C4 Therapeutics

Discovery of a Potent and Selective BRD9 BiDAC Degrader with Activity in a Preclinical Model of Synovial Sarcoma

Kate Jackson

4th Targeted Protein Degradation Summit
October 26-28, 2021

Forward-looking Statements and Intellectual Property

Forward-looking Statements

The following presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. These forward-looking statements include, but are not limited to, statements regarding the therapeutic potential of C4 Therapeutics, Inc.'s technology and products. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals, as well as the fact that the product candidates that we are developing or may develop may not demonstrate success in clinical trials. Prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. C4 Therapeutics, Inc. undertakes no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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BRD9: Drugging the Undruggable with a BiDAC Degrader Approach

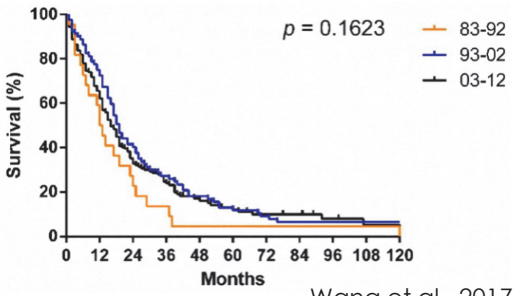
Strong Rationale for Degrader Approach

- Synovial sarcoma (SS) is dependent on BRD9 due to the oncogenic SS18-SSX translocation
- Inhibition of the BRD9 bromodomain is insufficient to ablate its oncogenicity

Brien et al. 2018

Clear Unmet Need

- Very limited benefit of treatments for metastatic or advanced synovial sarcoma, median survival ~18 months



Wang et al., 2017

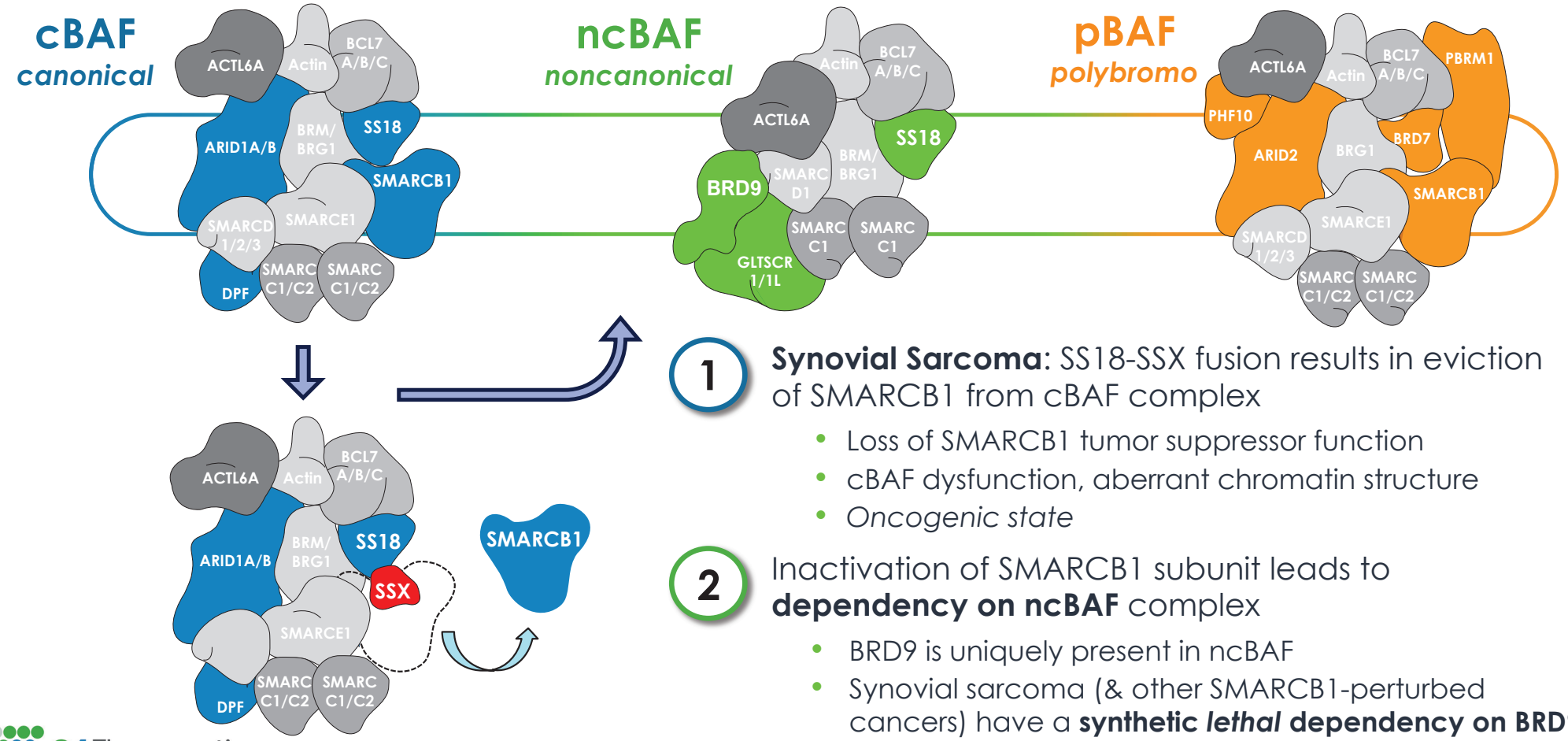
Defined Patient Population

- US incidence: ~900 cases/year
- ~10% of all soft tissue sarcomas
- Median age at diagnosis: 34 years old

Source: NIH SEER Database, Primary Literature Consensus

Patient figures represent estimated U.S. annual incidence

Synovial Sarcoma is Driven by Aberrant BAF Complex Biology



1 **Synovial Sarcoma**: SS18-SSX fusion results in eviction of SMARCB1 from cBAF complex

- Loss of SMARCB1 tumor suppressor function
- cBAF dysfunction, aberrant chromatin structure
- *Oncogenic state*

2 Inactivation of SMARCB1 subunit leads to **dependency on ncBAF** complex

- BRD9 is uniquely present in ncBAF
- Synovial sarcoma (& other SMARCB1-perturbed cancers) have a **synthetic *lethal* dependency on BRD9**

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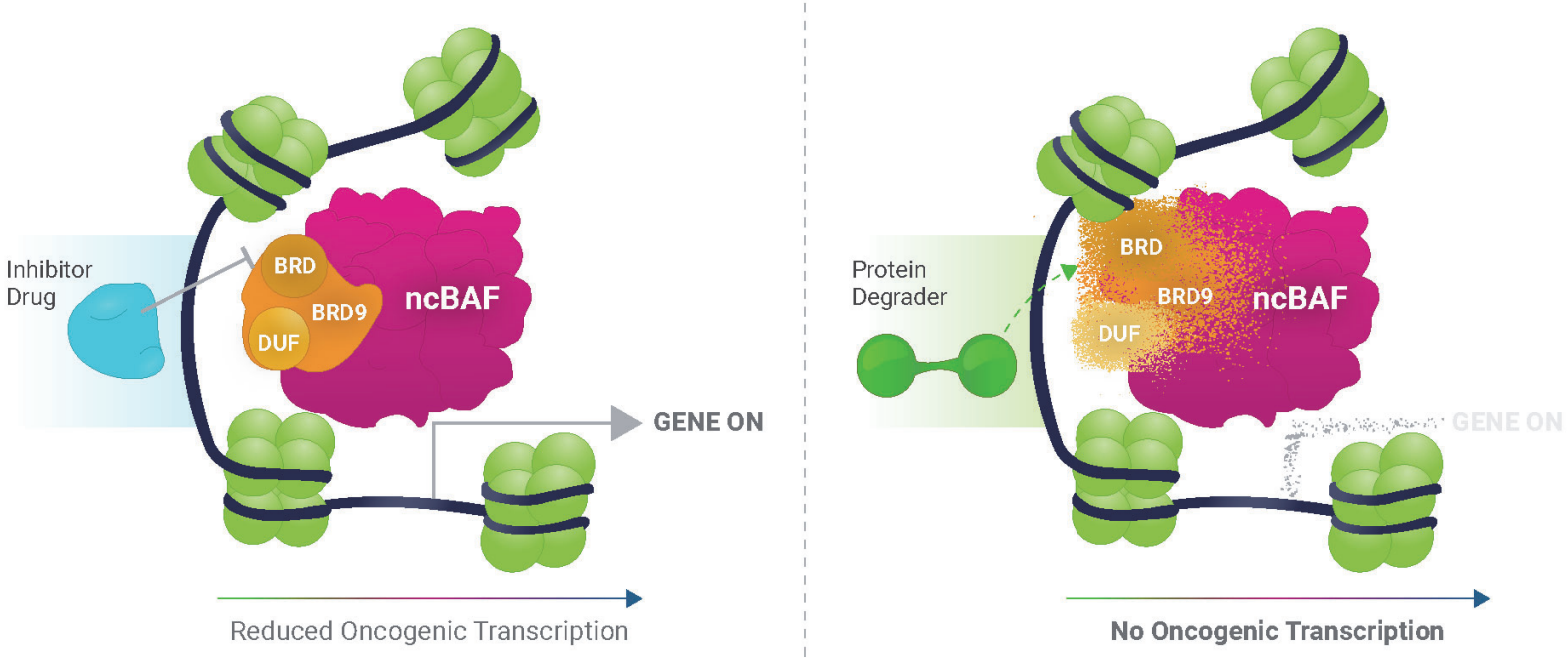
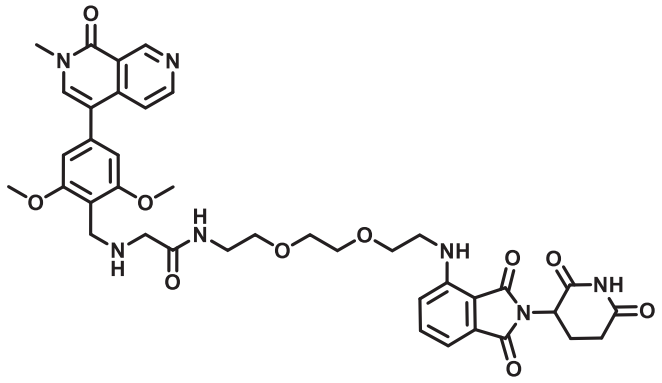
BRD9 Inhibition *vs.* Degradation



