Animal Model Workshop

Bridging the Gap: Humanized Drug Dosing in Mouse Models for Cancer Research

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September 11-13, 2025

Session 10: From Discovery to Delivery –
RCC Models Powering Therapies, Resistance Solutions, and Diagnostics

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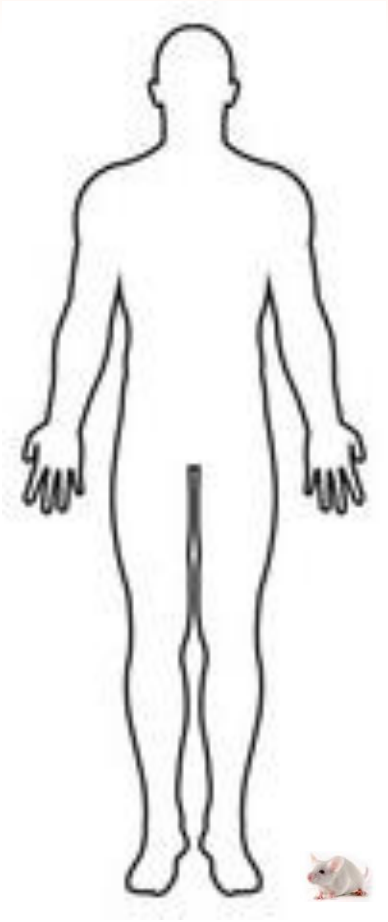
Kidney Cancer Program

The Problem



Parameter	Adult Male Human	Adult Male Mouse	Human/Mouse Ratio
Body Surface Area (cm^2)	19,000	91	209
Weight (kg)	75-90	0.02-0.035	3200
Blood Volume (mL)	5500	1.8	3056
Liver Blood Flow (mL/min/kg)	21	120	0.18
Kidney Blood Flow (mL/min/kg)	18	65	0.28
Cytochrome P450 Genes (pseudogenes)	57 (58)	102 (88)	
Plasma Esterases	absent CES	hi CES activity, extensive cleavage of ester bonds	

Sources: Davies, B.; Morris, T. *Pharm. Res.* **1993**, 10:1093-1095; Nelson, *et al Pharmacogenetics* **2004**, Vol 14:1-18

Potential Solutions

1. Allometric Scaling

a. body weight/surface area

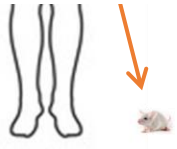
HED(mg/kg) = Animal dose (mg/kg) x (Animal K_m/Human K_m)

K_m = Avg body weight/Avg surface area

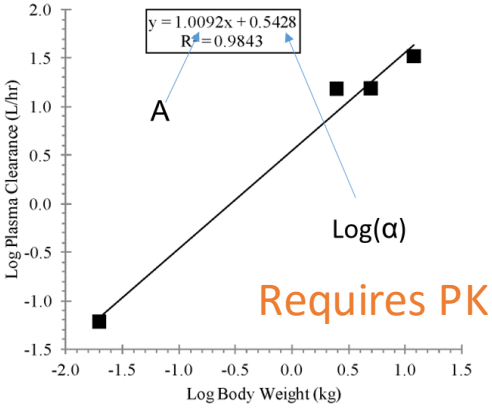
Mouse Km =3

Human Km = 37

Oversimplified method that does not account for differences in drug metabolism and transport



