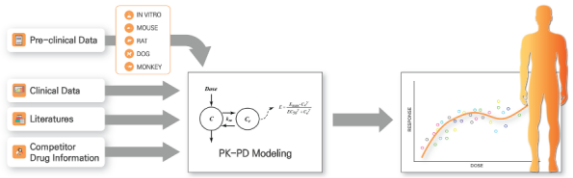
2019 KSCPT Spring Meeting Pre-course Workshop
Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

주요 *in vivo* 정보와 이를 활용한 인간 약동학 예측 이론



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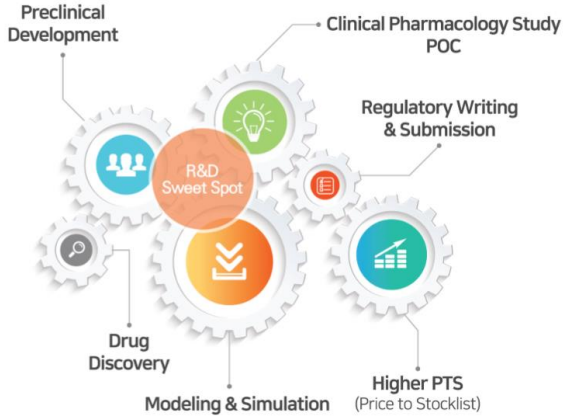

분당서울대병원 헬스케어 혁신파크 2019.04.25

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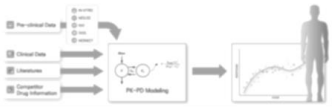


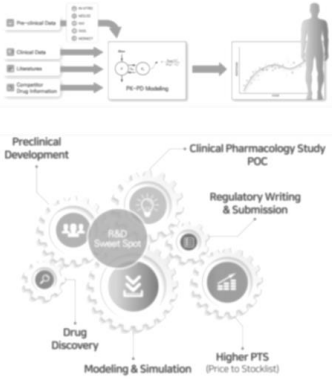
In vivo information in Dallphin

What is Dallphin-AtoM

- **D**rugs with
- **ALL**ometry and
- **PH**ysiology
- **IN**side
- **A**nimal **to**
- Hu**M**an

PBPK software for human PK parameters prediction

using physicochemical properties, in vitro and animal PK data



Dallphin: Inputs & Outputs

Input

In vitro data
- LogP
- Cb/Cp
- fu
- pKa
- Papp
- CLmet

Animal in vivo PK
- CLh
- Vc
- Vp
- CLr
- Q

Output

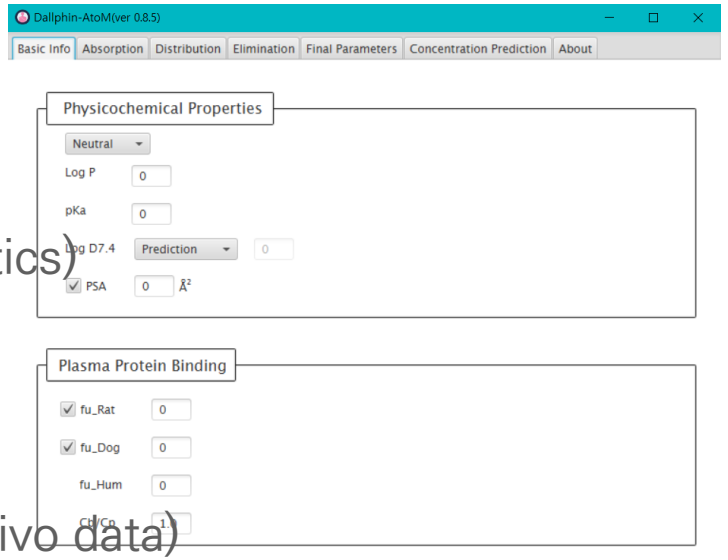
Human PK parameter
- Clearance (CL)
- Central volume (Vc)
- Peripheral volume (Vp)
- Intercompartment clearance (Q)
- Absorption rate constant (Ka)
- Bioavailability (F)

→ Vss

$$CL\ total = CLh + CLr$$

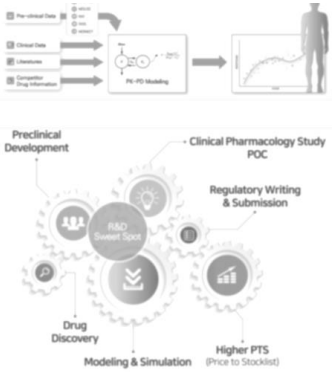
Major PK parameters Dallphin predicts

- [Absorption] Ka
- [Distribution] Vd (Vss, Vc, Vp), and Q
- [Elimination] CL
- [Absorption] F (if drug follows first-order kinetics)



In vivo data provides…

- ✓ Allometric methods to predict Vd, Q
- ✓ One of the methods to predict CLh & Fh (ex vivo data)
- ✓ Two methods to predict CLr



Dallphin methods: Clearance & F

$$CL_{hepatic} = \frac{Q_H \cdot fu \cdot CLint}{Q_H + fu \cdot CLint}$$

CL total = CL hepatic + CL renal

Microsome
1. MPPGL
2. Rat IVIV ratio
3. PS
4. PS(logD)