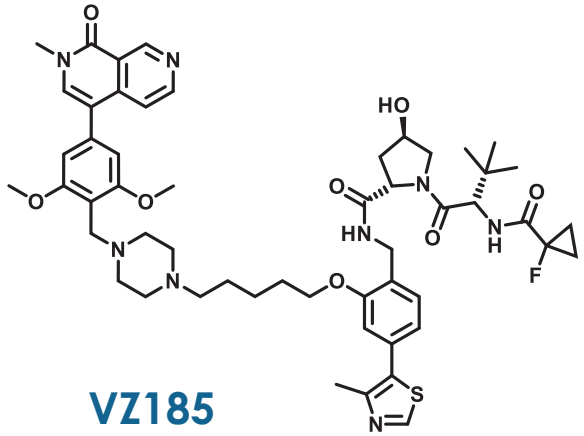
BRD9 associates with chromatin independent of its bromodomain, therefore traditional BRD9 inhibitors do not fully ablate oncogenic transcription

Brien *et al.* eLife 2018

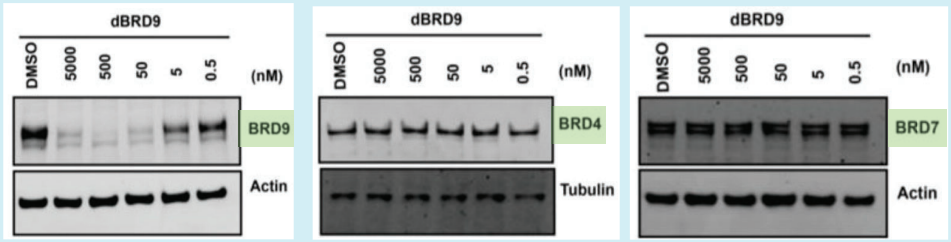
Published BRD9 Degraders – Excellent In Vitro Tool Compounds



dBRD9



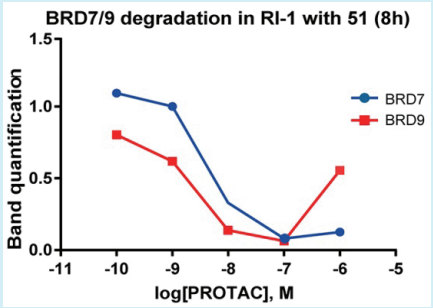
VZ185



Remillard et al. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 5738

RI-1 cells (8h):

BRD9 DC_{50} = 1.8 nM
BRD7 DC_{50} = 4.5 nM
D_{max} = 95%



Zoppi et al. *J. Med. Chem.* **2019**, *62*, 699

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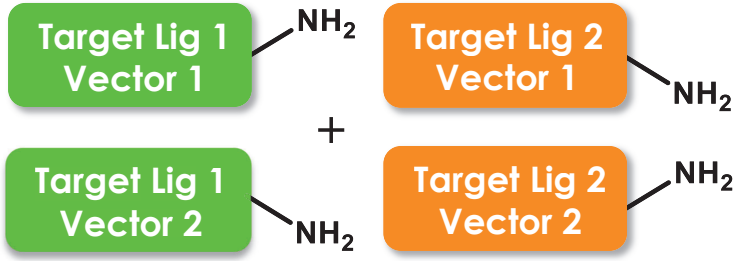
C4T's Approach to BiDAC Degrader Discovery

C4T TORPEDO™ Platform

An operationally refined, information rich approach that is successful ~75% of the time

Chemistry Design — 1

Strategy:
2 Targeting Ligands
x
2 Exit Vectors



Synthesis — 2

- Focused library campaign; ~60-90 compounds per target; interrogating multiple E3 ligases and linker lengths

Primary Profiling — 3

- Target engagement, E3 engagement, dimerization, and intracellular target degradation (HiBiT)

HITS ***(mechanistically-characterized)***

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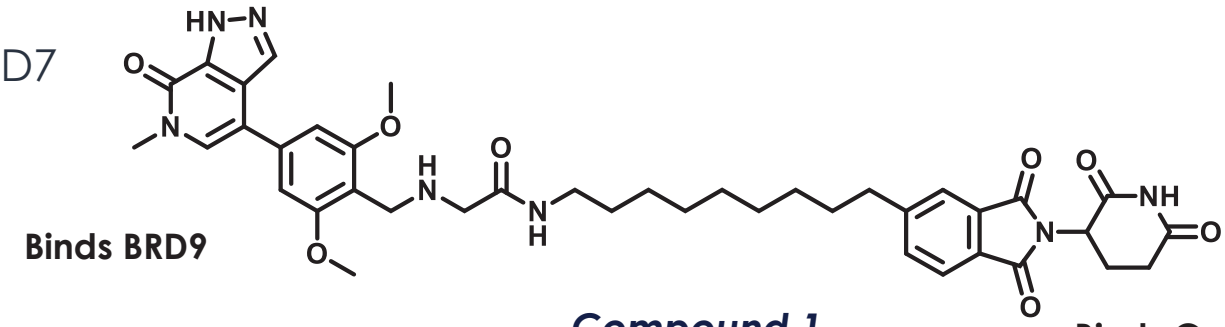
BRD9 BiDAC Degrader HIT

GOAL: Identify a drug-like compound with a mouse PK profile suitable to demonstrate proof-of-concept efficacy in a mouse xenograft model

- ✓ Potently degrades BRD9
- ✓ Selective over BRD4 & BRD7

- ✗ Drug-like properties
- ✗ Plasma stability
- ✗ Mouse PK



Compound 1

BRD9-HiBiT DC_{50} (2h)	E_{max} (2h)
5 nM	4 %

BRD9 BiDAC Degrader HIT: Design Objectives

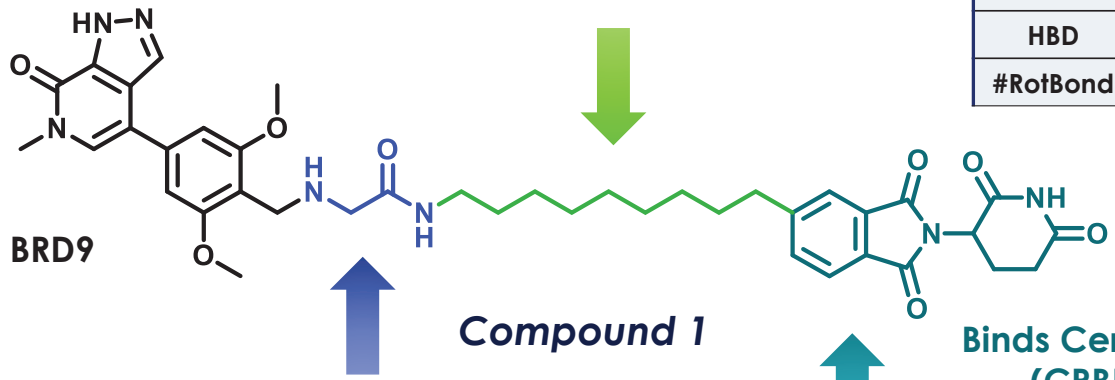
GOAL: Identify a drug-like compound with a mouse PK profile suitable to demonstrate proof-of-concept efficacy in a mouse xenograft model

