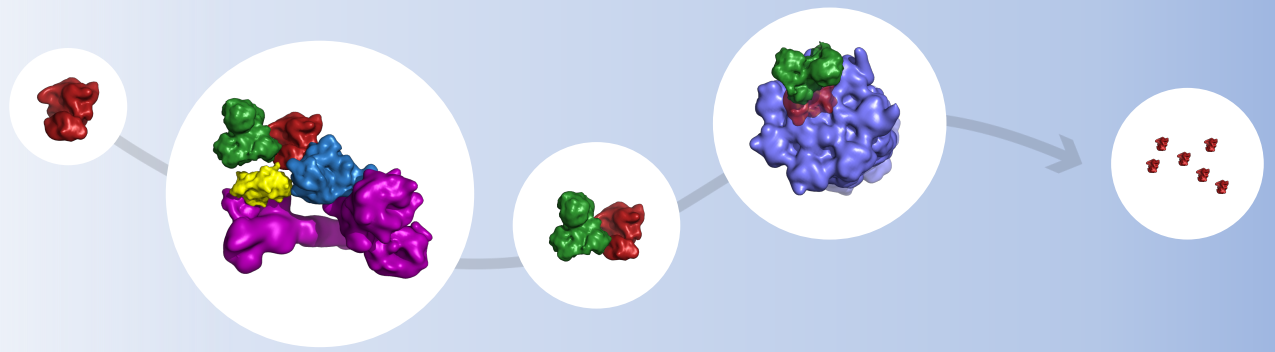
Understanding the Nuances of Targeted Protein Degradation



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

C4 Therapeutics

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

Stewart L. Fisher

Webinar

December 10, 2020

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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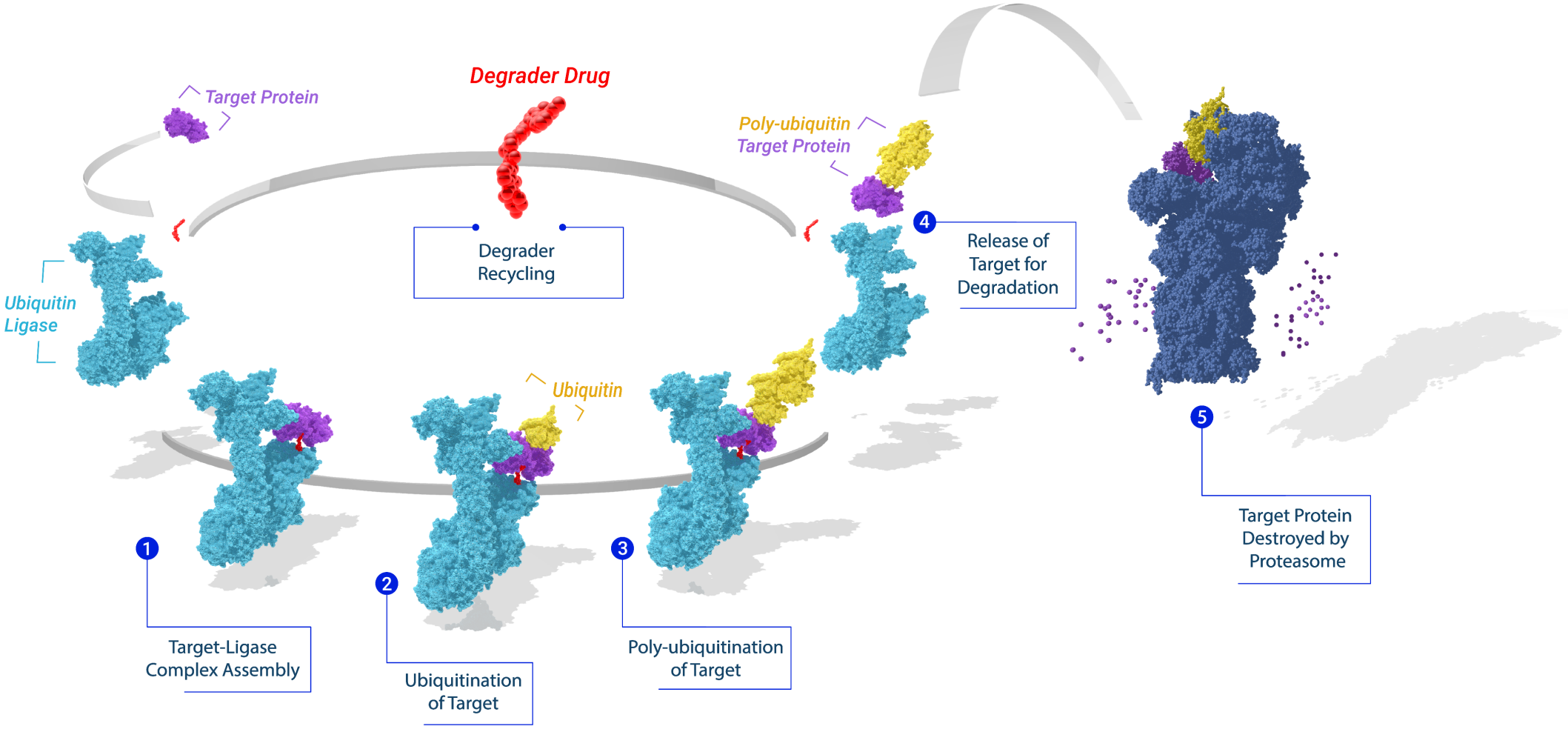
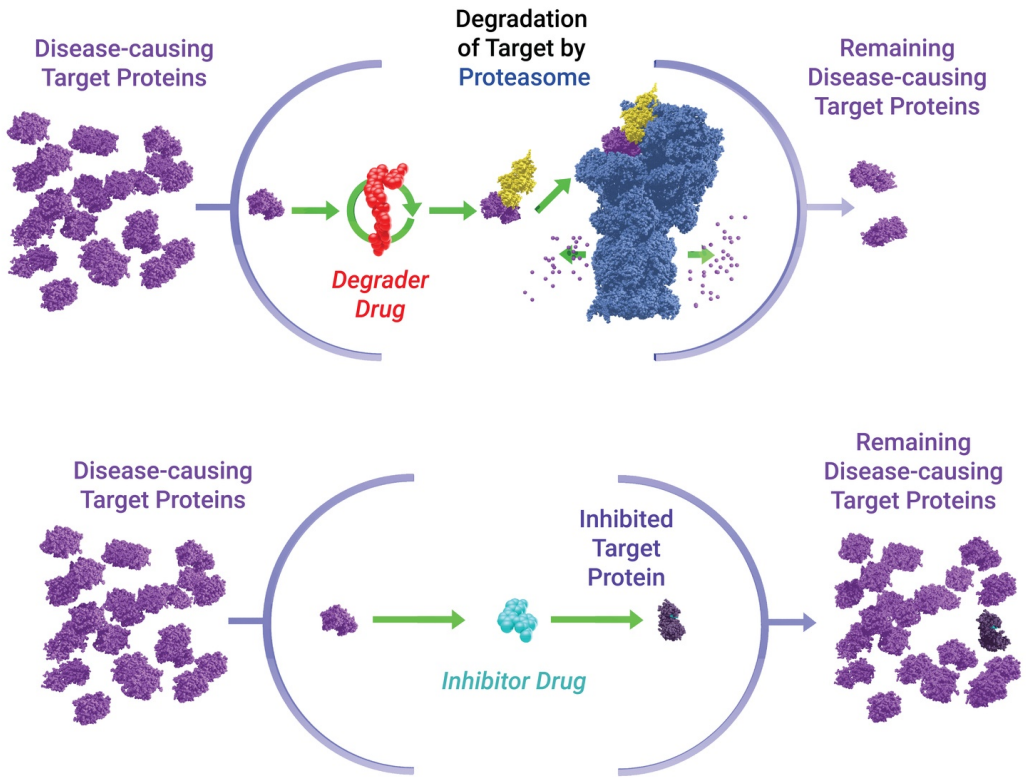
Degraders Enable a Catalytic Cycle that Destroys Disease-Relevant Proteins



Protein Degradation is Fundamentally Different than Protein Inhibition

Protein degraders allow for a **more potent and durable pharmacological response** at lower overall exposure levels than inhibitors



Key Advantages of Protein Degraders

1. **Improved Potency**

   Degraders are recycled and can engage multiple target proteins, resulting in improved activity against resistant proteins, greater depth of effect, and more durable outcomes

2. **Fast Response**

   Rapid degradation of target leads to strong and prolonged biological response

3. **High Selectivity**

   Degraders can leverage multiple layers of selectivity in cellular machinery

4. **Expansive Target Landscape**

   Degraders can be designed to bind to any part of the protein and are not limited to the active site, like most small molecule inhibitors, which means that previously undruggable targets may be degraded

