

A translational whole-body PBPK modelling framework to support the development of locally acting orally inhaled compounds

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Objectives

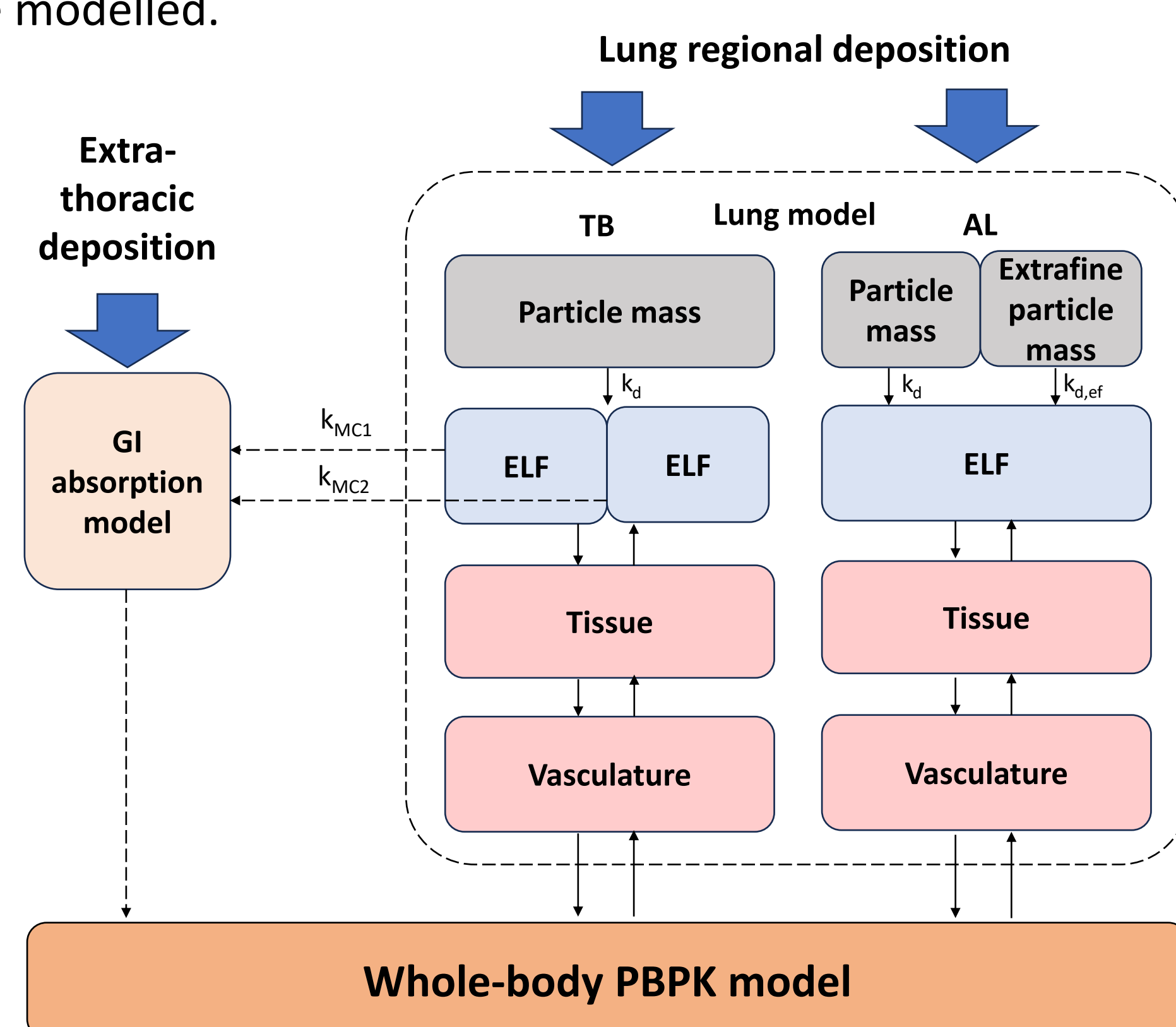
The evaluation of the target site exposure is essential for a better understanding of the PK-PD relationships of locally acting inhaled drugs. PBPK models are powerful tools in this context as their structure allows separation between drug- and system-specific properties, giving insights in which drug and/or formulation-specific properties modulate lung exposure leading to favorable PK-PD-safety profiles [1]. In addition, the parametrization based on physiology facilitates the translation updating the model with human system-specific properties [1].

