Application of Physiologically-Based Pharmacokinetic Model to Drug Development

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JSSX Kitagawa Memorial Award

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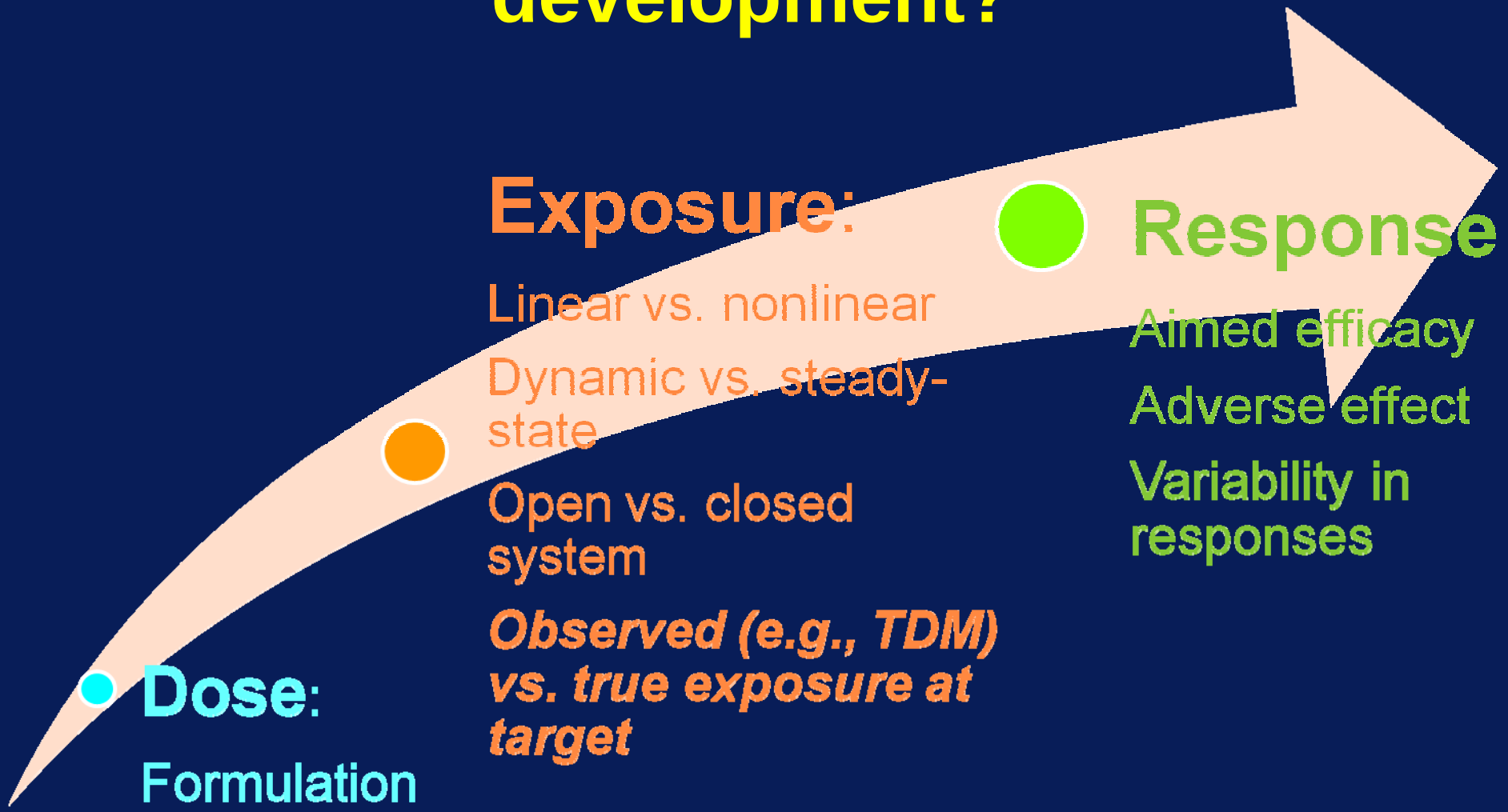
What's PKPD modeling for in drug development?



PKPD modeling in development process

H.Derendorf and B.Meibohm,
Pharm.Res. 16:176-185, 1999

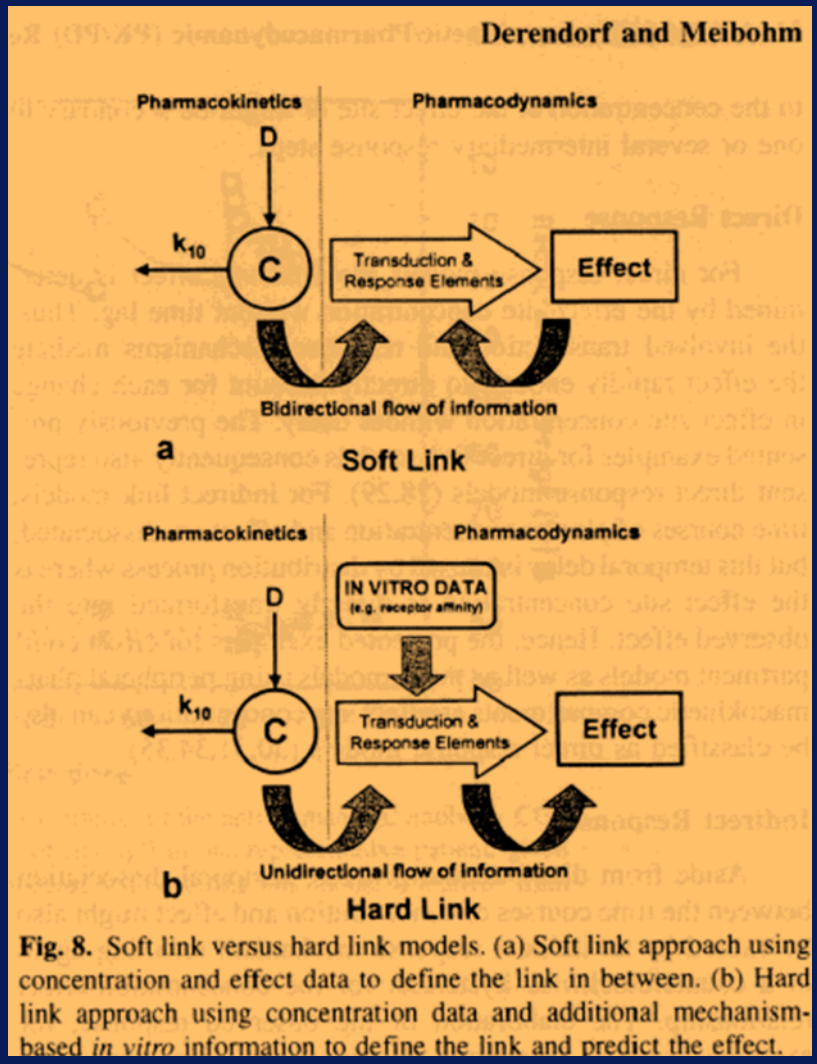


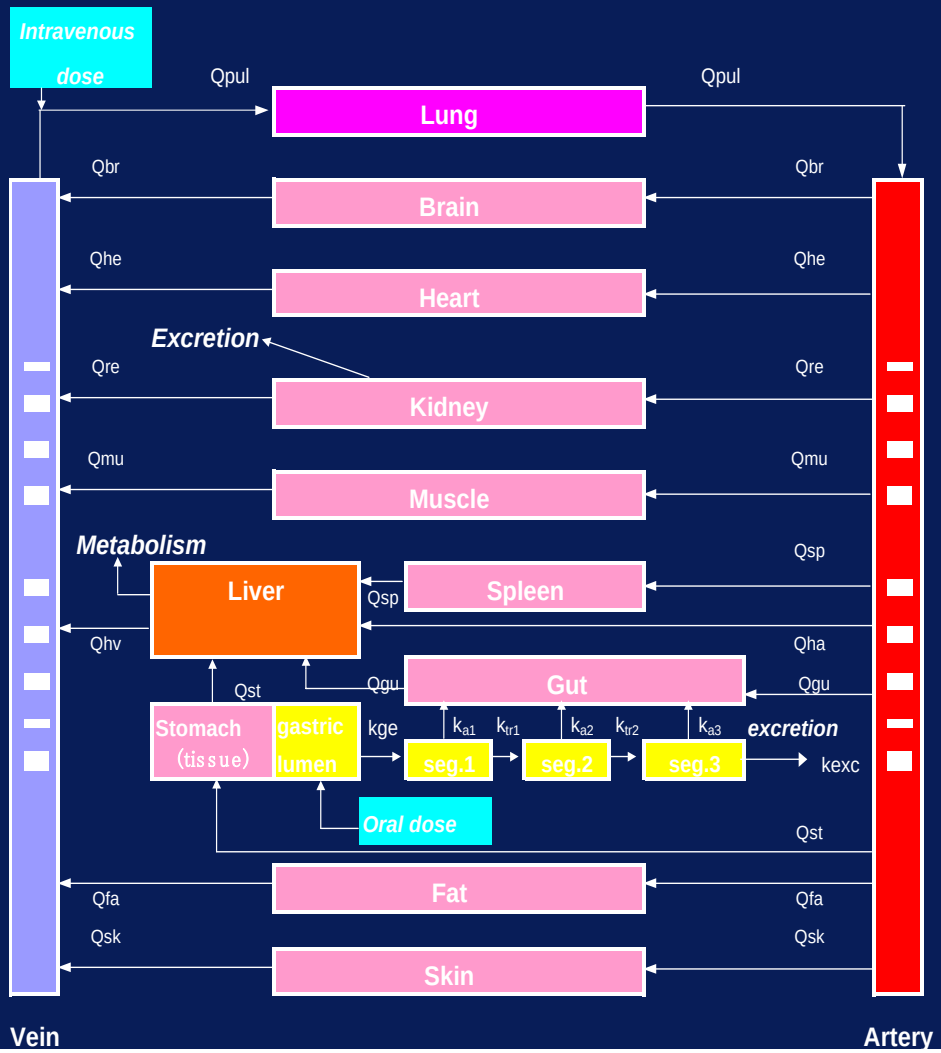
Fig. 8. Soft link versus hard link models. (a) Soft link approach using concentration and effect data to define the link in between. (b) Hard link approach using concentration data and additional mechanism-based *in vitro* information to define the link and predict the effect.

