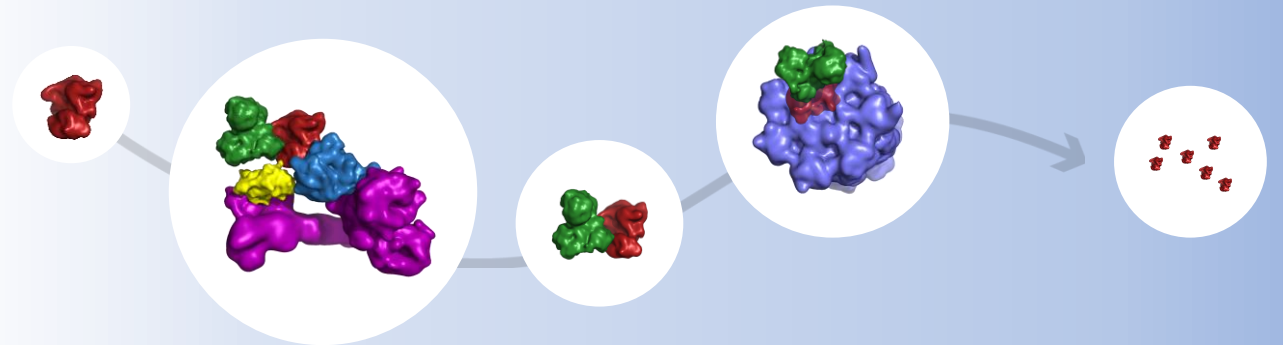


PIONEERING TRANSFORMATIVE **PROTEIN DEGRADATION** THERAPIES



A new class of small-molecule protein degraders harnessing powerful and universal cellular biology



C4Therapeutics

Destroying
~~Targeting~~ disease-causing
proteins to deliver hope

Targeted Protein Degradation Summit

Rhamy Zeid

October 14, 2020

Forward-looking Statements and Intellectual Property

Forward-looking Statements

The foregoing 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, and that our 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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C4 Therapeutics, Inc. owns various registered and unregistered trademarks in the U.S. and overseas, including, without limitation, C4 THERAPEUTICS, TORPEDO, BIDAC and MONODAC. All trademarks or trade names referred to in this presentation that we do not own are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the symbols ® and ™, but such those references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

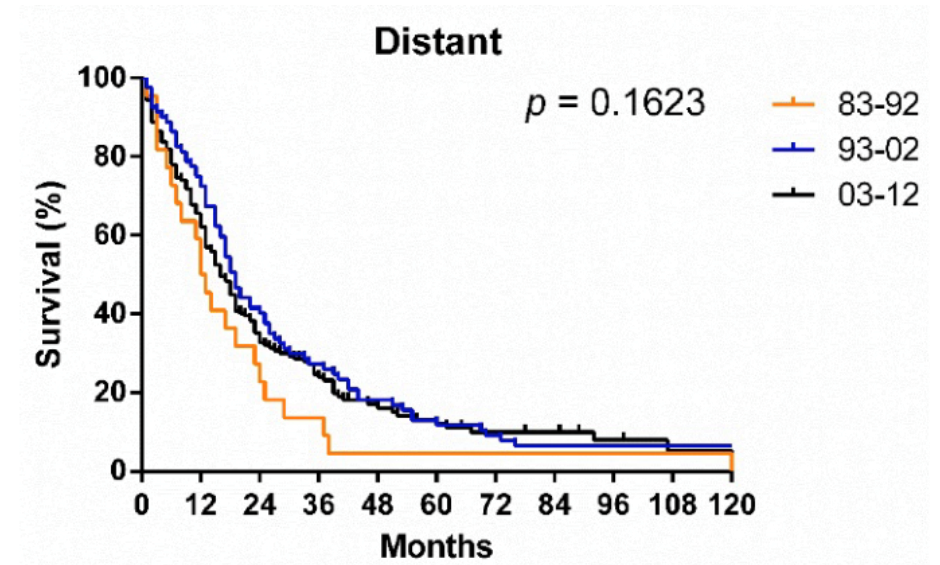
Synovial sarcoma

Clear Unmet Need

- **Very limited benefit of treatments** for metastatic synovial sarcoma or recurrence following surgery – metastatic **median survival ~18 months**
- Median age of diagnosis: **34 years old**

Defined Patient Population

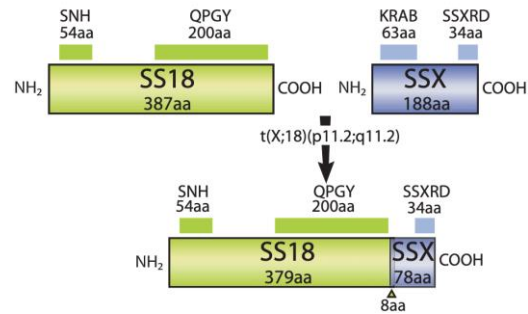
- **~900 US yearly incidence** of synovial sarcoma cases
- **~10% of all soft tissue sarcoma**



Wang et al., 2017

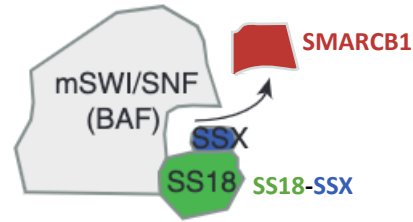
Lack of effective treatment strategies for metastatic disease or reoccurrence following surgery

Overview of BRD9 as a therapeutic target



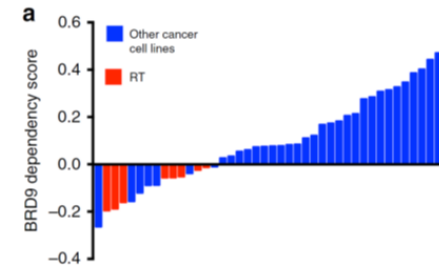
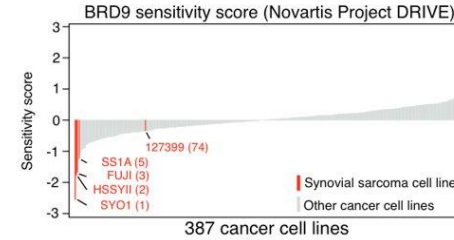
SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis



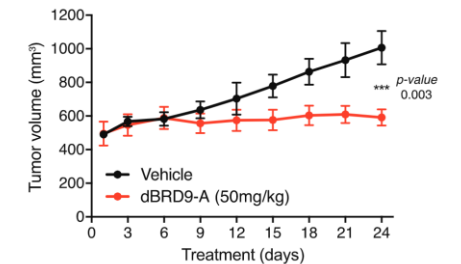
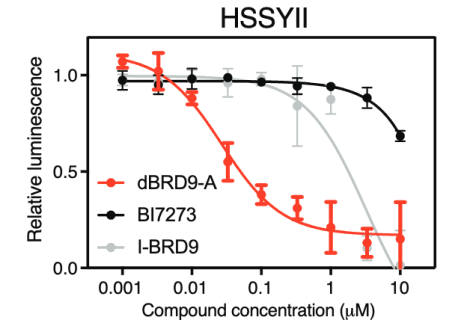
SMARCB1 eviction

Incorporation of the SS18-SSXX fusion ejects SMARCB1 from the BAF complex



BRD9 dependency

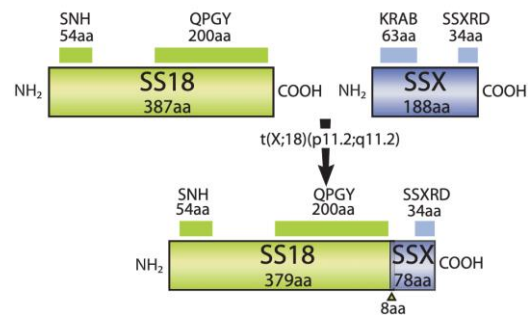
Loss of SMARCB1 results in a synthetic lethal relationship with BRD9



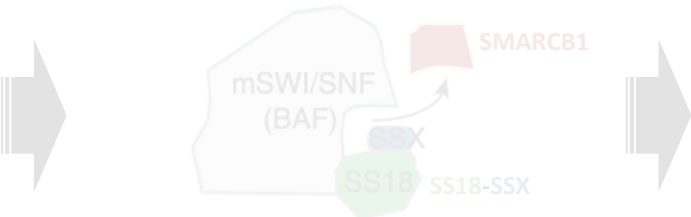
BRD9 degradation

Targeted protein degradation is an effective therapeutic strategy

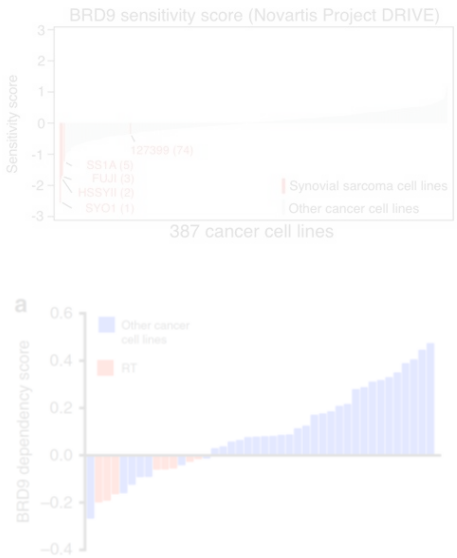
Overview of BRD9 as a therapeutic target



