C4 Therapeutics

North American Protein Degradation Congress

Rhamy Zeid

February 16, 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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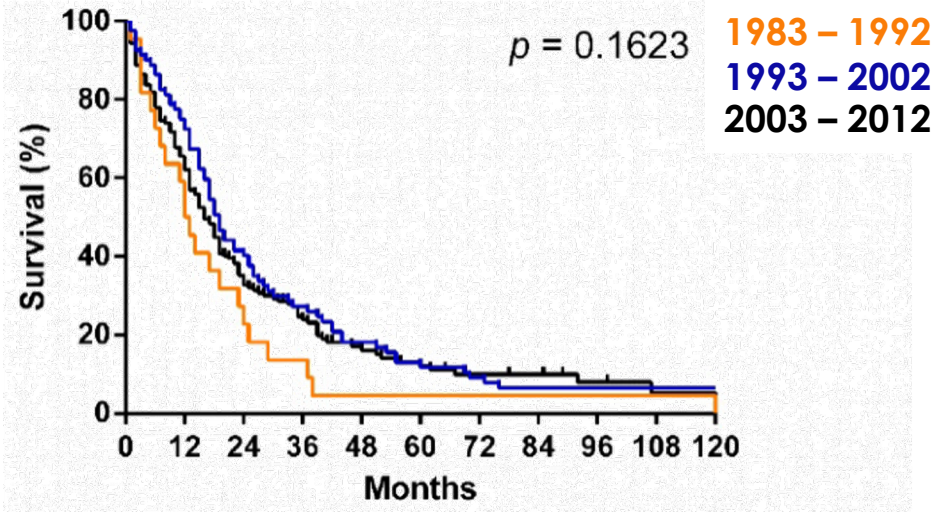
Synovial Sarcoma

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**

Kaplan-Meier Survival
Over time [3 decades]



Wang et al., 2017

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

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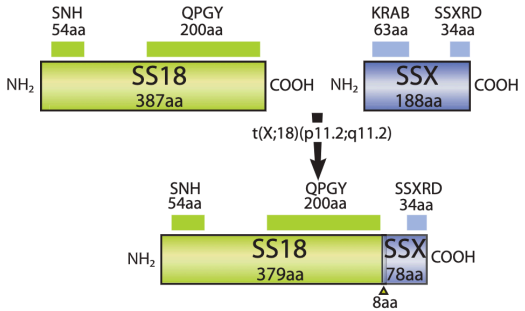
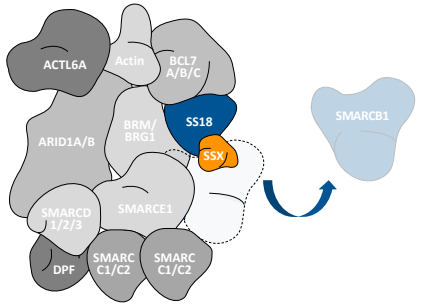
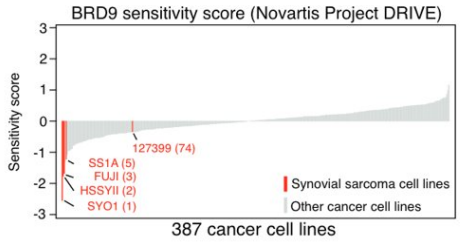
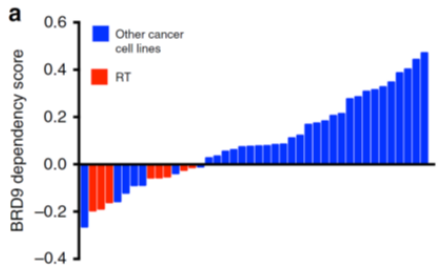
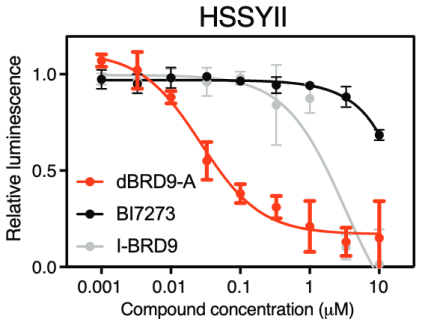
Overview of BRD9 as a Therapeutic Target

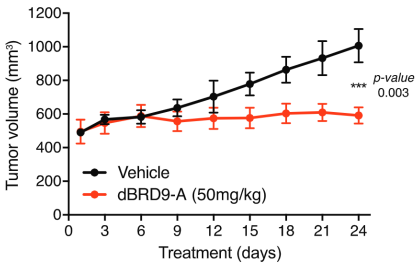












SS18-SSX fusion
Defining feature that underlies synovial sarcoma pathogenesis

SMARCB1 eviction
Incorporation of the SS18-SSX 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

Sources: Kadoch & Crabtree., 2013; McBride et al., 2018, Michel et al., 2018; Wang et al., 2019; Briens et al., 2018

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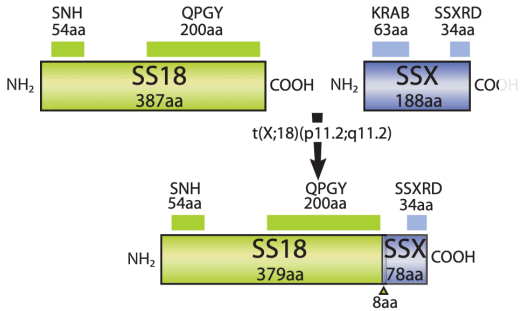
Overview of BRD9 as a Therapeutic Target



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Synovial Sarcoma – SS18-SSX Fusion

SS18-SSX fusion

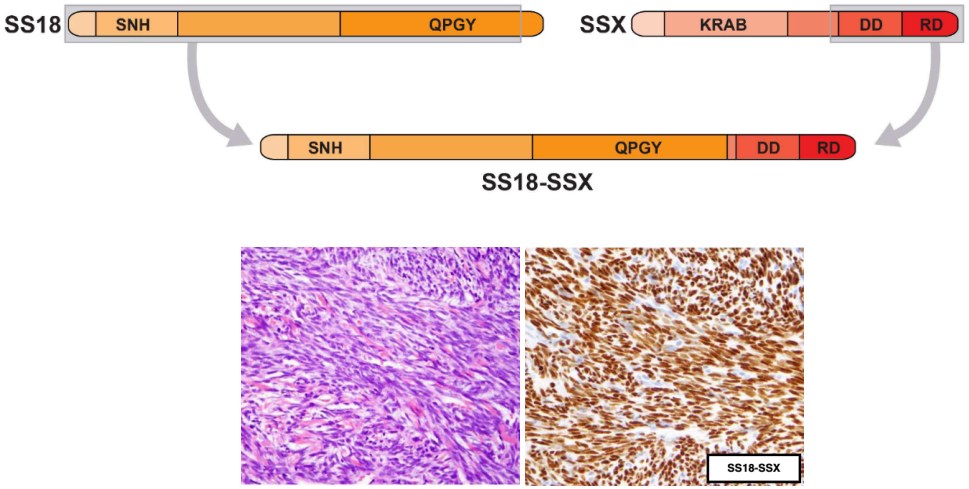
- Non-random chromosomal translocation t(X:18; p11:q11)
- Bona fide driver of pathogenesis

