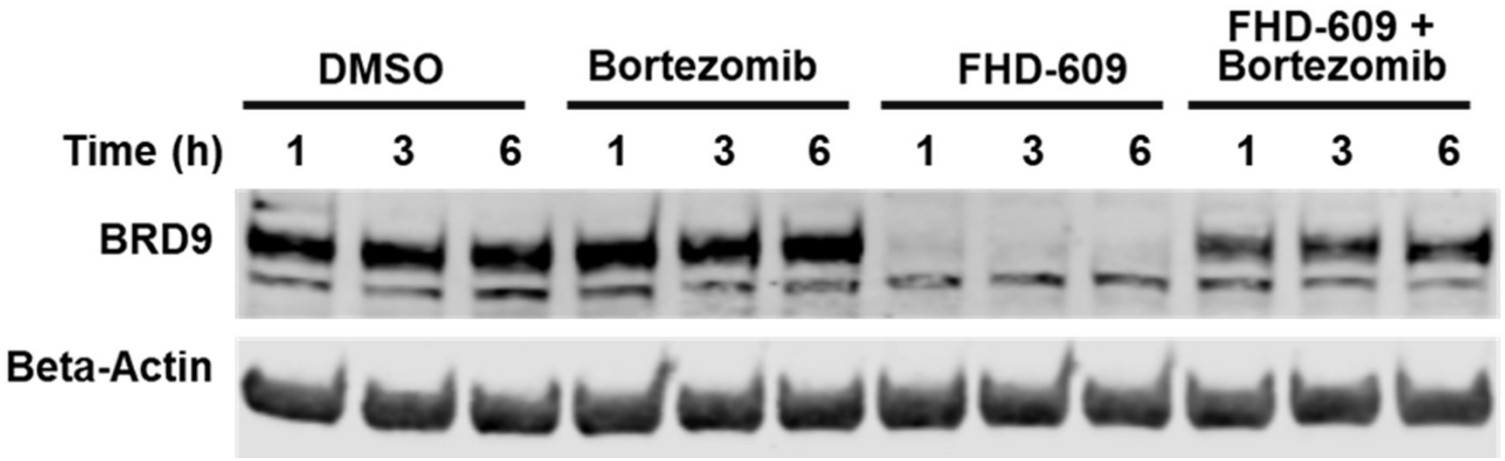
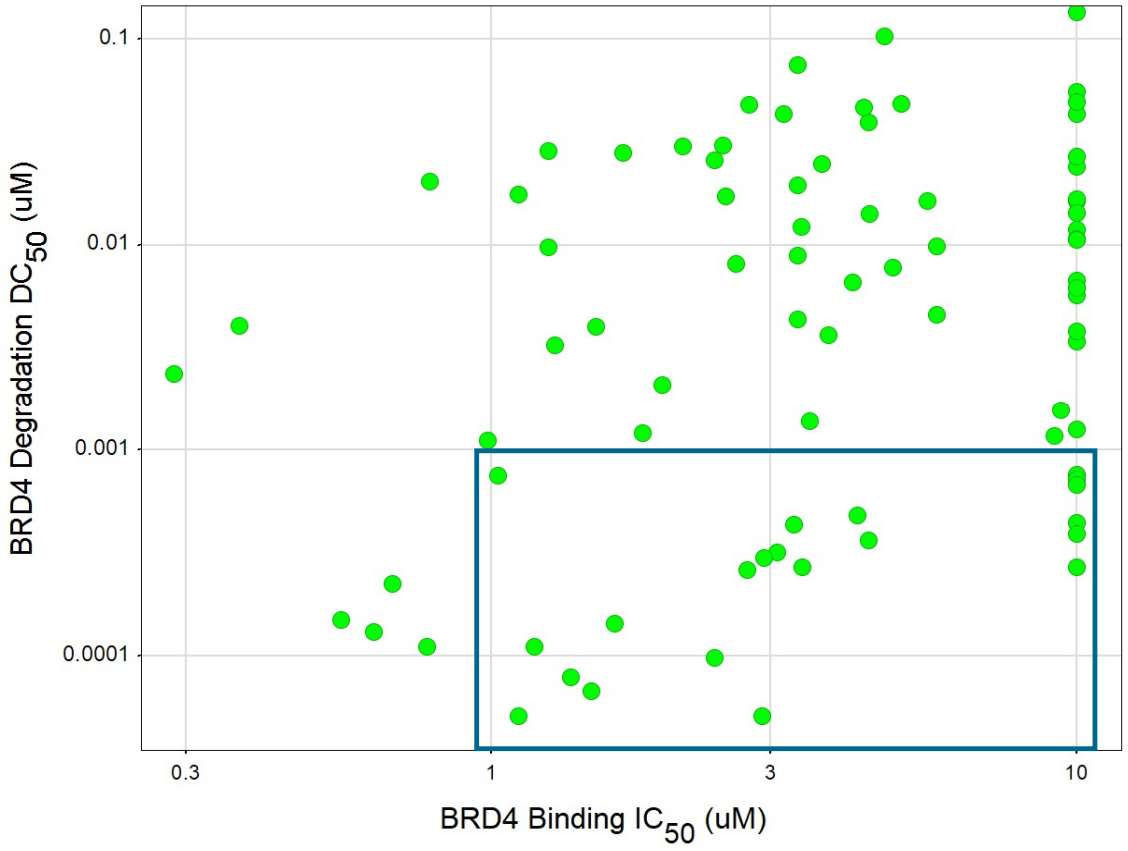
BRD9 Degradation by FHD-609 Is Proteosome Dependent

