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The Discovery and Characterization of CFT8634:

A Potent and Selective Degrader of BRD9 for the Treatment of SMARCB1-Perturbed Cancers

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Disclosure Information

Katrina L. Jackson, PhD

- I have the following financial relationships to disclose:
  - Stockholder in: C4 Therapeutics
  - Employee of: C4 Therapeutics
- I will not discuss off label use and/or investigational use in my presentation.

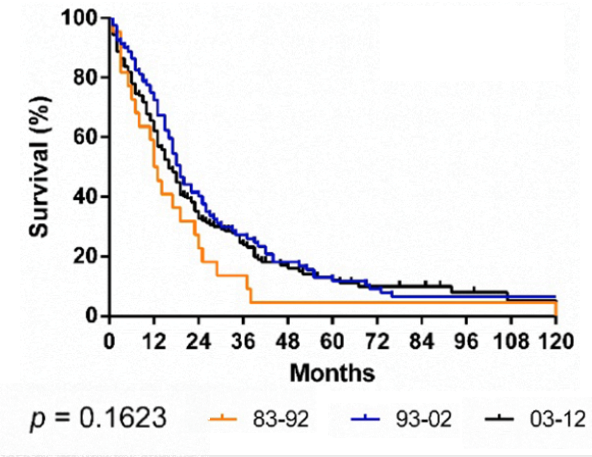
BRD9: Drugging the Undruggable with a Heterobifunctional Degrader Approach

Strong Rationale for Degrader Approach[1,2]

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

Clear Unmet Need[3]

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



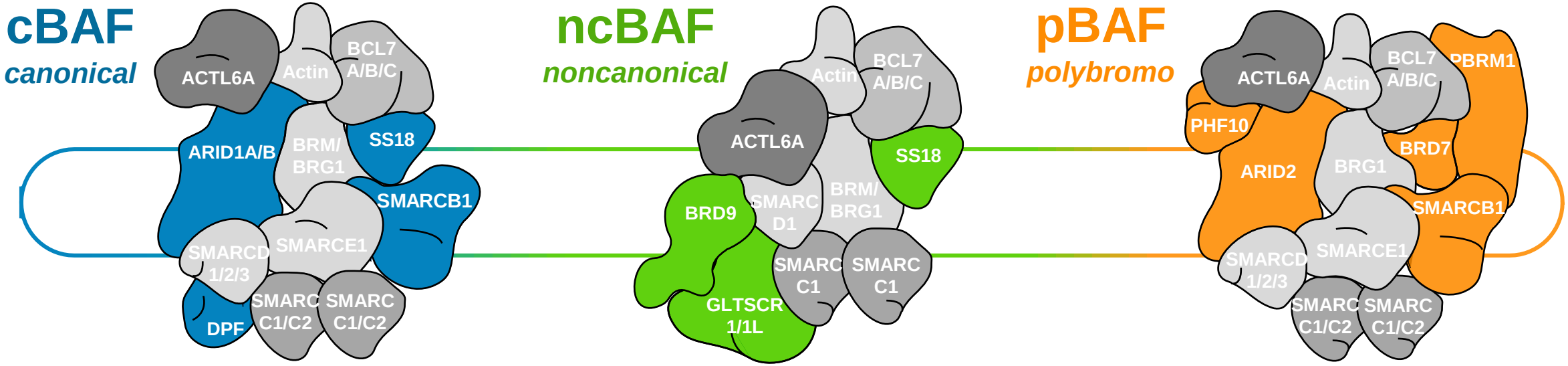
Defined Patient Population[a]

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

[a] Patient figures represent estimated U.S. annual incidence.
SS, synovial sarcoma.

1. NIH SEER Database, Primary Literature Consensus; 2. Brien GL et al. *eLife.* 2018;7:e41305; 3. Wang S et al. *J Cancer.* 2017;8(10):1759-1768.

BAF Complexes Regulate Chromatin State



Collaborative interplay between BAF complexes to collectively regulate chromatin state

cBAF, canonical BAF; ncBAF, noncanonical BAF; pBAF, polybromoBAF.

Oncogenic SS18-SSX Fusion Leads to BRD9 Dependency in Synovial Sarcoma

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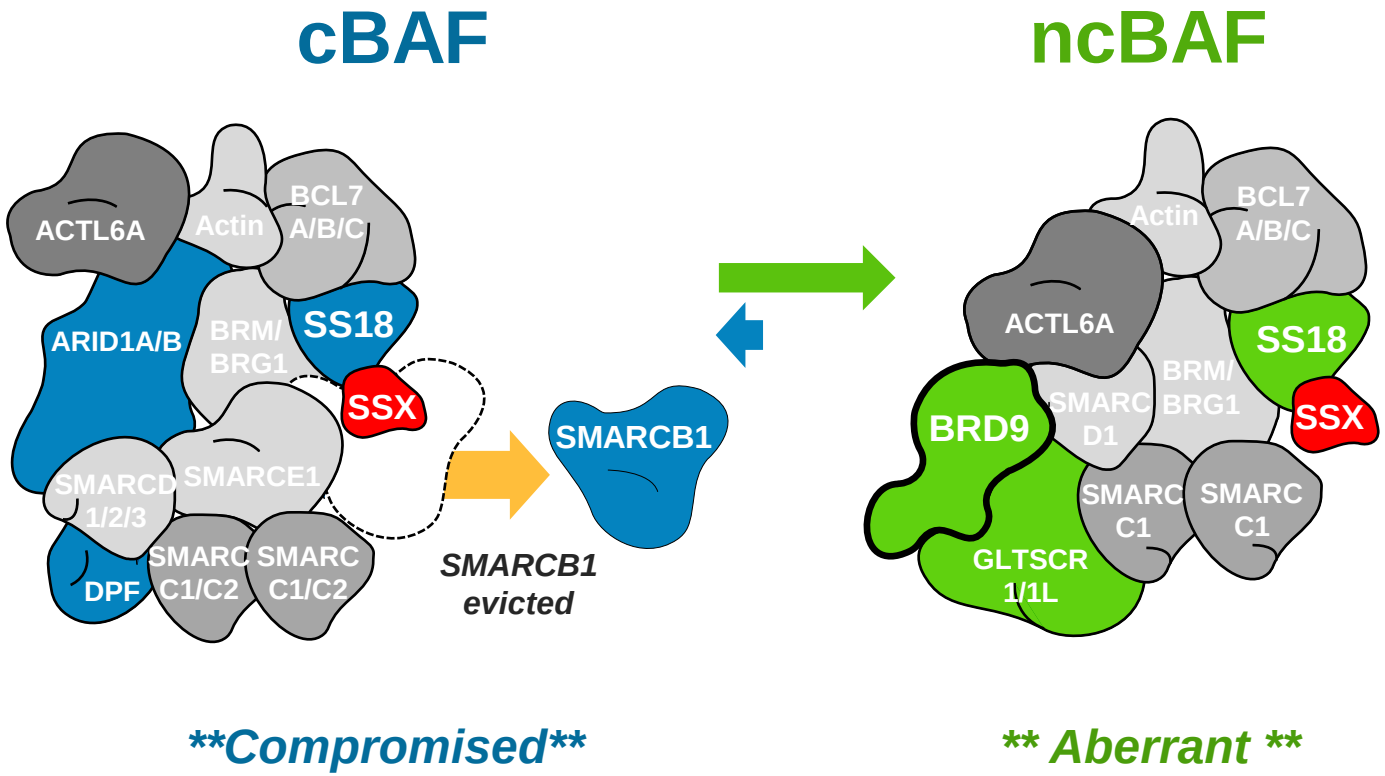


