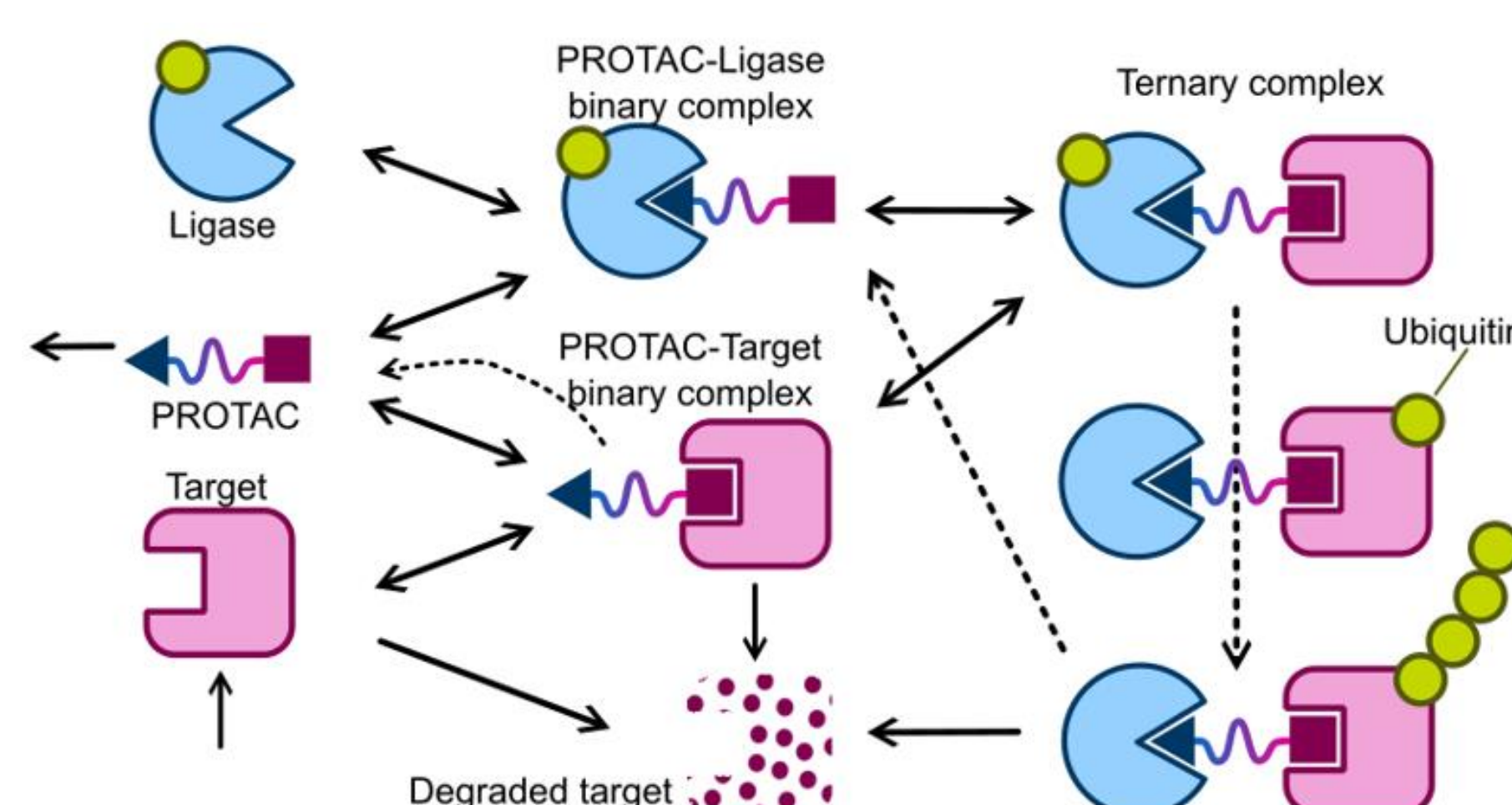


# A modelling framework for IVIV translation of PROTACs PKPD/E

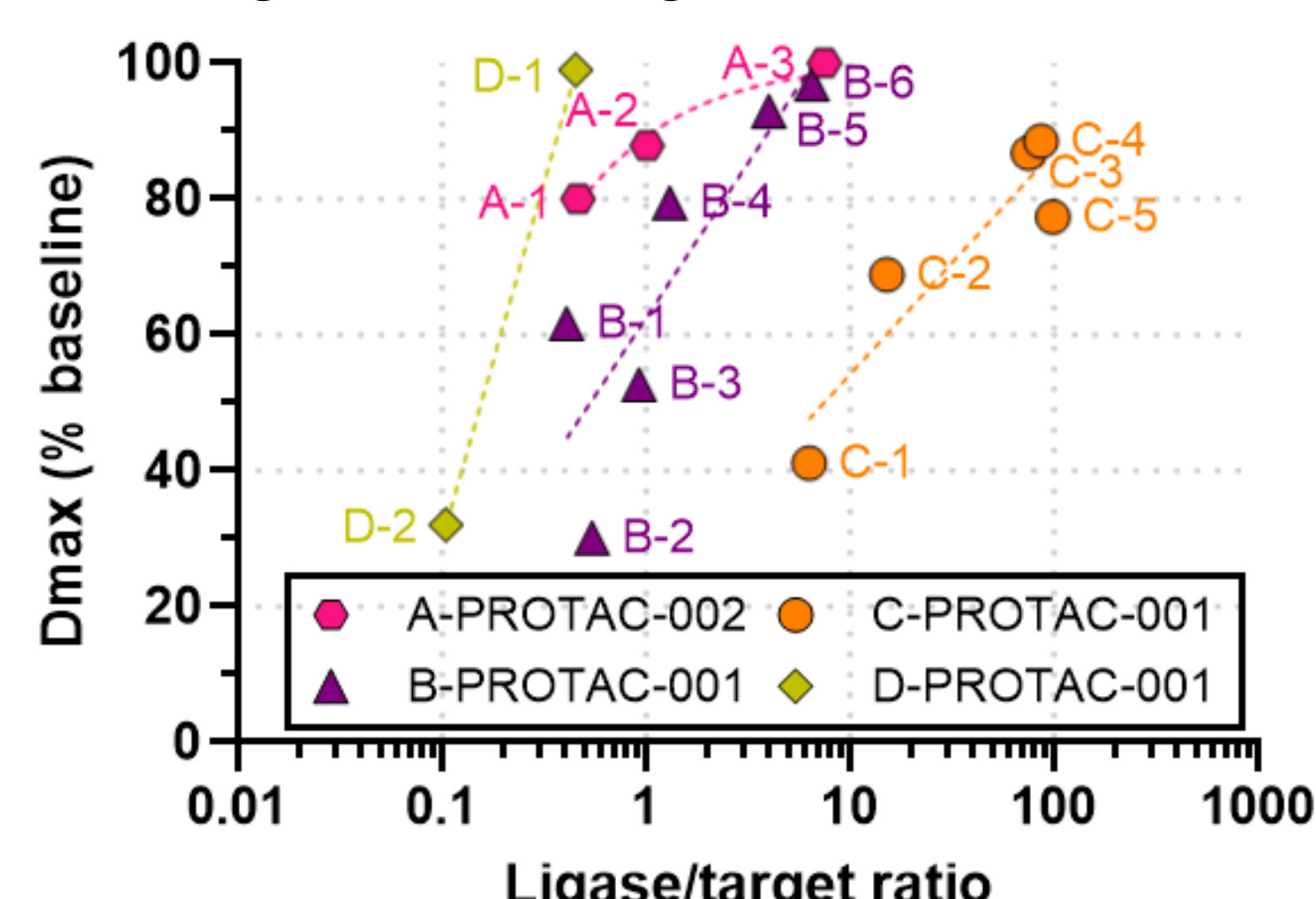
## Accelerating drug discovery of targeted protein degraders

