

Projecting MIW815 (ADU-S100) human tumor PK after intratumoral injection using a translational modeling approach combining preclinical and clinical data

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Background

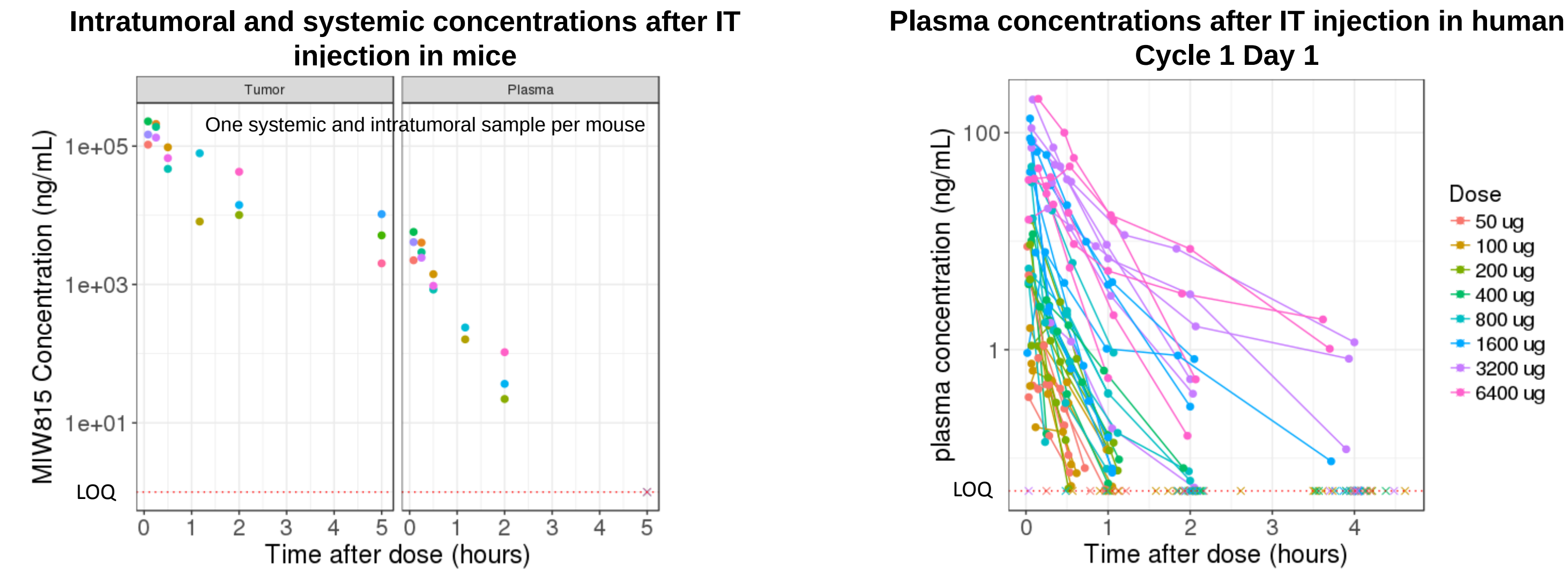
- MIW815 (ADU-S100):**
 - Novel **immuno-oncology** synthetic cyclic dinucleotide compound (MM=734.5 g/mol)
 - Agonist of STING** (Stimulator of Interferon Genes) **activating the innate and adaptive immune system against tumors**
- Findings from **preclinical studies**:
 - Intratumoral (IT) injection** needed to reduce high systemic exposure and thus increasing therapeutic window
 - Anti-tumor activity** on **treated** and **distal untreated lesions** via **systemic immune response**
- Currently being evaluated **in patients** with advanced/metastatic solid tumors or lymphomas:
 - IT injection, only systemic concentrations collected**

Objectives

Combine systemic and intratumoral preclinical and systemic clinical data through a semi-mechanistic PK model to simulate intratumoral PK in human and to enable support of dose selection for MIW815