Compromised

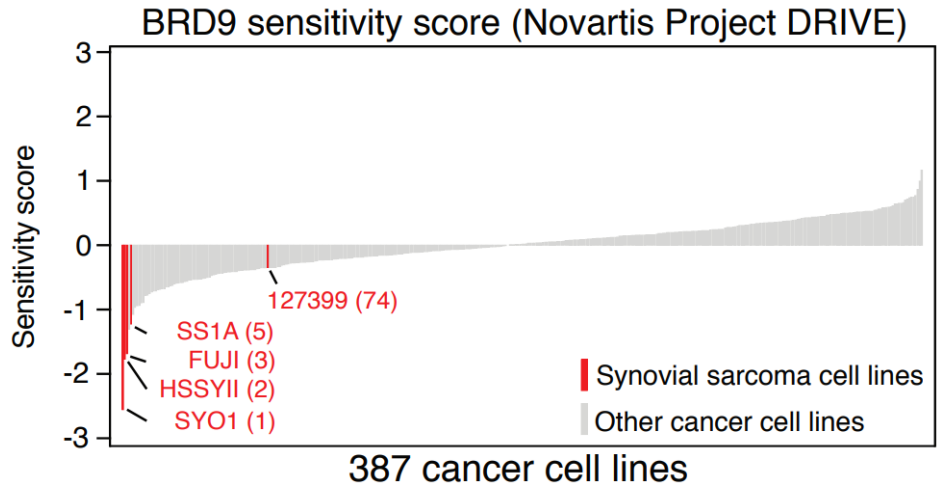
*** Aberrant ***

1. Incorporation of SS18-SSX fusion results in eviction of SMARCB1
   - cBAF complex compromised
   - Oncogenic state
2. Inactivation of SMARCB1 leads to dependency on ncBAF complex
   - BRD9 is uniquely present in ncBAF
   - ***Synthetic lethal dependency on BRD9*** in synovial sarcoma and other SMARCB1-deficient cancers

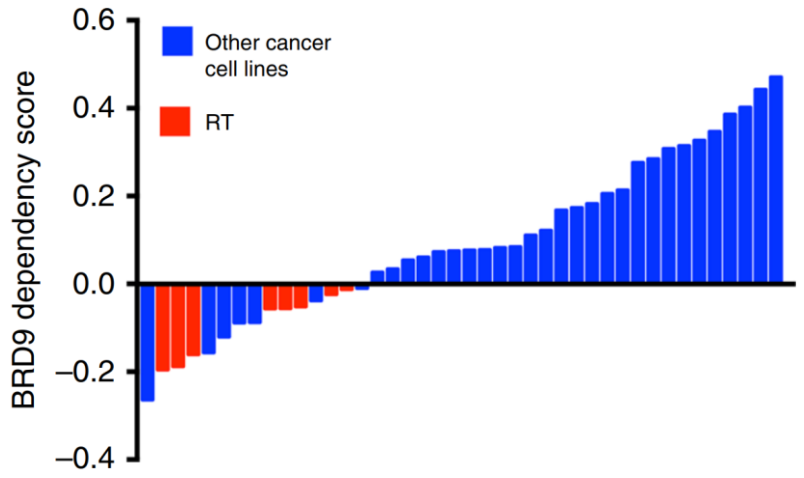
cBAF, canonical BAF; ncBAF, noncanonical BAF; pBAF, polybromoBAF.

BRD9 is a Selective Dependency in SMARCB1-Perturbed Contexts

Synovial Sarcoma
SS18-SSX fusion-driven ejection of SMARCB1[1]



Malignant Rhabdoid Tumor
Homozygous SMARCB1 deletion[2]

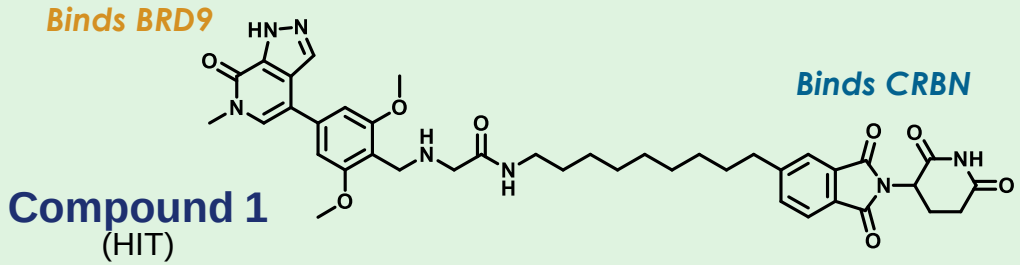


Genome-wide loss-of-function CRISPR screens identify BRD9 as a unique dependency in synovial sarcoma and malignant rhabdoid tumor cell lines

RT, rhabdoid tumor.

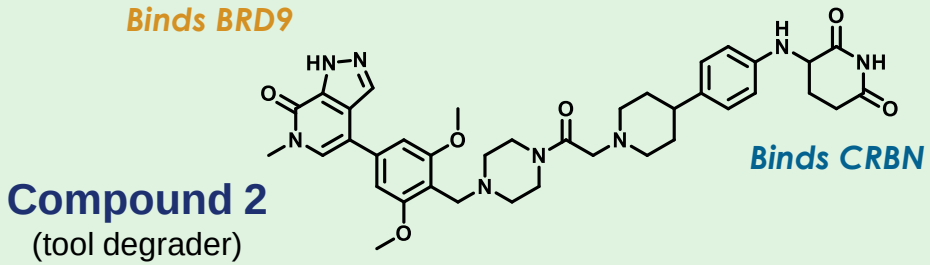
1. Brien GL et al. *eLife.* 2018;7:e41305; 2. Wang X et al. *Nat Commun.* 2019;10:1881.