### Introduction

PROTACs promote **protein degradation** by co-opting an **E3 ligase** to tag the targeted protein of interest for turnover by the **proteasome**<sup>1-2</sup>



**Potency and maximal degradation** can be highly **sensitive** to endogenous ligase and target **baselines**<sup>3</sup>



### Challenges:

- The criteria for **compound screening** based on activity and/or selectivity may heavily **depend on the choice of cell lines**
- Degradation in vitro** does not necessarily **predict degradation in vivo**
- Traditional metrics** for establishing a **PK/Efficacy relationship**, such as plasma exposure over a target concentration, are **inadequate** because the same exposure may not correspond to equivalent degradation

### PKPD: In vitro/in vivo extrapolation

- Degradation kinetics** are modelled with a **turnover model** with a **bi-sigmoidal degradation stimulus**, where  $D_{max}$  and  $DC_{50}$  are statistical functions of the **ligase/target baseline ratio** ( $\rho$ )<sup>3</sup>



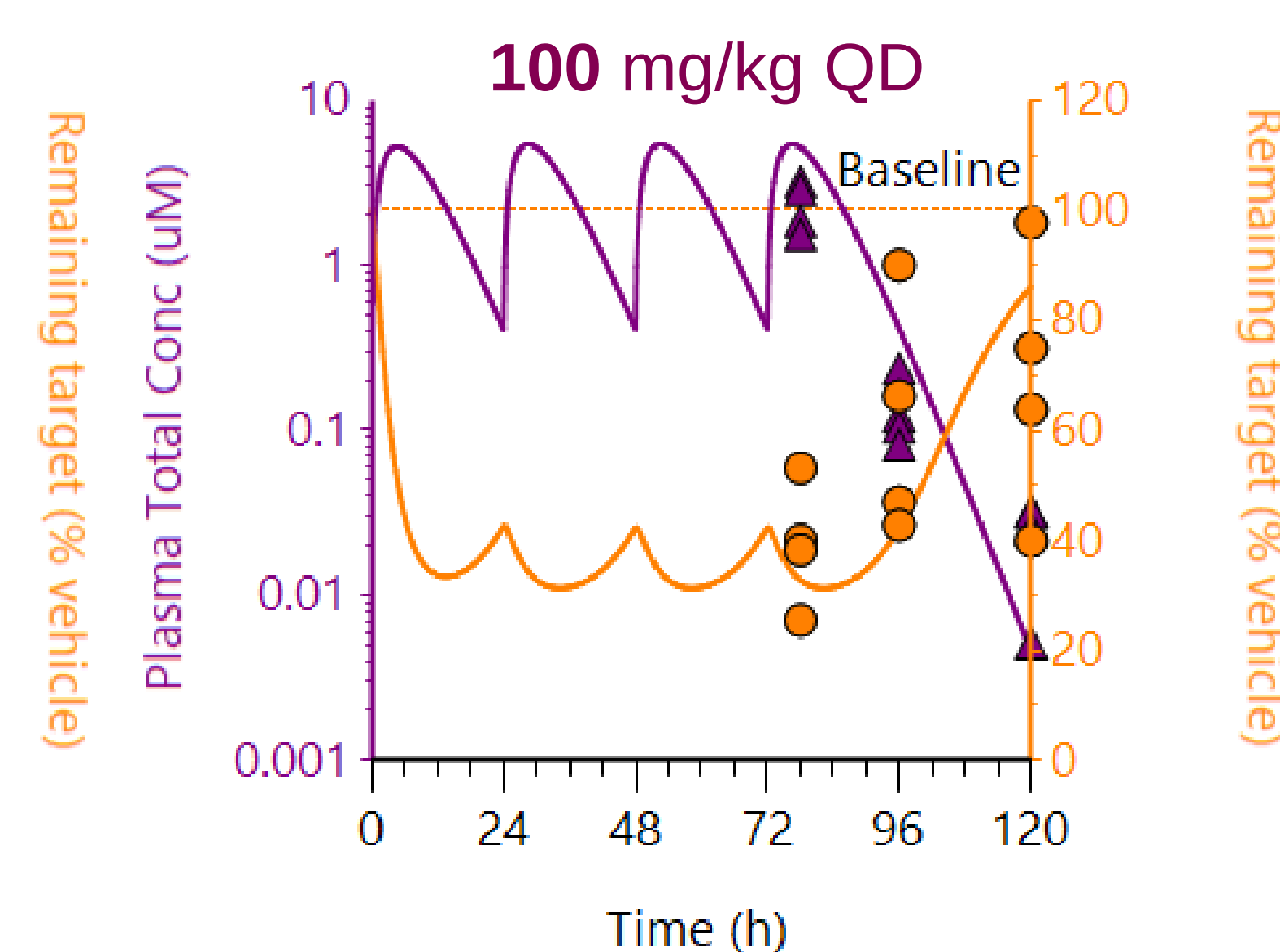
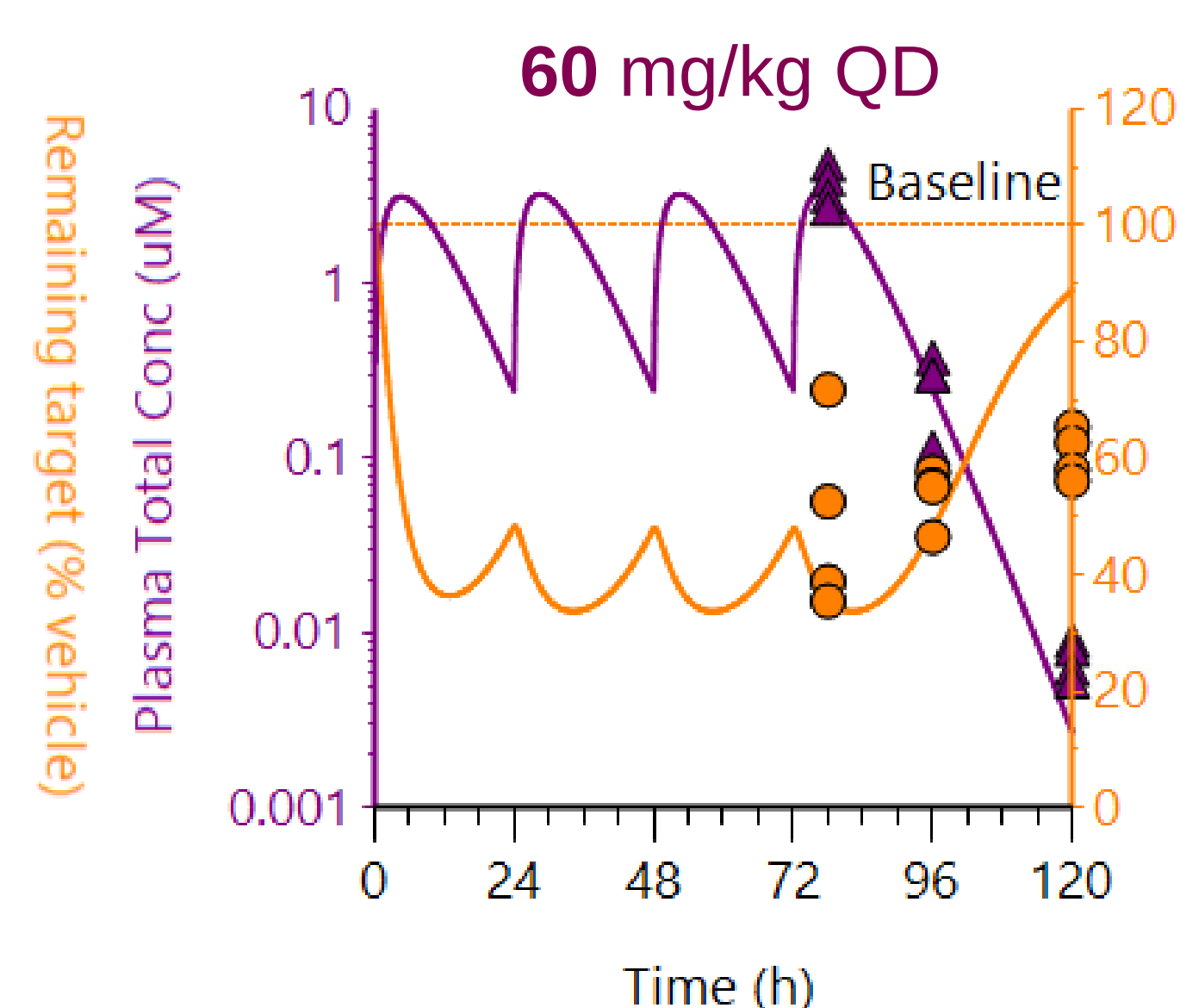
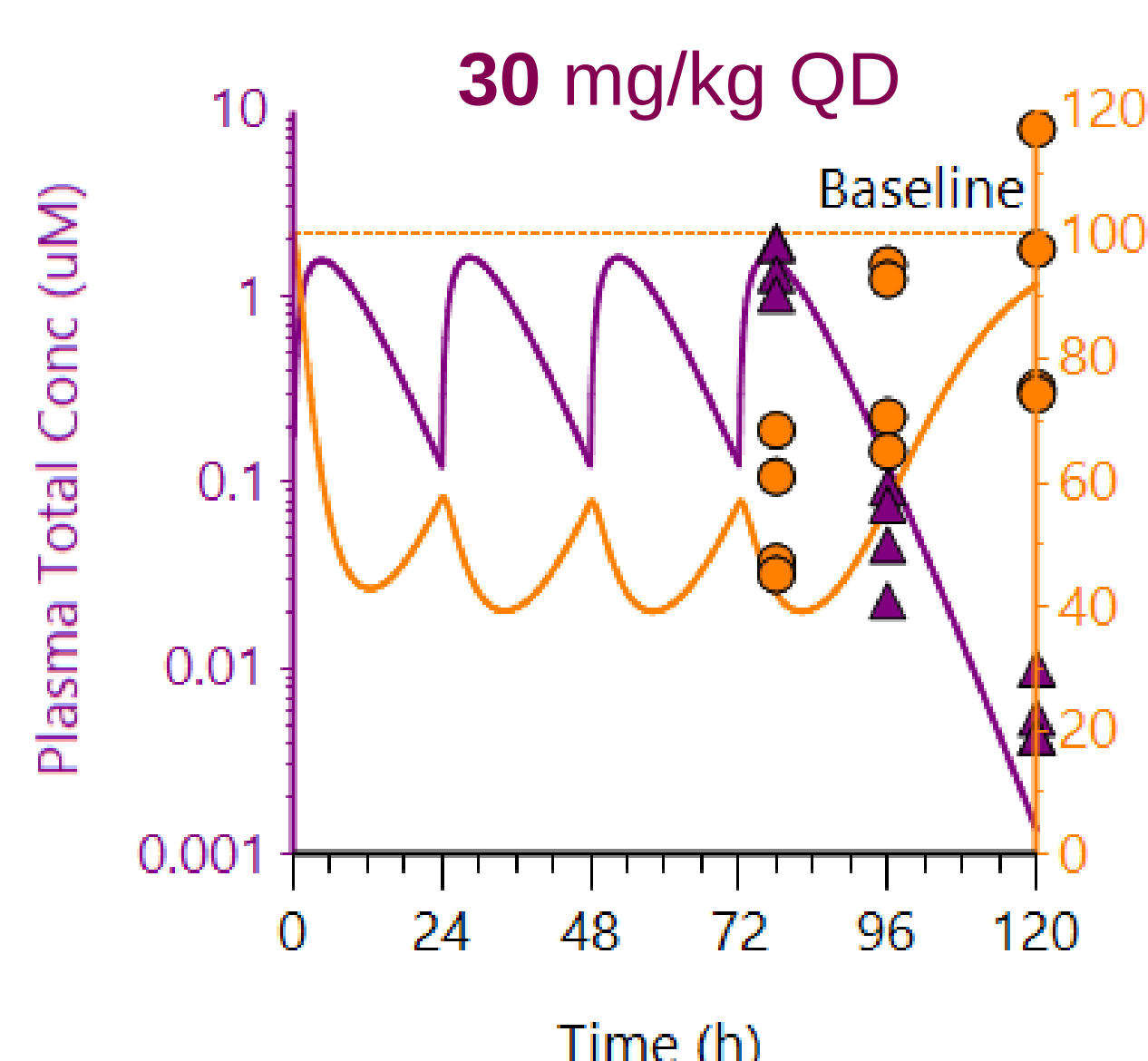
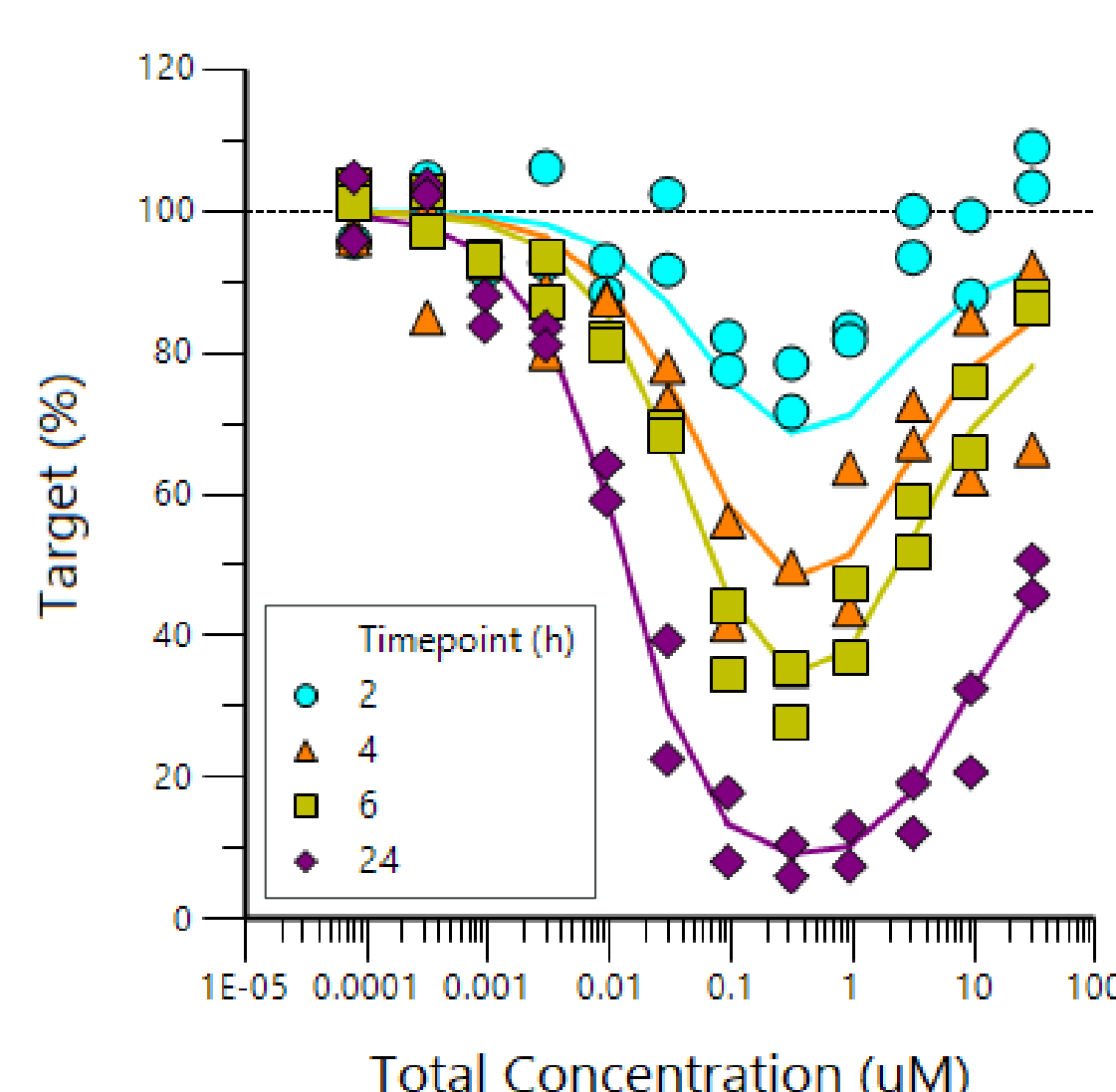
$$\frac{d\hat{P}}{dt} = k_{deg} - k_{deg} \cdot \left( 1 - D_{max} \frac{C\gamma}{C\gamma + DC_{50}^\gamma} \left( 1 - \frac{D_{loss}}{D_{max}} \frac{C}{C + IC_{50}} \right) \right)^{-1} \hat{P}$$