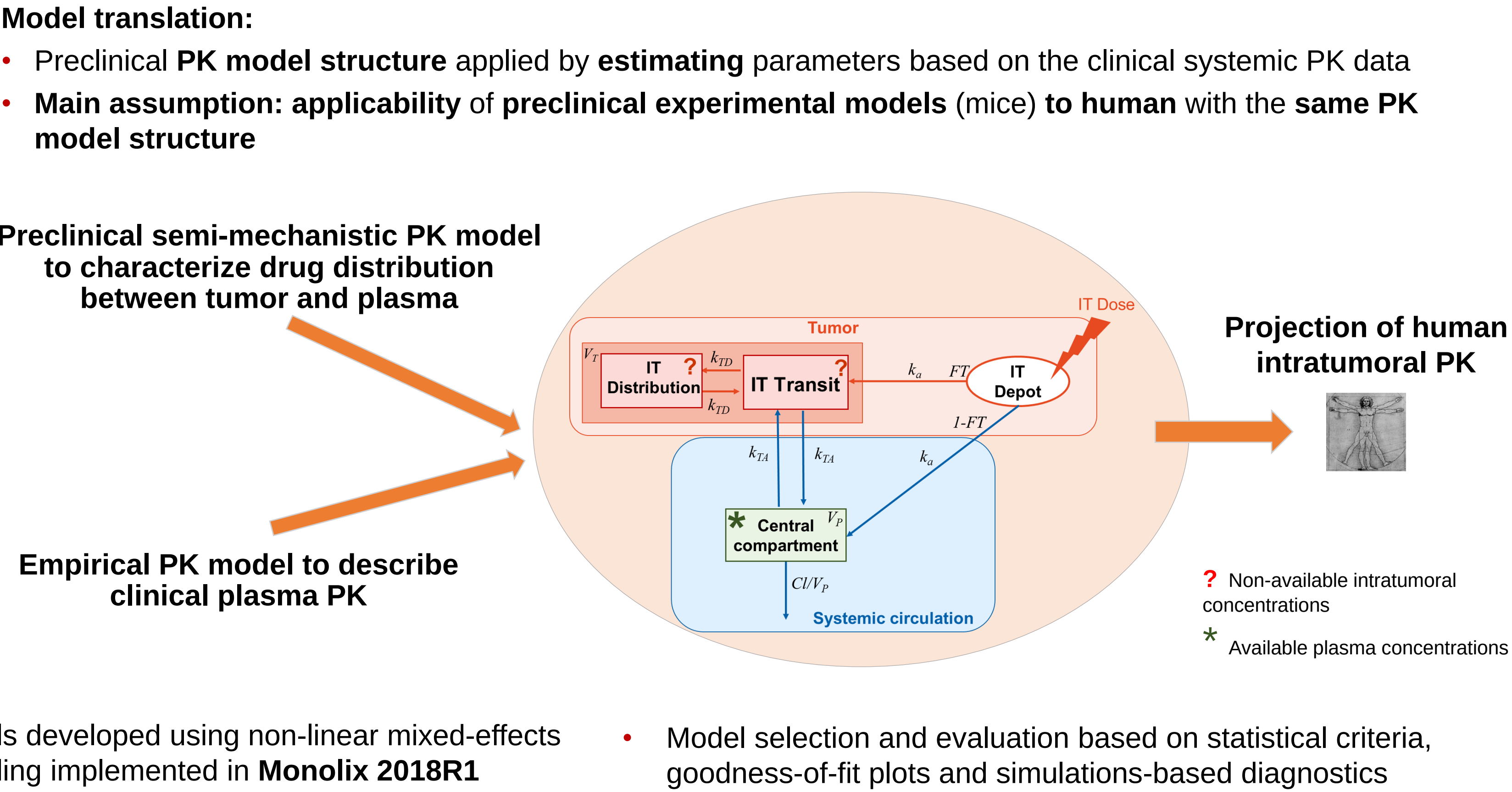
Data summary

Description	Mice data summary	Clinical data summary
Population	37 syngeneic mice (female C57BL/6) with B16.F10 tumor (melanoma)	47 patients with advanced/metastatic solid tumors or lymphomas from Phase I dose escalation study NCT02675439
Treatment	Single administration of MIW815 via: - IT injection of 20 mg/kg (~500 µg), - SC administration of 20 mg/kg, or - IV administration of 1 mg/kg	- Weekly MIW815 IT injection for 3 weeks followed by one week-off - Dose levels: 50 µg, 100 µg, 200 µg, 400 µg, 800 µg, 1600 µg, 3200 µg and 6400 µg - MIW815 injected volume (0.5 mL to 4.0 mL) varied based on the treated lesion size (11 mm to 100 mm)
PK	32 intratumoral concentrations up to 5 hours 54 systemic concentrations up to 5 hours (41% BLOQ)	- Full plasma PK profiles up to 4 hours after injected dose collected at cycle 1 day 1, cycle 1 day 15 and cycle 3 day 1 (32% BLOQ) - No intratumoral concentration