Ternary Complex Analysis Suggests Linker Excision is Possible

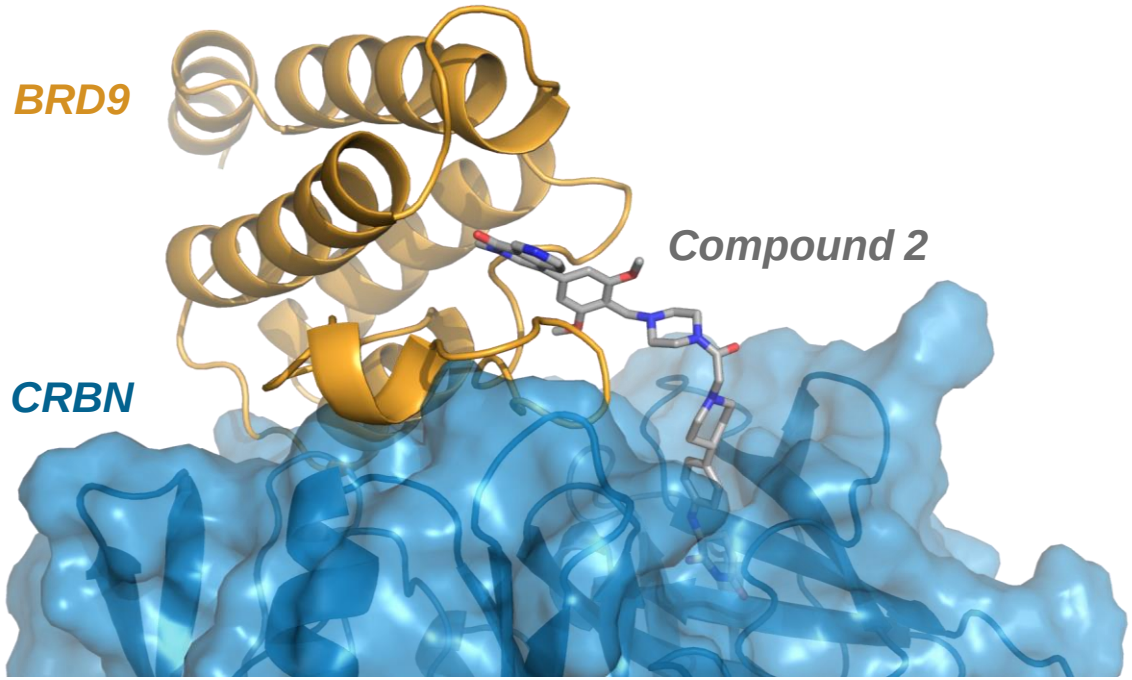


Compound 1
(HIT)

Medchem previously described



Compound 2
(tool degrader)



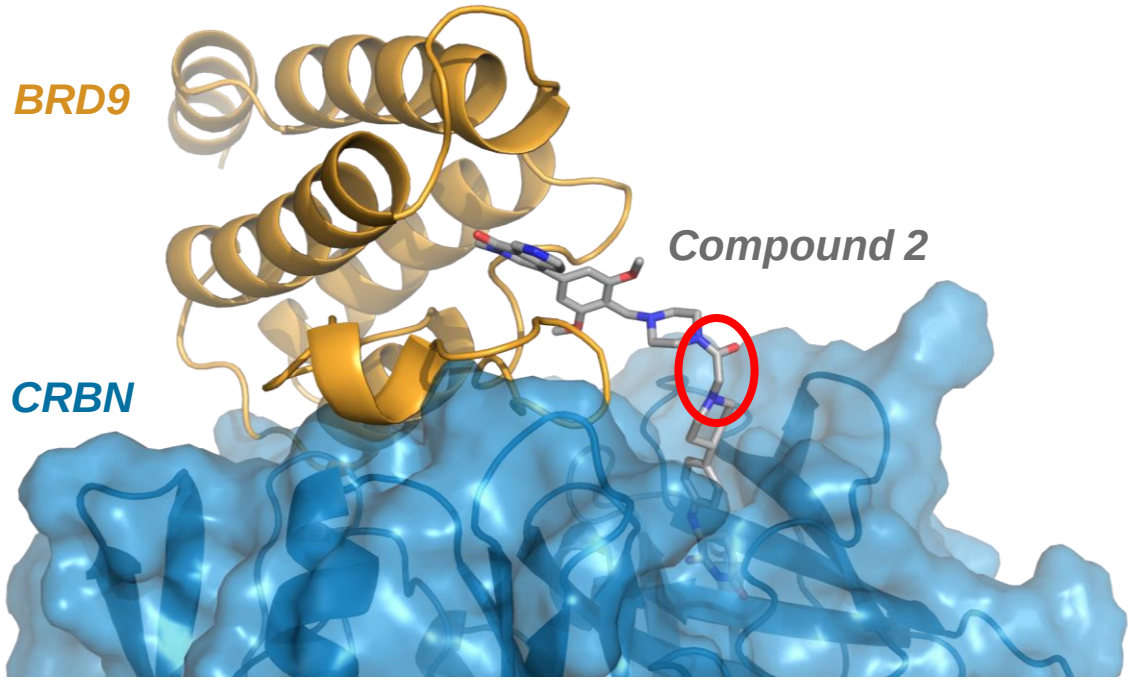
Features of tool degrader, Compound 2:

- Potent BRD9 degrader
- **Suboptimal selectivity over BRD4**
- Acceptable mouse IV PK profile
- **No oral exposure**

GOAL: Identify a potent & selective BRD9 degrader suitable for oral dosing

PK, pharmacokinetics ; CRBN, cereblon

Ternary Complex Analysis Suggests Linker Excision is Possible



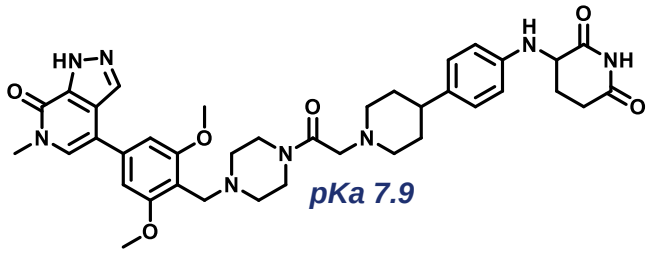
Hypothesis: Elimination of the linker will result in a tighter ternary complex