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

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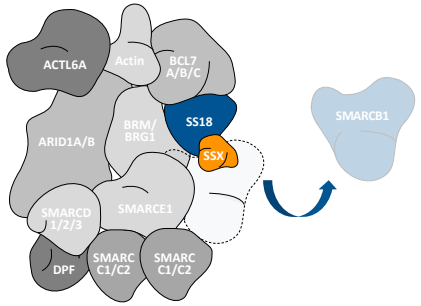
Overview of BRD9 as a Therapeutic Target

SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis



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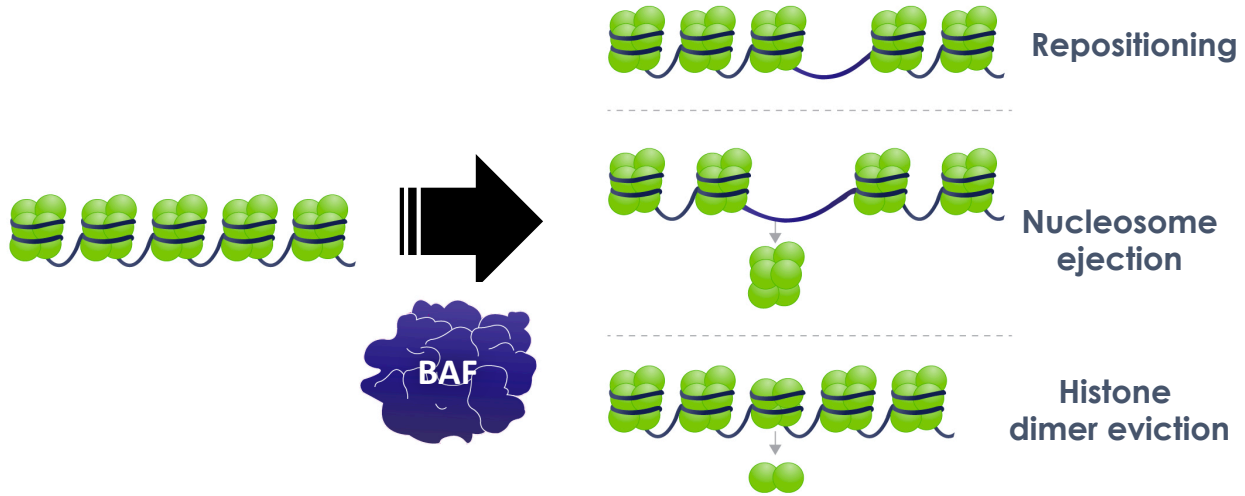
BAF Complexes are Critical Regulators of Chromatin State

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 Clapier el et al., 2017

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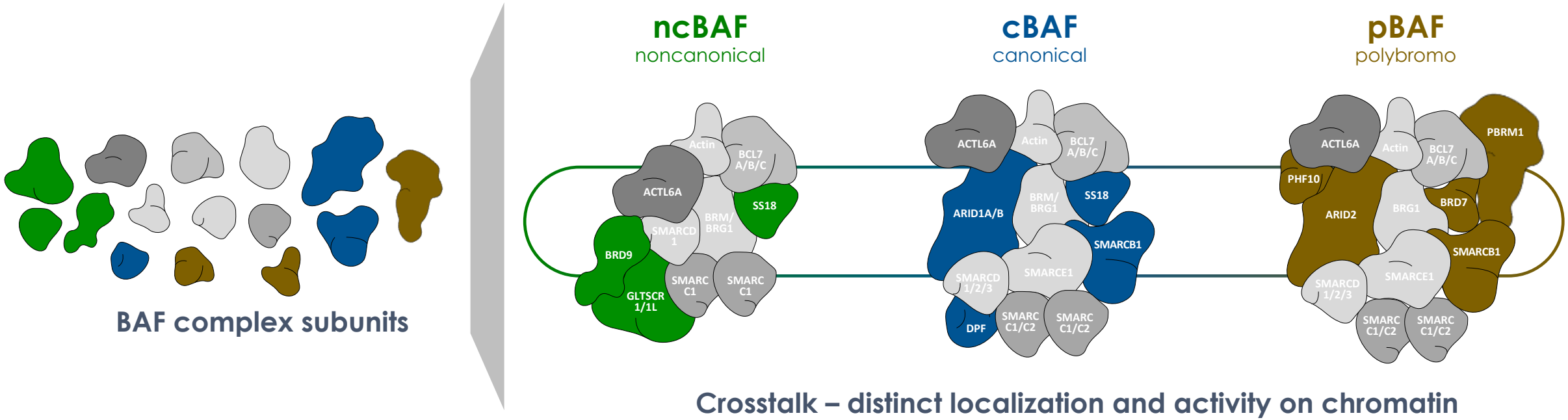
Three Versions of the BAF Complex



Crosstalk – distinct localization and activity on chromatin

Collaborative interplay between BAF complexes to collectively regulate chromatin state

Sources: Alpsoy et al., 2018; Gatchalian et al., 2018; Brien et al., 2018; Michel et al., 2018; Wang et al., 2019; Mashtalir et al., 2018; Inoue et al., 2019

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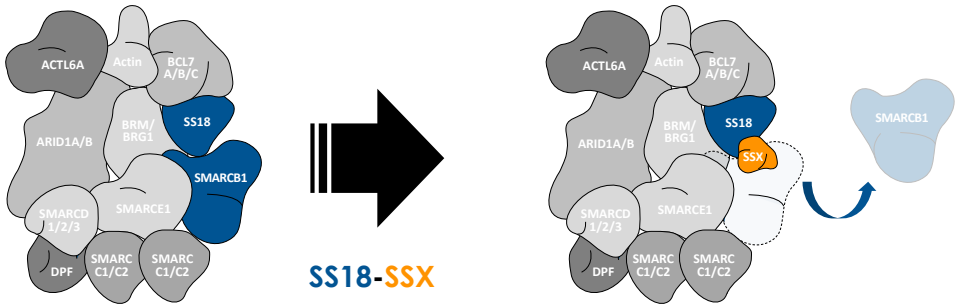
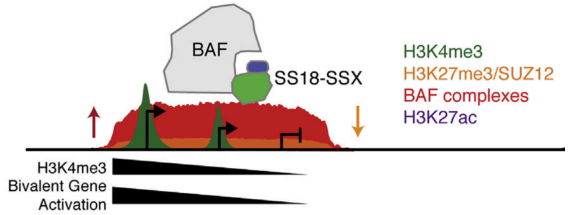
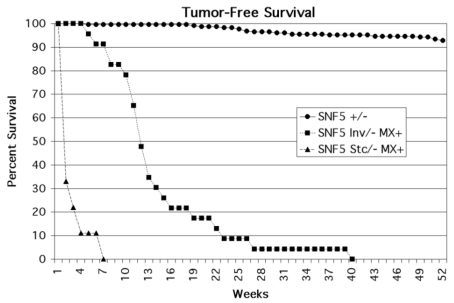
SS18-SSX Fusion Incorporation into the BAF Complex





