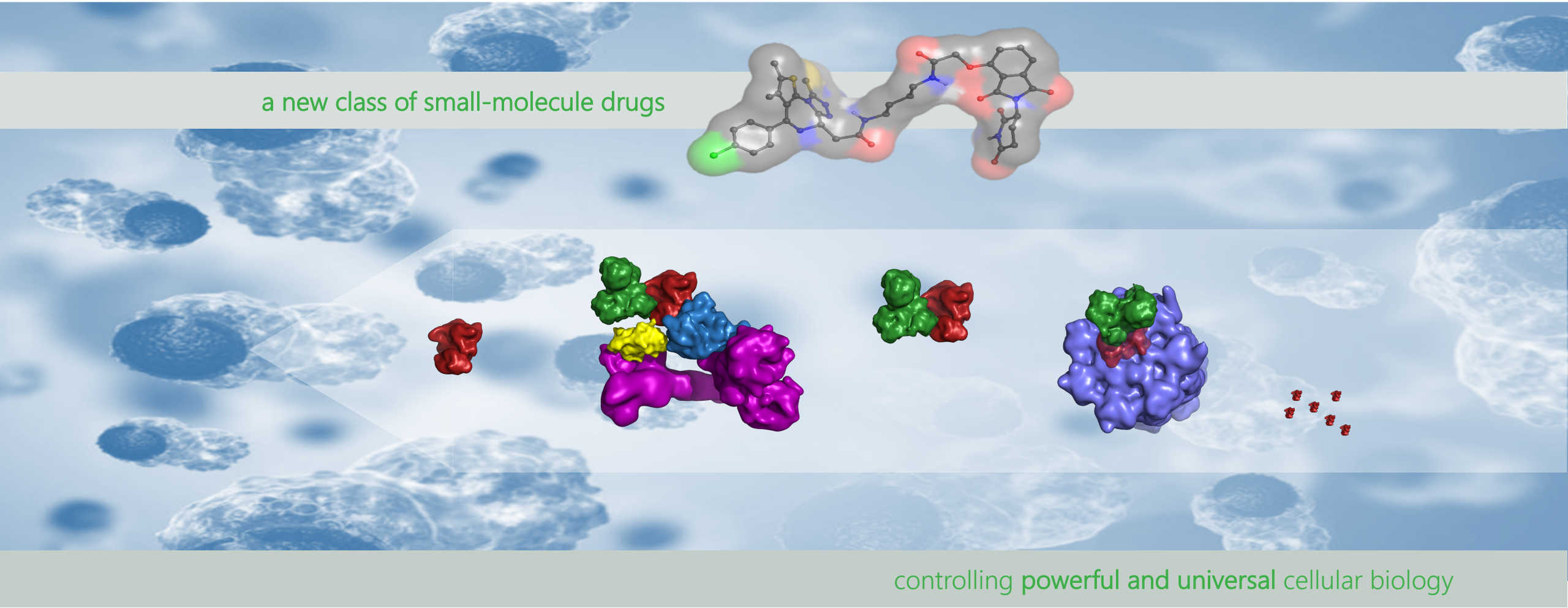

Translating Cellular Targeted Protein Degradation to in vivo Models using an Enzymology Framework

AACR Virtual Annual Meeting II
June 22, 2020

C4 Therapeutics

Disclosure Information

I am an employee of C4 Therapeutics.

I am a shareholder in C4 Therapeutics.

I will not discuss off label use and/or investigational use in my presentation.

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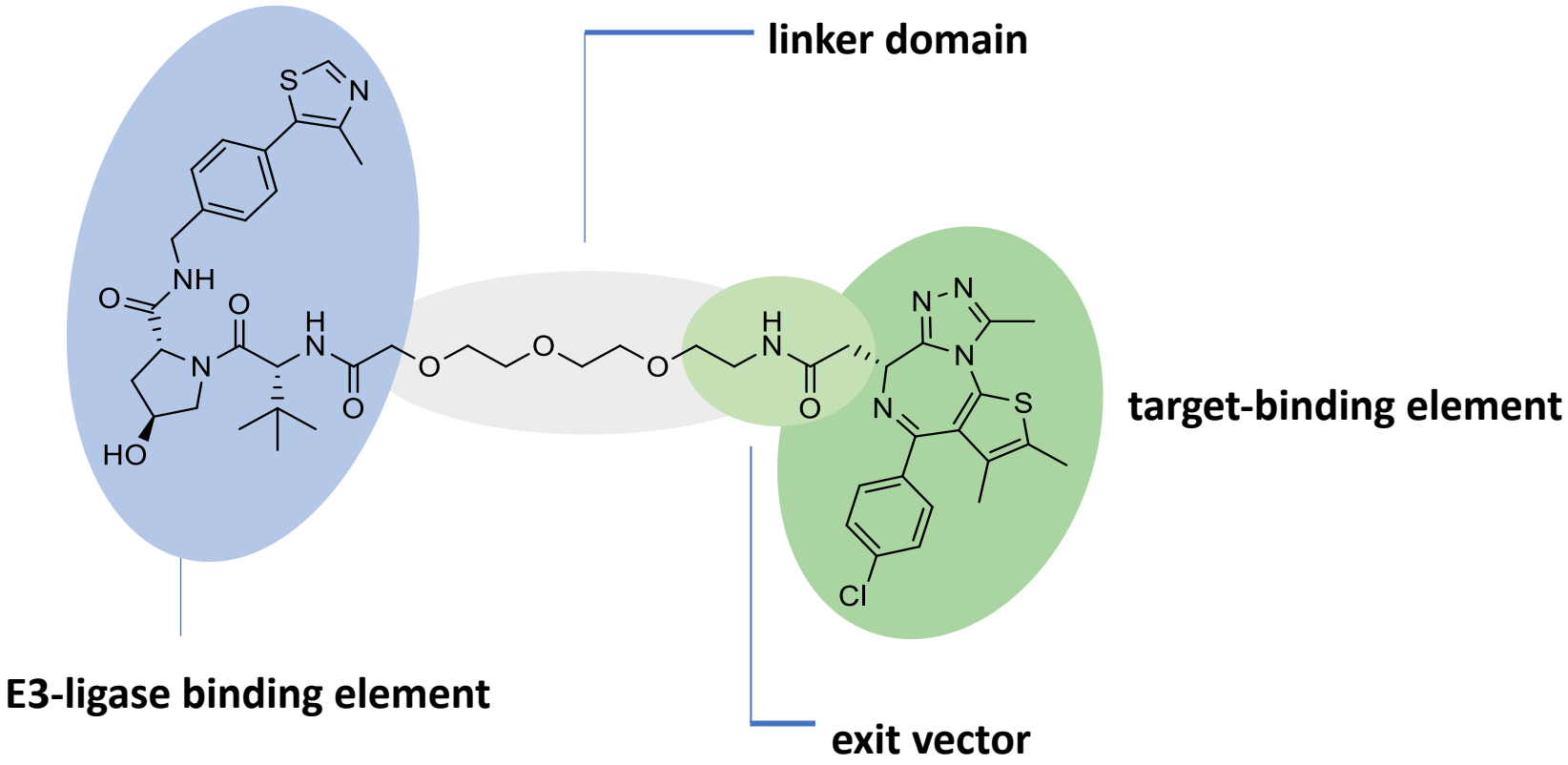
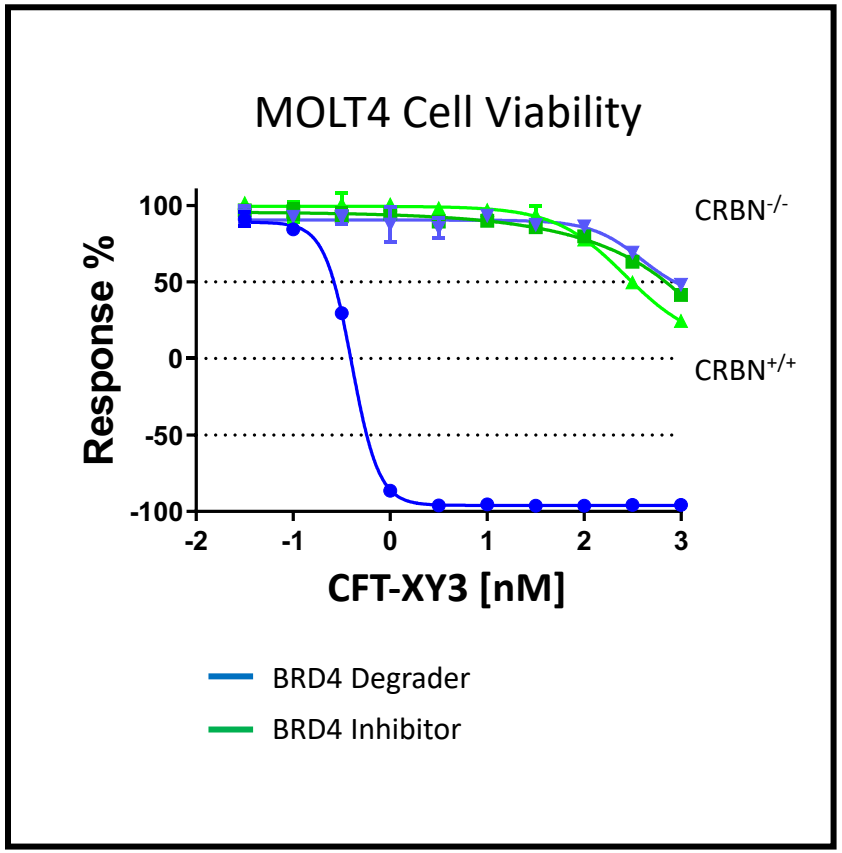
Degrader Anatomy

