3rd Annual TPD Targeted Protein Degradation

PK/PD RELATIONSHIP IN TARGETED PROTEIN DEGRADATION (TPD)

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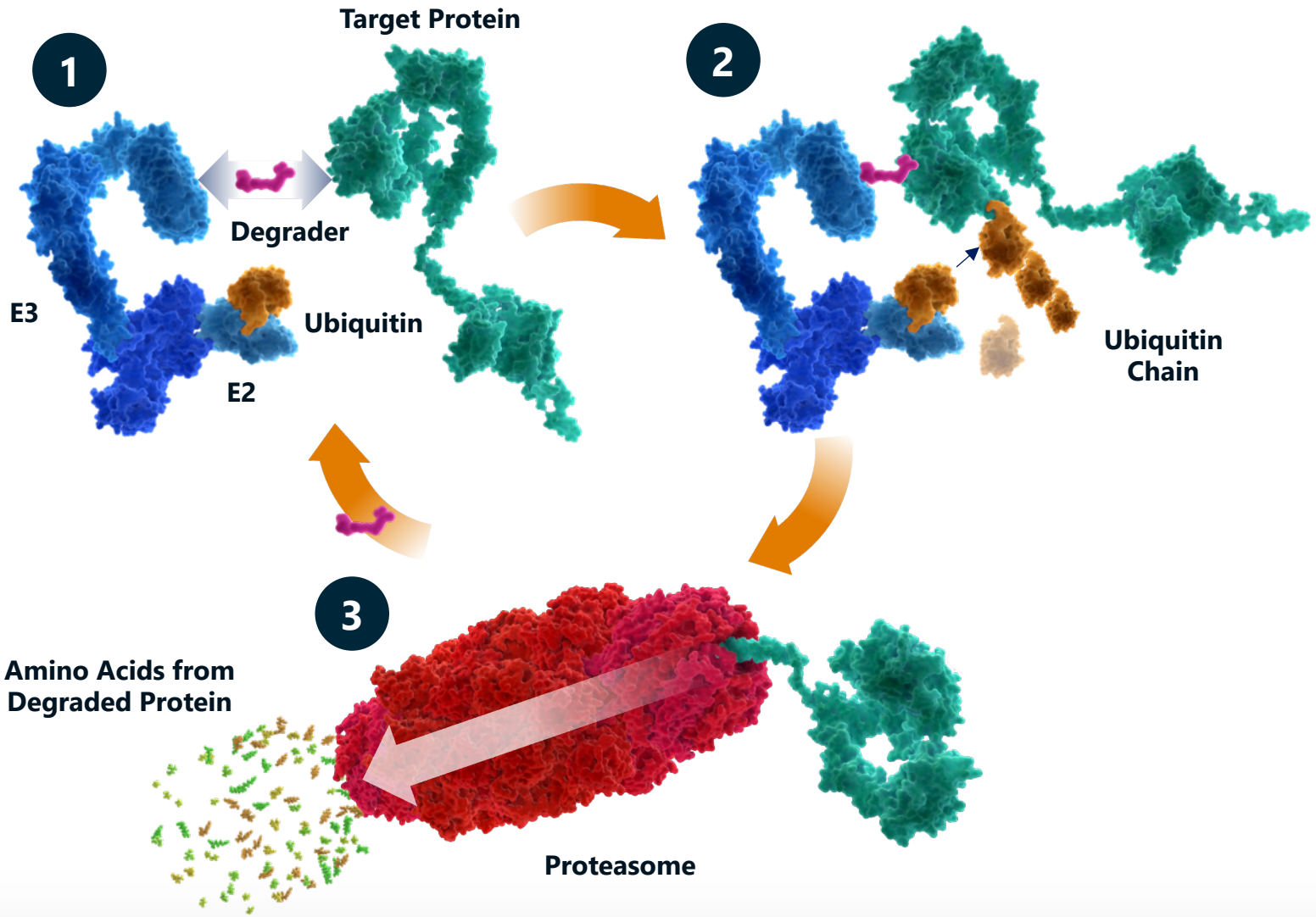
Biology of Targeted Protein Degradation



Heterobifunctional Targeted Protein Degrader

Broad Opportunity
Only Binding Site Required

Efficient
Catalytic

Prolonged Impact
Targeted Protein Degradation

In Vivo Protein Degradation: A Still-Evolving Field

Proven Clinical Benefit of Targeted Protein Degradation

Many Disease-Causing Proteins are Being Degraded

- **Scaffolding kinases**: HER2, ALK, FLT-3, FAK, RIPK2, **IRAK4**, BTK
- **Scaffolding proteins**: BRD9
- **Nuclear receptors**: AR, ERRα
- **E3 ligase**: MDM2
- **Transcription factors**: Ikaros, **STAT3**, ARNT

Questions on PK/PD

- Degradation/efficacies were seen at high dose and μM exposure (Watt et al, *DDT*, 2019)
  - Appeared to be inconsistent with the concept of "event-driven pharmacology"
  - Lack of good potency from degrader?
  - Faster synthesis rate of target protein?
- How do the drug- and system-dependent parameters interplay *in vivo*?
- How to predict *in vivo* degradation in human?

Kymera Proprietary Pegasus TPD Platform

E3 Ligase Whole-Body Atlas

Identification of the **expression profiles of the approximately 600 unique E3 ligases** to match a target protein with the appropriate E3 ligase based on expression, distribution, intracellular localization, and biology.

E3 Ligase Binders Toolbox

Leveraging the E3 Ligase Whole-Body Atlas, **a toolbox of proprietary ligands** designed to bind to novel E3 ligases to design protein degraders with specific degradation profiles for different target disease states.

Ternary Complex Modeling

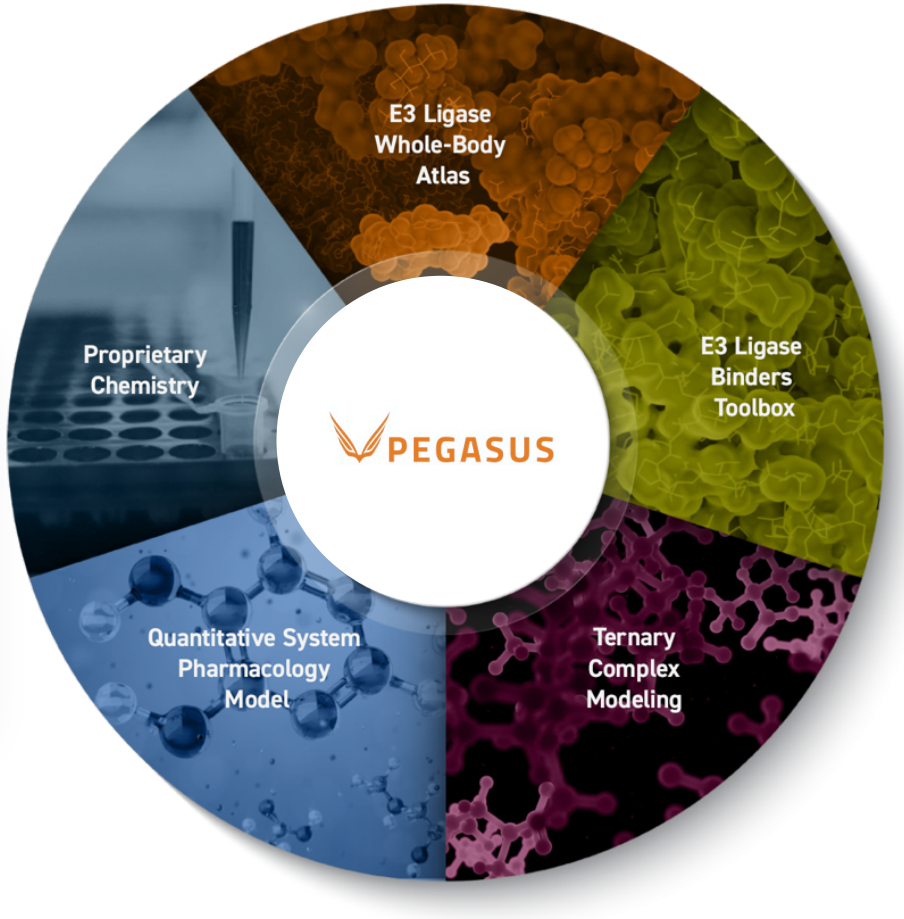
Characterization of ternary complex with both structural biology and biophysical techniques feeds a ternary complex modeling tool to optimize the development of highly efficient, and selective degrader therapeutics.