Endogenous syn/deg      Ternary complex formation      Ternary complex inhibition (hook effect)

- In vitro** degradation kinetics data are fitted and used to **predict** degradation kinetics **in vivo**

- Plasma or tumor PK in vivo** is fitted and used as a **driver** of the **in vitro** PD model

$$D_{max}(\rho) = \frac{\rho^\delta}{\rho^\delta + \rho_{50}^\delta} \quad DC_{50}(\rho) = (DC_{50,max} - DC_{50,min}) e^{-\kappa \cdot \rho} + DC_{50,min}$$

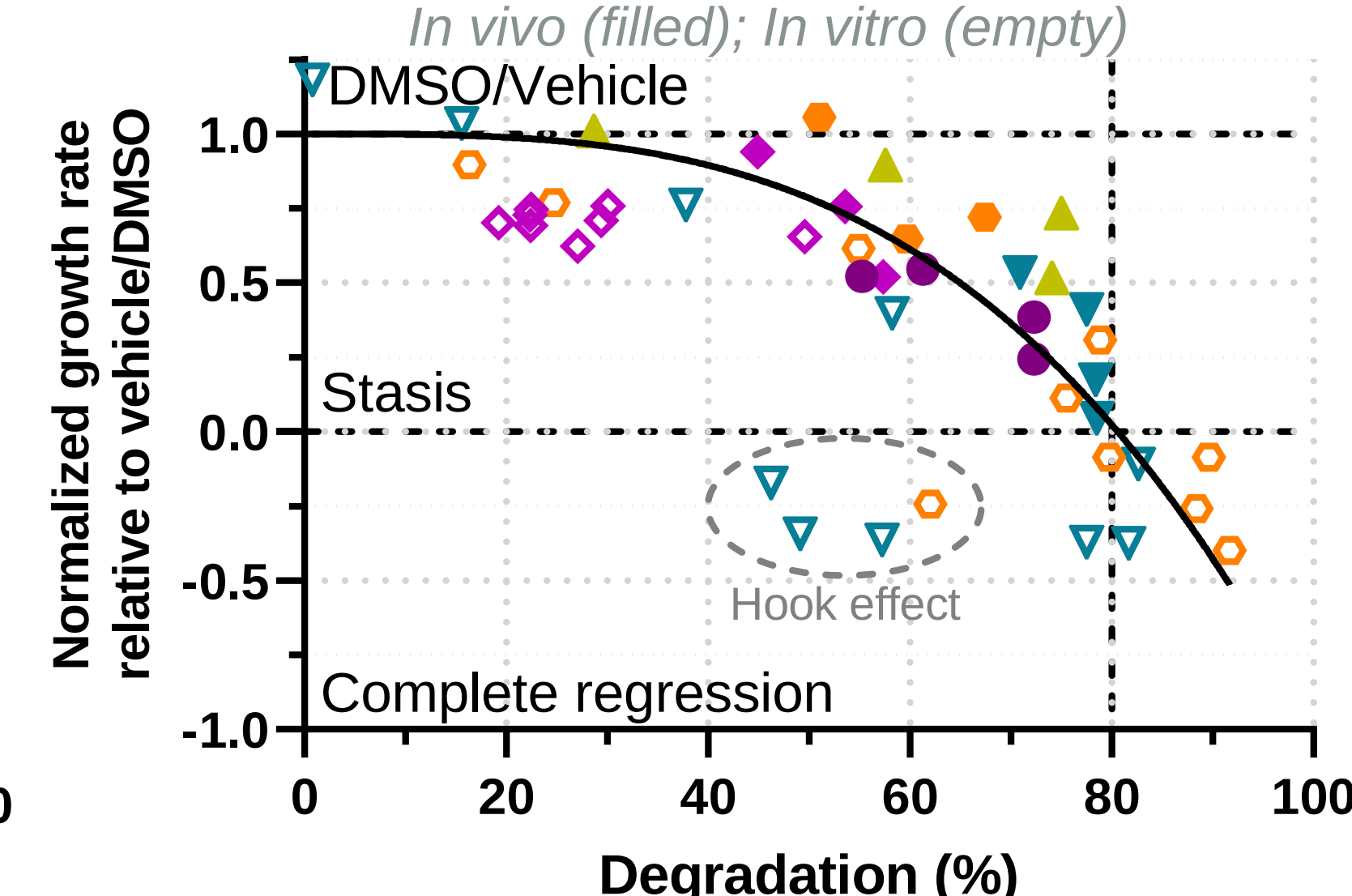
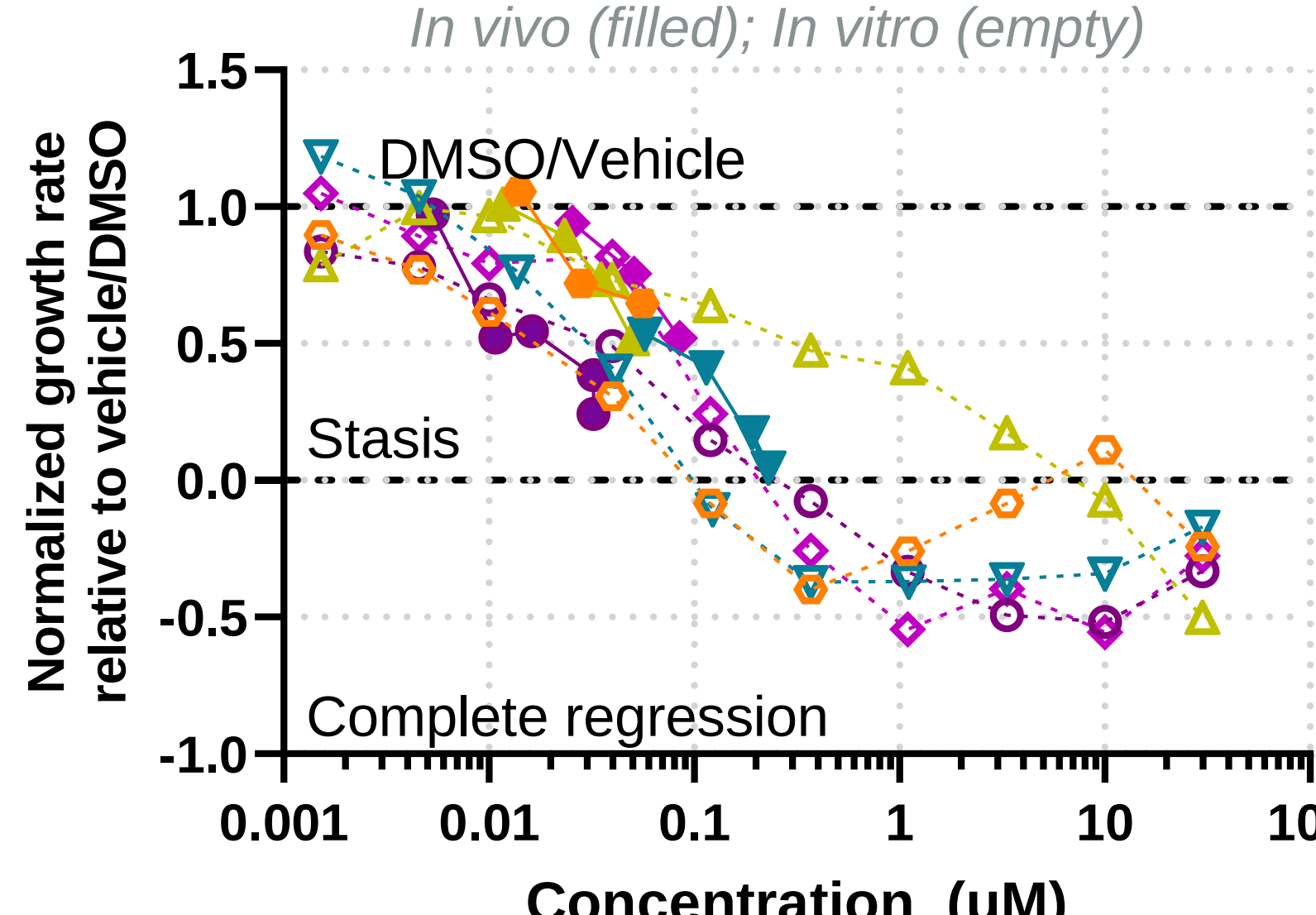
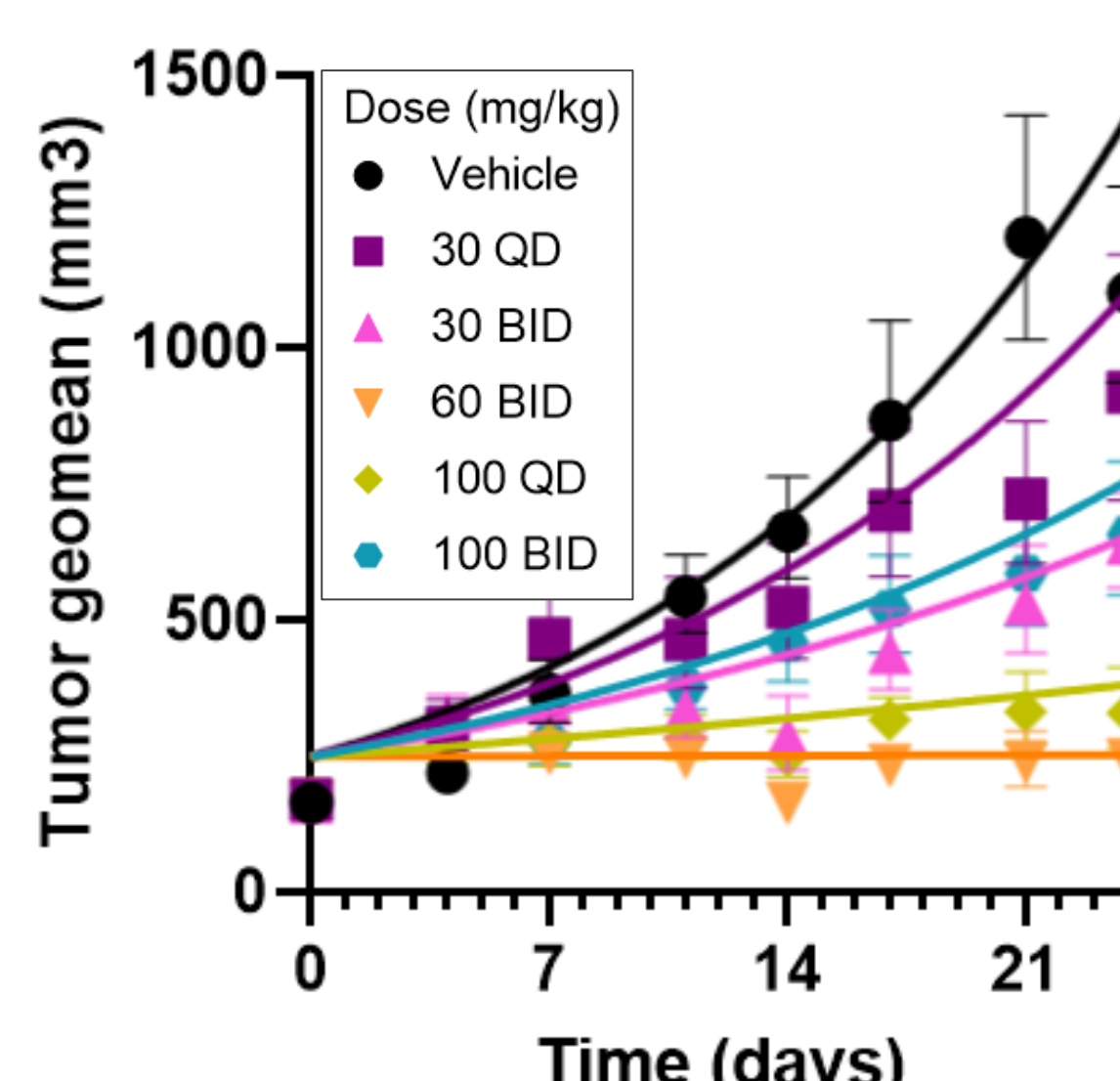
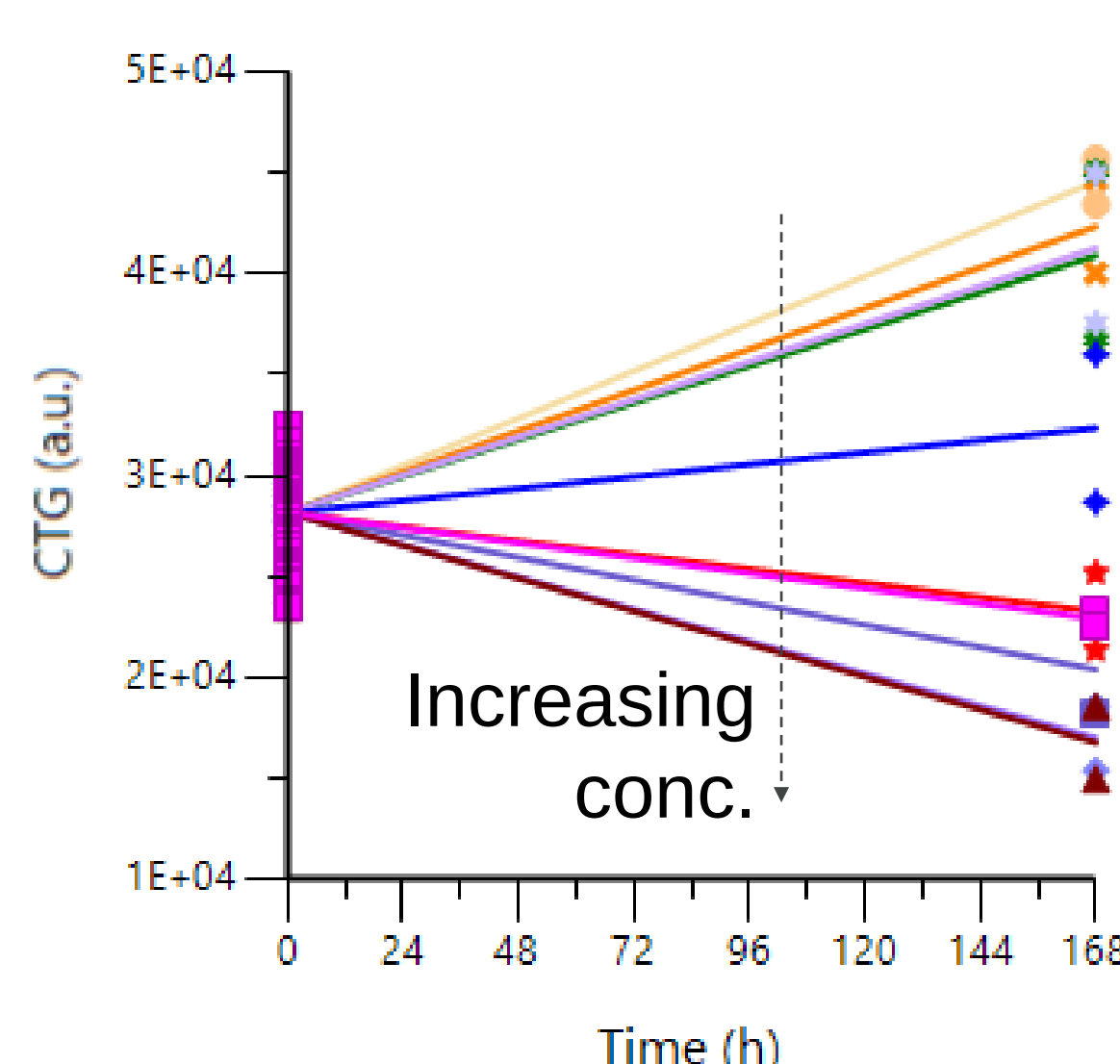


