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ANNUAL MEETING 2022 New Orleans
APRIL 8-13, 2022 • #AACR22

The Discovery and Characterization of CFT7455:

A Potent and Selective Degrader of IKZF1/3 for the Treatment of Relapsed/Refractory Multiple Myeloma

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C4 Therapeutics, Inc
Watertown, MA USA

Disclosure Information

James A. Henderson, 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.

CFT7455: Potent Small Molecule IKZF1/3 Degrader with Enhanced Catalytic & Pharmacologic Properties

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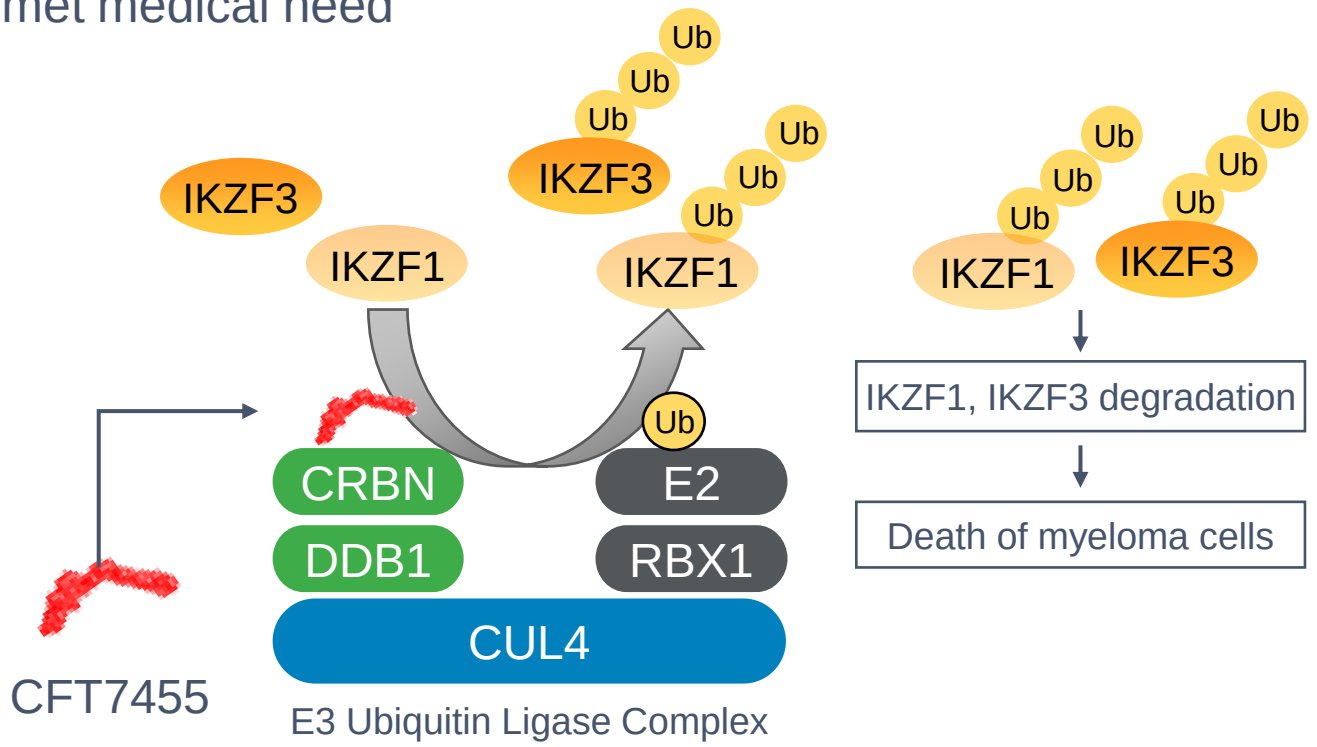
- IKZF1/3 are transcription factors required for cancer cell growth and survival in multiple myeloma (MM)
- IKZF1/3 degrading IMiDs are widely used in MM treatment (lenalidomide, pomalidomide)
- Relapsed/refractory MM remains a high unmet medical need

Goal: Develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC) with these properties:

- Class-leading catalytic activity to enable potent, rapid, and deep target degradation
- High binding affinity to overcome IMiD resistance
- Selective to reduce off-target liabilities
- Pharmacologic profile that enables sustained IKZF1/3 degradation

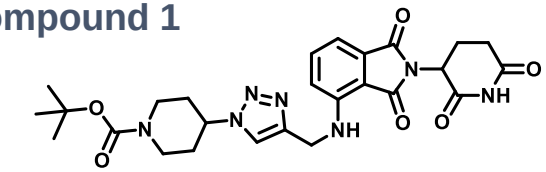


CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; IMiD, immunomodulatory imide drug; monoDAC, monofunctional degradation activating compound; MM, multiple myeloma; RBX1, ring box protein 1; Ub, ubiquitin.

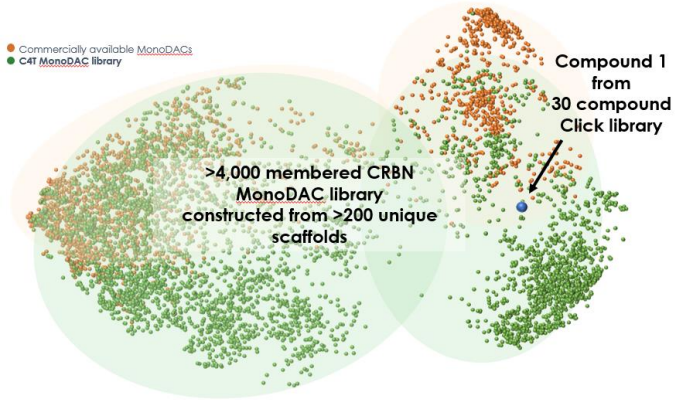
IKZF1/3 Degrader Lead Derived from MonoDAC Library Hit

Potent Hit from MonoDAC Library

Compound 1

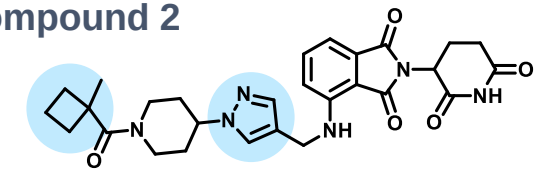


IKZF1 DC_{50}, E_{max} @ 6 hr = 16 nM,16% (HiBiT H929)