SYO1 cell line

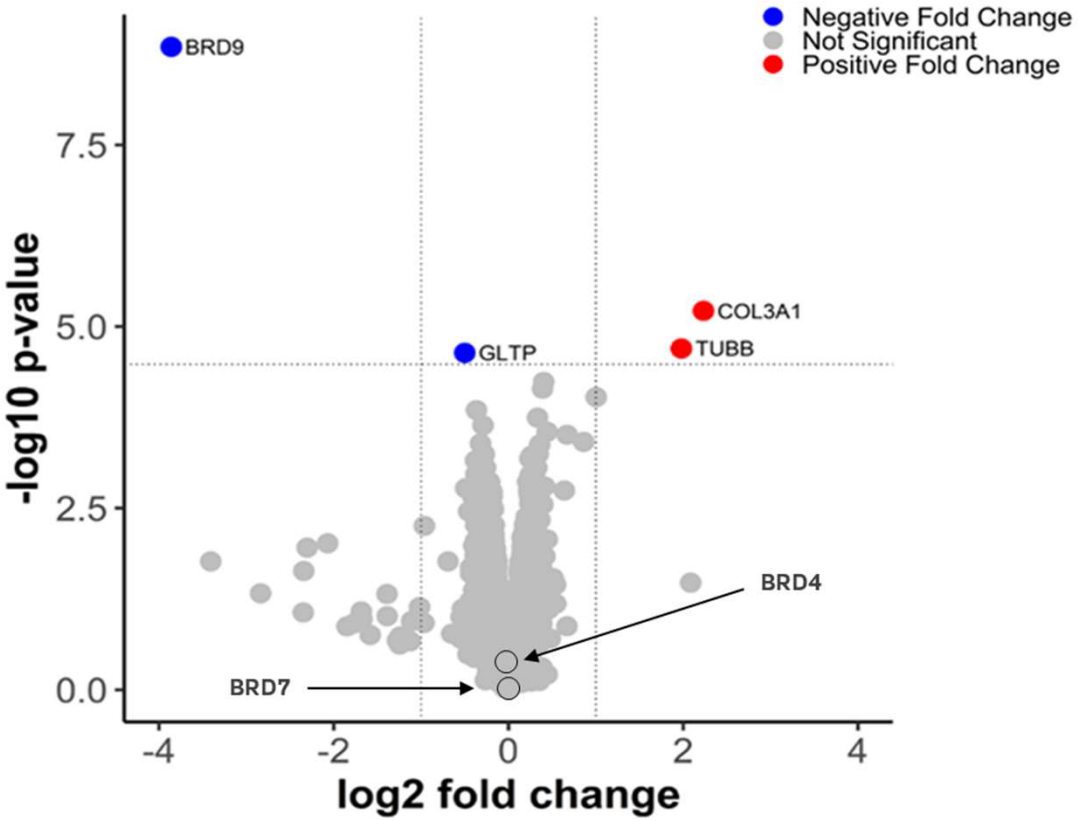


Weak Binding Can Lead to Potent Degradation



- Very weak binding can lead to extremely potent and efficient degradation
- Binding assays may provide misleading data as degrader molecules grow
- Biophysical methods and cellular degradation assays may be more reliable
- Proteomics is the most reliable assay