Quantitative System Pharmacology Model

A model to measure and predict the diverse sets of parameters that impact protein levels. Based on **understanding of PK/PD both *in vitro* and *in vivo***, and across different tissues and cell types.

Proprietary Chemistry

Expertise in proprietary chemistry enables the design and optimizes both E3 and target protein binders and convert them into **degraders with optimal pharmaceutical properties** tailored to specific patient populations and diseases.



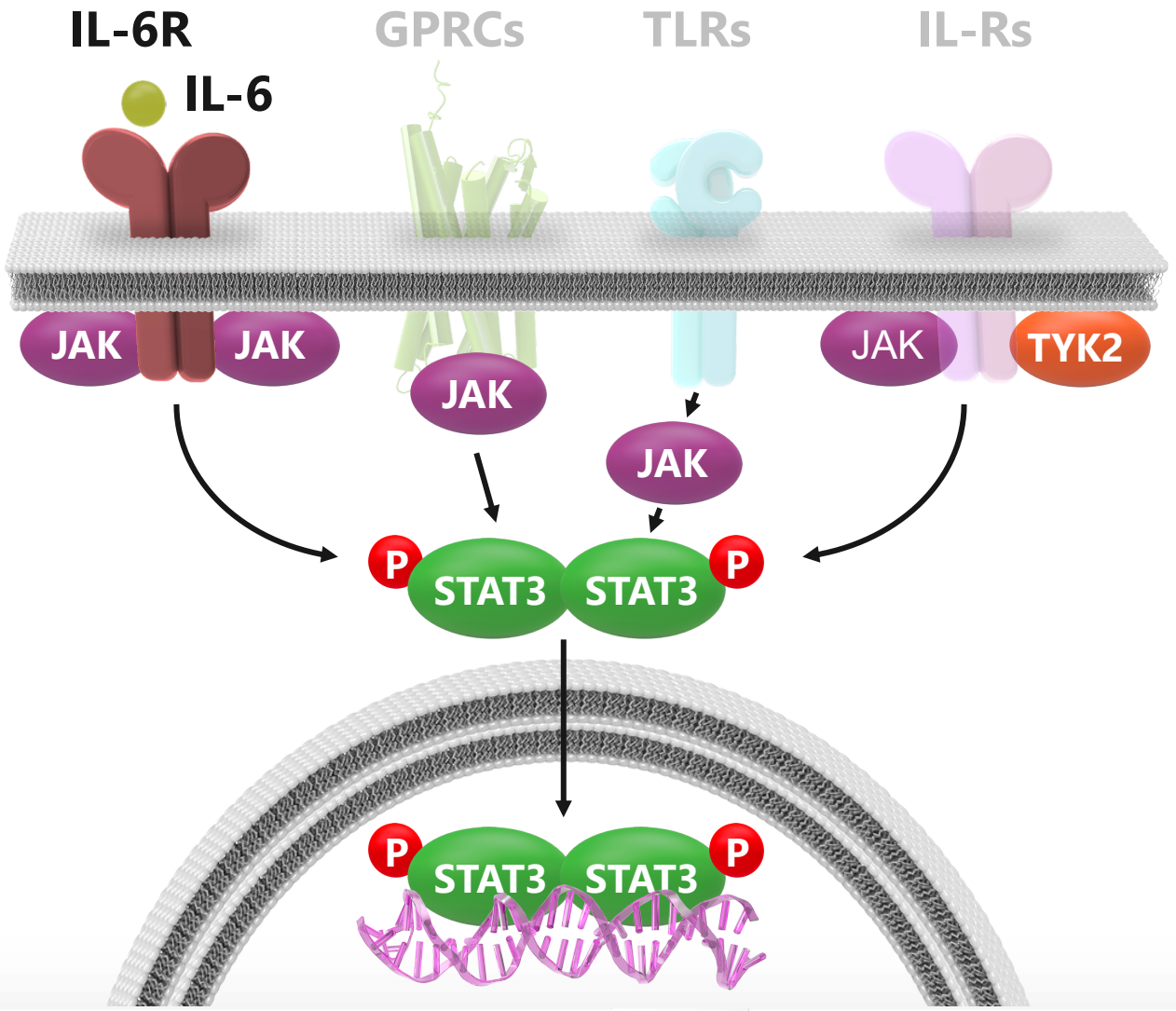
Case Study

PK/PD of STAT3 Degradation *in vivo* and Mechanistic Modeling

- "Undruggable" therapeutic target STAT3: the biology and degrader rationale
- Potency, selectivity and efficacy of STAT3 degrader KTX-201 *in vitro* and *in vivo*
- PK and PD profiles of KTX-201 in SU-DHL-1 tumor *in vivo*
- Mechanistic PK/PD modeling of KTX-201 to dissect drug- and system-parameters and enable mouse to human translation
- Summary

STAT3 Biology and Degrader Rationale

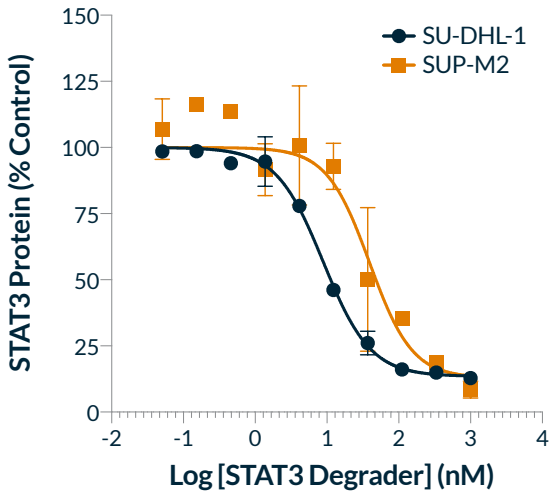
- STAT3 is a traditionally largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAKs mediated mechanisms
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported also by numerous publications
- STAT3 plays a role in tumor biology, evasion of immune surveillance and inflammation/fibrosis
- No known drugs specifically affect STAT3 broadly across all relevant cell types
- First in class opportunity to address STAT3 driven pathology across large and diverse indications