McBride et al., 2018

SS18-SSX fusion oncogenic program



Roberts et al., 2002

Loss of SMARCB1 tumor suppressor function

SS18-SSX fusion incorporation results in the ejection of SMARCB1, rendering the cBAF complex dysfunctional and driving an oncogenic state

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Overview of BRD9 as a Therapeutic Target

SS18-SSX fusion

Defining feature that underlies synovial sarcoma pathogenesis

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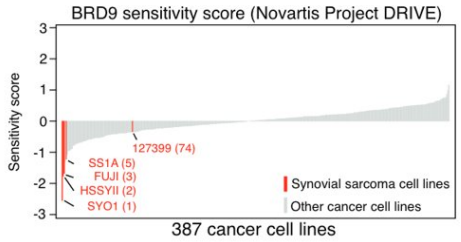
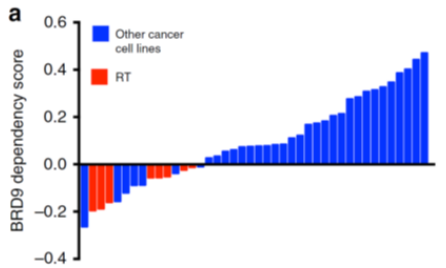
Incorporation of the SS18-SSX fusion ejects SMARCB1 from the BAF complex





BRD9 dependency

Loss of SMARCB1 results in a synthetic lethal relationship with BRD9

BRD9 degradation

Targeted protein degradation is an effective therapeutic strategy

Sources: Kadoch & Crabtree., 2013; McBride et al., 2018, Michel et al., 2018; Wang et al., 2019; Briens et al., 2018

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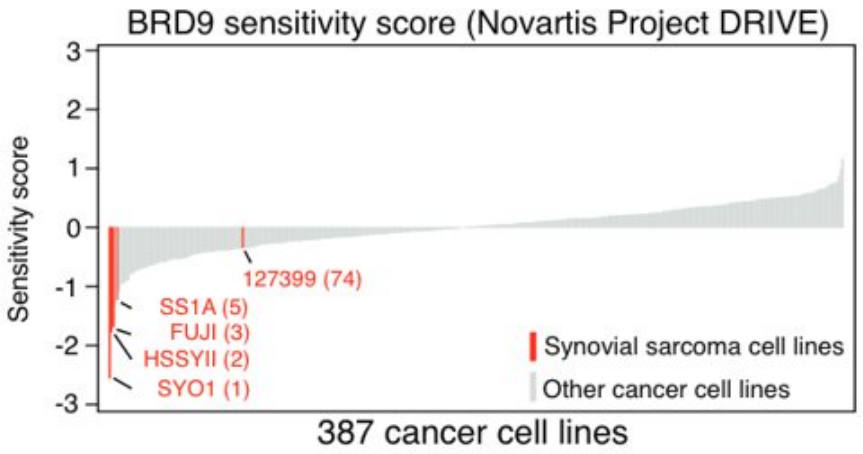
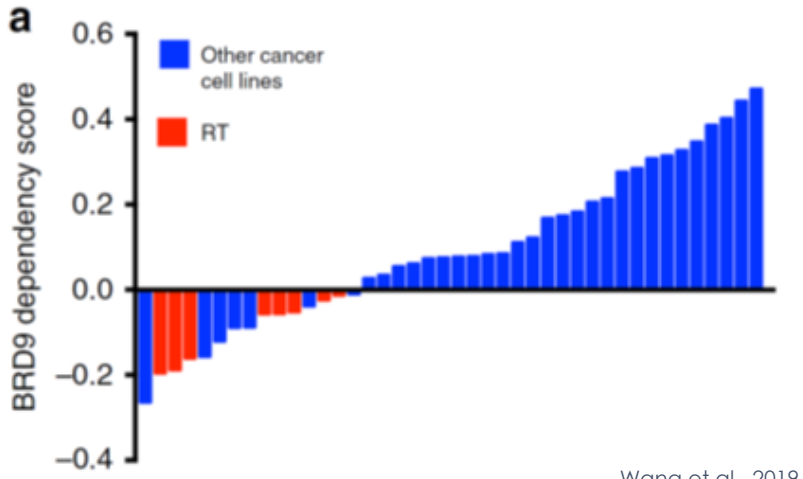
BRD9 is a Selective Dependency in SMARCB1 Perturbed Contexts

Synovial Sarcoma
SS18-SSX fusion driven ejection of SMARCB1



Briens et al., 2018

Malignant Rhabdoid Tumor
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

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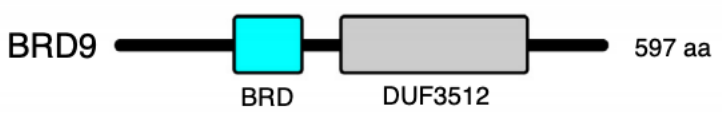
Role of BRD9 in BAF Complexes

BRD9

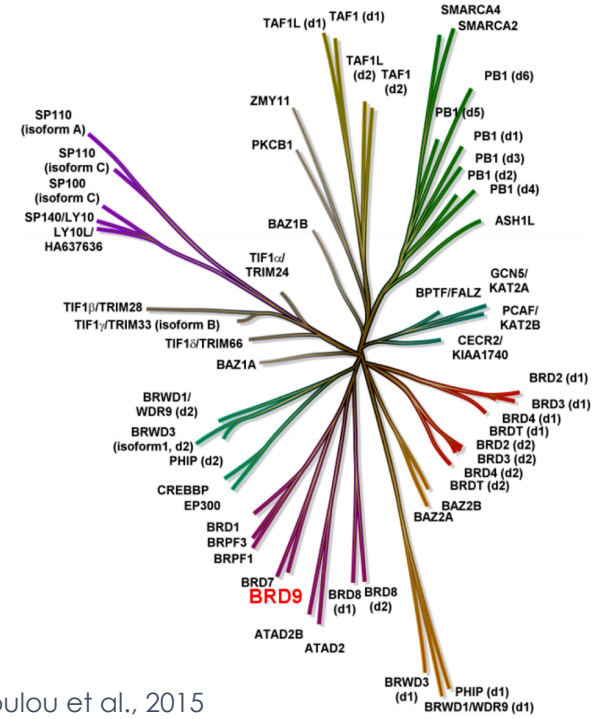
- **Br**omo**d**omain containing protein 9
  - Alternate names
    - Sarcoma antigen NY-SAR-29
    - rhabdomyosarcoma antigen MU-RMS-40.8