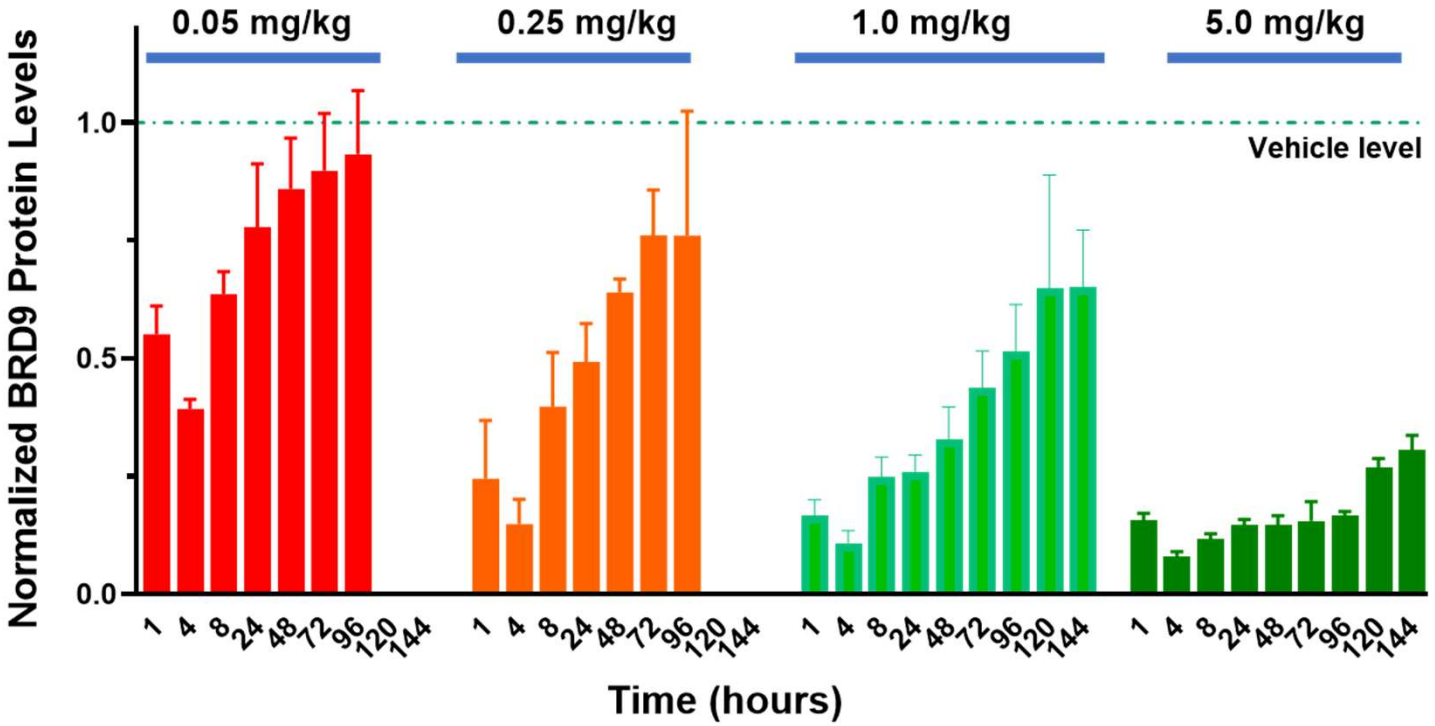
FHD-609 Selectively Degrades BRD9 - Global Proteomics



- Data shown for SYO1 synovial sarcoma cells treated with 16nM of FHD-609 (~200x DC50) for 4h
- BRD9 is the only protein significantly degraded, with 16-fold reduction, by quantitative MS analysis. About ~9k detectable proteins
- Similar selectivity observed for 24h treatment of 16nM FHD-609, or higher concentration of 78nM (~1000x DC50) for 4h, data not shown

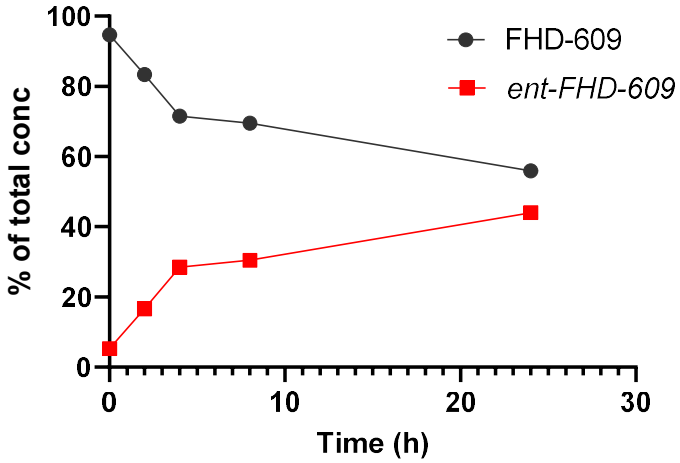
Dose- and Time-dependent *in vivo* BRD9 Degradation