KTX-201 Exhibited High Potency and Selectivity

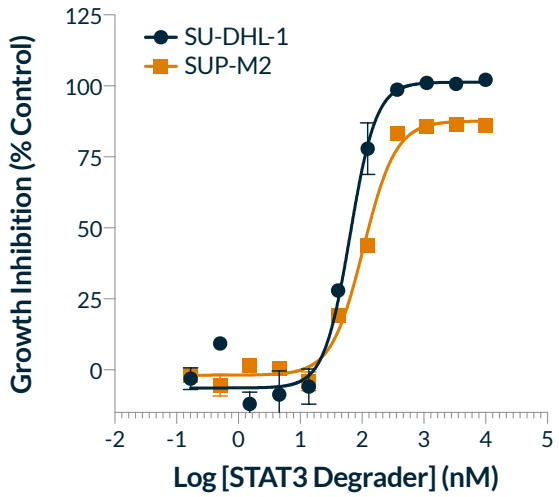
High Potency in SU-DHL-1 and SUP-M2 Cell Lines

Degradation Potency



SU-DHL-1 24h DC_{50} 15 nM
SUP-M2 24h DC_{50} 86 nM

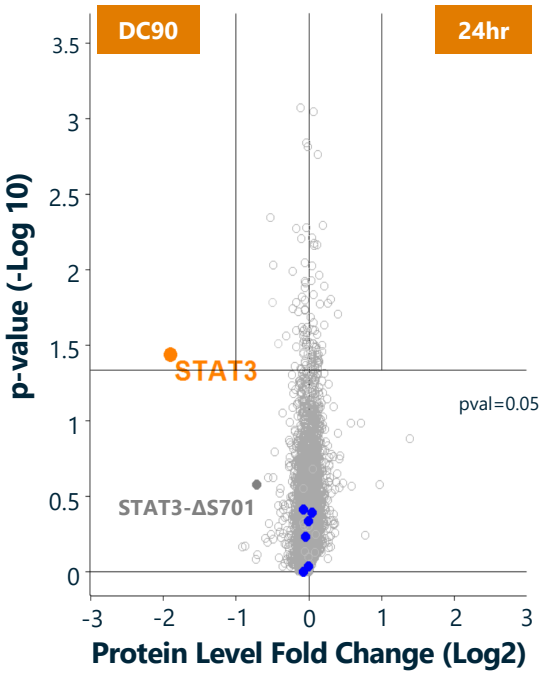
Growth Inhibition Potency



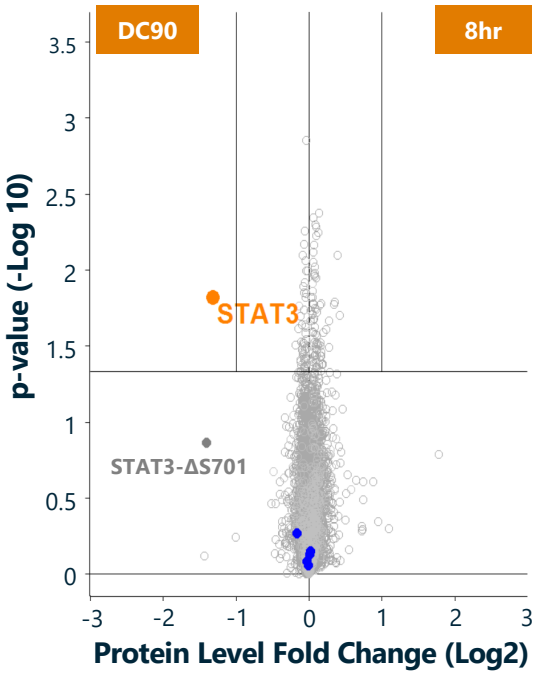
SU-DHL-1 IC_{50} 64 nM
SUP-M2 IC_{50} 105 nM

High Selectivity in huPBMCs and SUDHL-1 Cell

huPBMCs



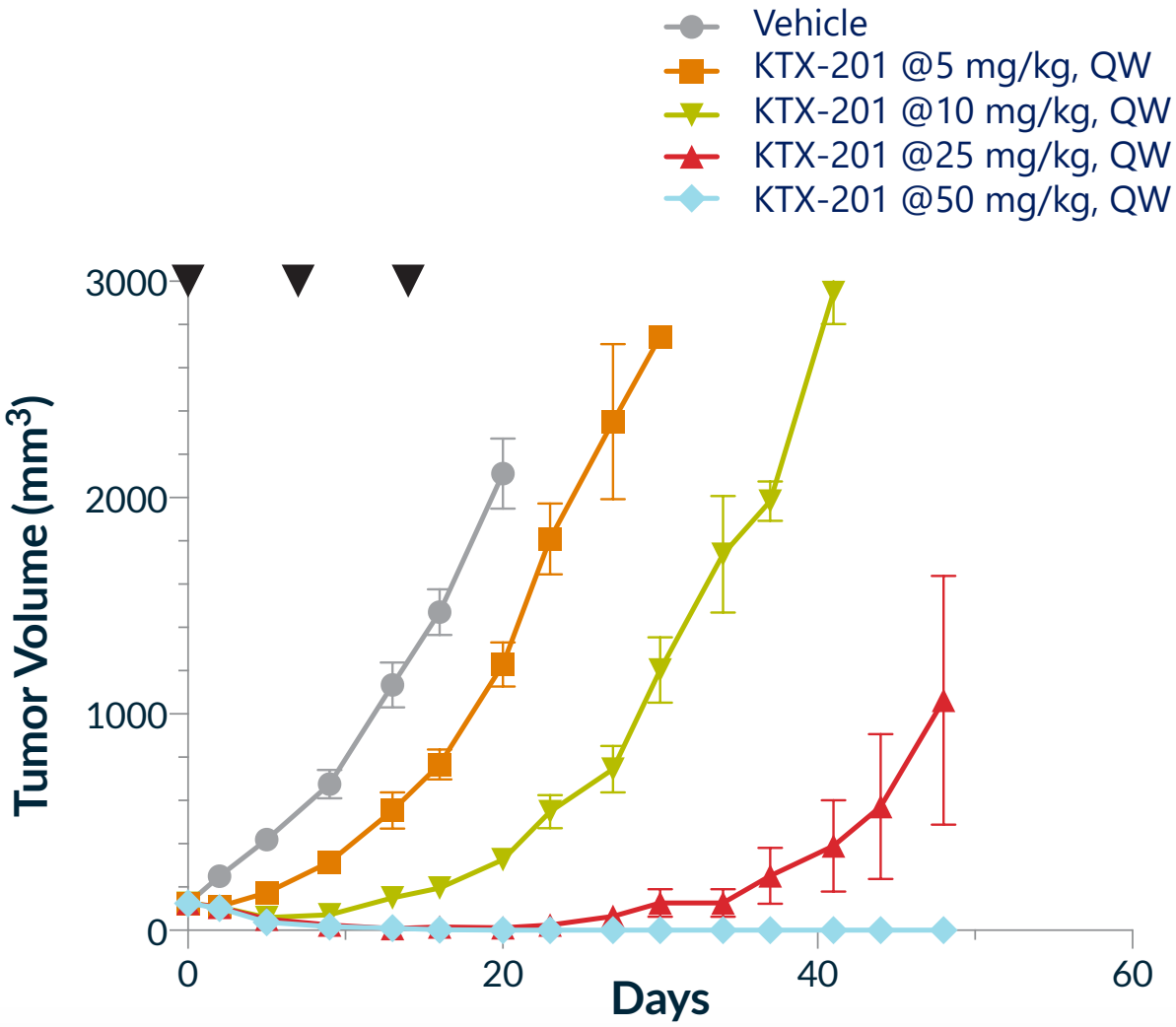
SU-DHL-1



● STAT Family Members: **STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6**