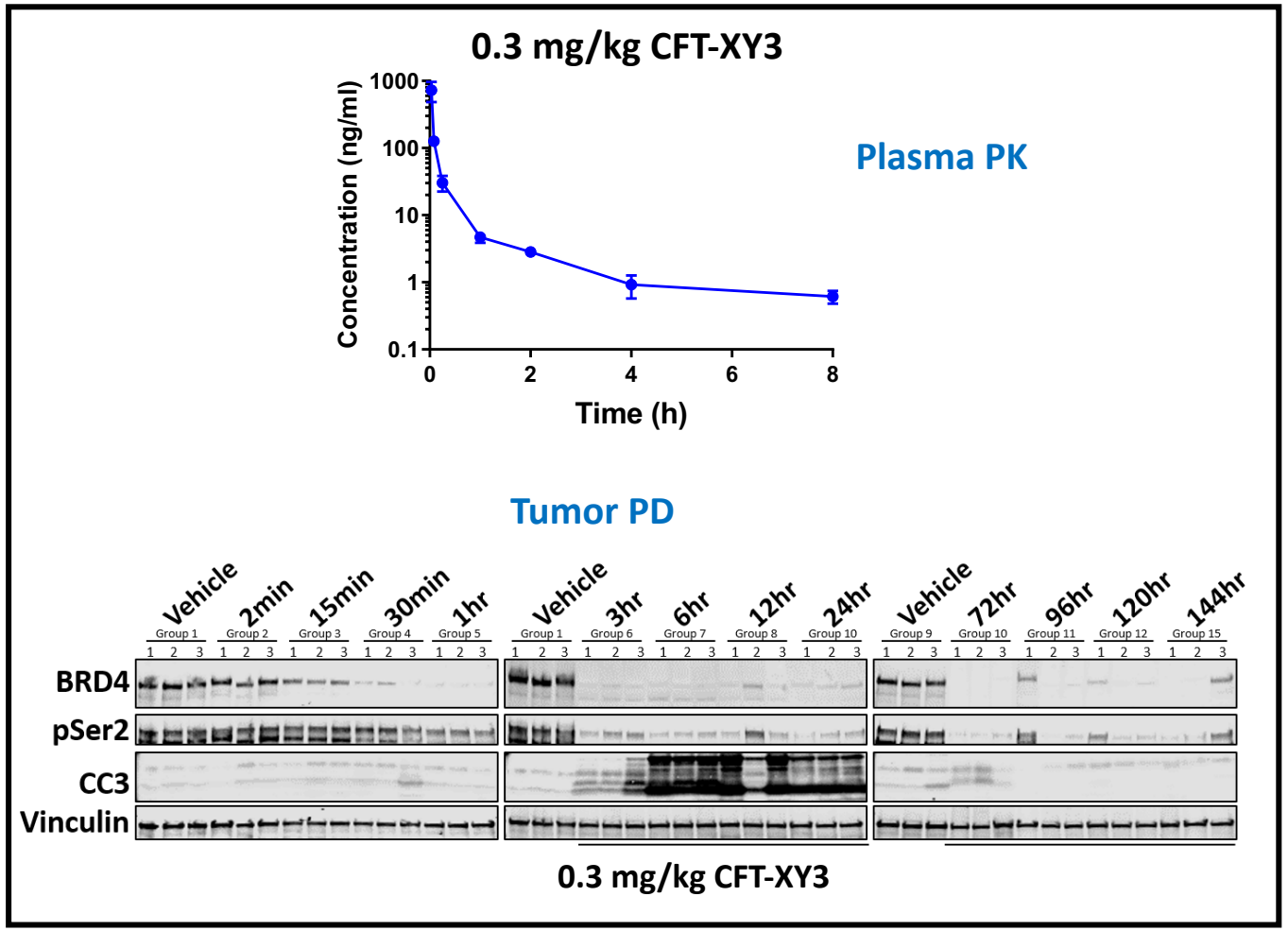


Potent BRD4 degrader induces rapid tumor apoptosis

Cellular



in vivo



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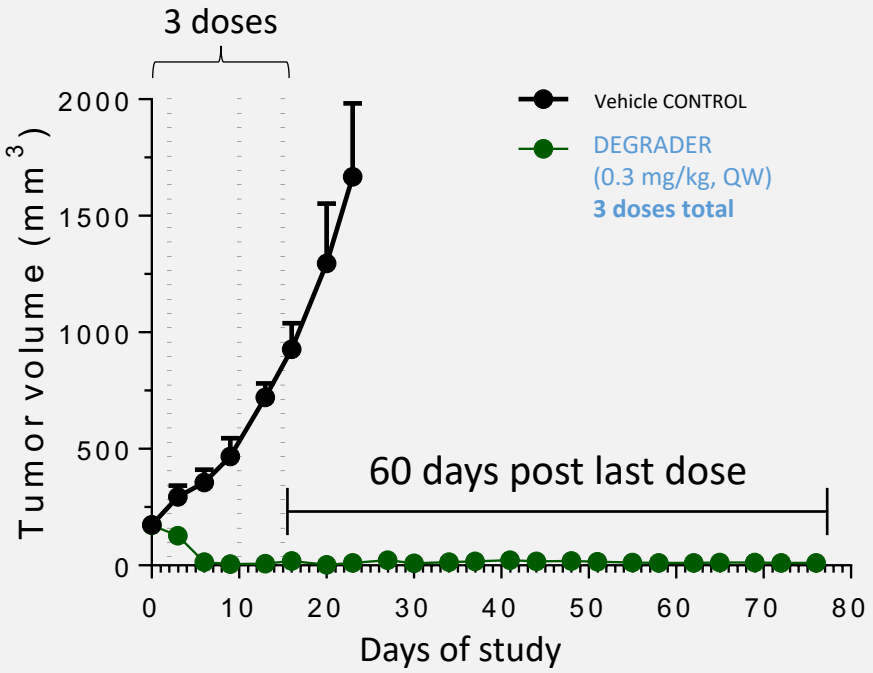
An Advanced Example: BRD4 Degraders Dosed Intermittently Yield Complete Responses