Hepatocyte
1. Human hepatocyte

1. CL renal_rat
2. CL renal_dog
3. CL renal_user input

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

F total = Fh x Fa

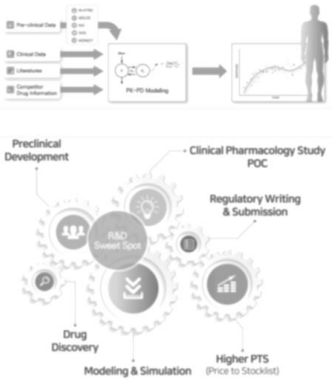
$$Fh = 1 - \frac{CL_{hepatic}}{Q_H}$$

Microsome
1. MPPGL (CLint)
2. Rat IVIV ratio
3. PS
4. PS(logD)

Hepatocyte
1. Human hepatocyte

1. Fa_Caco
2. Fa_PSA

CLint: intrinsic metabolic or hepatic clearance
Fh: hepatic availability
Fa: fraction absorbed from intestinal tract
PS: permeability surface area coefficient
Q_H: hepatic blood flow
PSA: dynamic polar molecular surface area



Dallphin methods: Vd & Q

Allometric approaches

1. Vss: 1-compartment model
2. Vss, Vc, Vp, Q: 2-compartment model

PBPK approach[12,13]

1. Vss: 1-compartment model (Vc:well-perfused organs)

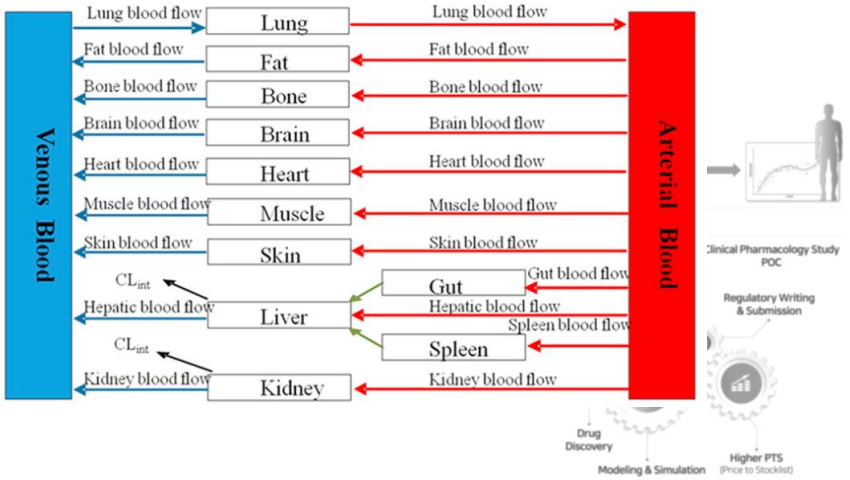
PBPK approach

Predicted human tissue distribution — One-Compartment Model

Bone	1.8884	L/kg	Lung	0.0194	L/kg
Brain	0.3767	L/kg	Muscle	3.0453	L/kg
Gut	0.3683	L/kg	Skin	0.6641	L/kg
Heart	0.0188	L/kg	Spleen	0.0196	L/kg
Kidney	0.0292	L/kg	Plasma	0.0449	L/kg
Liver	0.3970	L/kg	Adipose	29.143	L/kg

Human | WT : 70kg | VSS : 36.02 L/kg

$$V_{ss} = V_p + \sum (V_t \times K_{pt})$$



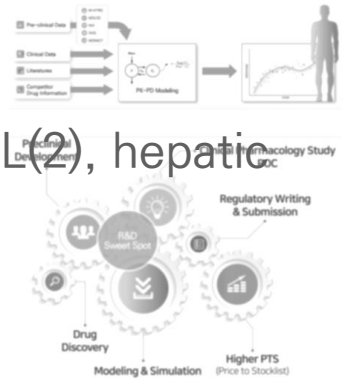
1. Dallphin 에서 사용하는 in vivo 정보

- [Basic info] Plasma protein binding (ex-vivo data)

- Rat fraction unbound => human hepatic CL(2), hepatic availability(2), human renal CL
- Dog fraction unbound => human renal CL
- Human fraction unbound => human hepatic CL (1)-(4), hepatic availability (1)-(4)
- Blood to plasma ratio

- [Distribution] Allometric approaches: Animal IV PK parameters
- Weight, Q, Volume of distributions (Vss, Vc, Vp)

- [Elimination] Microsome:
- Rat CLint,initial, rat hepatic CL (observed) => human hepatic CL(2), hepatic availability(2)