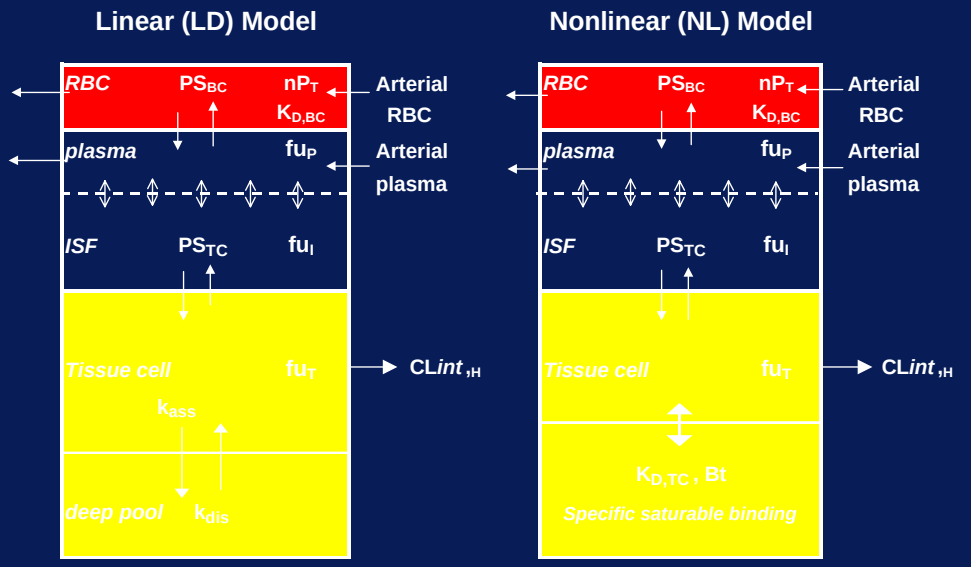
Since 1990's, "top-down " and "bottom-up" approaches were identified as essential for drug development

From discovery to PoC stage, bottom-up constructive approach is demanded

PBPK model is “only framework” to assess globally R&D data/info to support rational drug development

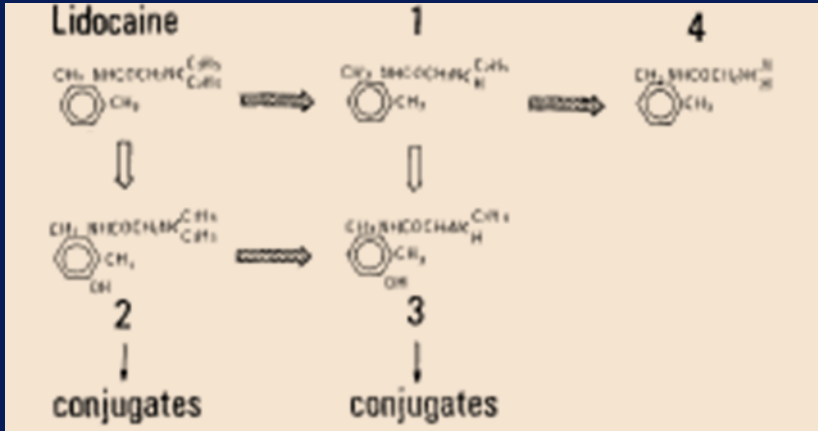
Malcolm Rowland





Started with "nonlinear kinetics" to explain efficacy (bioavailability) and safety (toxic metabolite) in early to mid 1980's

Kawai et al., J.Pharm.Sci. 74:1219-1224 (1985)



Scheme I —Metabolic pathways of lidocaine. Key: (□) 3-hydroxylation; (▨) N-deethylation.

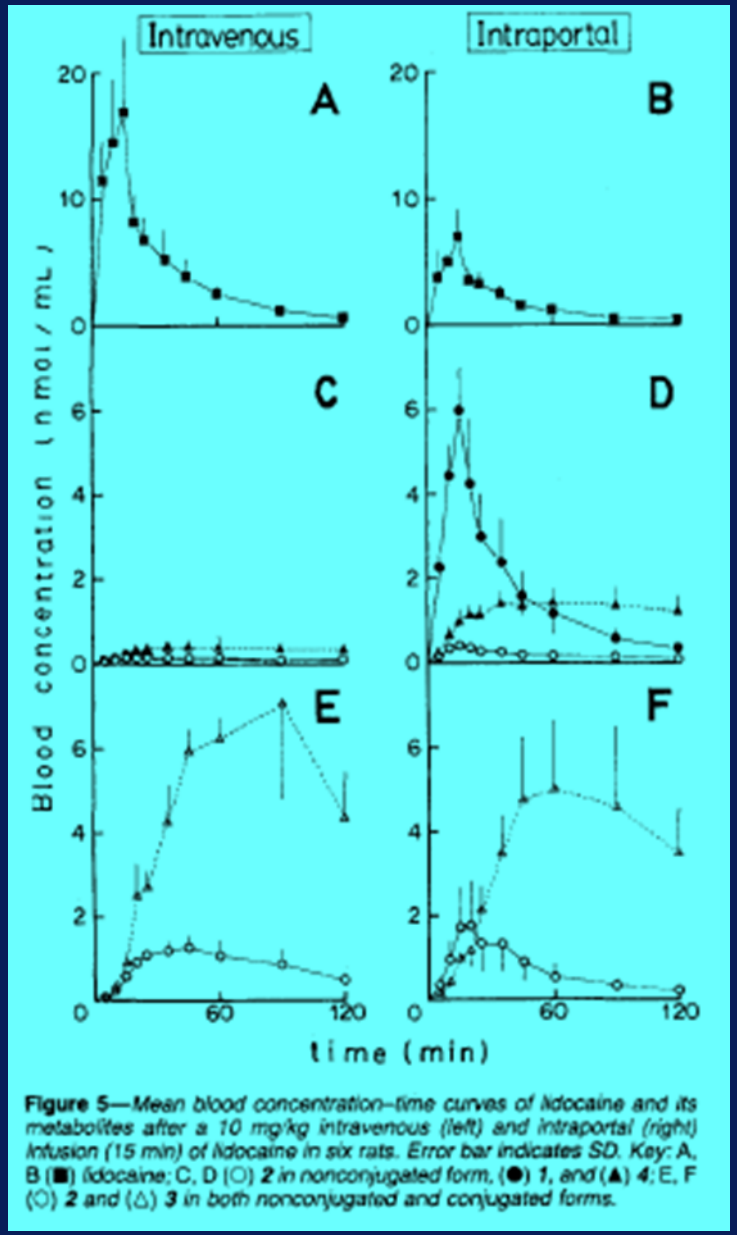


Figure 5—*Mean blood concentration–time curves of lidocaine and its metabolites after a 10 mg/kg intravenous (left) and intraportal (right) infusion (15 min) of lidocaine in six rats. Error bar indicates SD. Key:* A, B (■) *lidocaine;* C, D (○) ***2*** *in nonconjugated form,* (●) ***1***, *and* (▲) ***4***; E, F (◇) ***2*** *and* (△) ***3*** *in both nonconjugated and conjugated forms.*

Explored use of PK models to clarify drug – target (biophase) interaction with physiology and anatomy in late 1980's

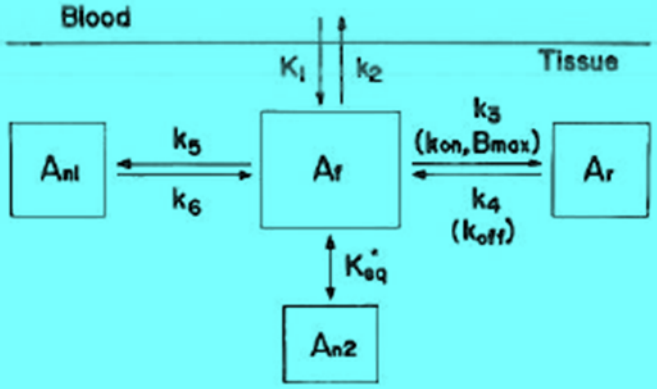


FIG. 1. The compartmental model adopted in this study consists of free, unbound ligand (A_f), receptor-bound ligand (A_r), nonspecifically bound with measureable rate constants (A_{n1}), and "instantaneously" bound (A_{n2}). K_1 and k_2 are the influx (blood clearance) and efflux rate constants across the blood–brain barrier, respectively; k_{on} and k_{off} are the receptor association and dissociation rate constants, respectively; B_{max} is the concentration of receptors; k_5 and k_6 are the nonspecific binding association and dissociation rate constants, respectively; K^*_{eq} is the "instantaneous" nonspecific binding equilibrium constant. Under linear (tracer) conditions, receptor association (k_{on}, B_{max}) and dissociation (k_{off}) processes can be expressed by k_3 and k_4, respectively.