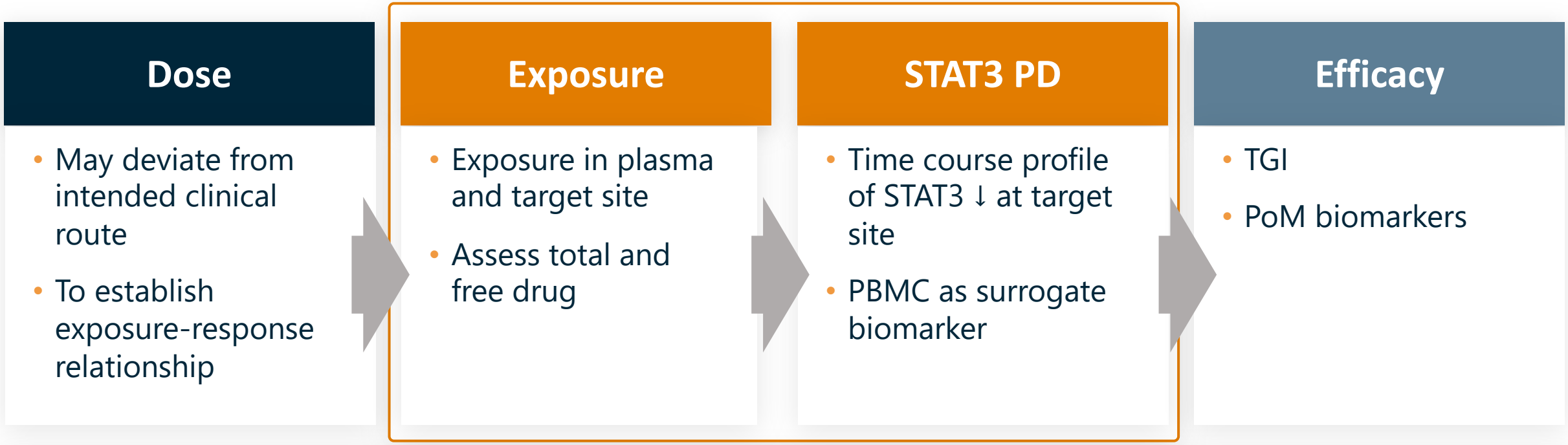
KTX-201 Showed Significant Anti-Tumor Activity *In Vivo* with Weekly Dosing Regimen

- SU-DHL-1 Xenograft Mouse
- KTX-201
  - IV bolus at 5 to 50 mg/kg
  - Weekly dosing
  - Treatment on D1, D8, D15
- The treatments were well tolerated, with no significant body weight loss
- Three doses sufficient to drive durable complete responses



Understanding PK/PD Relationship to Enable Human Translation

PK/PD Relationship *In Vivo*



Account for species difference in translation

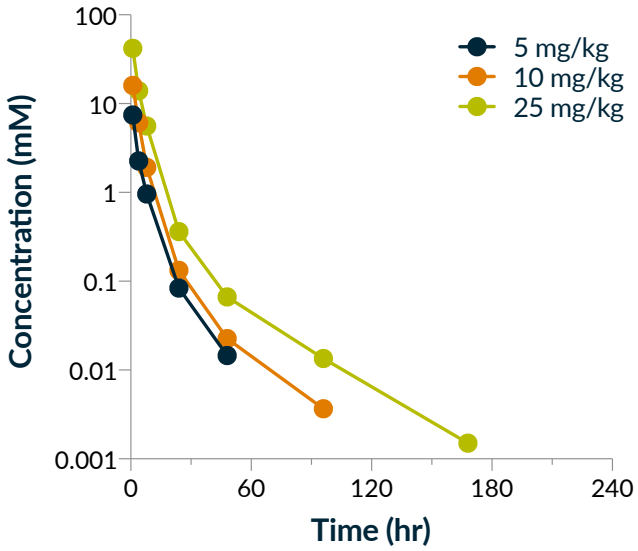
- Pharmacokinetics: drug metabolism and disposition
- Drug distribution in tissues and its kinetics
- Target protein properties:
  - Turnover rate (synthesis and degradation)
  - Disease status

KTX-201 Exhibited Prolonged Half-life in Tumor

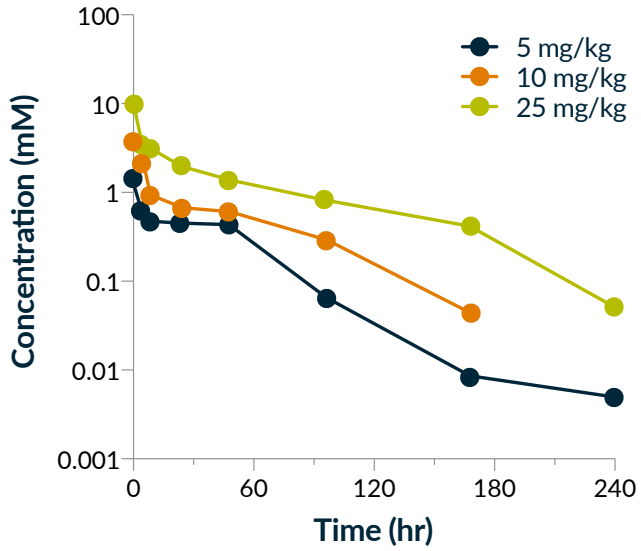
PK in Plasma and Tumor

- Plasma and tumor exposure increase as increase of dose
- $T_{½}$ in tumor > plasma
- Tumor/Plasma AUC ratio *Kp* ~1; consistent across 5 mpk to 25 mpk dose range