2. Input parameter for human PK prediction[1,2]

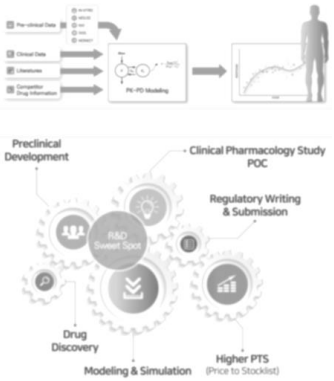
- [Basic info] Plasma protein binding

1. fu_Rat –〉 CL int, rat(in vivo observed) –〉 CL int_rat_iviv_ratio
   =〉 human hepatic CL CLh_fromRativivc
   =〉 human bioavailability F(CLh_fromRativivc)
   =〉 human renal CL CLr (rat to human prediction)

$$CLh\_fromRativivc = \frac{Q_{H,B} \cdot fu_B \cdot \mathrm{CLu}_{int,H}}{Q_{H,B} + fu_B \cdot \mathrm{CLu}_{int,H}} \times CLint\_rat, IVIV\ ratio$$

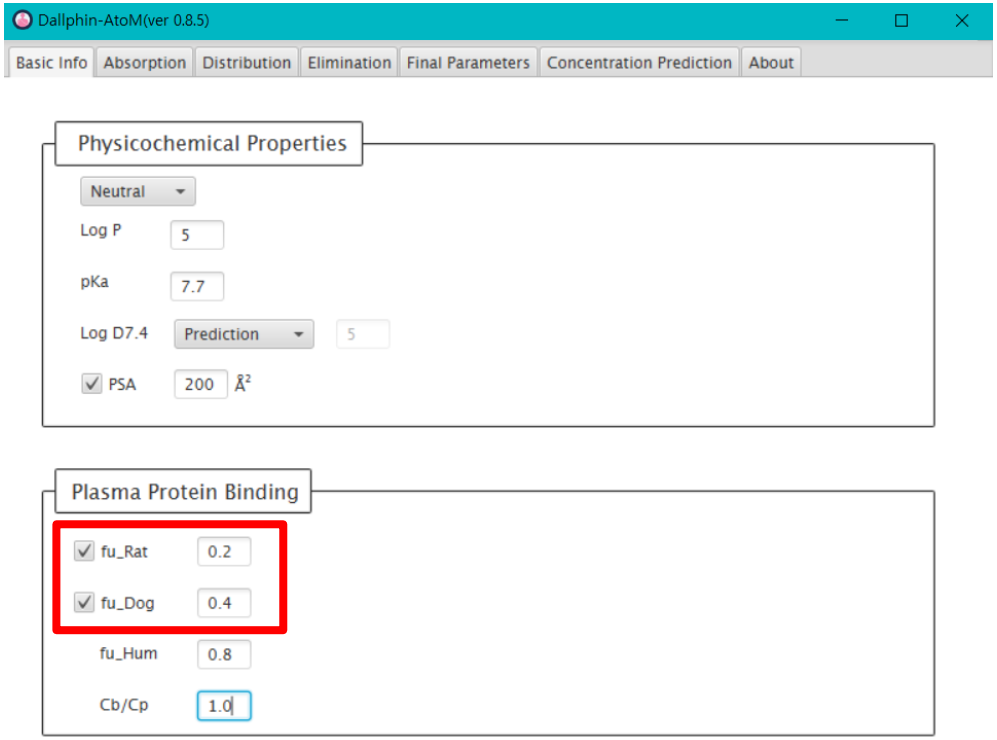
2. fu_Dog =〉 human renal CL CLr (dog to human prediction)

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$



[Basic info]

- Plasma protein binding
  - fu_Rat
  - fu_Dog



CL renal[2]

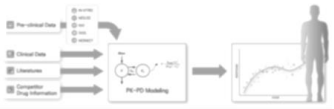
- Three animal scaling techniques for the prediction of human CL renal:

1. Direct correlations between CLr in man and each of the two main preclinical species (rat and dog)

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

2. Simple allometry $CLr = a(W)^b$

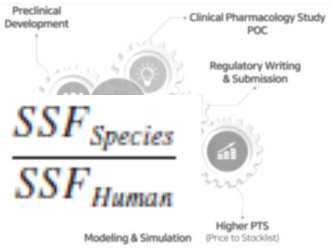
$$CLr_{Predicted\ total} = CLr_{Predicted\ unbound} \times fu_{Human}$$



3. Mahmood's renal clearance scaling method

$$\text{SSF} = \frac{(\text{Glomerular filtration} \times \text{kidney blood flow})}{(\text{body weight} \times \text{kidney weight})}$$

$$\text{Correction factor} = \frac{SSF_{Species}}{SSF_{Human}}$$



CL renal[2]