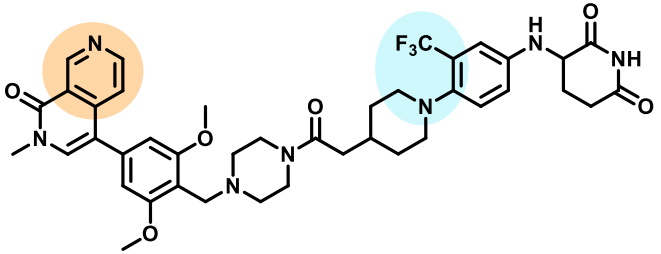
Potential advantages:

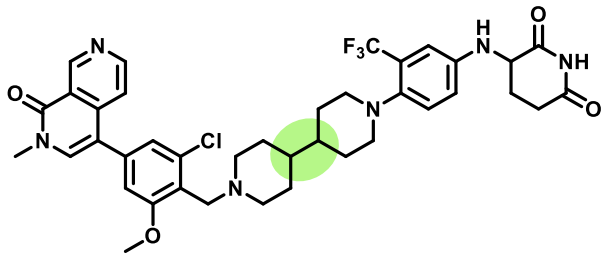
- Greater selectivity over BRD4, BRD7
- Smaller degraders with better properties and higher oral bioavailability

PK, pharmacokinetics ; CRBN, cereblon

Linker Excision & Properties Tuning Results in Encouraging Oral Bioavailability



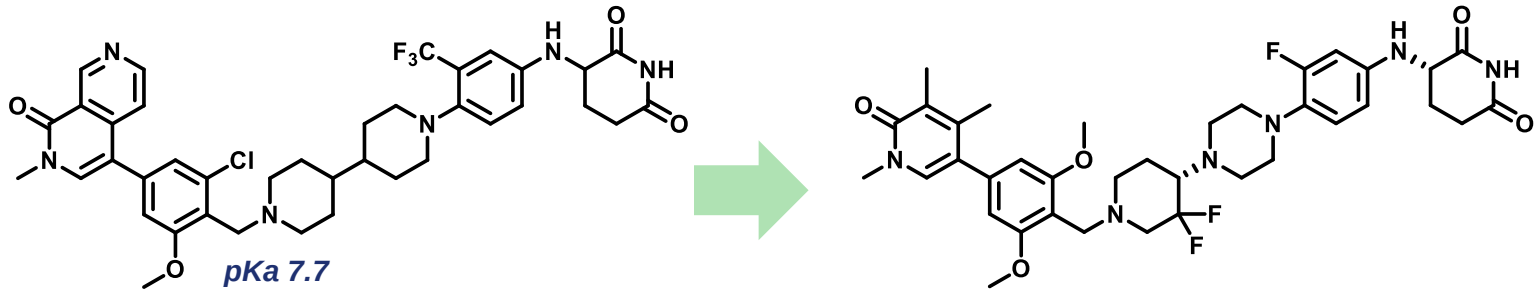




	Compound 2	Compound 3	Compound 4
BRD9 DC_{50} / E_{max} [2 h]	**5 nM / 5%**	**4 nM / 6%**	**11 nM / 5%**
$LogD_{7.4}$	1.2	2.5	3.5
TPSA	152	▼ 137	▼ 107
H-Bond Donors	3	▼ 2	2
Most Basic pKa [calc]	7.9	▼ 5.8	7.7
Mouse F [%]	**<1**	**21**	**100**

TPSA, topological polar surface area.
C4 Therapeutics data on file.

Further Refinement Leads to CFT8634

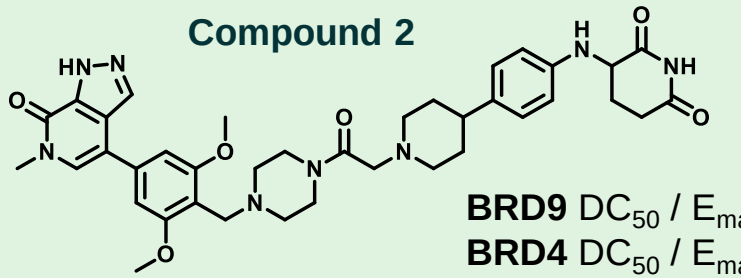


	Compound 4	CFT8634
BRD9 DC_{50} / E_{max} [2 h]	11 nM / 5%	3 nM / 4%
$LogD_{7.4}$	3.5	▼ 2.7
Most Basic pKa [calc]	7.7	▼ 5.1
CL_{obs} Mouse / Rat [mL/min/kg]	30 / 74	6 / 22
F % Mouse / Rat	100 / 48	74 / 83
Cyp Inhibition 3A4 / 2C19 / 2D6 [μM]	5.6 / 1.9 / >30	27 / >30 / >30
hERG Inhibition [μM]	7.5	>30

Cyp, cytochrome P450; hERG, human ether-à-go-go-related gene.
C4 Therapeutics data on file.

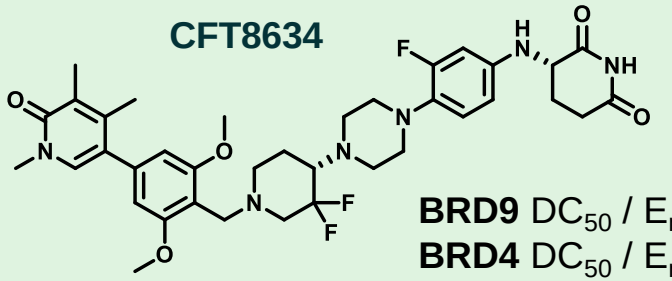
Selectivity Rationalized with Ternary Complex Models