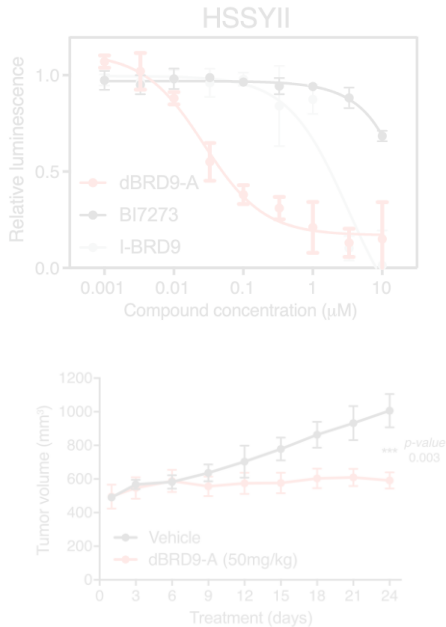
SS18-SSX fusion
Defining feature that underlies
synovial sarcoma pathogenesis



SMARCB1 eviction
Incorporation of the SS18-SSXX fusion
ejects SMARCB1 from the BAF complex



BRD9 dependency
Loss of SMARCB1 results in a synthetic
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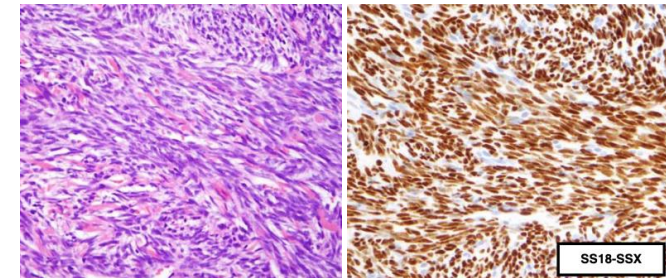
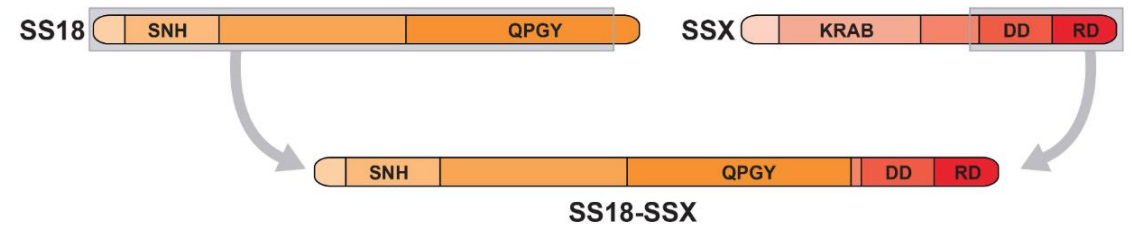


BRD9 degradation
Targeted protein degradation is an
effective therapeutic strategy

Synovial sarcoma

SS18-SSX fusion

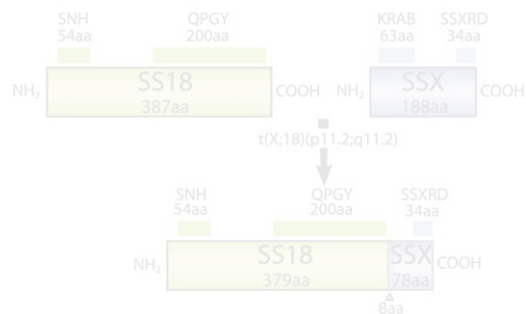
- Non-random chromosomal translocation t(X:18; p11:q11)
- Bona fide driver of pathogenesis
- SS18
 - Epigenetic chromatin regulator
 - Member of the BAF chromatin remodeling complex
- SSX
 - Potent transcriptional repressor via its KRAB domain (not included within the fusion)



Baranov et al., 2020

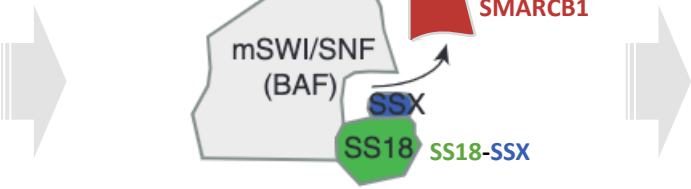
SS18-SSX fusion is the defining molecular feature of synovial sarcoma

Overview of BRD9 as a therapeutic target



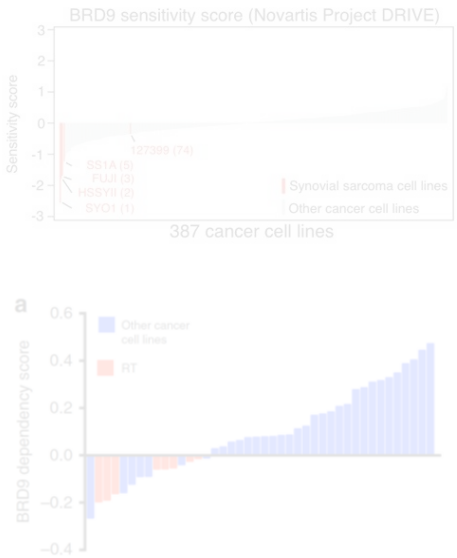
SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis



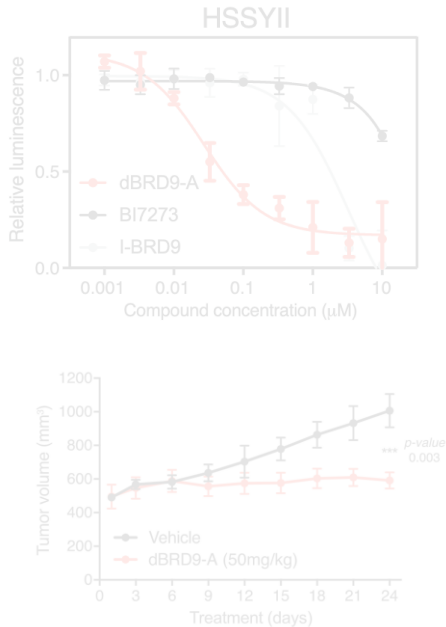
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Loss of SMARCB1 results in a synthetic lethal relationship with BRD9



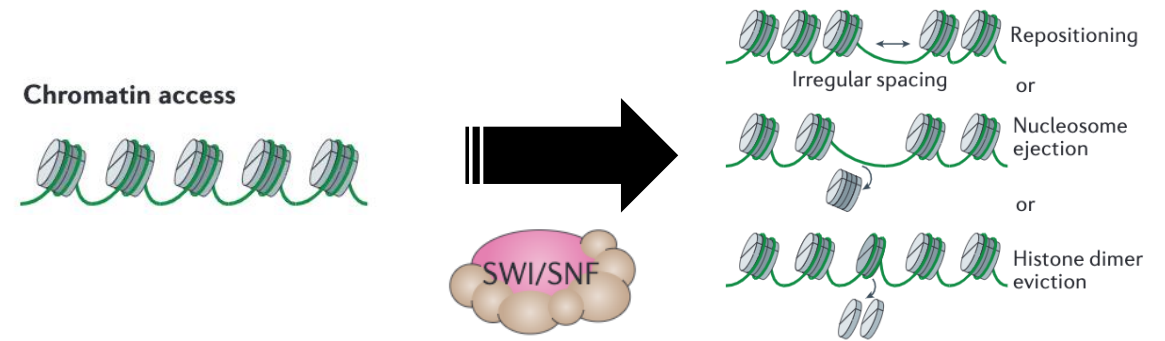
BRD9 degradation

Targeted protein degradation is an effective therapeutic strategy

BAF complexes are critical regulators of chromatin state

BAF (Brg/Brahma associated factors) or mSWI/SNF complexes

- Multi sub-unit (~15 proteins) ATP dependent chromatin remodeling complexes
- Compaction and decompaction of DNA in the nucleus
- Enables replication, selective gene expression and repression