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

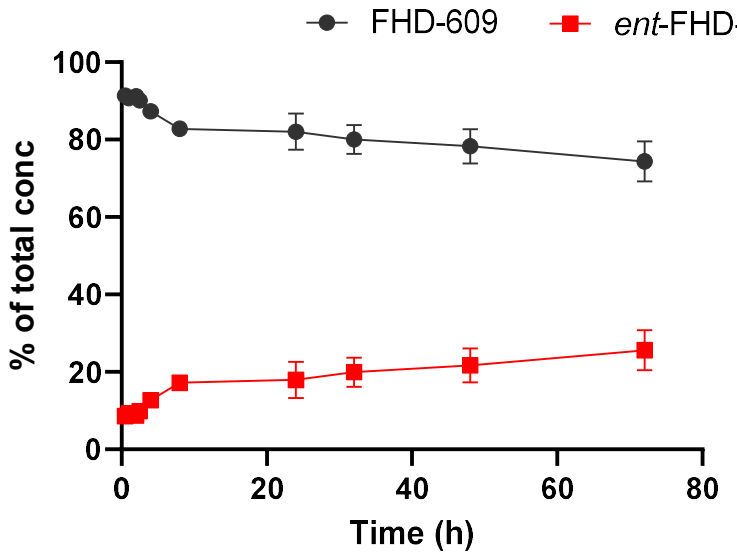


FHD-609 Epimerization: *in vivo* and *in vivo* Differences

In vitro, FHD-609, monkey plasma



In vivo after FHD-609 2h IV infusion, monkey



	% of total AUC
FHD-609	89.9
ent-FHD-609	9.1

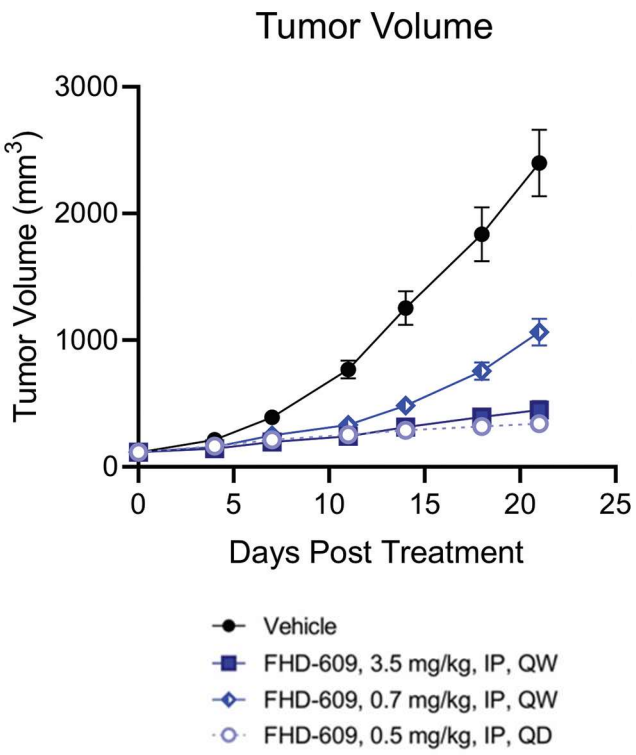
- In vitro models of epimerization may not be indicative of in vivo rate
- Apparent in vivo conversion can be affected by multiple factors such as tissue distribution, B/P partitioning, and pH

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

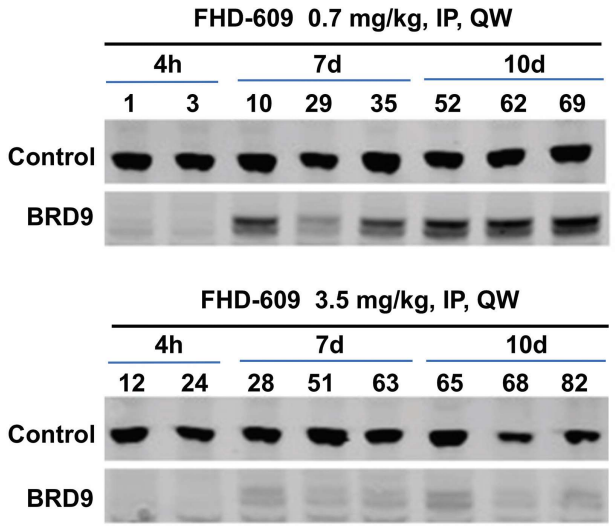
Weekly dosing of racemic FHD-609* achieved sustained BRD9 degradation