Compound 2

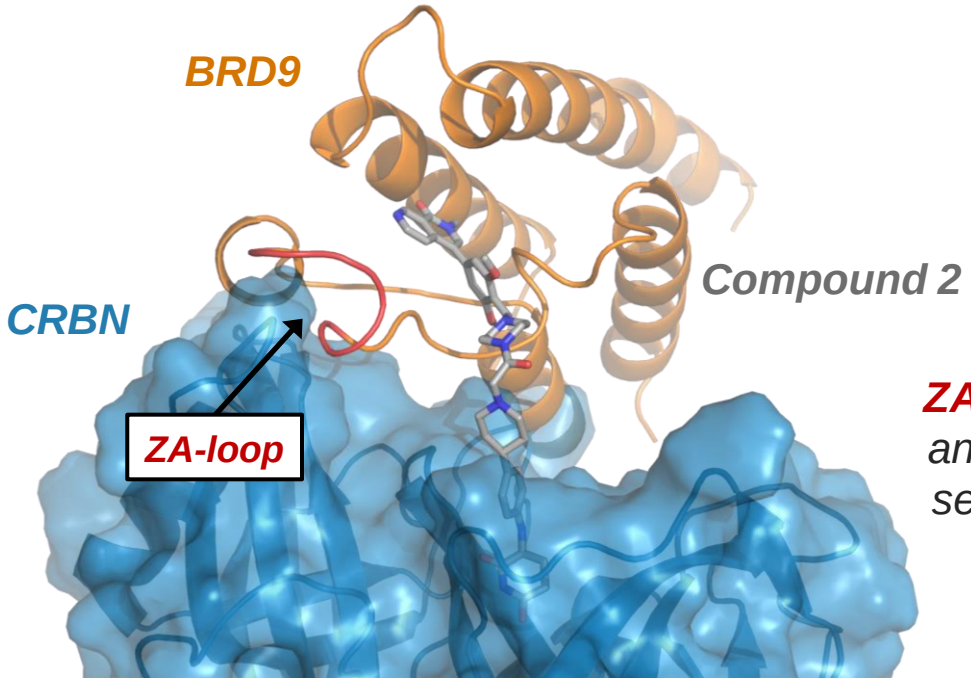


BRD9 DC_{50} / E_{max} = **5 nM / 5%**
BRD4 DC_{50} / E_{max} = **130 nM / 30%**

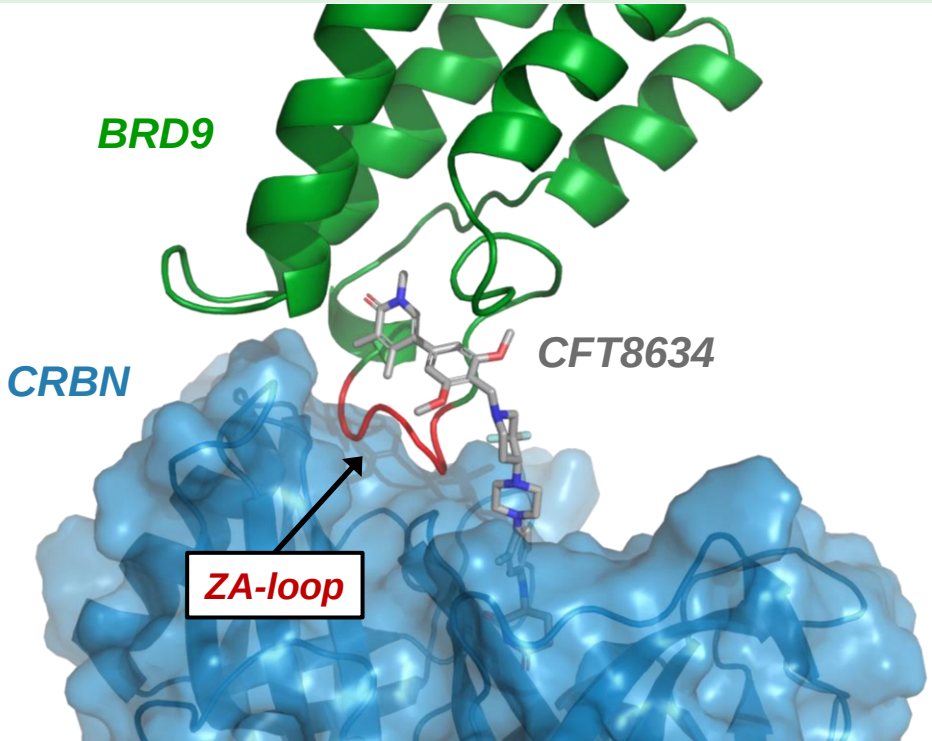
CFT8634



BRD9 DC_{50} / E_{max} = **3 nM / 4%**
BRD4 DC_{50} / E_{max} = **>10 µM / 75%**

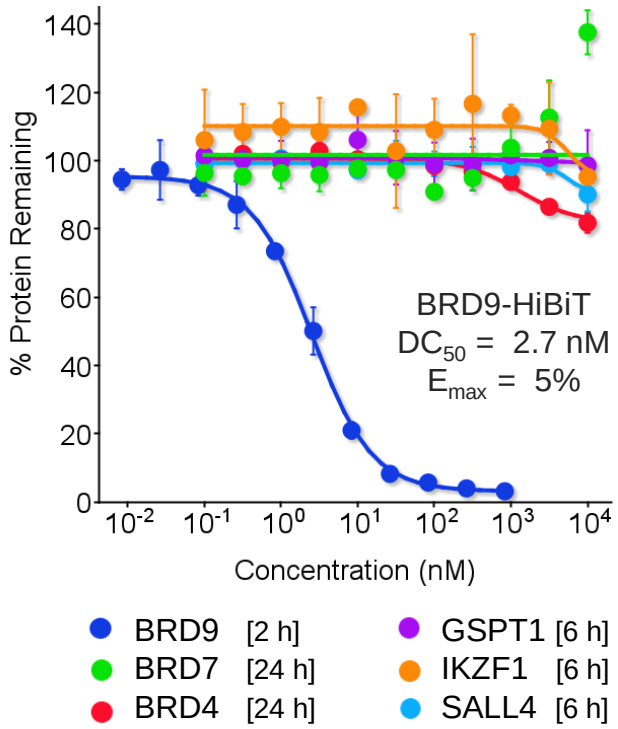


ZA-loop *hypothesized to be an important determinant of selectivity vs. BRD4, BRD7*