Kawai et al., J.Cereb.Blood Flow Metab. 11:529-544 (1991)

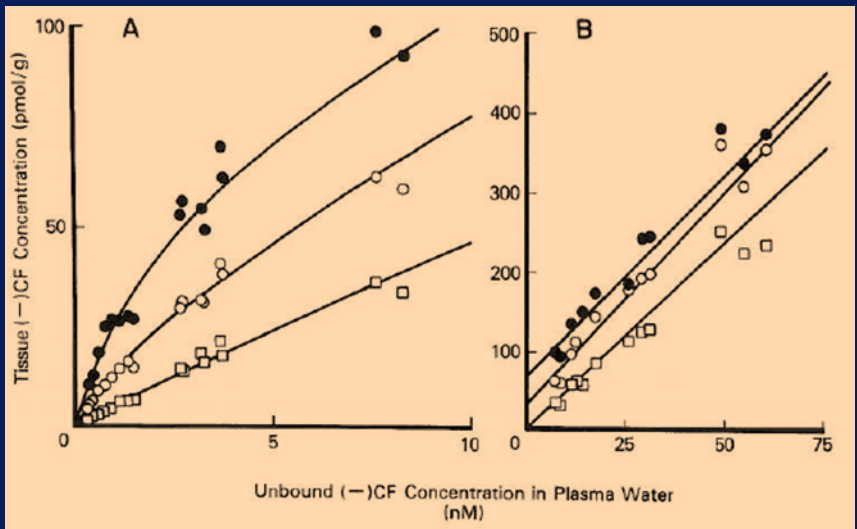


TABLE 2. *Receptor binding parameters B_{max} and K_D and nonspecific tissue binding (K_{eq}) of [^{3}H](−)-CF in rat brain*

Structures	B_{max} (pmol/g)	K_D (nM)	K_{eq}
Cerebellum	−0.1 ± 2.9	5.54 ± 1.23	5.20 ± 0.28
Frontal cortex	28.0 ± 6.7	1.87 ± 0.58	7.95 ± 0.49
Parietal cortex	17.1 ± 5.2	1.70 ± 0.67	7.45 ± 0.44
Occipital cortex	16.8 ± 5.8	1.63 ± 0.73	8.01 ± 0.50
Thalamus	58.4 ± 9.9	2.00 ± 0.45	7.05 ± 0.59
Caudate	74.3 ± 16.8	2.90 ± 0.80	7.37 ± 0.85
Midbrain	42.2 ± 6.4	1.73 ± 0.37	5.77 ± 0.44
Hippocampus	17.1 ± 6.3	1.41 ± 0.71	7.30 ± 0.57
Medulla	27.5 ± 6.2	2.06 ± 0.59	5.29 ± 0.42
White matter	15.4 ± 4.5	1.78 ± 0.68	5.18 ± 0.37

Estimated values, ± SEM of the estimate.

Established PBPK model for development with cyclosporin and its derivatives in 1990's

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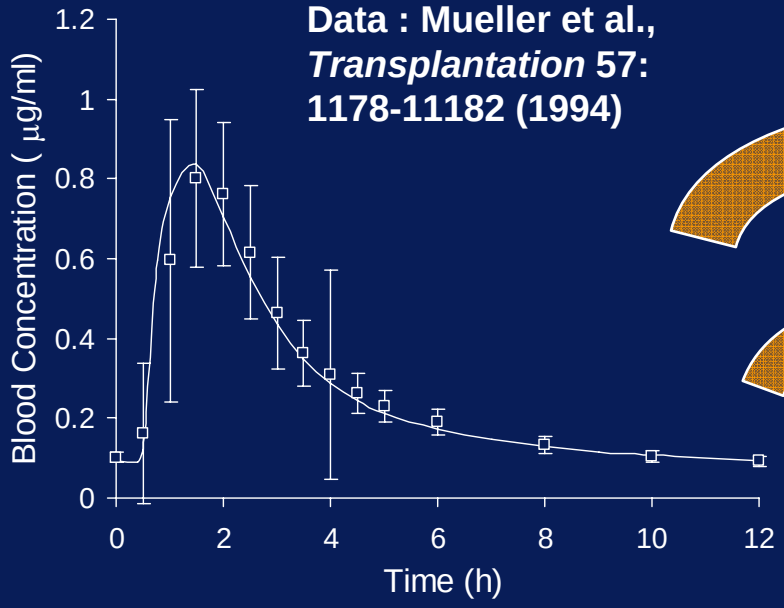


Data : Mueller et al., *Transplantation* 57: 1178-11182 (1994)

translation

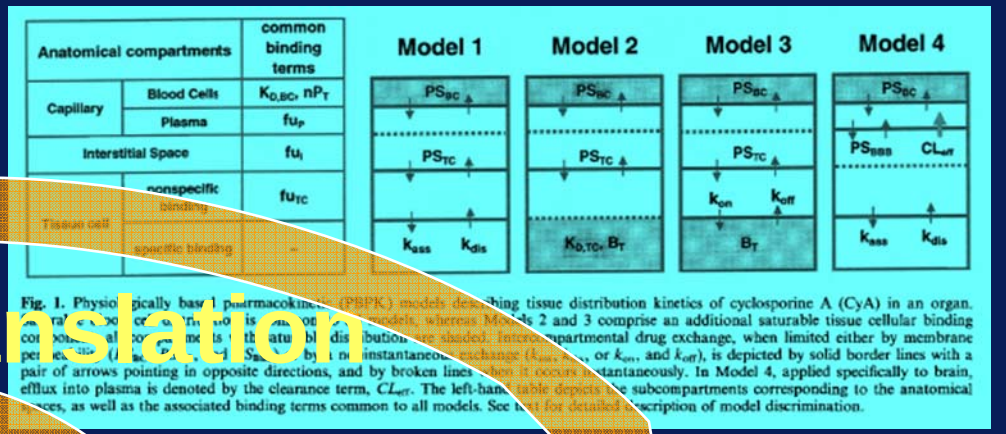
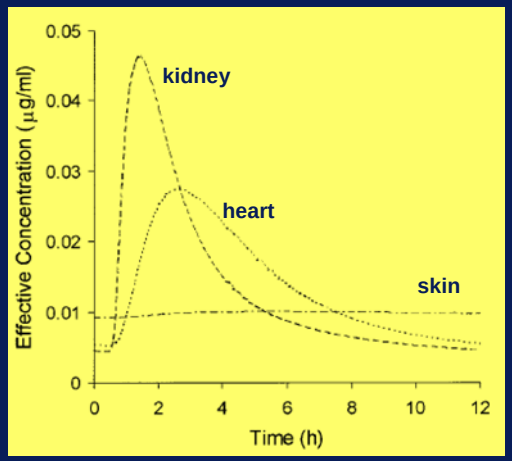


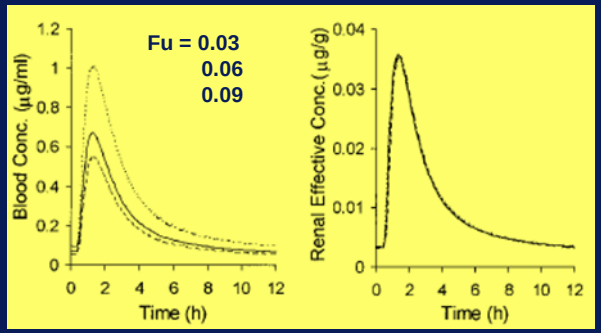
Fig. 1. Physiologically based pharmacokinetic (PBPK) models describing tissue distribution kinetics of cyclosporine A (CyA) in an organ. ... Models 2 and 3 comprise an additional saturable tissue cellular binding ... compartmental drug exchange, when limited either by membrane ... instantaneous exchange (k_{ass}, ..., or k_{on}, and k_{off}), is depicted by solid border lines with a pair of arrows pointing in opposite directions, and by broken lines ... when it occurs instantaneously. In Model 4, applied specifically to brain, efflux into plasma is denoted by the clearance term, CL_{eff}. The left-hand ... depicts the subcompartments corresponding to the anatomical ... spaces, as well as the associated binding terms common to all models. See text for detailed description of model discrimination.

Tanaka et al., .Pharmacokinet. Biopharm. 27: 597-623 (1999)

Exposure to diverse targets



Apparent vs. true exposure



Measured and PBPK simulated concentration of cyclosporine A in renal transplant patients (1.5 mg/kg bid); from Kawai et al., J Pharmacol Exp Ther 287: 457-468 (1998).

General PBPK model applicatiton as a framework to integrate R&D data

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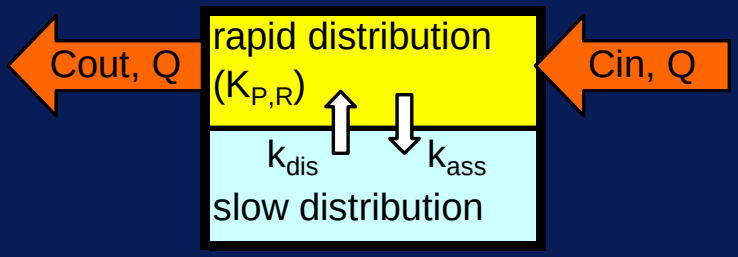
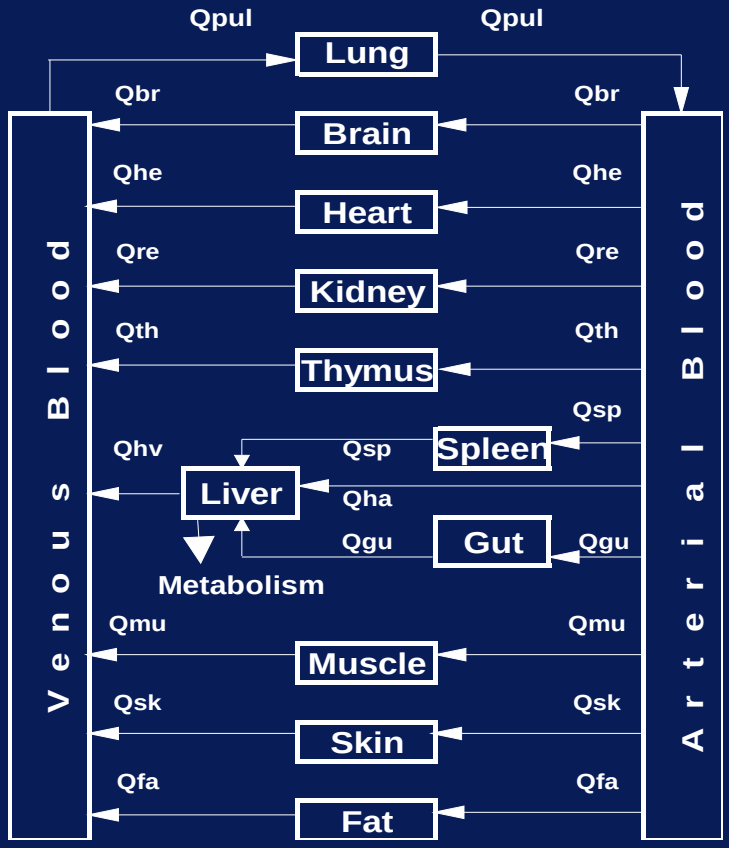
A typical organ model