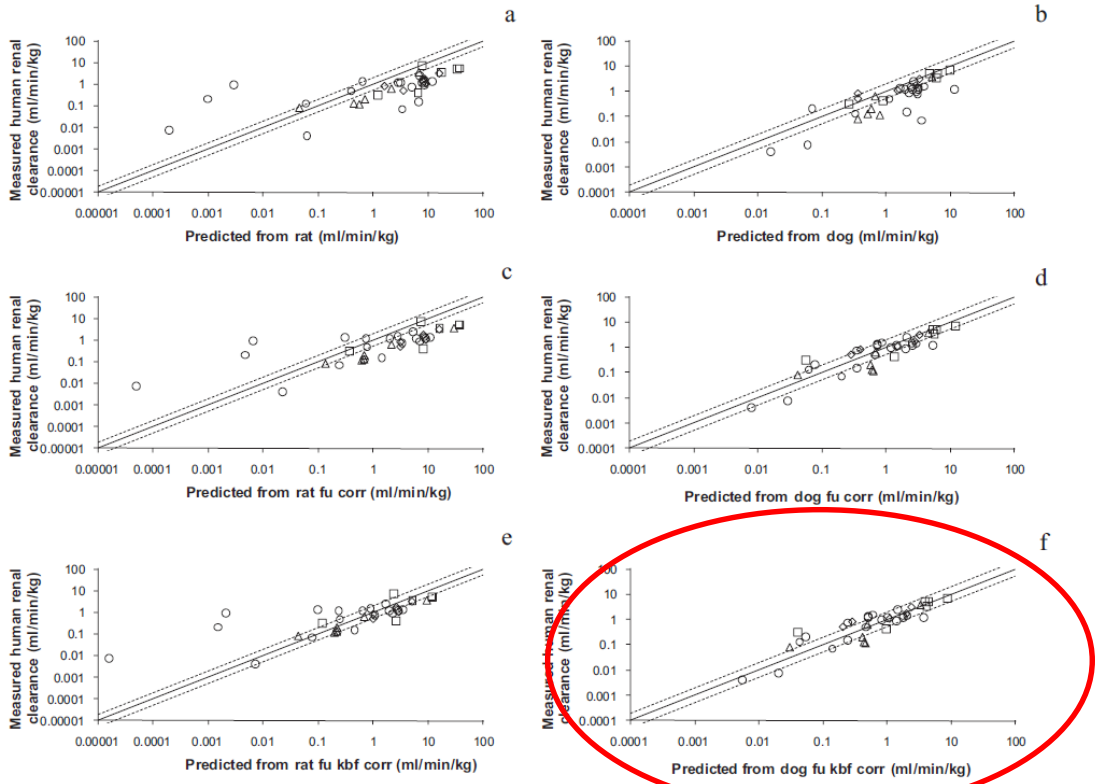
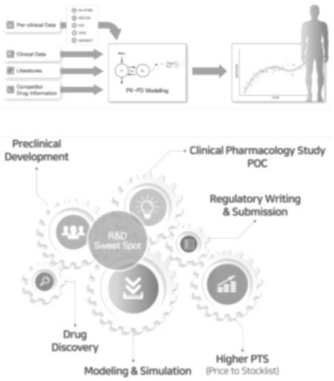


FIG. 2. Measured human renal clearance versus measured renal clearance from rat (a), dog (b), rat corrected (corr.) for fu differences (c), dog corrected for fu differences (d), rat corrected for both KBF and fu differences (e), and dog corrected for both KBF and fu differences (f). Circles, acids; squares, bases; triangles, neutrals; diamonds, zwitterions.

- Most accurate prediction: 1. Direct correlation with the dog renal clearance with PPB and KBF corrections (R^2 = 0.84)



2. Input parameter for human PK prediction[1,2]

- [Elimination] Microsome

1. CL int_ini Rat –〉 CL int,rat (in vitro)
2. CLh_ratinvivo –〉 CL int,rat (in vivo)

} =〉 CLint_rat,iviv ratio

=〉 human hepatic CL CLh_fromRativivc

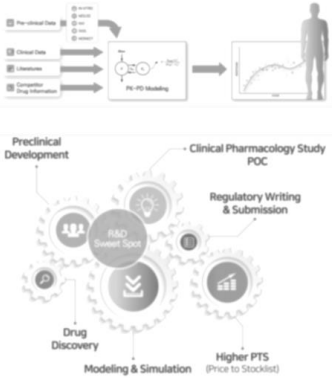
=〉 human bioavailability Fh (CLh_fromRativivc)

$$CLh\_fromRativivc = \frac{Q_{H,B} \cdot fu_B \cdot \boxed{CLu_{int,H} \times CLint\_rat, IVIV\ ratio}}{Q_{H,B} + fu_B \cdot \boxed{CLu_{int,H} \times CLint\_rat, IVIV\ ratio}}$$

$$CLint\_rat, IVIV\ ratio = \frac{CLint\_rat\ (in\ vivo\ observed)}{CLint\_rat\ (in\ vitro\ predicted)} \quad <- CLh\_rat\ (in\ vivo\ observed)$$

$$CLh\_rat\,(in\ vivo\ observed) = \frac{Q_{H,rat} \cdot furat \cdot CLint_{,rat}}{Q_{H,rat} + fur_{at} \cdot CLint_{,rat}}$$

$$CL_{int,rat} = CL_{int\ ini,rat} \cdot MPPGLrat \cdot Liver\ wt\_rat$$



[Elimination]

- Hepatic Clearance (CLh)