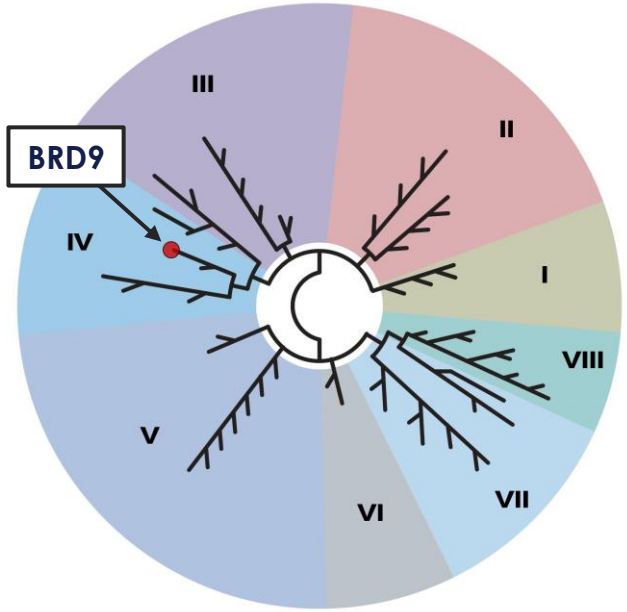


In vitro: CFT-8634 is a Highly Selective BRD9 Degrader

Selectivity over BRD4, BRD7, and Neo-Substrates of CRBN



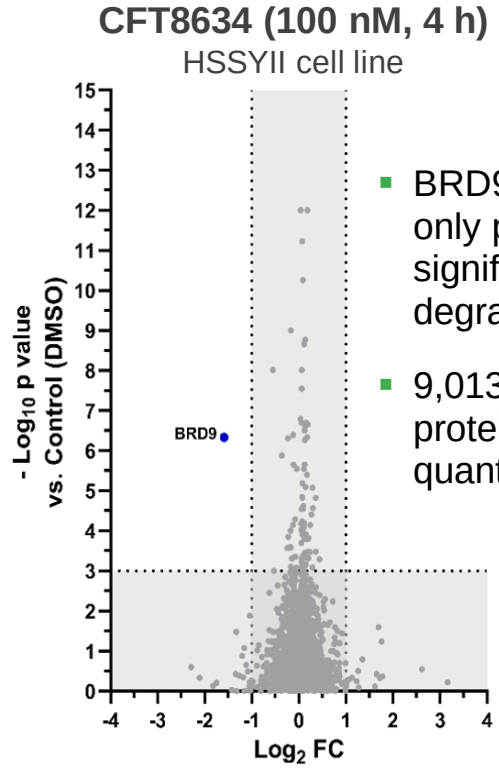
Bromodomain Binding Specificity



BromoScan®

100 nM CFT8634

Global Proteomic Evaluation



- BRD9 is the only protein significantly degraded
- 9,013 proteins quantified

HiBiT; high affinity bioluminescent tag.
C4 Therapeutics data on file.

CFT8634-Induced BRD9 Degradation Leads to Selective Growth Inhibition in BAF-Perturbed Cells

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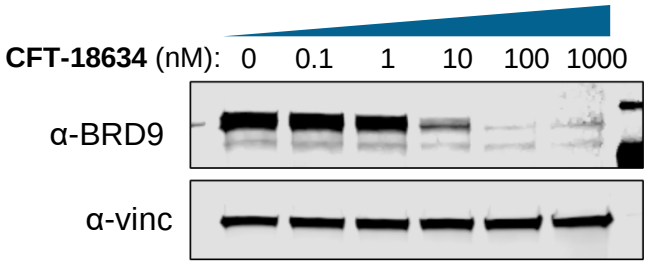
Endogenous BRD9 Degradation

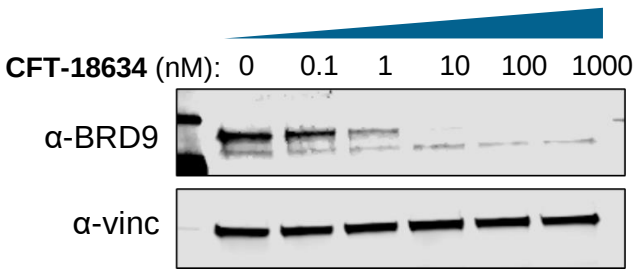
Yamato-SS

Synovial sarcoma [SS18-SSX1 fusion]

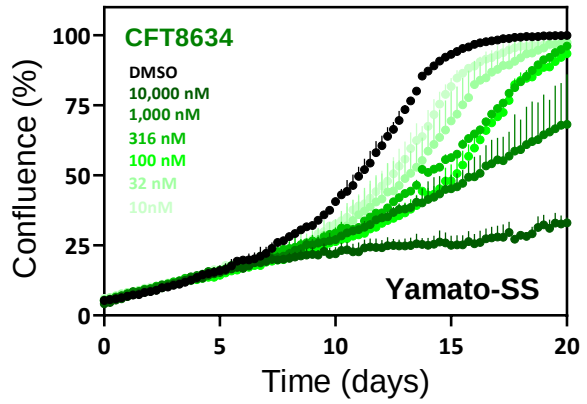


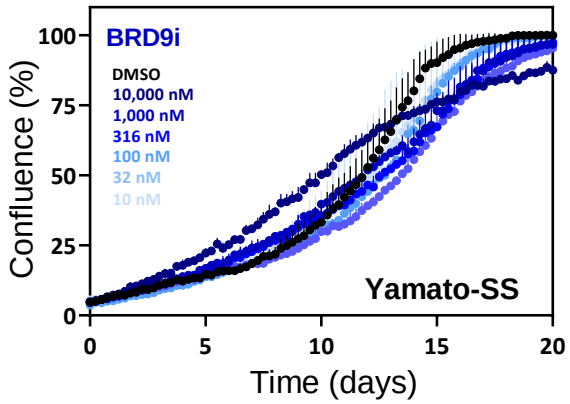
SW982

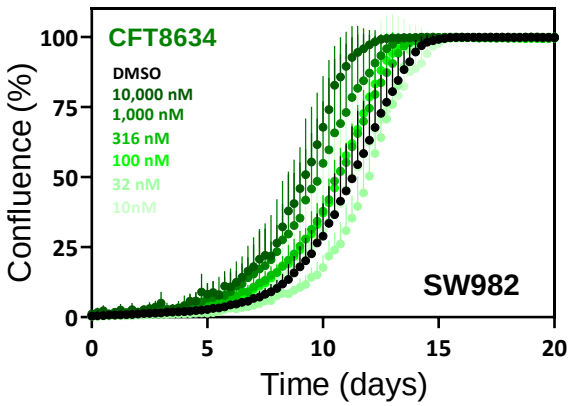
Soft-tissue sarcoma [BAF wildtype]