KTX-201 Plasma PK Profiles



KTX-201 Tumor PK Profiles



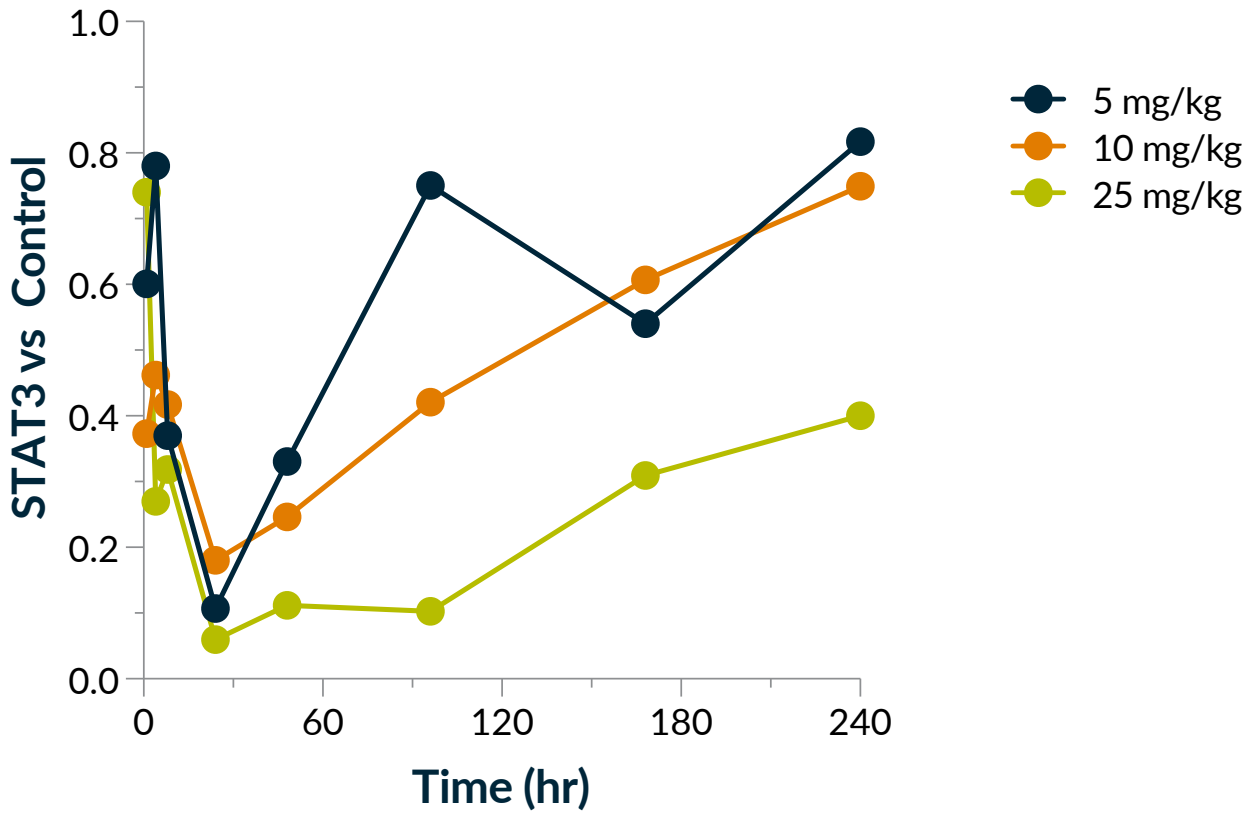
KT-5679		5 mpk		10 mpk		25 mpk	
PK Parameters	Unit	Plasma	**Tumor**	Plasma	**Tumor**	Plasma	Tumor
$T_{1/2}$	hr	6.8	**24**	16	**31**	16	**36**
AUC_{last}	µM*h	40	**36**	87	**78**	229	**231**

Degrader Exhibited Dose-Dependent STAT3 Degradation in Tumor

Degrader Dose-Dependent PD

- Maximal STAT3 degradation occurred at 24 h post dose for all the doses
- Maximal degradation is dose-dependent, >90% at 25 mg/kg
- Recovery of STAT3 is dose-dependent
  - Lower doses back to baseline 10 days post dose
  - High dose, 25 mg/kg, maintained ~50% degradation 10 days post dose

STAT3 Degradation (PD) Profiles in SU-DHL-1 Tumor

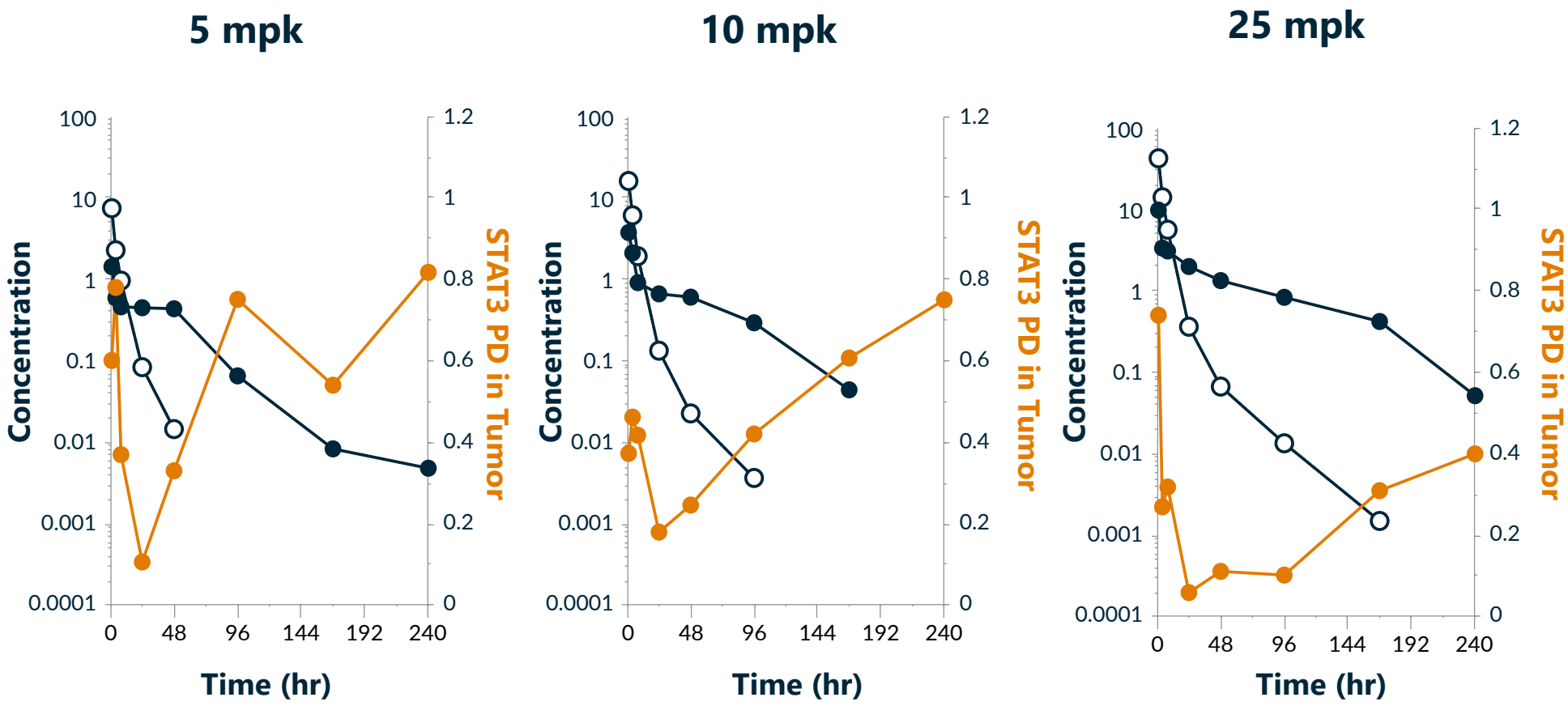


STAT3 Degradation in Tumor Was Exposure-Dependent

- Prolonged degradation in tumor is partially due to longer drug half-life in tumor
- $T_{½}$ of STAT3 return to baseline is dose-dependent → higher dose/higher exposure/ prolonged degradation

