



Physiologically based pharmacokinetic modeling of TLL-018 for prediction of human pharmacokinetics and in vitro-in vivo extrapolation

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Introduction & Objectives

TLL-018 is a novel selective Janus Kinase 1 / Tyrosine Kinase 2 (JAK1/TyK2) inhibitor which is being developed for the treatment of several inflammatory diseases. TLL-018 was evaluated in early phase clinical trials as an oral immediate-release (IR) formulation and the extended-release (ER) formulation was expected to be developed.

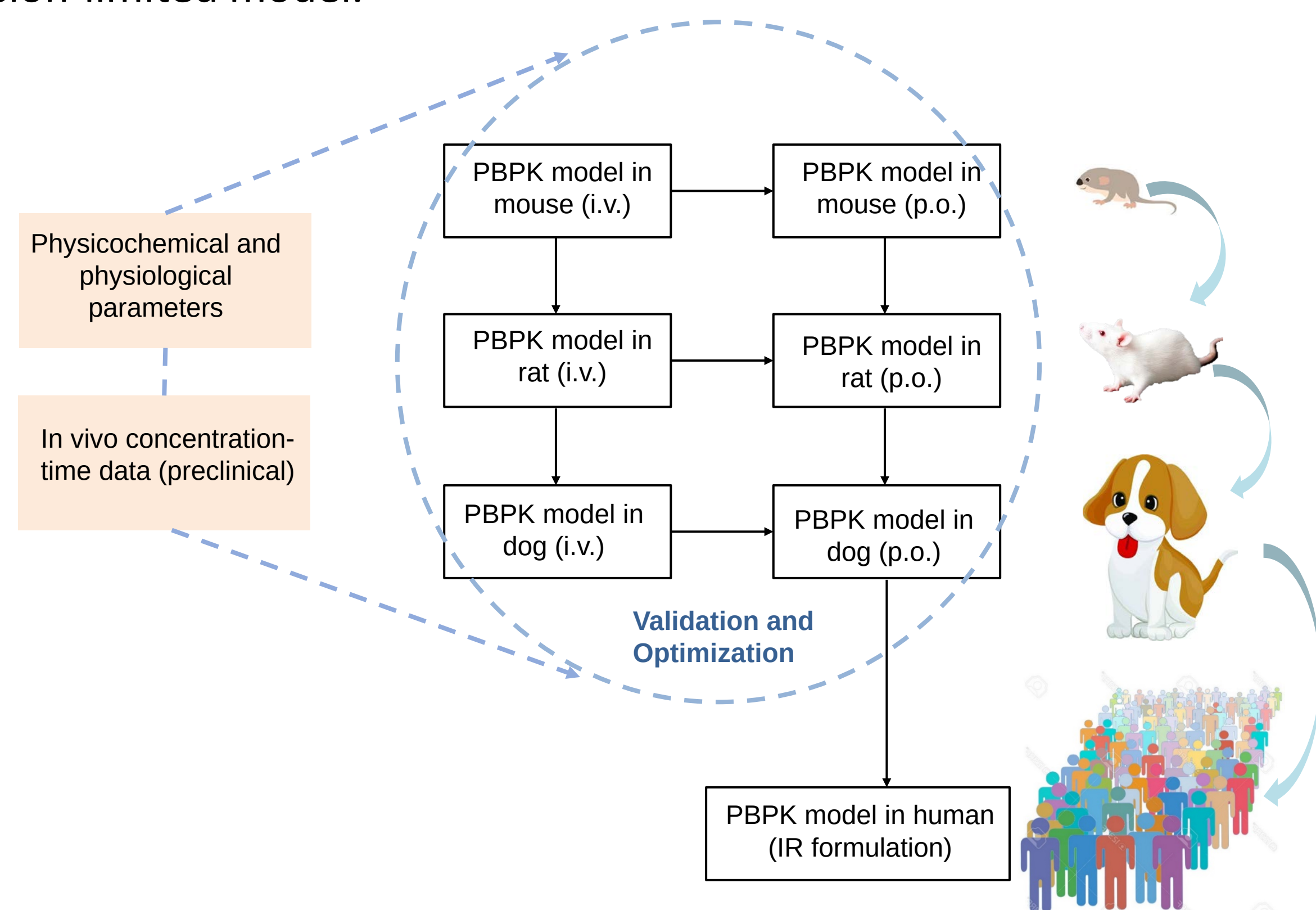
This study aims to develop a physiologically based pharmacokinetic (PBPK) model to predict the pharmacokinetics (PK) of TLL-018 IR formulation in humans based on the in vitro and in vivo PK data of animals, and to use the validated PBPK model of IR formulation to predict the in vivo plasma concentration curves of TLL-018 ER formulations according to the in vitro dissolution profiles and the in vivo concentration data in dog.