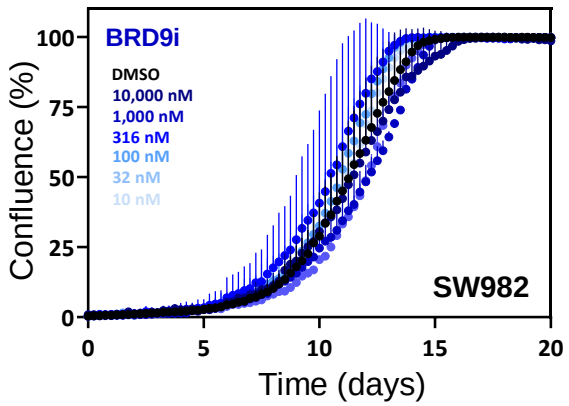


Single Dose, Long-Term Growth Evaluation





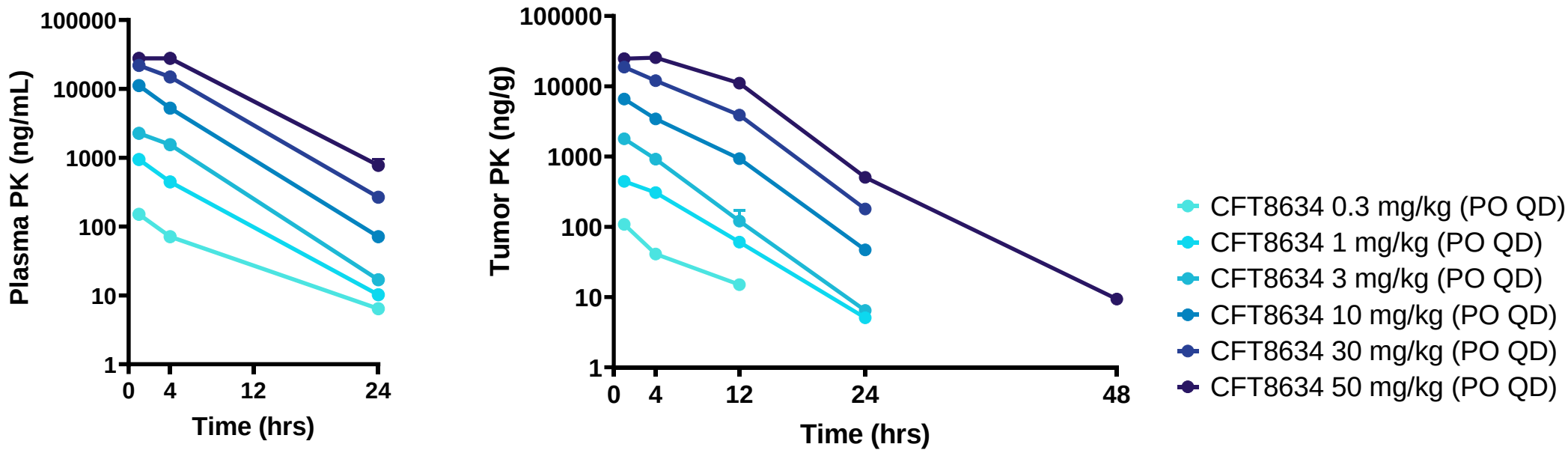




C4 Therapeutics data on file.

Dose Proportional Exposure in a Cell-Derived Model

Plasma vs. Tumor PK – Yamato-SS CDX Model

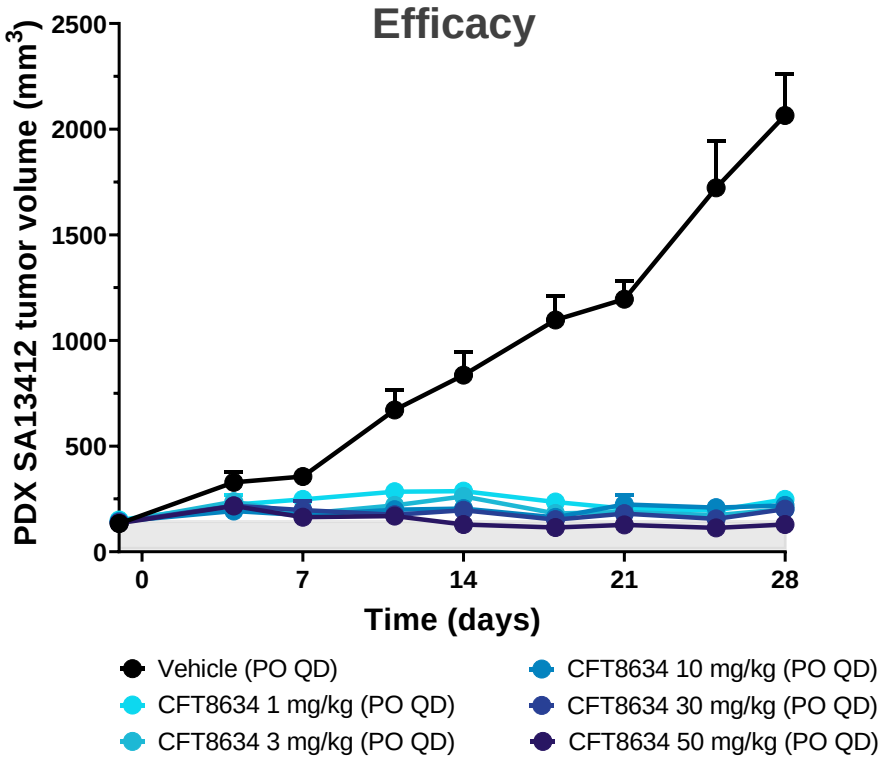


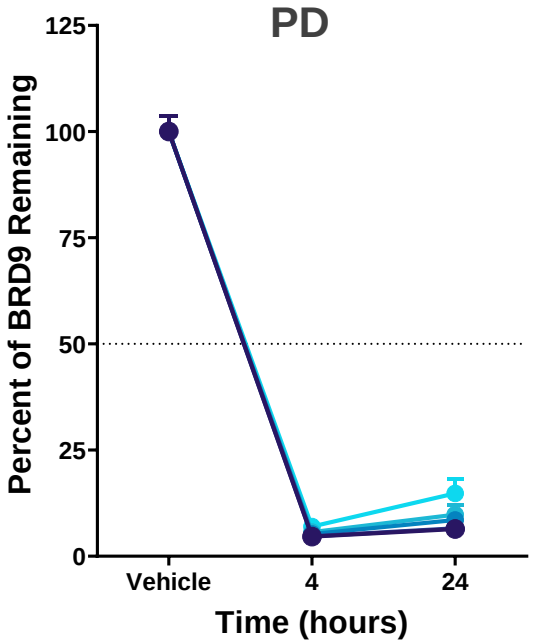
Dose-Proportional Exposure & Concordant Cross-Species PK Profile

PK, pharmacodynamics; PO, by mouth; QD, once daily; SS, synovial sarcoma.
C4 Therapeutics data on file.