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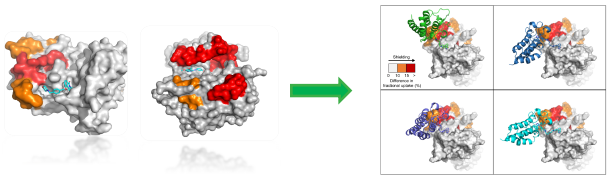
TORPEDO Platform: Robust Drug Discovery and Higher Confidence in Clinical Outcomes

Design

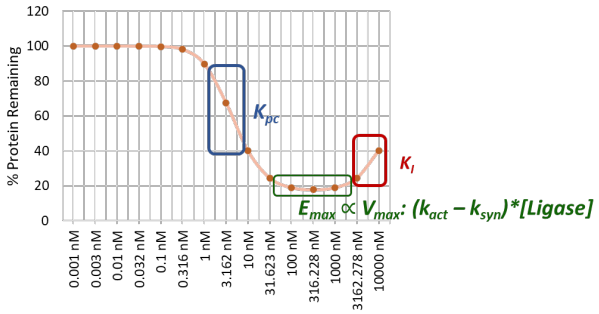


HDX-MS

Predicted ternary complexes

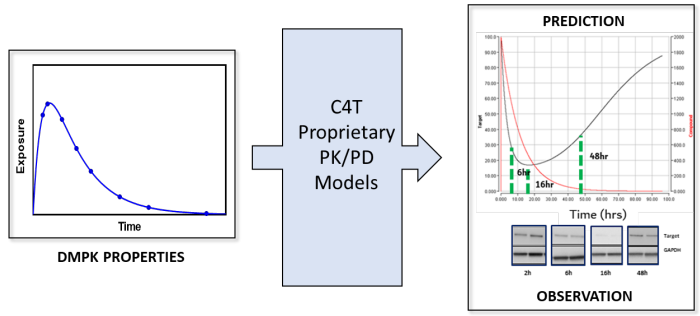
- **Computational method** incorporates **experimental data** to identify top models
- **Atomic-level degrader design** utilized to **improve selectivity** and **exquisite potency**

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

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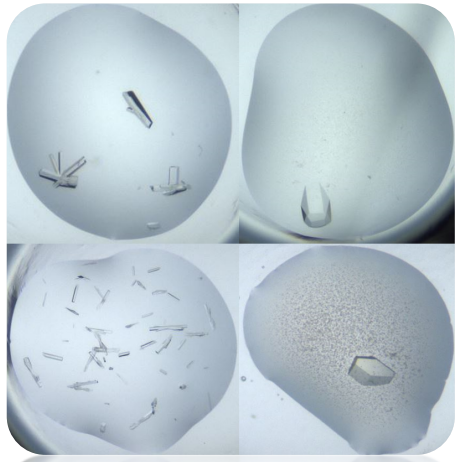
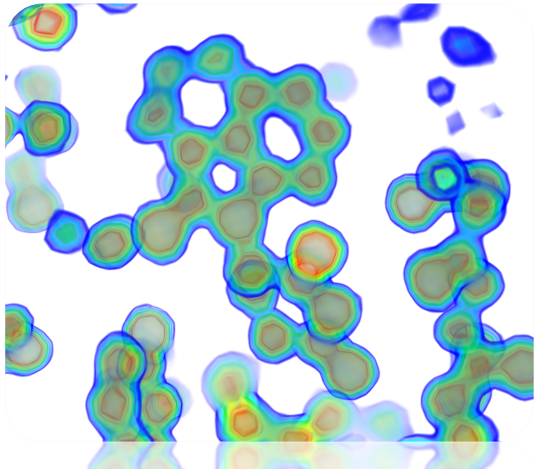
The TORPEDO Platform Employs Cutting Edge Structure-based Design

X-RAY CRYSTALLOGRAPHY

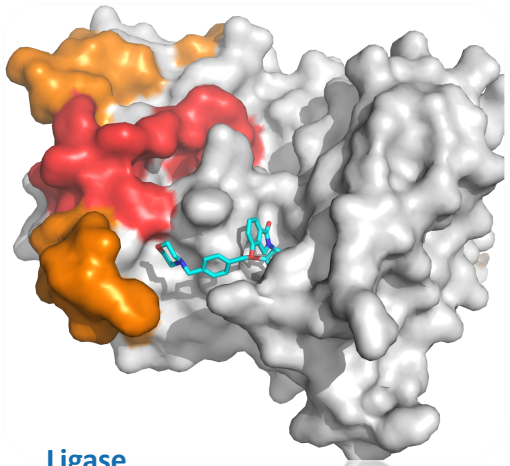


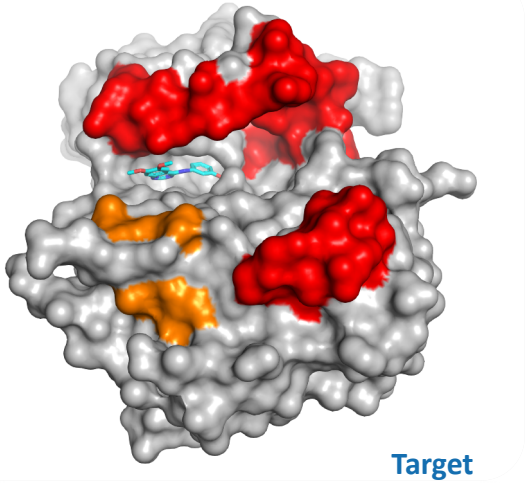


- *>70 proprietary X-ray structures solved*
- *Coverage includes key E3 ligases, ~70% of targets*
- *Supports rapid degrader chemical optimization*

HYDROGEN-DEUTERIUM EXCHANGE MASS SPEC

(HDX-MS)

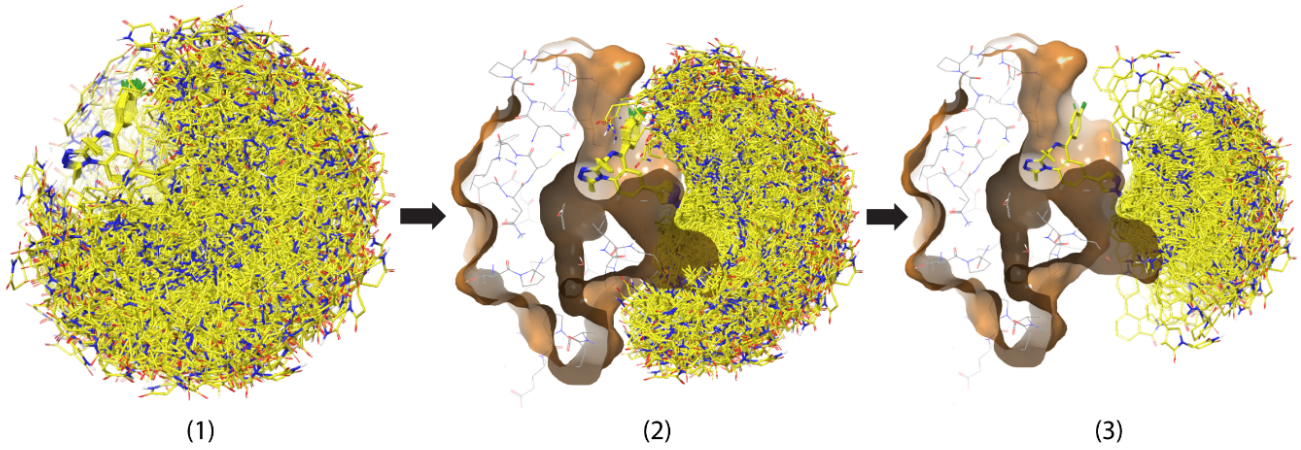




- *Established in 2018 via open access labs at UMass Amherst*
- *Allows in solution mapping of degrader promoted complexes*
- *Enables C4T proprietary ternary complex prediction pipeline*