In this work, a translational PBPK modelling framework to support the preclinical to clinical translation of inhaled compounds is presented. The ability of the model to describe lung and plasma PK in rats after intratracheal (IT) administration was evaluated. The model performances in extrapolating the human PK after inhalation were evaluated focusing on plasma PK of highly soluble compounds with negligible oral bioavailability or co-administered with charcoal, to have insights on the ability to describe the pulmonary absorption process [2].

Methods

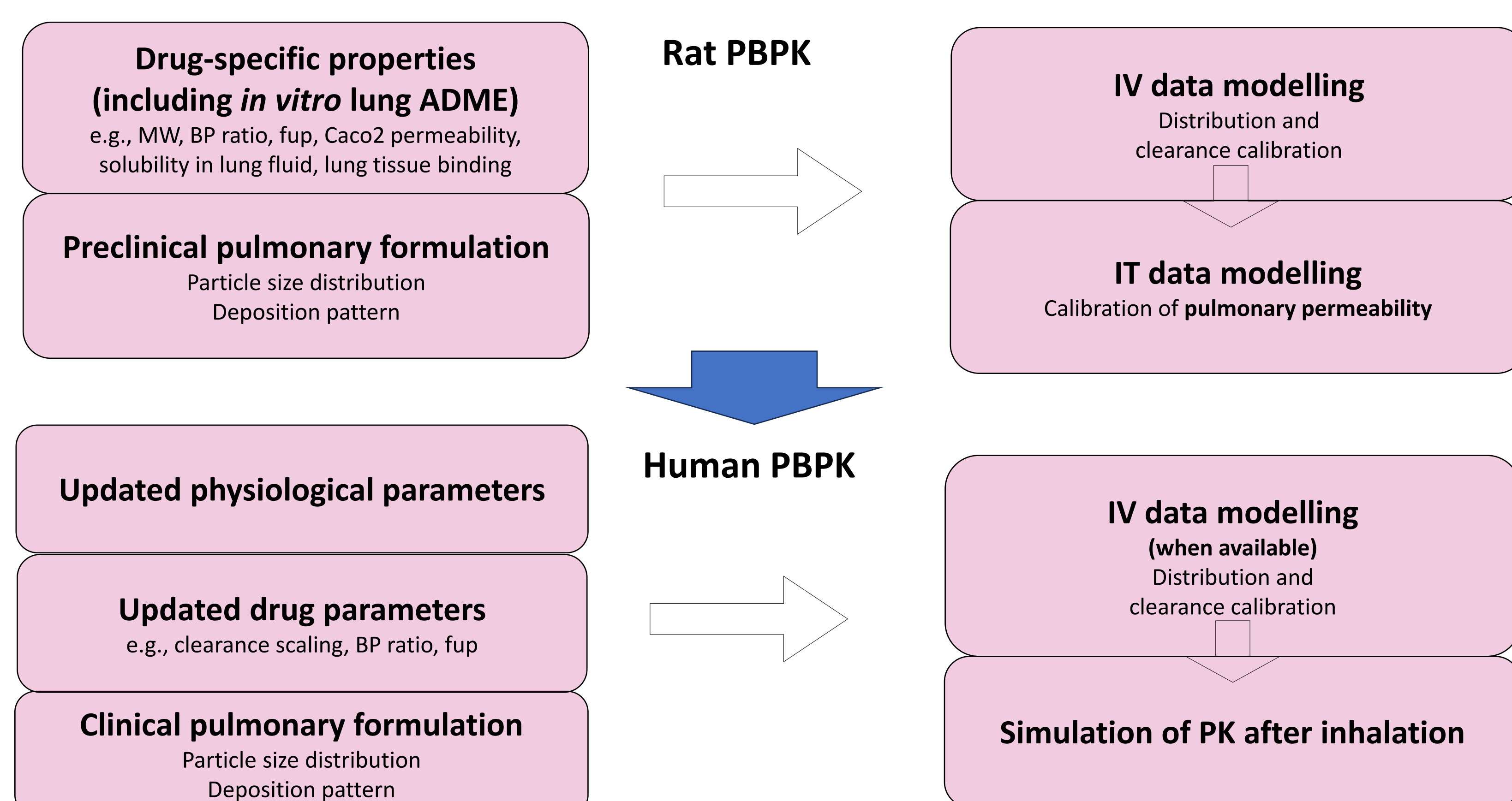
The model

The PBPK model consists of a whole-body structure including a gastrointestinal absorption model [3]. A pulmonary model is integrated to describe the PK of inhaled compounds [4]. The lung is modelled as two regions representing the tracheobronchial (TB) and the alveolar region (AL). The main processes governing the pulmonary PK i.e., deposition, dissolution, mucociliary clearance and absorption are modelled.



The translational workflow

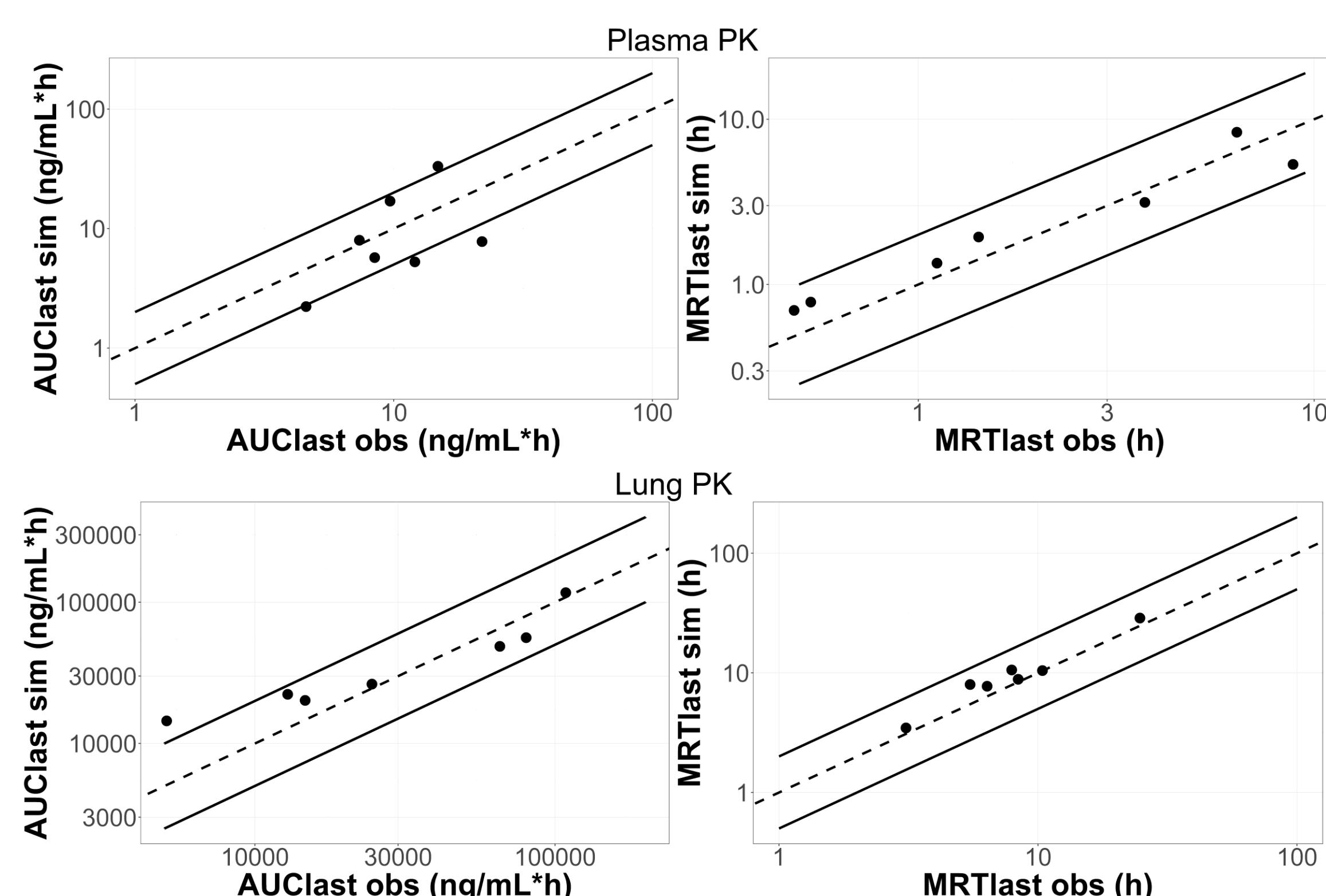
The translational workflow consists of different steps. Initially, rat lung and plasma PK data after IT administration are modelled. Subsequently, for the translational step, species-specific parameters were updated with the human ones, lung drug-specific parameters were kept fixed from the previous step. The regional deposition in humans was computed based on the characteristics of the inhalation device and the particle size distribution of the formulation.