b. PK parameter-based scaling



$$Cl/F = \alpha \times BW^{A}$$

α = allometric coefficient

A = allometric exponent

BW = body weight

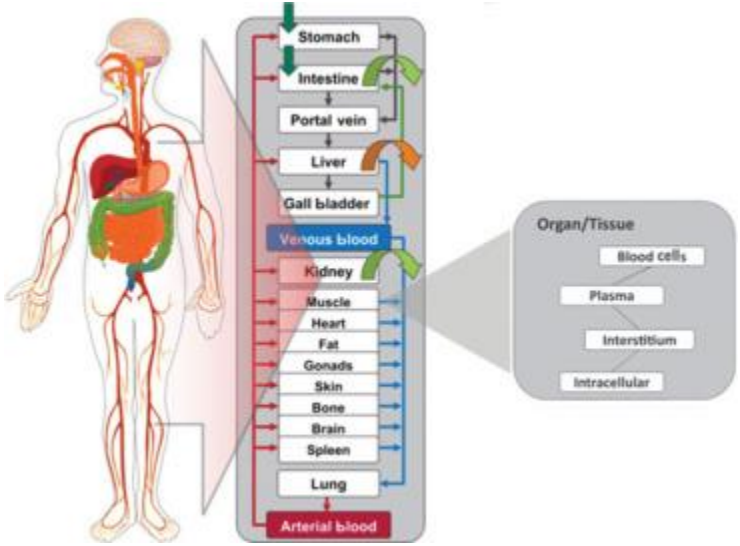
Requires PK data from multiple species

$$Dose(mg) = Animal\ AUC(h * \mu g/mL) \times scaled\ human\ Cl/F(L/h)$$

Nair, AB and Jacob, S. *J Basic Clin Pharma* **2016**;7:27-31; Amantana A, *et al PLOS ONE* **2013**, 8(4): e61514.

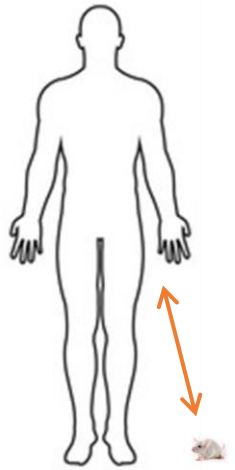
Potential Solutions

2. PBPK Modeling for Interspecies Scaling



Requires extensive information

1. Information on physiometric difference such as organ size and tissue composition between species
2. Unbound fraction (fu) in plasma between species
3. Kinetic parameters V_{max} and K_m for primary biochemical route of degradation/elimination
4. Information on gene expression profiles of metabolizing enzymes and transporters



3. 8Hum mice –

34 murine cytochrome P450s from the major gene families involved in drug disposition in humans replaced by 6 human P450 genes and human PXR and CAR.

Does not take into account differences in physiometrics (size, blood flow)

Henderson, CJ., *et al. Drug Metab Dispos*, **2019**, 47:601–615

Our Approach

Pharmacokinetically-guided dose adjustment in mice to simulate human exposure

1. Gather PK data in rodent models and in humans from the literature.
2. Seek guidance from the literature on PK parameter that informs efficacy (Peak/C_{max} conc., Time above threshold conc., AUC, etc)
3. Perform mouse PK at dose estimated to most closely match human exposure.
4. Repeat PK at different doses until relevant parameter(s) most closely matched