SYO1 Synovial Sarcoma CDX Model

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



Sustained BRD9 Degradation

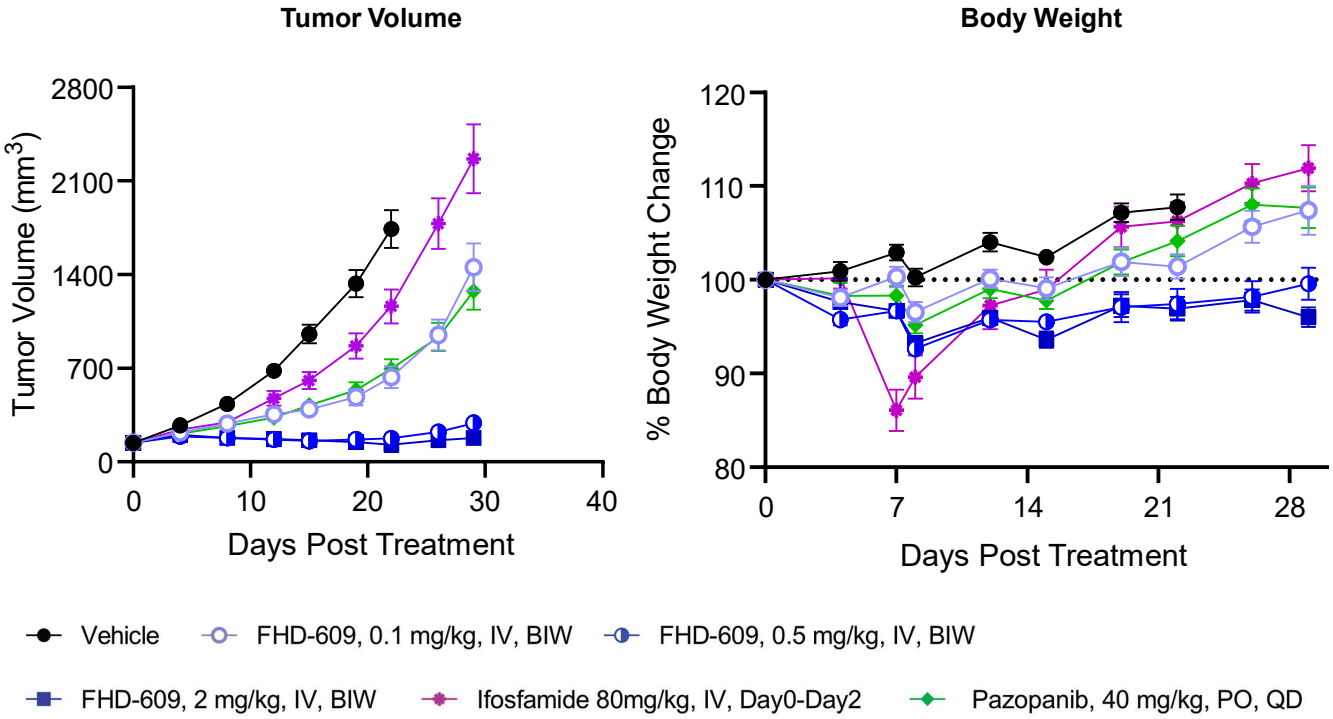


***Racemic FHD-609 utilized in this study**

Superior Tumor Growth Inhibition of FHD-609* in a Synovial Sarcoma Model as Compared to Ifosfamide and Pazopanib