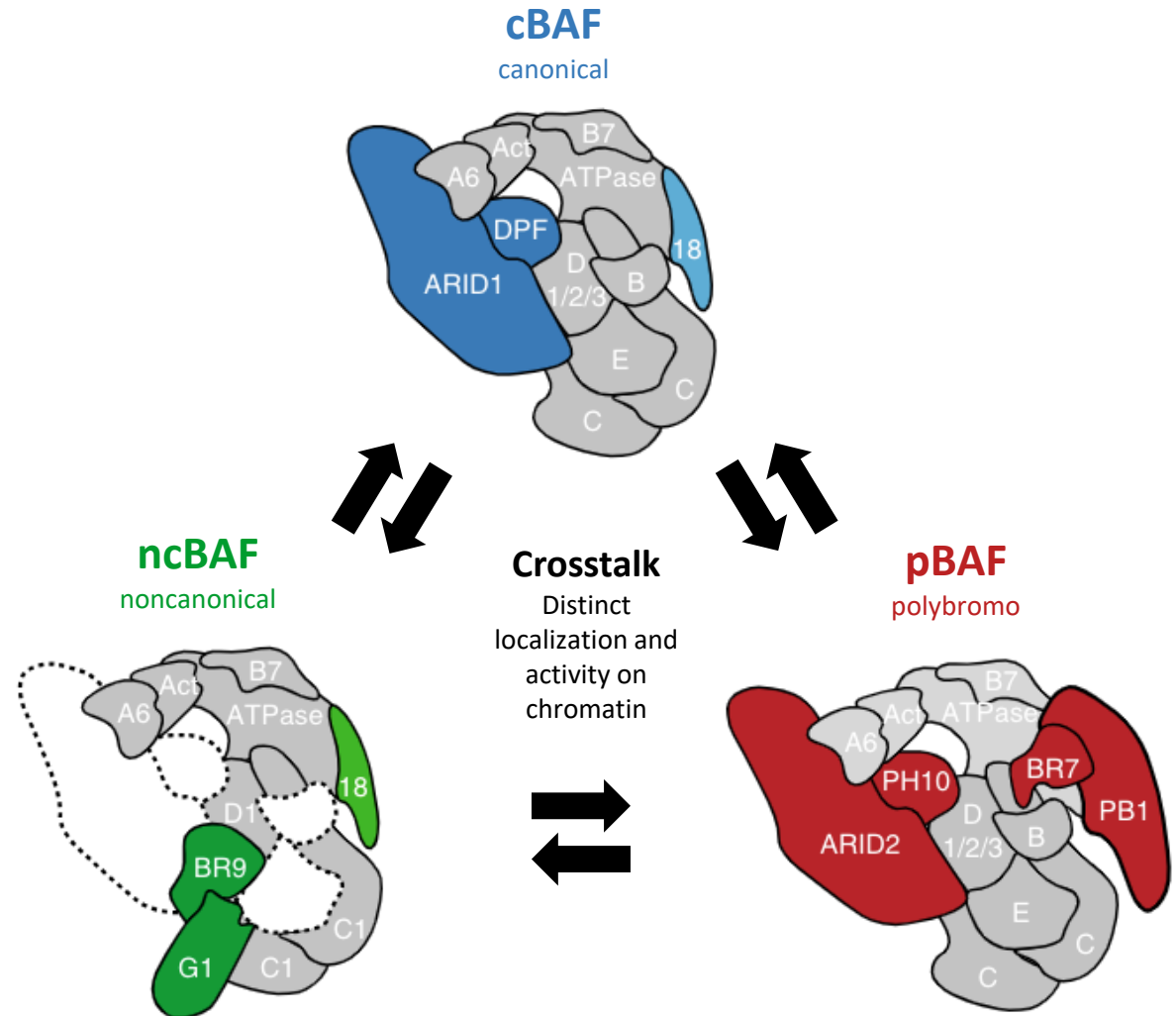


Adapted from Clapier et al., 2017

Three versions of the BAF complex collectively regulate chromatin state

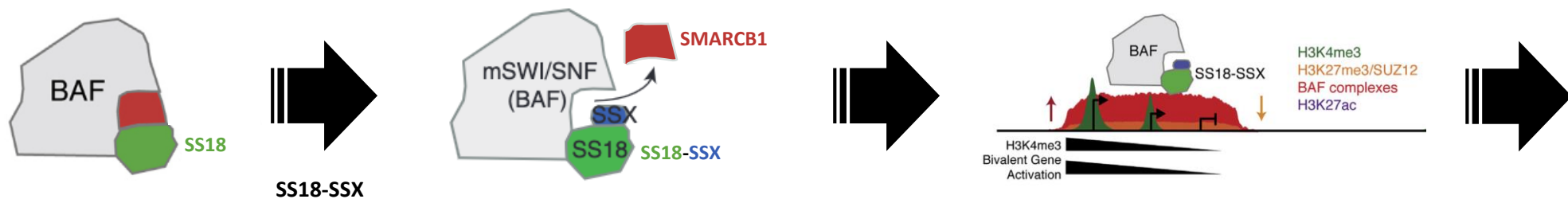
BAF complexes

- Three distinct versions with unique sub-unit combinations
 - SS18 → ncBAF, cBAF
 - SMARCB1 → cBAF, pBAF
 - BRD9 → ncBAF
- Collaborative interplay between the complexes to regulate chromatin state

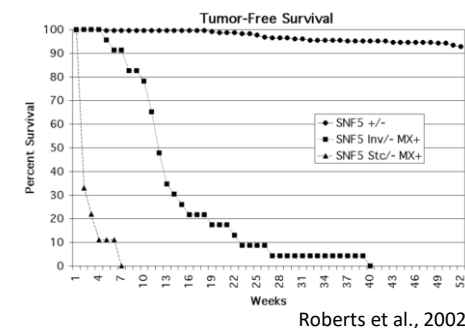
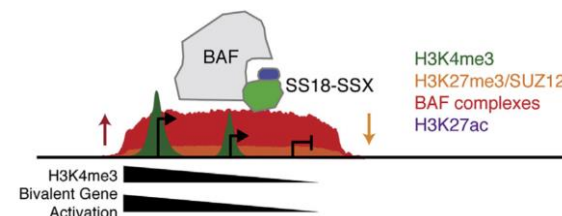


Adapted from Michel et al., 2018

SS18-SSX fusion incorporation into the BAF complex



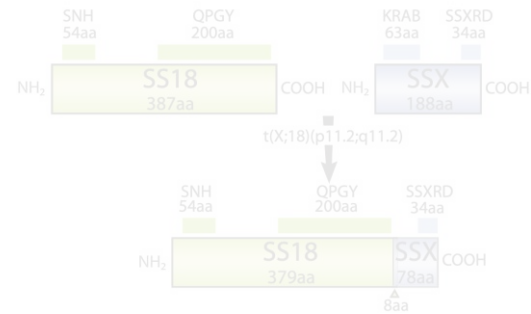
Adapted from McBride et al., 2018



Roberts et al., 2002

SS18-SSX fusion incorporation results in the ejection of SMARCB1, rendering the cBAF complex dysfunctional and driving an oncogenic state
Redistribution of BAF complexes, aberrant chromatin structure, loss of SMARCB1 tumor suppressor function

Overview of BRD9 as a therapeutic target



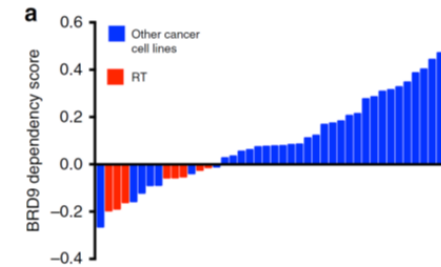
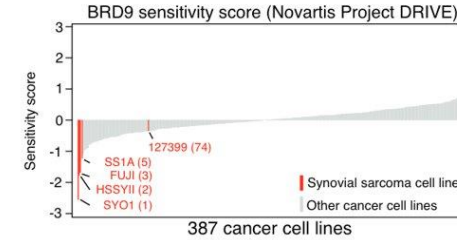
SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis



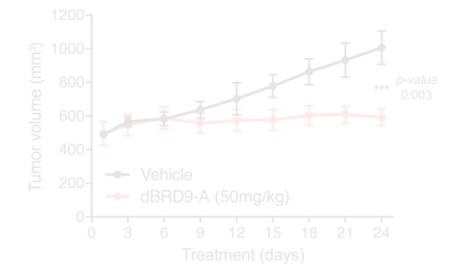
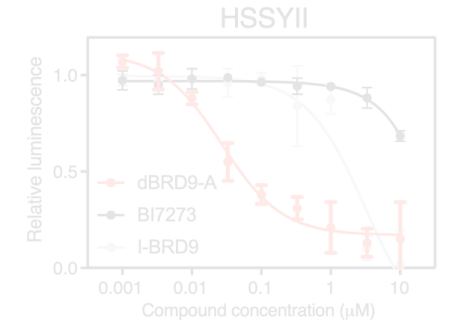
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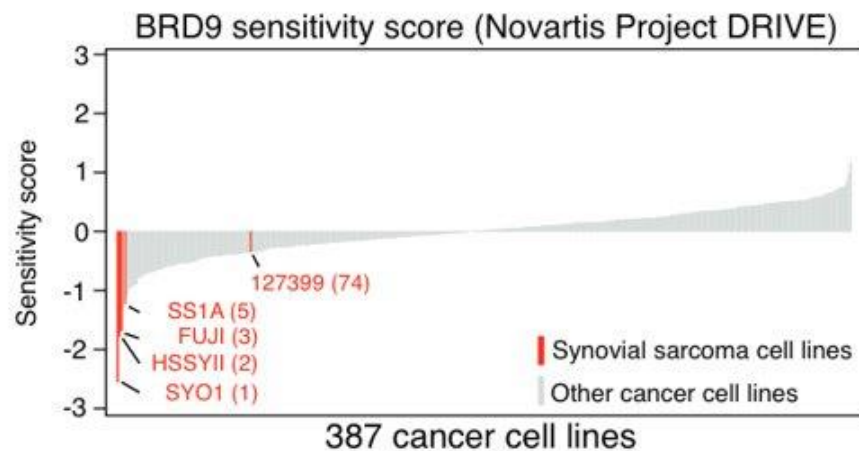
BRD9 degradation