- ✔ Potently degrades BRD9
- ✔ Selective over BRD4 & BRD7

- ✘ Drug-like properties
- ✘ Plasma stability
- ✘ Mouse PK

MW	754
ClogP	4.4
TPSA	194
#RotBond	18

Shorten linker length
(reduce MW and # rotatable bonds)



Binds BRD9

Compound 1

Binds Cereblon (CRBN)

Replace BRD9 exit vector moiety
(improve stability)

Try alternative CRBN binders
(improve physicochemical properties)

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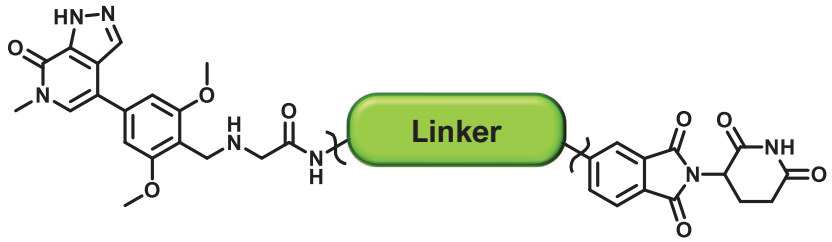
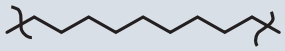
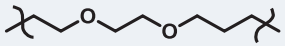
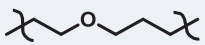
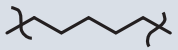
Linker Length and Composition

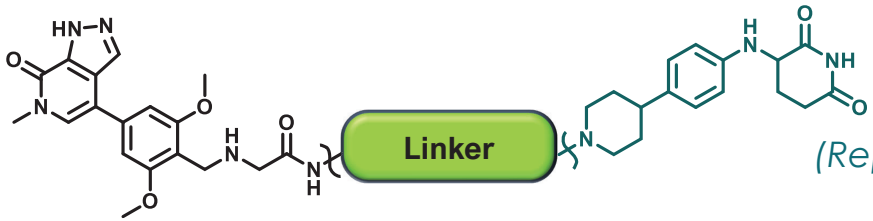


Compound	Linker	BRD9 DC_{50} 2h (nM)	E_{max} 2h (%)
1 (HIT)		5	4
2		91	3
3		3	3
4		67	4
5		242	23
6		>9990	67

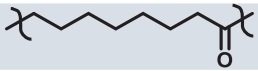
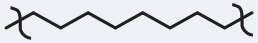
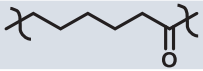
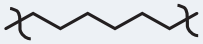
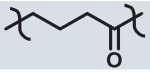
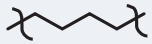
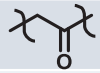
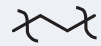
- Alkyl >> PEG
- Reduction of linker length tolerated with some loss of potency

Will shorter linker lengths be tolerated with non-phthalimide CRBN binders?

Shorter Linker Length Tolerated with Alternate CRBN Binder



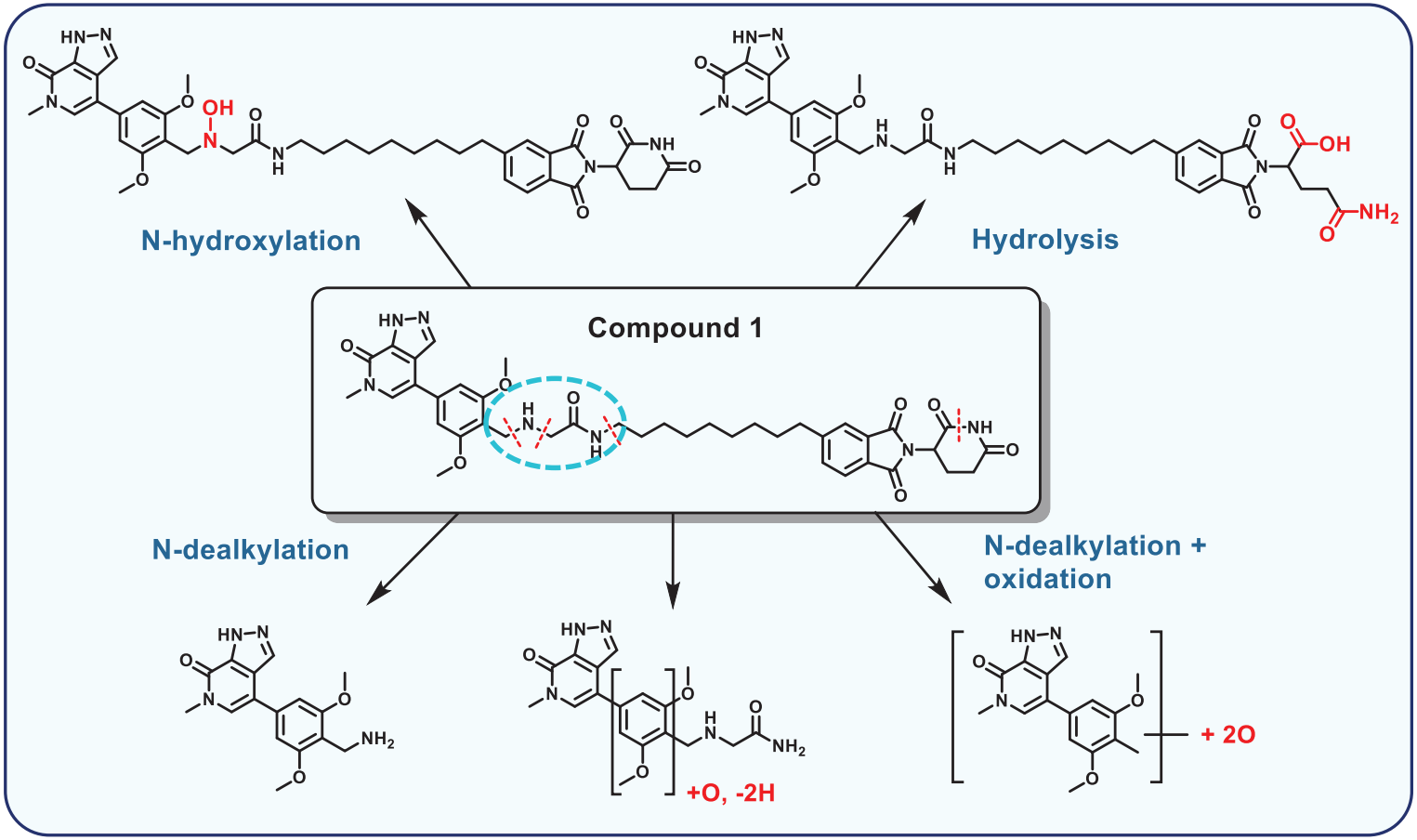
N-aryl glutarimide
(Replacement for phthalimide)

Compound	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
7		160	23	107
8		>9990	67	--
9		>9990	67	--
10		>9990	62	--
11		135	5	--
12		>9990	58	--
13		249	4	--
14		187	9	93
15	***none*** *(piperidine amide)*	>9990	55	25

- Easy to miss degradation signal if not exploring systematically

- Desirable reduction in MW
- Key analogs for next round of optimization

How to Improve PK? Metabolite-ID for the Original HIT

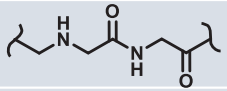
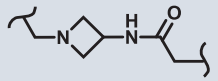
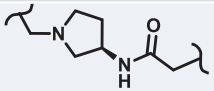
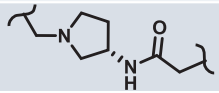
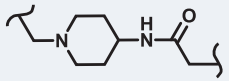
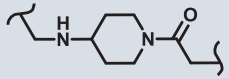
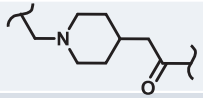
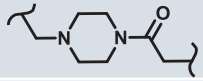
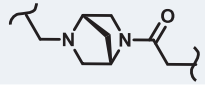
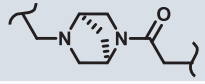
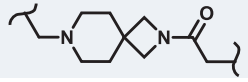


- Met-ID studies suggest glycyl in exit vector region is a source of metabolic instability
- **Next SAR step →** Identify alternative structural feature to replace glycine

