



Undruggable Leaders Forum Europe

Stewart Fisher

April 13, 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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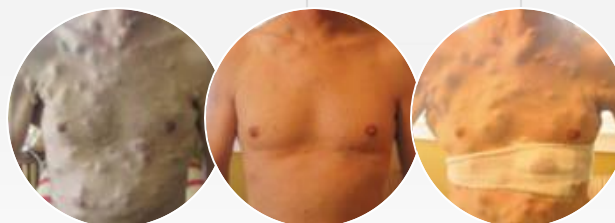
Targeted Protein Degradation Has the Potential to Transform Treatment of Disease



<15%

**Of Human Proteome
Addressable by Small
Molecule Inhibitors**

Substantial opportunity to develop treatments for targets previously considered undruggable



Before

15 weeks

23 weeks

Adapted from Wagle et al, J Clin Oncol, 2011

Cancers become resistant to standard therapies and treatment options are then limited



\$63B

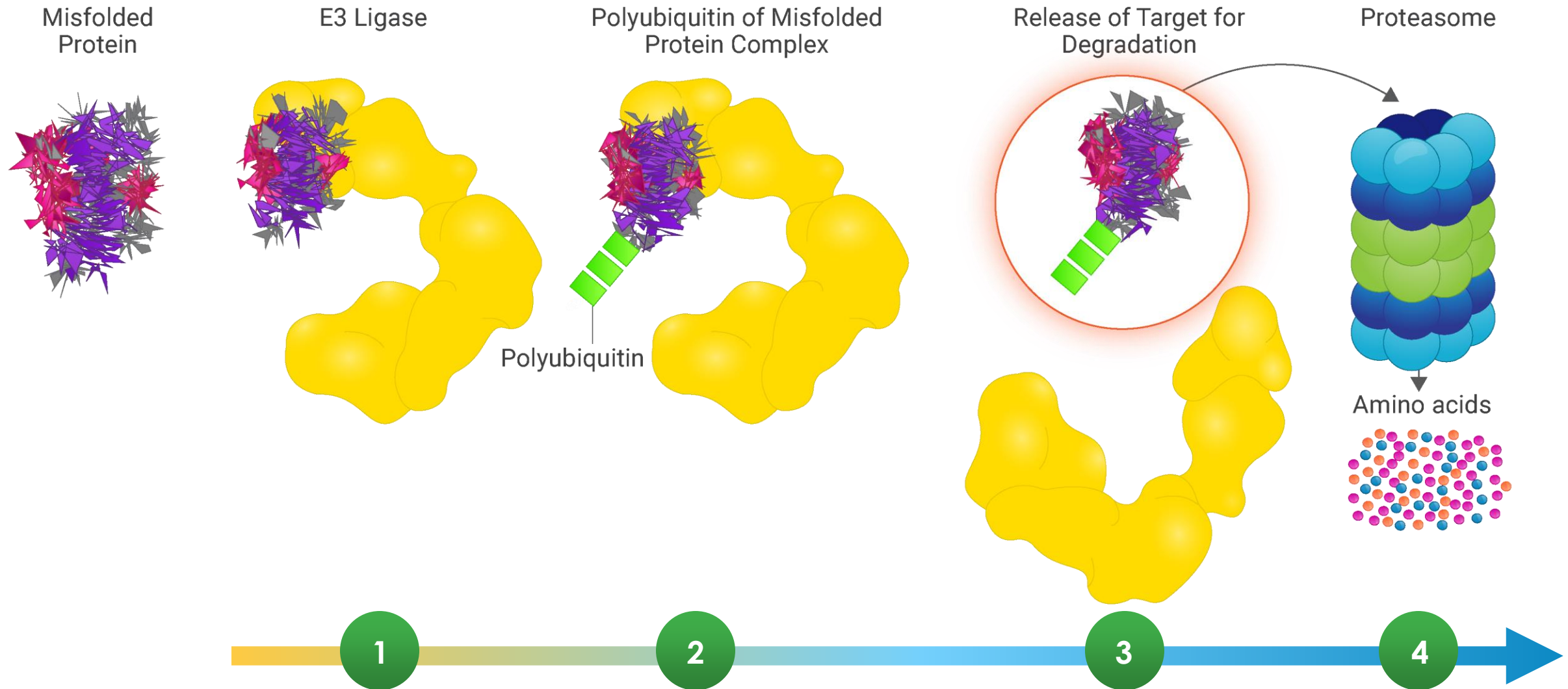
**2018 Global
Revenue**

Oncology small molecule therapies generate significant revenue despite known limitations

Targeted Protein Degradation Has Potential to Drug the Remaining ~85% of the Human Proteome and Overcome Resistance to Existing Inhibitor Medicines

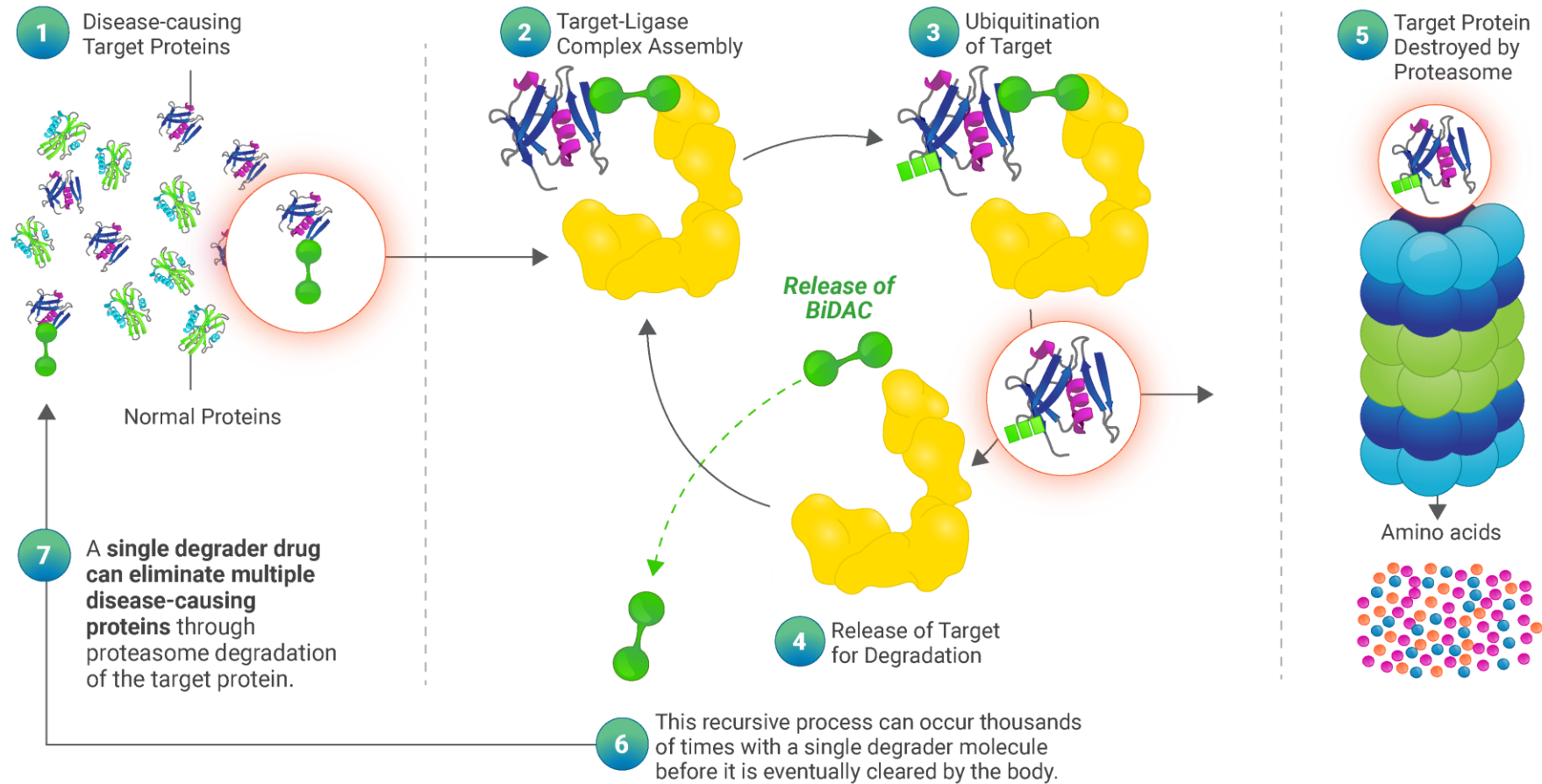
Sources: Hopkins, A., Groom, C. The druggable genome. Nat Rev Drug Discov 1, 727–730 (2002). <https://doi.org/10.1038/nrd892>; "A view on drug resistance in cancer" Nature | Vol 575 | 14 November 2019; Fact.MR: <https://www.factmr.com/report/3747/oncology-small-molecule-drugs-market>