Targeted protein degradation is an effective therapeutic strategy

BRD9 is a selective dependency in SMARCB1 perturbed contexts

Synovial sarcoma

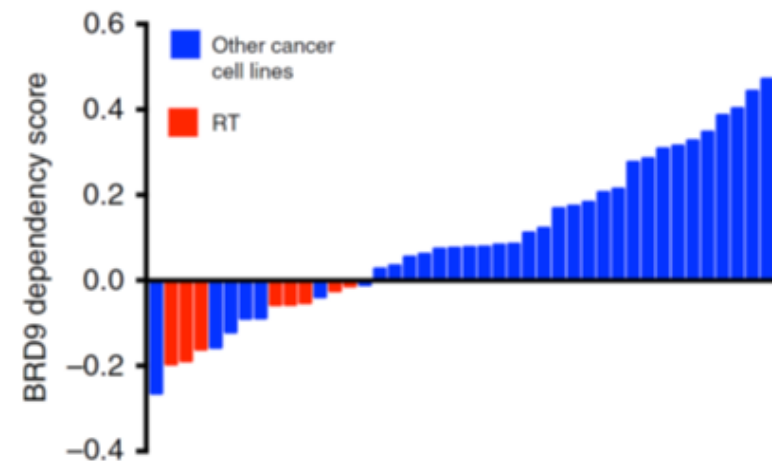
SS18-SSX fusion driven ejection of SMARCB1



Briens et al., 2018

Malignant rhabdoid tumor (MRT)

Homozygous SMARCB1 deletion



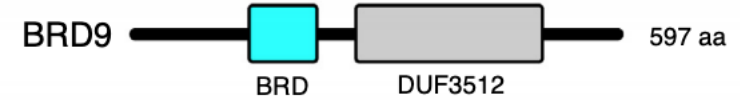
Wang et al., 2019

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

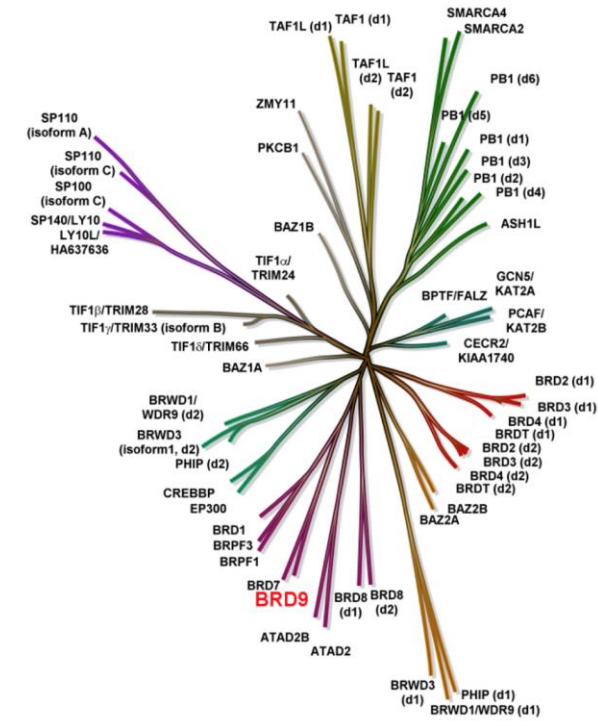
Targeting aberrant BAF complexes via BRD9 degradation

BRD9

- Bromodomain containing protein 9
 - Alternate names
 - Sarcoma antigen NY-SAR-29
 - Rhabdomyosarcoma antigen MU-RMS-40.8
- Small and compact with two annotated domains
 - Bromodomain: acetyl lysine reader function
 - DUF3512 domain: mediates incorporation into the BAF complex
- BRD9 is *selectively* incorporated into the ncBAF complex



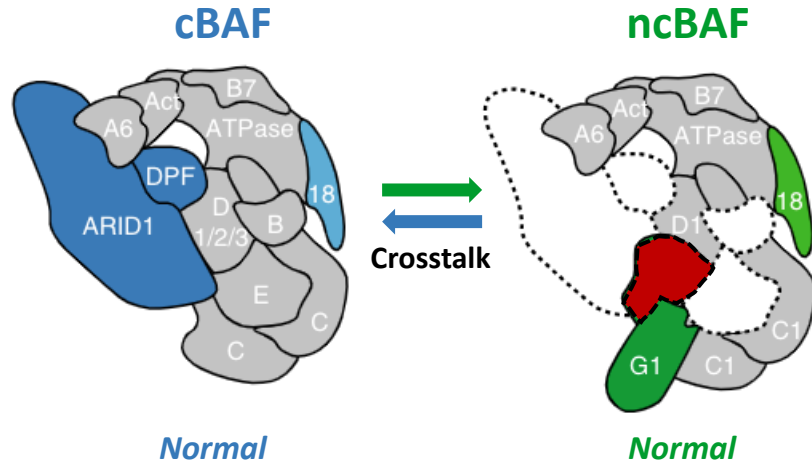
St. Pierre & Kadoch., 2017



Theodoulou et al., 2015

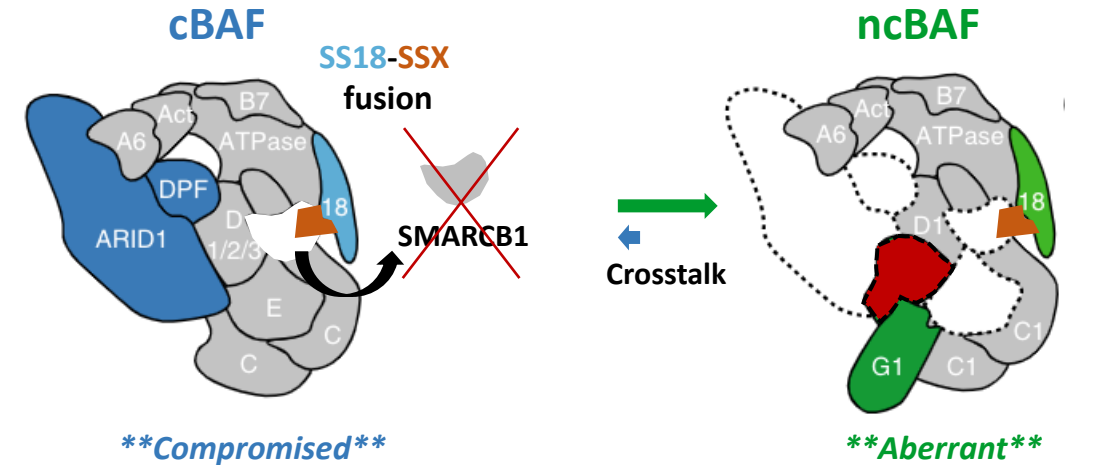
BRD9 dependency in synovial sarcoma

Normal cells



Normal cells spared

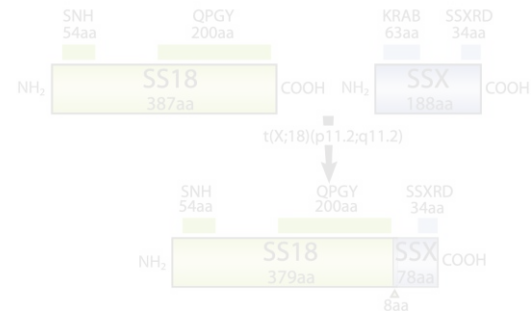
Synovial sarcoma cells



Anti-tumor response via eliminating oncogenic ncBAF activity in BAF perturbed state

Target rationale: synovial sarcoma tumors are uniquely dependent on BRD9 (synthetic lethal) and degradation is a safe and effective targeted therapy