- 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

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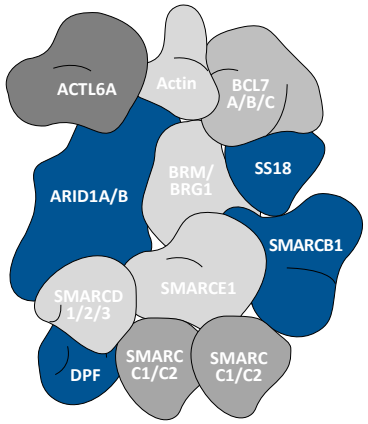
BRD9 Dependency in Synovial Sarcoma

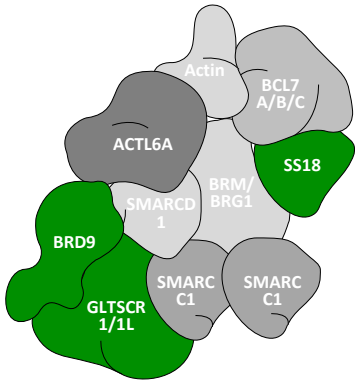
NORMAL CELLS

cBAF



Crosstalk

ncBAF



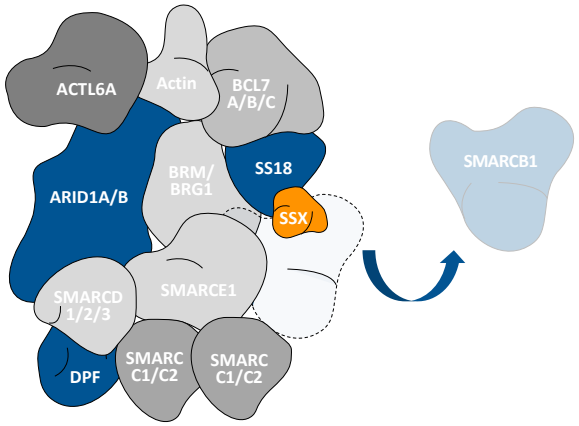
Normal

Normal

- Normal chromatin structure
- Wild type transcription

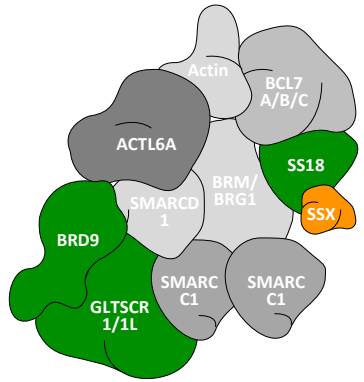
SYNOVIAL SARCOMA CELLS

cBAF



Crosstalk

ncBAF



****Compromised****

****Aberrant****

- SMARCB1 null state
- Aberrant chromatin structure
- Oncogenic transcription

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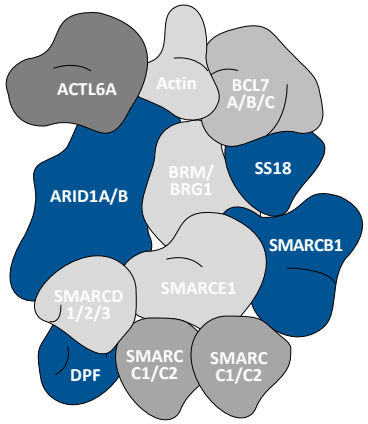
Sources: Michel et al., 2018; Briens et al., 2018

BRD9 Dependency in Synovial Sarcoma

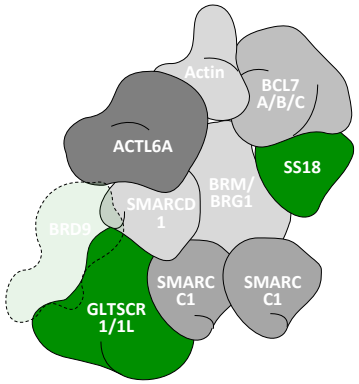
NORMAL CELLS

cBAF



Crosstalk

ncBAF

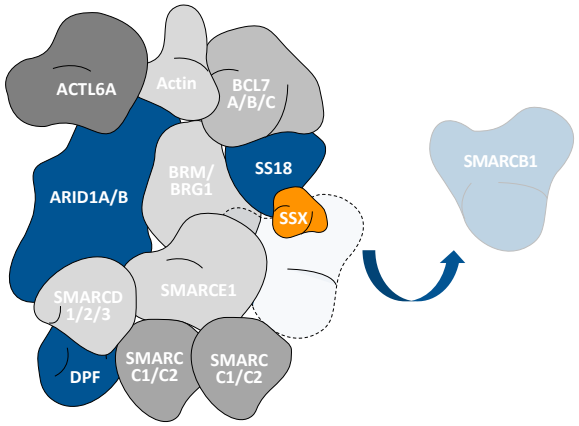


Normal *Normal*

Normal cells spared

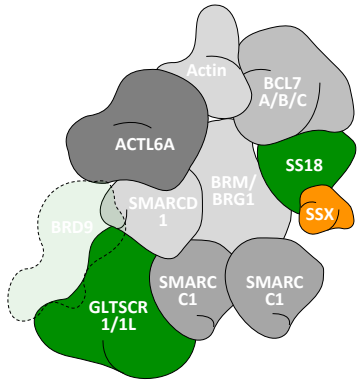
SYNOVIAL SARCOMA CELLS

cBAF



Crosstalk

ncBAF



Compromised ***Aberrant***

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

Target rationale: The role of BRD9 in the ncBAF complex results in a synthetic lethal dependency in SS18-SSX fusion driven synovial sarcoma

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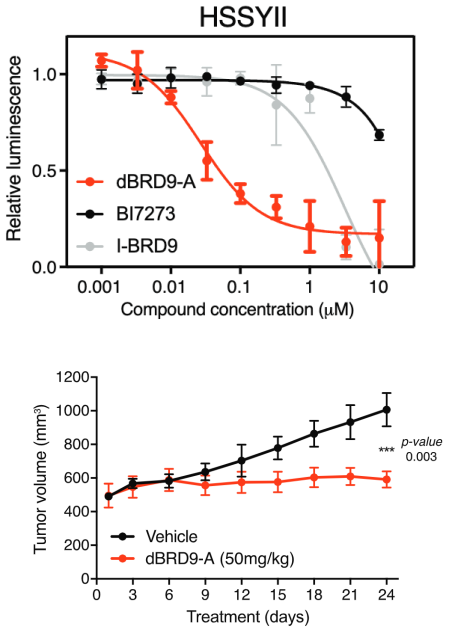
Sources: Michel et al., 2018; Briens et al., 2018