Incorporation of Solution State Data is Critical for Predictive Ternary Complex Models

in silico modeling of BRD4 degraders



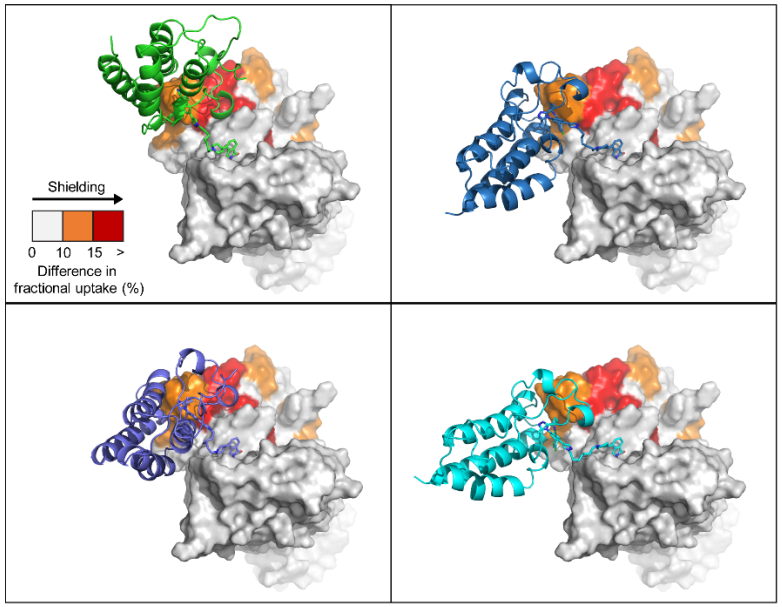
Degrader Only
>10,000 Conformations

Remove BRD4 Steric Clashes
~3,200 Conformations

Virtual Docking with CRBN
~430 Conformations

Utilize HDX-MS Surface Mapping as Constraints

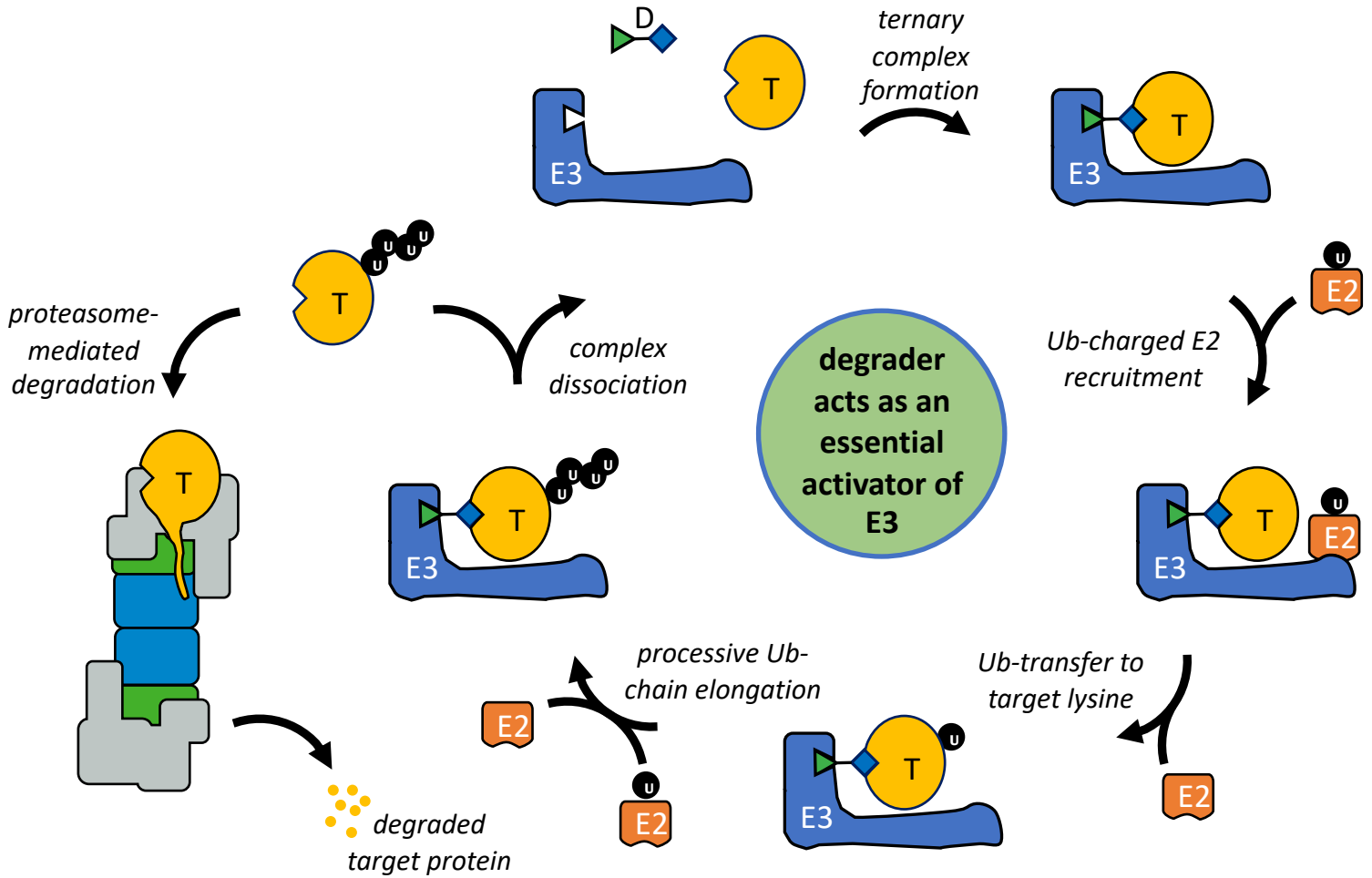
Ternary complex ranking using HDX-MS Data



Rank Conformers on HDX Constraints
4 Conformations

Ternary Complex Modeling Approach Validated using CRBN-based BRD4 Degraders

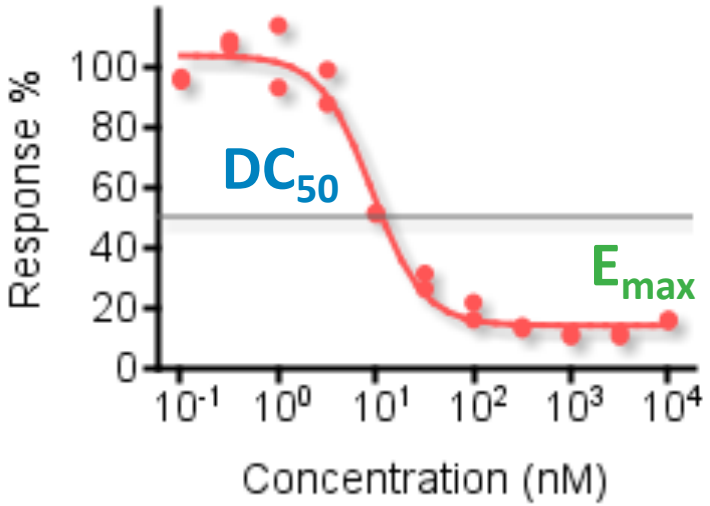
Degraders are Essential Catalytic Activators



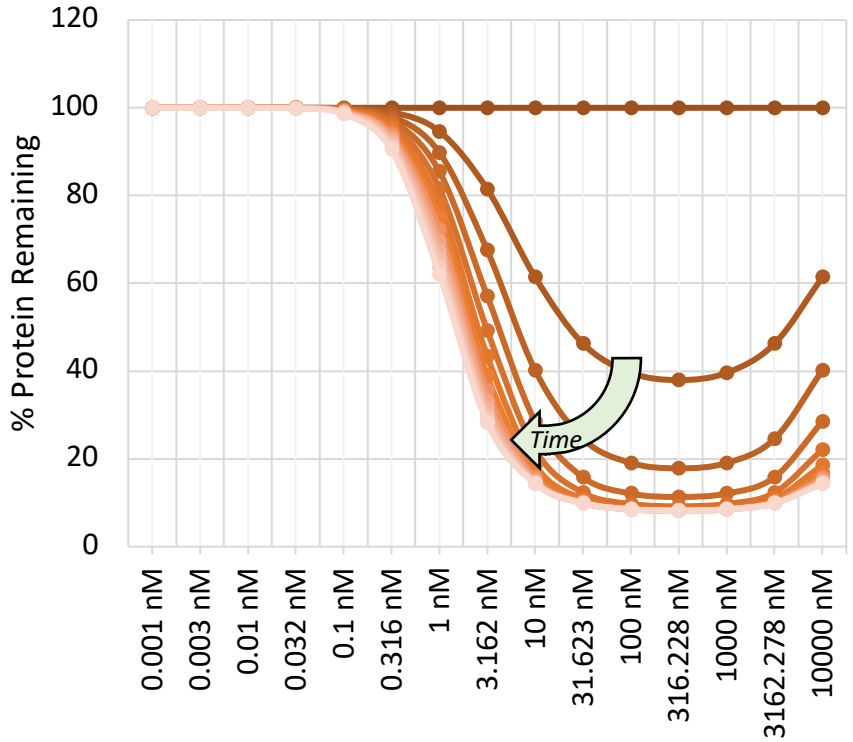
Fisher and Phillips, *Curr Opin Chem Biol.* **2018,** *44*, 47

Cellular Degradation is Time Dependent

Single Timepoint



Time Course



DC_{50} – [degrader] for 50% target depletion
(≈ cellular potency)

E_{max} – % remaining target @ assay timepoint
(maximal degradation ≈ degradation rate)