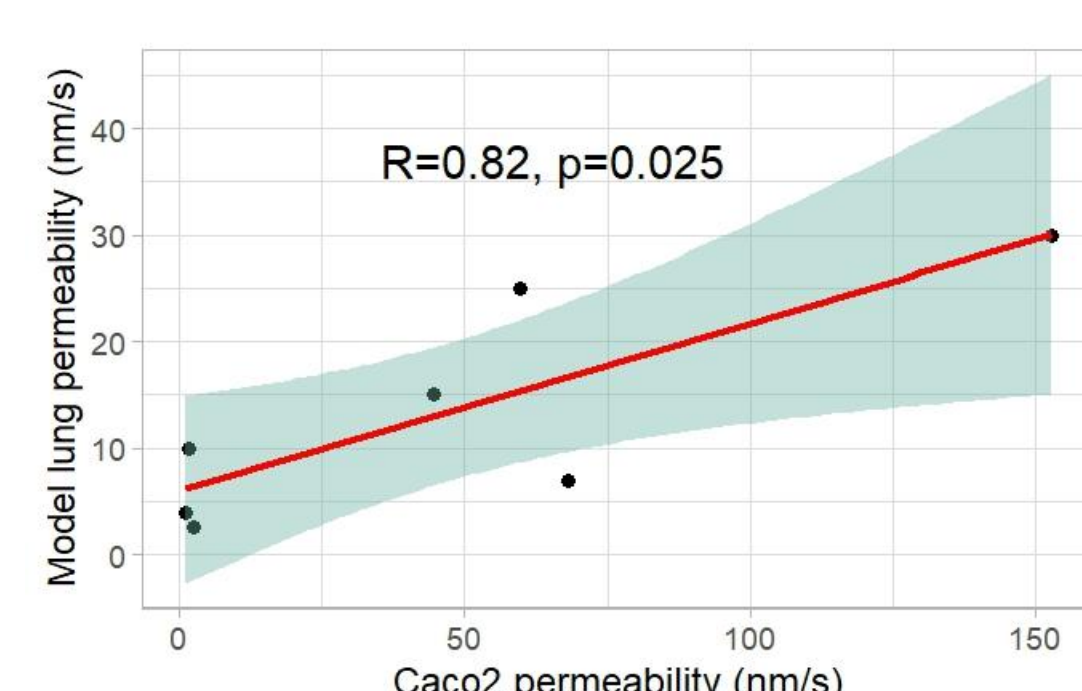
Results

The model was able to describe plasma and lung PK profiles in rats after IT administration. The human plasma PK after inhalation was successfully predicted leveraging *in vitro* compound and formulation data, and calibration on preclinical PK data. With a few exceptions, for all the compounds, all the computed metrics were within the 2-fold error. In addition, during the model calibration step on *in vivo* rat PK data a correlation between the model pulmonary and the *in vitro* Caco2 permeability was found.

Preclinical performances: prediction of rat PK after intratracheal administration



Correlation between calibrated model pulmonary permeability and Caco2 cells permeability