Microsome

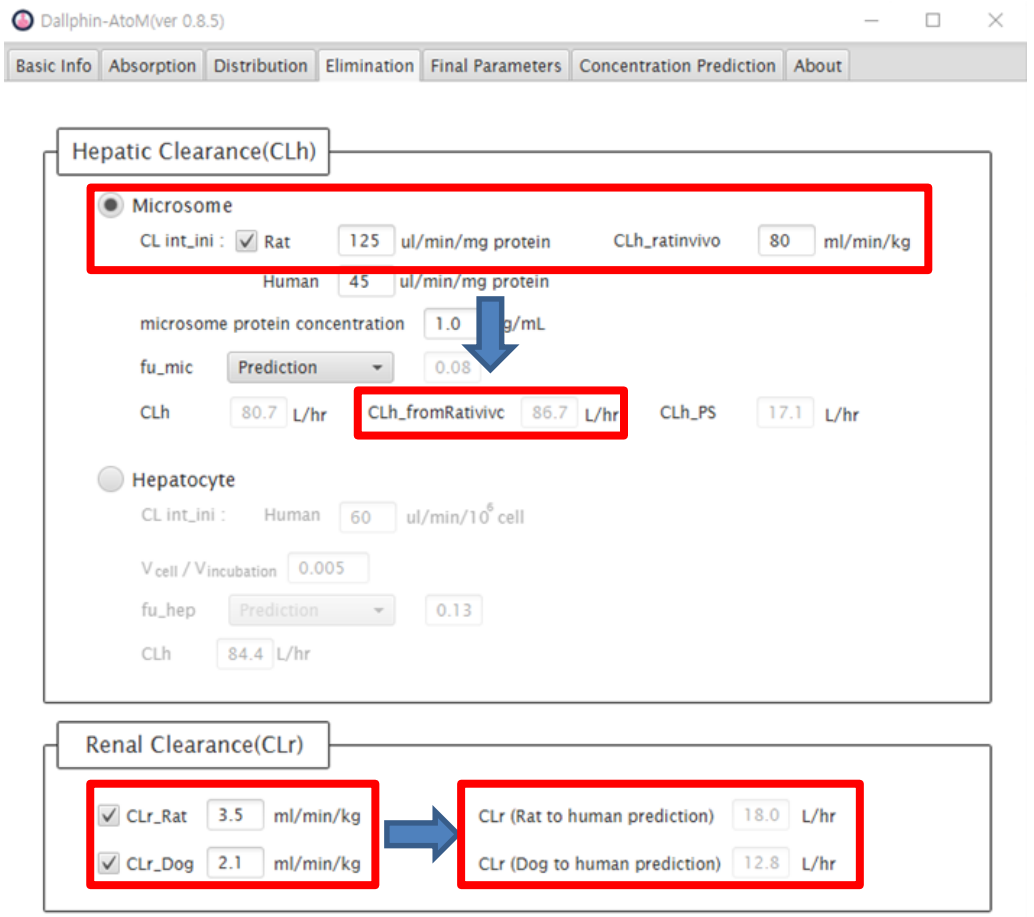
–CL int_ini Rat (ul/min/mg protein)

–CLh_ratinvivo (ml/min/kg)

- Renal Clearance (CLr)

–CLr_Rat (ml/min/kg)

–CLr_Dog (ml/min/kg)



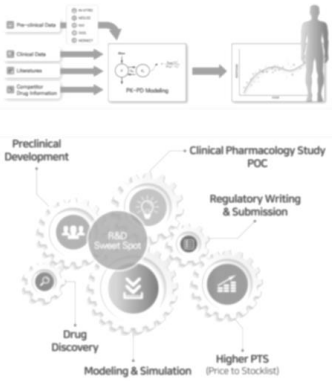
2. Input parameter for human PK prediction [Distribution]

- Mouse, rat, monkey, dog 총 4종의 정보 입력 가능
- 각 종 별 Weight
- Model structure – 1 compartment vs. 2 compartment
- Model 을 통해 구한 각 종 별 Vss 또는 Q, Vss (Vc, Vp)

- [Prediction] 을 통해 Allometric scaling 수행 =〉
  70 kg-human Q, Vc, Vp, Vss 구함

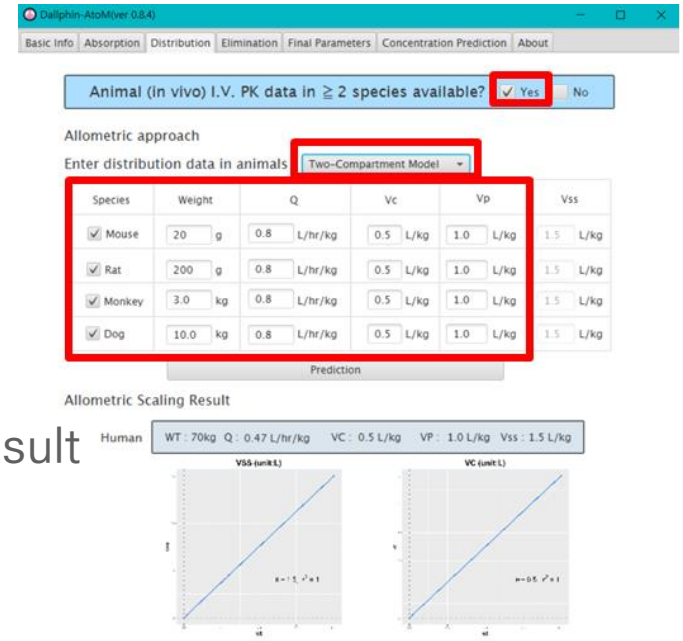
- Vc ➡ Ka $k_{a,eq} = \frac{P_m S}{V_c}$