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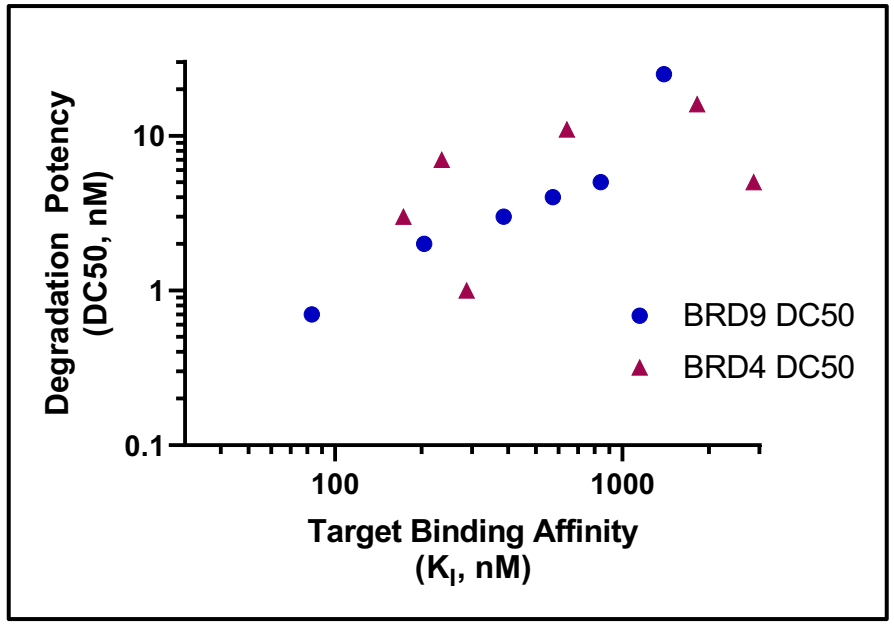
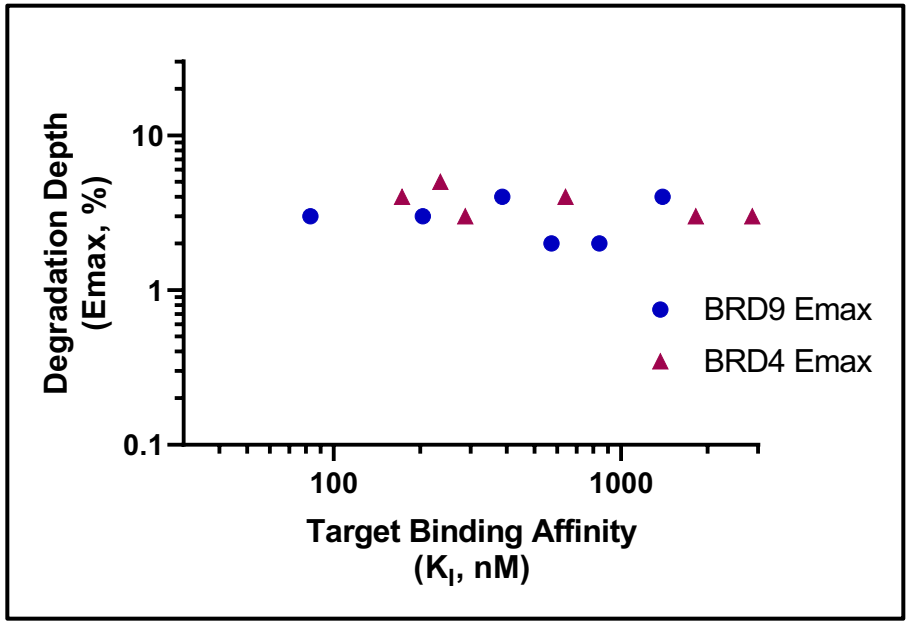
BiDAC Degradation Activity is *Not* Strictly Dependent on Target Binding Affinity





- Excellent degradation observed with reduced (weak) target binding affinity
- Can be leveraged to obtain coverage of clinically-relevant, secondary resistance mutations to inhibitor therapies

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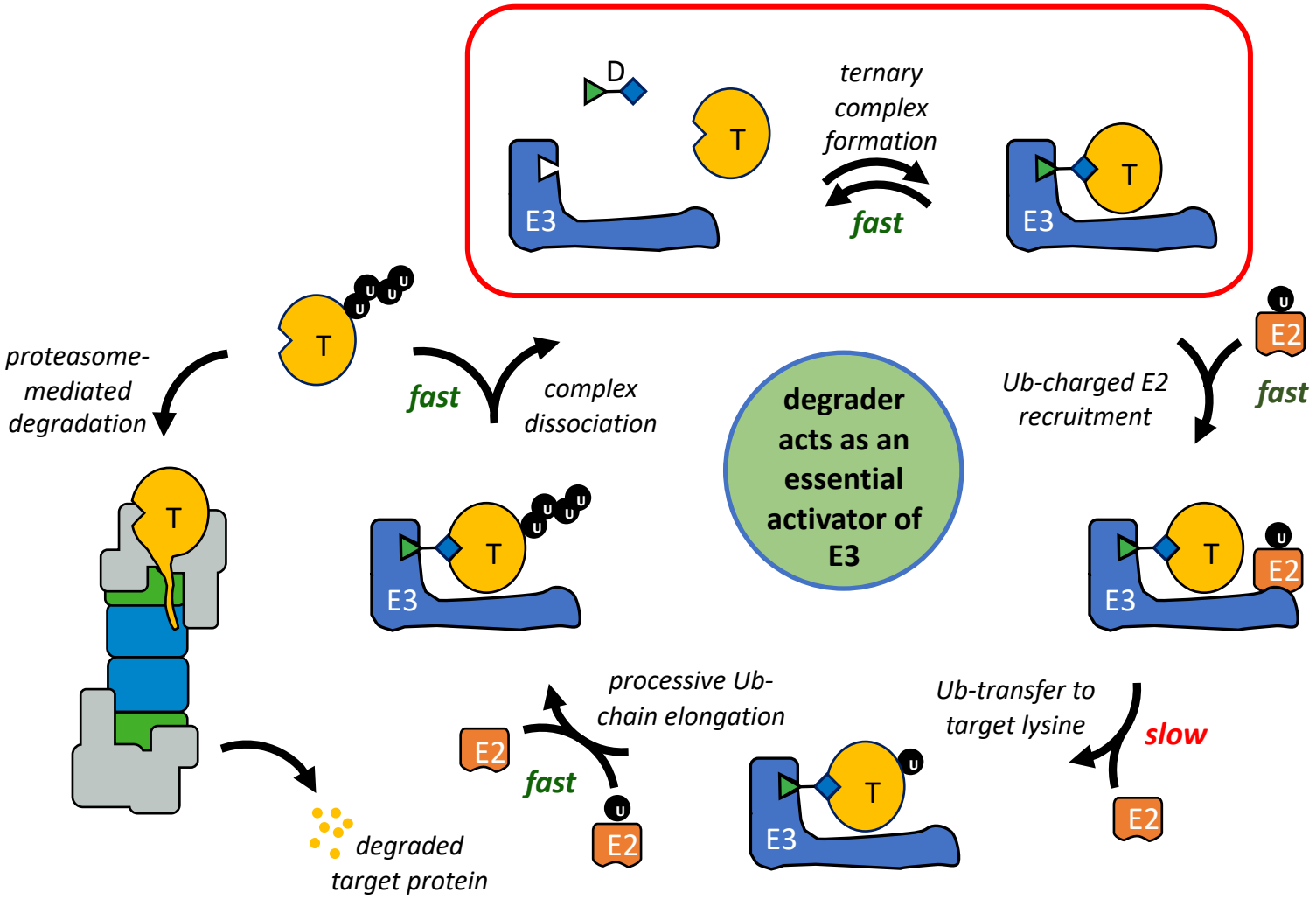
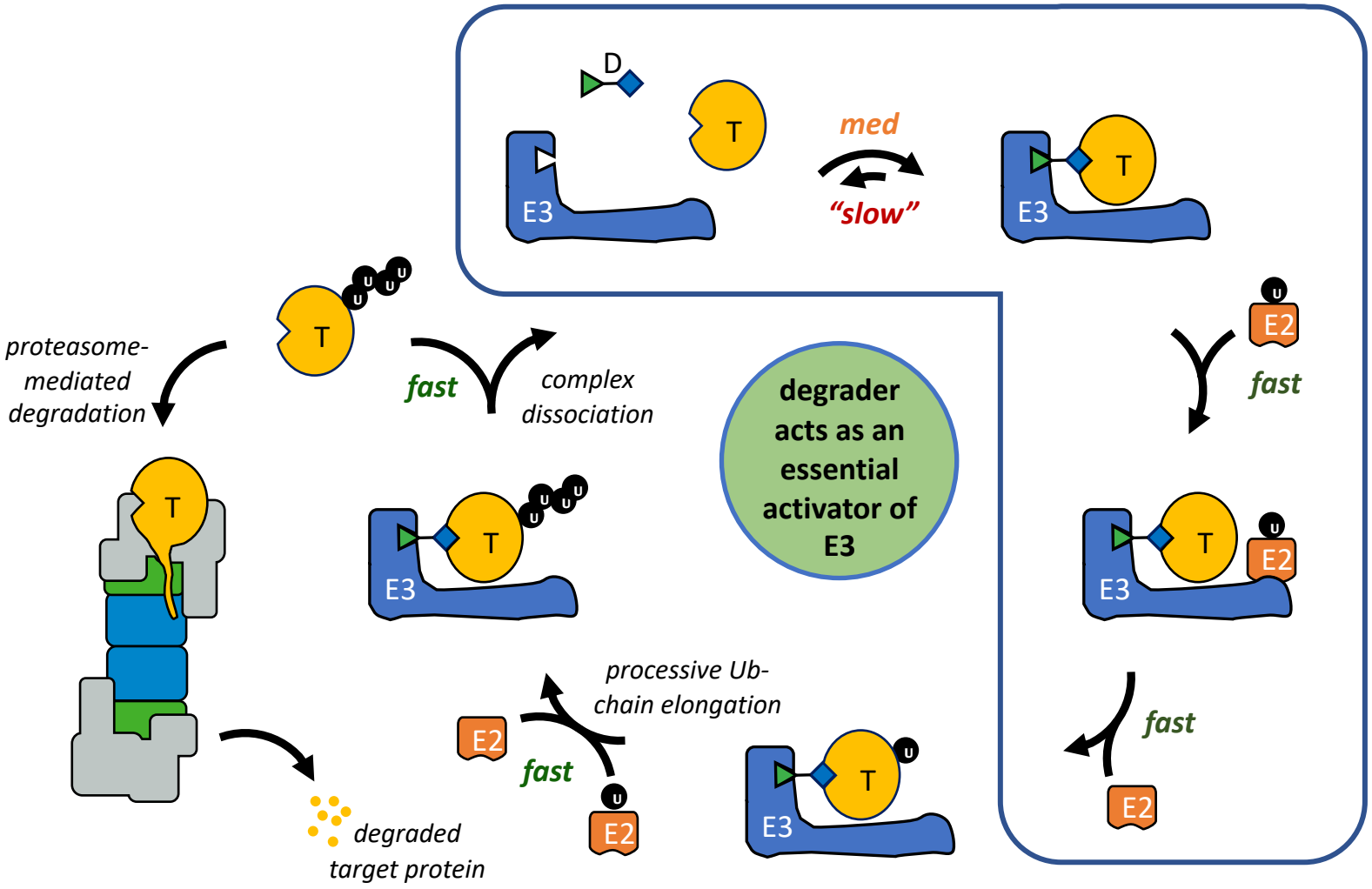
Prevailing Assumption: Ternary Complex Formation Drives Potency