Two compartment model per organ usually suffices to describe kinetic event in tissues



A whole-body PBPK model



Organ mass and blood flow database

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	mouse		rat		dog		human	
	mass (g)	perfusion (mL/h)	mass (g)	perfusion (mL/h)	mass (kg)	perfusion (L/h)	mass (kg)	perfusion (L/h)
Blood	1.7	-	16.9	-	0.425	-	5.40	-
lung	0.12	337 [a]	1	2571 [a]	0.085	58 [a]	1.17	314 [a]
brain	0.36	4.8	1.7	80	0.05	8.7	1.45	42.0
heart	0.08	17	0.8	235	0.043	2.6	0.27	9.0
kidney	0.32	78	2.3	554	0.097	10.2	0.31	66.0
bone [b]	1.04	21	15.8	152	1.21	1.3	8.70	15.0
muscle	10	55	122	450	4.25	10.2	30.0	45.0
pancreas	0.22	2.8	1.3	31	0.018	1.0	0.08	8.0
stomach	0.13	15	1.1	68	0.024	0.6	0.16	2.3
spleen	0.10	5.4 [c]	0.6	38 [c]	0.022	0.8 [c]	0.19	4.6 [c]
liver	1.75	21	10.3	120	0.213	2.7	1.69	18.1
gut	1.50	90	10	451	0.204	15.3	1.65	66.0
thymus	0.14	1.6	0.7	18	0.007	0.6	0.03	4.8
skin	2.9	25	40	350	0.364	1.1	7.80	18.0
fat	0.51	1.5	10	24	1.5	3.0	10.0	15.6
total	21	-	235	-	8.5	-	68.9	-
body weight	22		250		8.5		70.00	
(% BW)	(95)		(94)		(100)		(98)	

a) sum of perfusion in all organs; b) mass and perfusion for bone marrow are 30 and 100% of respective bone values; c) liver perfusion means that by arterial blood (excludes portal flow)

Prediction of intrinsic (metabolic) clearances based on in vitro data in various species

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Predicted interspecies ratio in CLint (/kg) vs. rat[a,b]

an example for an actual drug under development

species	slice	S9	microsomes
mouse	3.3	-	58
rat	1	1	1
dog	0.59	-	-
human	0.54	0.45-0.93[c]	0.23

a) The same conditions (initial substrate conc.) in all species.

b) Liver mass/body weight in mouse (1.4g/22g), rat (10.3g/250g), dog (213g/8.5kg) and human (1.69kg/70kg) are standard values.

c) Give ranges for uncertainty.

Scaling-up toxicological exposure

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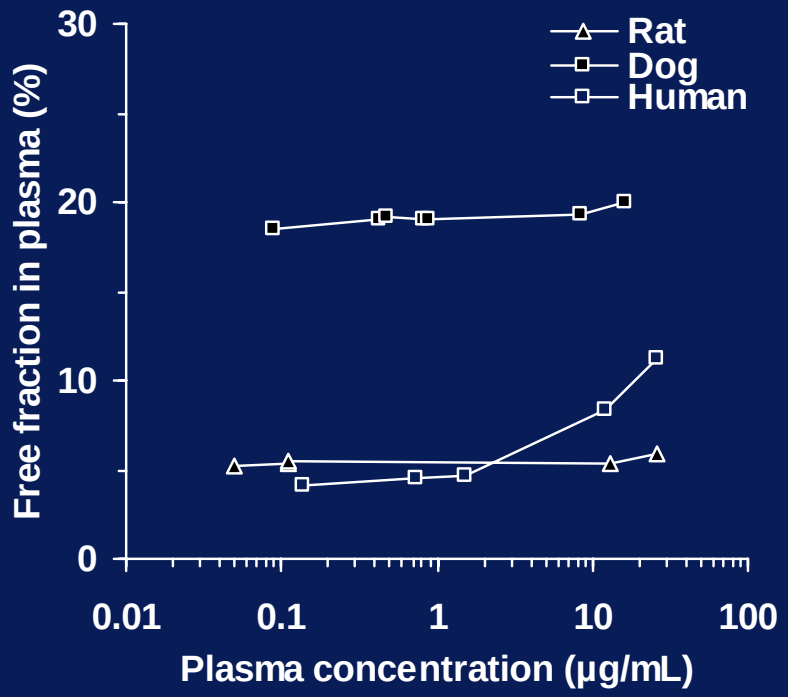
Plasma protein binding often differs largely across species



PBPK simulations of organ exposure after single dose expressed as AUC in rat, dog and human

Species	Dose (mg/kg)	Dose (mg/44 kg)	AUC[a] (µg*h/mL or g) Plasma	Liver
Rat	60[b,c]	-	45.4	2173
Dog	10[b]	-	5.86	979
Human[d]	5.8	250[e]	15.3-77.1	589-2948

a; AUC calculated up to 7 days post-dose (i.e., when more than 99.5 % dose eliminated).
b; hepatotoxicity critical dose in 13-week oral study.
c; hepatotoxicity critical dose in 2-week oral study.
d; CSF was varied from 0.068 to 0.36 for PBPK simulations.
e; liver toxicity occurred at this dose.

Procedure 1 : develop model with ADME data

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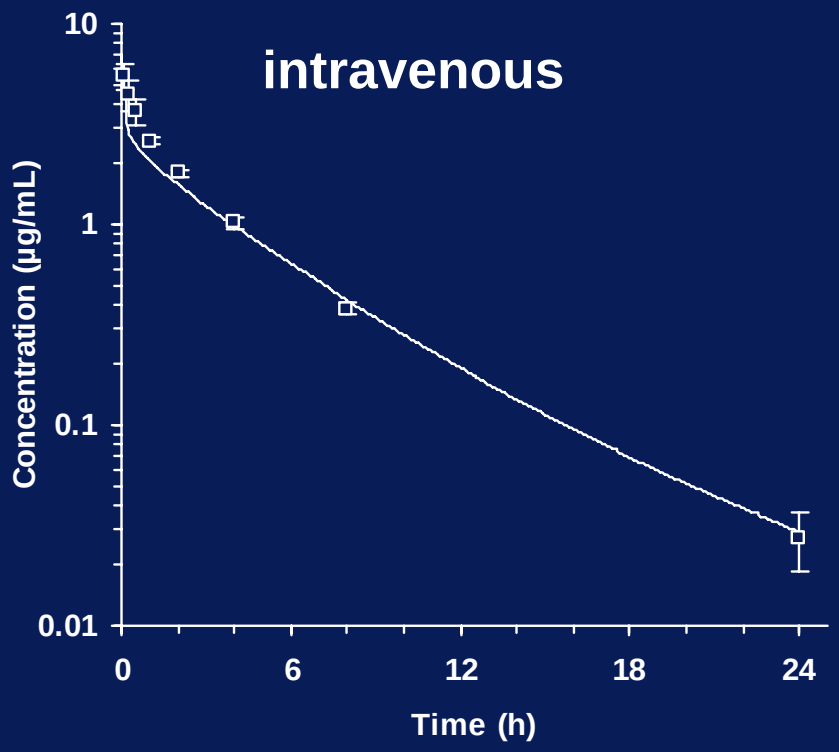
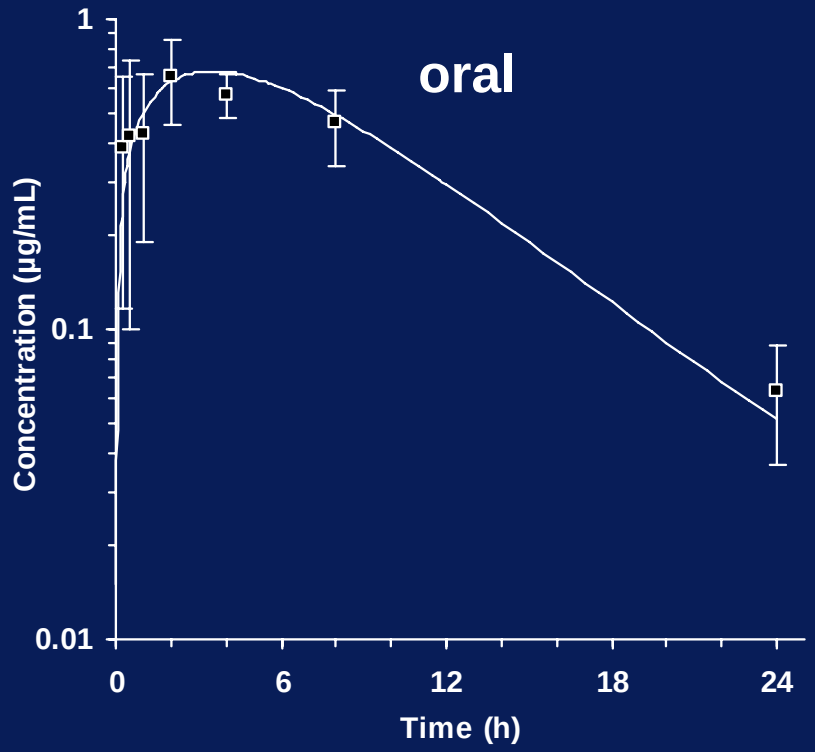
Measured vs PBPK model simulated plasma concentrations in rats following a single intravenous and oral doses (mean ± SD, n=3)