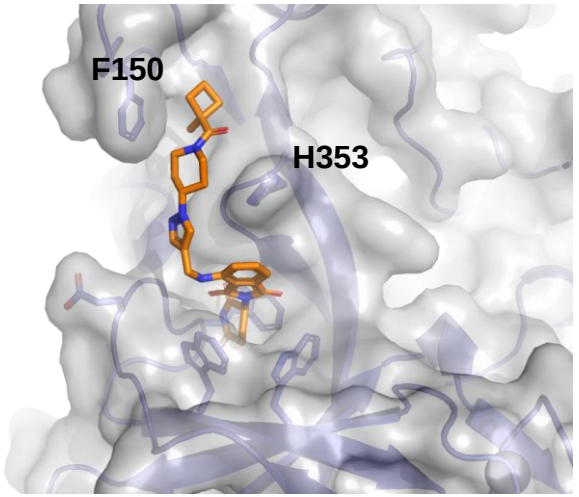


Improvement Using SBDD

Compound 2

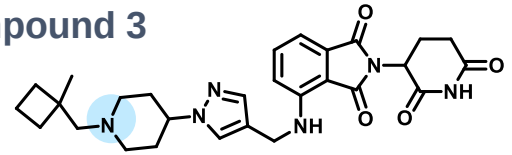


6 hr = 1 nM, 13%



PK & In Vivo Screening

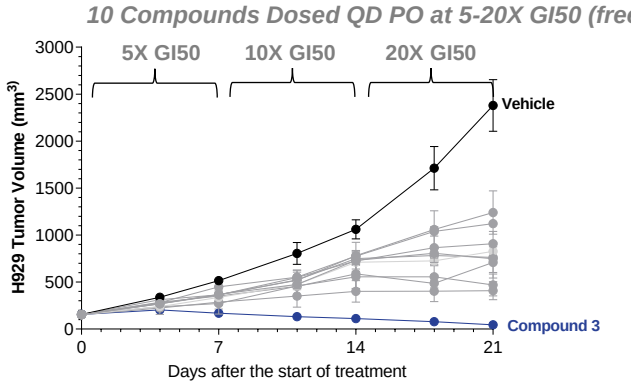
Compound 3



6 hr = 0.6 nM, 12%
1.5 hr = 4.2 nM, 25%

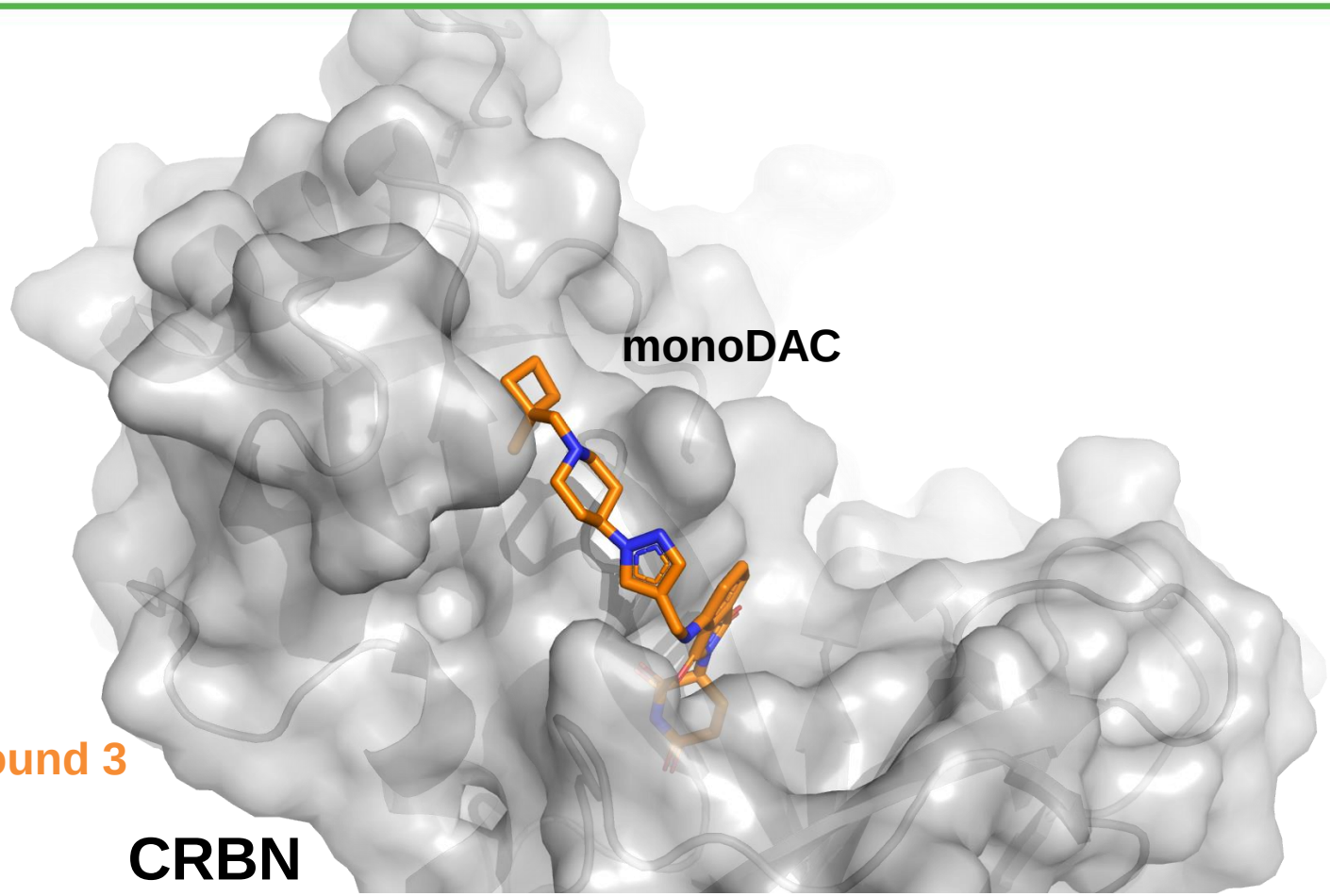
Goal >10x Increase

Screening Efficacy in H929 Xenografts



IKZF1/3, Ikaros family zinc finger proteins 1 and 3; HiBiT; high affinity bioluminescent tag; monoDAC, monofunctional degradation activating compound; PK, pharmacokinetics; SBDD, structure-based drug design.