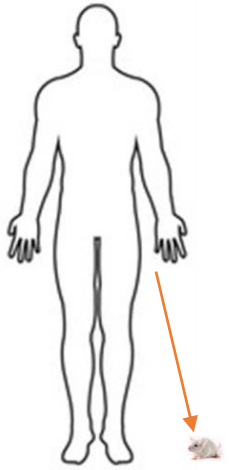


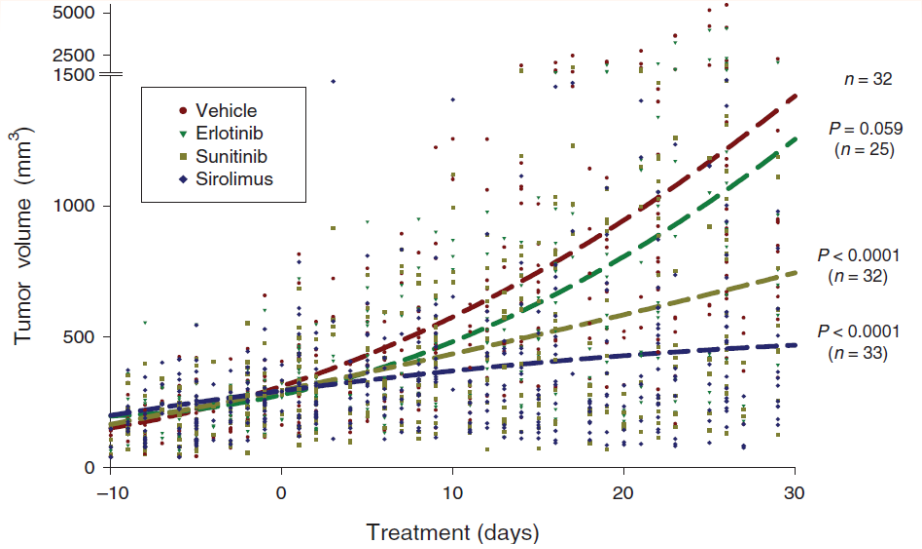
Table 6. Pharmacokinetic analysis of drug regimens in mice with reference to human studies. Pharmacokinetic (PK) parameters (mean ± SE) based on noncompartmental analysis using WinNonlin (Pharsight Corp.). IP, intraperitoneal; IV, intravenous; PO, orally; G, gavage; qwk, weekly; qd, daily.

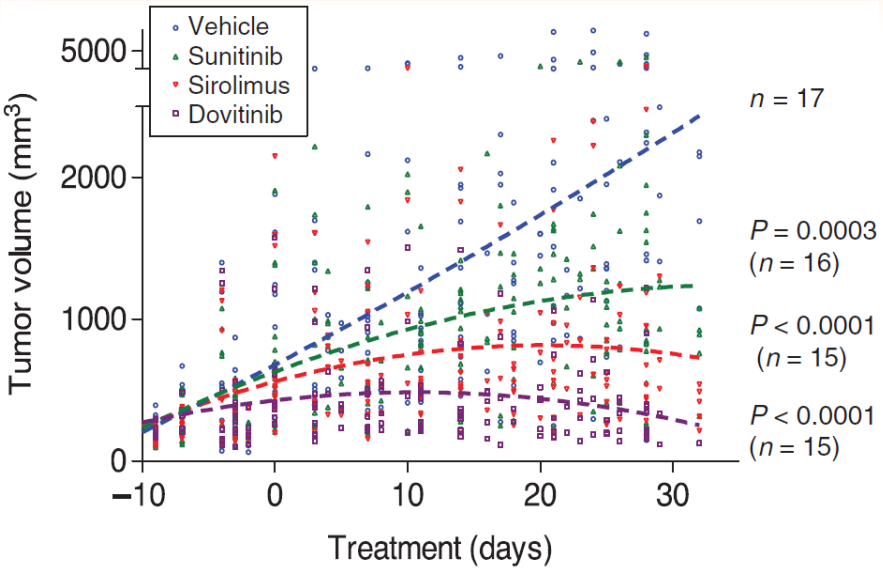
Drug	Species	Dose	Route	Schedule	PK data at	Analyte	AUC_{last} (ng h/ml)	C_{max} (ng/ml)	T_{max} (hours)	Terminal $t_{1/2}$ (hours)	C_{min} (ng/ml)	Reference
Sirolimus	**Mouse**	**0.5 mg/kg**	**IP**	**q48h**	**48 h**	**Sirolimus**	**4,276 ± 329**	**983 ± 98**	**1**	**13.6**	**14.9 ± 2.0**	
Temsirolimus	Human	25 mg	IV	qwk	D7 or D28	Temsirolimus	1,580 ± 270	595 ± 102	0.5	12.8		(*50*)*
						Sirolimus	3,810 ± 2,210	66 ± 35	1	48.8		
						Sum	5,860 ± 2,340					
Everolimus	Human	10 mg	PO	qd		Everolimus	514 ± 231	61 ± 17			13.2 ± 7.2	(*55*)*
Sunitinib malate	**Mouse**	**10 mg/kg**	**G**	**q12h**	**12 h (D1)**	**Sunitinib**	**449.8 ± 41.1**	**108.5 ± 5.5**	**2**	**2**	**4.2 ± 0.1**	
						Desethyl sunitinib	**174.4 ± 24.0**	**37.8 ± 0.2**	**2**	**2.6**	**3.0 ± 0.1**	
						Sum	**624.2**				**7.2**	
Sunitinib malate	Human	50 mg	PO	qd (D1–28)	24 h (D1)	Sunitinib	420 ± 210	27.7 ± 14.1	5			(*68*)*
						Desethyl sunitinib	63.6 ± 33.7	4.1 ± 2.2	5			
						Sum	483.6					
Sunitinib malate	Human	50 mg	PO	qd (D1–28)	24 h (D28)	Sunitinib	1,296 ± 609	72.2 ± 31.0	8.5		44.0 ± 26.0	(*68*)*
						Desethyl sunitinib	592 ± 391	33.7 ± 24.6	6.5		18.8 ± 8.5	
						Sum	1,888				62.8	
Erlotinib	**Mouse**	**12.5 mg/kg**	**G**	**q12h**	**12 h (D1)**	**Erlotinib**	**27,042 ± 2,569**	**3,513 ± 271**	**3**	**3.1**	**521 ± 169**	
						Desmethyl erlotinib	**3,970 ± 330**	**526 ± 77**	**3**	**2.5**	**50 ± 23**	
Erlotinib	Human	150 mg	PO	qd	24 h (D1)	Erlotinib	11,860 ± 5,010	872 ± 399	3		385 ± 213	(*57*)*
						Desmethyl erlotinib	835 ± 479	68 ± 45	3.6		25 ± 18	
Erlotinib	Human	150 mg	PO	qd	24 h (D28)	Erlotinib	43,760 ± 22,560	2,528 ± 1,187		24.2	1,473 ± 877	(*56*)*
Dovitinib	**Mouse**	**30 mg/kg**	**G**	**qd**	**24 h (D1)**	**Dovitinib**	**6,078 ± 710**	**373 ± 14.6**	**6**	**5.4**	**41.2 ± 9.3**	
Dovitinib	Human	500 mg	PO	5 d on/ 2 d off	24 h (D1)	Dovitinib	2,200 – 8,251	180 – 487				(*69*)*
Dovitinib	Human	500 mg	PO	qd	24 h (D1)	Dovitinib	3,734 ± 2,115	223 ± 128				(*70*)*
					(D15)	Dovitinib	4,340 ± 3,775	267 ± 178		21		