The Human Body Has A Natural Process to Destroy Unwanted Proteins



Targeted Protein Degradation Leverages the Body's Natural Process to Destroy Disease-Causing Proteins

Focus on Overall Catalytic Degradation



Targeted Protein Degradation Offers Fundamental Advantages Over Protein Inhibition

1

Improved Potency

2

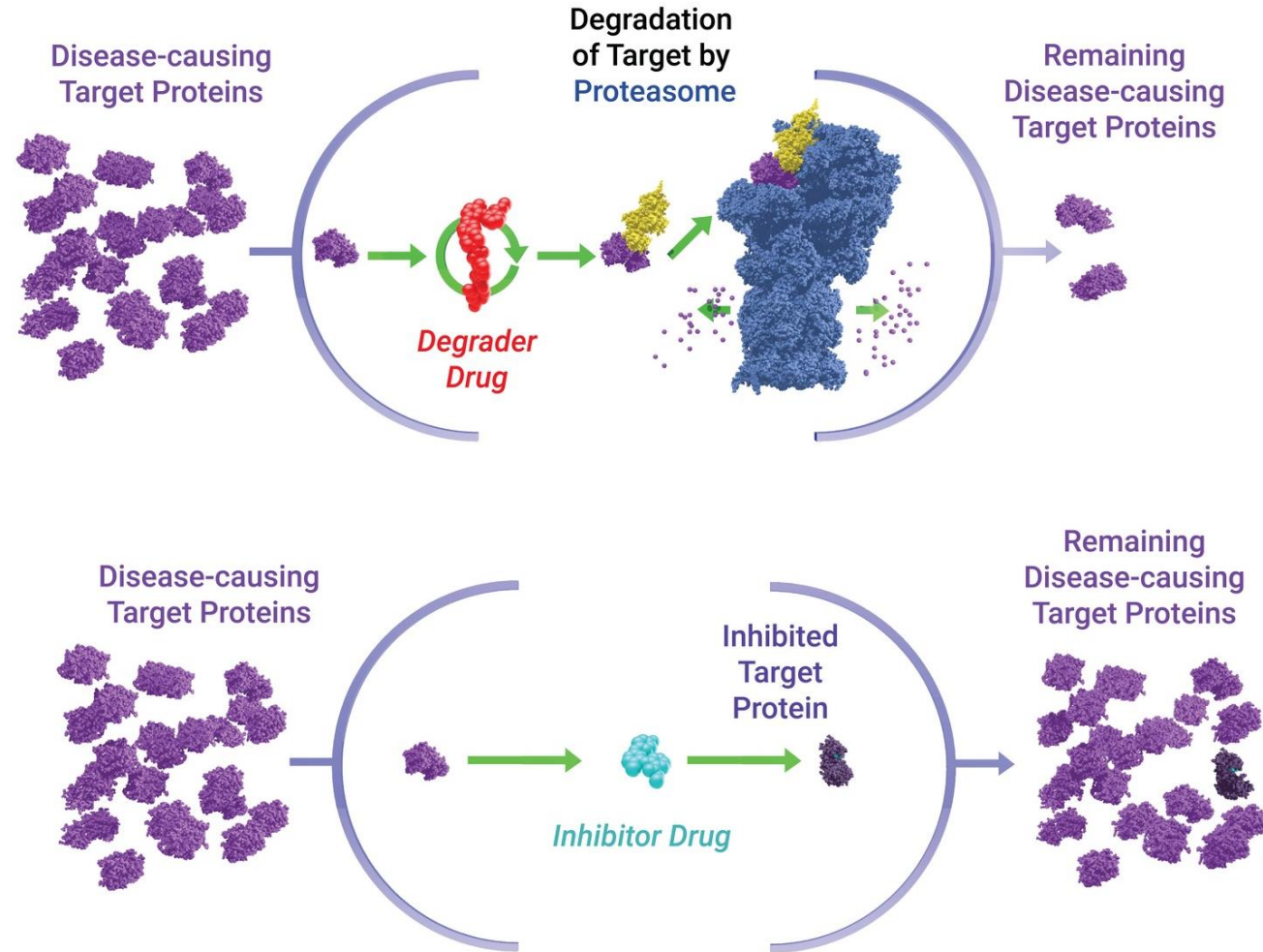
Fast Response

3

High Selectivity

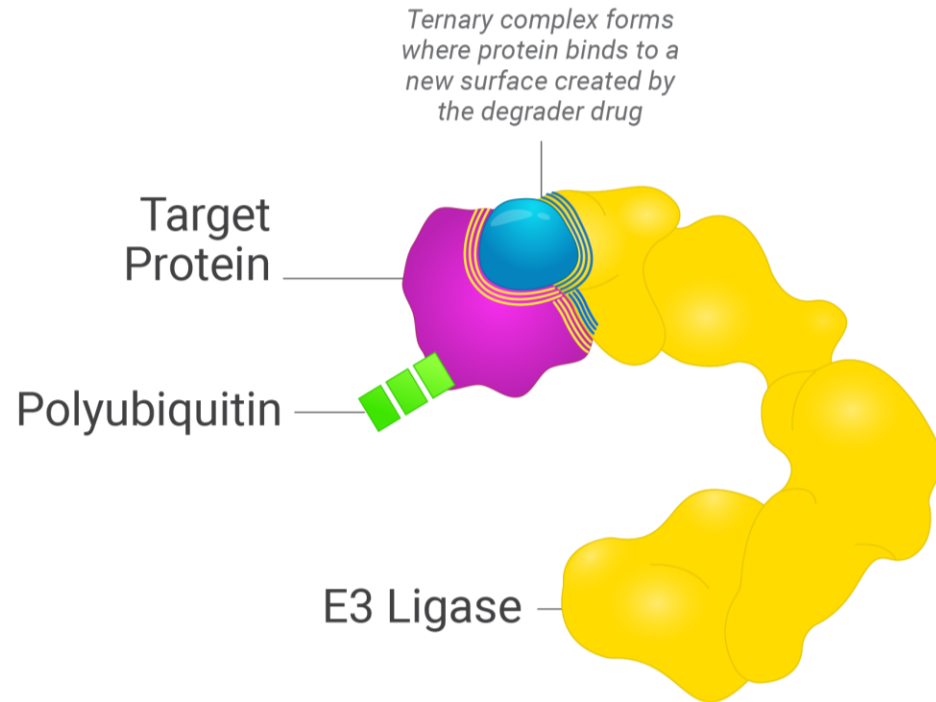
4

Expansive Target Landscape

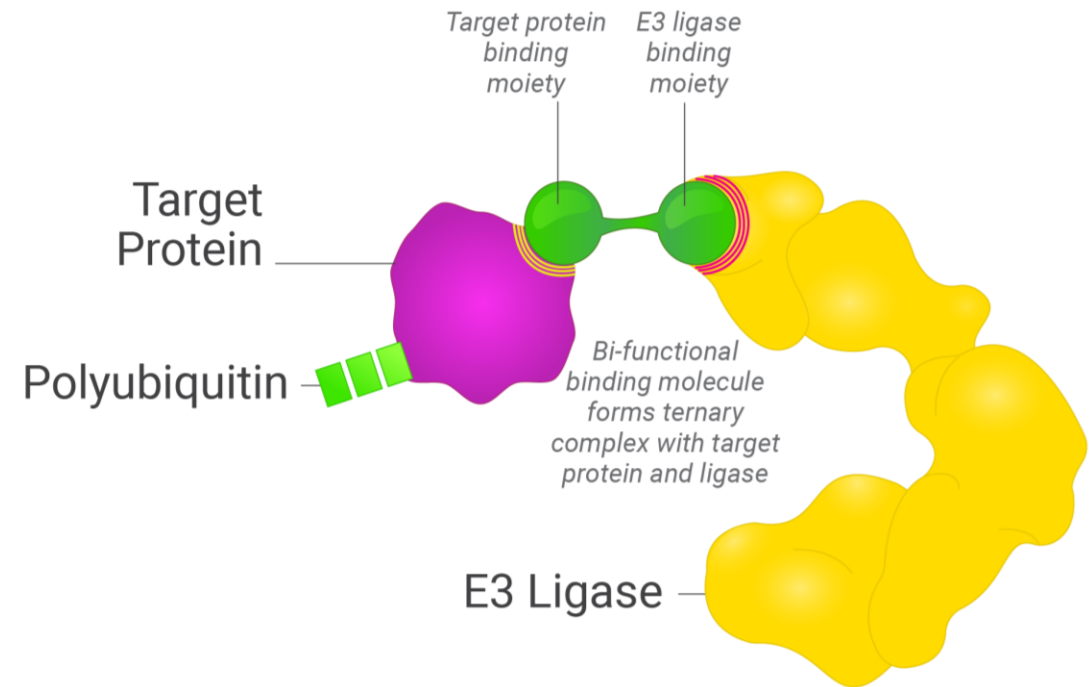


TORPEDO Platform Offers Flexibility to Design MonoDAC and BiDAC Degraders

MonoDAC Degradar



BiDAC Degradar



Flexibility to Address Different Targets with Tailored Approach

TORPEDO Platform Has Delivered a Robust Degradader Pipeline; Four Clinical Programs Expected by End of 2022

Target	Indication(s)	Discovery	Preclinical	Clinical	Ownership
IKZF1/3 (CFT7455)	Multiple Myeloma & Lymphoma				C4 Therapeutics
BRD9 (CFT8634)	Synovial Sarcoma & SMARCB1 Deleted Tumors				C4 Therapeutics
BRAF V600E	Drug-Resistant BRAF mutant Melanoma & NSCLC				C4 Therapeutics
RET	Drug-Resistant RET-Altered Tumors				C4 Therapeutics
EGFR	Drug-Resistant EGFR+ NSCLC				C4 Therapeutics
Transcriptional Control	Undisclosed Solid Tumors				C4 Therapeutics