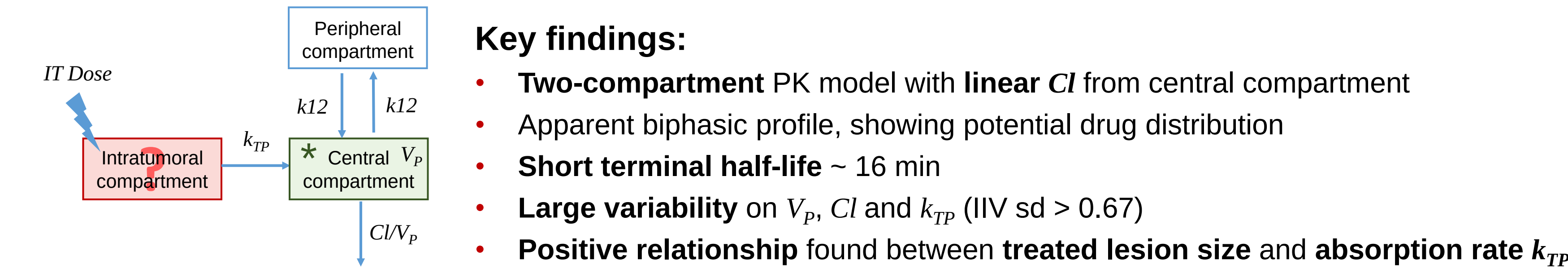


Methods

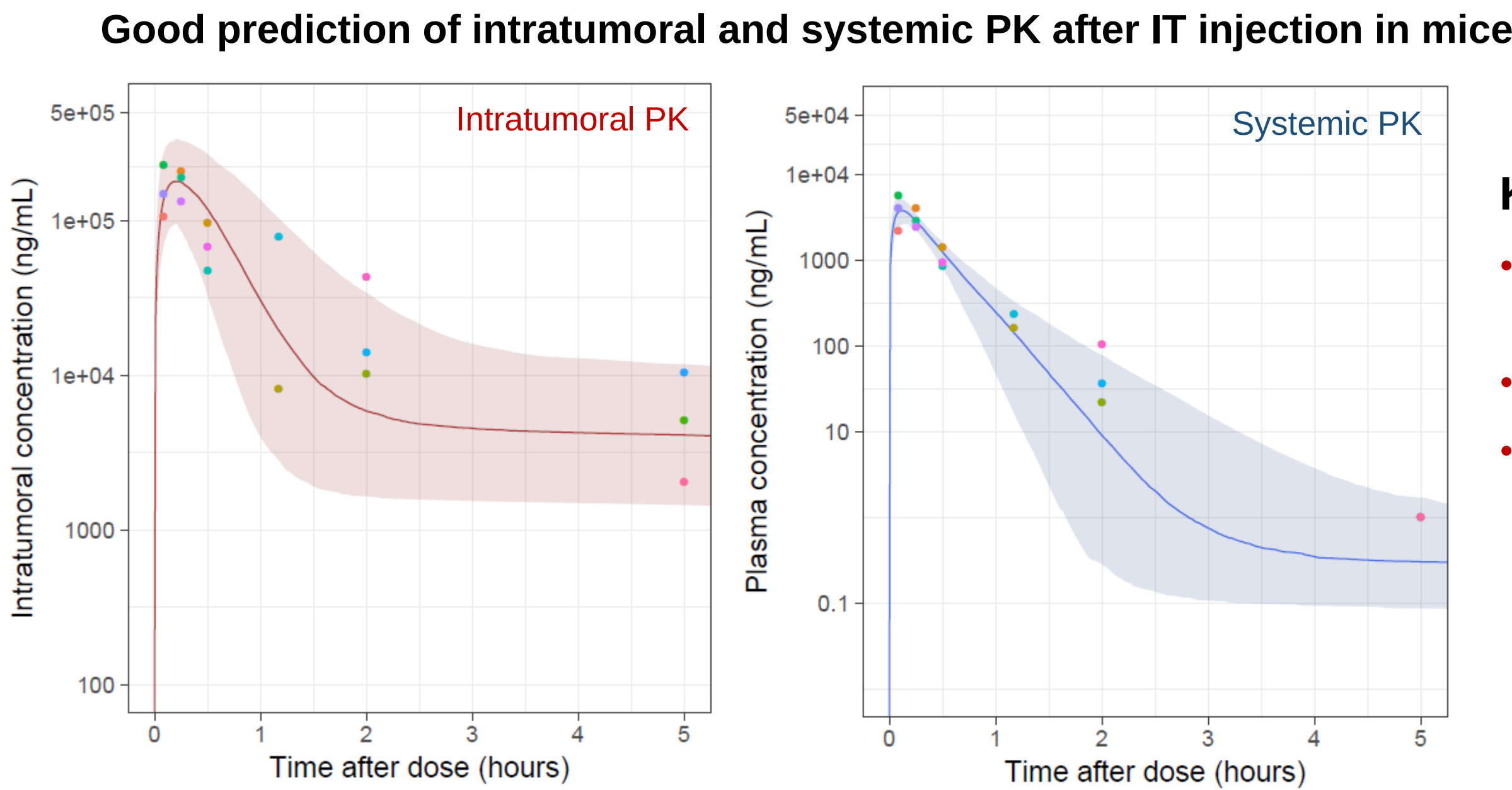
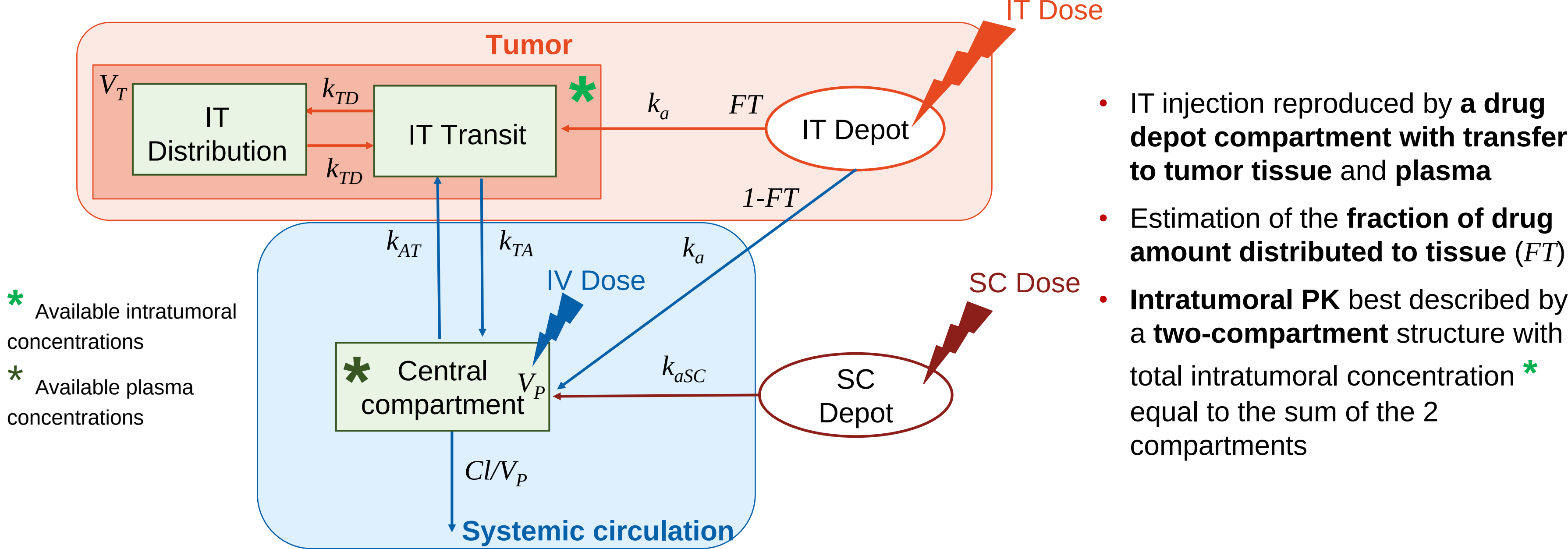
Modeling strategy



1- Empirical clinical PK model



2- Preclinical semi-mechanistic PK model



- Key findings:**
- Available fraction of dose for tumor (FT) estimated at 43% (RSE=10%)
 - Fast transfer rates k_{TA} and k_a (~ 4 h^{-1})
 - Slower transfer rates k_{AT} and k_{TD} (~ 0.02 h^{-1})

Results

3- Model translation to human

- Key findings:**
- Faster transfer rates in humans compared to mice
 - Large variability on V_p , Cl and k_a (IIV sd > 0.73)
 - Positive relationship found between treated lesion size and transfer rate from depot k_a
 - Apparent biphasic profile described by tumor distribution
 - Similar model performance and goodness-of-fits compared to the empirical clinical PK model

- Assumptions:**
- Same FT between species
 - Apparent V_T fixed to 1L
 - $k_{AT} = k_{TA}$

4- Projection of human intratumoral PK