COMPLETE RESPONSE

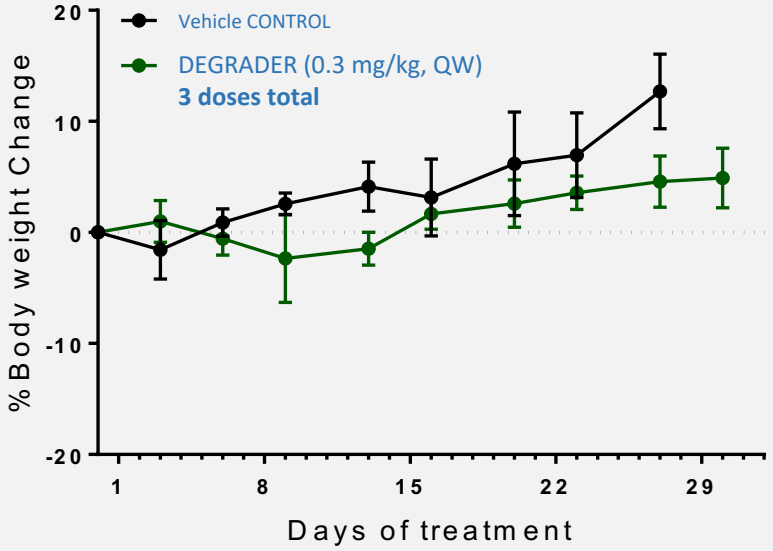
advanced BRD4 degraders show complete responses in MV4;11 AML models



degrader dosed once weekly

WELL TOLERATED

advanced BRD4 degraders have minimal effect on mouse body weight



degrader dosed once weekly

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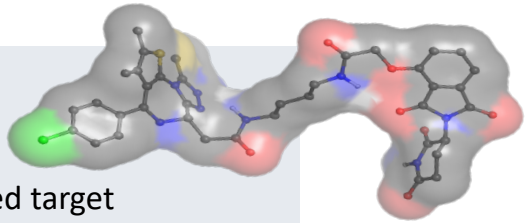
Degraders: Programmable Function in Molecules with Pharmaceutical Properties

Medicinal chemistry provides degraders with diverse, and desirable, physicochemical and pharmacological properties



MW	600-1300 Da
Degradation potencies	50pM (maximum); routinely 0.15-10nM
Selectivity*	High. Routinely observe only degradation of desired target
Catalytic efficiency	K_{cat} = 6 (high catalysis); K_{cat} = 1 (moderate catalysis)
log D	1 – 4 (experimentally determined)
Protein binding	78 - 99%
V_{dss} (L/kg)	0.13 – 14 L/kg
$T_{1/2}$ (h)	0.3 – 26.7 hour
Clearance	0.14 – 150 ml/min/kg
Plasma Stability	0 – 98%
Kinetic Solubility	0.5 – 500 µM
Oral bioavailability	**YES**. F% up to **100%** with examples in all settings where pursued Good oral exposures (AUC/dose >1200 h*ng/ml achieved)

* Control over degradation of known Cereblon neosubstrates (Ikaros, Aiolos, GSPT1, CK1α, SALL4 etc) can be achieved by medicinal chemistry

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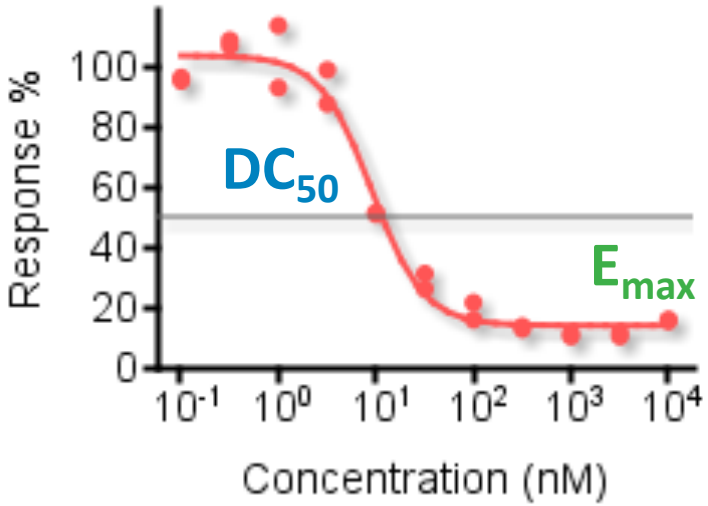
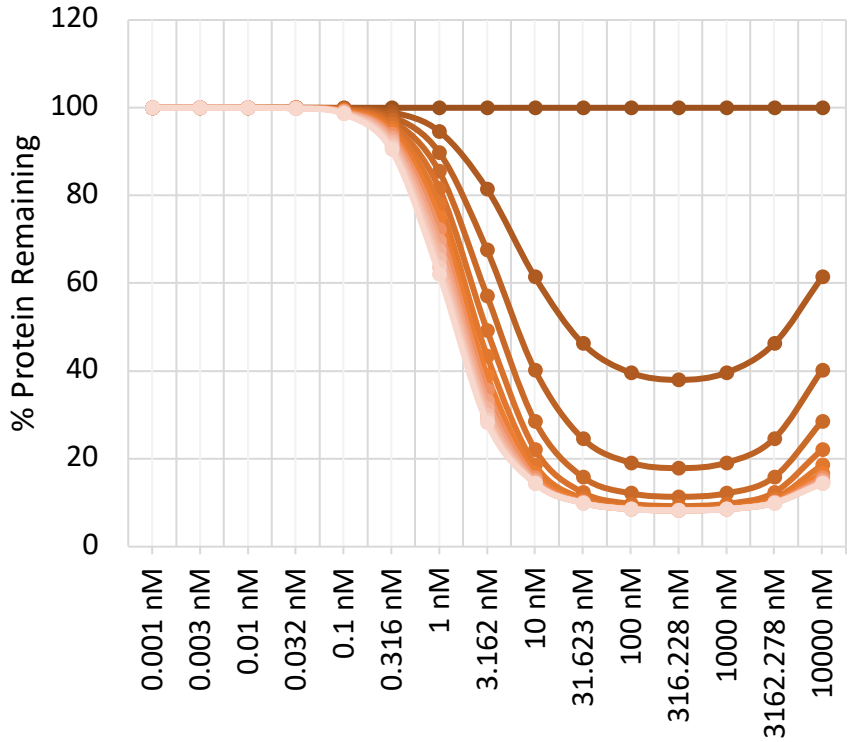
Cellular Degradation is Time Dependent