Robust Efficacy Response Observed in Two PDX Models of Synovial Sarcoma

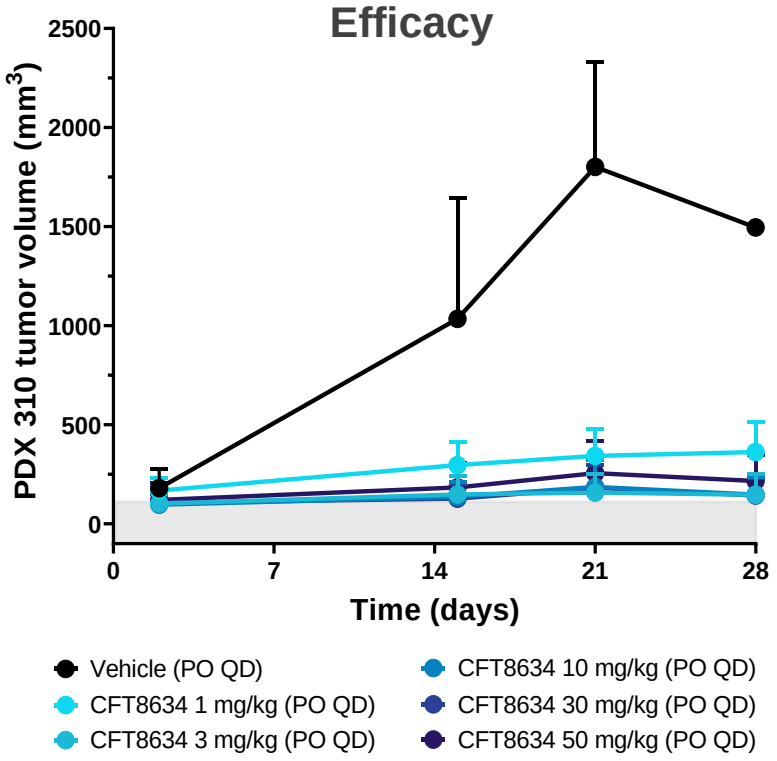
PDX SA13412
Synovial Sarcoma Harboring SS18-SSX1





- PD analysis at 4 h and 24 h post-Day 18 dose

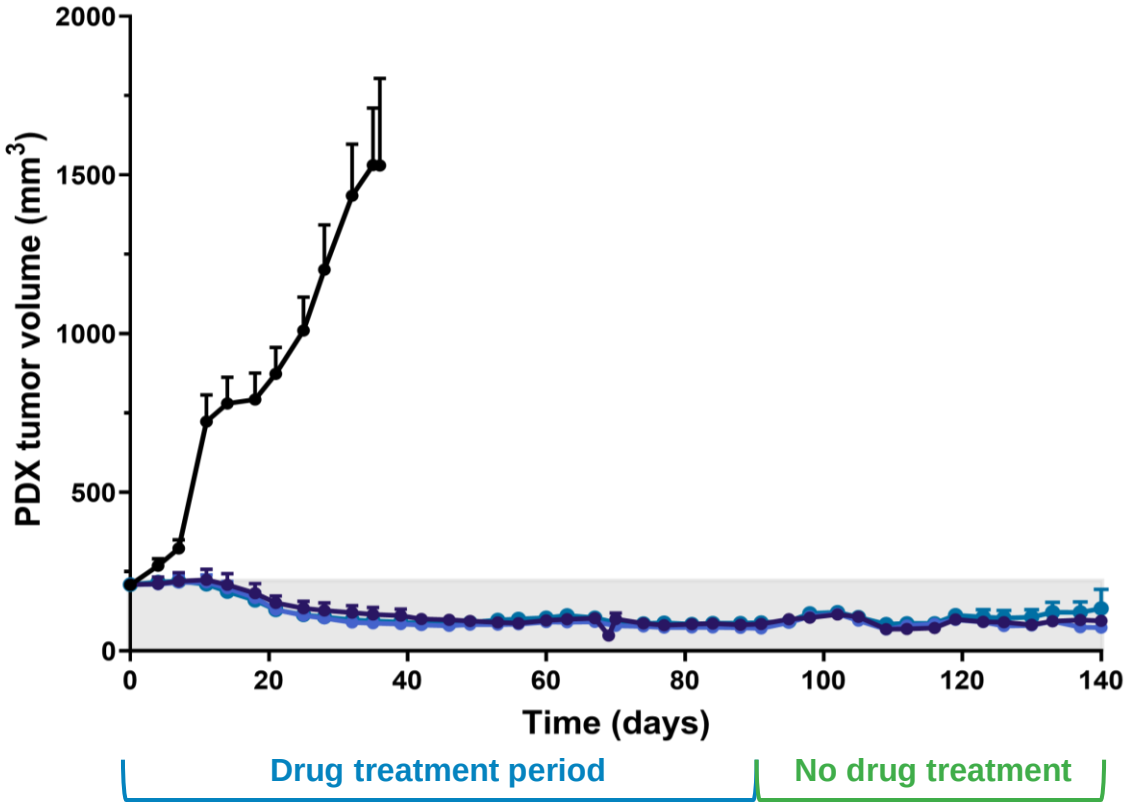
PDX 310
Synovial Sarcoma Harboring SS18-SSX2



PO, by mouth; QD, once daily; PD, pharmacodynamics
C4 Therapeutics data on file.

Durable Response Observed in a PDX Model of Synovial Sarcoma

Durable Tumor Regression in PDX SA13412



- Treatment administered for 89 days followed by 51-day observation period
- Tumor regressions were durable with no regrowth observed

BID, twice daily; PO, by mouth; TID, thrice daily; QD, once daily.
C4 Therapeutics data on file.

Conclusions

- Extensive medicinal chemistry efforts leading to CFT8634, a potent, selective, and orally bioavailable BiDAC™ degrader, highlight the potential of the TORPEDO® platform to create degrader medicines that may drug the undruggable with a BiDAC™ degrader approach
- CFT8634 selectively inhibits the growth of BAF-perturbed cell lines and demonstrates robust efficacy in clinically-relevant patient-derived xenograft models of synovial sarcoma
- Based on the pre-clinical profile of CFT8634, a Phase 1/2 trial in patients with synovial sarcoma and SMARCB1-null solid tumors is planned to initiate in the first half of 2022

Acknowledgments

Thank you to the C4T scientists & our CRO partners across the globe who made this work possible