Cancer Signaling	Undisclosed Cancers				C4 Therapeutics
Transcriptional Control	Undisclosed Liquid Tumors				C4 Therapeutics
Cancer Signaling	Undisclosed Solid Tumors				C4 Therapeutics

Nine Additional Undisclosed Collaborator Programs in Discovery

Three Strategic Target Platform Collaborations Expand Platform Potential



Signed March 2016
and continues until
completion of six
programs

Focus is on oncology
treatments targeting a
specified set of proteins

Calico

5-year term
beginning March 2017

Focus is on treating
diseases of aging,
including cancer



4.5-year term beginning
January 2019

Focus is on neurological
conditions with up to
five targets total

TORPEDO Platform: Robust Drug Discovery Process Enabling Higher Confidence in *In Vivo* Efficacy



Design

Computational method incorporates experimental data to identify top models

Atomic-level degrader design utilized to improve selectivity and potency



Analyze

Cellular degradation data fitted using an enzymology framework

Key parameters describe intrinsic degradation activity



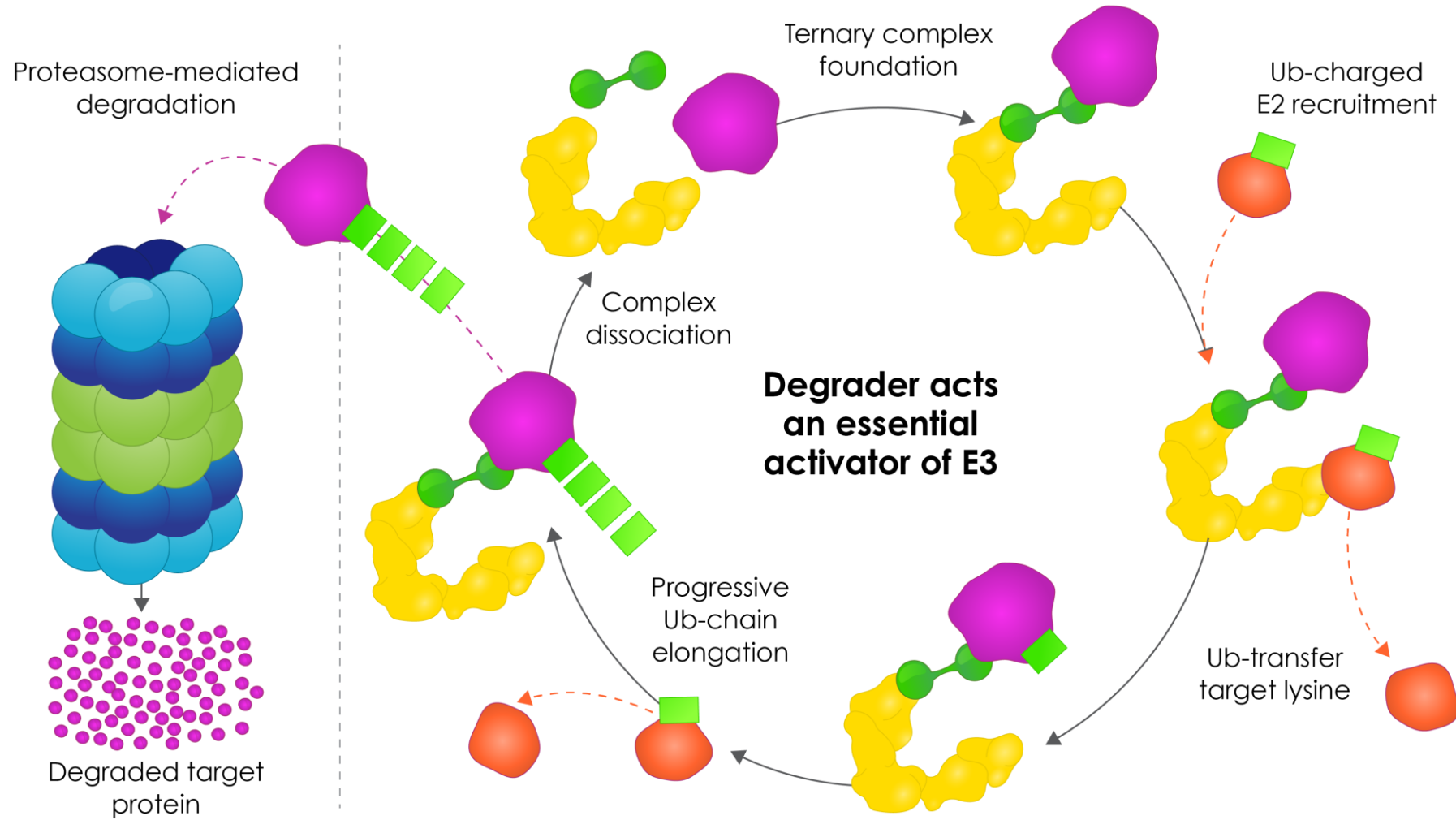
Predict

Universal modeling framework merges degradation activity with degrader exposure

Robust predictions of depth and duration of *in vivo* target degradation at any dose