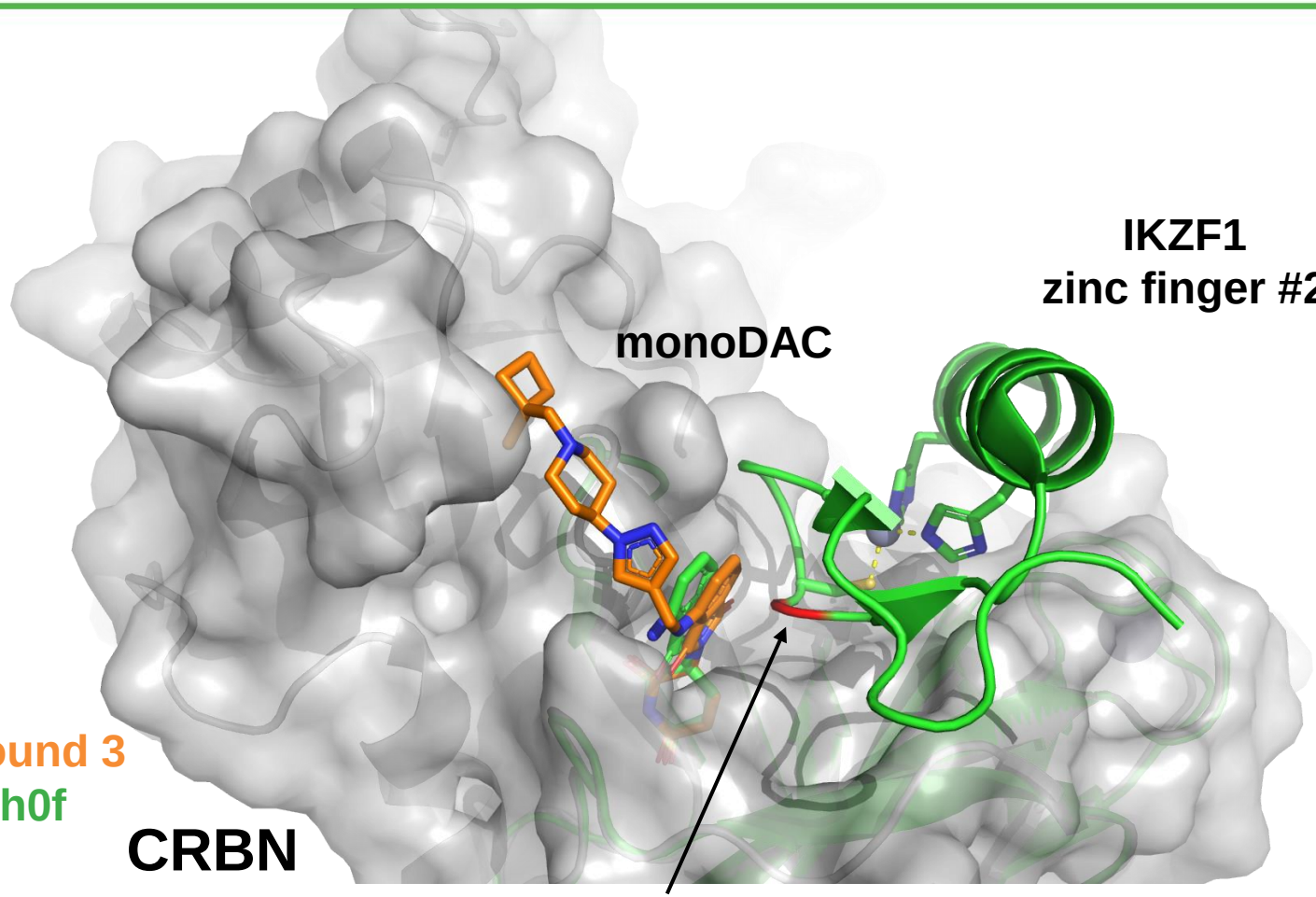
Need for Speed: Structural Biology Highlights Areas for Chemistry Exploration



- The monoDAC degrader binds to CRBN and modulates the surface to accommodate an interaction with neosubstrate

CRBN, cereblon; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; monoDAC, monofunctional degradation activating compound; PDB: 6h0f, pomalidomide CRBN complex bound to IKZF1(ZF2).
Sievers et al. *Science.* 2018:(2);362(6414):eaat0572. doi:10.1126/science.aat0572

Need for Speed: Structural Biology Highlights Areas for Chemistry Exploration



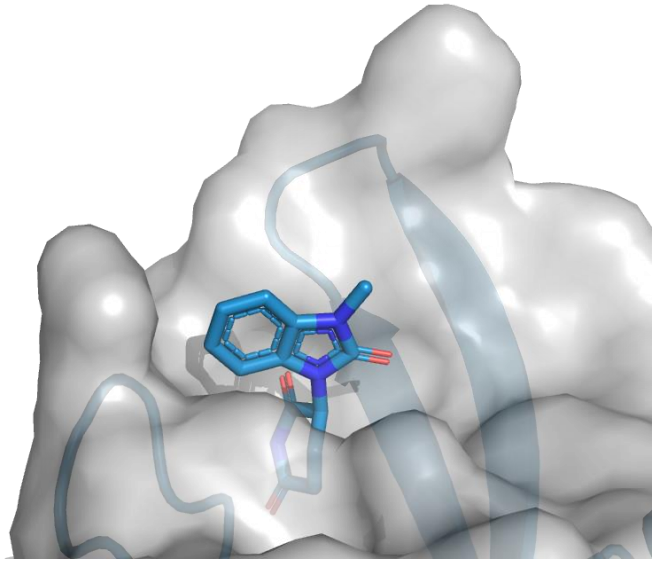
- The monoDAC degrader binds to CRBN and modulates the surface to accommodate an interaction with neosubstrate
- The second zinc finger of IKZF1 lands on top of the CRBN-monoDAC degrader complex
- The β-hairpin glycine interaction with the monoDAC is critical for IKZF1/3 degradation

CRBN, cereblon; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; monoDAC, monofunctional degradation activating compound; PDB: 6h0f, pomalidomide CRBN complex bound to IKZF1(ZF2).
Sievers et al. *Science.* 2018:(2);362(6414):eaat0572. doi:10.1126/science.aat0572

CRBN X-Ray Structures Inspire the Design of the Tricyclic Core

Benzoimidazolone

C4T unpublished
1.17 Å

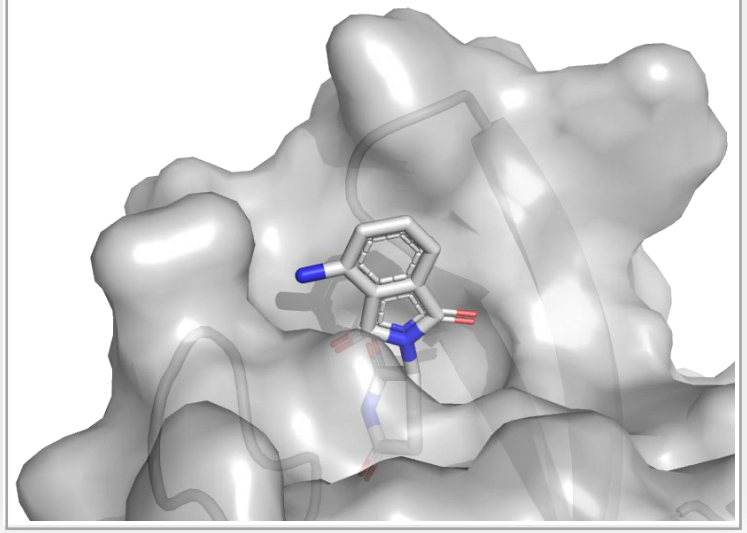


Compound 4
CRBN FP K_D = 830 nM

IKZF1▼

Pomalidomide

PDB 6h0f



Pomalidomide
K_D = 1600 nM

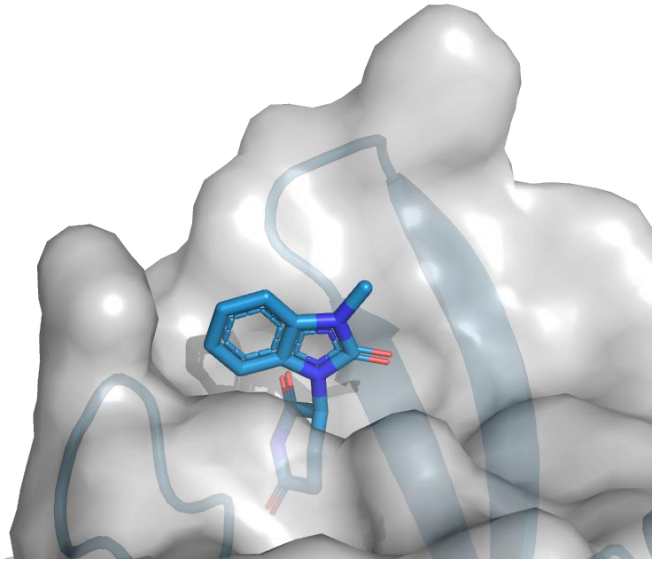
IKZF1▼

CRBN, cereblon; FP, fluorescence polarization; IKZF1, Ikaros family zinc finger protein 1.