Overview of BRD9 as a therapeutic target



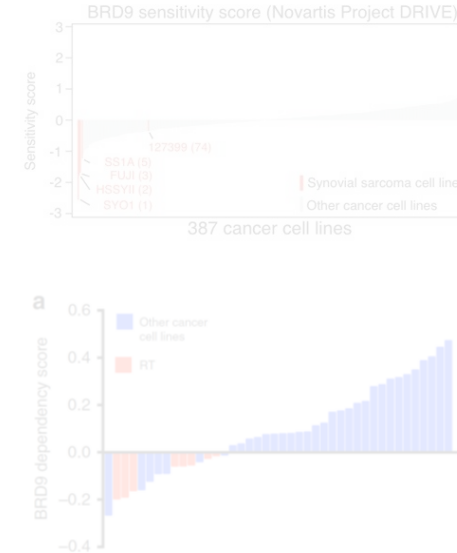
SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis



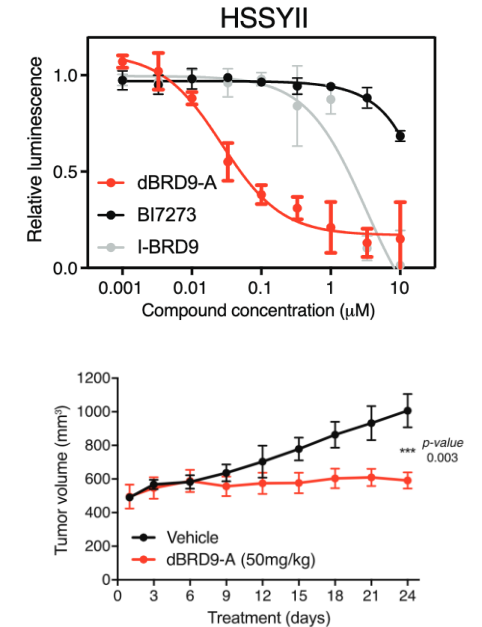
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Incorporation of the SS18-SSXX fusion ejects SMARCB1 from the BAF complex



BRD9 dependency

Loss of SMARCB1 results in a synthetic lethal relationship with BRD9



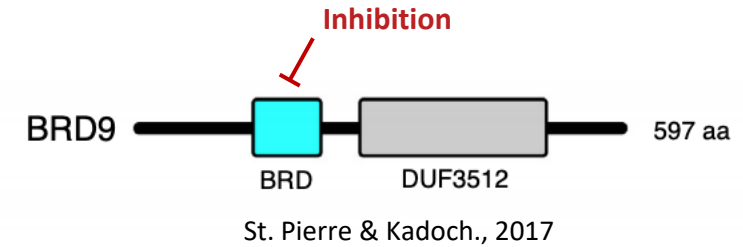
BRD9 degradation

Targeted protein degradation is an effective therapeutic strategy

Targeted protein degradation of BRD9 is an effective therapeutic strategy

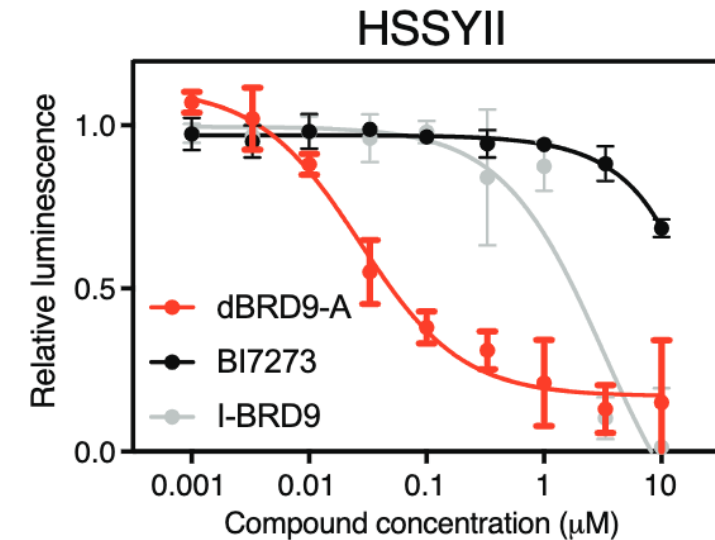
Small molecule inhibition of BRD9 is ineffective

- Limited to the disruption of acetyl-lysine bromodomain reader function alone

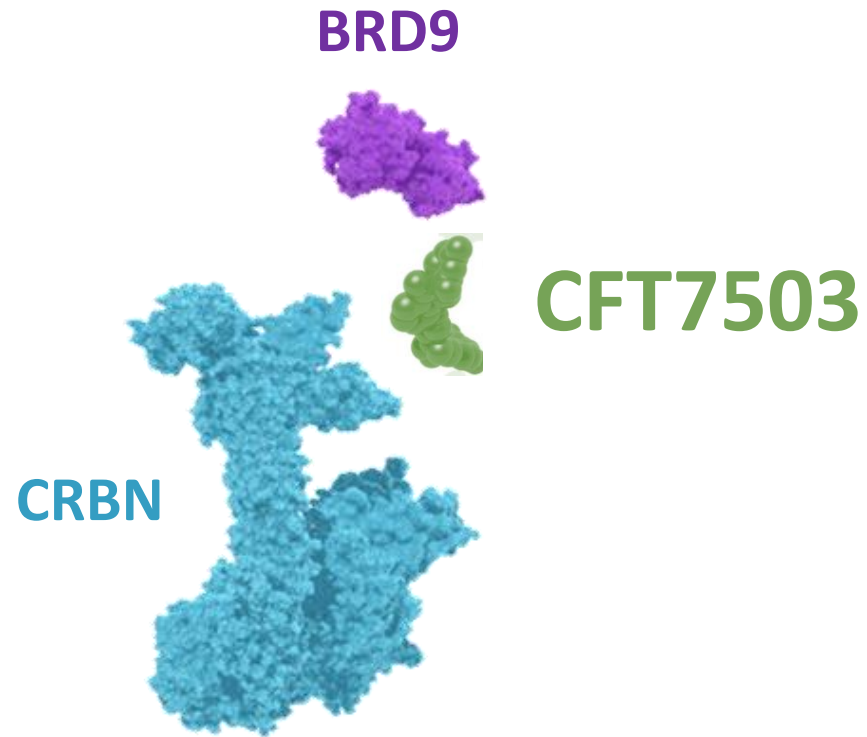


Targeted protein degradation results in the complete loss of BRD9

- Maximal disruption of the ncBAF complex oncogenic activity



Opportunity to develop a first and best-in-class BRD9 degrader



Degradation activity

- Potent
- Selective
- Complete
- Durable

Complete disruption of oncogenic BRD9/ncBAF activity

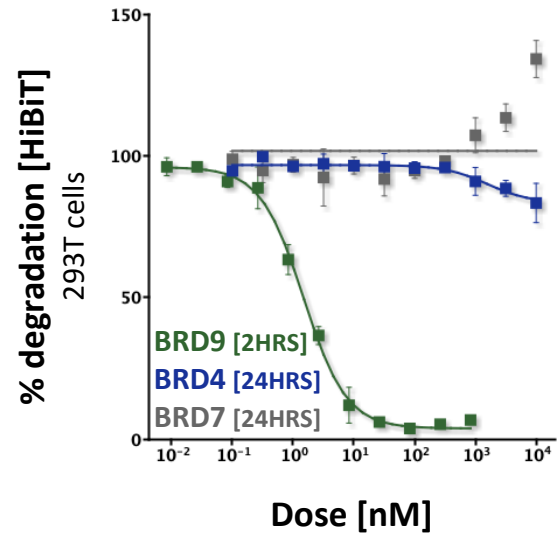
- Selective *in vitro* growth inhibitory activity in human synovial sarcoma cell lines
- Complete tumor growth inhibition across CDX and PDX models of synovial sarcoma

Enabling pharmacokinetic profile and drug properties

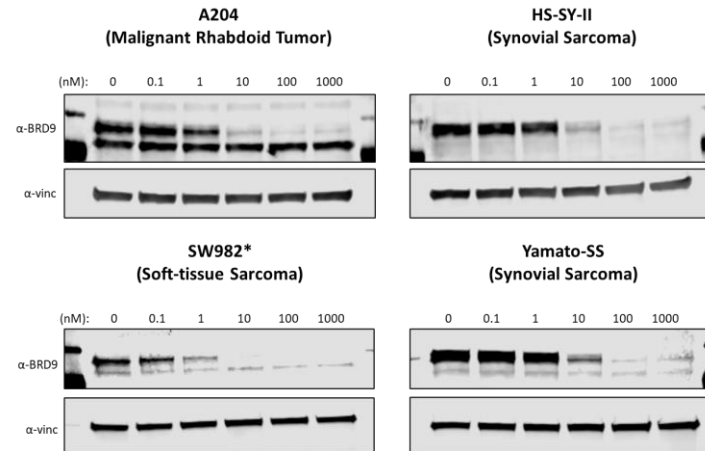
- Oral dosing
- Dosing frequency flexibility

Note: CFT7503 is the parent compound of CFT8634, C4 Therapeutics' lead compound for BRD9.