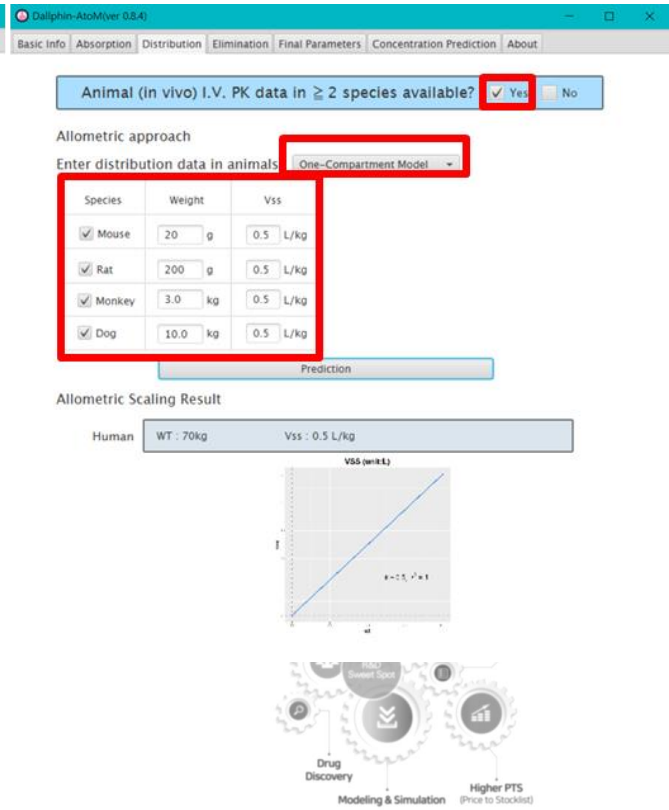
P_m : drug permeability across intestinal mucosa (Caco-2 Papp)
S : absorptive surface area



[Distribution]

- Animal data available ? YES
  - One-compartment model
  - Two-compartment model

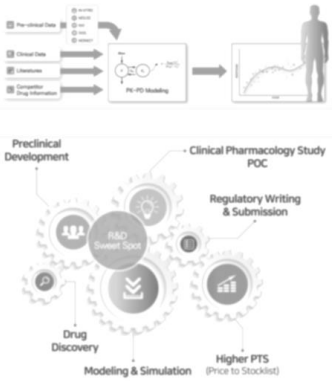




- [Prediction]
- Allometric scaling result

Volume of distribution

- Allometric scaling as choice of method to predict human Vd
- Plasma protein binding should be considered[3]
- Multiple methods available for prediction of volume of distribution[3,4,6]
  - ✓ Simple allometric scaling
  - ✓ Allometry with correction factors
  - ✓ Average fraction unbound tissue
  - ✓ Proportionality (dog-human)
  - ✓ QSAR



Volume of distribution[3,4]

- Simple allometric scaling
- Allometry with correction factors*
- Average fraction unbound tissue*
- Proportionality (dog–human)*
- QSAR

*Pertains plasma protein binding data as an essential element

$$\log_{10}VD = a \cdot \log_{10}\text{body weight}_{(kg)} + b$$

$$VD_{free} = \frac{VD_{total}}{f_u}$$

Table 4. Methods for prediction of volume of distribution (V_d).

Method	Equation		Comment *	Ref.
Simple AS	$V = a(W)^b$	(93)	The prediction of V_d is well predicted equally with using two species in AS	[108]
Average fraction unbound in tissue [1]	$V = V_{Plasma}(1 + R_{E/I}) + f_u \cdot V_P(\frac{V_E}{V_p} - \frac{V_R \cdot f_u}{\alpha_R})$	(94)	It is useful to analyze and predict an alteration in apparent V_d then identify the cause of alteration. It is particularly useful for drugs with low V_d (<15 L or 0.2 L/kg)	[119]
Proportionality	$V_{human,pred} = \frac{V_{animal} \cdot f_{u,human}}{f_{u,animal}}$	(95)	It is assumed that the volume of distribution at a steady state of free drug is identical between species	[120]
One species AS	$V_{human,pred} = -0.35V_{rat}^{0.91}$	(96)	Statistical modeling is applied in this model	[121]
QSAR	$\log(Vd_{ss,human}) = 0.1859 \cdot \log(Vd_{ss,rat}) \times \log(Vd_{ss,rat}) - 0.3887 \cdot \log(Vd_{ss,rat}) \times \log(MW) + 0.3089 \cdot \log(Vd_{ss,dog}) \times \log(MW) + 0.003306 \cdot \log(MW) \times c\log P + 1.71$	(97)	$Vd_{ss,\ human}$ (mL/kg) is predicted by QSAR modeling with quadratic term descriptors	[122]

* Each comment corresponds to all the equations within each major section of the table defined by horizontal lines.