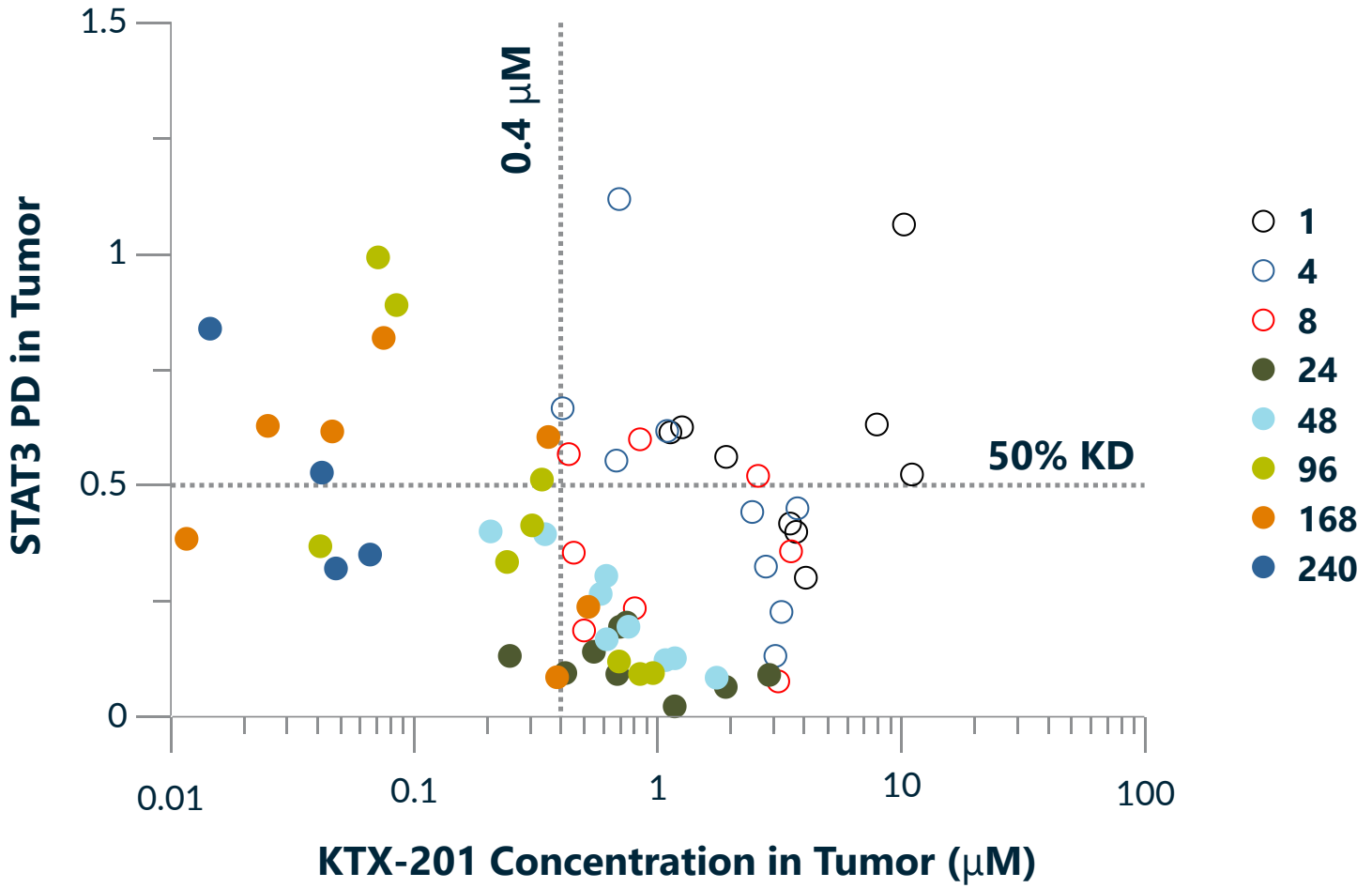
KTX-201 Conc. vs. Time
- Plasma PK
- Tumor PK

STAT3 vs. Control vs. Time
- Tumor PD



In Vivo Degradation Driven by Potency and Free Drug Exposure at Target Site

- Hysteresis was observed, suggesting indirect PK and PD relationship (time delay)
- Initial estimate showed that degrader conc. of >0.4 µM in tumor is associated with 50% STAT3 KD
- *in vivo tumor* DC_{50} is expected to be 0.46 µM (based on in vitro DC_{50} with PPB correction)
- Data suggested that *in vivo* degradation is driven by degradation potency and free drug exposure at target site



*10% FBS fu = 0.15; SUDHL-1 fu,t = 0.0049

Mechanistic PK/PD Modeling of Target Protein Degradation

PK

Drug
IV, SC, PO k_a

Plasma
C_p

k_{eo}

Tumor
C_t

k_{el}
Elimination

$$\frac{dR}{dt} = k_{syn} - k_{deg}\left(1 + \frac{E_{max} \times C_t}{EC_{50} + C_t}\right) R$$