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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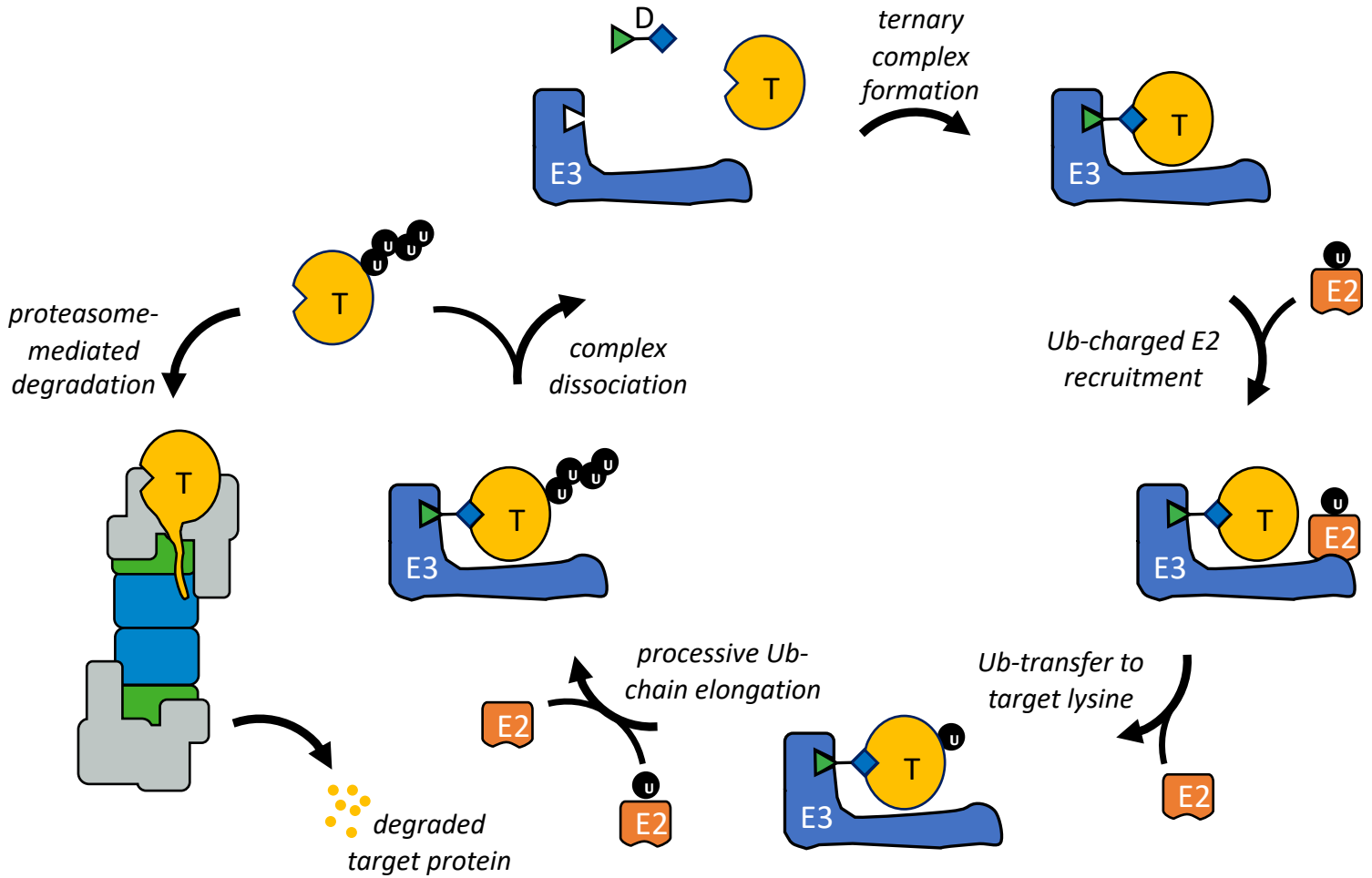
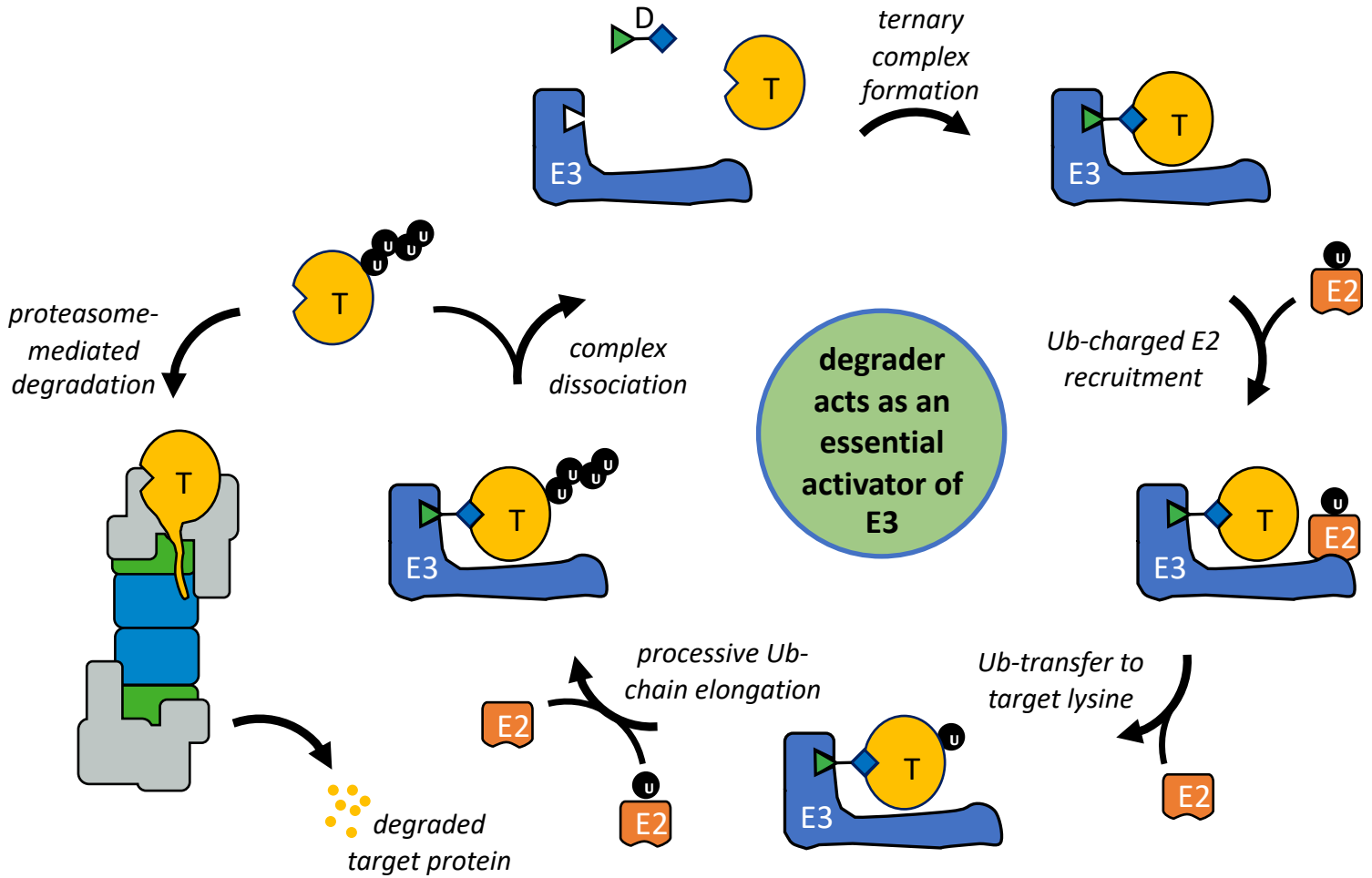
The Catalytic Cycle of Degradation



Fisher and Phillips *Curr Opin Chem Biol.* **2018**, *44*: 47-55

Degraders are Essential Catalytic Activators



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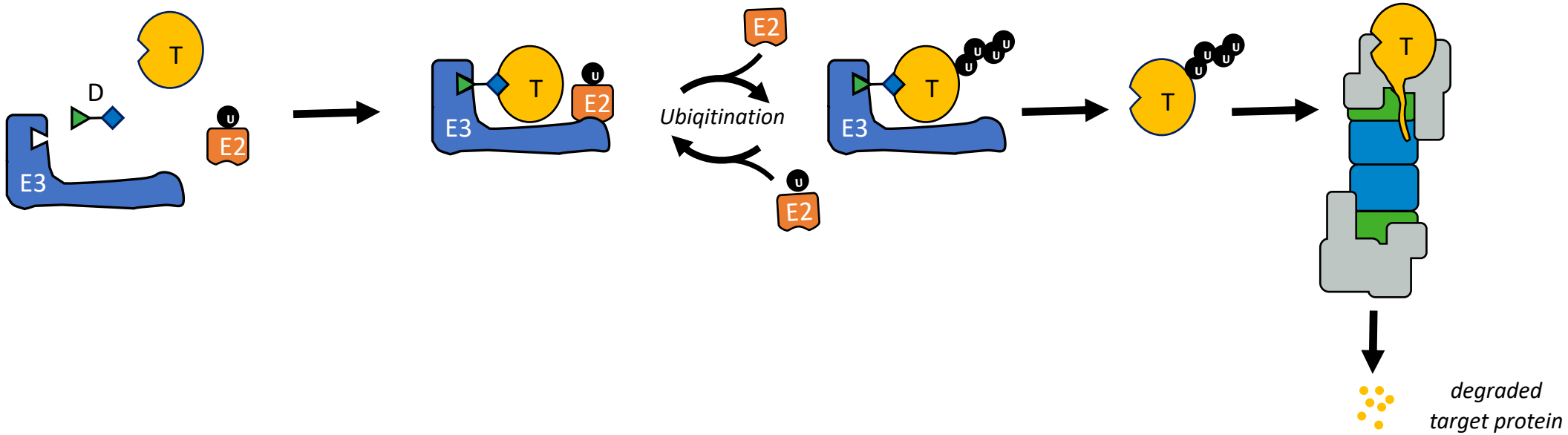
Fisher and Phillips *Curr Opin Chem Biol.* **2018**, *44*: 47-55