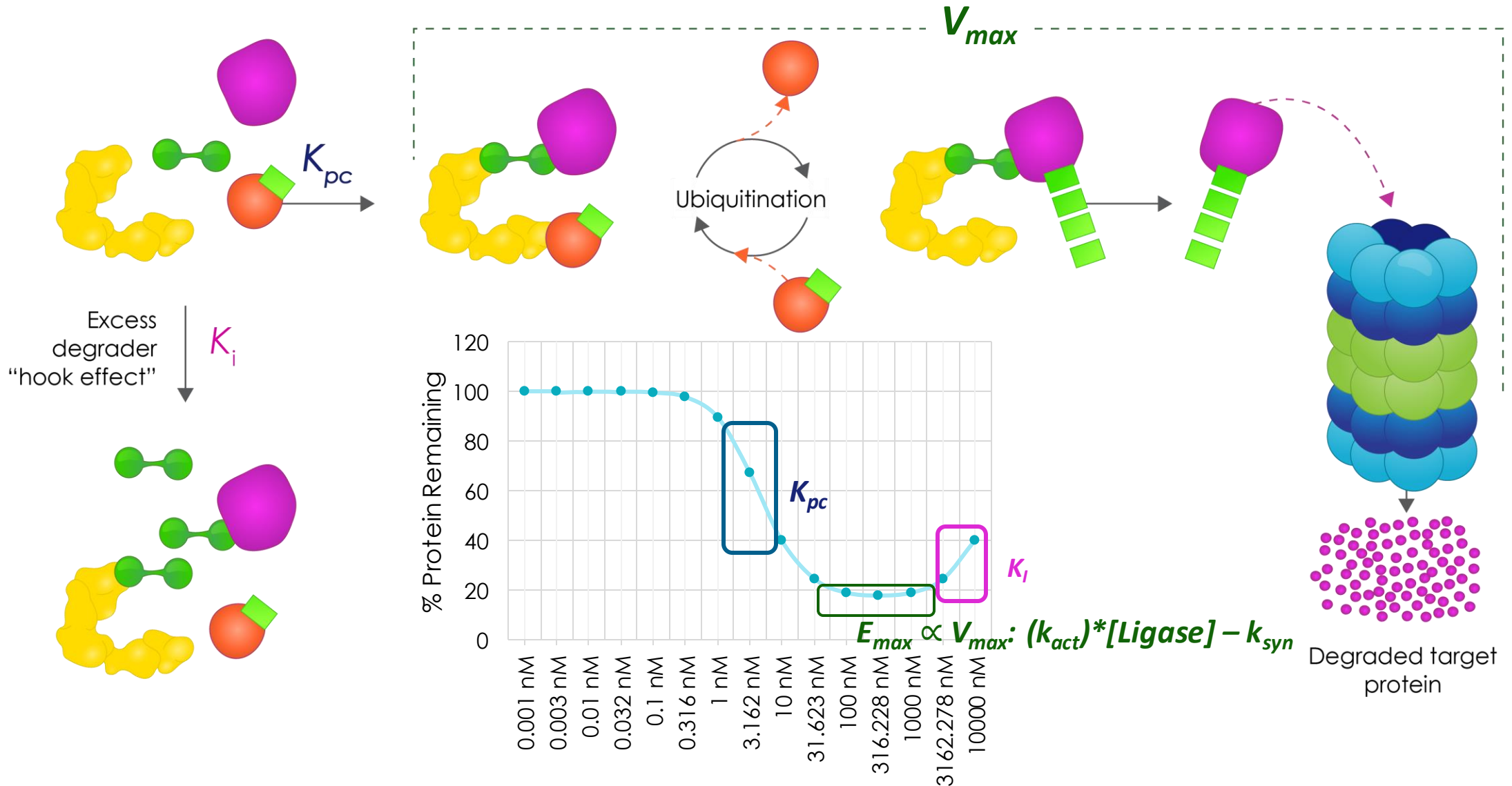
Rapid Delivery of Potent Drug Candidates Through Informed and Efficient Drug Discovery

Degraders Are Essential Catalytic Activators



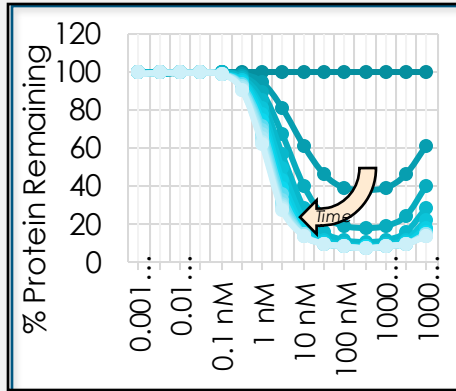
Fisher and Phillips, Curr Opin Chem Biol. 2018, 44, 47

Applying an Enzymology Framework Provides Quantitative Assessments of Degradator Activity

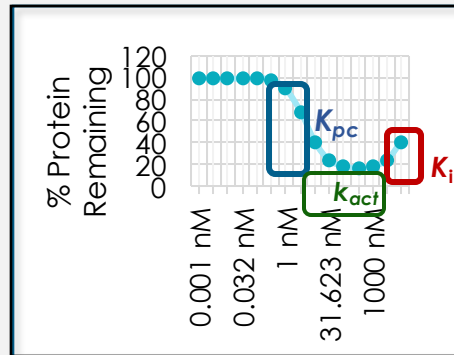


Proprietary PK/PD Models Founded on Degradation Enzymology Framework

Enzymology Framework

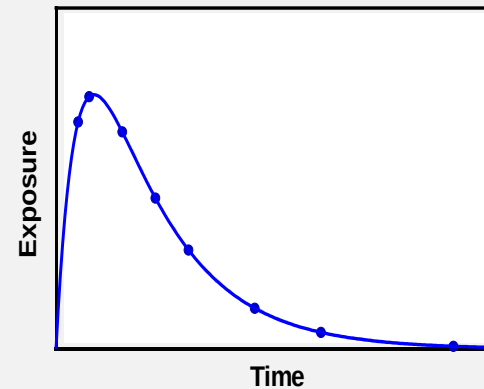


Time Dependence



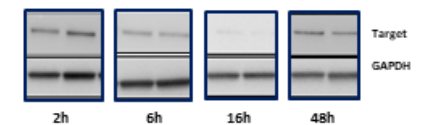
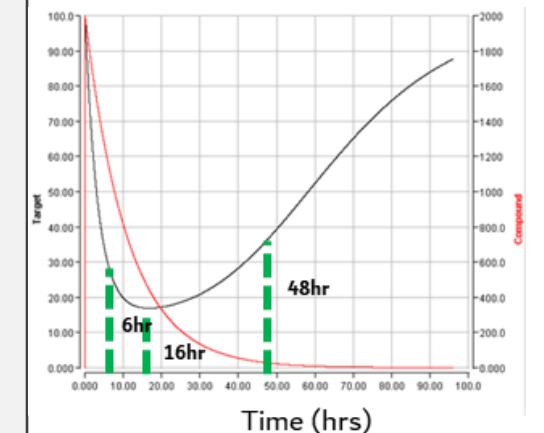
Key Parameters