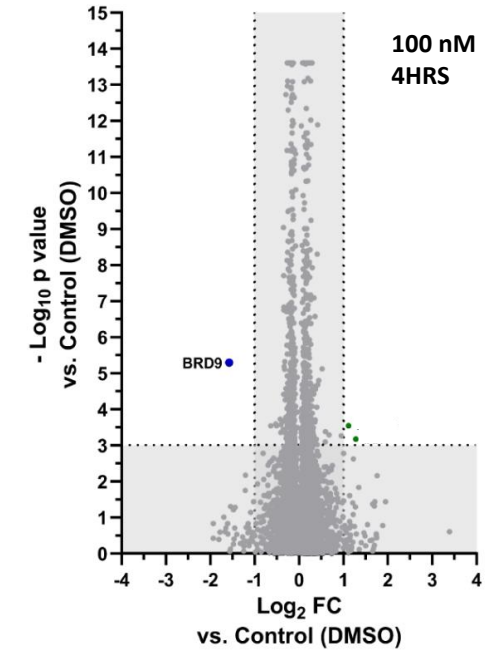
Cellular degradation activity



Dose response degradation
Engineered 293T HiBiT cell lines



Degradation across cellular contexts
Endogenous degradation across representative cellular contexts



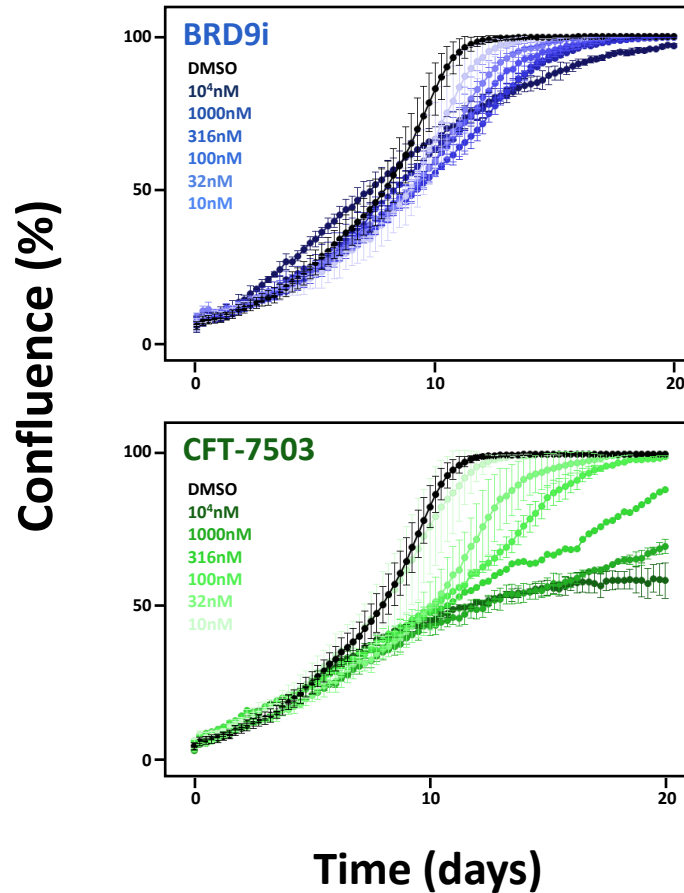
Degradation selectivity
Global proteomic profiling

Potent, complete, selective, and durable dose responsive BRD9 degradation

Cellular consequences of BRD9 degradation

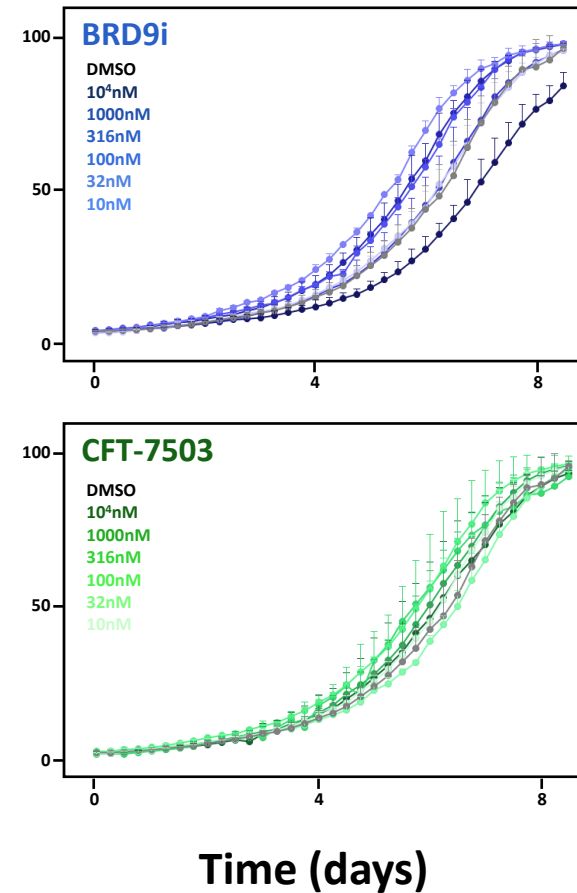
Yamato [SS18-SSX fusion; BAF perturbed]

Single dose long term growth evaluation



SW982 [BAF wildtype]

Single dose long term growth evaluation

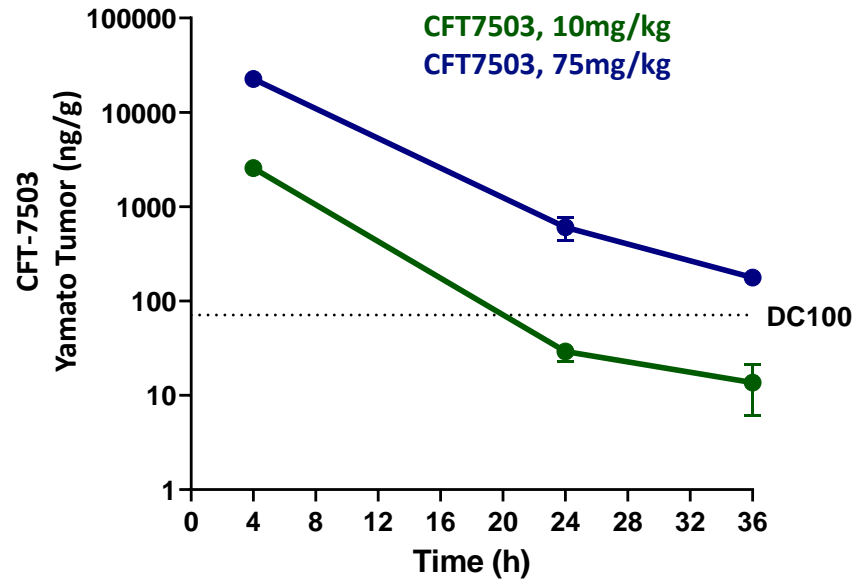


Degradation induced selective growth inhibition in BAF perturbed synovial sarcoma cells

In vivo properties – pharmacokinetics (PK) and pharmacodynamics (PD)

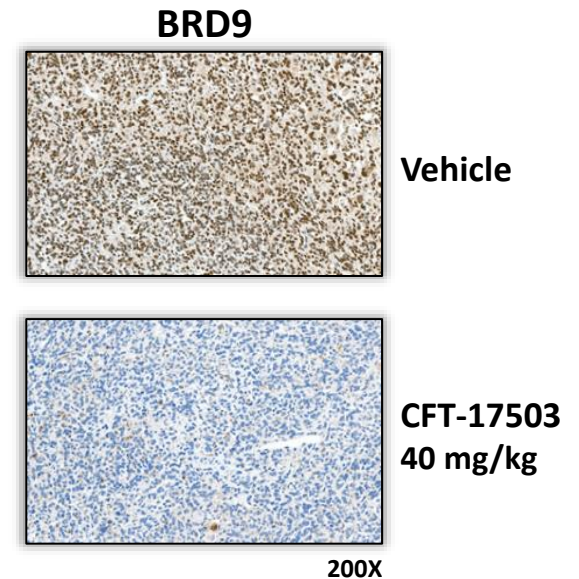
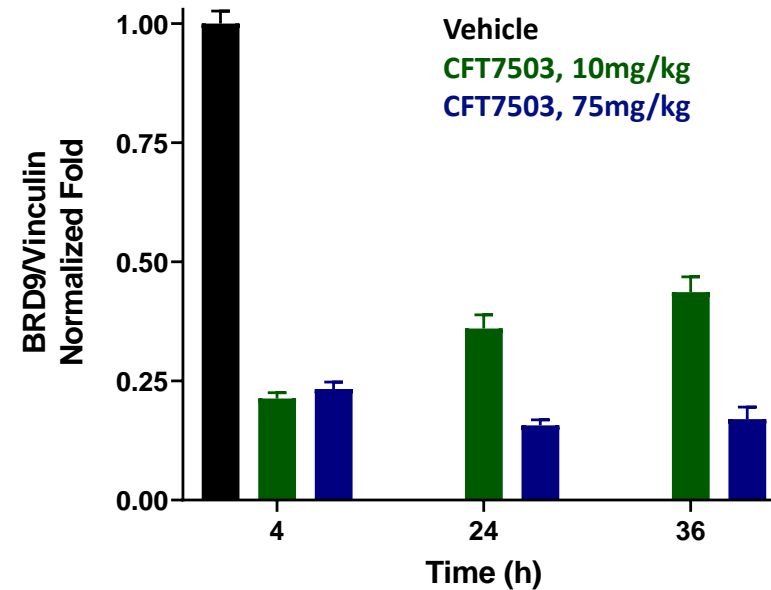
Tumor PK