Procedure 2 : confirm model with other data

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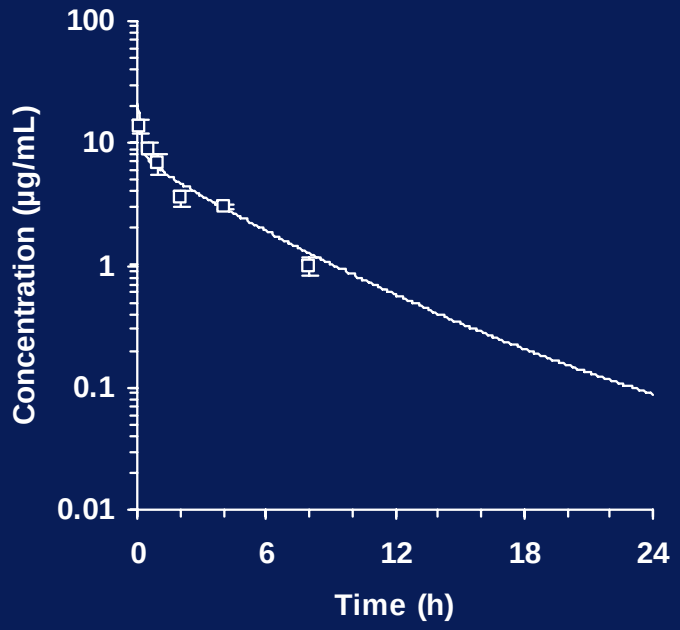
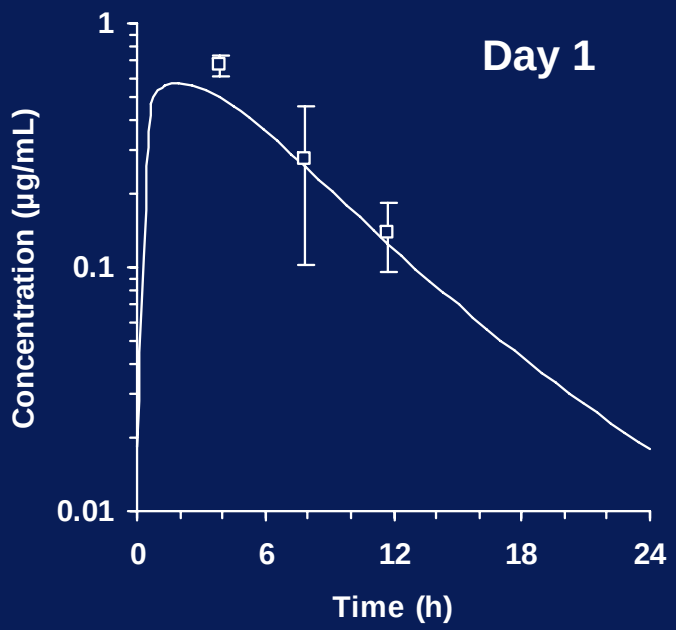
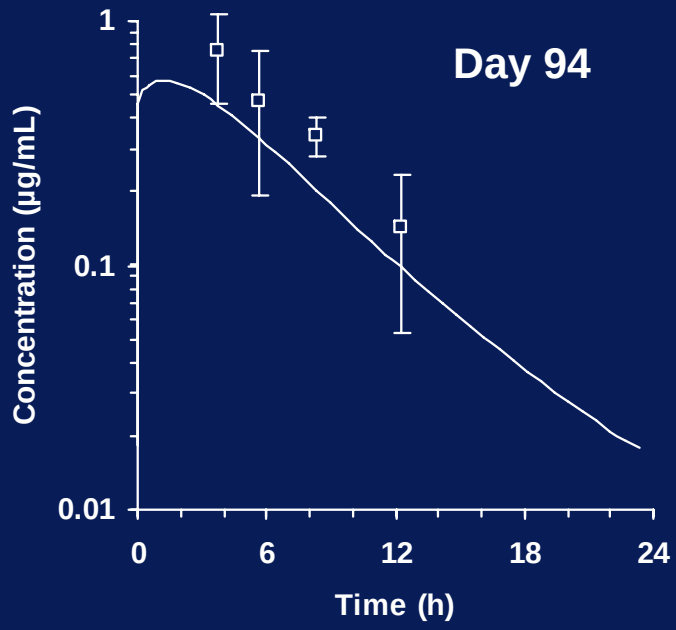
PBPK simulation and TK measurements of plasma concentrations in rats

Intravenous dose



Oral dose: 13-week toxicokinetic study





Procedure 2 : confirm model with other data

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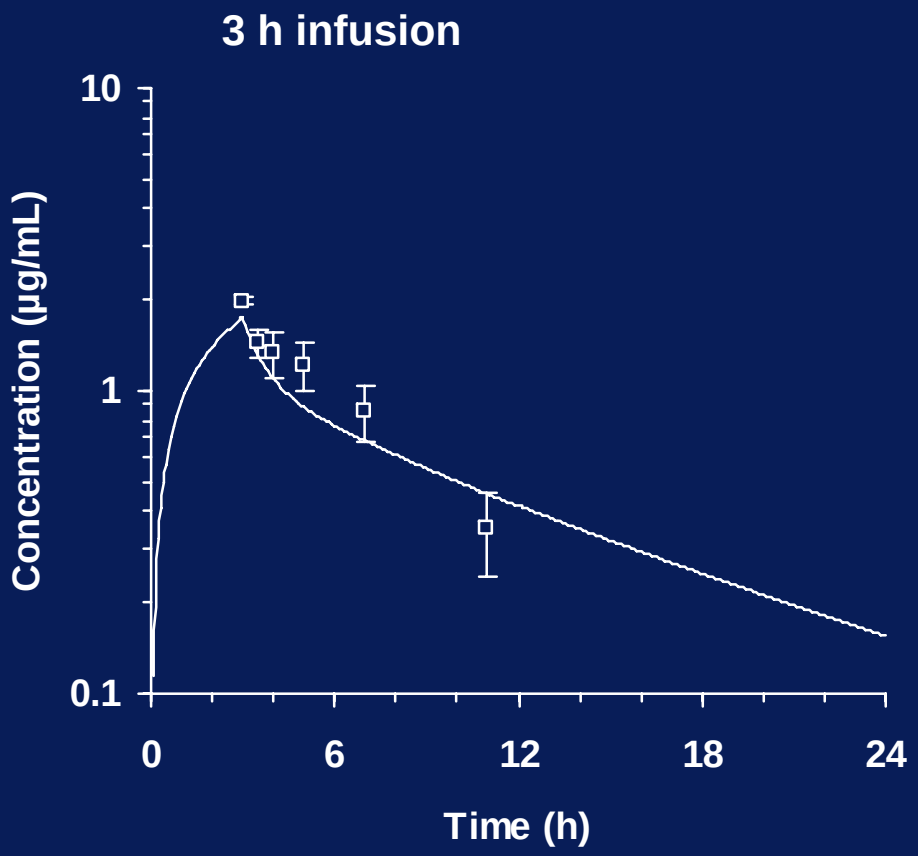
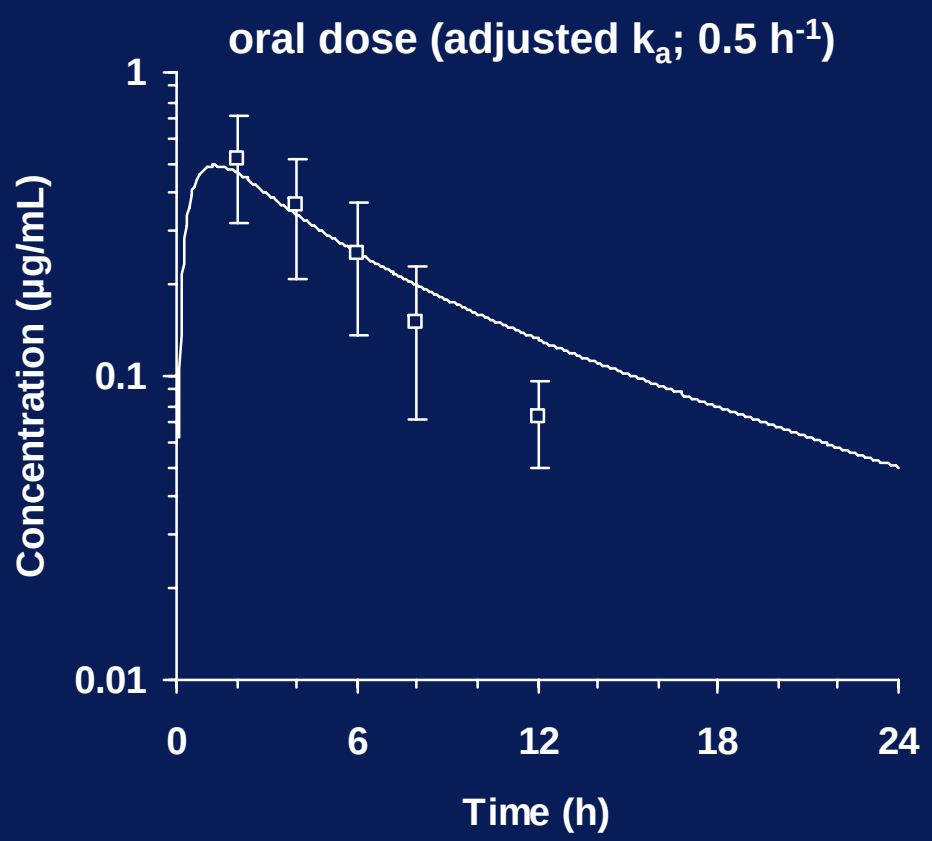
PBPK simulation with median clearance scaling factor and TK measurements of plasma concentrations in dog