Overview of BRD9 as a Therapeutic Target

SS18-SSX fusion
Defining feature that underlies synovial sarcoma pathogenesis

SMARCB1 eviction
Incorporation of the SS18-SSX 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

Sources: Kadoch & Crabtree., 2013; McBride et al., 2018, Michel et al., 2018; Wang et al., 2019; Briens et al., 2018

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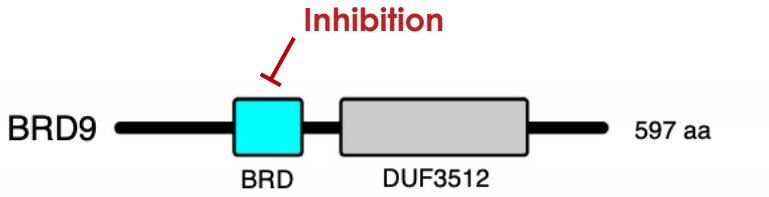
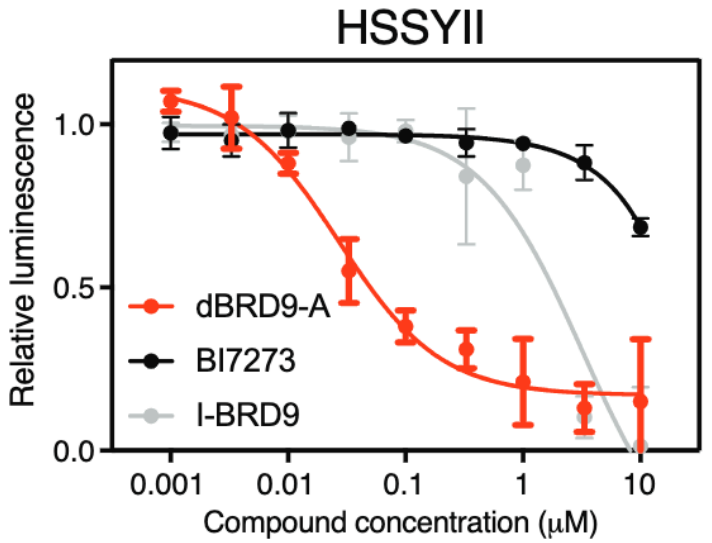
Targeted Protein Degradation of BRD9 is an Effective Therapeutic Strategy

- Small molecule inhibition of BRD9 is ineffective
  - Limited to the disruption of acetyl-lysine bromodomain reader function alone



St. Pierre & Kadoch., 2017

- Targeted protein degradation results in the complete loss of BRD9
  - Maximal disruption of the ncBAF complex oncogenic activity



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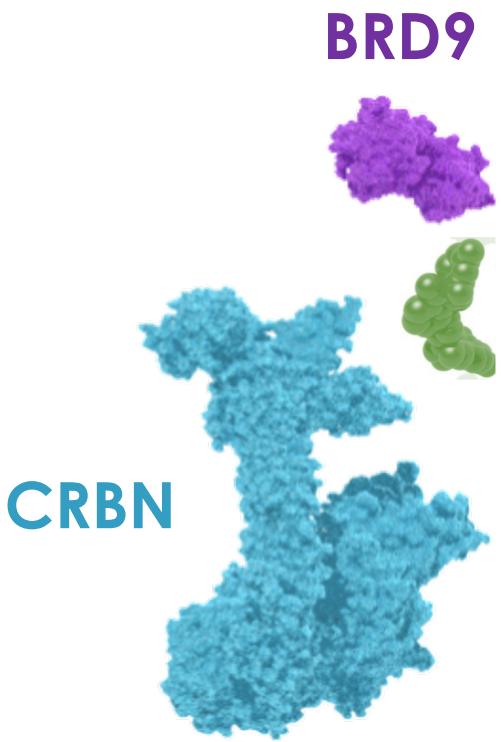
Opportunity to Develop a First and Best-in-class BRD9 Degrader



CFT8634

CFT7503 (racemate)

- 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

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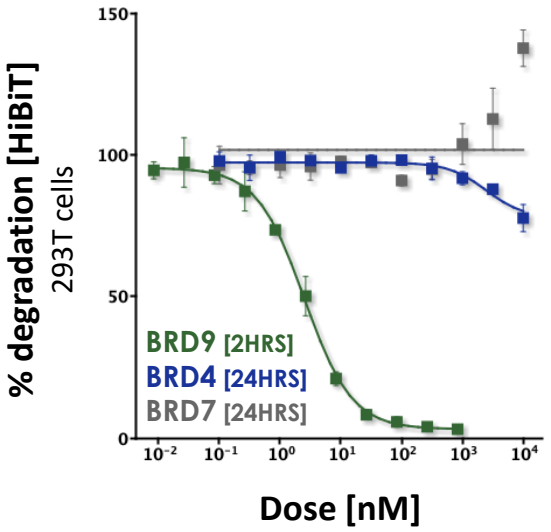
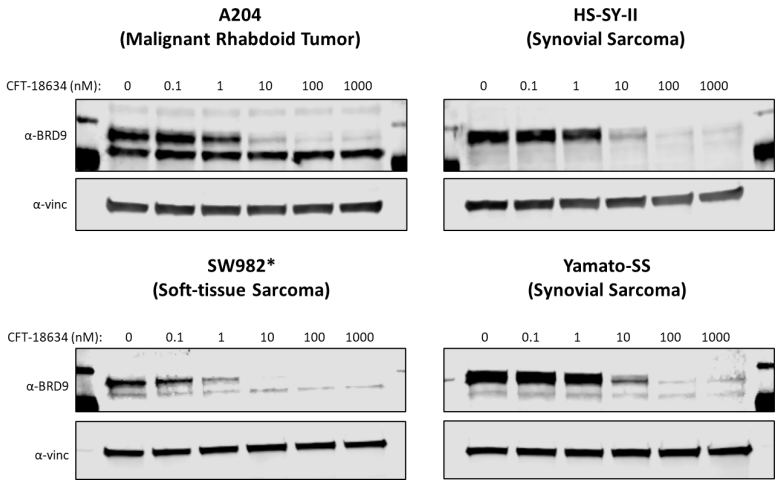
CFT8634 – Degradation Activity

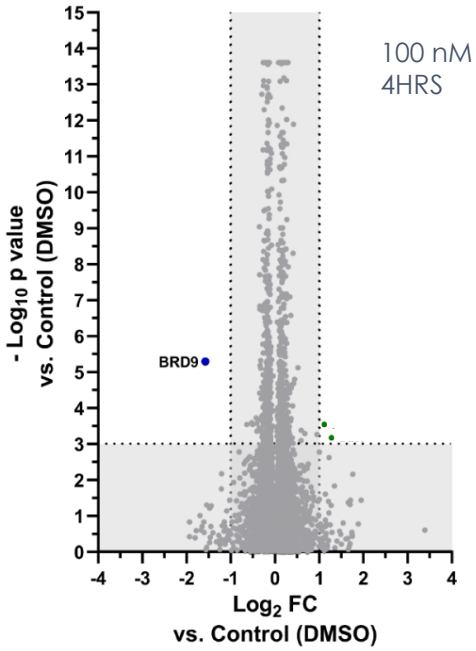
Dose Response Degradation
Engineered 293T HiBiT cell lines