Applying an Enzymology Framework



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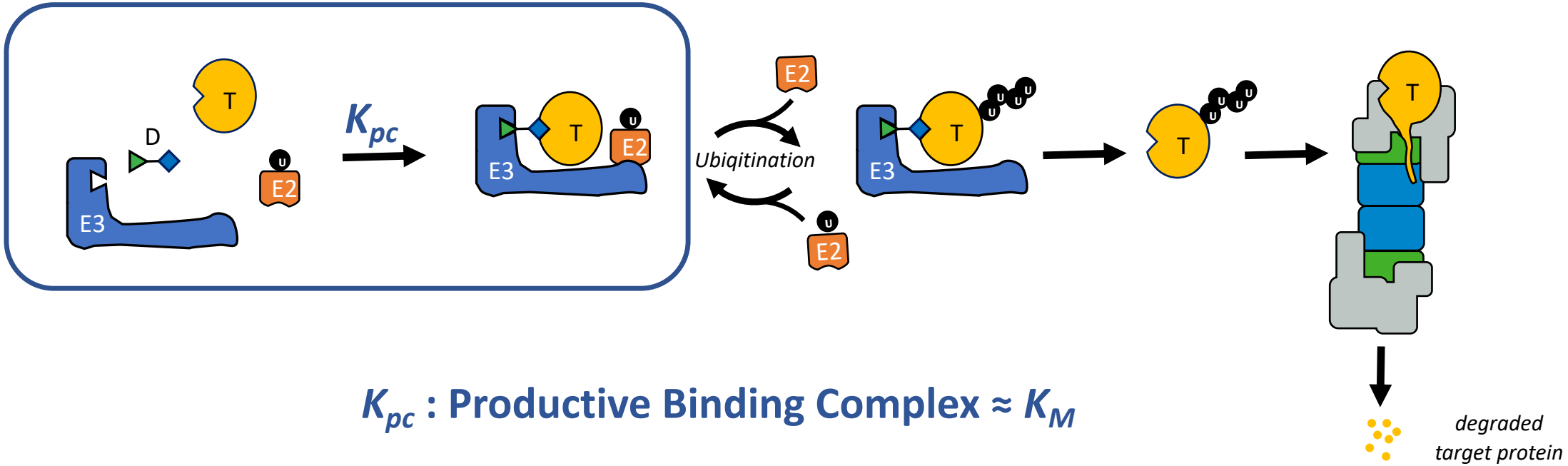
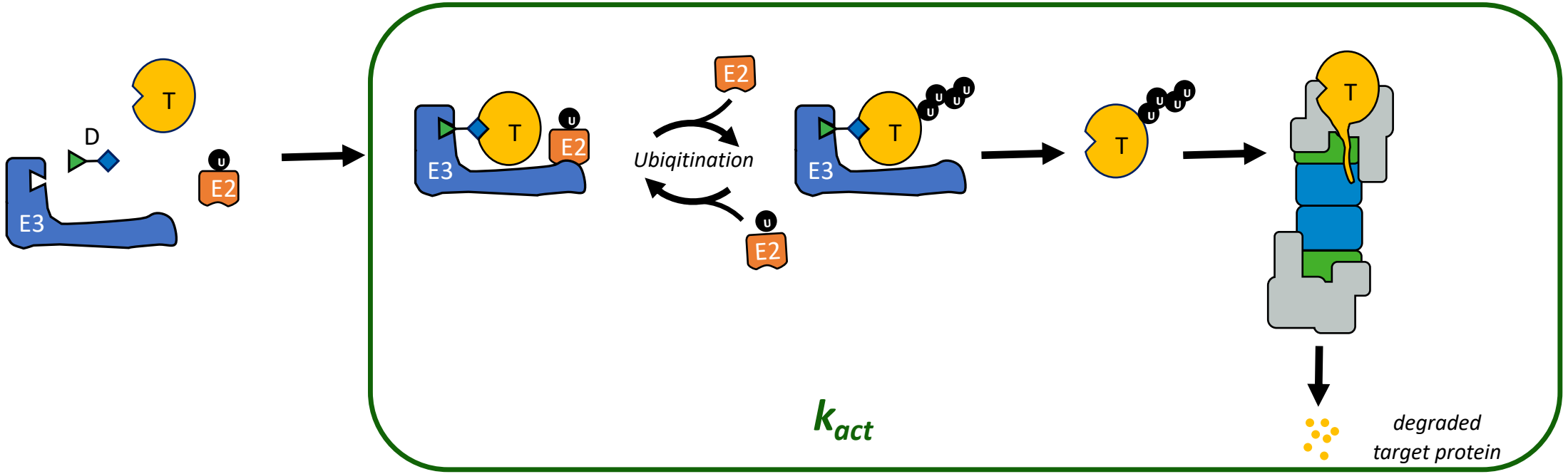
Applying an Enzymology Framework: Binding



K_{pc} : Productive Binding Complex ≈ K_M

Applying an Enzymology Framework: Catalysis



k_{act} : Target turnover rate ≈ k_{cat}

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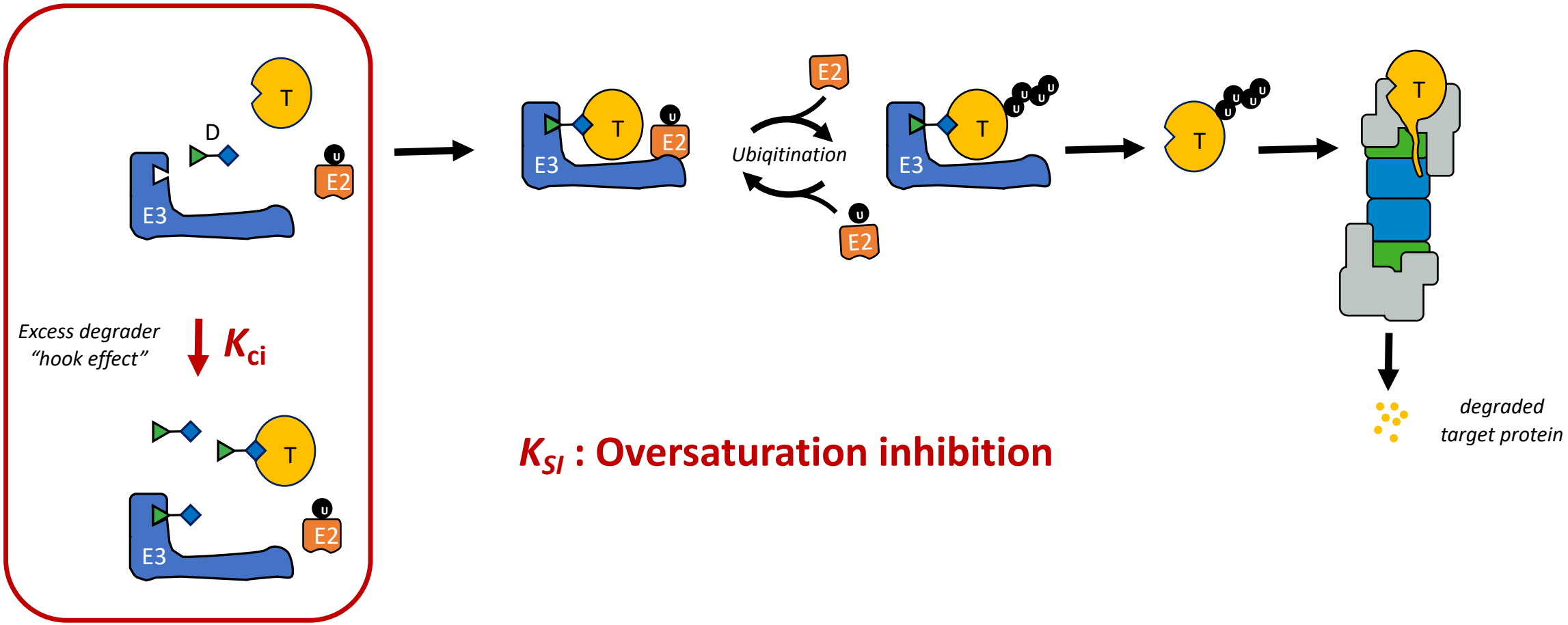
Applying an Enzymology Framework: Inhibition