Implications:

- Ternary complex $K_{tf} = K_M$
- Ternary Complex Max Fraction $\propto V_{max}$
- Positive binding cooperativity $\propto V_{max}$

What about Kinetically-driven Systems?

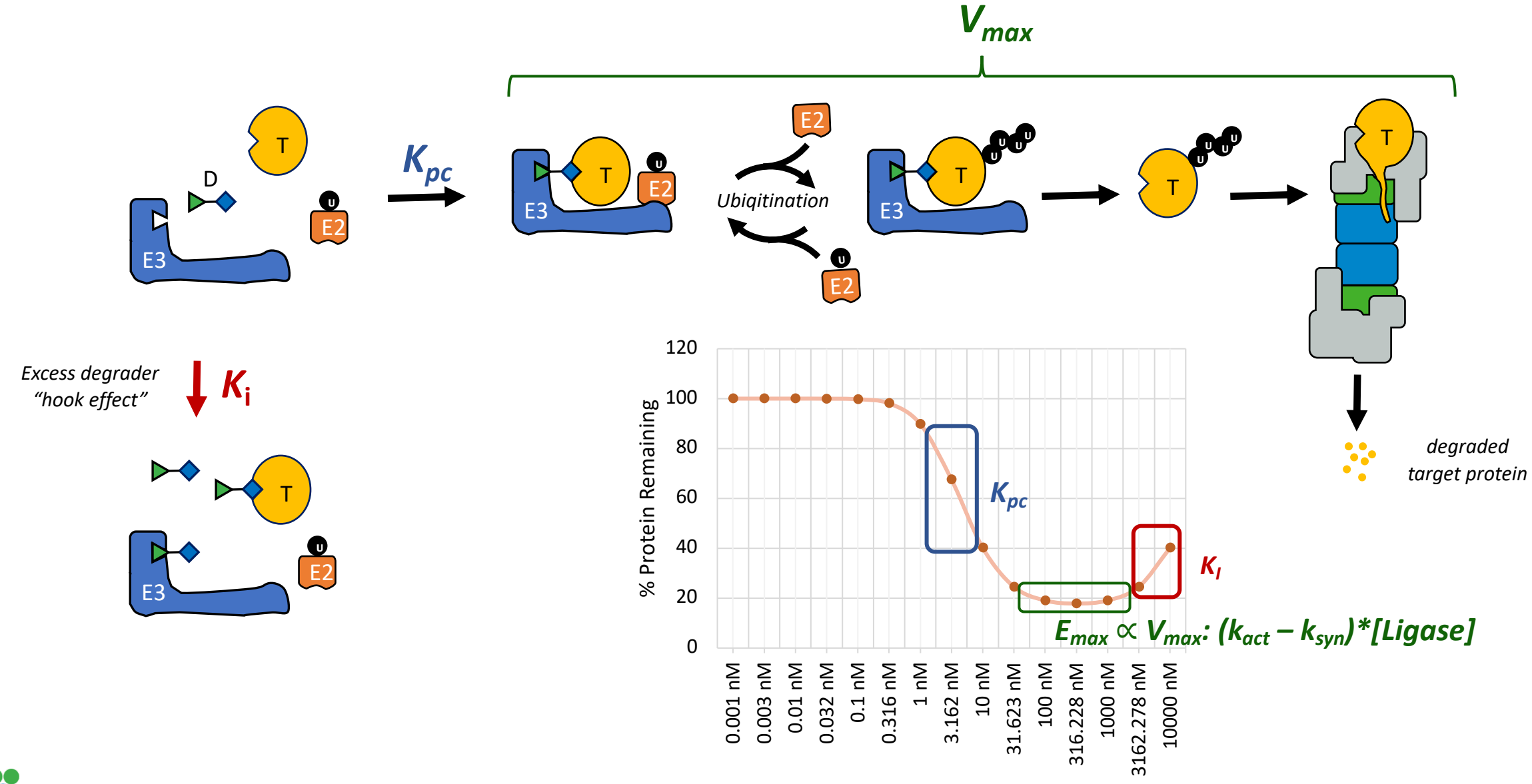


Implications:

- ***No correlations*** between ternary complex formation and catalysis
- Negative binding cooperativity ***tolerated***

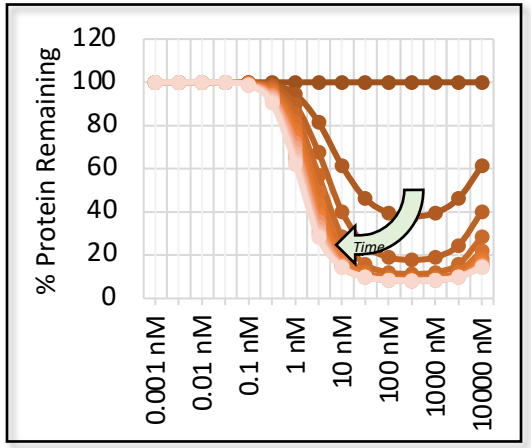
"Optimal catalysis does not necessarily result from a high affinity for the substrate"
– William P. Jencks, 1997

Applying an Enzymology Framework Provides Quantitative Assessments of Degrader Activity