DMPK Properties



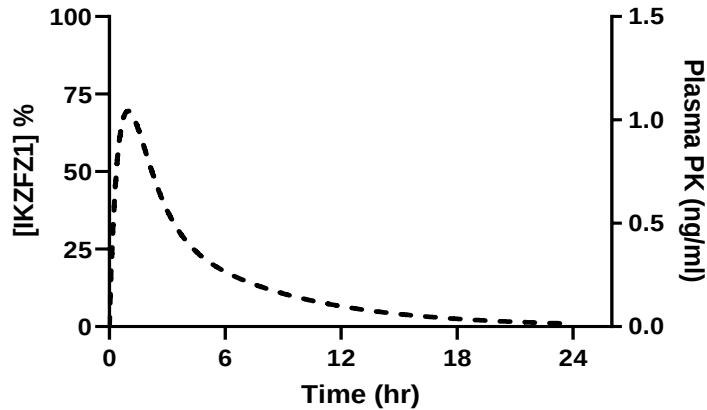
C4T Proprietary PK/PD Models

Prediction

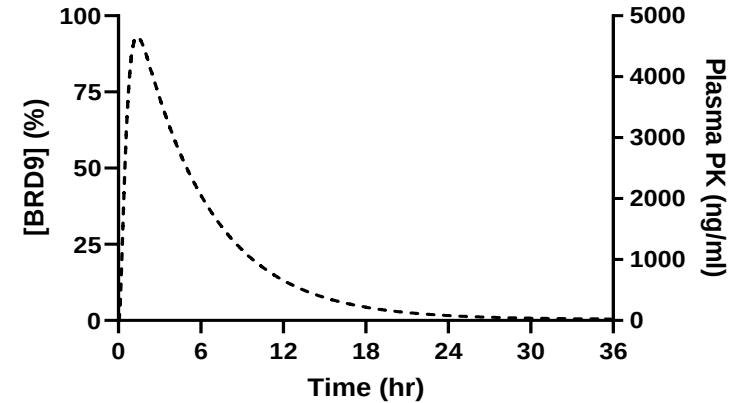


Observation

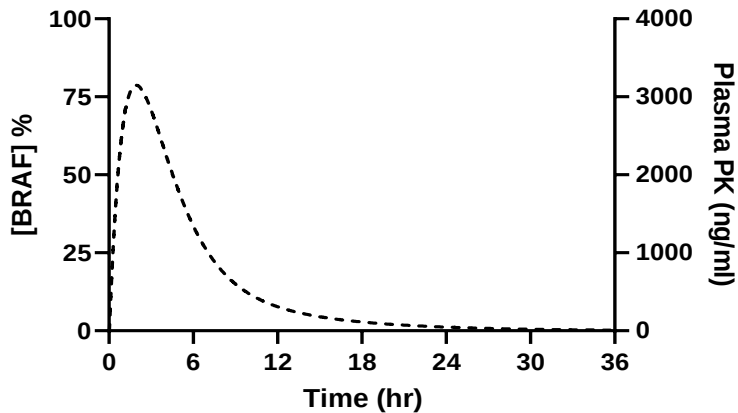
PK/PD Models Provide Robust Predictions Across Diverse Targets and Degradation Classes



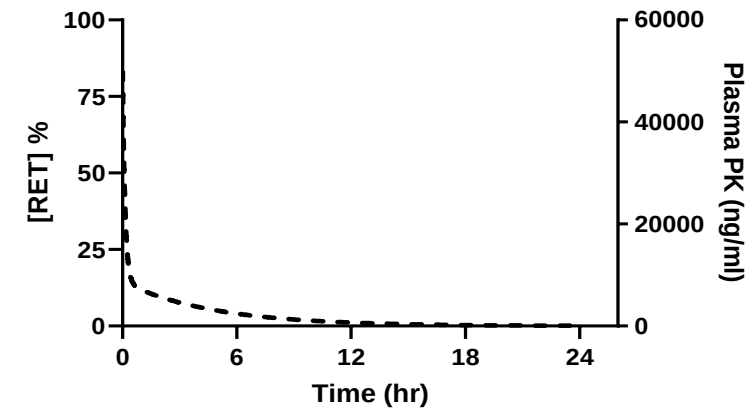
CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model



CFT7503, 10 mg/kg dose po, Yamato Synovial Sarcoma model

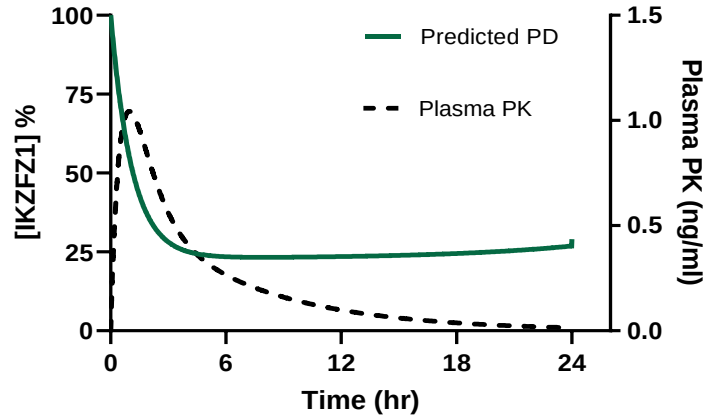


CFT-17977, 30 mg/kg dose po, A375 model

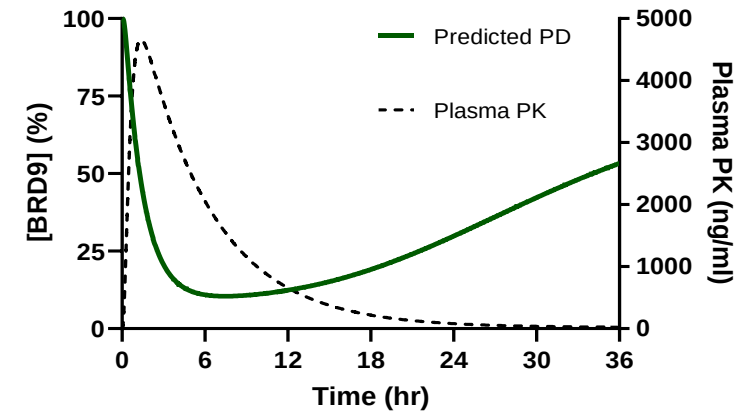


CFT-12521, 30 mg/kg dose iv, KIF-5B:RET Fusion model

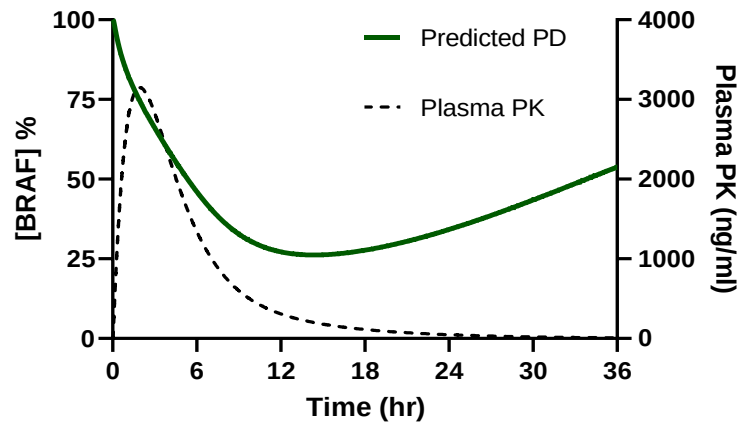
PK/PD Models Provide Robust Predictions Across Diverse Targets and Degradation Classes



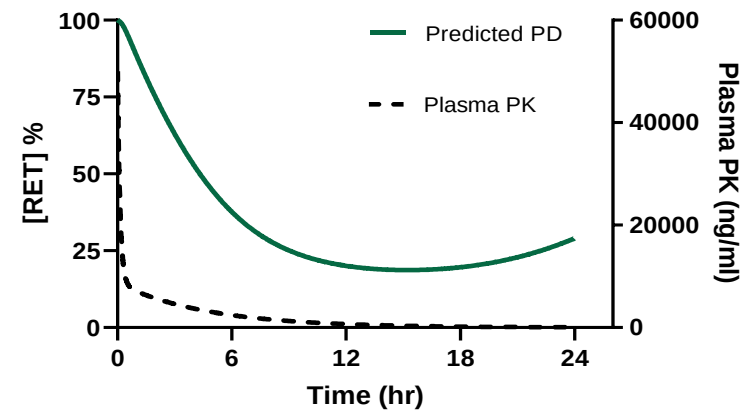
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CFT7503, 10 mg/kg dose po, Yamato Synovial Sarcoma model