CRBN X-Ray Structures Inspire the Design of the Tricyclic Core

Benzoimidazolone

C4T unpublished
1.17 Å

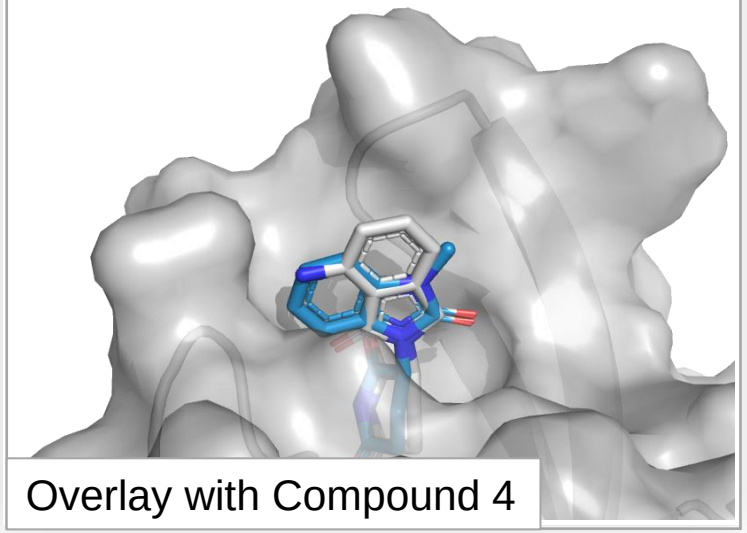


Compound 4
CRBN FP K_D = 830 nM

IKZF1▼

Pomalidomide

PDB 6h0f



Overlay with Compound 4

Pomalidomide
K_D = 1600 nM

IKZF1▼

CRBN, cereblon; FP, fluorescence polarization; IKZF1, Ikaros family zinc finger protein 1.

CRBN X-Ray Structures Inspire the Design of the Tricyclic Core

Benzoimidazolone

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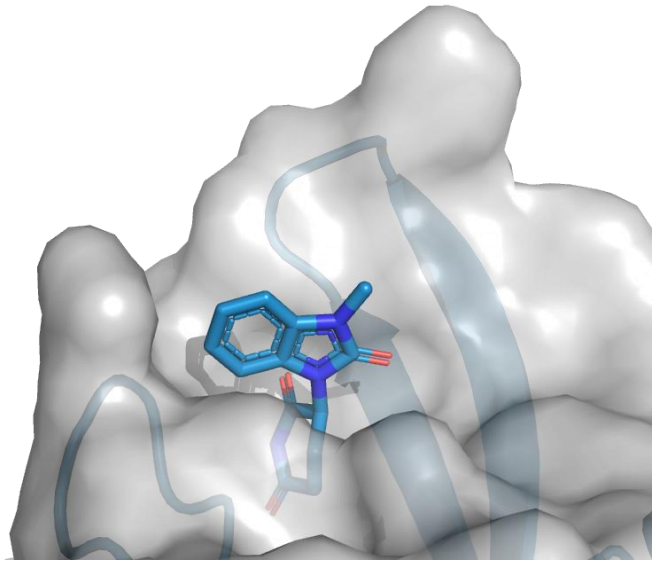
1.17 Å