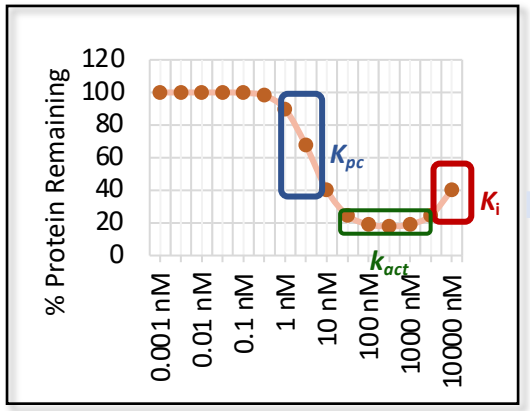


Proprietary PK/PD Models Founded on Degradation Enzymology Framework

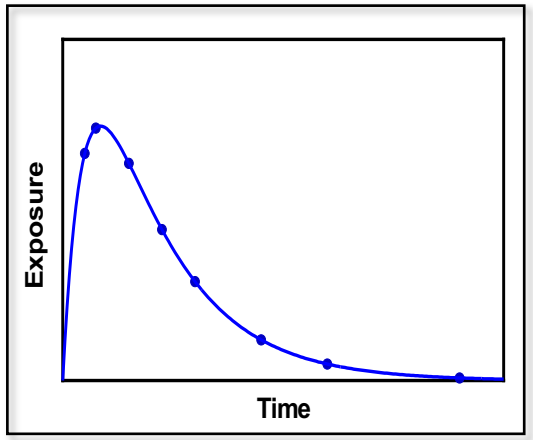
Enzymology Framework



TIME DEPENDENCE

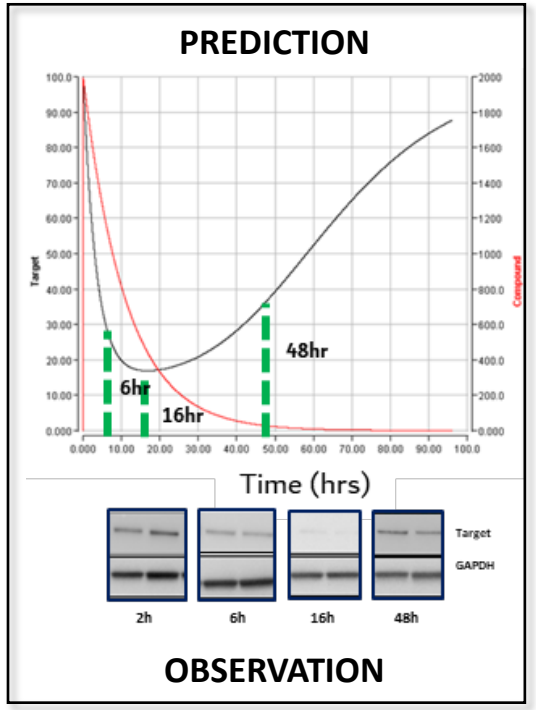


KEY PARAMETERS



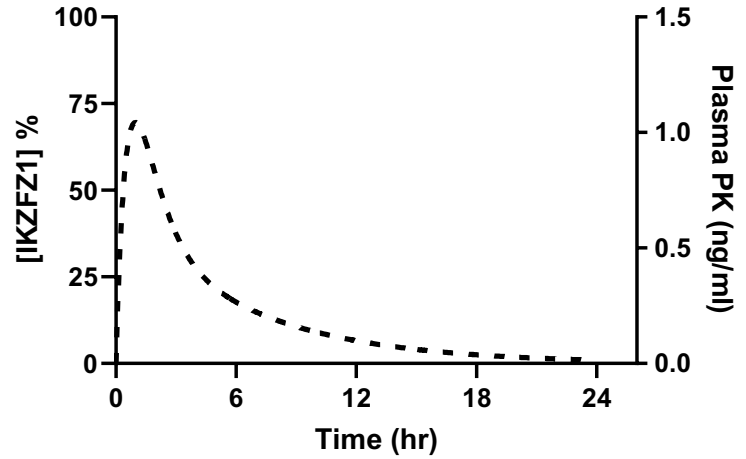
DMPK PROPERTIES

C4T Proprietary PK/PD Models

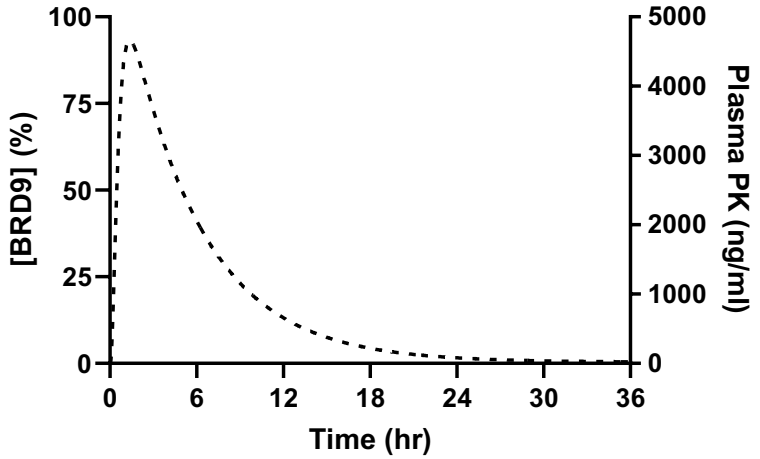


OBSERVATION

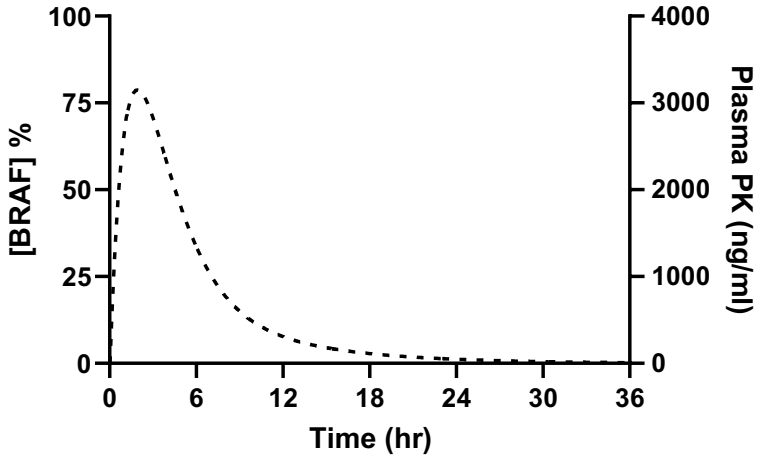
PK/PD Models Provide Robust Predictions Across the Diverse Targets and Degrader Classes



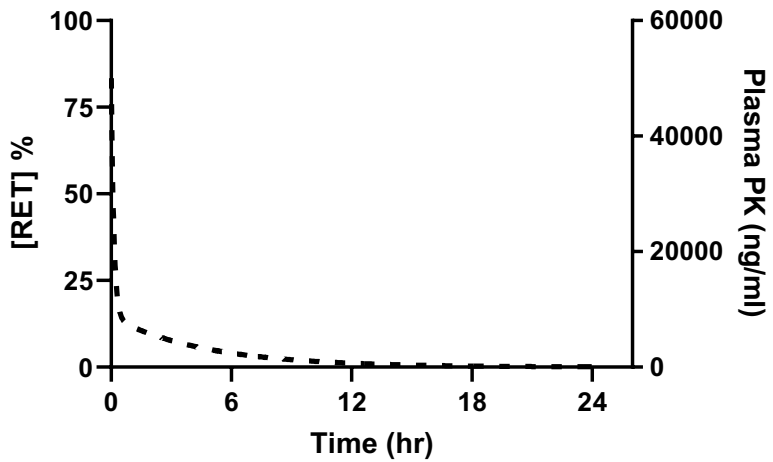
CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model



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

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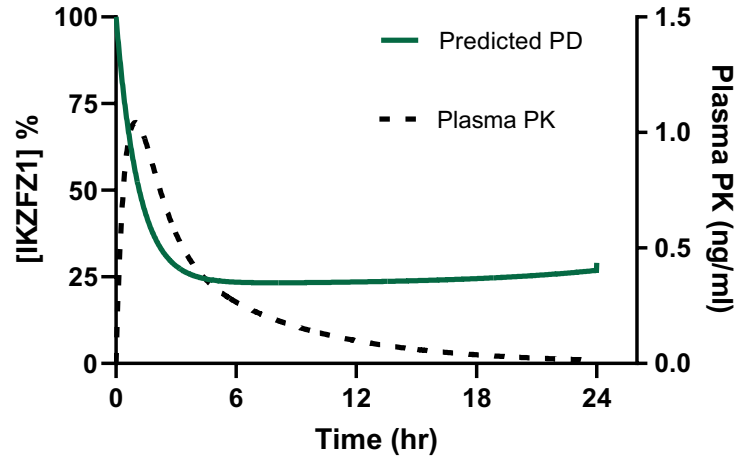
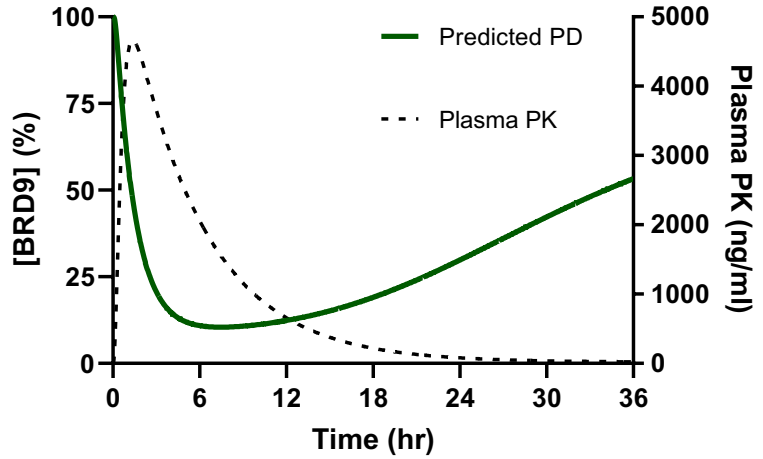
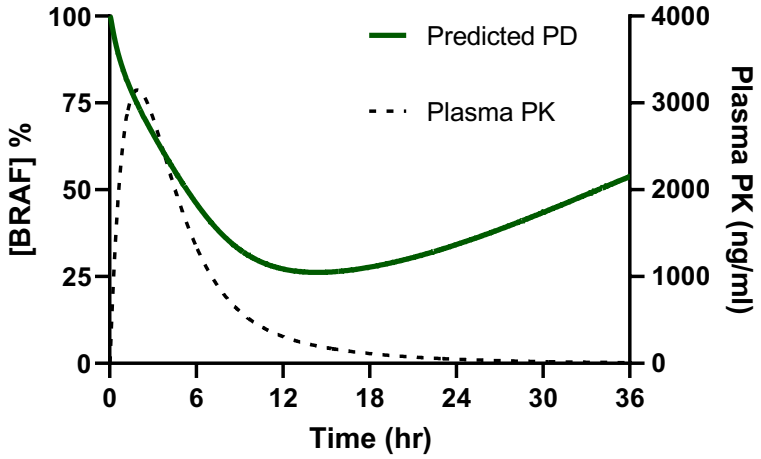
PK/PD Models Provide Robust Predictions Across the Diverse Targets and Degrader Classes