[1] Where V_d is apparent volume of distribution, V_{plasma} is plasma volume, V_E is extracellular space minus the plasma, V_R is physical volume into which the drug distributes minus the extracellular space, f_u is the fraction unbound in plasma, and $R_{E/I}$ is the ratio of distributed albumin in the extravascular space to that in the intravascular space. It is 1.4. α_R equals to C_u/C_R where C_u is unbound drug concentration at distribution equilibrium and C_R is concentration in V_R.

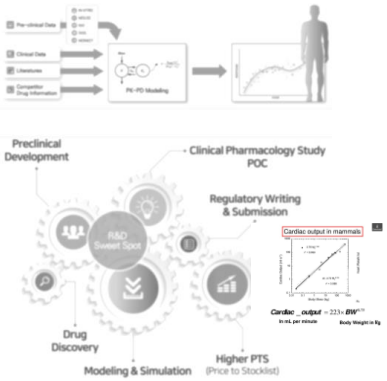
3. Allometry[5,6]

- "Study of size and its consequences"
- Based on the assumption that there are anatomical, physiological, and biochemical similarities among animals which can be described by simple mathematical models
- Choice of method for projection to human PK

- Possible with in vivo IV PK data from 2 species, but ≥ 3 species provide more accurate prediction
- Plasma protein binding data in two or more species and human should be emphasized
- Completed after each species modeling to predict human PK parameters, which is used for simulations
- Different allometric approaches available

For which PK parameter prediction?

- Human Vd
- Human CL



General allometric approaches[3,4,5]

- Simple allometry $Y = a(BW)^b$ $logY = \log(a) + b \cdot \log(BW)$

- Allometry with standard correction factors for Vd – PPB (plasma protein binding)

$$\log(VD) = \log(a) + b \cdot \log(BW)$$

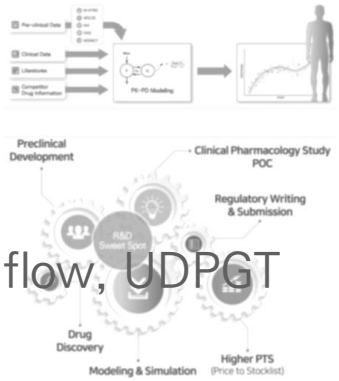
$$\mathrm{VD_{free}} = \frac{\mathrm{VD_{total}}}{\mathrm{f_u}}$$

- Allometry with standard correction factors for CL – MPL (product of maximum life-span), brain weight

$$Clearance = aBW^b$$

$$Clearance \times MLP = aBW^b$$

$$Clearance \times BrainWeigh\ t = aBW^b$$



cf) Correction factors for renally/biliary excreted drugs – GFR/bile flow, UDPGT

$$Clearance / GFR = aBW^b$$

$$Cl \times Bile\_flow = aBW^B$$

$$Cl \times UDPGT = aBW^b$$

Different allometric approaches for CL[10]

- Simple allometry
- Rule of exponents
- Correction factor – MLP, brain weight
- Two-term method
- Multiexponential
- Normalized

Table 5. Statistical Evaluation of Various Methods to Predict Human Plasma CL for the 10 Drugs[a]