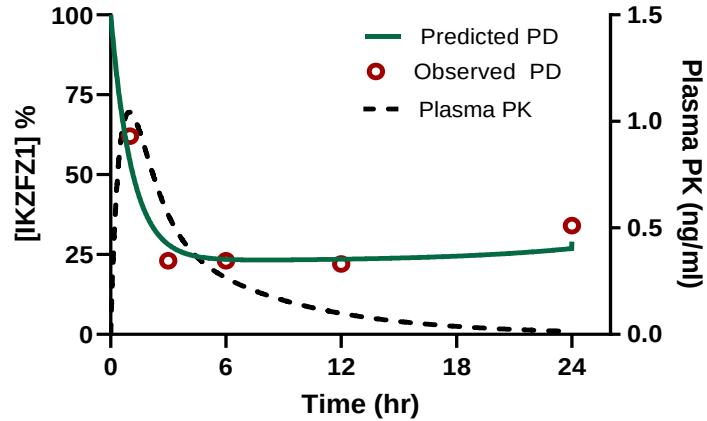


CFT-17977, 30 mg/kg dose po, A375 model

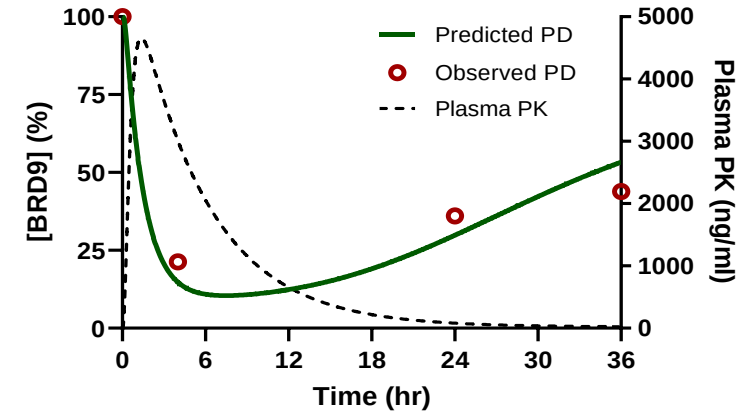


CFT-12521, 30 mg/kg dose iv, KIF-5B:RET Fusion model

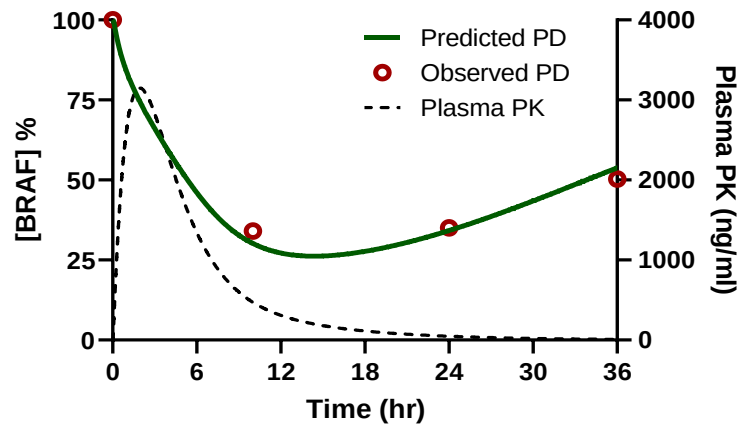
PK/PD Models Provide Robust Predictions Across Diverse Targets and Degradable Classes



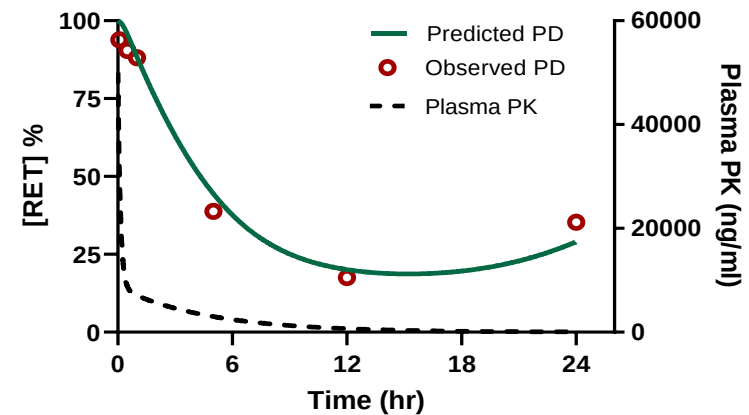
CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model