Synovial sarcoma CDX (Yamato-SS)



Tumor PD

BRD9 degradation in synovial sarcoma tumors

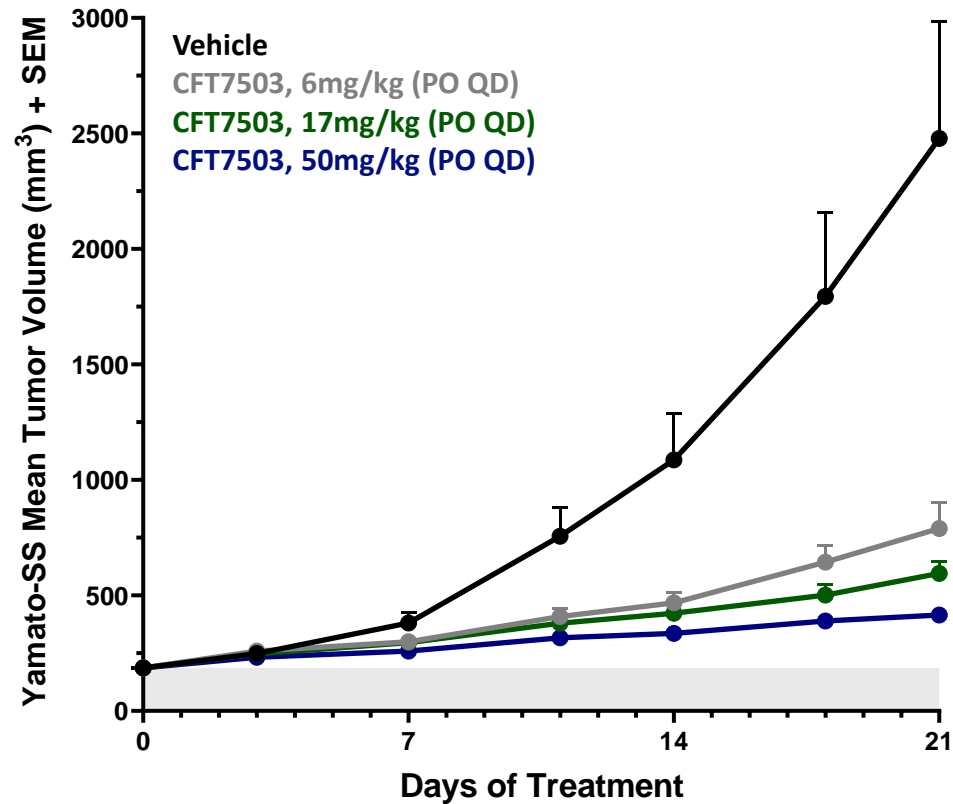


CFT7503 induces deep and durable BRD9 degradation upon oral administration in a xenograft model of synovial sarcoma

In vivo activity – efficacy in synovial sarcoma

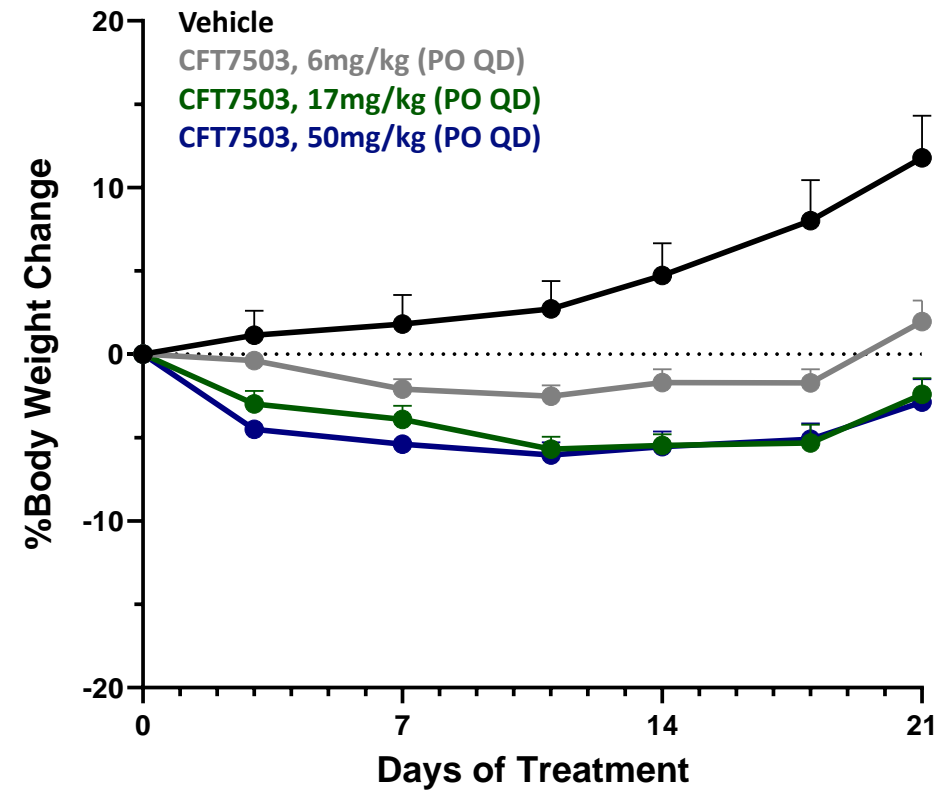
Efficacy

Synovial sarcoma CDX (Yamato-SS)



Tolerability

Synovial sarcoma CDX (Yamato-SS)

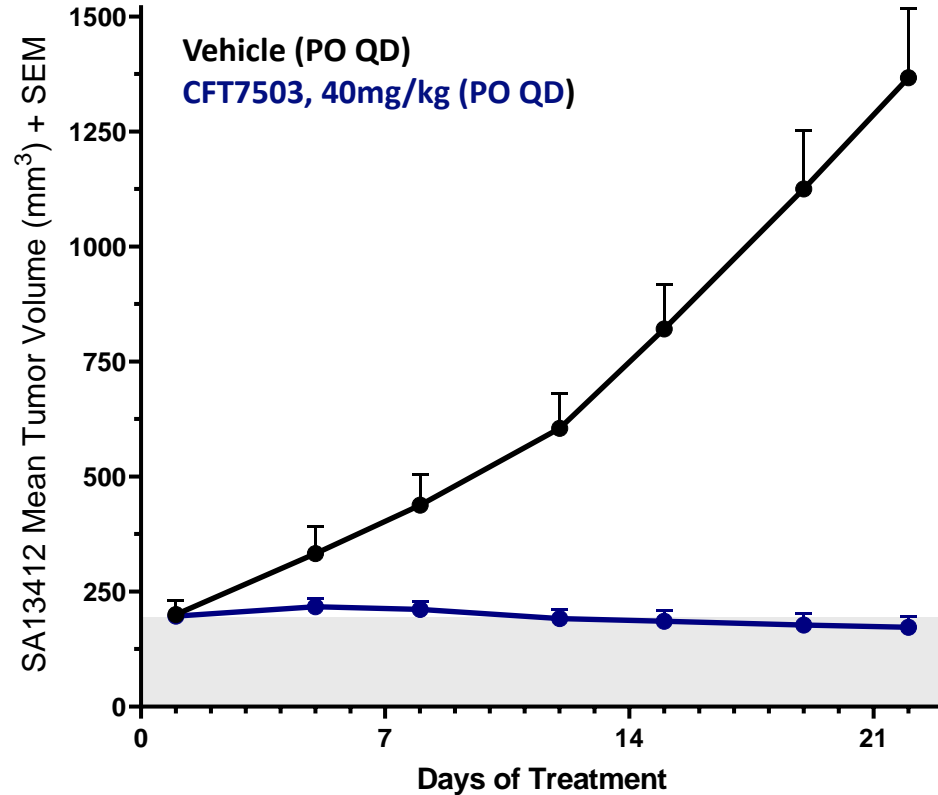


CFT7503 demonstrates dose dependent efficacy in synovial sarcoma and is well tolerated