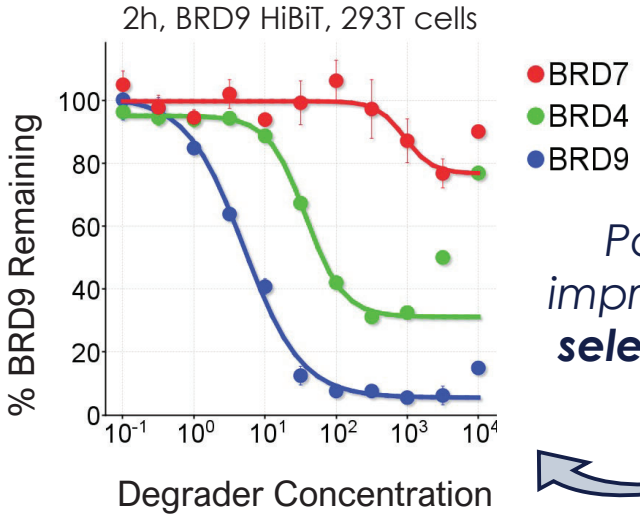
Glycyl Replacement Can Offer Potency & Metabolic Stability Improvement

Goals:

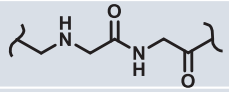
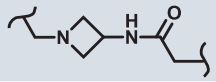
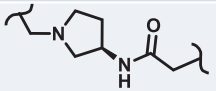
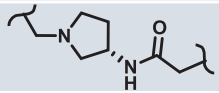
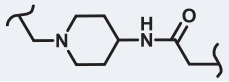
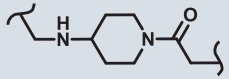
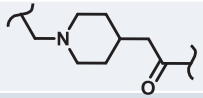
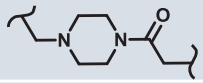
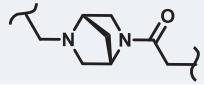
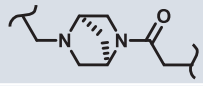
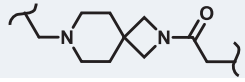
- Improve potency
- Improve metabolic stability

Cmpd	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
14		187	9	93
15		88	3	102
16		305	24	88
17		224	11	56
18		25	10	68
19		98	18	79
20		**7**	4	157
21		**5**	4	**36**
22		35	8	103
23		43	8	86
24		63	19	**31**

Glycyl Replacement Can Offer Potency & Metabolic Stability Improvement



*Potency & PK improvement…**but selectivity eroded***

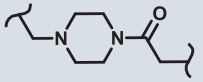
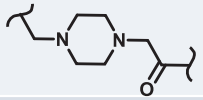
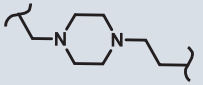
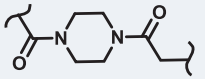
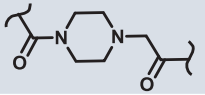
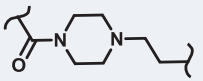
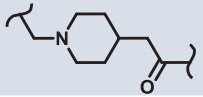
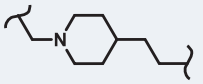
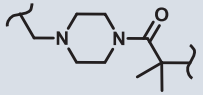
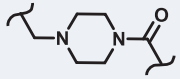
Cmpd	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
14		187	9	93
15		88	3	102
16		305	24	88
17		224	11	56
18		25	10	68
19		98	18	79
20		**7**	4	157
21		**5**	4	**36**
22		35	8	103
23		43	8	86
24		63	19	**31**

C4 Therapeutics

Single Atom Change is Beneficial for Bromodomain Selectivity

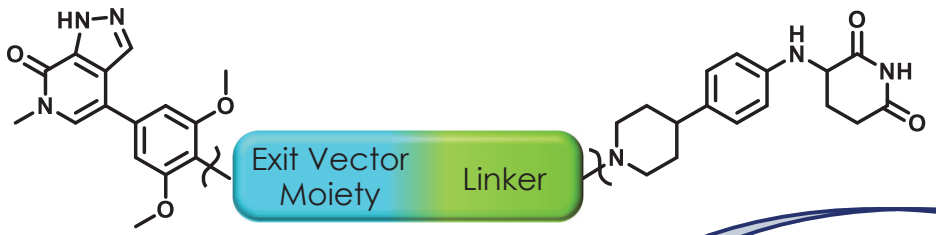
Hypothesis:

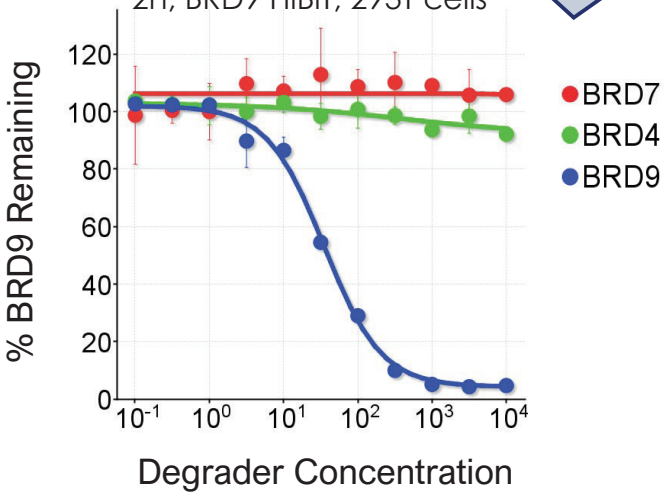
- Small modification in exit vector region could influence exit trajectory & ternary complex structure, thereby influencing selectivity over BRD4 and BRD7

Cmpd	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
21		5	4	36
25		15	8	154
26		158	36	10
27		**39**	5	**31**
28		>5000	45	42
29		55	7	55
30		7	4	157
31		286	24	42
32		>1000	58	--
33		6	15	786

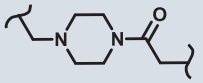
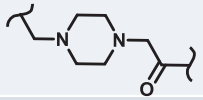
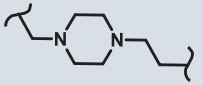
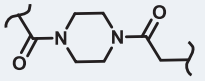
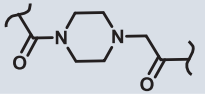
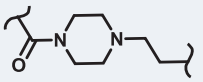
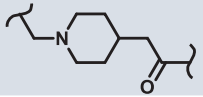
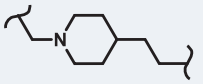
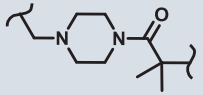
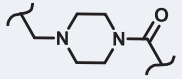
C4 Therapeutics

Single Atom Change is Beneficial for Bromodomain Selectivity



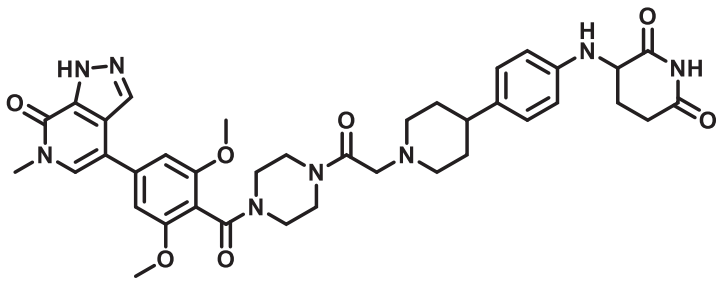


Some potency lost….but ***selectivity restored***

Cmpd	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
21		5	4	36
25		15	8	154
26		158	36	10
27		**39**	5	**31**
28		>5000	45	42
29		55	7	55
30		7	4	157
31		286	24	42
32		>1000	58	--
33		6	15	786

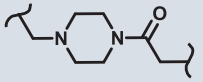
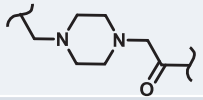
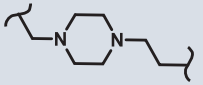
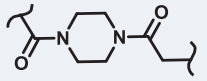
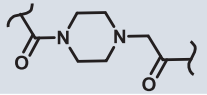
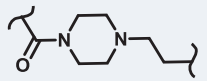
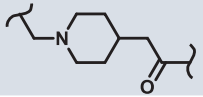
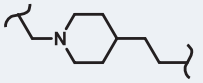
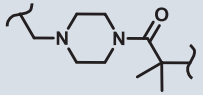
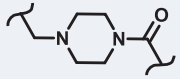
C4 Therapeutics