Procedure 3 : adjust model with human data

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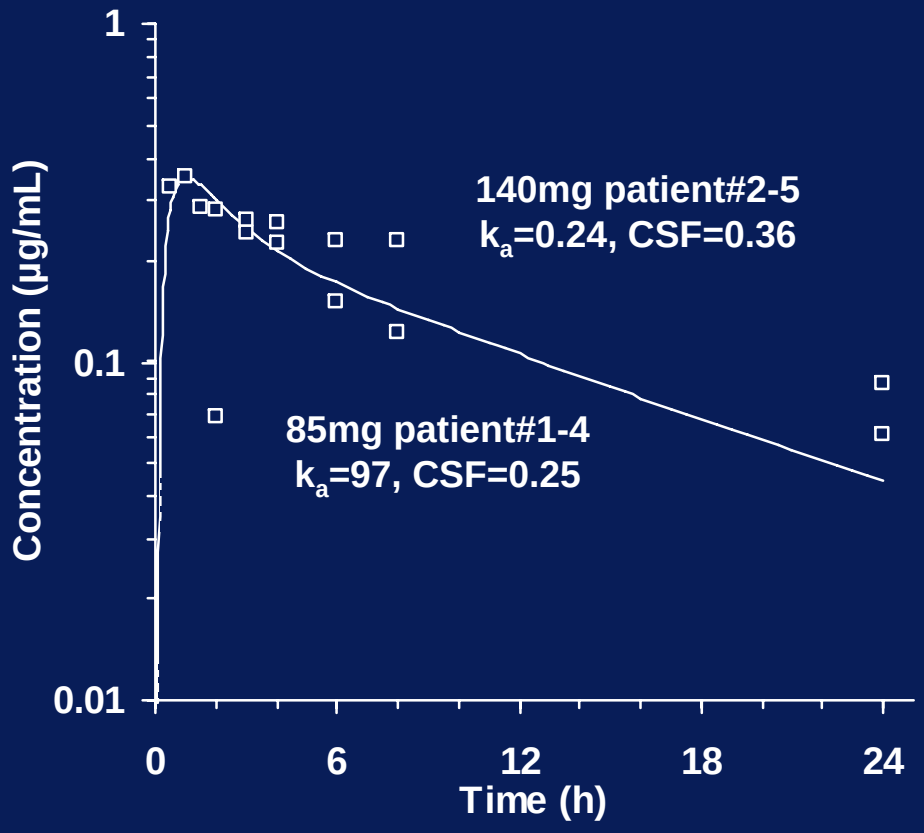
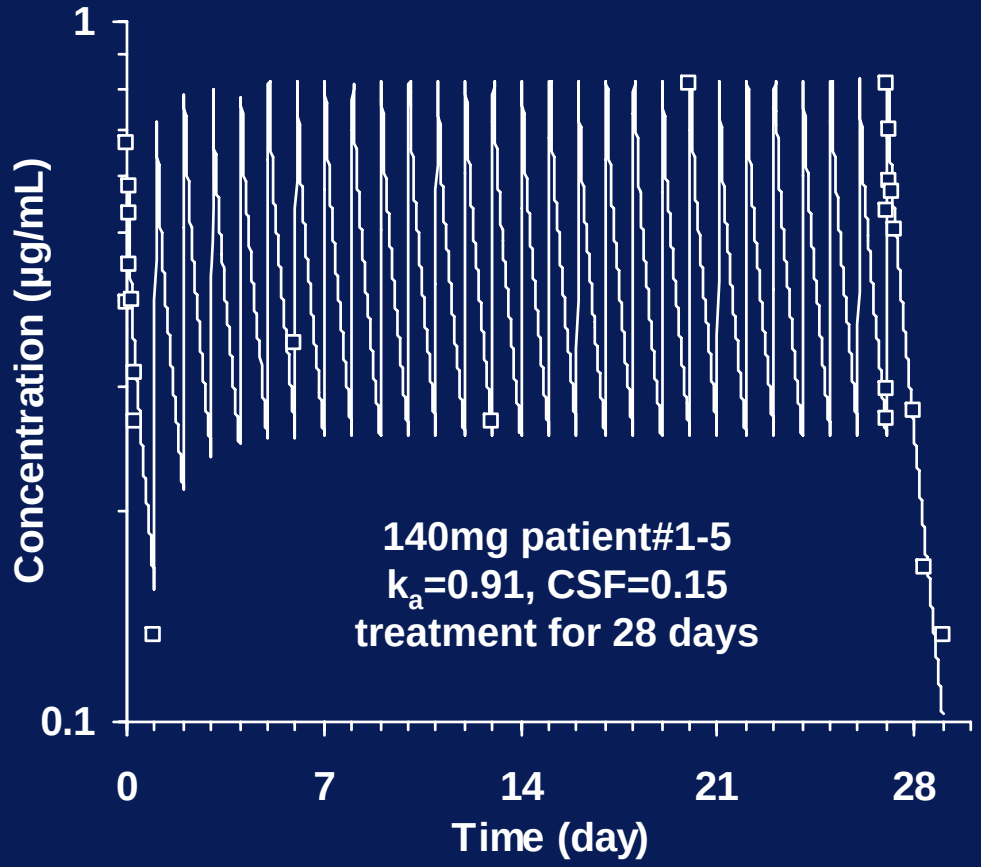
PBPK model was adjusted to each subject by fitting the plasma data with f_{abs} = 1 varying k_a and CSF (within the range given from *in vitro* biotransformation data)





Procedure 4: Assessment of relevant factors in man [altered plasma binding]

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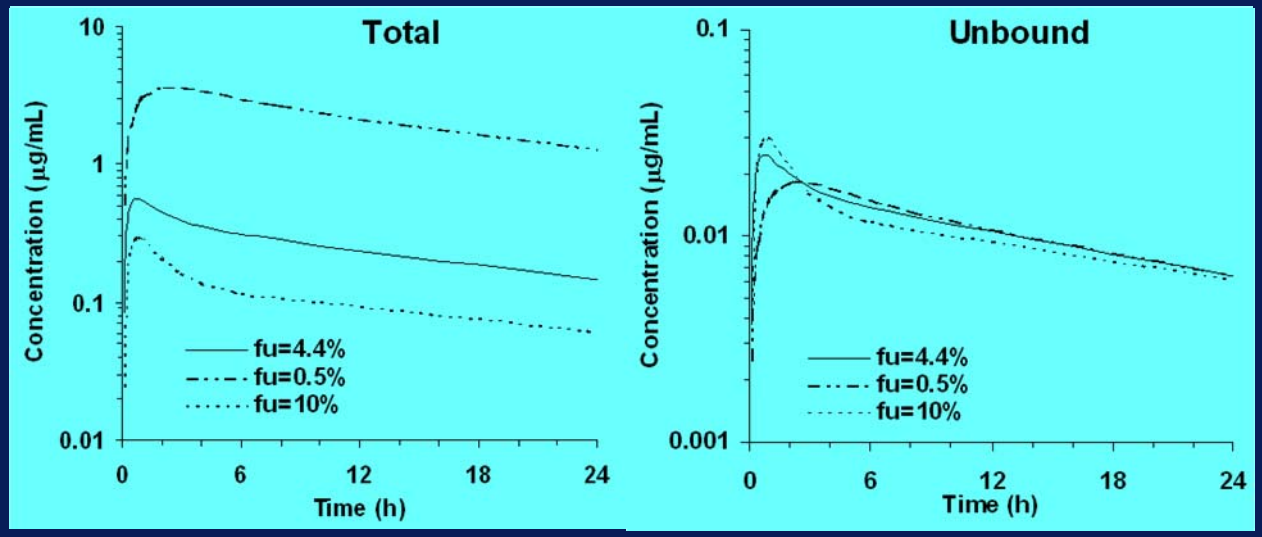

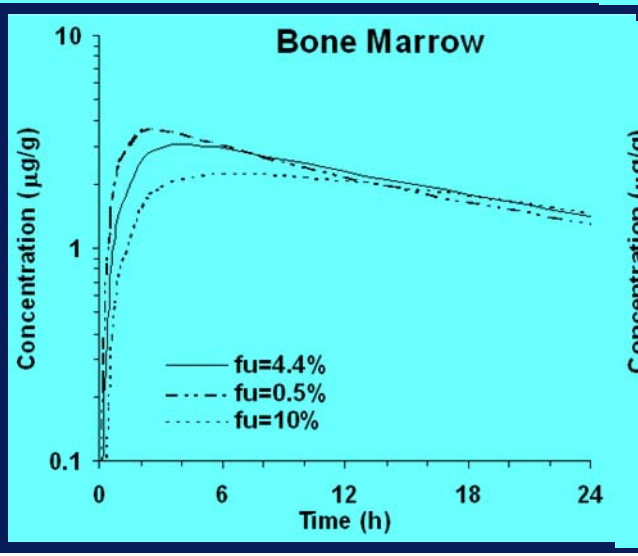

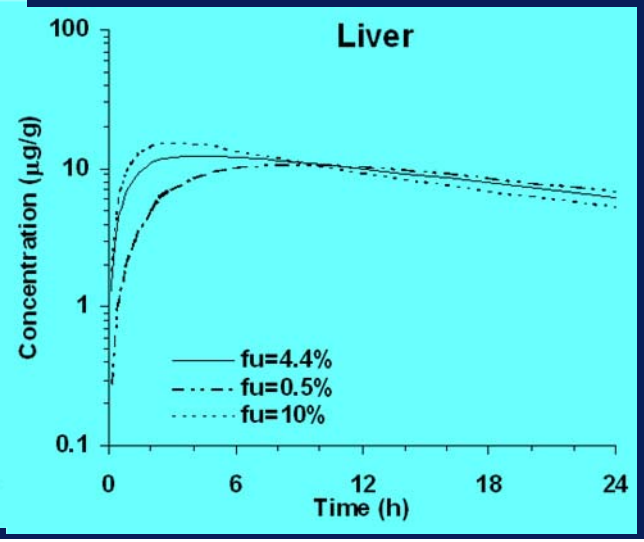

A kinetic model describing presystemic disposition of cyclosporin derivative dry powder after inhalation