Conclusions

- The model performances in the preclinical species support the use of the framework to evaluate PK-PD relationships in animals.
- The encouraging results related to the human PK extrapolation support further investigations with poorly soluble compounds for its use to guide the design of FIH trials.
- The correlation to calculate the model pulmonary permeability could be potentially used for the prediction of human lung PK of new compounds at early stages directly from *in vitro* data, guiding the optimization of preclinical experiments and potentially reducing the animal testing.

Acknowledgments

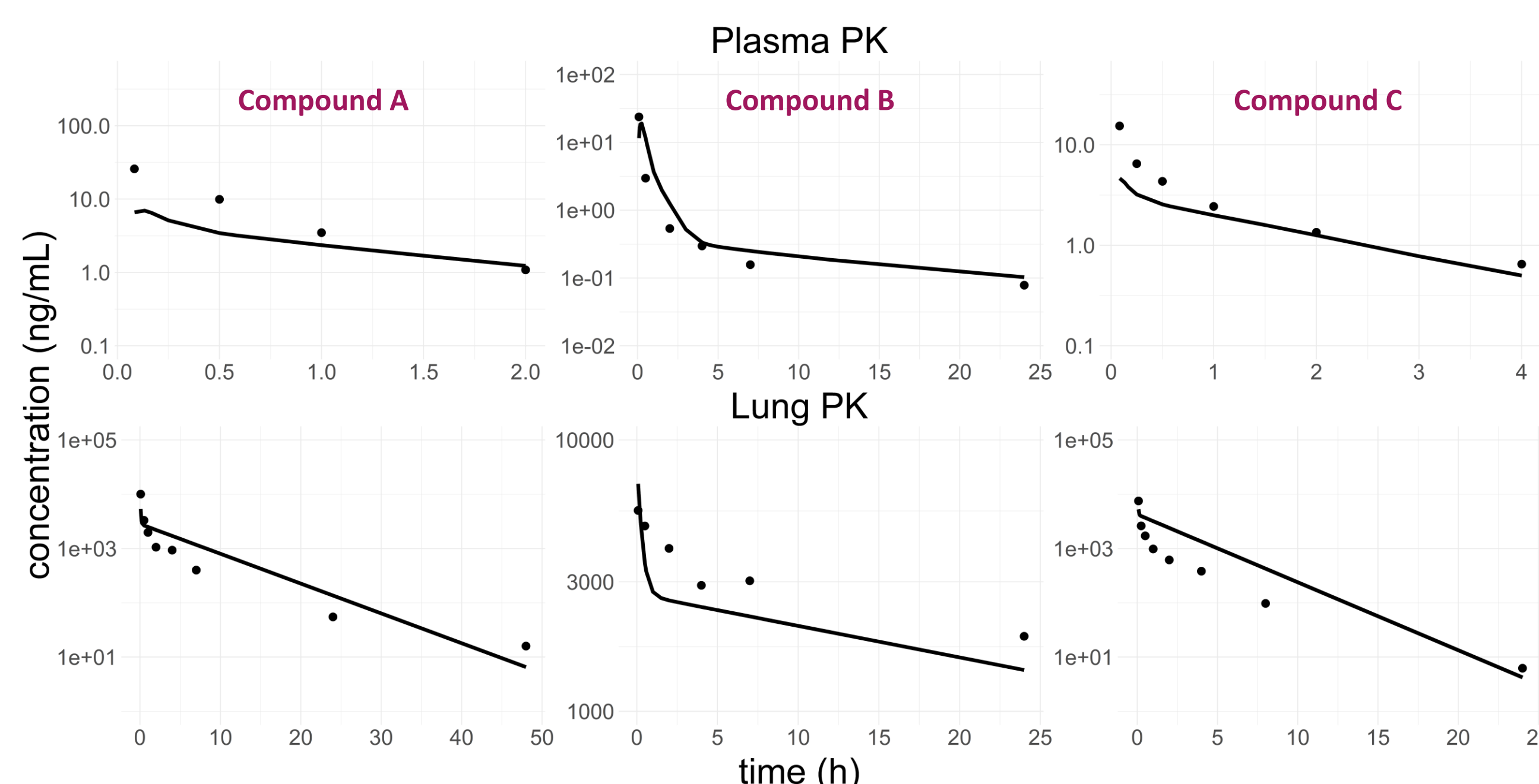
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References