Single Atom Change is Beneficial for Bromodomain Selectivity



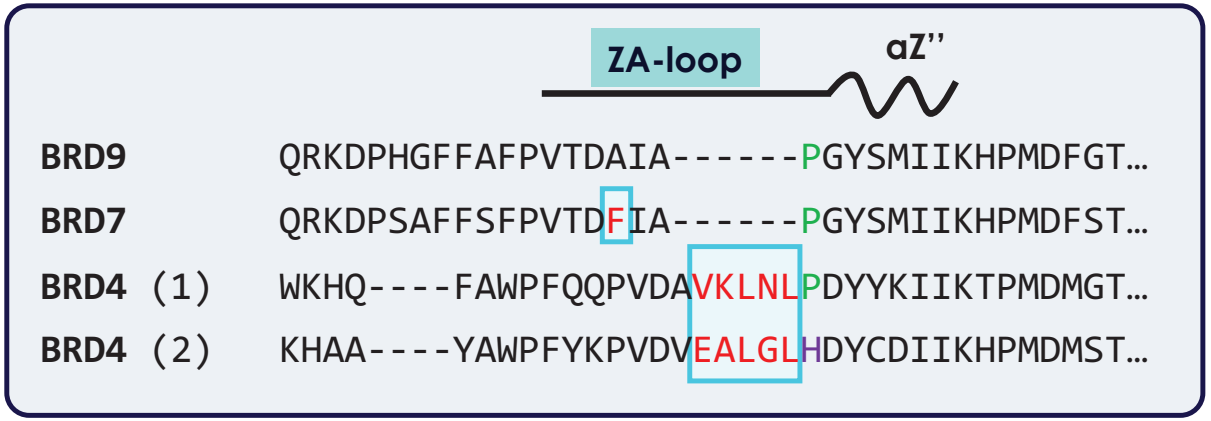
Compound 27: Reasonable balance of potency, mouse IV PK, and selectivity

Mouse IV PK (2 mg/kg)			Mouse PO PK (10 mg/kg)
CL (mL/min/kg)	$T_{1/2}$ (h)	$V_{d,ss}$ (ng*h/mL)	%F
31	7	4.8	0.1

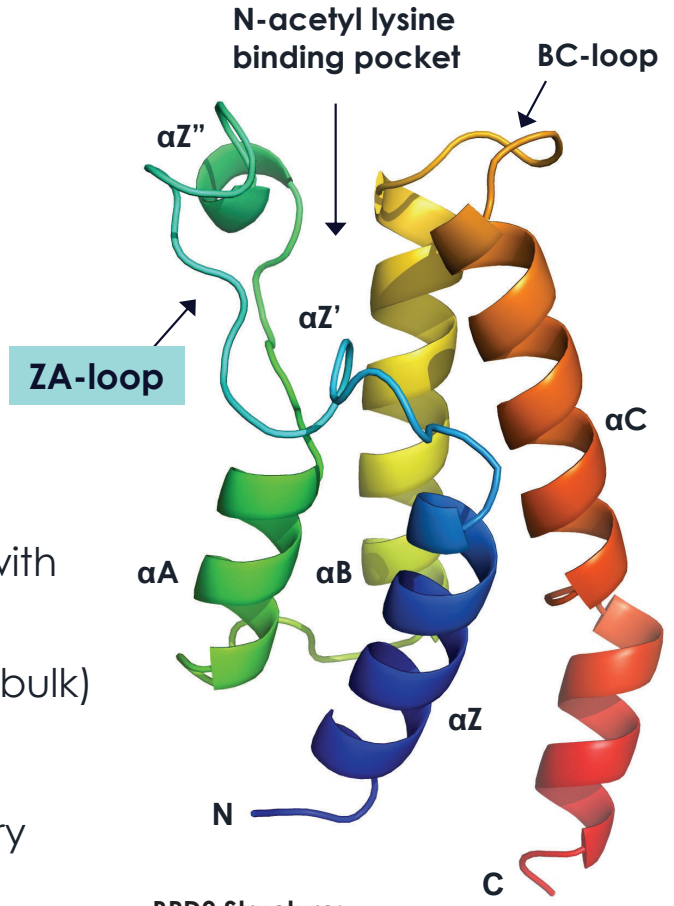
Cmpd	Linker	BRD9 DC_{50} 2h, (nM)	E_{max} 2h (%)	Mouse IV CL [mL/min/kg]
21		5	4	36
25		15	8	154
26		158	36	10
27		**39**	5	**31**
28		>5000	45	42
29		55	7	55
30		7	4	157
31		286	24	42
32		>1000	58	--
33		6	15	786

C4 Therapeutics

Selectivity Considerations: BRD Sequence Alignments Diverge at ZA-loop

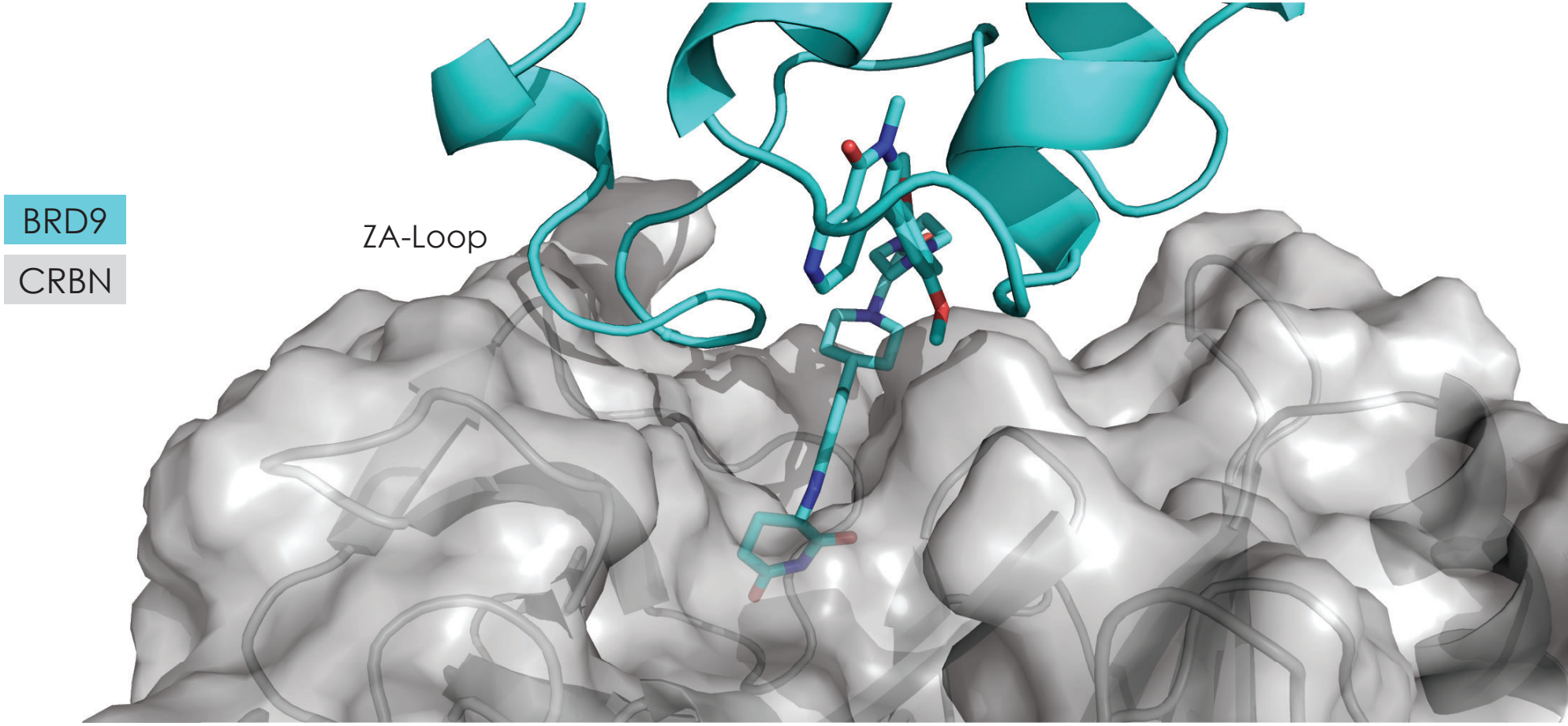


- Bromodomain sequences deviate within the ZA-loop near αZ''
  - Modeling and HDX data suggest this region might interact with CRBN in the ternary complex
- In **BRD7**, there is Phe just before ZA-loop rather than Ala (added bulk)
- In **BRD4**, there is ≥4 residue insertion in ZA-loop relative to BRD9
- Selectivity partially attributed to involvement of ZA-loop in ternary complex