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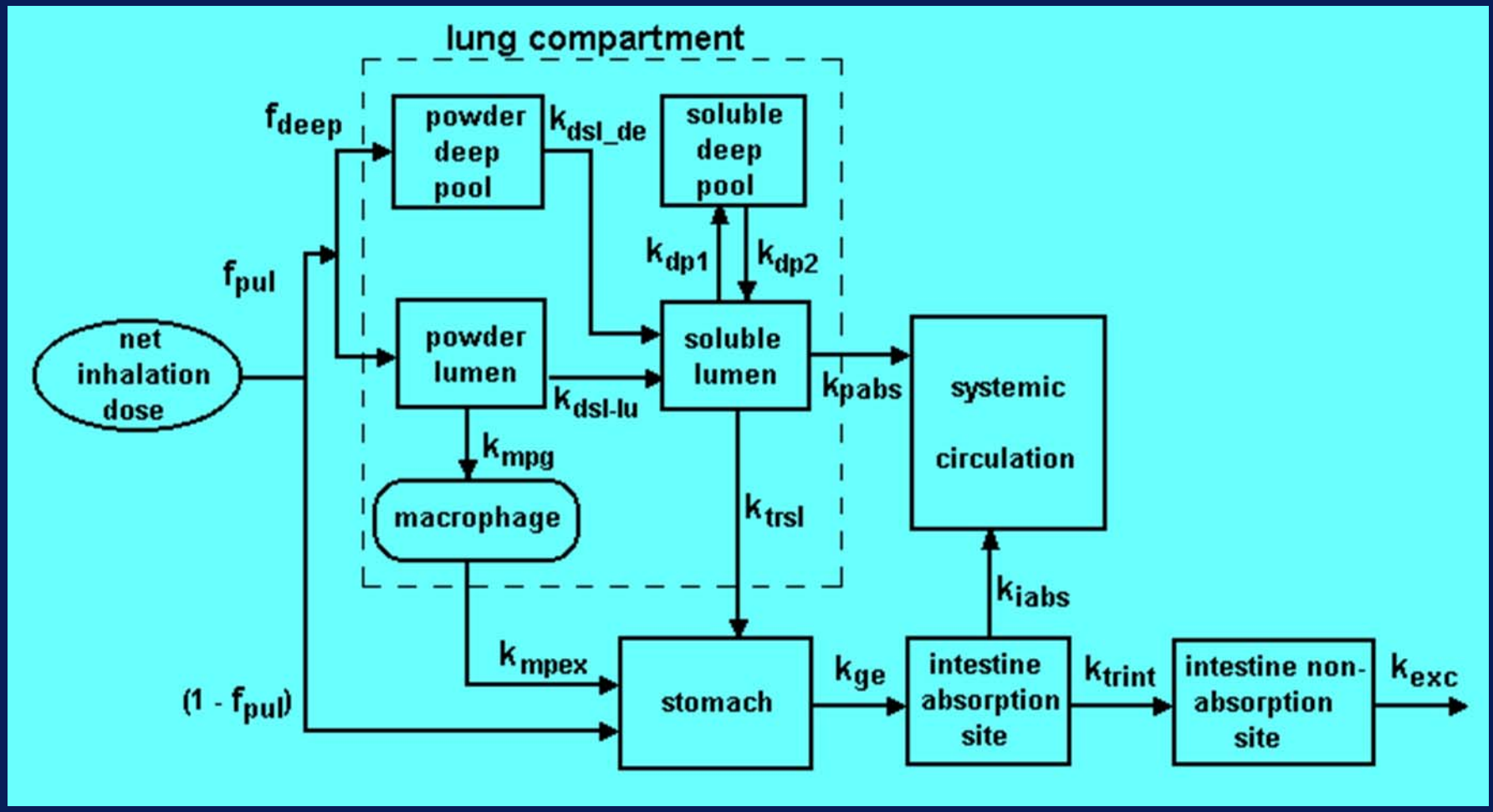

Drugs recovered in various body sites in rats after intra-tracheal dose (solution) and dry powder inhalation fitted to PBPK model.

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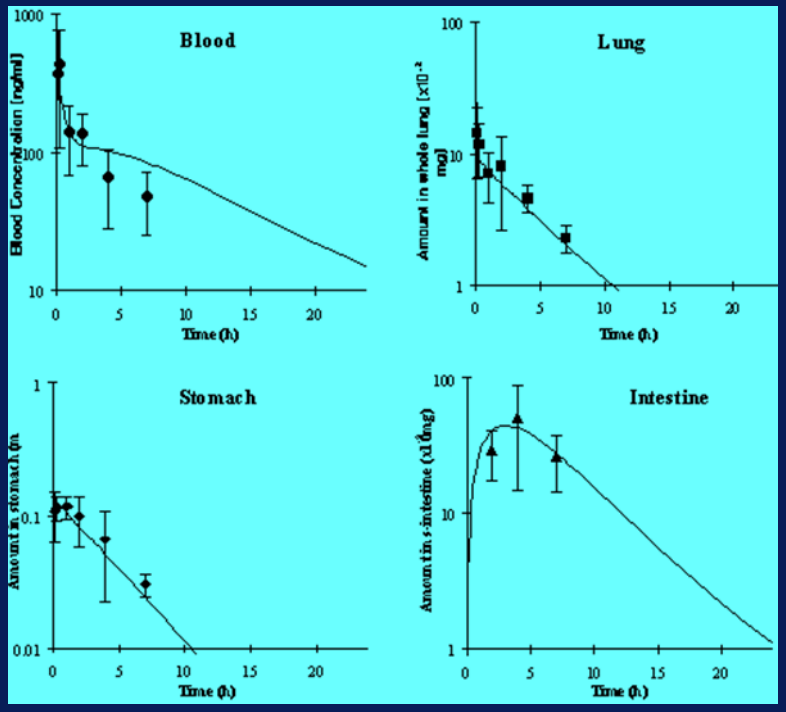
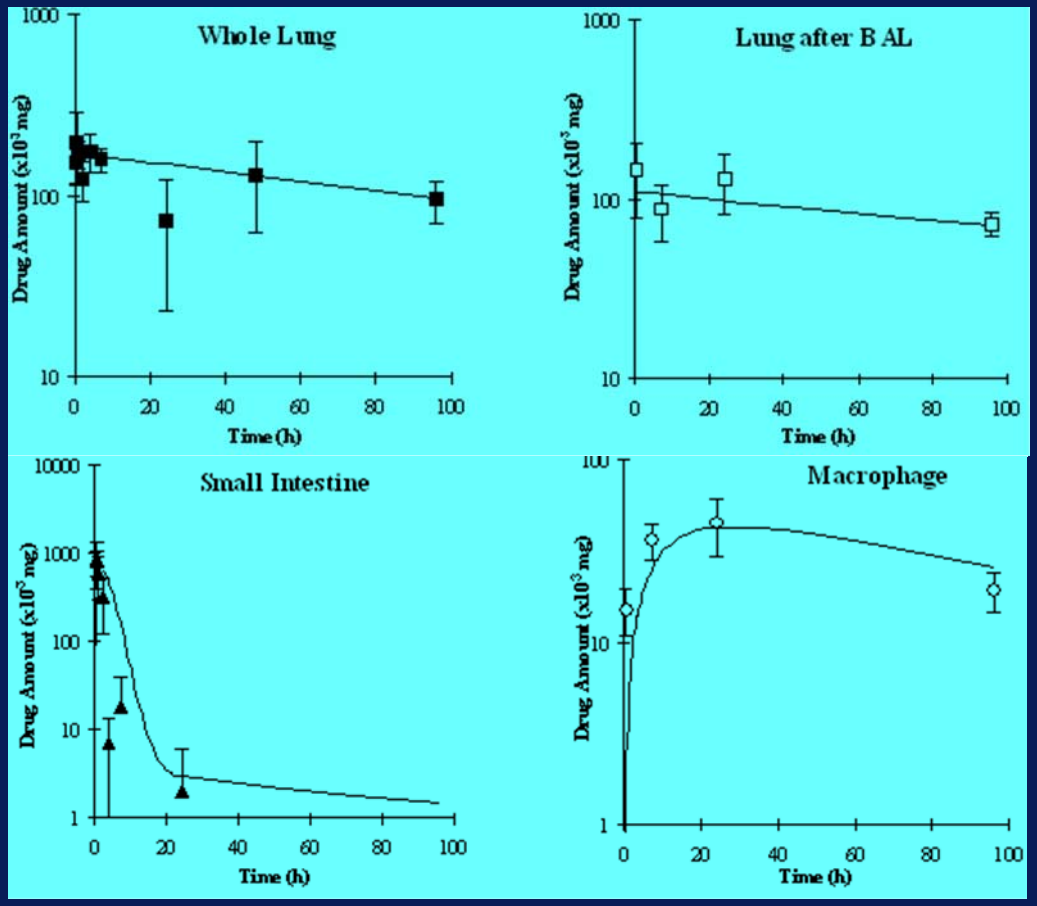
Intra-tracheal (solution) dose