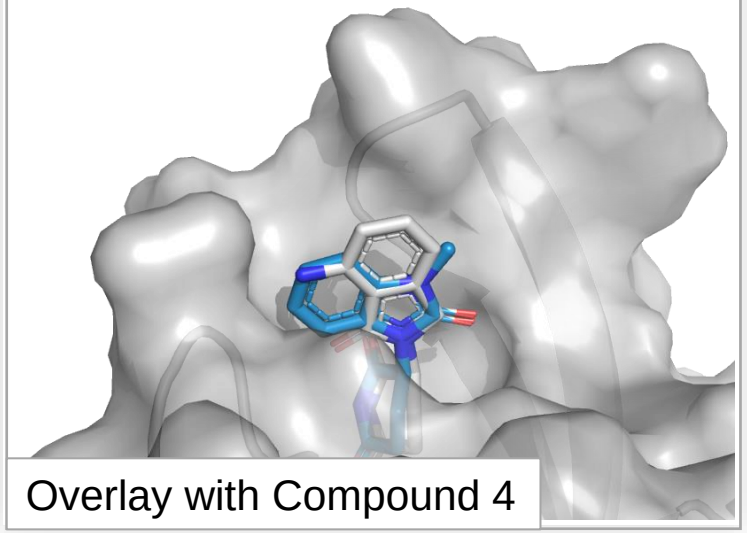


Compound 4
CRBN FP K_D = 830 nM

IKZF1▼

Pomalidomide

PDB 6h0f



Overlay with Compound 4

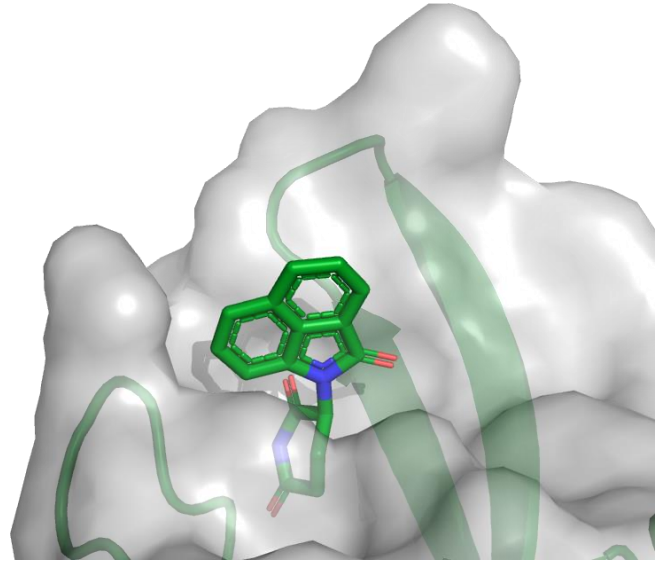
Pomalidomide
K_D = 1600 nM

IKZF1▼

50-fold affinity increase

Benzoisoindolinone

C4T unpublished
1.06 Å



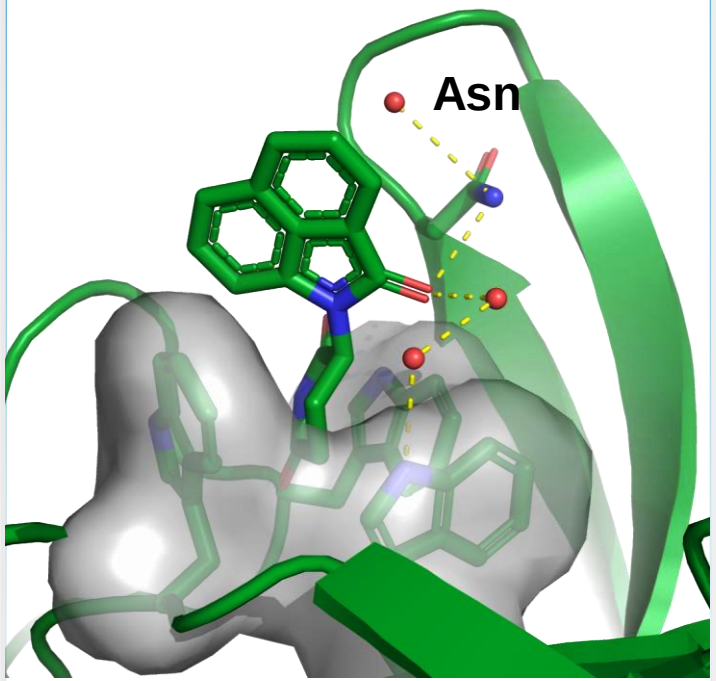
Compound 5
K_D = 34 nM

IKZF1▼

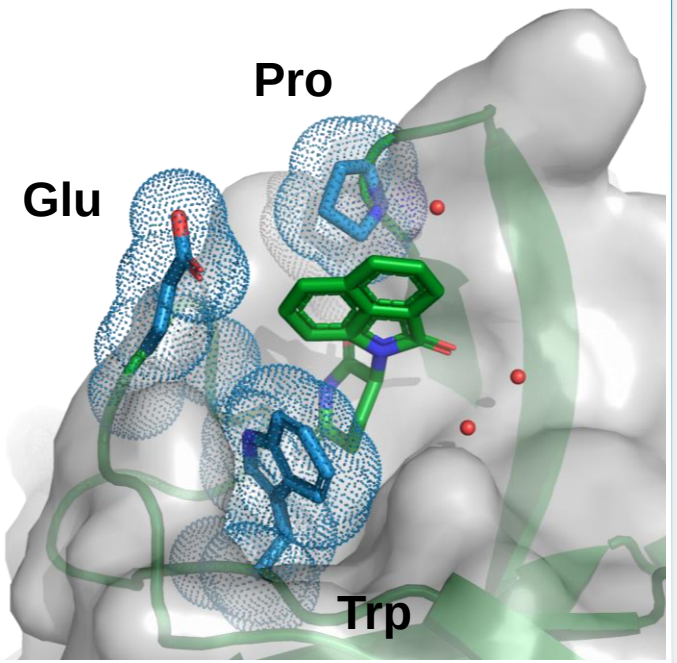
CRBN, cereblon; FP, fluorescence polarization; IKZF1, Ikaros family zinc finger protein 1.

Exploring CRBN Interactions with the Potent Tricyclic Core

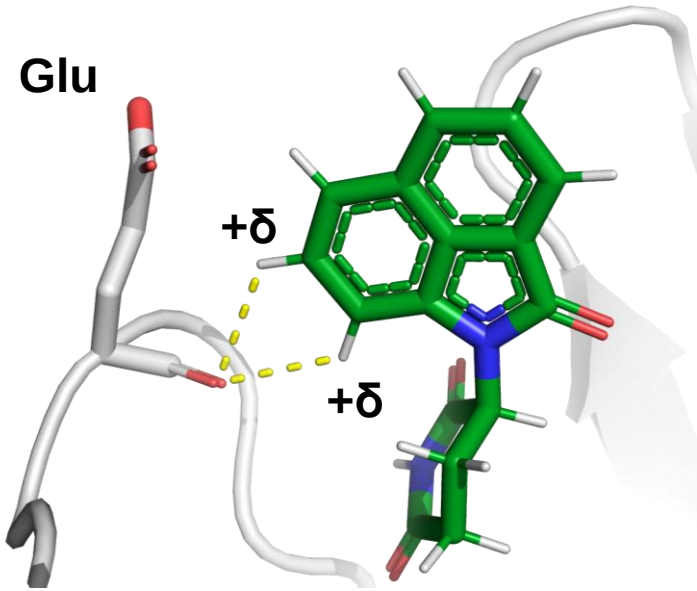
Tri-Trp Pocket Interactions



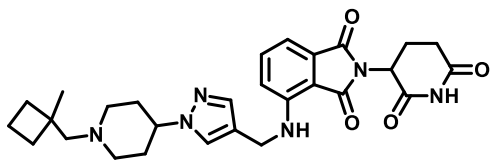
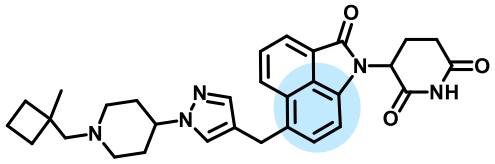
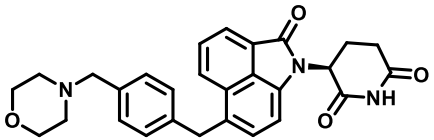
Increased Hydrophobic Contacts with CRBN



+δ Aromatic C-H Interactions with Backbone Carbonyl



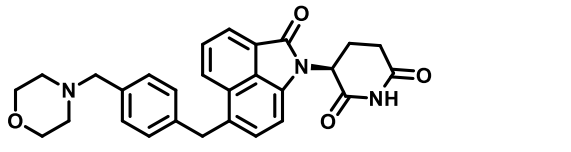
From First Generation Lead to CFT7455

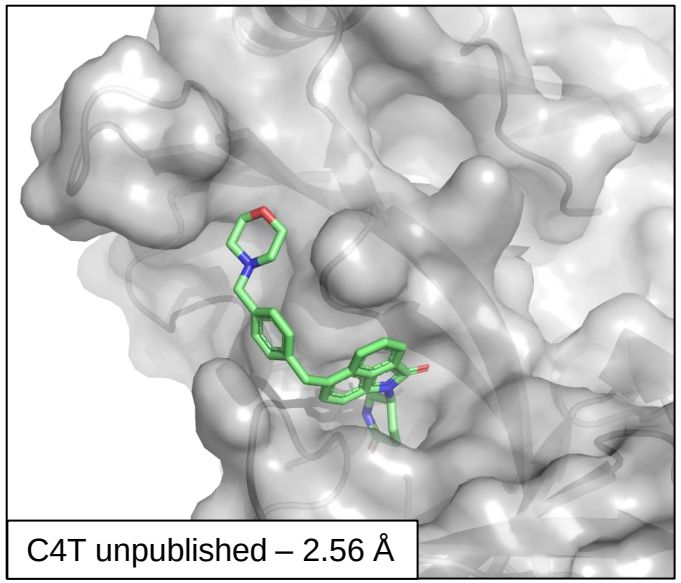
			
	Compound 3	**Compound 6**	**CFT7455**
CRBN IC_{50} (293T NanoBRET)	9 nM	0.3 nM	0.4 nM
IKZF1 DC_{50}, E_{max} **(1.5 hr)** H929 HiBiT	4.2 nM, 25%	0.3 nM, 22%	0.17 nM, 20%
H929 IC_{50} (96 hr)	2.3 nM	0.009 nM	0.07 nM
PPB mouse/human (% bound)	94.3 / 96.2	97.2 / 98.6	93.4 / 94.6
Mouse Vd_ss, T1/2, %F	6.2 L/kg, 1.7 h, 9%	2.9 L/kg, 1.3 h, 23%	5.6 L/kg, 2.0 h, 48%

CRBN, cereblon; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; monoDAC, monofunctional degradation activating compound; PPB, plasma protein binding
C4 Therapeutics data on file.