CFT7503, 10 mg/kg dose po, Yamato Synovial Sarcoma model

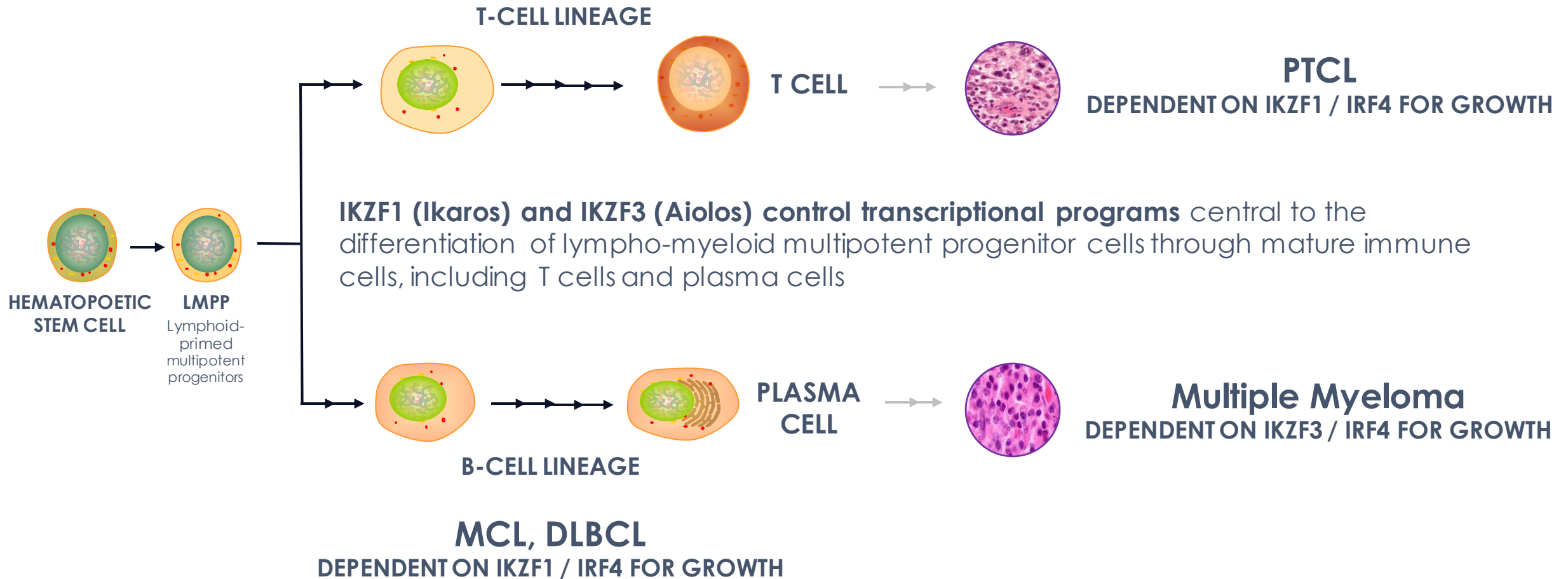


CFT-17977, 30 mg/kg dose po, A375 model



CFT-12521, 30 mg/kg dose iv, KIF-5B:RET Fusion model

Ikaros Transcription Factors Are Central to Lymphoid Differentiation and Myeloma

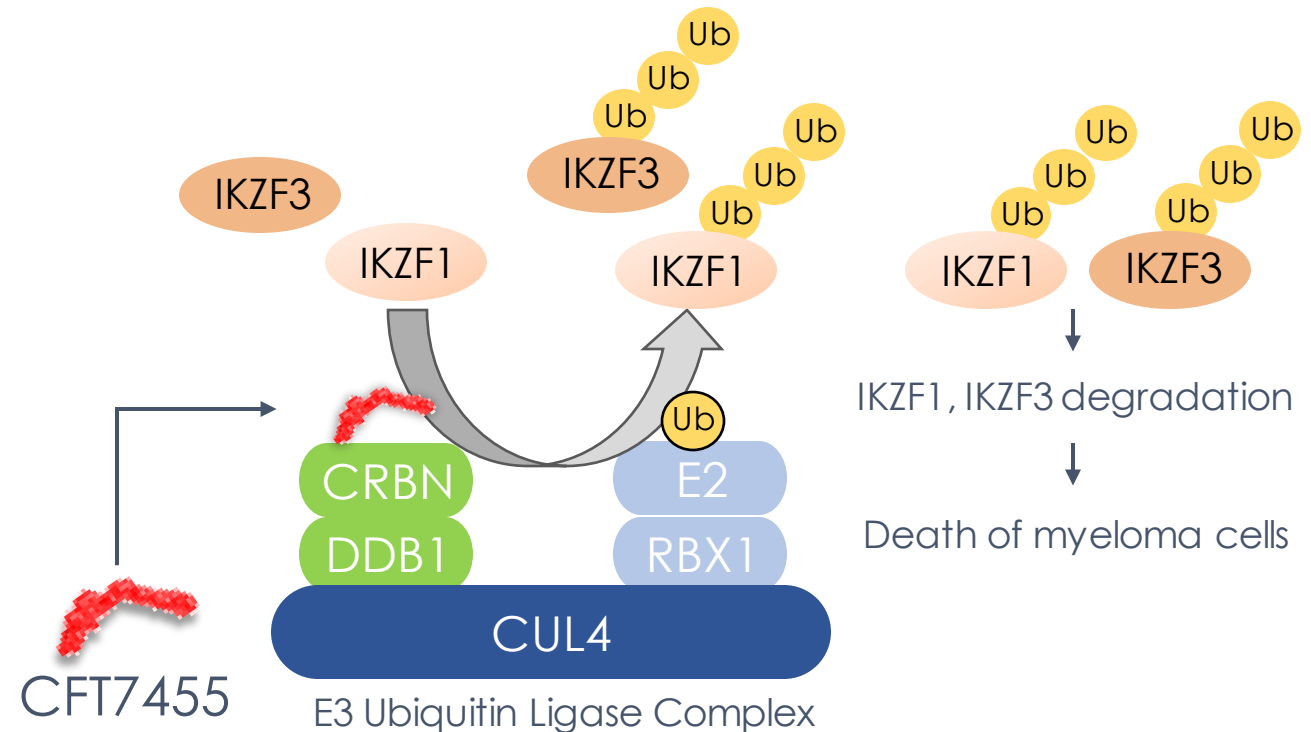


DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma

CFT7455: Potent Small Molecule IKZF1/3 Degradator Optimized for Catalytic and Pharmacologic Properties

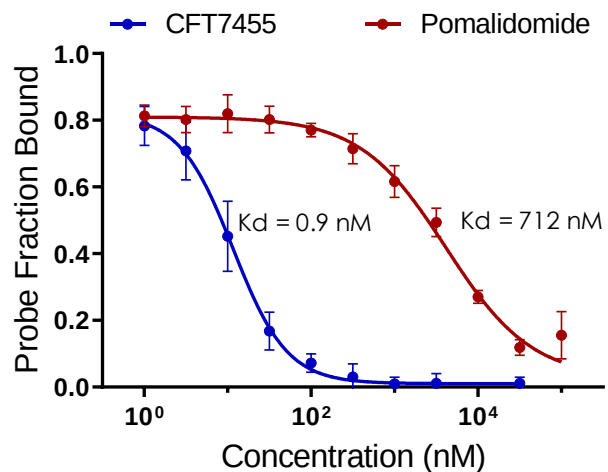
Goal: Develop an IKZF1/3 Monofunctional Degradation Activating Compound (MonoDAC) with these properties:

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

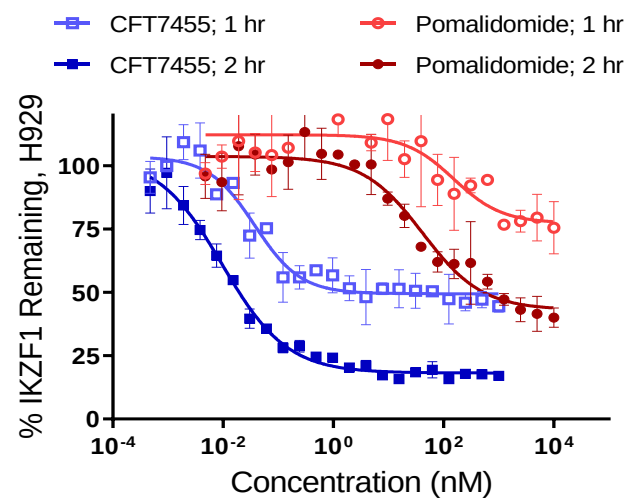


High Catalytic Activity of CFT7455 Improves Anti-Cancer Activity in H929 MM Cells

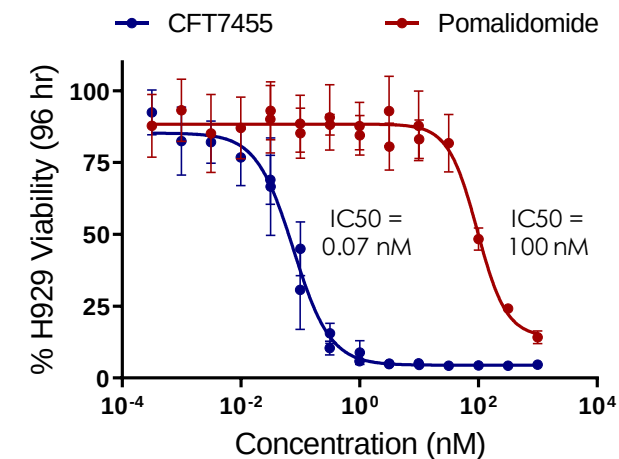
Binding Affinity (FP)



Degradation Kinetics



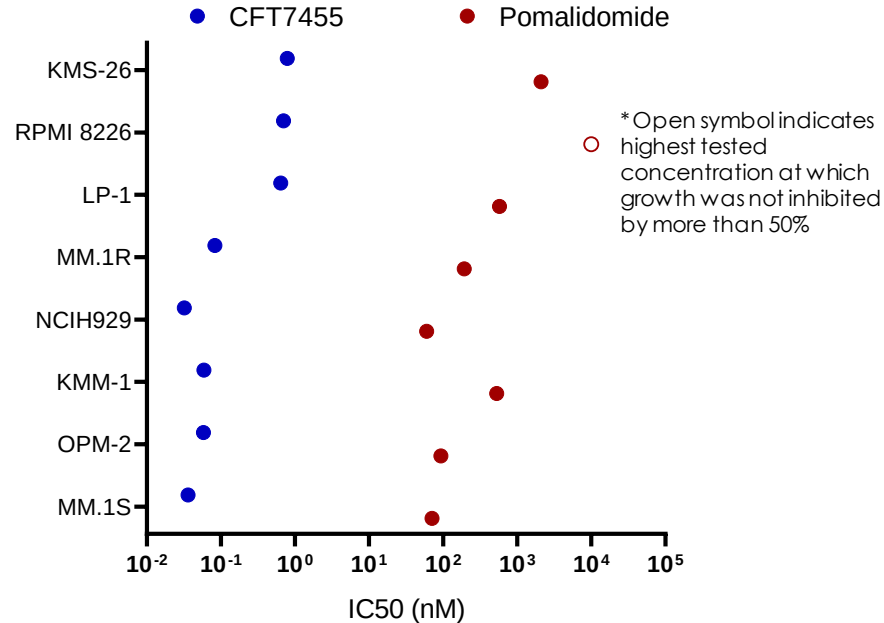
MM Cell Viability



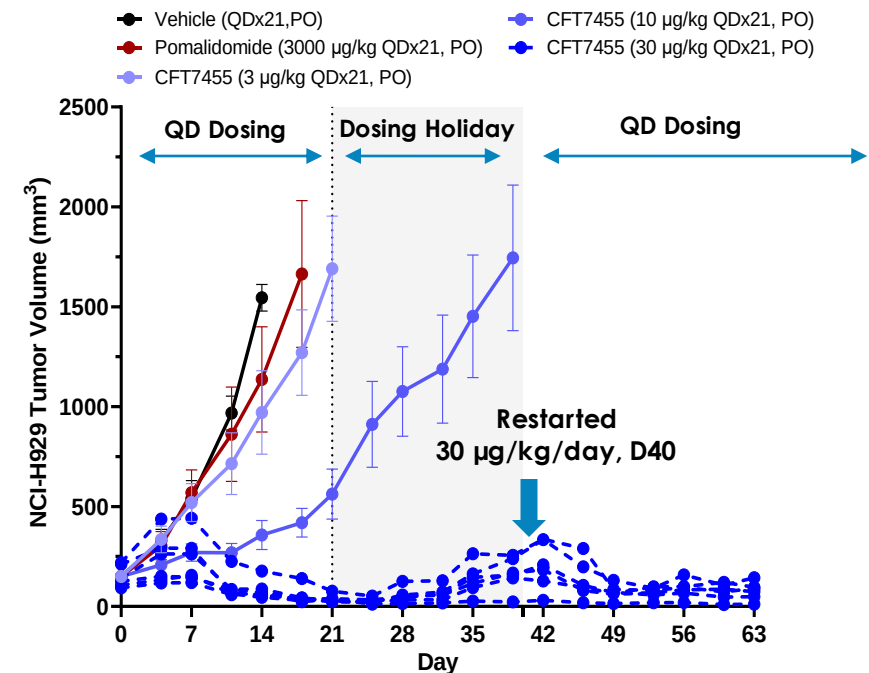
Optimization of Catalytic Activity Resulted in >5,000-fold Improvement in Potency