Degradation Across Cellular Contexts
Endogenous degradation



Degradation Selectivity
Global proteomic profiling



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

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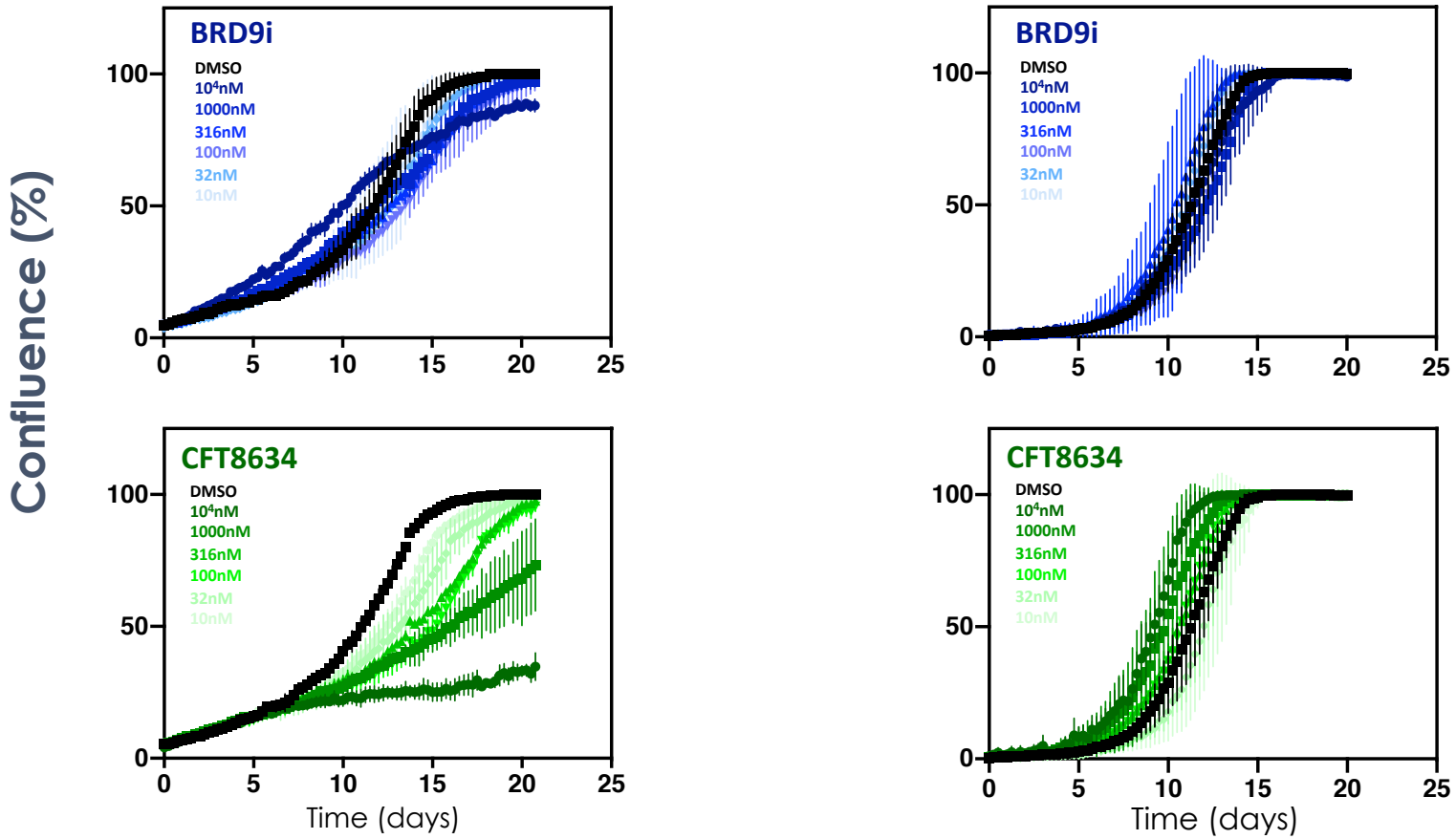
Cellular Consequences of BRD9 Degradation

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

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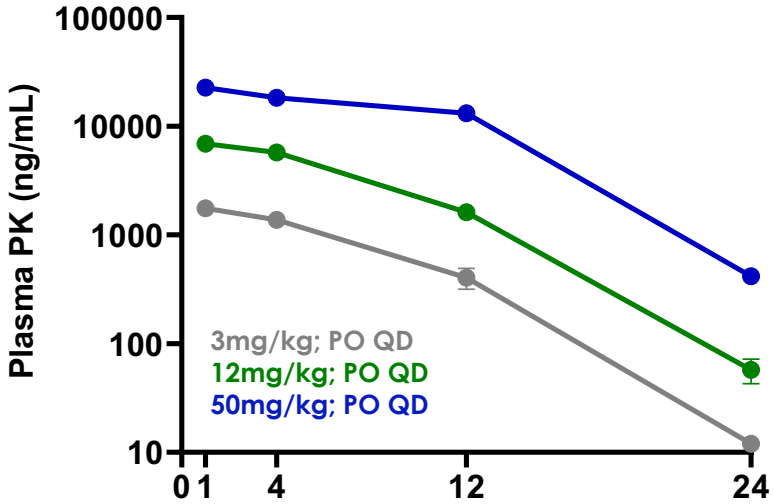
In vivo properties – Pharmacokinetics (PK) and Pharmacodynamics (PD)

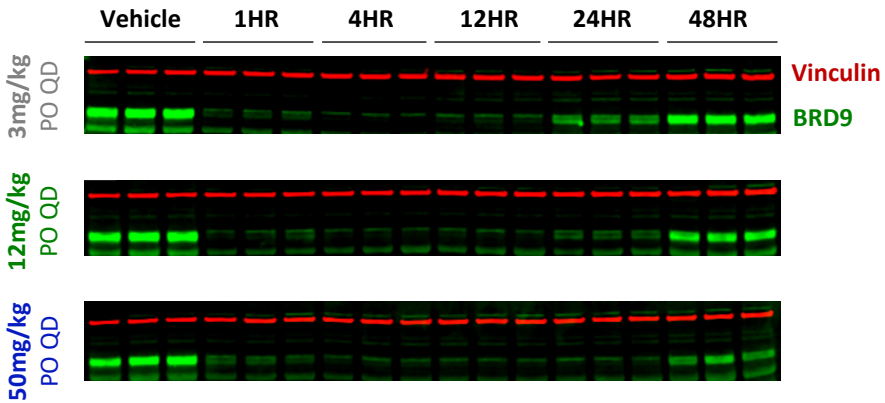
Tumor PK

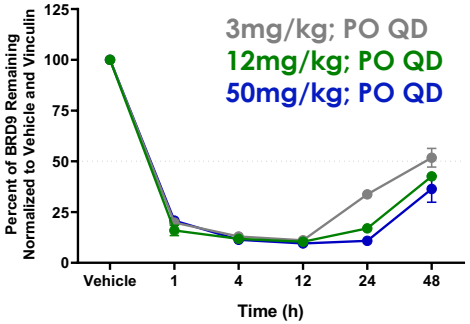
Synovial Sarcoma CDX (Yamato-SS)