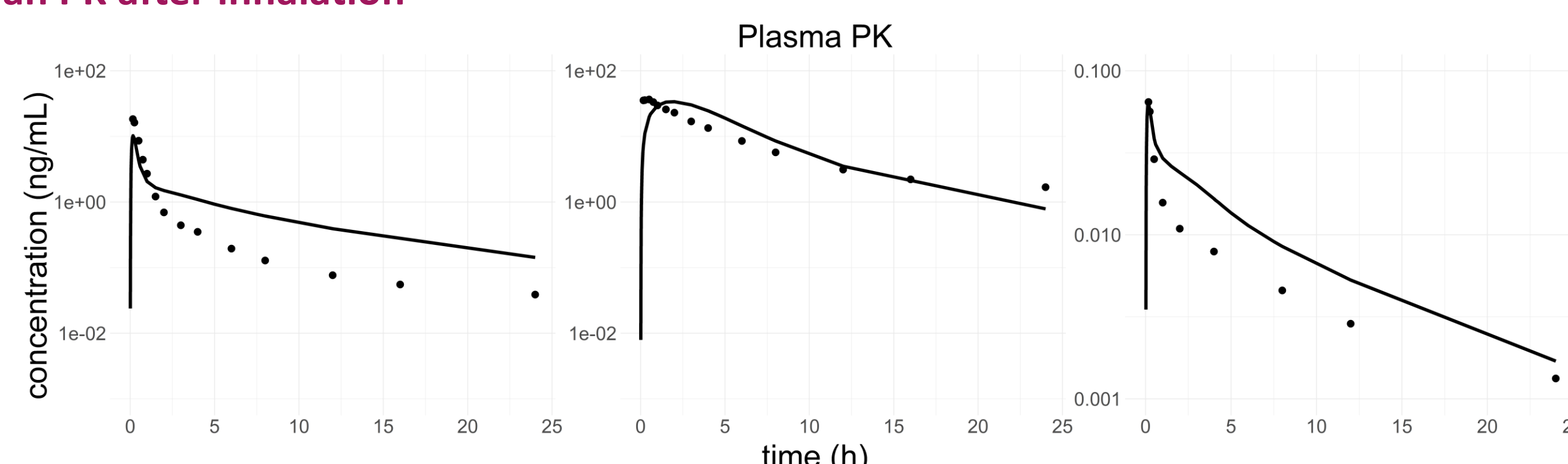
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Translational performances: extrapolation of human PK after inhalation

Rat PK after intratracheal administration



Human PK after inhalation



	Compound A	Compound B	Compound C
AUC _{last} fold error	1.54	1.28	1.82
C _{max} fold error	0.56	0.93	0.99
MRT _{last} fold error	2.5	0.95	0.97