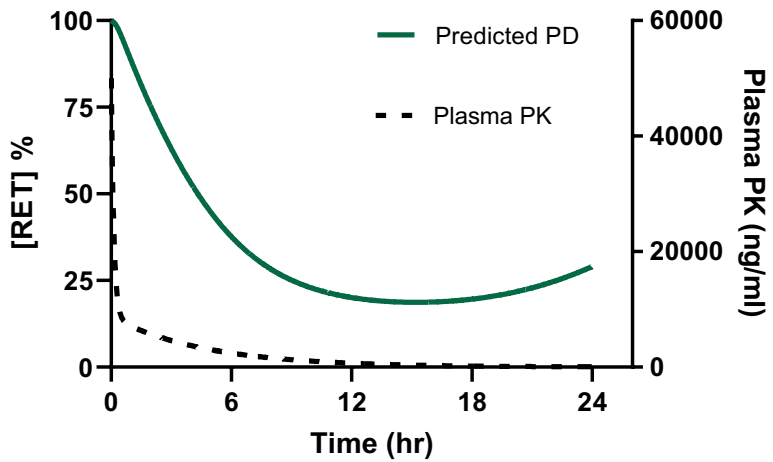
CFT7455, 1 mg/kg dose po, KI-KJ Anaplastic Large Cell Lymphoma model



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



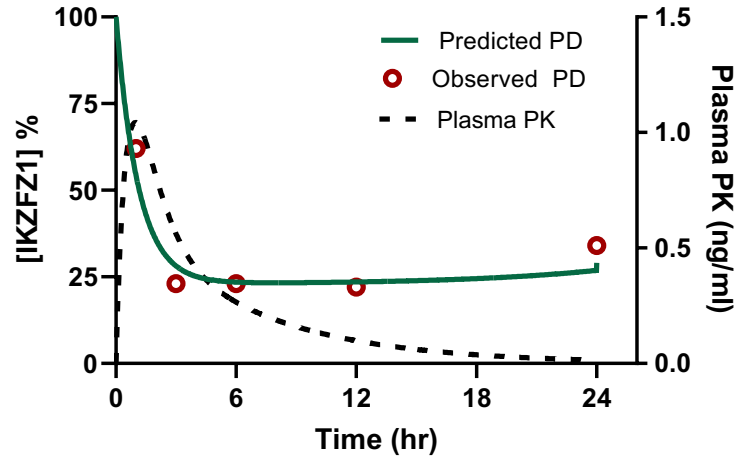
CFT-17977, 30 mg/kg dose po, A375 model



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

C4 Therapeutics

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



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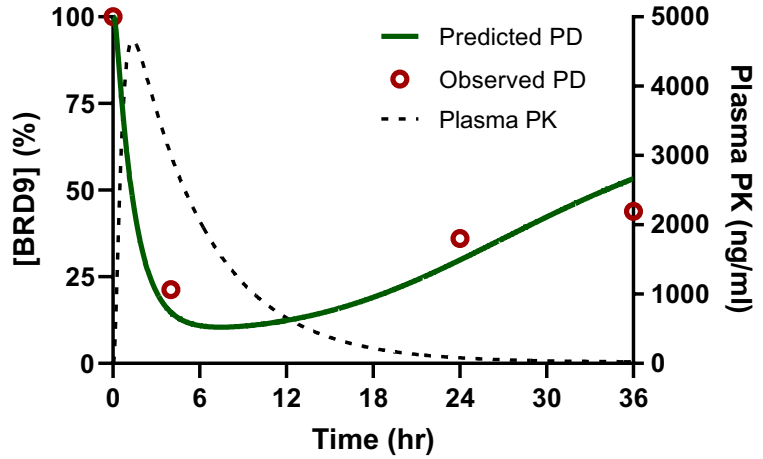
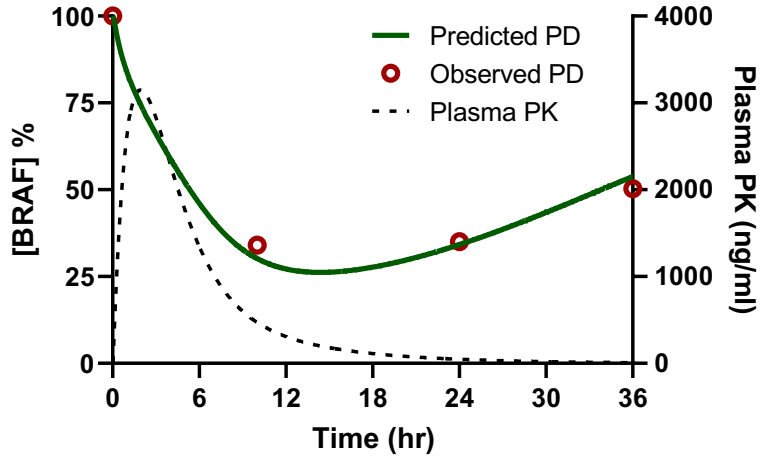
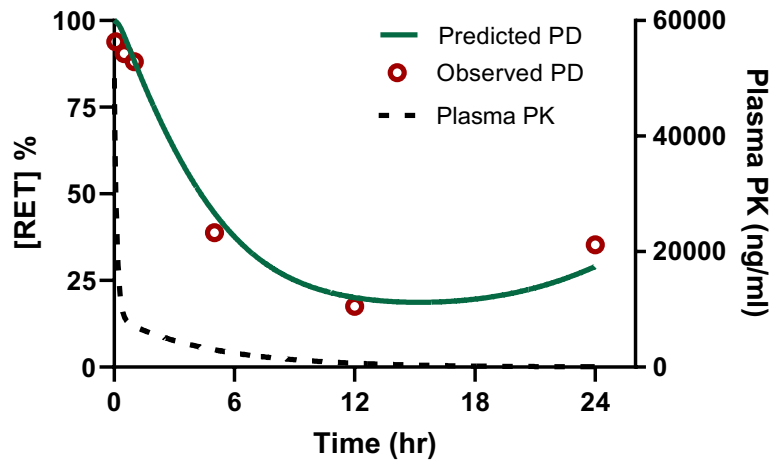


CFT7503, 10 mg/kg dose po, Yamato Synovial Sarcoma model



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



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

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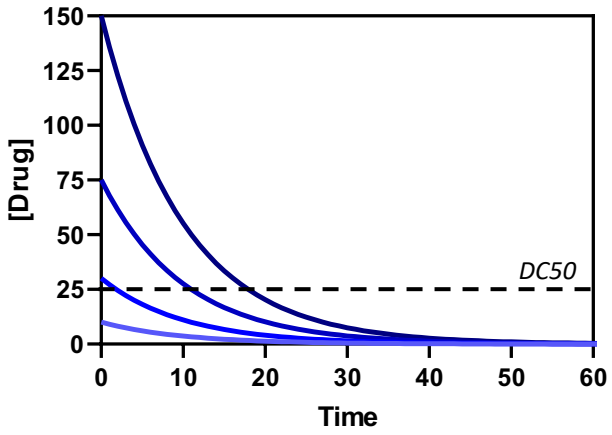
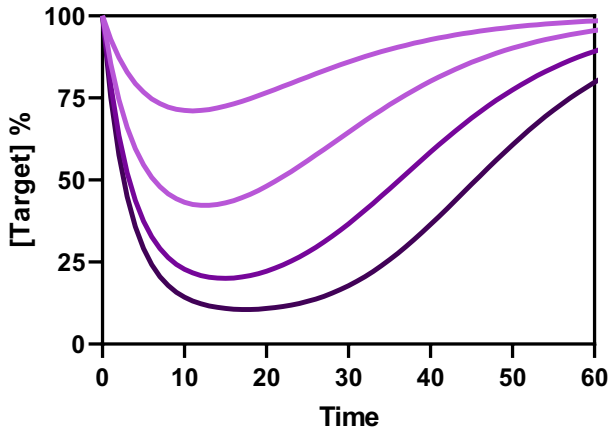
Pharmacodynamic Threshold: Linking Pharmacodynamics to Efficacy