Inhalation of dry powder



Pharmacodynamic “biophase”prediction by PBPK

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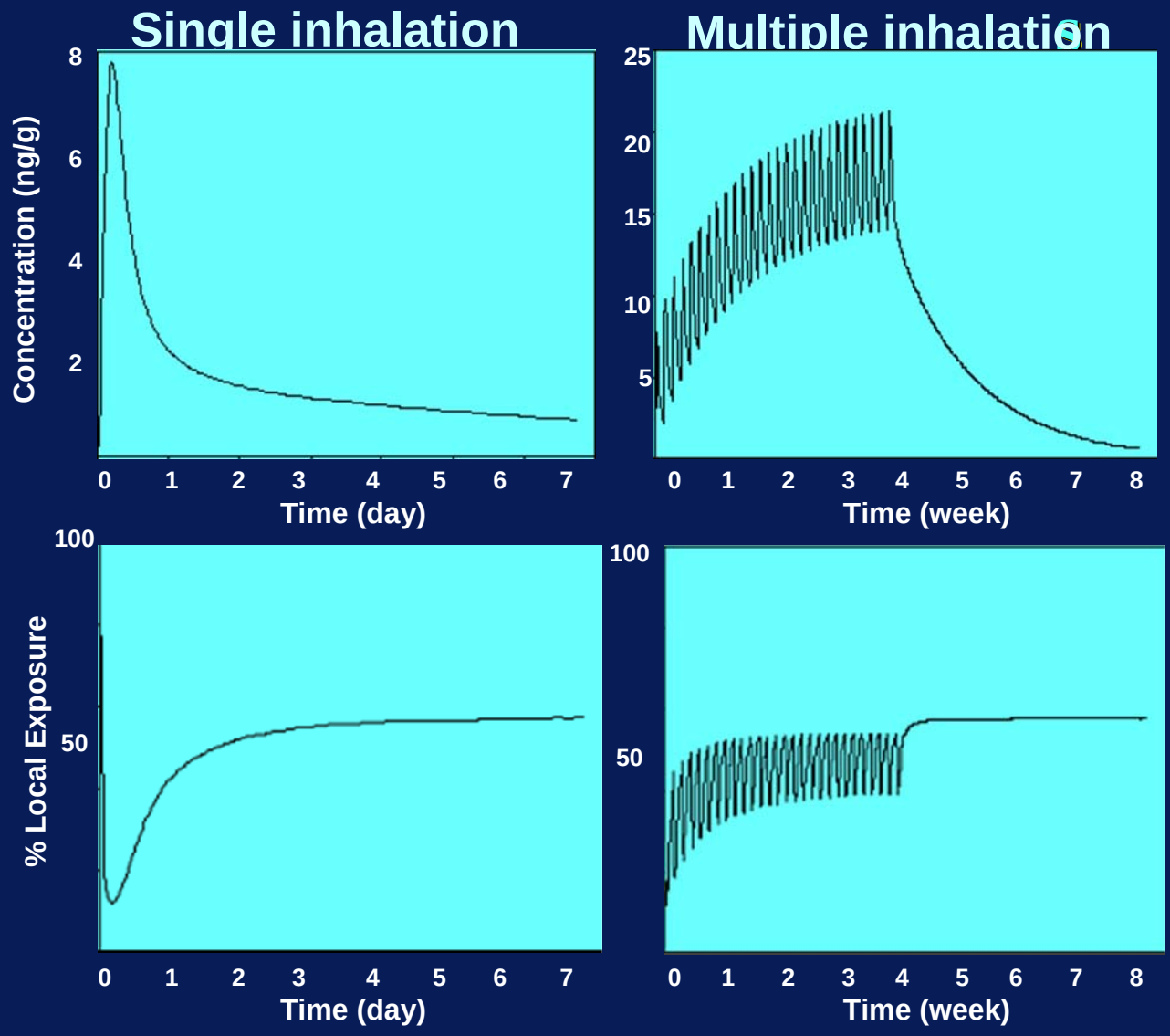
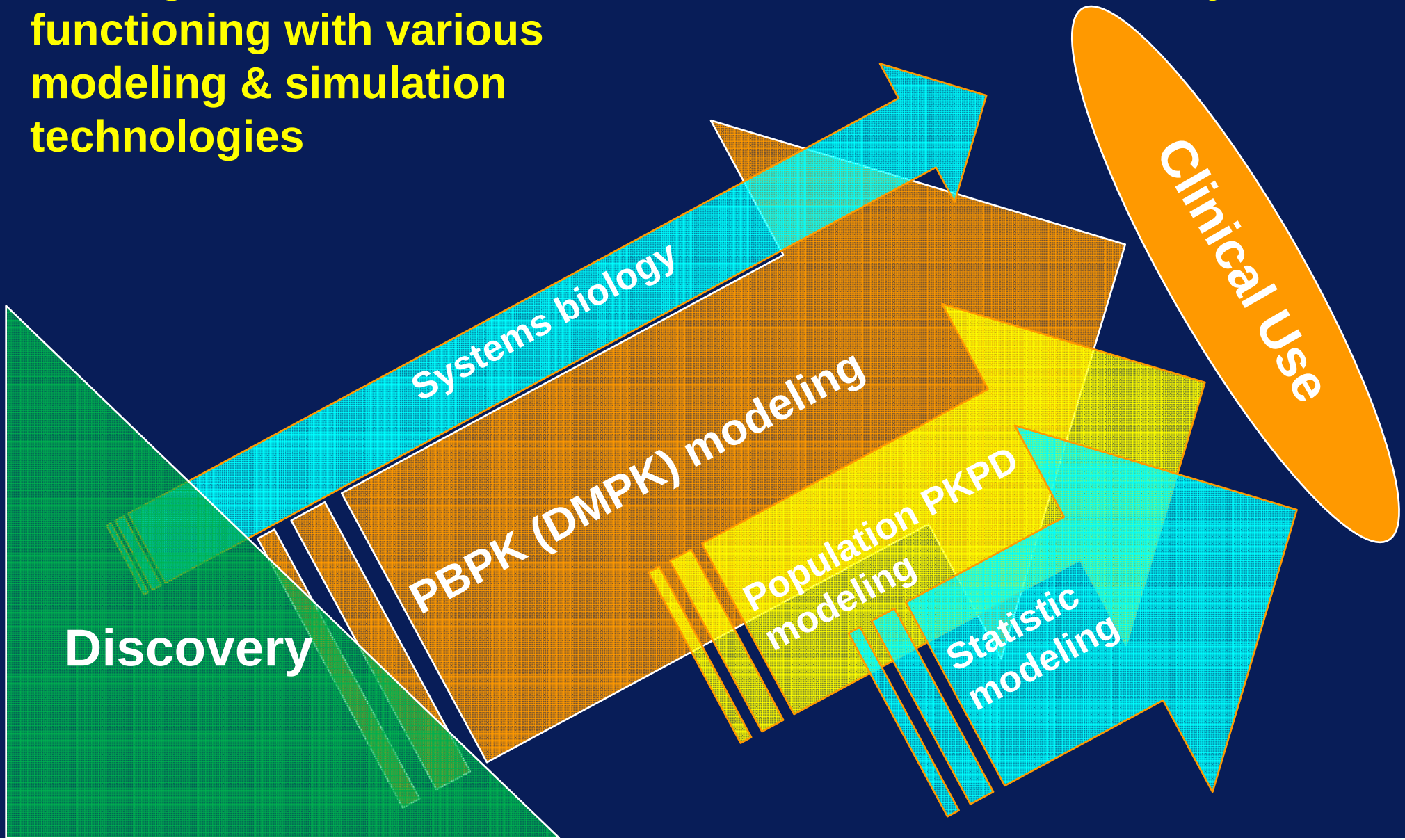
Prediction of effective concentrations

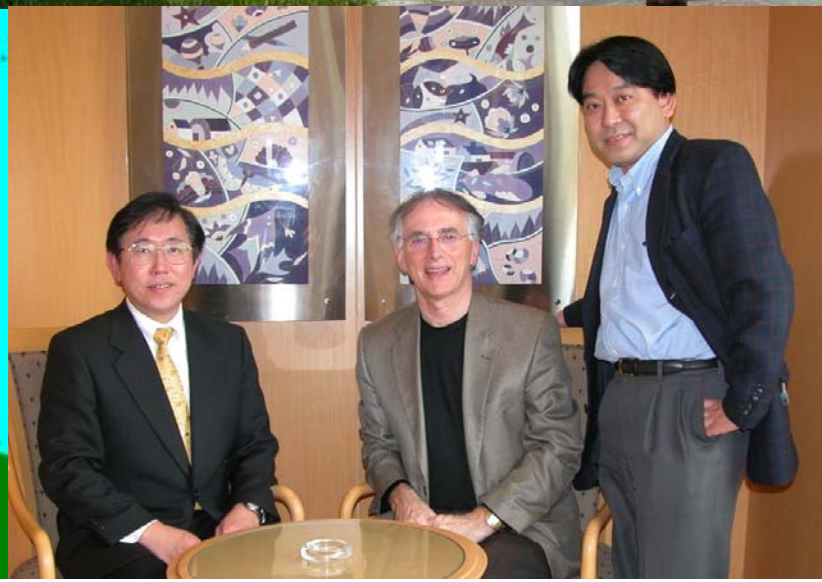
Local vs. systemic drug deliveries



PBPK model aided rational development strategy and decision making, however, there remain much rooms to evolve by cross-functioning with various modeling & simulation technologies



All my works were supported by wonderful mentors and co-workers around world



Thanks to JSSX and all the members for the ever lasting stimulation, encouragement, and opportunities