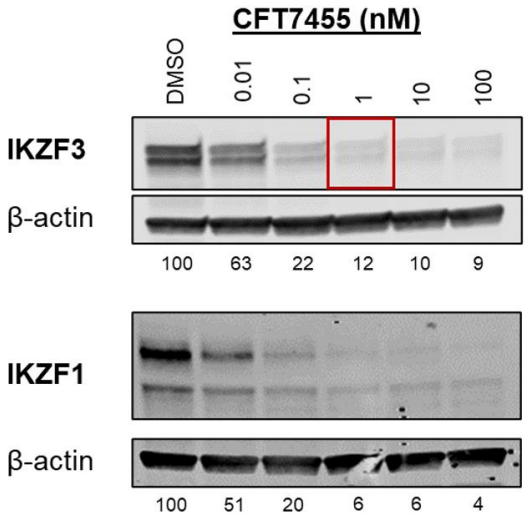
CFT7455: Potent, Rapid and Selective Degradation of IKZF1/3

CFT7455



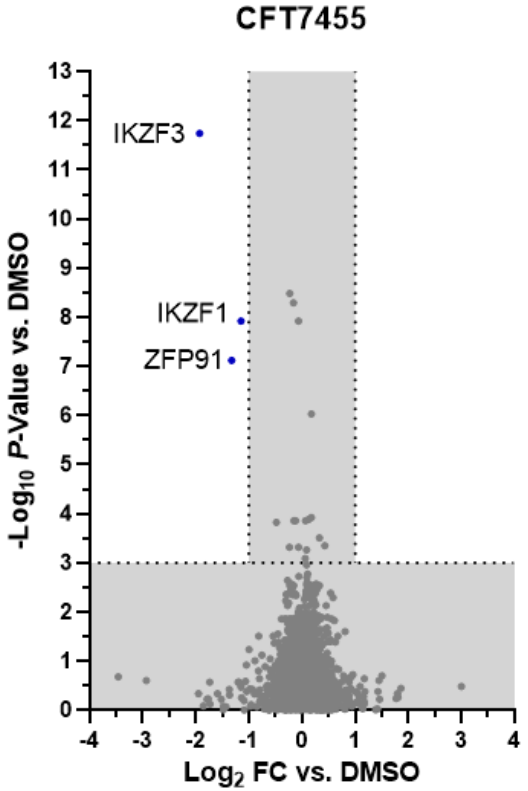


IKZF1/3 Degradation, H929 (4 hr)



H929 cells, 4 hr

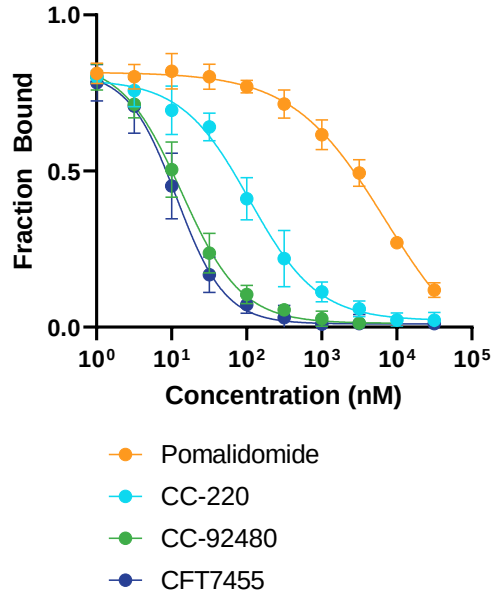
GPE in RPMI-8226, 10 nM (4 hr)



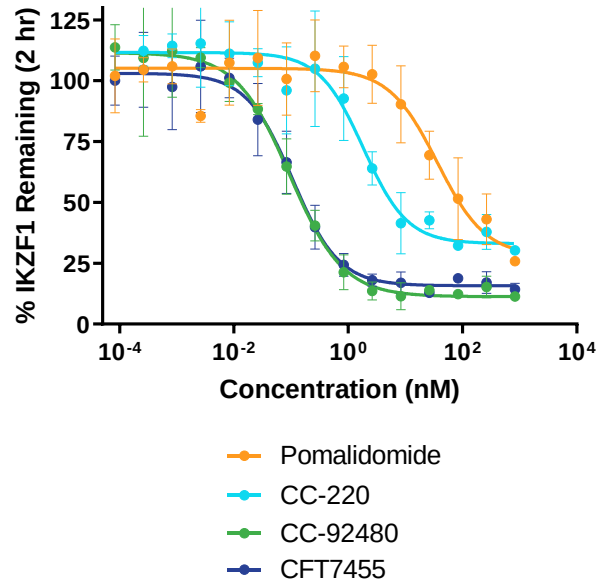
GPE, global proteomics experiment; IKZF1/3, Ikaros family zinc finger proteins 1 and 3.
C4 Therapeutics data on file.

High Catalytic Activity of CFT7455 Improves Anti-Cancer Activity in H929 MM Cells

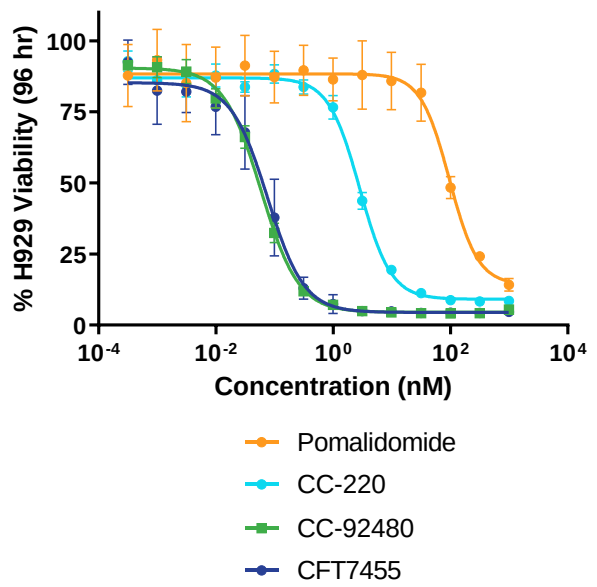
Binding Affinity (FP)



Degradation Potency



MM Cell Viability



Catalytic activity enhancement resulted in >1000-fold improvement in potency vs. Pom*

*POM is an approved IKZF1/3 degrader while CC-220, CC-92480 and CFT7455 are all investigational compounds. Hansen JD, et al. *J Med Chem*. 2020;63(13):6648-6676. Matyskiela ME, et al. *J Med Chem*. 2018;61(2):535-542. IKZF1, Ikaros family zinc finger protein 1; MM, multiple myeloma; FP, fluorescence polarization.
C4 Therapeutics data on file.