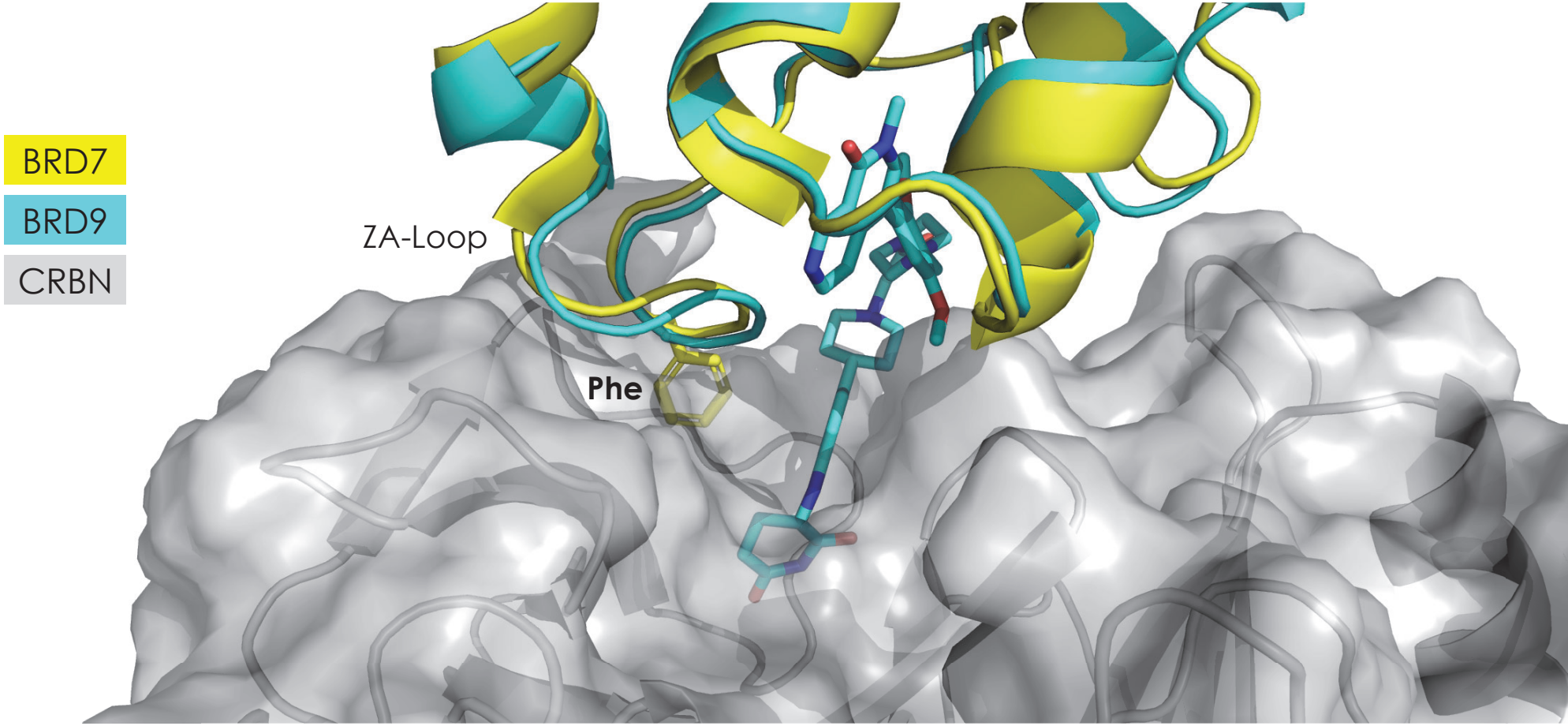


BRD9 Structure:
Martin et al. *J. Med. Chem.* **2016**, *59*, 4462

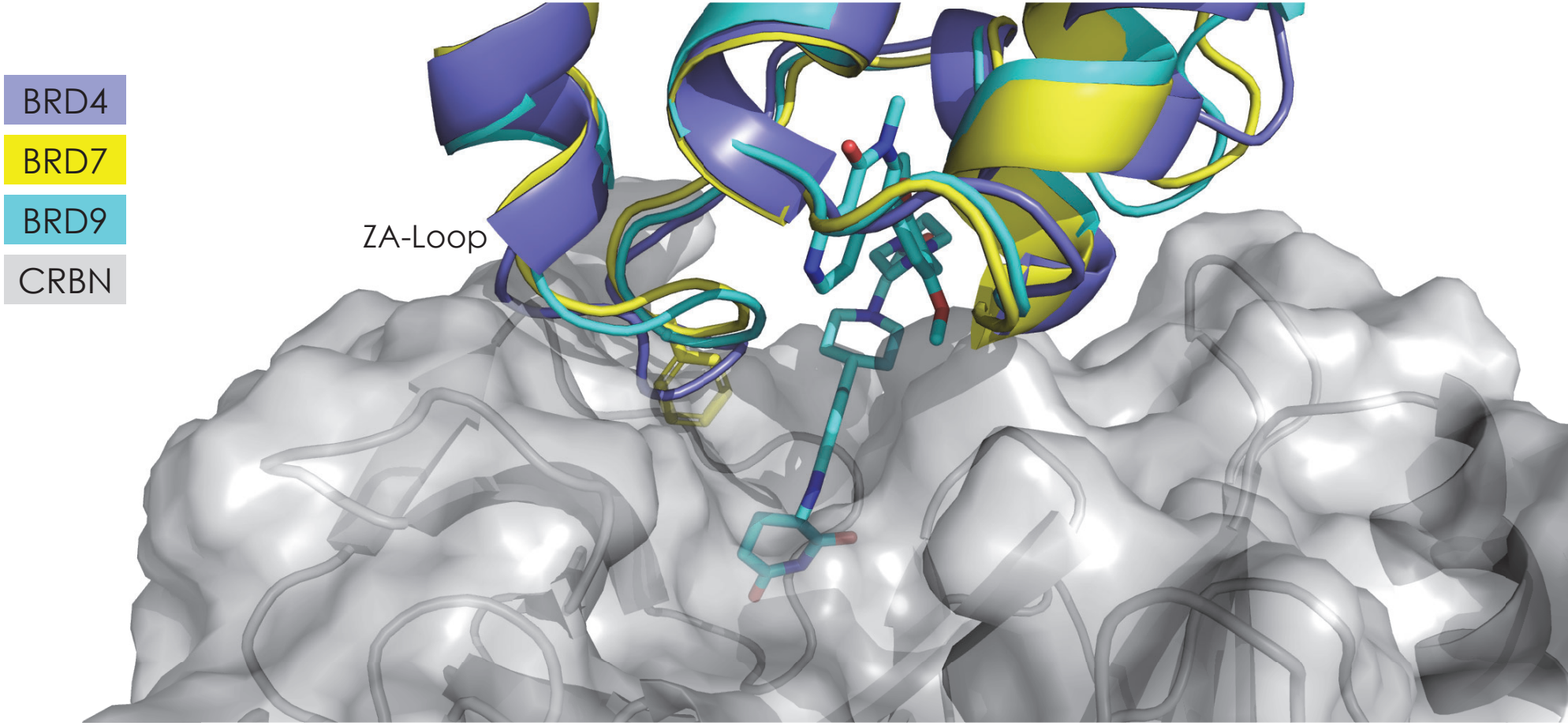
Compound 21 Ternary Complex Model



Compound 21 Ternary Complex Model

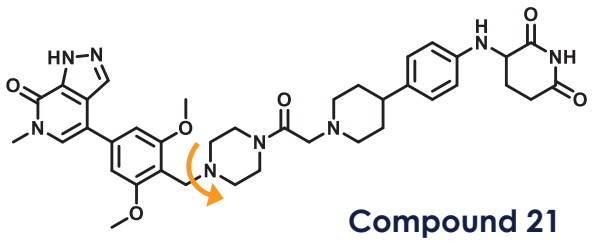


Compound 21 Ternary Complex Model

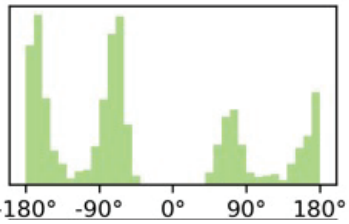


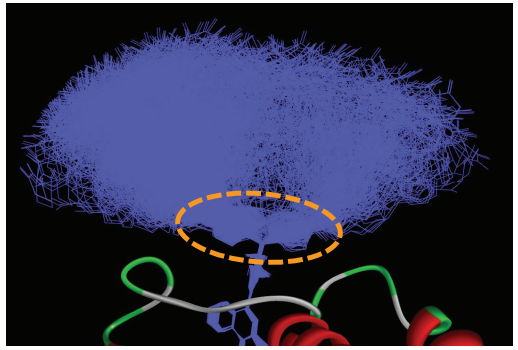
Comparing Ternary Complex Models for Compound 21 and 27

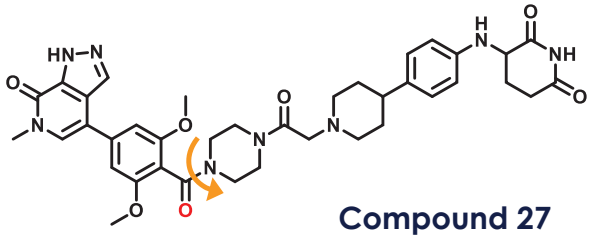
- ~1.5k TCMs generated for Compounds 21 & 27, **superimposed using BRD9** (*CRBN removed*)
- **Compound 21**: TCMs cover broad conformational space due to flexible C-N bond in exit vector
- **Compound 27**: TCMs occupy two major clusters due to more narrowly-defined amide conformation