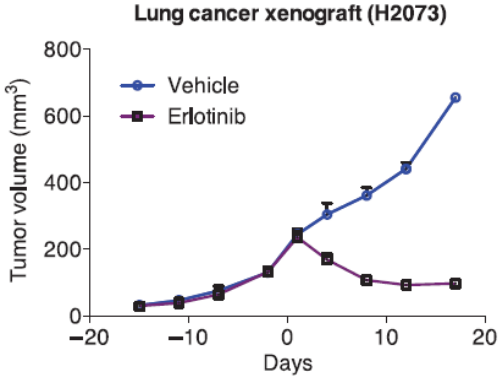
*Mean ± SD.

Sivanand, S., *et al, Sci Transl Med*, 2012, 4(137):137ra75

RCC







Sivanand, S., *et al, Sci Transl Med*, 2012, 4(137):137ra75

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Application to HHT (Omacetaxine) and Cabozatinib

Table 1: Pharmacokinetic analysis of HHT in mice.

	0.4 mg/kg	0.7 mg/kg	2 mg/kg
Terminal $t^{½}$ (hr)	1.86	2.80	6.74
T_{max} (hr)	0.17	0.17	1.50
C_{max} (ng/ml)	28.8	57.8	97.2
AUC_{inf} (hr*ng/ml)	251.0	439.8	905.2
Vz/F (ml)	87.7	123.2	453.3
Cl/F (ml/hr)	32.7	30.5	46.6

HHT Human Pharmacokinetics (*Cancer Chemother Pharmacol* (2013) 71:35–41) (1.25 mg/m^2 SC BID)						
Study Day	Cmax (ng/ml)	Tmax (hr)	T 1/2	AUC inf (hr*ng/ml)	Cl/F (L/h/m^2)	Vz/F (L/m^2)
1	25.1	0.55	6.96	136.2	13.5	126.8
11	36.2	0.6	7.03	188	10.5	66.2