ASKA CDX Model

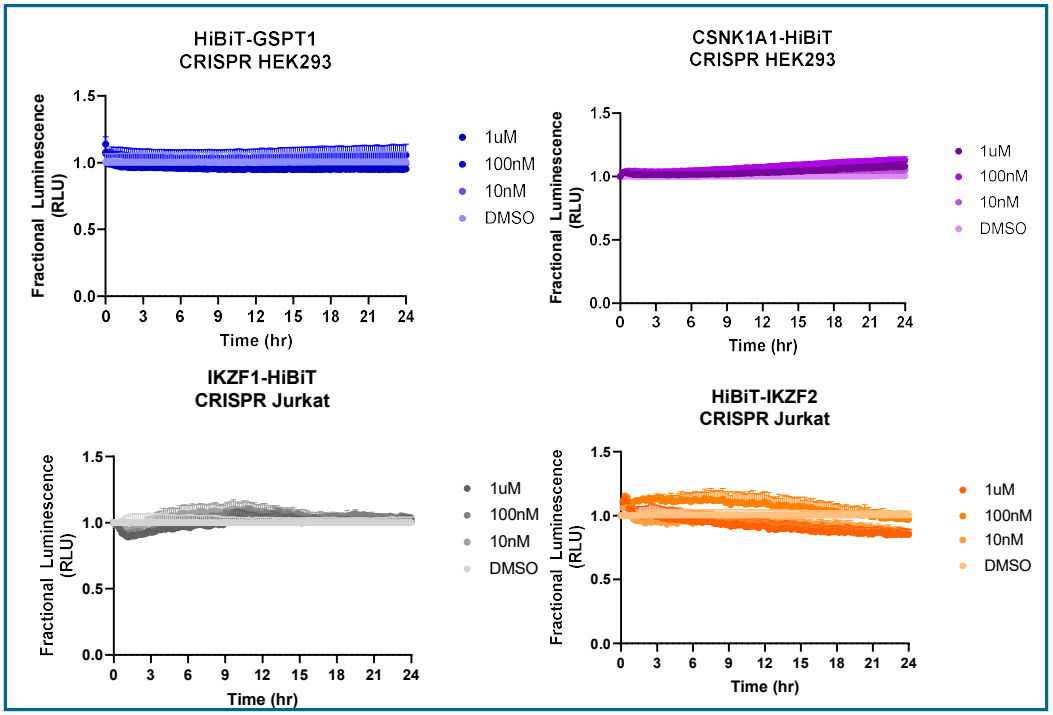
- Mutation: **SS18-SSX1**
- Superior tumor growth inhibition compared to ifosfamide and pazopanib
- Complete suppression observed over 30 days at 2 mg/kg of FHD-609



