The Discovery and Characterization of CFT8634:
A Potent and Selective Degrader of BRD9 for the Treatment of SMARCB1-Perturbed Cancers


C4 Therapeutics, Inc
Watertown, MA USA
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\textsuperscript{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\textsuperscript{3}

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

Defined Patient Population\textsuperscript{a}

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

\textsuperscript{a} Patient figures represent estimated U.S. annual incidence. SS, synovial sarcoma.

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

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

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

Malignant Rhabdoid Tumor
Homozygous SMARCB1 deletion

RT, rhabdoid tumor.

Ternary Complex Analysis Suggests Linker Excision is Possible

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
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
Linker Excision & Properties Tuning Results in Encouraging Oral Bioavailability

![Chemical structures with pKa 7.9](image)

<table>
<thead>
<tr>
<th></th>
<th>Compound 2</th>
<th>Compound 3</th>
<th>Compound 4</th>
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<tbody>
<tr>
<td>BRD9 DC&lt;sub&gt;50&lt;/sub&gt; / E&lt;sub&gt;max&lt;/sub&gt; [2 h]</td>
<td>5 nM / 5%</td>
<td>4 nM / 6%</td>
<td>11 nM / 5%</td>
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<tr>
<td>LogD&lt;sub&gt;7.4&lt;/sub&gt;</td>
<td>1.2</td>
<td>2.5</td>
<td>3.5</td>
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<tr>
<td>TPSA</td>
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<td>▼ 137</td>
<td>▼ 107</td>
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<td>H-Bond Donors</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Most Basic pKa [calc]</td>
<td>7.9 ▼ 5.8</td>
<td>7.7</td>
<td></td>
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<tr>
<td>Mouse F [%]</td>
<td>&lt;1</td>
<td>21</td>
<td>100</td>
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TPSA, topological polar surface area. C4 Therapeutics data on file.
Further Refinement Leads to CFT8634

<table>
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<tr>
<th></th>
<th>Compound 4</th>
<th>CFT8634</th>
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</thead>
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<tr>
<td>BRD9 DC&lt;sub&gt;50&lt;/sub&gt; / E&lt;sub&gt;max&lt;/sub&gt; [2 h]</td>
<td>11 nM / 5%</td>
<td>3 nM / 4%</td>
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<td>▼ 2.7</td>
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<tr>
<td>CL&lt;sub&gt;obs&lt;/sub&gt; Mouse / Rat [mL/min/kg]</td>
<td>30 / 74</td>
<td>6 / 22</td>
</tr>
<tr>
<td>F % Mouse / Rat</td>
<td>100 / 48</td>
<td>74 / 83</td>
</tr>
<tr>
<td>Cyp Inhibition 3A4 / 2C19 / 2D6 [μM]</td>
<td>5.6 / 1.9 / &gt;30</td>
<td>27 / &gt;30 / &gt;30</td>
</tr>
<tr>
<td>hERG Inhibition [μM]</td>
<td>7.5</td>
<td>&gt;30</td>
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</table>

Cyp, cytochrome P450; hERG, human ether-à-go-go-related gene.
C4 Therapeutics data on file.
Selectivity Rationalized with Ternary Complex Models

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

**Compound 2**

**CFT8634**

**BRD9**

**CRBN**

**ZA-loop**

- **BRD9** $D_{50}/E_{\text{max}} = 5$ nM / 5%
- **BRD4** $D_{50}/E_{\text{max}} = 130$ nM / 30%

- **BRD9** $D_{50}/E_{\text{max}} = 3$ nM / 4%
- **BRD4** $D_{50}/E_{\text{max}} = >10$ µM / 75%
**In vitro: CFT-8634 is a Highly Selective BRD9 Degrader**

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

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

Bromodomain Binding Specificity

Global Proteomic Evaluation

**BromoScan®**

100 nM CFT8634

BRD9-HiBiT

DC_{50} = 2.7 nM

E_{max} = 5%

CFT8634 (100 nM, 4 h)

HSSYII cell line

- 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

**Endogenous BRD9 Degradation**

**Yamato-SS**
- Synovial sarcoma [SS18-SSX1 fusion]

**SW982**
- Soft-tissue sarcoma [BAF wildtype]

**Single Dose, Long-Term Growth Evaluation**

- **Yamato-SS**
  - **CFT8634**
    - DMSO
    - 10,000 nM
    - 1,000 nM
    - 316 nM
    - 100 nM
    - 32 nM
    - 10 nM
  - **BRD9i**
    - DMSO
    - 10,000 nM
    - 1,000 nM
    - 316 nM
    - 100 nM
    - 32 nM
    - 10 nM

- **SW982**
  - **CFT8634**
    - DMSO
    - 10,000 nM
    - 1,000 nM
    - 316 nM
    - 100 nM
    - 32 nM
    - 10 nM
  - **BRD9i**
    - DMSO
    - 10,000 nM
    - 1,000 nM
    - 316 nM
    - 100 nM
    - 32 nM
    - 10 nM

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

Efficacy

Time (days)

Vehcle (PO QD)  CFT8634 10 mg/kg (PO QD)
CFT8634 1 mg/kg (PO QD)  CFT8634 30 mg/kg (PO QD)
CFT8634 3 mg/kg (PO QD)  CFT8634 50 mg/kg (PO QD)

PD

Percent of BRD9 Remaining

Time (hours)

Vehicle  4  24
0  25  50
75  100  125

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

PDX 310
Synovial Sarcoma Harboring SS18-SSX2

Efficacy

Time (days)

Vehicle (PO QD)  CFT8634 10 mg/kg (PO QD)
CFT8634 1 mg/kg (PO QD)  CFT8634 30 mg/kg (PO QD)
CFT8634 3 mg/kg (PO QD)  CFT8634 50 mg/kg (PO QD)

PO, by mouth; QD, once daily; PD, pharmacodynamics
C4 Therapeutics data on file.
Durable Response Observed in a PDX Model of Synovial Sarcoma

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

Durable Tumor Regression in PDX SA13412

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