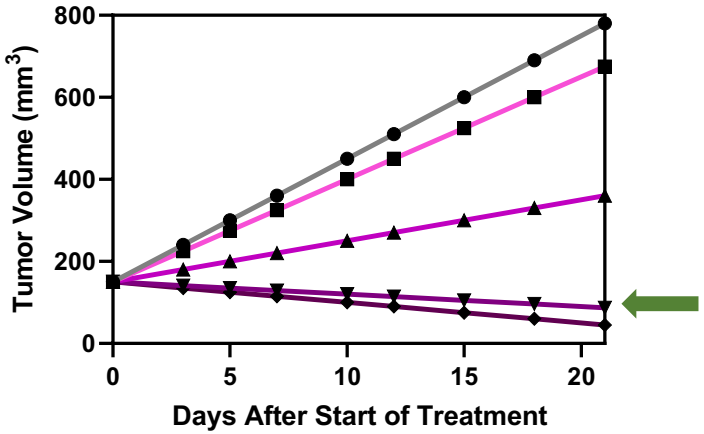
ASCENDING DOSE PK



PHARMACODYNAMIC RESPONSE



DOSE RESPONSE EFFICACY



- PDT = Pharmacodynamic threshold required for *desired efficacious response*
  - Function of target engagement/degradation and exposure
  - Dependent on target biology and tumor; not dependent on drug modality

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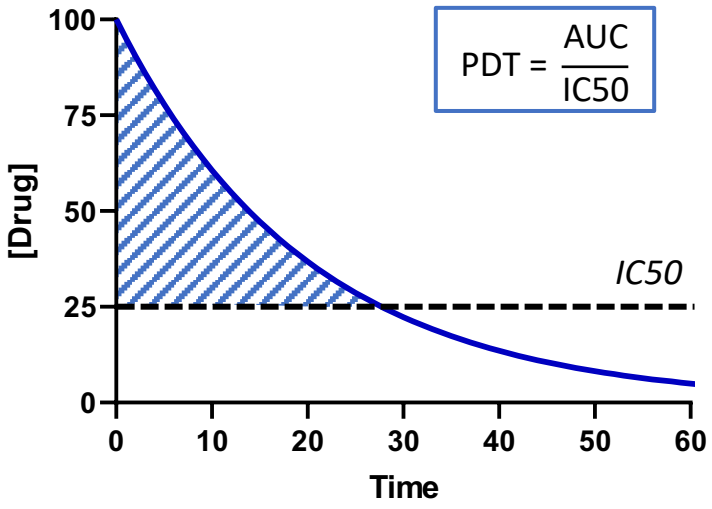
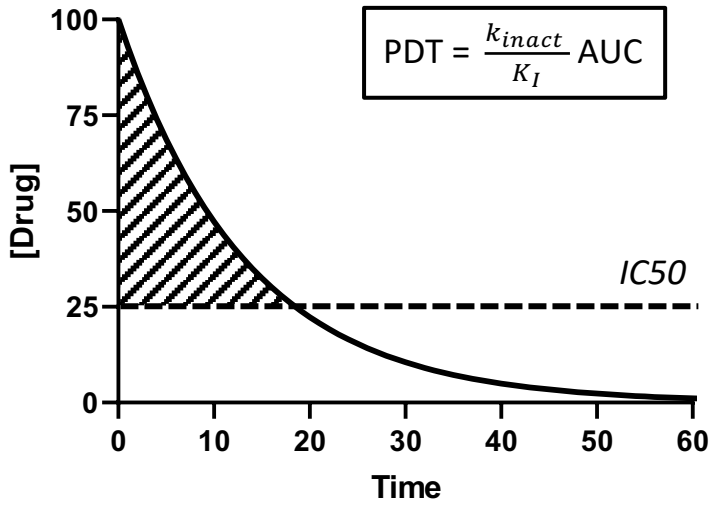
Degrader Catalytic Activity Drives Pharmacology: Lower Exposures Required

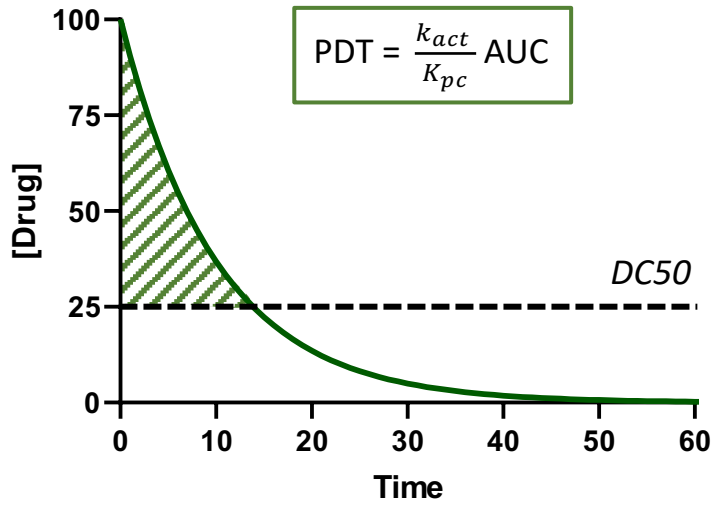
REVERSIBLE INHIBITOR



COVALENT INHIBITOR



DEGRADER



$AUC_{Degrader}$ < $AUC_{Inhibitor}$ to Achieve Equivalent Target Efficacious Response

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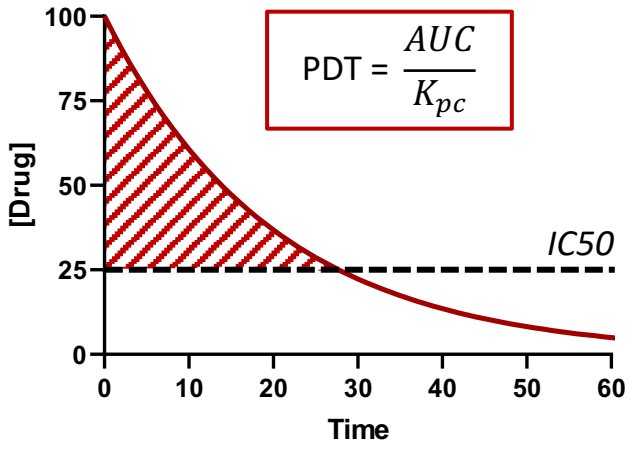
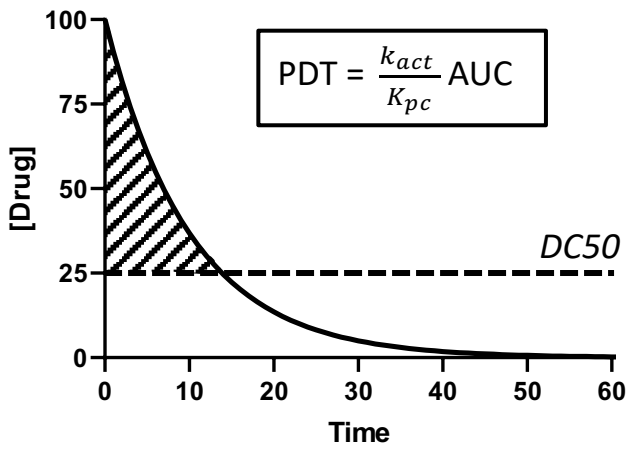
Degrader Pharmacodynamic Driver Landscape

POOR DEGRADER



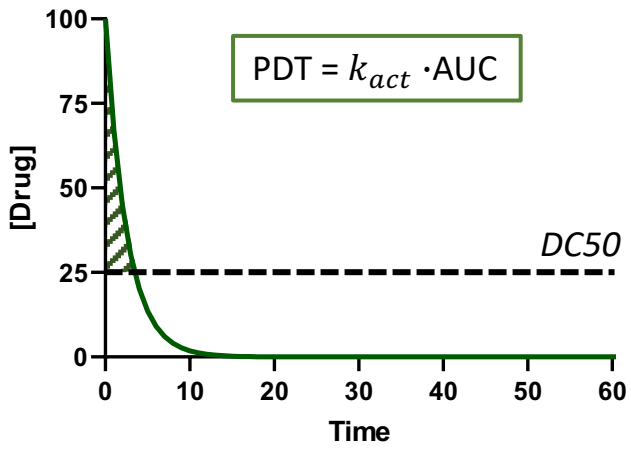
$k_{act} << K_{pc}$

GOOD DEGRADER



$k_{act} >> K_{pc}$

EXCELLENT DEGRADER



- Low catalytic activity
- Pharmacological effect driven by binding/inhibition
- High AUC required to maintain target engagement

- High catalytic activity
- Rapid target degradation drives effect
- No threshold required

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Potential Advantages of Degraders over Inhibitors

- PDT analysis assumes equivalent pharmacological response for degraders and inhibitors

- Degraders are expected to exhibit one or more of the following attributes over inhibitors (target dependent):
  - Prolonged activity duration due to target resynthesis requirement (PK/PD hysteresis)
  - Amplified activity against requisite dimers
  - Activity against scaffolding functions
  - Enhanced selectivity
  - Activity against secondary mutations

Degraders ≠ Inhibitors

Degraders are expected to have *enhanced* pharmacological response over inhibitors

C4 Therapeutics

The C4 Therapeutics Team