K_{SI} : Oversaturation inhibition

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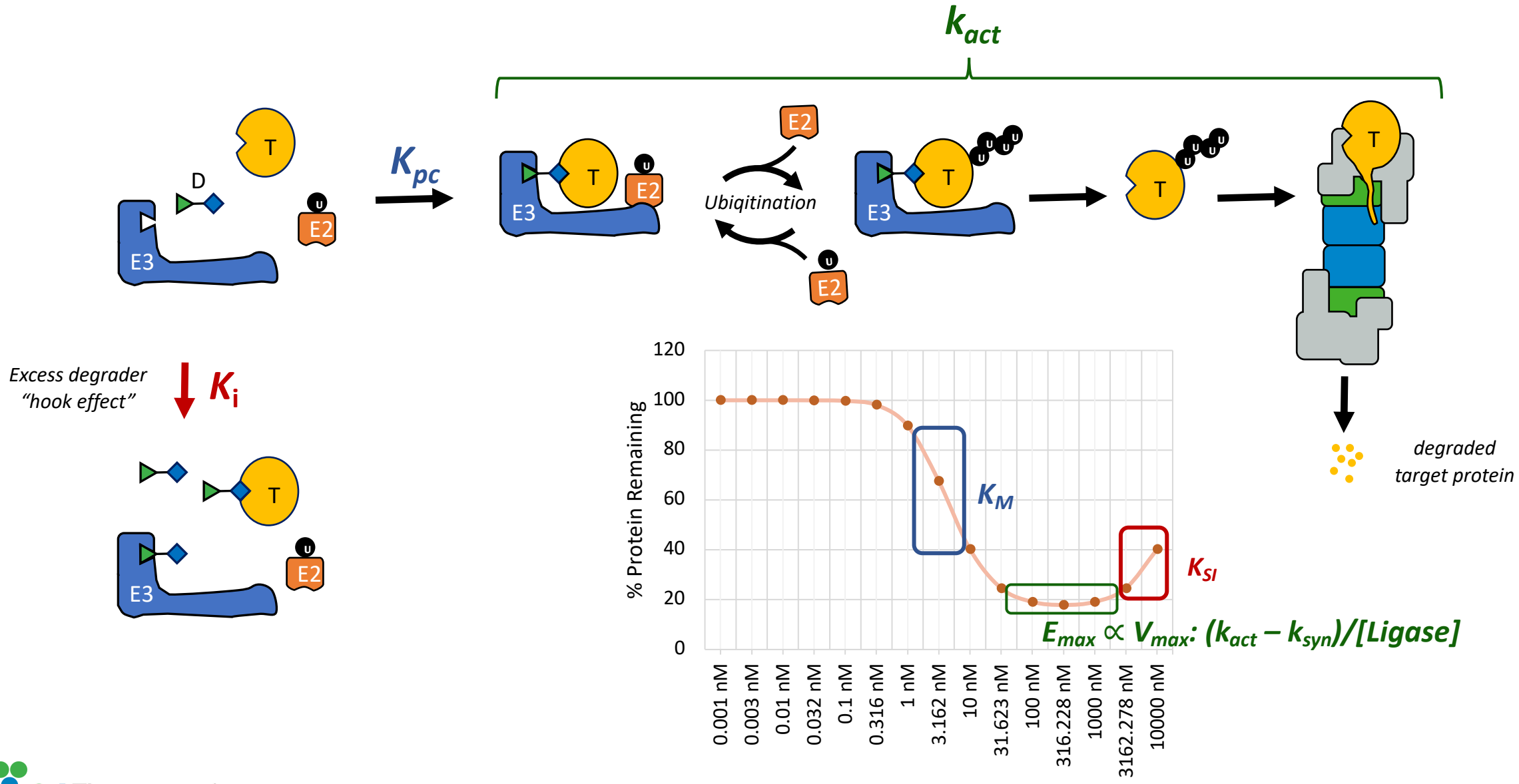
Applying an Enzymology Framework: Qualitative Mapping



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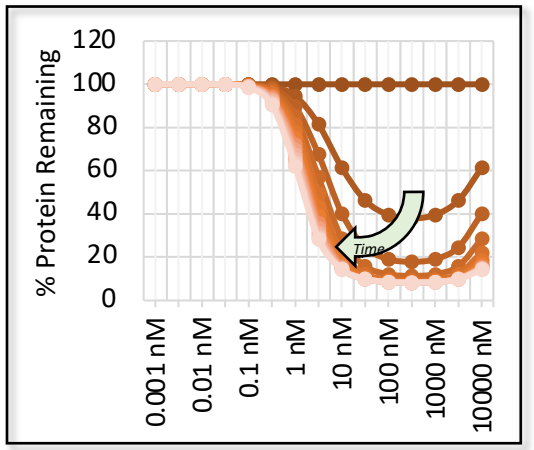
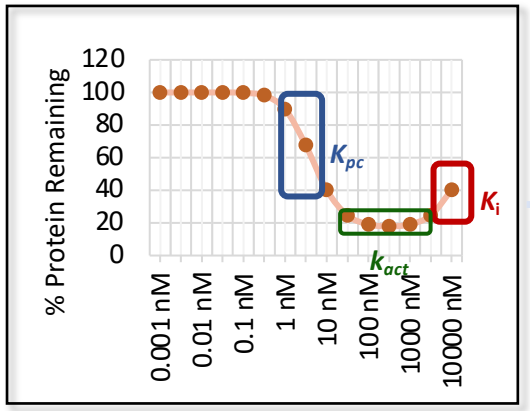
Assays and framework support predictions of *in vivo d*egradation