Tumor PD

BRD9 Degradation in Synovial Sarcoma Tumors





CFT8634 induces deep and durable BRD9 degradation upon oral administration in a xenograft model of synovial sarcoma

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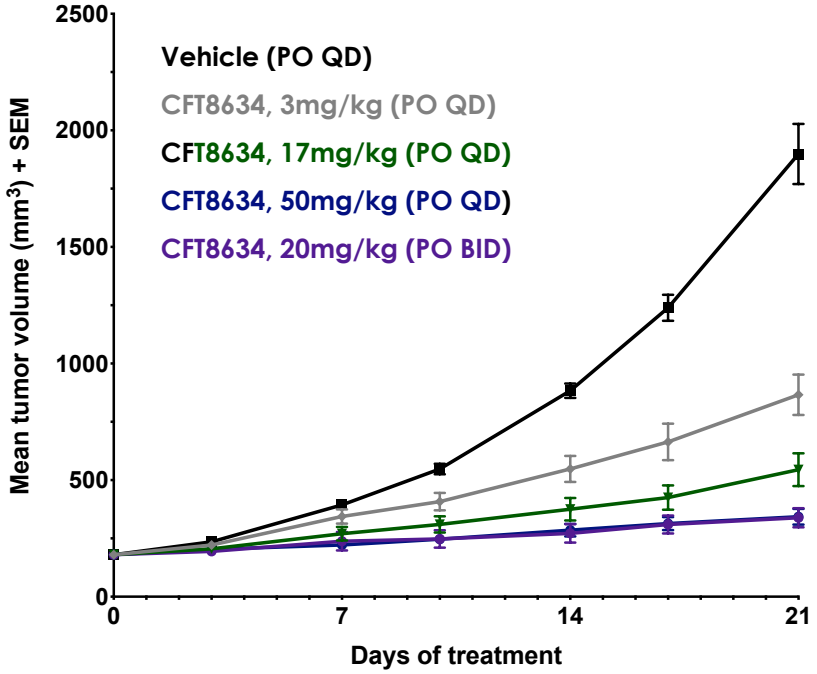
In vivo Activity – Efficacy and Tolerability in Synovial Sarcoma

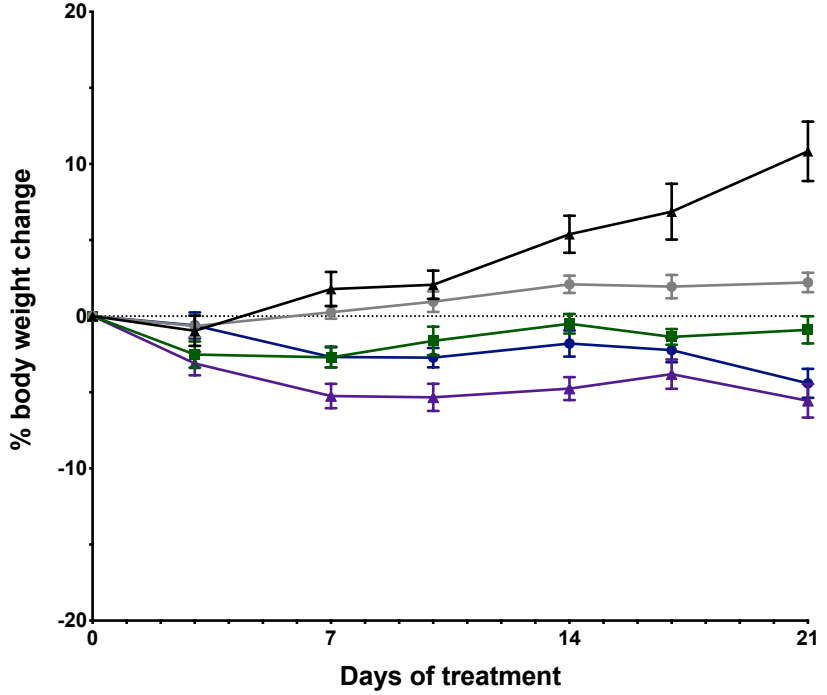
Efficacy

Synovial Sarcoma CDX (Yamato-SS)



Tolerability

Synovial Sarcoma CDX (Yamato-SS)



CFT8634 demonstrates dose dependent efficacy in synovial sarcoma and is well tolerated

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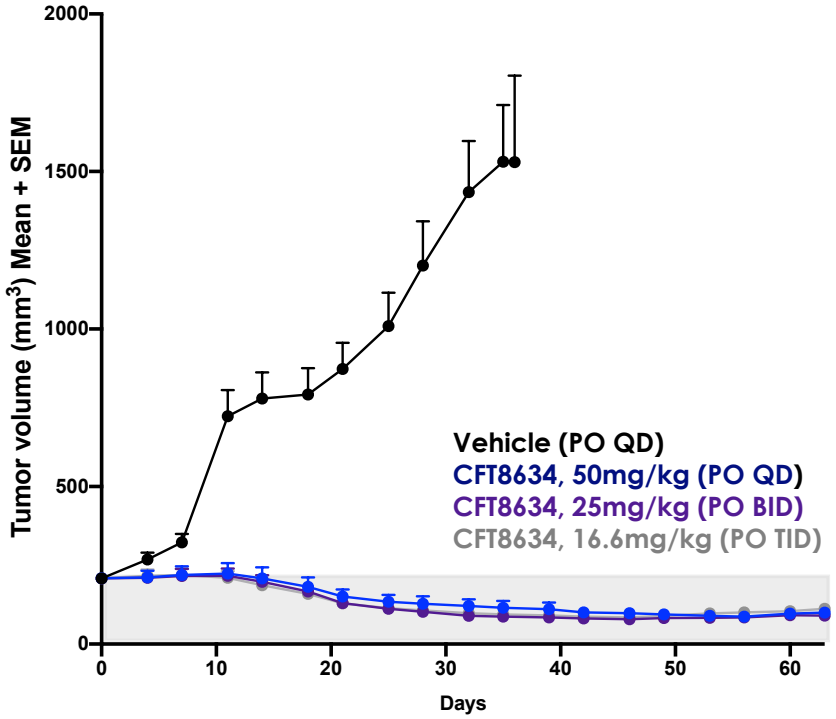
In vivo Activity – Efficacy and Tolerability in Synovial Sarcoma