Methods

Predicting the PK of TLL-018 IR formulation in human

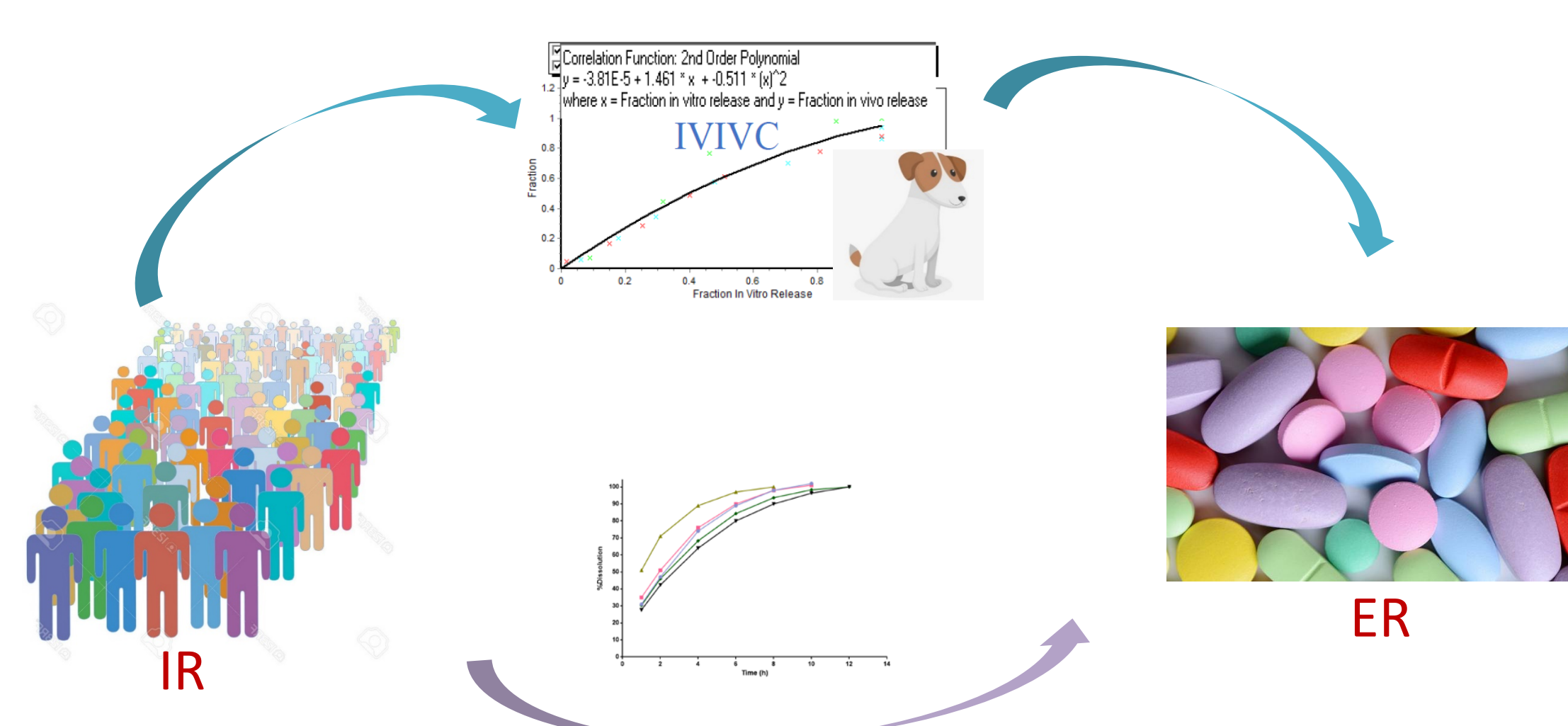
The physicochemical and physiological parameters of TLL-018, including molecular weight, solubility, lipophilicity, permeability, pKa, plasma protein binding, and blood/plasma ratio were used to establish a PBPK model in mouse firstly. These parameters were mainly gained from the in vitro experiments, or predicted by ADMET Predictor® (Version 10.2, Simulations Plus, Inc., CA, United States).