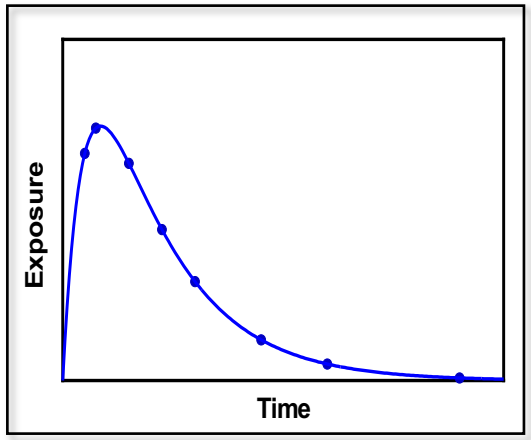
Enzymology Framework



TIME DEPENDENCE

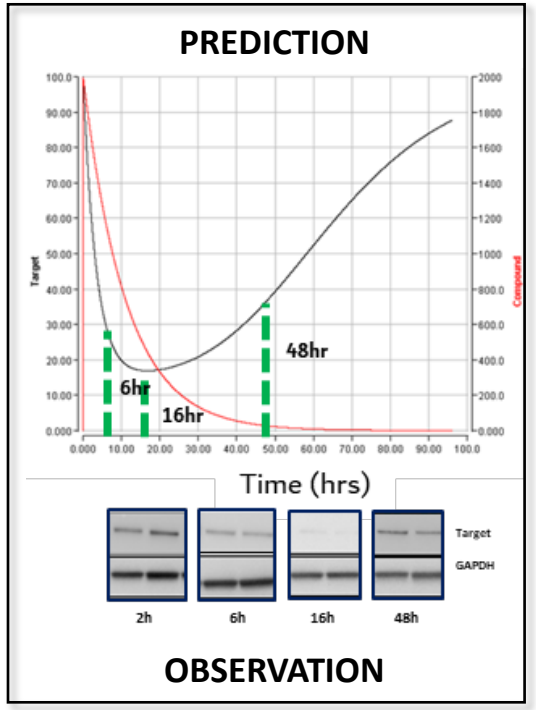


KEY PARAMETERS



DMPK PROPERTIES

C4T Proprietary PK/PD Models



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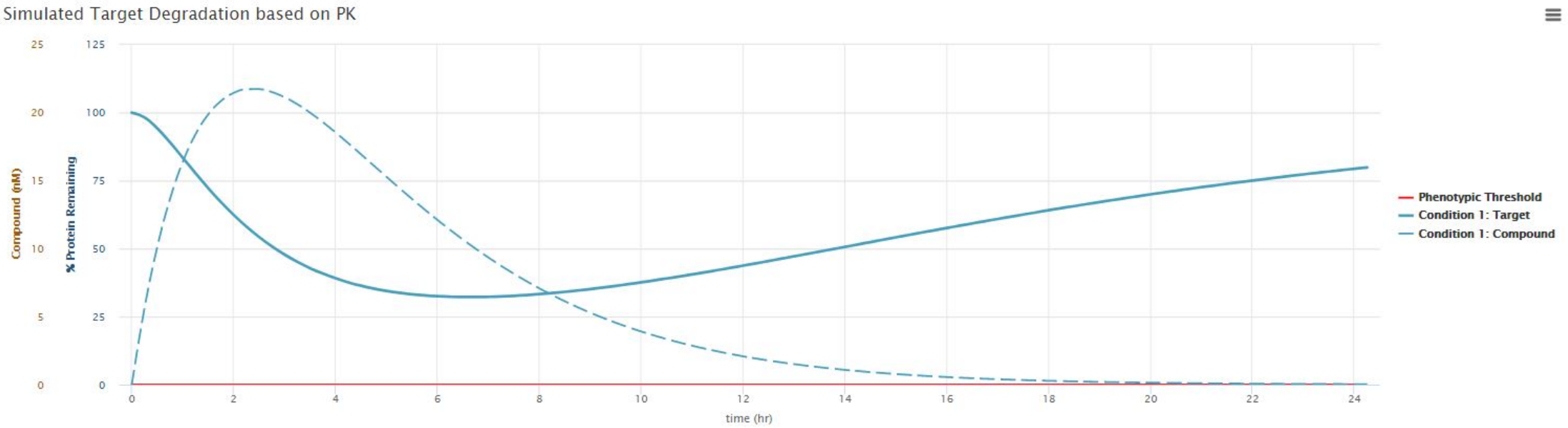
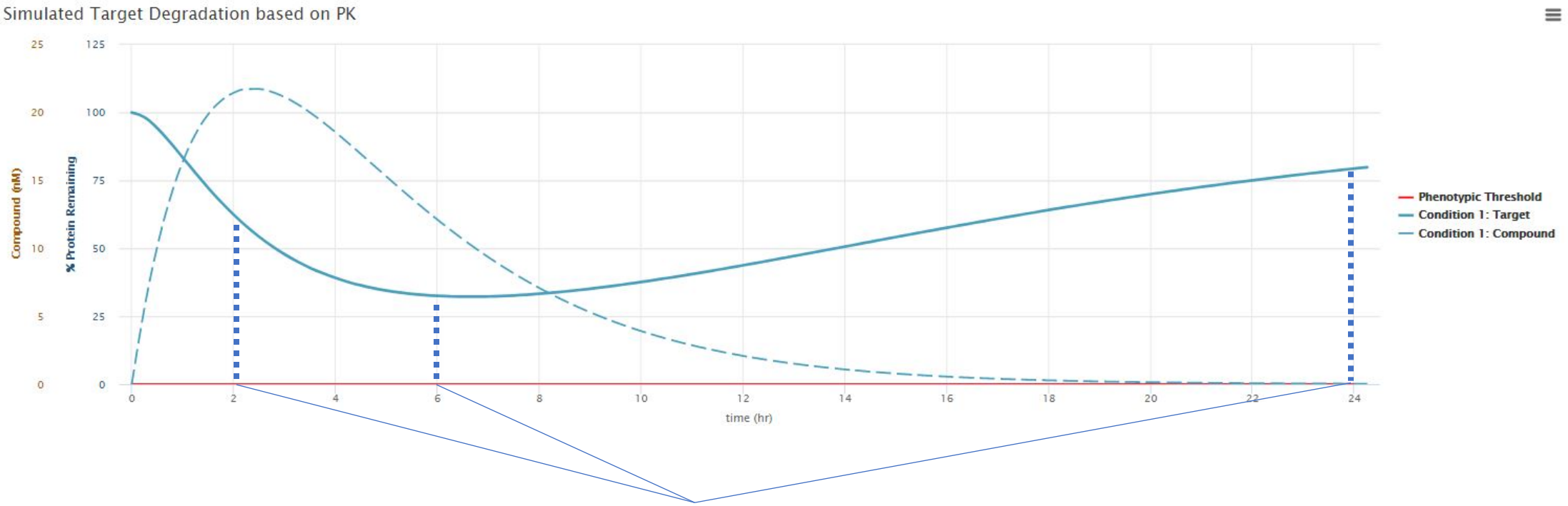
Quantitative Framework can be extended to PKPD Simulations



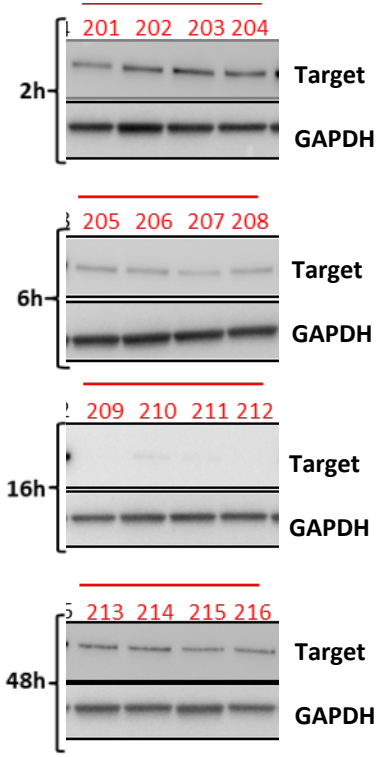
Quantitative Framework can be extended to PKPD Simulations



Optimal PD sampling points

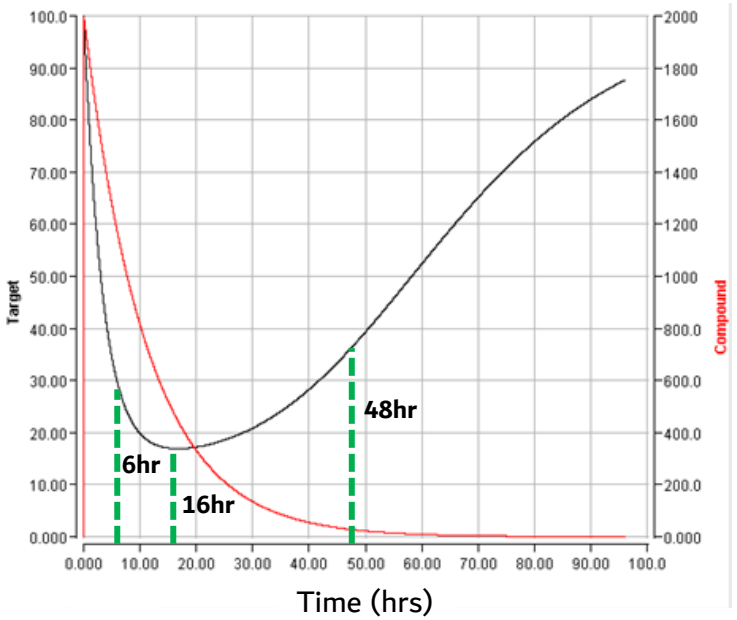
Validation of PKPD modeling

Mouse tissue samples
Western Blot analysis

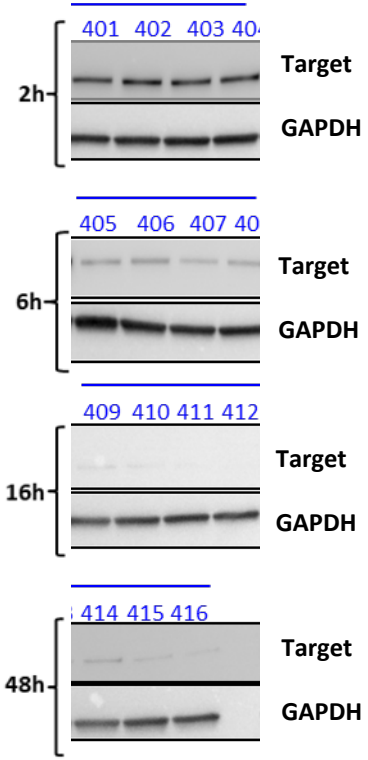


Example 1

(protein levels shown as black line)