PD

k_{syn}

PD (R)
Target
Protein

k_{deg}

Efficacy

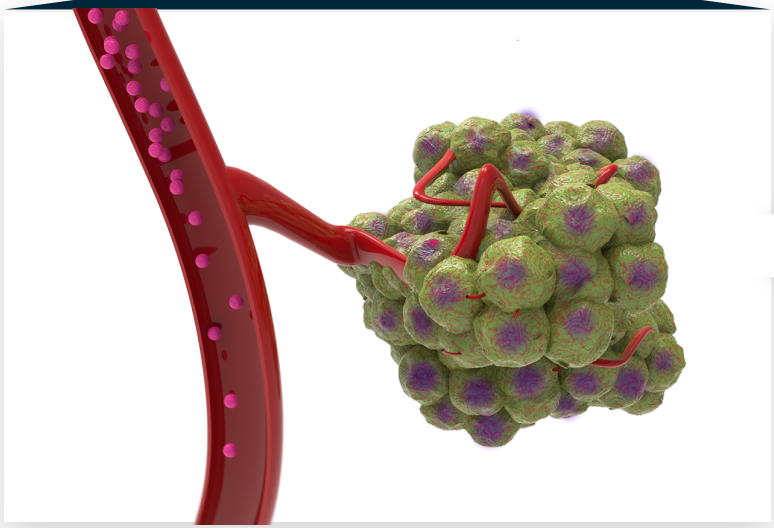
k_{growth}

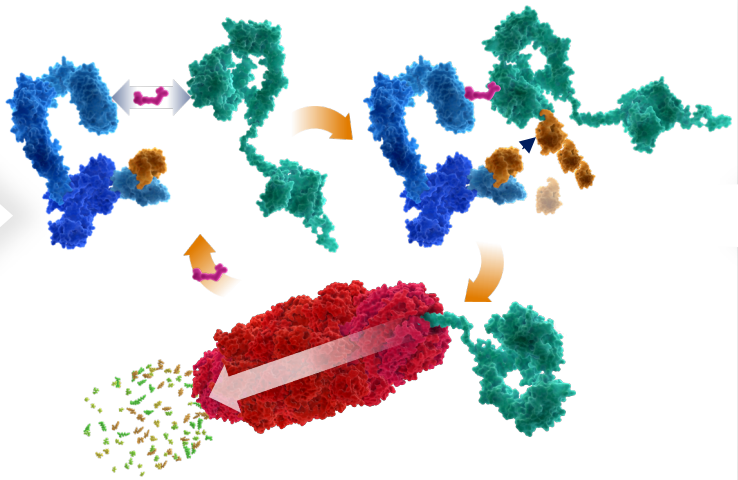
Cancer
Cells

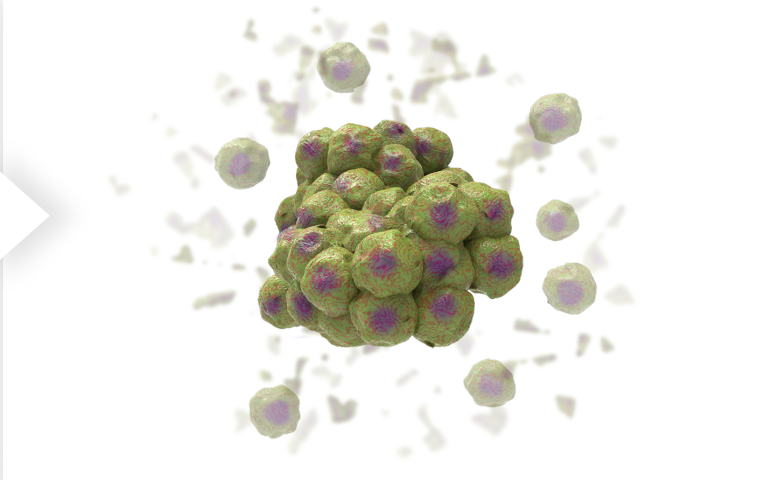
Growth Inhibition

Stimulation through TM immune activation

Loss

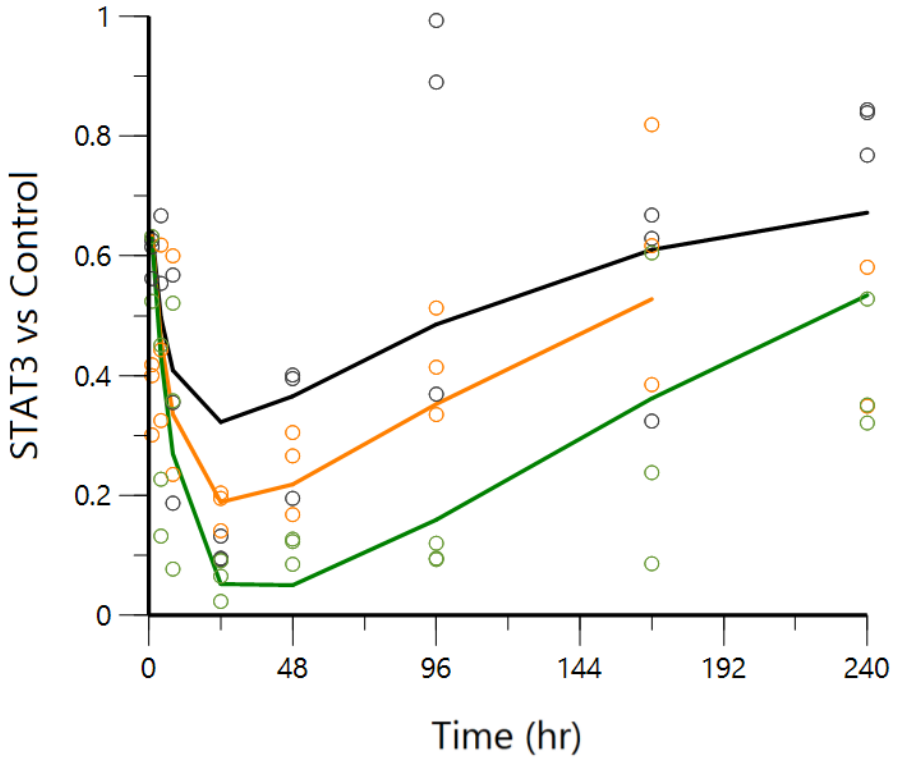






Important *In Vivo* PD Parameter Estimated by PK/PD Modeling to Enable Human Dose Projection

PK/PD Modeling Captures The PD Profiles of STAT3 Degradation in SU-DHL-1 Tumor *In Vivo*



5, 10, 25 mg/kg

Solid lines (simulations); Open circles (observed data)

PK/PD Parameter of KTX-201 in SUDHL-1 Tumor Estimated with Good Precision

Parameters	Description	Estimate	CV
k_{deg}	Degradation Rate	0.0356 hr^{-1} ($T_{½}$ 19 hr)	17%
E_{max}	*In vivo* max. effect	14	16%
EC_{50}	*In vivo* potency	2.5 µM	16%

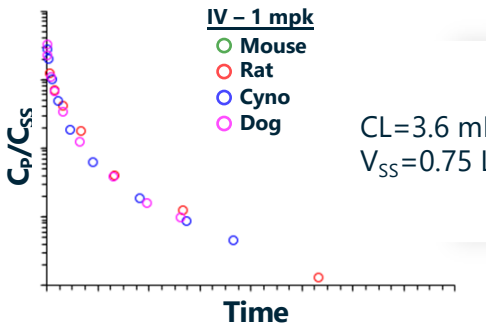
- Important *in vivo* PD parameter estimated by PK/PD modeling
  - Half-life of STAT3 in SU-DHL-1 tumor: 19 hr
  - *In vivo* DC_{50} in SU-DHL-1 tumor: 2.5 µM
- These PK/PD parameters are used to project degradation profiles in human

Apply Mechanistic PK/PD Modeling to Translating Degradation from Mouse to Human

- Combine allometric scaling methods and Wajima superposition approach to project KTX-201 IV PK profiles in human
- Feed human PK parameter to mechanistic PK/PD model, established by PK/PD in XG mouse, to project STAT3 PD profiles in human

Project IV PK Profile of STAT3 Degrader in Human

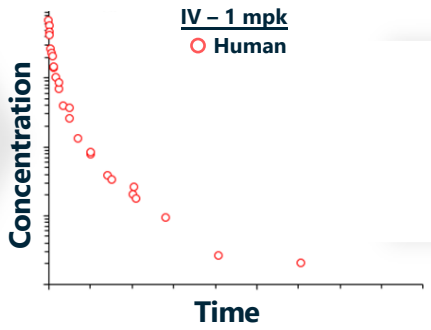
Wajima Superposition (C_{ss}-MRT)