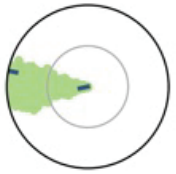
Compound 21
(moderately BRD4 / BRD7 selective)

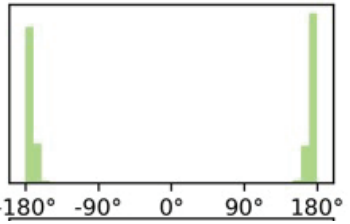


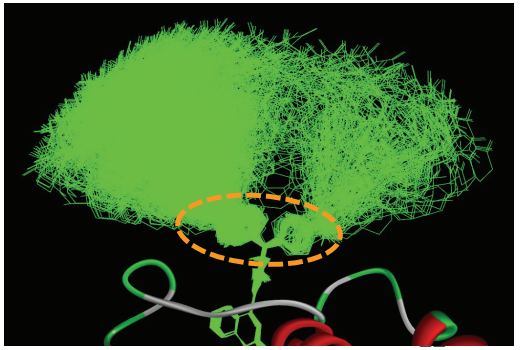




Compound 27
(BRD4 / BRD7 selective)



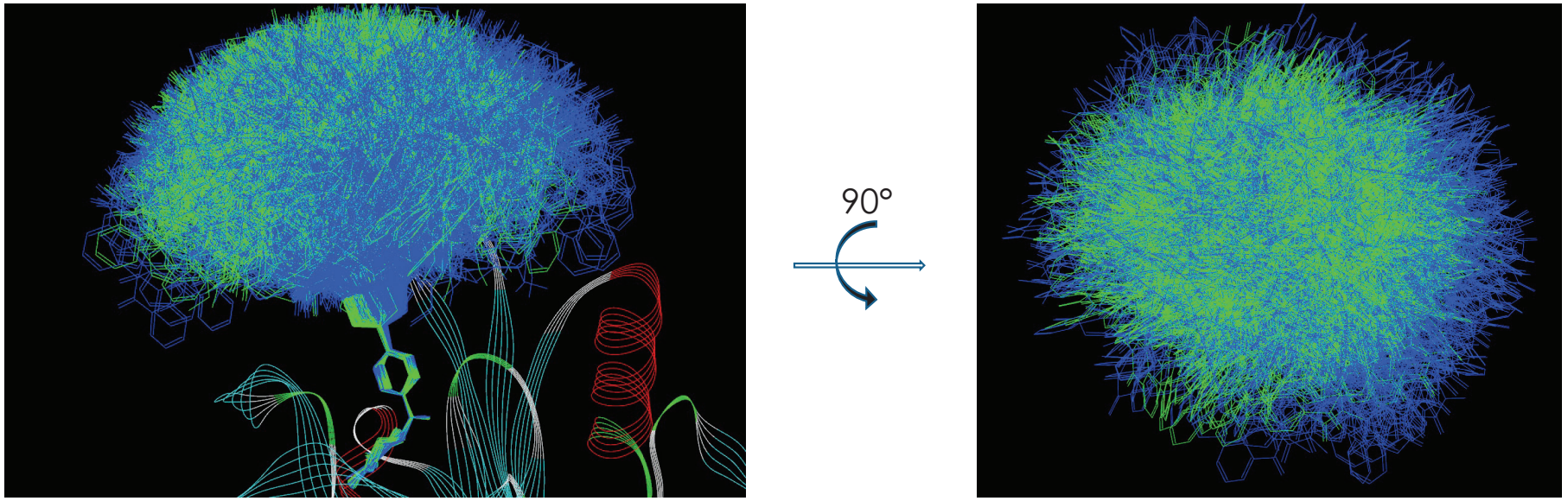




C4 Therapeutics

Comparing Ternary Complex Models for Compound 21 and 27

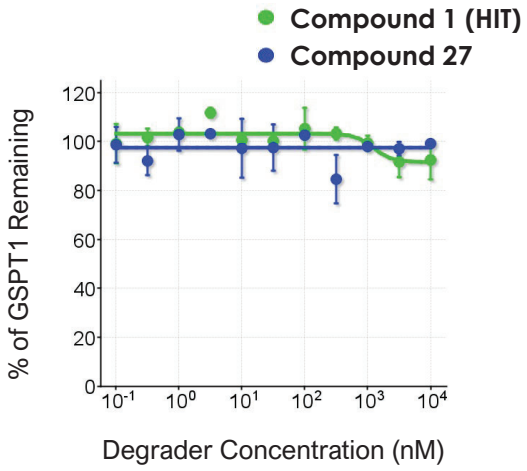
- ~1.5k TCMs generated for Compounds 21 & 27 **superimposed using CRBN** (*BRD9 removed*)
- **Compound 21**: Broader conformational space, larger radius sampled → *less selective*
- **Compound 27** : Smaller radius sampled → *more selective*



Selectivity: Compound 27 Does Not Degrade Neomorphic Off-targets

GSPT1
(G1 to S phase transition 1)

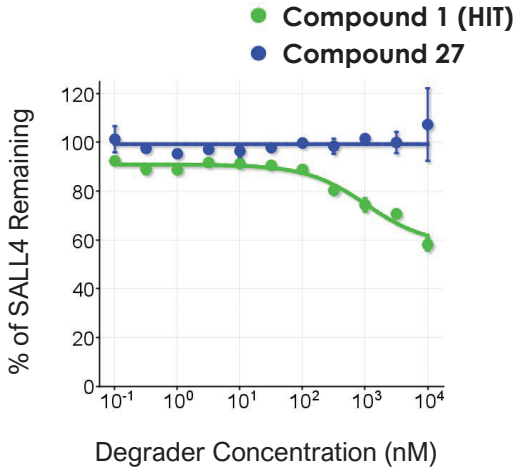
HEK 293T cells



- Plays a central role in mRNA translation (translation termination factor)

SALL4
(Spalt-like transcription factor 4)

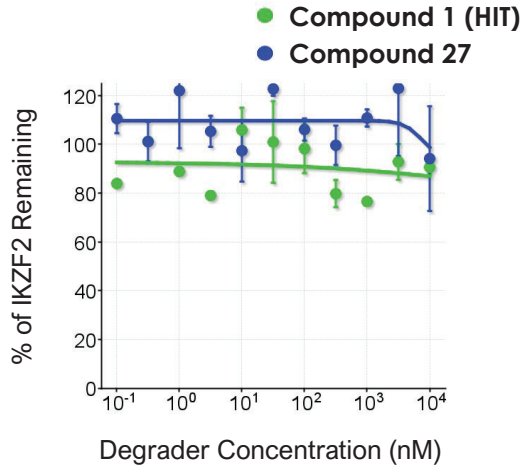
KELLY cells



- Essential for embryonic development
- Linked to the teratogenicity associated with thalidomide and other IMiDs

IKZF1
(Ikaros Family Zinc Finger 1)

NCI-H929 cells

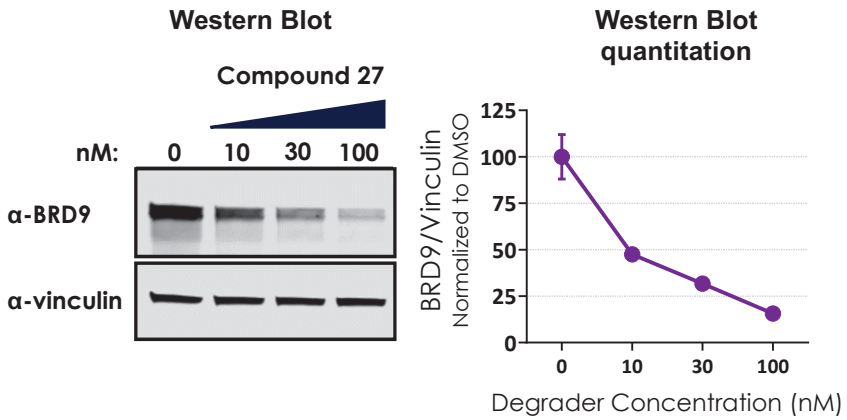


- Important for lymphocyte development and other physiological processes

Compound 27 Degrades Endogenous BRD9, Inhibits Synovial Sarcoma Cell Growth

Endogenous BRD9 Degradation

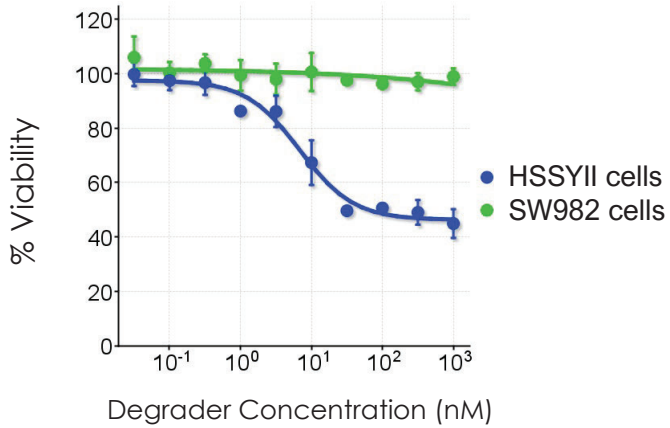
Yamato-SS Synovial Sarcoma cells (2 hours)