CFT7455 Demonstrates High Potency in MM Cell Lines and Xenografts

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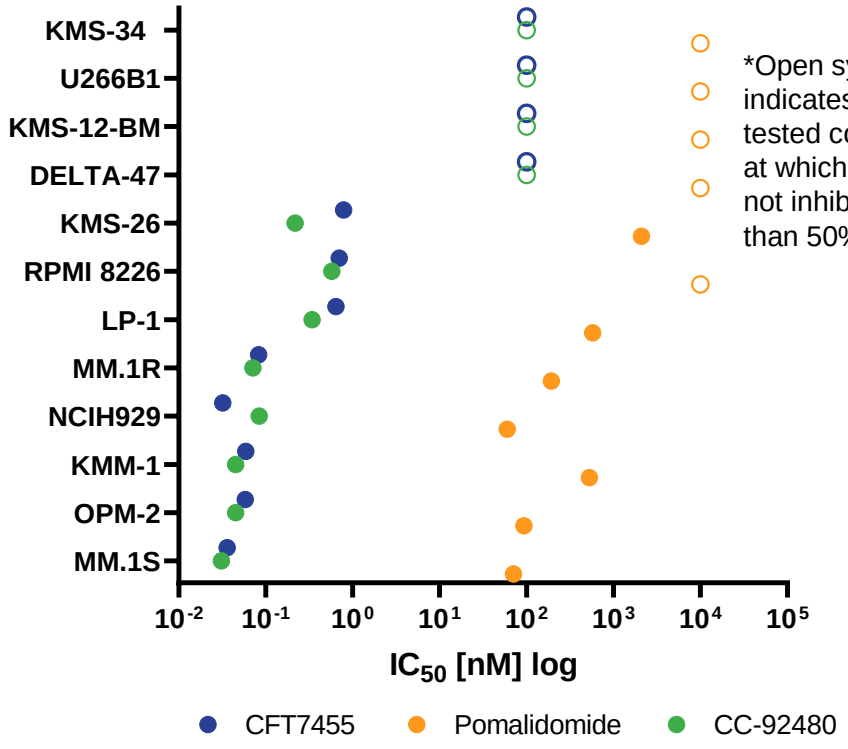
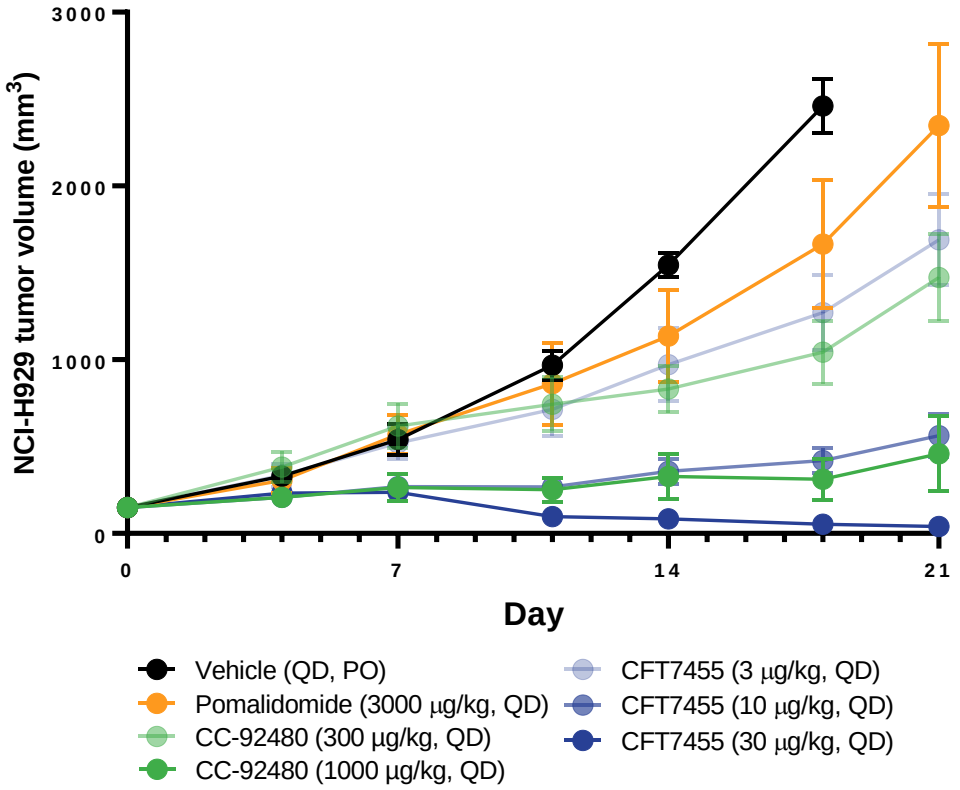
CFT7455 Has Broad Antiproliferative Activity



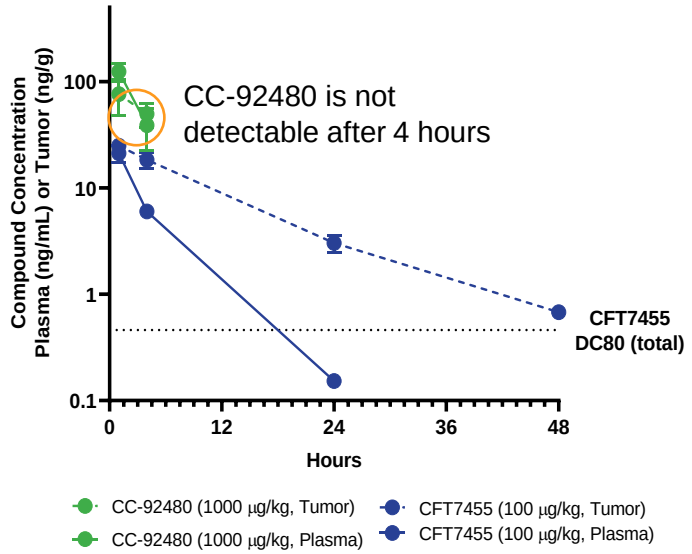
CFT7455 Promotes Durable Tumor Regression



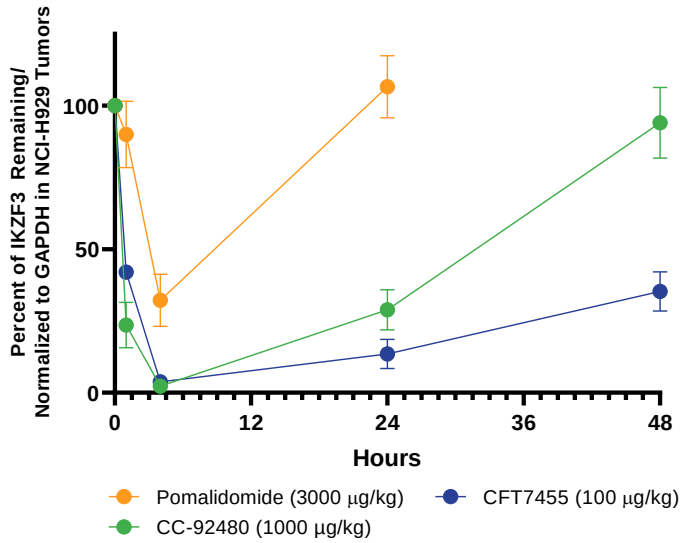
MM, multiple myeloma, QD, once daily.
C4 Therapeutics data on file.