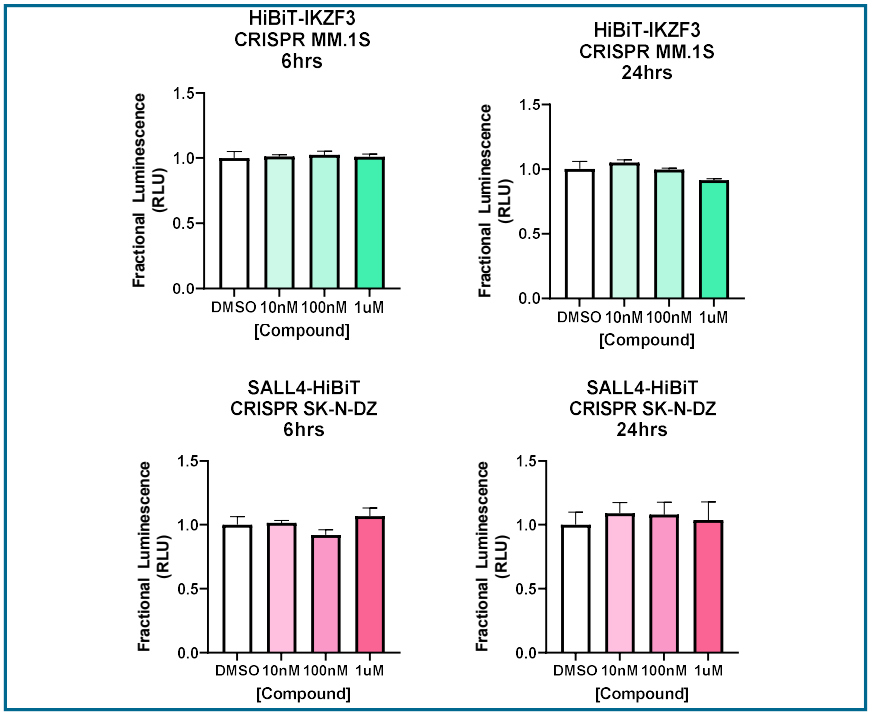
*Racemic FHD-609 utilized in this study

FHD-609: Off-target IMiD Neosubstrate Degradation Activity

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



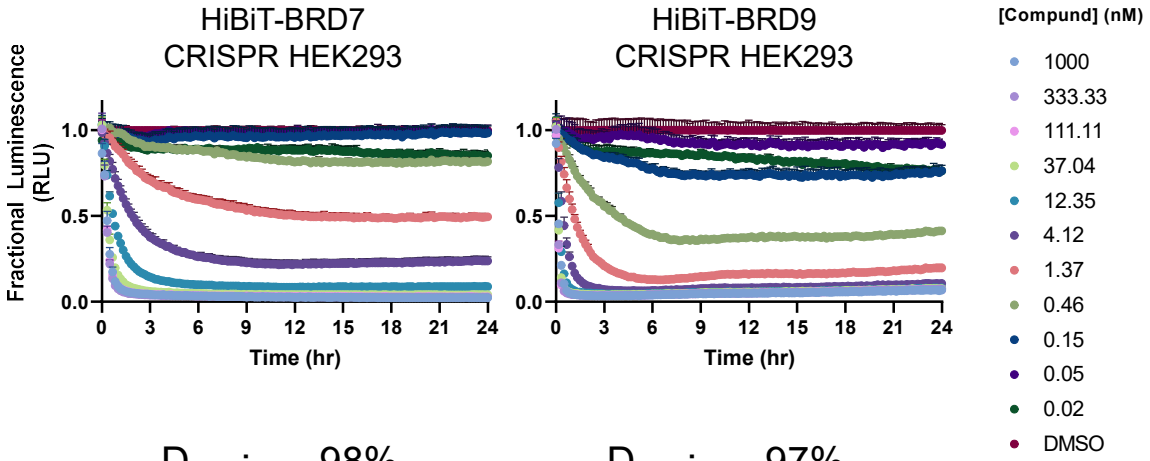
Endpoint degradation (6hr and 24hr) profiling of IKZF3 and SALL4 with FHD-609



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

From Selective BRD9 Degradation to Robust Dual BRD7 and BRD9 Degradation

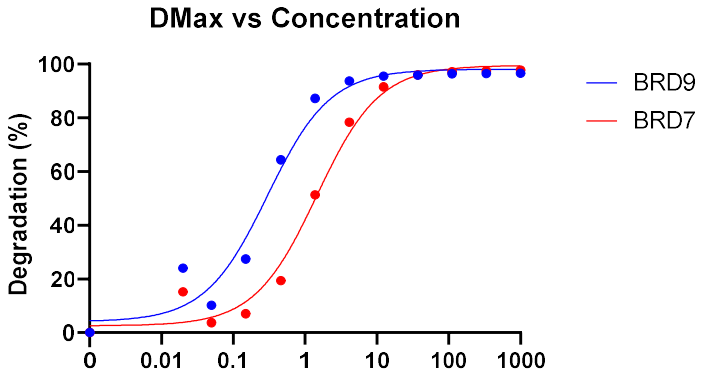
Dual BRD7 and BRD9 kinetic degradation



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

D_{max}: 97%
D_{max50}: 300pM
Rate λ: 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

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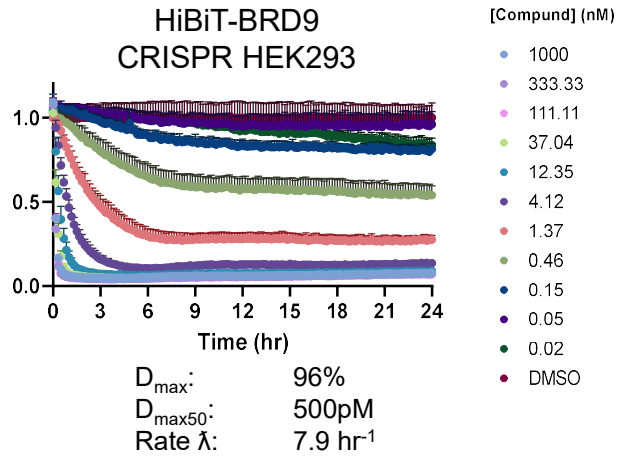
Development of Orally Bioavailable Selective Degraders