CFT7455 Demonstrates High Potency in MM Cell Lines and Xenografts

CFT7455 Has Broad Anti-proliferative Activity



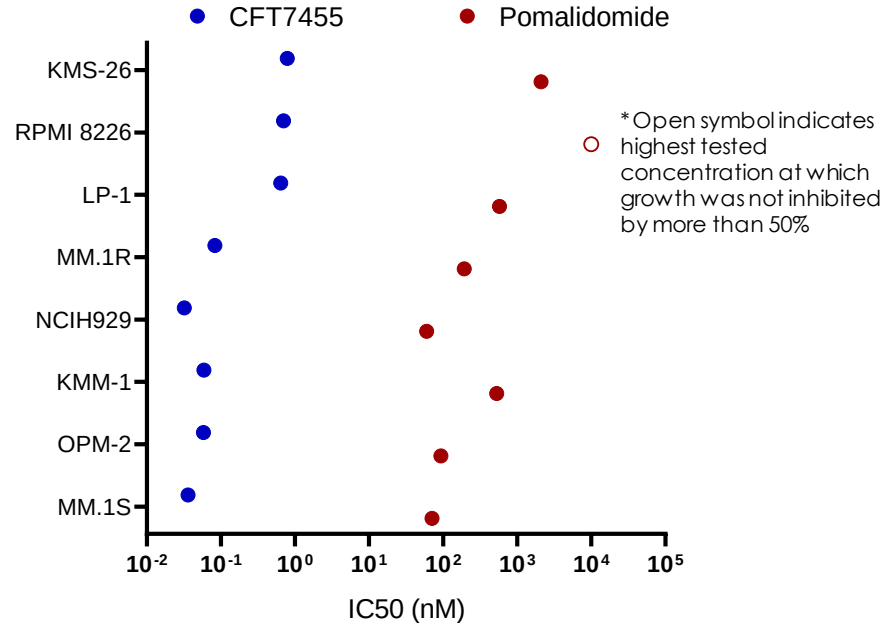
CFT7455 Promotes Durable Tumor Regression



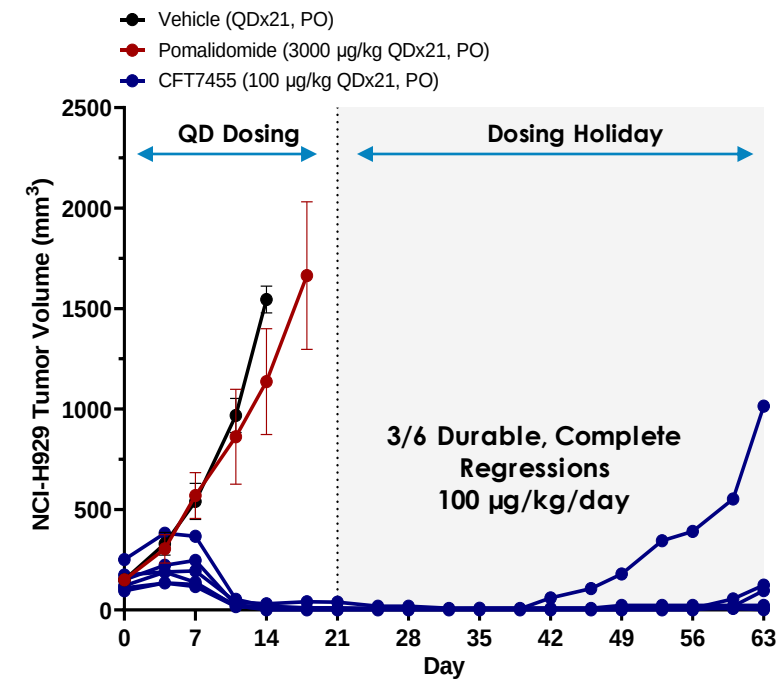
D, day; QD, once daily

CFT7455 Demonstrates High Potency in MM Cell Lines and Xenografts

CFT7455 Has Broad Anti-proliferative Activity



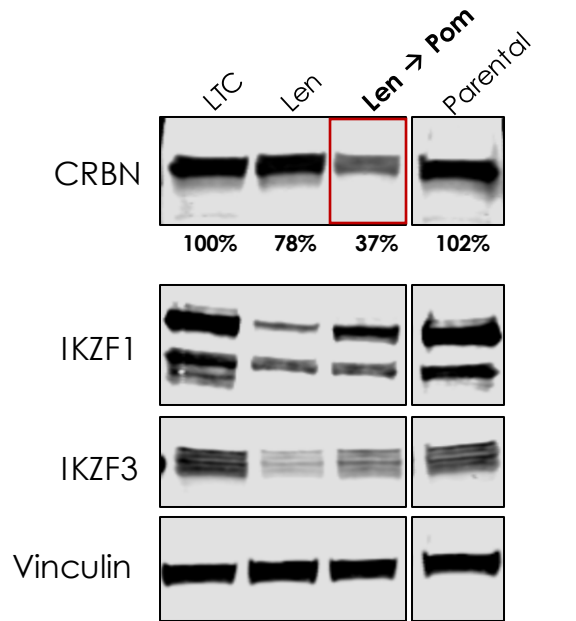
CFT7455 Promotes Durable Tumor Regression



D, day; QD, once daily

CFT7455 is Efficacious in MM Models Resistant or Insensitive to IMiDs

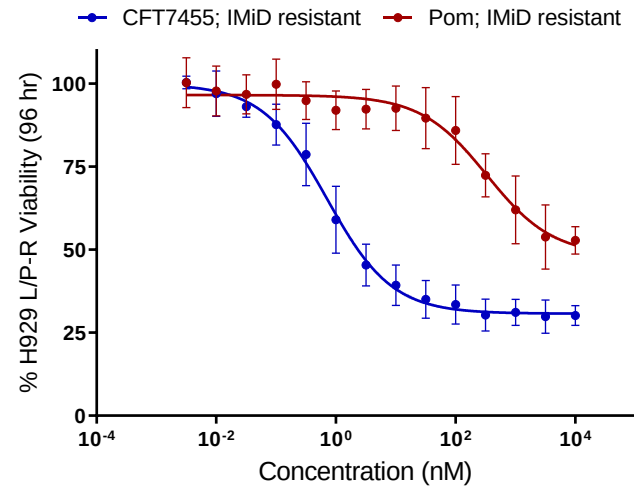
Reduction in CRBN Expression with Chronic IMiD Dosing



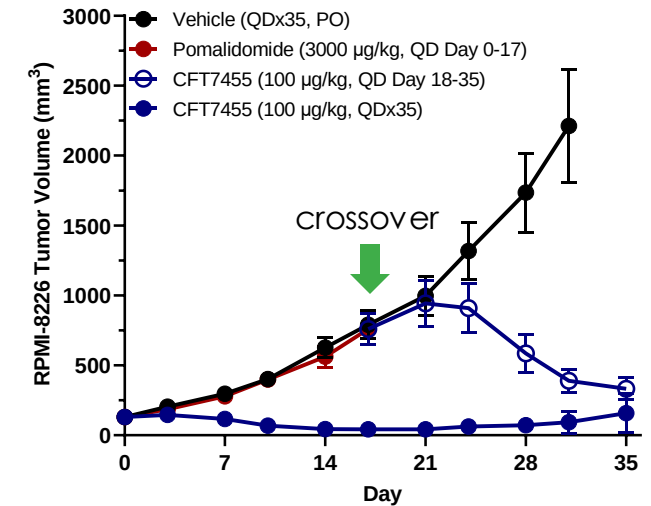
LTC = long term culture in DMSO
Parental = Original, naive H929 cells

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





C4 Therapeutics

Thank You