CL=3.6 mL/min/kg
V_{SS}=0.75 L/kg

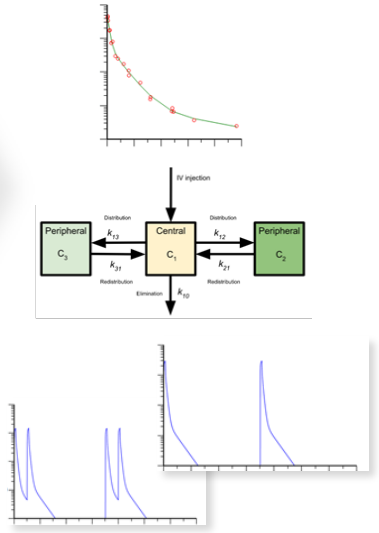
- Scale and normalize rat, dog and monkey profiles

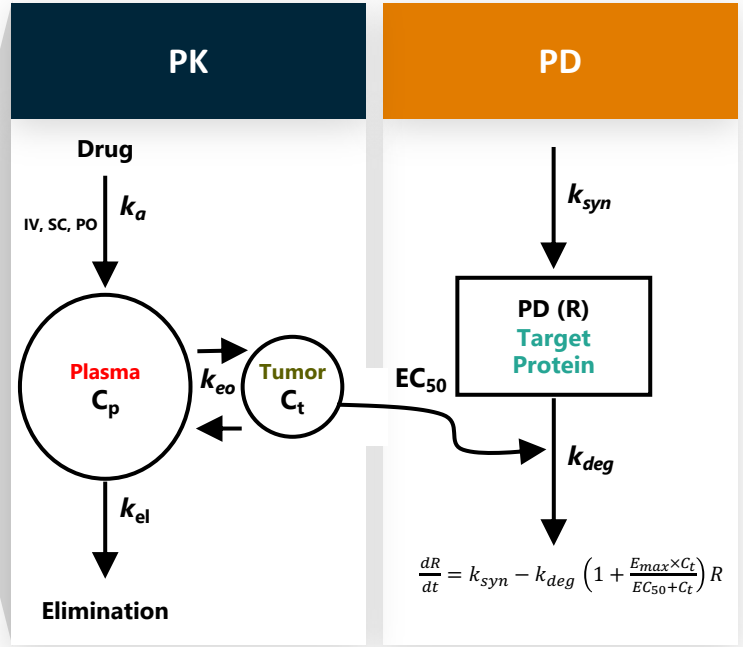
Prediction of Human IV Profile



- Apply projected human CL and V_{ss} to Wajima superposition

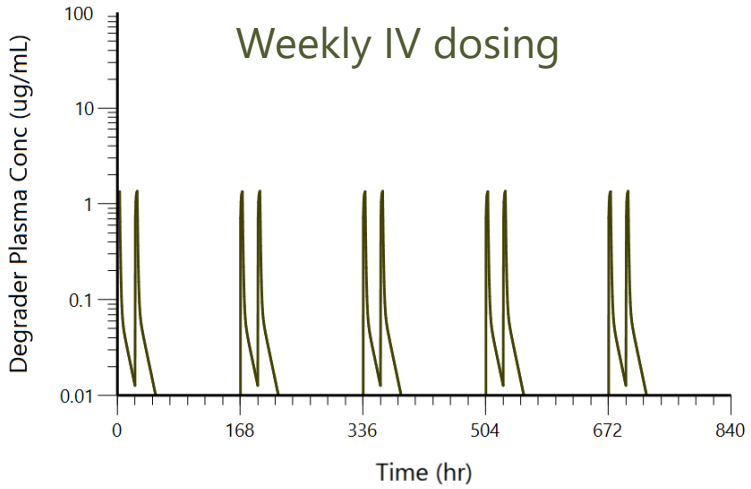
Modeling and Simulation



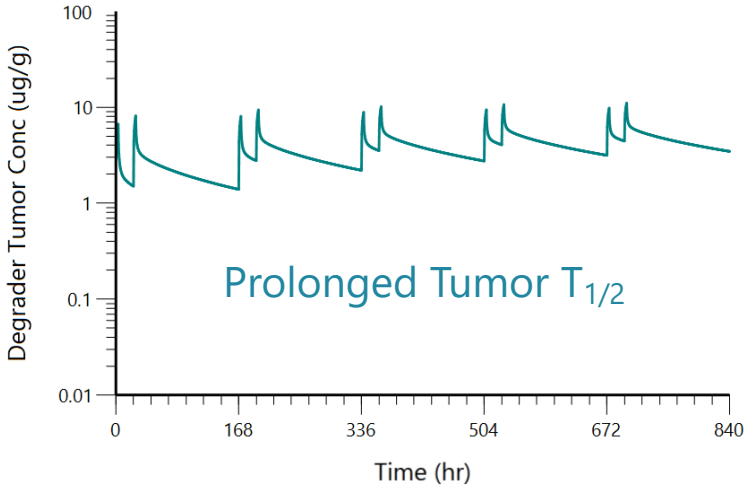


Mechanistic Modeling to Project STAT3 Degradation in Human

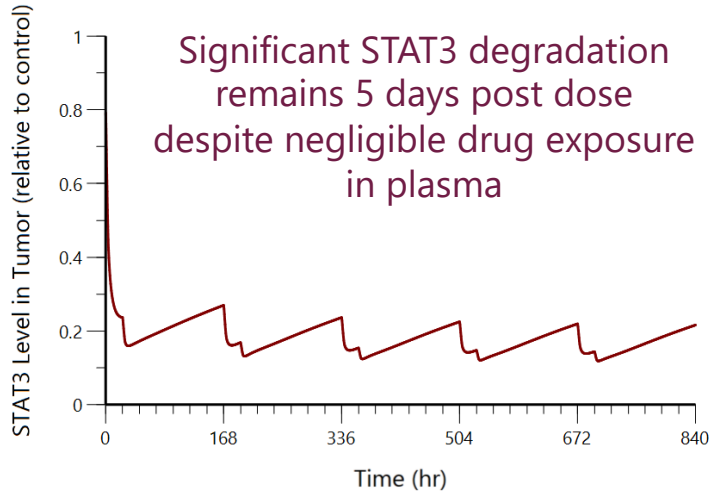
Simulated Plasma PK Profile in Human



Simulated Tumor PK Profile in Human



Simulated Tumor PD Profile in Human



Integration of human PK, tissue distribution, and *in vivo* degradation potency (EC_{50}) and efficacy (E_{max}) enables projection of target protein degradation in human for dose optimization in clinic.

Summary

- The delay in PK/PD relationship of TPD largely stems from its mechanism of action
  - Stimulation of degradation is an indirect pharmacological response
  - Multiple system parameters, i.e. target protein expression level and its half-life, contribute to the kinetics of target protein degradation
- Study the temporal PK/PD relationship *in vivo* is key to understand the interplay between drug- and system- parameters
- Mechanism PK/PD modeling is a useful tool to dissect the PK/PD interplay *in vivo* and to facilitate human dose projection

Q & A

THANK YOU

October 2020