- 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}

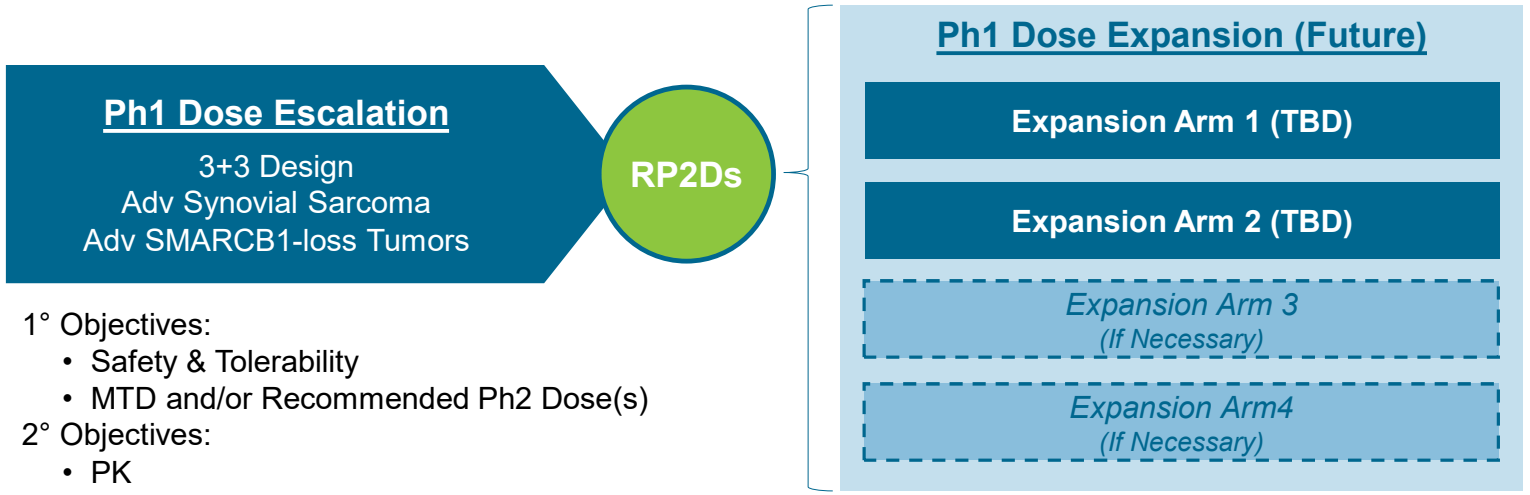
Selective degradation and oral bioavailability

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

FHD-609 Phase 1 Study Overview and Progress



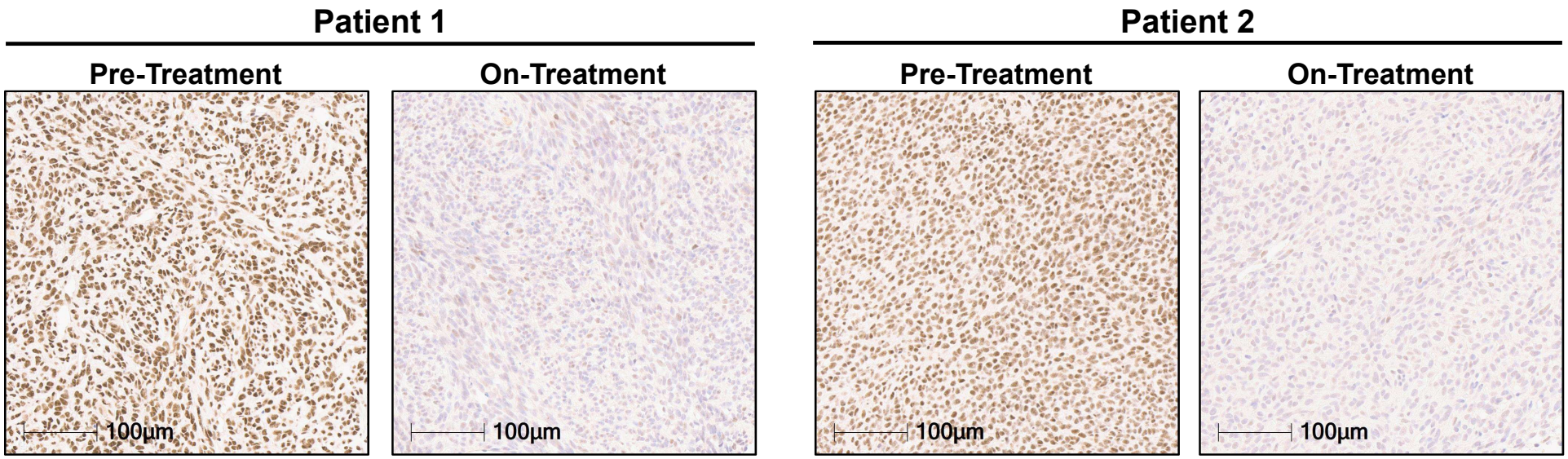
1° Objectives:
- Safety & Tolerability
- MTD and/or Recommended Ph2 Dose(s)

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

Conclusion and Summary

- FHD-609 is a heterobifunctional degrader with proteosome dependent and picomolar potency for BRD9 degradation with selectivity over BRD7, BRD4 and the wider proteome
- Demonstrates picomolar growth inhibitory and colony formation effects in vitro against several synovial cell sarcoma cell lines
- Demonstrates potent degradation in vivo PKPD with dose and time dependence
- Displays potent and sustained degradation of BRD9 in SS xenograft models, with robust tumor growth inhibition that is superior to standards of care
- FHD-609 is in phase 1 clinical trials for synovial sarcoma

Acknowledgements

Thank you!

Questions?