Wolff, NC, *et al Oncotarget*, **2015,** 6(19):16951-16962

Table 5. Pharmacokinetic analyses of cabozantinib in mice compared with humans

Species	Experimental/estimated	Single dose/steady state	Dose	C_{max} (ng/mL)	AUC_{0-last} (h*ng/mL)
Mouse	Experimental[A]	Single dose	10 mg/kg	3,180	25,174
Mouse	Estimated[B]	Steady state	5 mg/kg bid	1,505	22,330
Human	Experimental[C]	Single dose	60 mg	343	3,880
Human	Estimated[D]	Steady state	60 mg qd	1,235	21,728

Prakasam, G., *et al J Clin Invest*. **2024**;134(7):e170559

Overcoming Cl problems with iPrecio Pumps

Human Cefepime PK (2g q8hr)

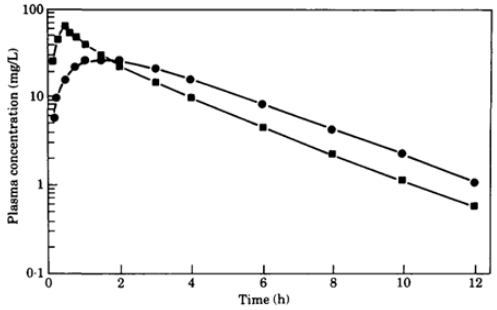
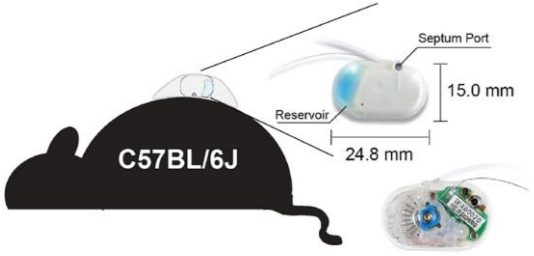
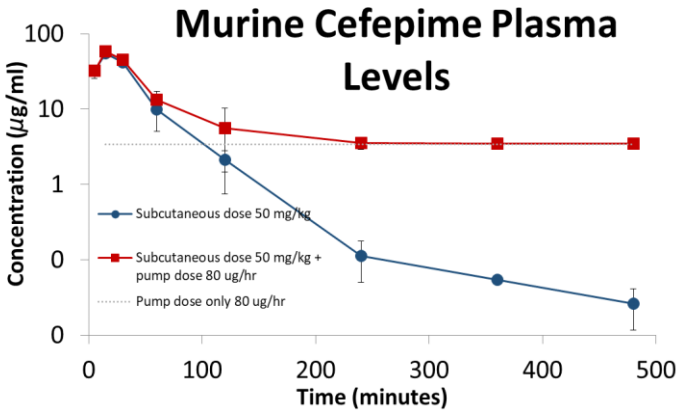


Figure 2. Mean plasma cefepime concentration following single 2000-mg im (■) and iv (●) administration (from Barbhaiya *et al.* (1990*b*), with permission). $n = 6$.



Target Goal in patients: >70% fT>MIC (3-5 µg/mL)



Approach*

1. Determine single dose PK by SC route. Calculate Cl
2. Use Cl, to calculate required pump concentration and rate of release

(Infusion rate (µg/hr) = Cl/F x Css; desired concentration)

3. Implant pump and initiate bolus therapy by desired route.
4. Refill pump at required intervals.

*Requires sufficient drug solubility

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Rodrigues, M., *et al, Cell Host and Microbe*, **2024**, 32(3):396-410

Acknowledgements

Preclinical Pharmacology Core

Lorraine Morlock

Xiaoyu Wang

Brugarolas Lab

Gopinath Prakasam

Sharanya Sivanand

Vanina T. Tcheuyap

Nick Wolff

Toprak Lab

Marinelle Rodrigues

Koh Lab

Laura Coughlin

Marguerite Monogue

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