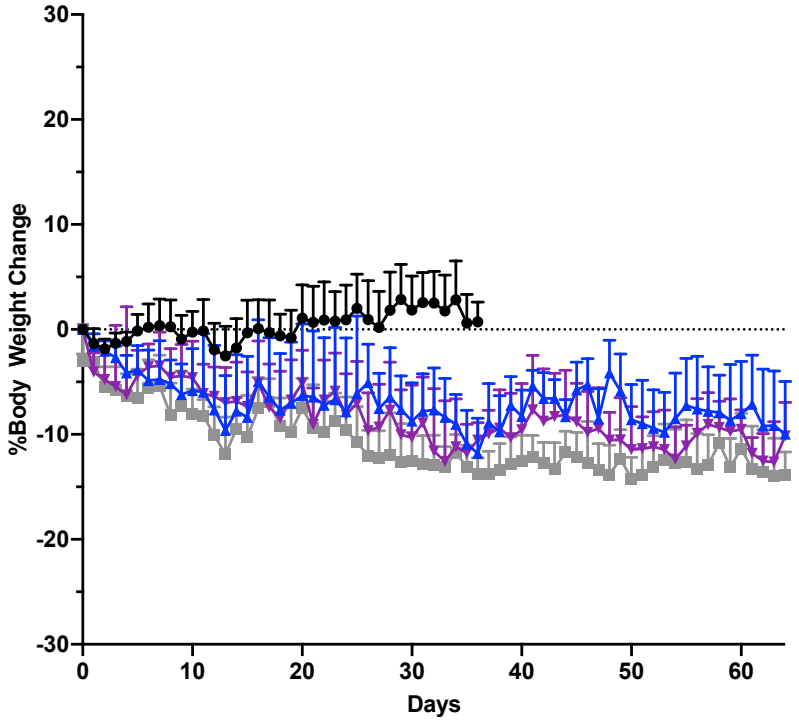
Efficacy

Synovial Sarcoma PDX (SA13412)



Tolerability

Synovial Sarcoma PDX (SA13412)



CFT8634 is efficacious (durable, regressions) in an adult PDX model of synovial sarcoma

SA13412 PDX: Pretreated 22YO female w/ metastatic, multifocal synovial sarcoma in right upper lobe lung; SS18/SSX fusion positive

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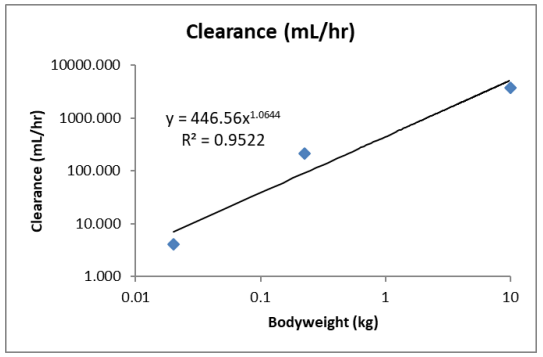
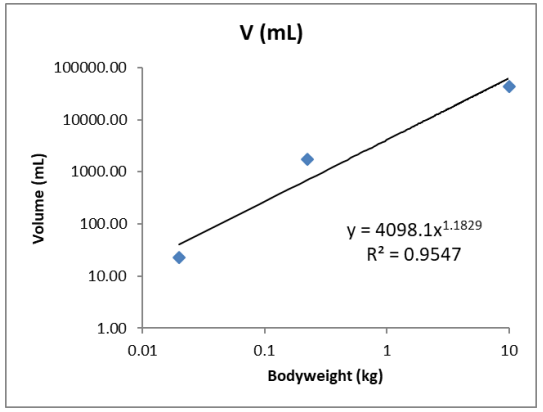
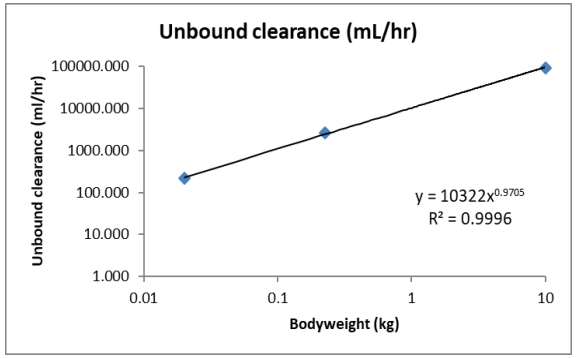
Cross-species PK Profiles

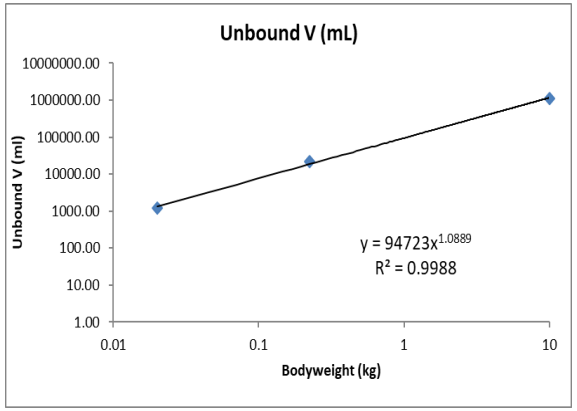
Clearance





Volume





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

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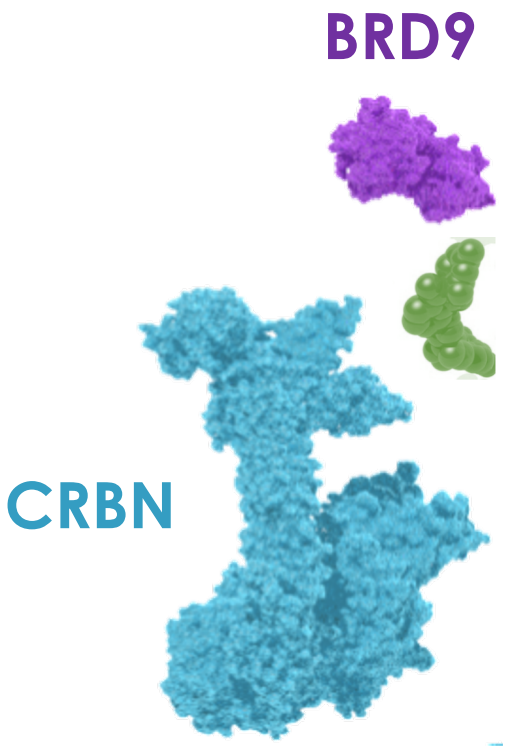
Opportunity to Develop a First and Best-in-class BRD9 Degrader



CFT8634

CFT7503 (racemate)

- 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 an effective therapeutic agent with applicability across SMARCB1 deleted cancers
Synovial sarcoma, Malignant Rhabdoid Tumor, Epithelioid sarcoma

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Thank you