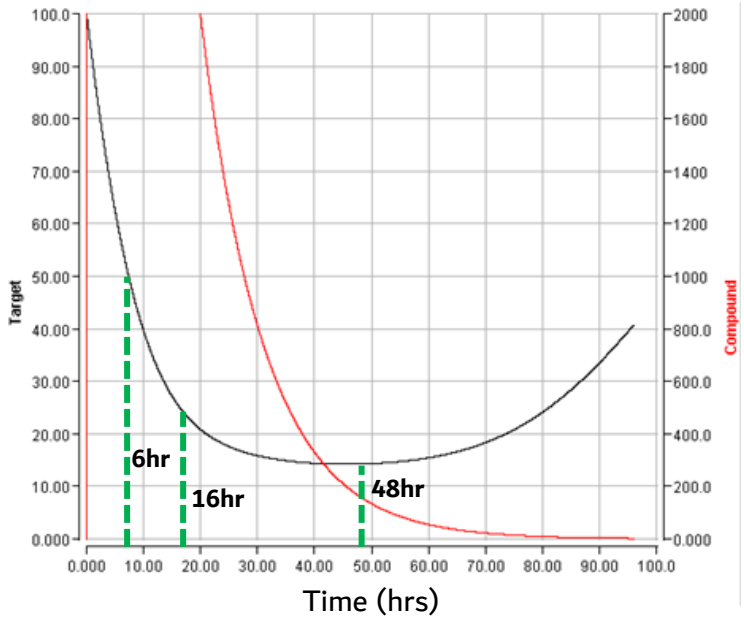


Mouse tissue samples
Western Blot analysis



Example 2

(protein levels shown as black line)



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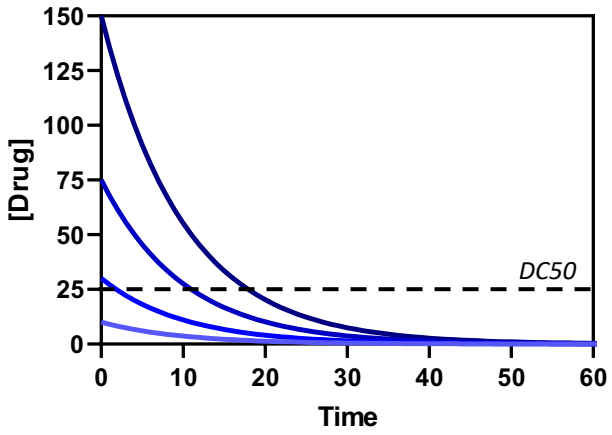
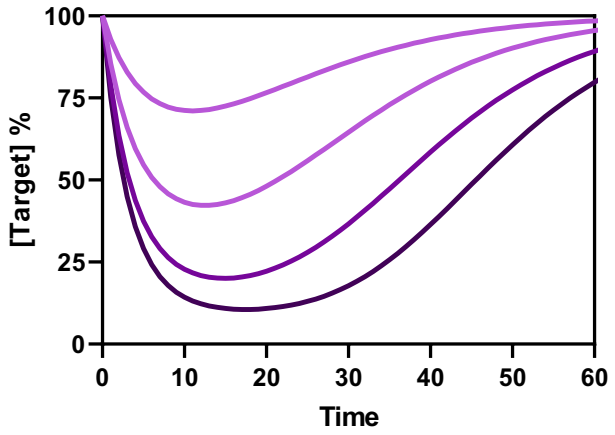
Pharmacodynamic Threshold: Linking Pharmacodynamics to Efficacy

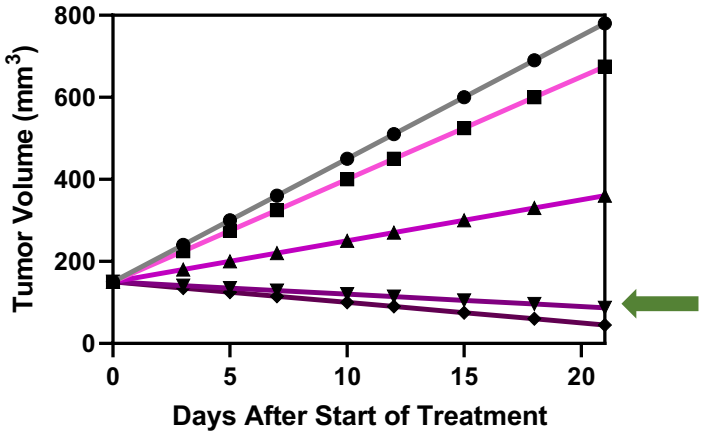
ASCENDING DOSE PK



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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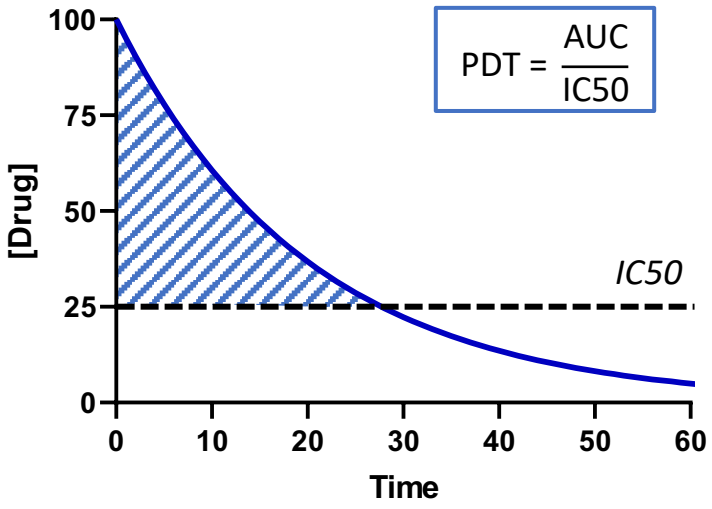
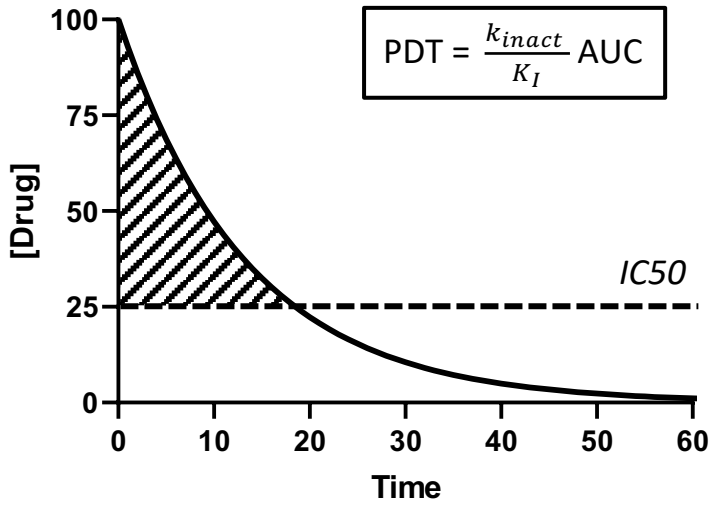
Degrader catalytic activity drives pharmacology: lower exposures required

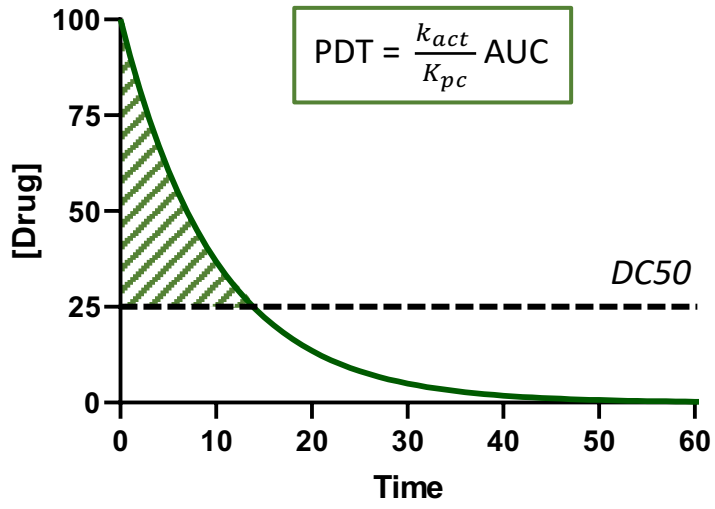
REVERSIBLE INHIBITOR



COVALENT INHIBITOR



DEGRADER



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

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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 (PKPD hysteresis)
  - Amplified activity against requisite dimers
  - Activity against scaffolding functions
  - Enhanced Selectivity
  - Activity against secondary mutations

Degraders ≠ Inhibitors

Degraders expected to have *enhanced* pharmacological response over inhibitors

C4 Therapeutics

The C4 Therapeutics Team

C4 Therapeutics