Advanced Compartmental Absorption and Transit (ACAT) model built in GrastroPlus™ software (Version 9.8.2, Simulations Plus, Inc., CA, United States), consisting of nine compartments corresponding to different segments of the digestive tract, was used for absorption. All tissues were represented by a perfusion-limited model.



Predicting the PK of TLL-018 ER formulation in human

After establishing the PBPK model of the IR formulation of TLL-018 in human, the in vitro dissolutions of the ER formulations were substituted into the model to predict the PK of different ER formulations in humans. In addition, the in vitro-in vivo correlation (IVIVC) for TLL-018 ER formulations in dog was used to predict the PK of TLL-018 ER formulations in human. The model predictions were validated based on the measured results of an ER formulation (Formulation A).



Results

Predicting the PK of TLL-018 IR formulation in human

The established PBPK model proved to be effective in describing the observed plasma concentrations of TLL-018 in animals. The predicted C_{max} , T_{max} and AUC of human IR formulation extrapolated from animal PBPK model were all within the two-fold of the observed value.

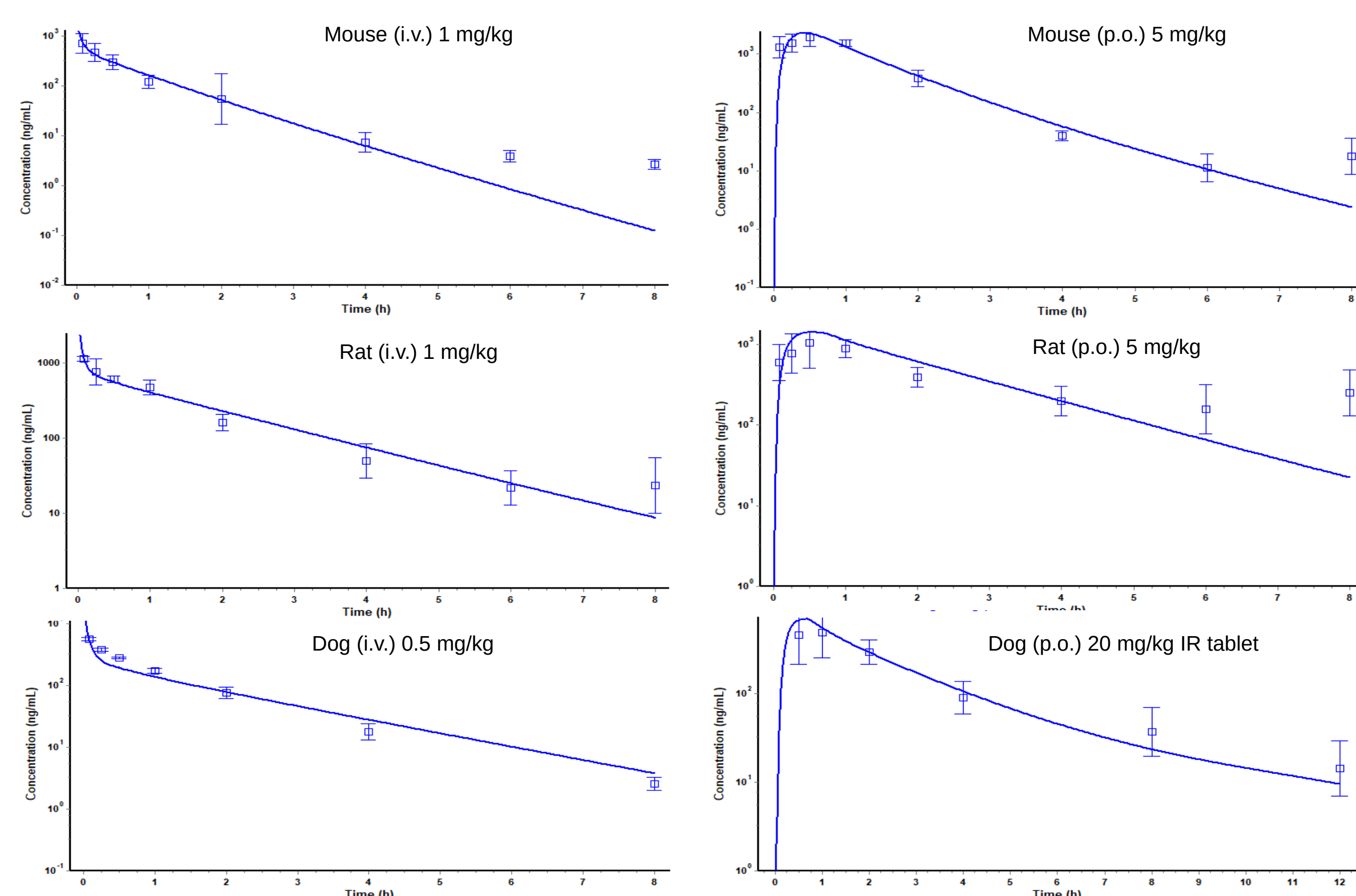


Figure 1. Observed and PBPK model simulated PK profiles in animals.

Table 1. Ratios of simulated/observed PK parameters of TLL-018 IR formulation in human.

	4 mg	8 mg	16 mg	24 mg	64 mg	120 mg
	Sim/Obs	Sim/Obs	Sim/Obs	Sim/Obs	Sim/Obs	Sim/Obs
C_{max}	0.63	0.65	0.70	0.87	0.81	0.69
T_{max}	1.92	1.92	0.96	0.96	1.00	1.22
AUC_{0-inf}	0.86	0.76	0.88	0.81	0.79	0.79
AUC_{0-t}	0.90	0.80	0.89	0.83	0.80	0.80

Predicting the PK of TLL-018 ER formulation in human

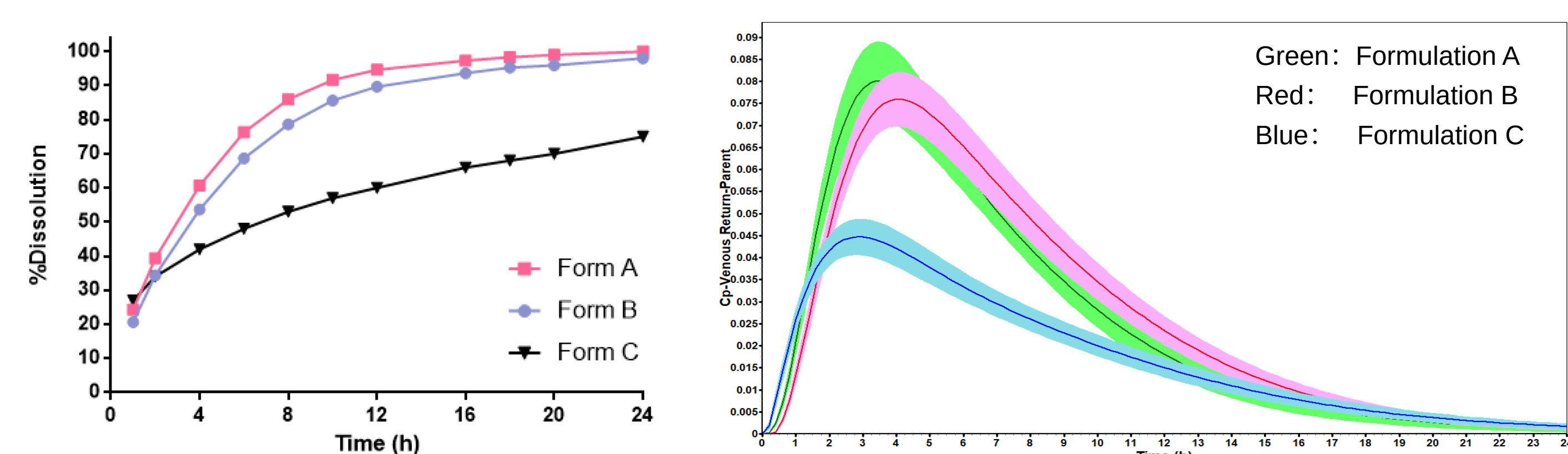


Figure 2. In vitro dissolution profiles (left), and simulated PK profiles of TLL-018 ER formulations using IVIVC method.

Table 2. Ratios of simulated/observed PK parameters of TLL-018 ER formulation A in human.

Formulation A	C_{max}	T_{max}	AUC_{0-inf}	AUC_{0-t}
Pred _{IVIVC} /Obs	1.00	1.40	1.05	1.10
Pred _{PH6.8} /Obs	0.83	1.00	0.95	1.00
Pred _{PH1.2} /Obs	0.95	1.00	1.03	1.08

Conclusion

PBPK model played a significant role in the development of new drug TLL-018 and the selection of ER formulations.

Reference

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