CFT7455 Efficacy Attributed to Durable Tumor PK and IKZF3 PD in NCI-H929 MM Model

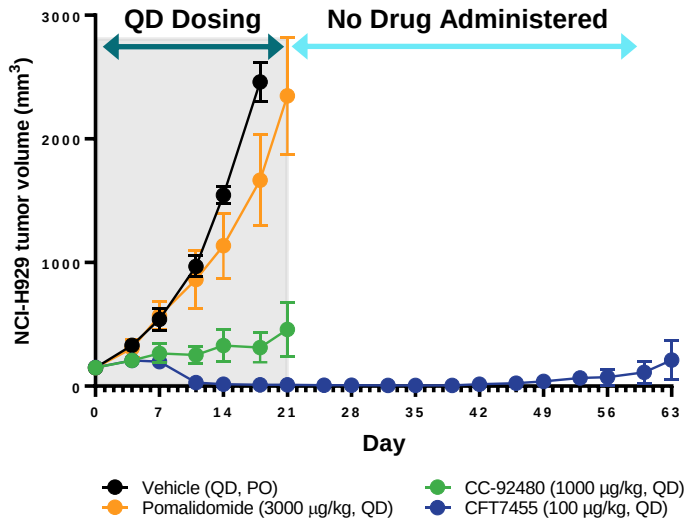
Linear, Durable Tumor PK



48 hr Degradation Kinetics



IKZF3 PD Associated with Efficacy



CFT7455 displays linear and durable tumor PK translating into deep IKZF3 degradation and regression in MM xenograft models

IKZF3, Ikaros family zinc finger protein 3; MM, multiple myeloma; PD, pharmacodynamics; PK, pharmacokinetics, QD; once daily.
C4 Therapeutics data on file.

CFT7455 is Efficacious in MM Models Resistant or Insensitive to IMiDs

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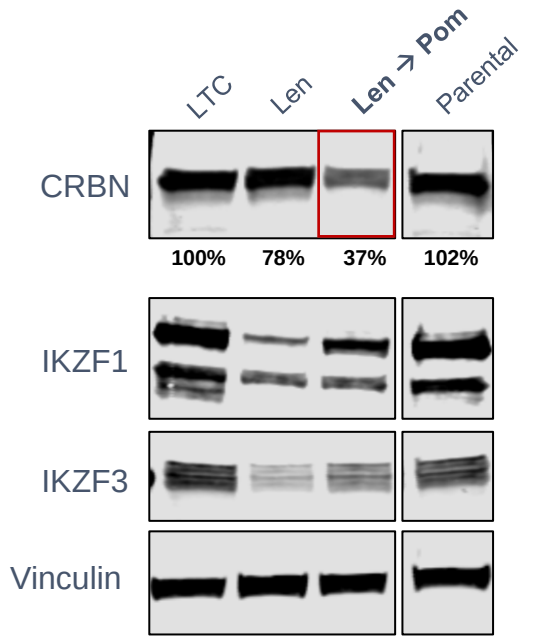
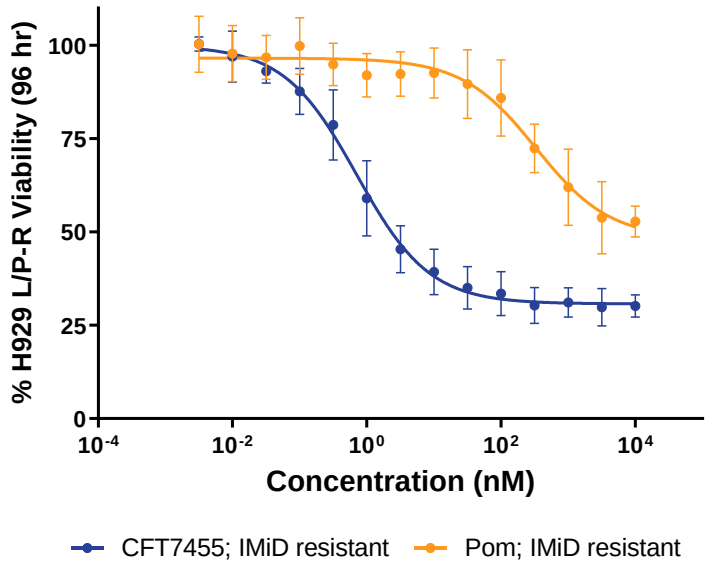
Reduction in CRBN Expression with Chronic IMiD Dosing



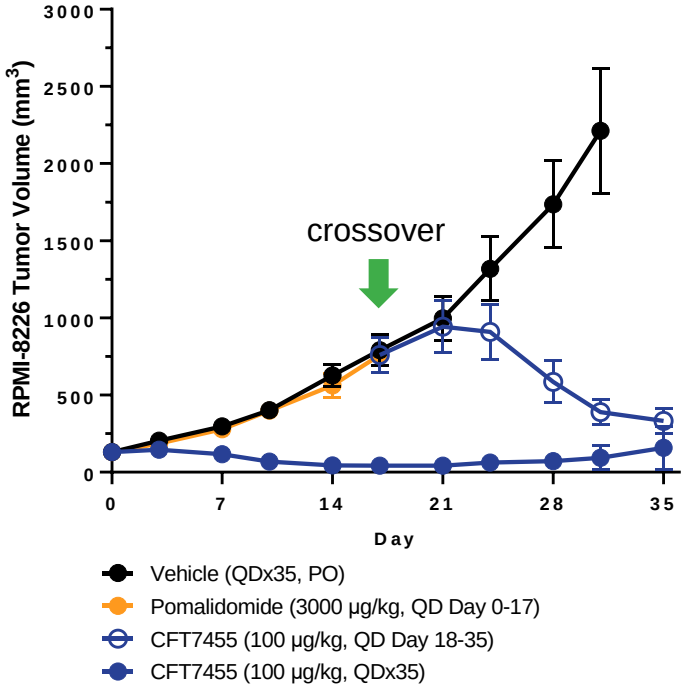
LTC = longterm culture in DMSO
Parental = original, naïve H929 cells

Len, lenalidomide; L/P-R, Len/Pom-Resistant

CFT7455 Retains Activity in Len- & Pom-Resistant MM Cells



CFT7455 Promotes Regression in Tumors Insensitive to Pom



CRBN, cereblon; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; IMiDs, immunomodulatory imide drug; Len; lenalidomide; PO, orally; Pom, pomalidomide; QD, once daily.
C4 Therapeutics data on file.

Summary

- Discovery efforts were aimed at identifying an IKZF1/3 degrader with class-leading activity
- Structure-based design and in vivo screening were employed to discover CFT7455

In vitro data with CFT7455 demonstrated:

- High CRBN binding affinity (K_D = 0.9 nM)
- Rapid, selective, and deep degradation of IKZF1/3 that is associated with apoptosis
- Broad, potent antiproliferative activity in a panel of MM cell lines

In vivo MM models treated with CFT7455 demonstrated:

- Regression in the treatment-naïve H929 MM tumor models at doses ≥10 µg/kg/day
- Durable antitumor responses consistent with long-lived pharmacodynamic activity
- Single-agent efficacy in models unresponsive to approved IMiDs

A Phase 1/2 clinical trial to assess the safety and tolerability of CFT7455 in patients with R/R MM or non-Hodgkin's lymphoma (NCT04756726) is ongoing and early clinical data is presented in poster #CT186

CRBN, cereblon; IKZF1/3, Ikaros family zinc finger proteins 1 and 3; IMiDs, immunomodulatory imide drug; K_D, dissociation constant; MM, multiple myeloma; R/R, relapsing/refractory.

Acknowledgements

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