In vivo activity – efficacy in synovial sarcoma

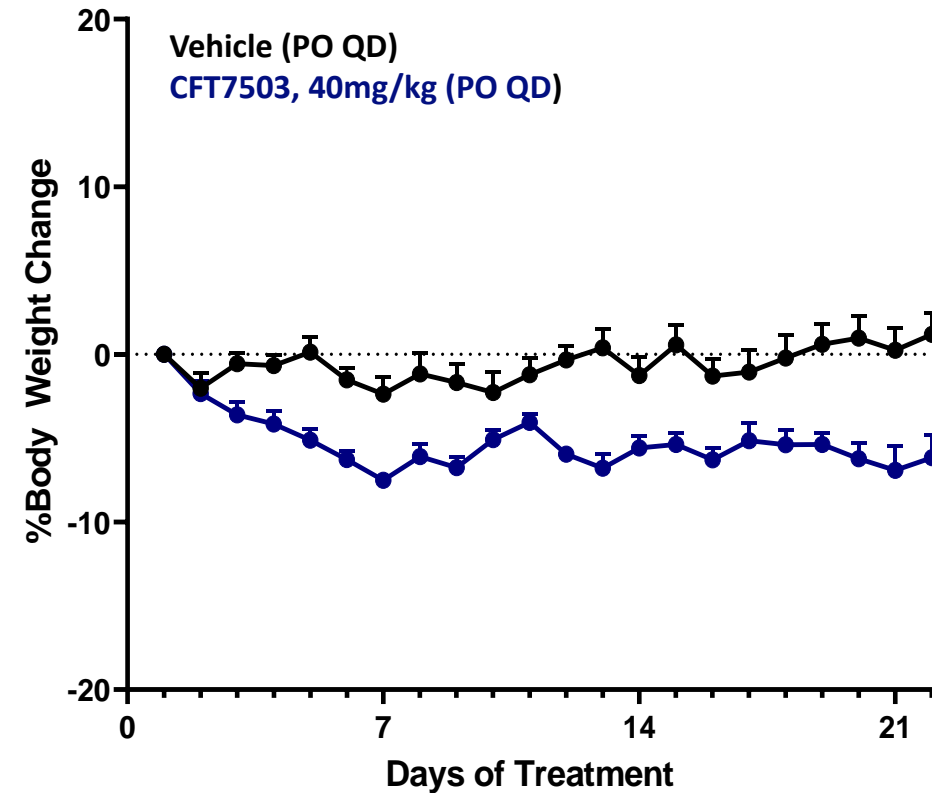
Efficacy

Synovial sarcoma PDX (SA13412)



Tolerability

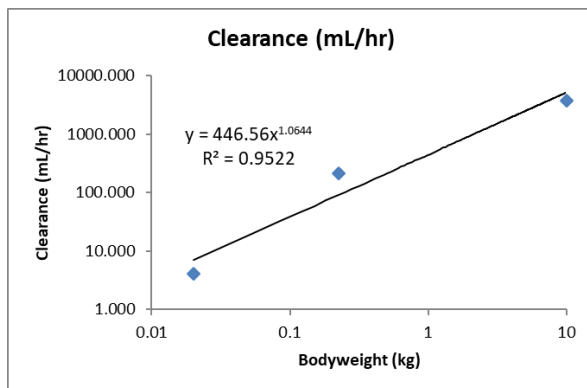
Synovial sarcoma PDX (SA13412)



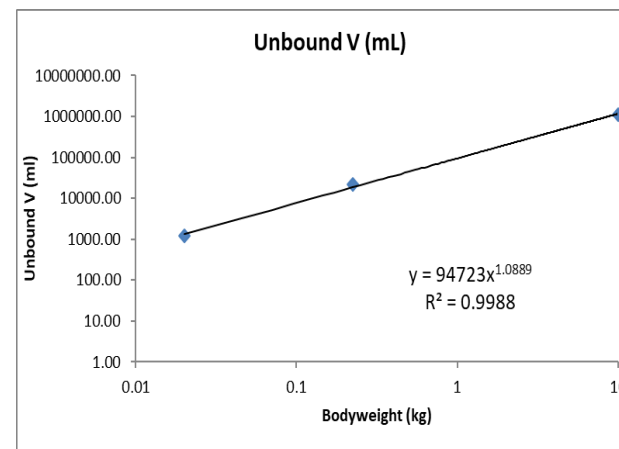
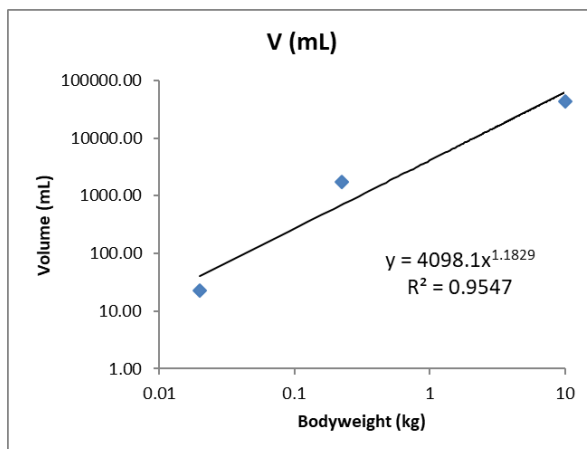
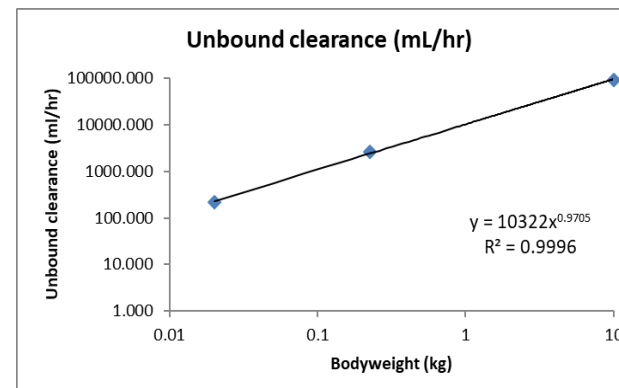
CFT7503 is efficacious in an adult patient derived xenograft (PDX) model of synovial sarcoma

Cross-species pharmacokinetic profiles

CLEARANCE

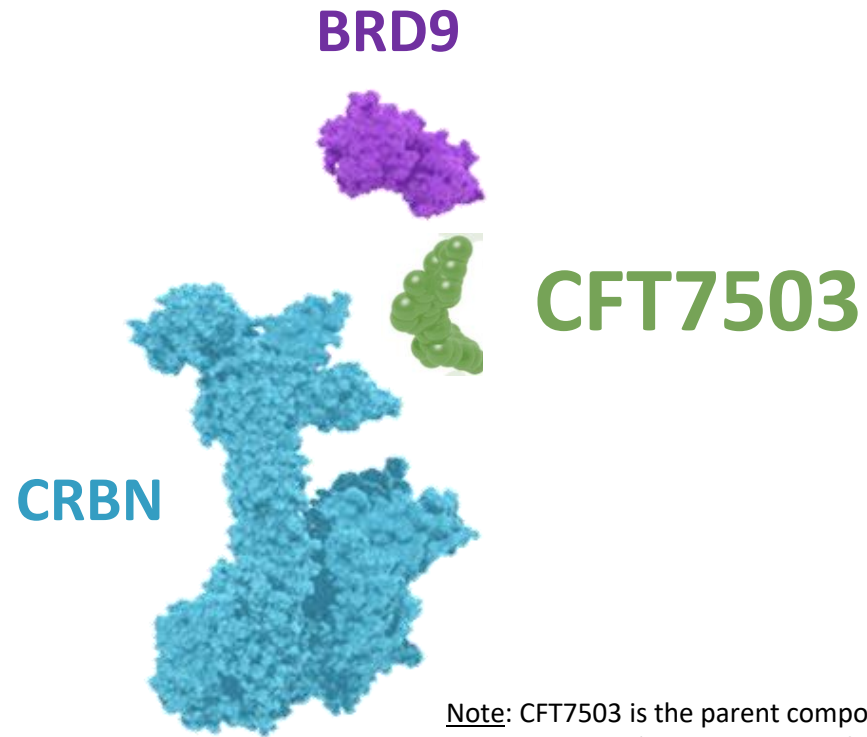


VOLUME



Concordant cross-species PK profiles enable confident and favorable human dose predictions

Opportunity to develop a first and best-in-class BRD9 degrader



Degradation activity ✓

- Potent
- Selective
- Complete
- Durable

Complete disruption of oncogenic BRD9/ncBAF activity ✓

- Selective *in vitro* growth inhibitory activity in human synovial sarcoma cell lines
- Complete tumor growth inhibition across CDX and PDX models of synovial sarcoma

Enabling pharmacokinetic profile and drug properties ✓

- Oral dosing
- Dosing frequency flexibility

Potential for a safe and effective therapeutic agent with applicability across SMARCB1 deleted cancers

Synovial sarcoma, malignant rhabdoid tumor, epithelioid sarcoma

The C4 Therapeutics Team