### PKPD/Efficacy: In vitro/in vivo extrapolation

$GR = 2^{\frac{k_{gro}}{k_{veh}}} - 1$  is calculated from *in vitro* CTG data and *in vivo* tumor volume for each compound<sup>4</sup>

The **GR dose-responses in vitro** are consistent with PK/E relationship **in vivo**

**PD/E relationship translates from in vitro to in vivo**

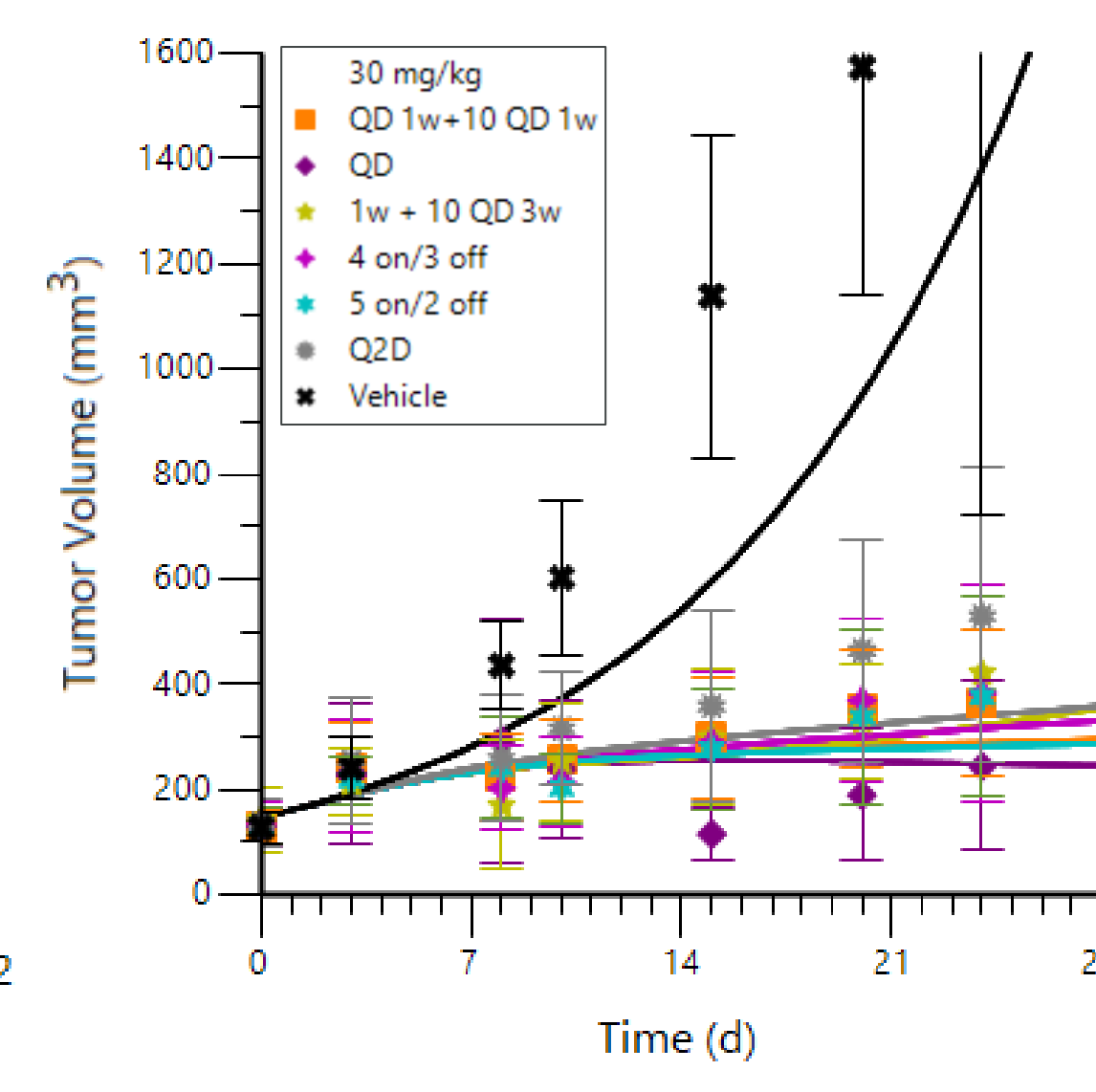
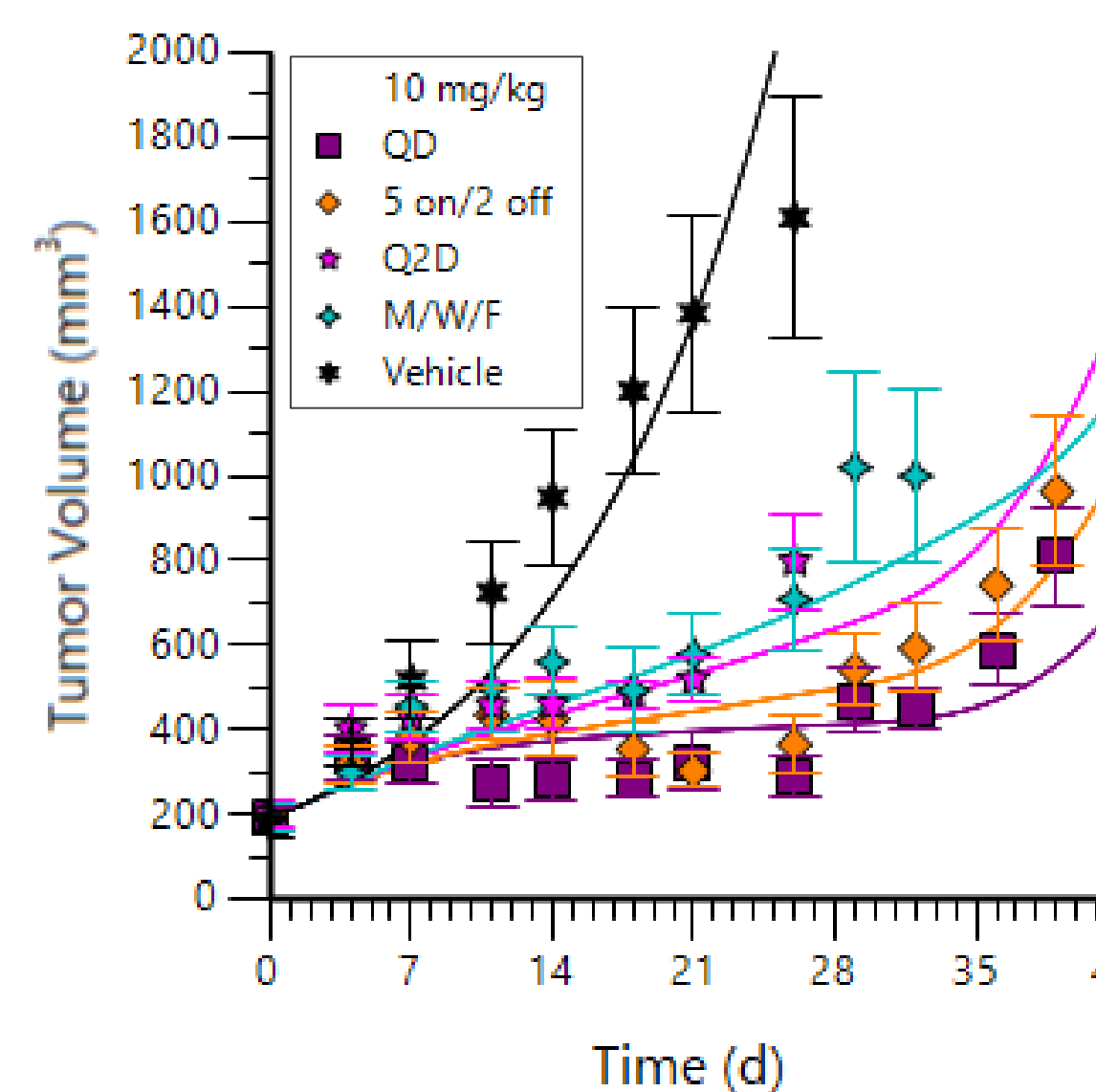
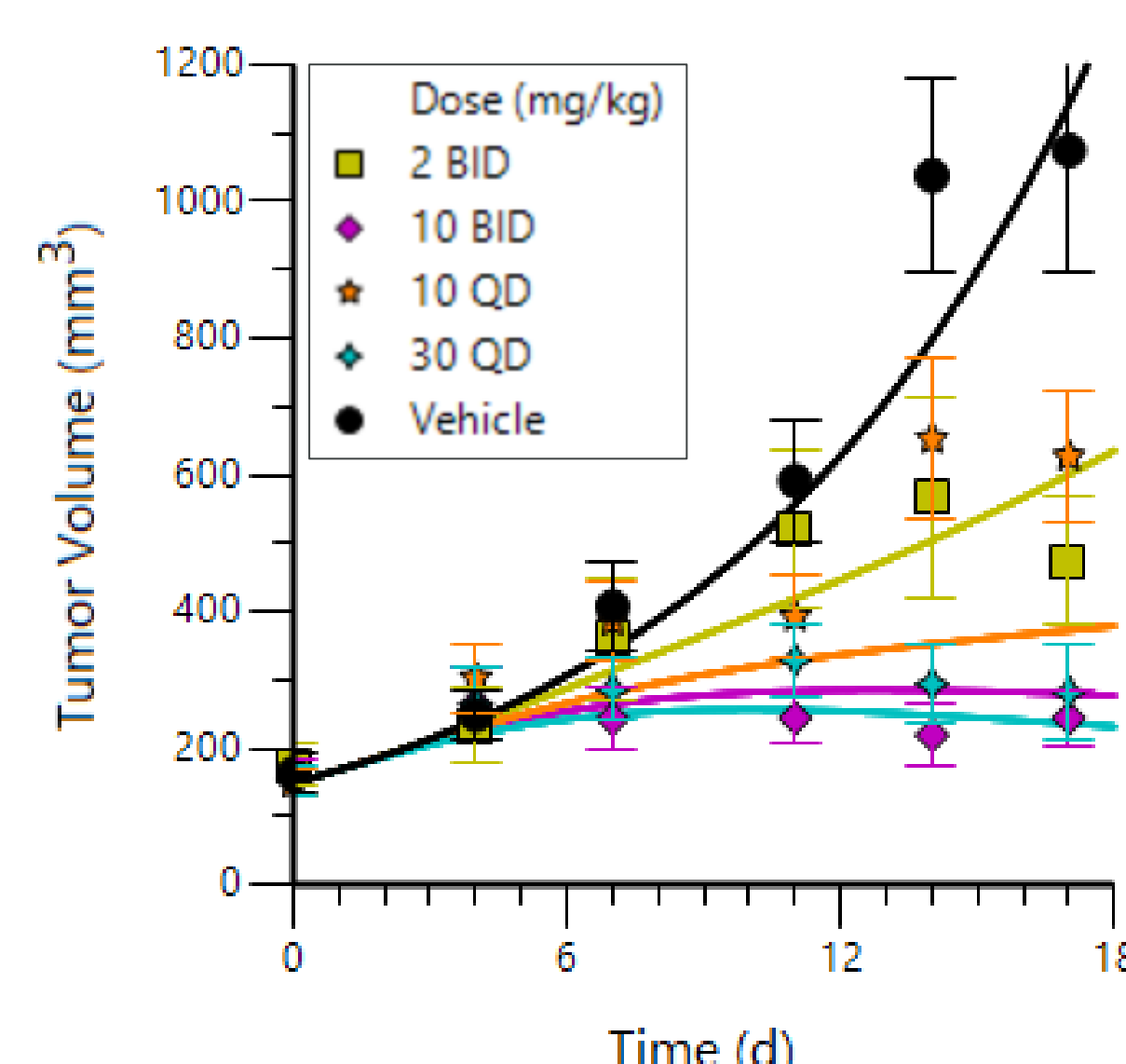
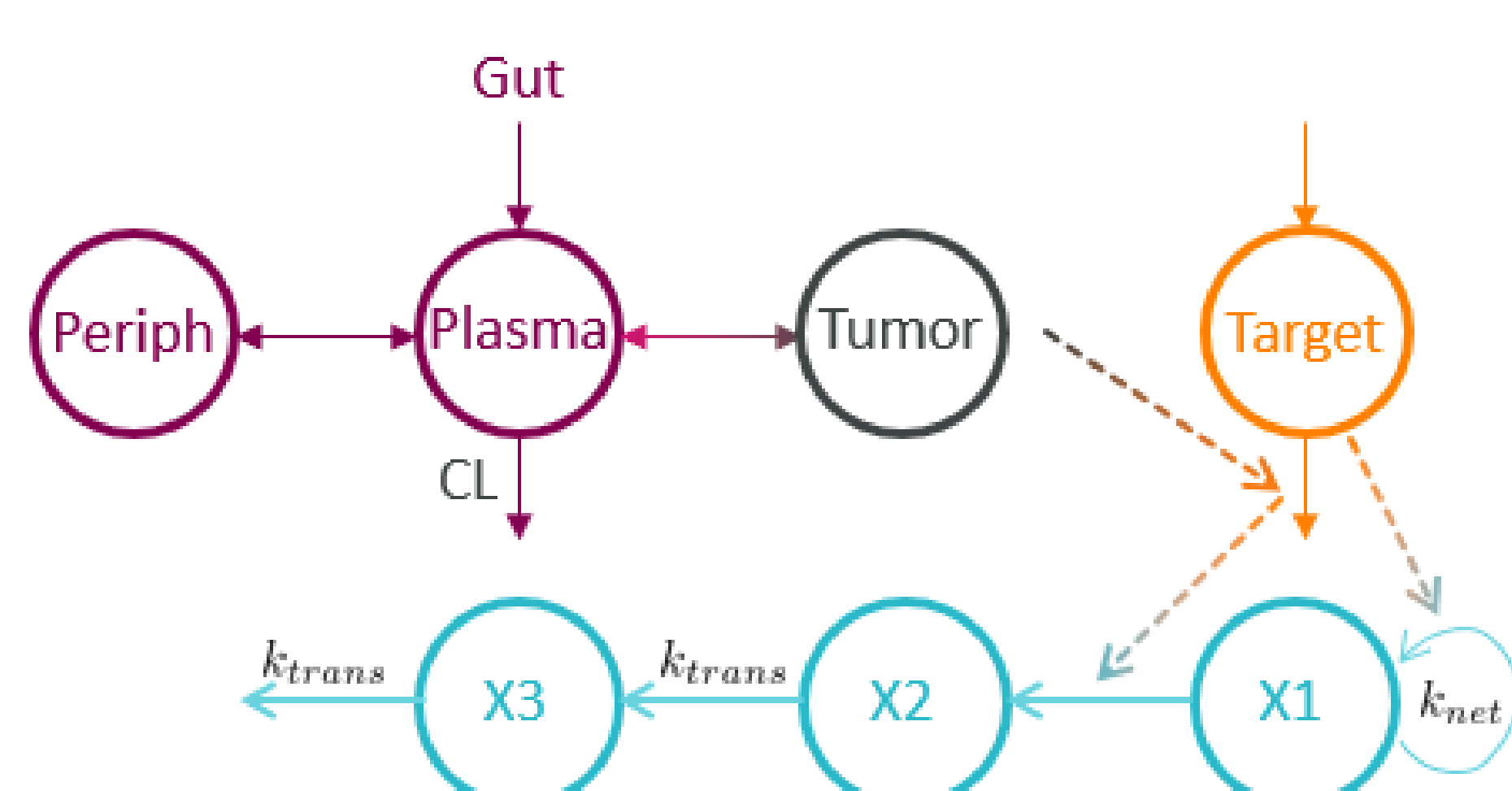


### Bespoke PKPD/Efficacy semi-mechanistic modelling

**Delayed efficacy model**<sup>5</sup> driven by **turnover model**, in turn driven by **tumor PK**

The PKPD/E model is **fitted** to dose-response on **continuous dosing**

The PKPD/E model **successfully predicts** efficacy dose-responses with **intermittent scheduling**



### Conclusions

The challenges related to the IVIV translation of PROTACs PKPD/E relationship can be overcome by a **pragmatic modelling approach** which accounts for the **sensitivity of degradation to endogenous conditions** (i.e. ligase/target baselines), as well as mechanistic **efficacy metrics based on cell/tumor growth kinetics** rather than single timepoint data (such as cell viability or TGI). This enables **acceleration of drug discovery programs**.

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