- Compound 27 degrades endogenous BRD9 in the Yamato-SS synovial sarcoma cell line

Viability Effects

HSSYII Synovial Sarcoma cells (144 hours)

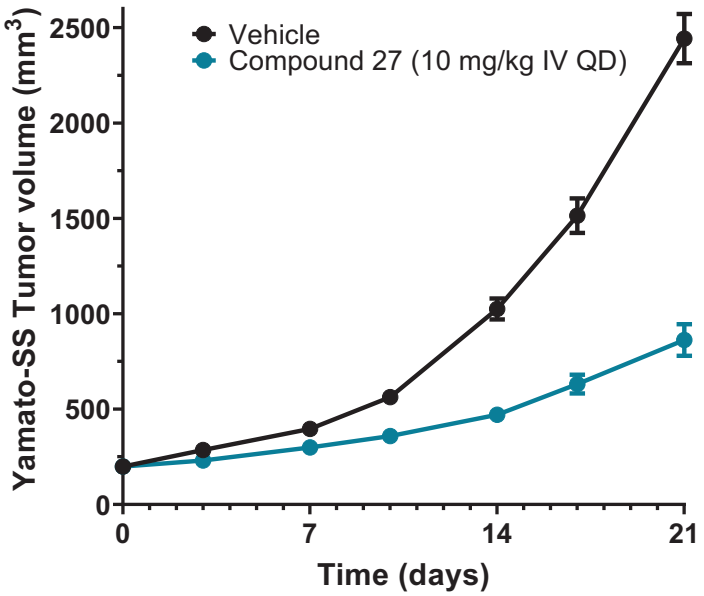


- Compound 27 results in growth inhibition of BAF-perturbed HSSYII synovial sarcoma cells but not BAF-*wild type* SW982 soft tissue sarcoma cells

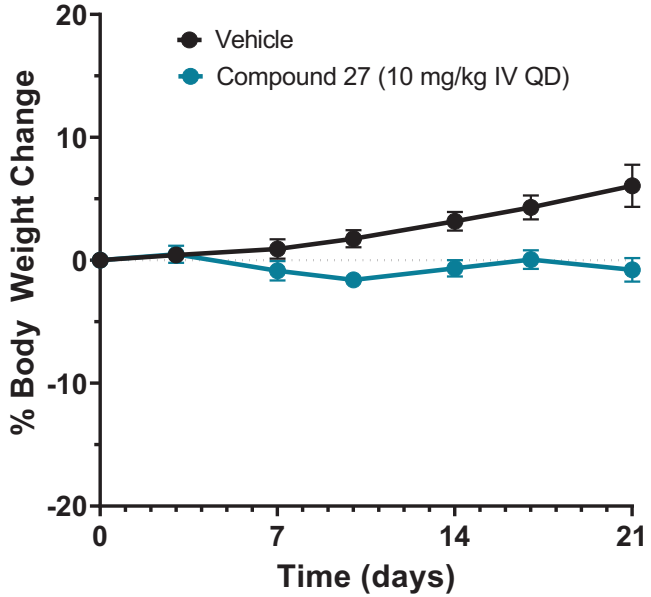
Compound 27 Inhibits Growth of Synovial Sarcoma Xenograft Model

Synovial Sarcoma CDX (Yamato-SS)

Activity



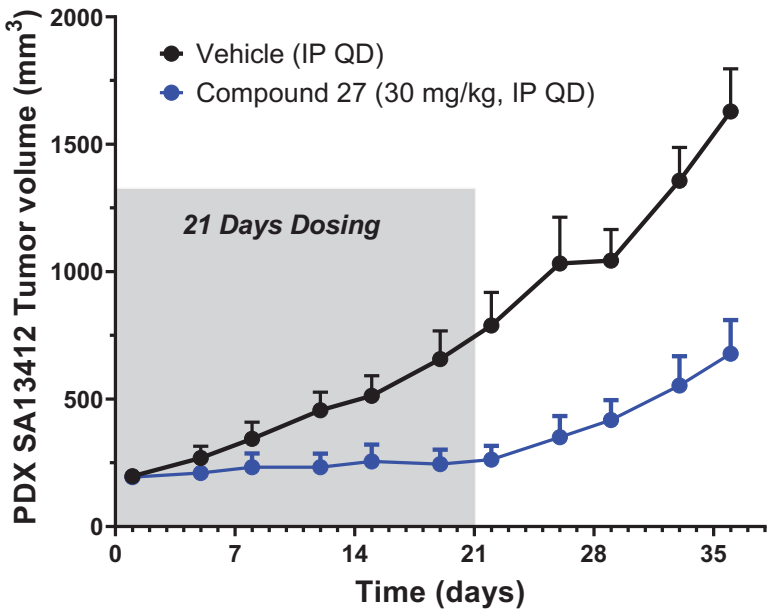
Tolerability



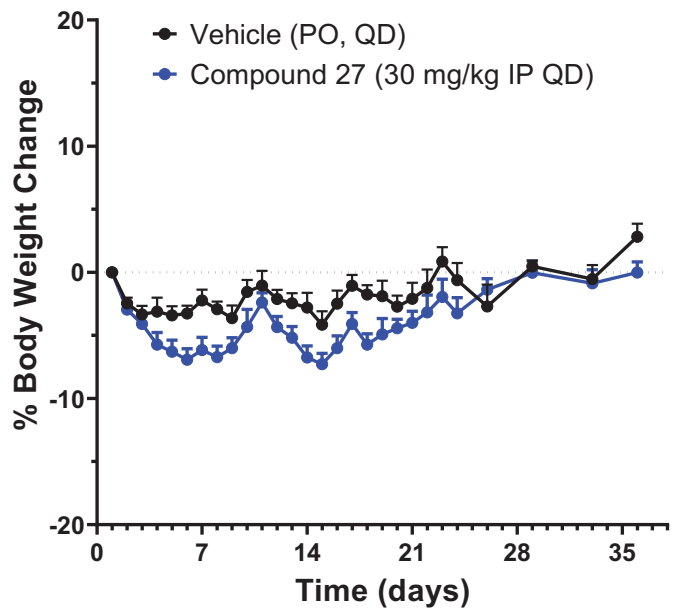
Compound 27 is Efficacious in a PDX Model of Synovial Sarcoma

Synovial Sarcoma PDX (SA13412)

Activity

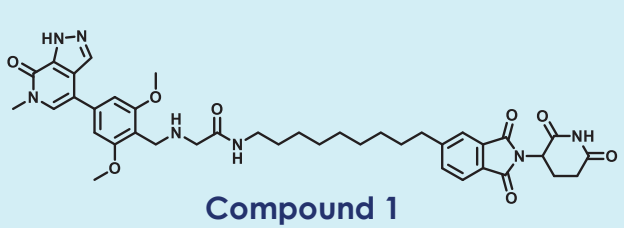


Tolerability



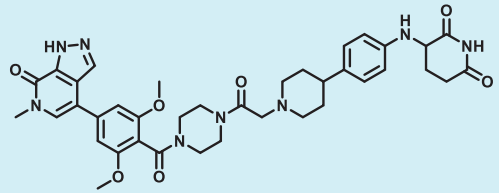
Conclusions

- Compound 27 is a potent and selective BiDAC degrader of BRD9 with improved drug-like properties relative to the HIT Compound 1
- Compound 27 demonstrated efficacy in both cell-derived and patient-derived models of synovial sarcoma (IV or IP dosing)
- Compound 27 was used as a launching point for further optimization, eventually leading to the discovery of the orally-bioavailable BRD9 BiDAC degrader, CFT8634



Compound 1

MW	754
ClogP	4.4
TPSA	194
HBD	4
#RotBond	18



Compound 27

MW	724
ClogP	2.3
TPSA	165
HBD	3
#RotBond	9

Orally bioavailable BRD9 BiDAC degrader

CFT8634

Thank You