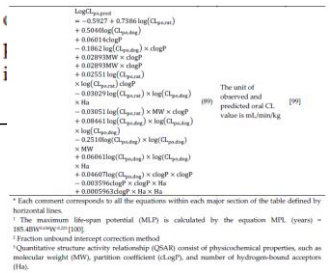
		Prediction of Human CL (mL/min/kg)									
Model Numbers Listed in Table 1	Prediction Methods of CL	n	% < 2-Fold	% < 3-Fold	% < 10-Fold	AFE	AAFE	RMSE	r	CCC	Reasons of Exclusion or Indication of Poor Predictability[b]
Conventional allometry											
CL1	SA	18	50	56	83	2.16	3.14	0.66	0.22	0.40	
CL2	MA	18	56	72	94	1.71	2.47	0.52	0.04	0.48	
CL3	SA_{fup}	18	44	56	94	1.22	2.91	0.59	0.39	0.45	
CL4	MA_{fup}	18	50	83	94	1.18	2.16	0.42	0.26	0.62	
CL5	ROE	18	72	83	100	1.05	1.71	0.33	0.84	0.76	
CL6	ROE_{fup}	18	61	78	100	0.65	2.02	0.40	0.68	0.68	
CL7	NAS	4	75	75	100	0.78	2.07	0.36	−0.44	−0.15	$n < 9$
CL8	NAS_{fup}	4	25	75	100	0.63	2.52	0.45	−0.39	−0.10	$n < 9$
CL9	FCIM	18	72	83	100	0.77	1.63	0.28	0.76	0.80	Selected method
Species-based allometry											
CL10	$SS_{LBF-rat}$	19	47	68	100	1.5	2.1	0.40	0.61	0.67	
	$SS_{LBF-dog}$	19	17	67	100	2.3	2.8	0.49	0.81	0.55	
	$SS_{LBF-monkey}$	6	67	83	83	0.83	2.64	0.52	0.20	0.16	$n < 9$
CL11	$SS_{LBF-rat-fup}$	18	53	84	100	1.2	2.1	0.36	0.67	0.73	
	$SS_{LBF-dog-fup}$	18	39	83	100	1.3	2.1	0.37	0.79	0.69	
	$SS_{LBF-monkey-fup}$	4	50	75	75	0.44	2.47	0.57	0.83	0.26	$n < 9$
CL12	SS_{monley}	6	33	83	83	0.98	2.73	0.51	0.26	0.18	$n < 9$
CL13	SS_{dog}	18	72	72	100	1.16	1.73	0.37	0.70	0.69	
CL14	SS_{rat}	19	47	79	100	0.76	2.13	0.38	0.60	0.69	
CL15	SSS_{rat}	18	50	72	100	1.0	2.0	0.35	0.72	0.70	
CL16	SSS_{dog}	17	47	65	100	0.96	2.2	0.41	0.75	0.69	
CL17	$TS_{rat-dog}$	18	67	94	100	0.83	1.69	0.30	0.75	0.79	Selected method
CL18	$TS_{rat-monkey}$	6	50	67	100	0.64	2.33	0.42	0.24	0.21	$n < 9$
Calculation Method—QSAR											
CL19	$QSAR_{rat-dog}$	15	60	87	100	0.74	1.71	0.29	0.79	0.87	Selected method
In Vitro–In Vivo Correlation (IVIVC)											
CL20	$PBSF_{mic}$	14	43	79	100	1.54	1.97	0.35	0.30	0.20	
CL21	$PBSF_{mic-fup}$	14	29	43	64	0.15	6.70	1.06	0.55	0.18	%<10-fold < 80%
CL22	$PBSF_{mic-fup/fuinc-meas}$	12	75	83	92	0.52	2.18	0.52	0.44	0.23	
CL23	$PBSF_{mic-fup/fuinc-calc}$	14	57	57	79	0.31	3.42	0.76	0.55	0.23	%<10-fold < 80%
CL24	$PBSF_{hep}$	9	78	78	100	1.53	1.69	0.32	0.13	0.05	
CL25	$PBSF_{hep-fup}$	9	22	22	56	0.08	12.7	1.46	0.30	0.04	%<3-fold < 40%,%<10-fold < 80%
CL26	$PBSF_{hep-fup/fuinc-meas}$	2	50	50	100	0.37	2.71	0.52	1.00	0.31	$n < 9$
CL27	$PBSF_{hep-fup/fuinc-calc}$	9	22	56	78	0.19	5.69	1.01	0.32	0.06	%<10-fold < 80%
CL28	RSF_{mic}	13	39	62	100	0.79	2.53	0.48	0.74	0.41	
CL29	RSF_{hep}	4	0	75	100	0.51	2.83	0.49	−0.36	0.01	$n < 9$

[a]CL prediction methods are numbered similar to those in Table 1 wherein each method is presented in detail. See Table 2 for scaling factors (PBSF) used with IVIVC approaches. The three methods with the best predictive performance based on the statistical criteria defined for the purpose of the present study[1] are highlighted and those eliminated from further analysis due to $n < 9$ are italicized. Data consists of 19 drugs for which i.v. data were available.
[b]Models excluded due to $n < 9$ or an indication of poor predictability as outlined in a companion study.[1]
n, number of predicted values per method; AFE, average fold-error; AAFE, absolute average fold-error; RMSE, root mean squared error; r, correlation coefficient; CCC, concordance correlation coefficient.

Different allometric approaches for CL[4,11]

Table 3. Methods for prediction of clearance (CL) using allometric scaling (AS).

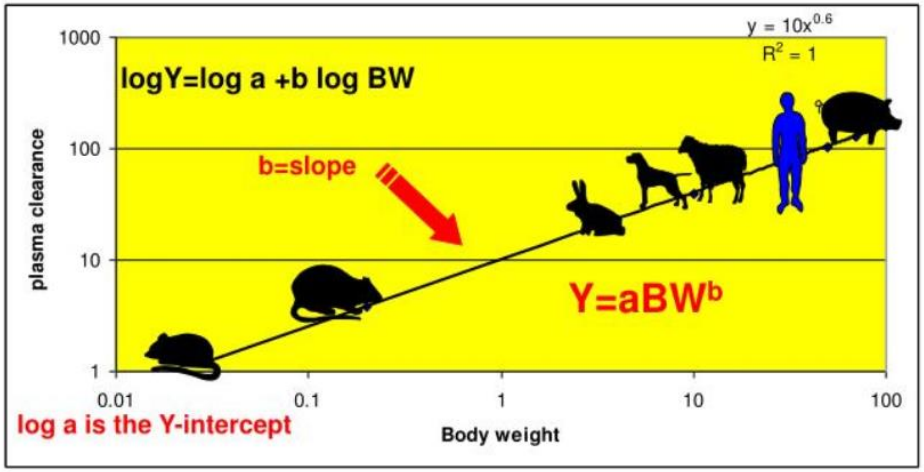
Method	Equation		Comments *	Ref.
Simple AS	$CL = a(W)^b$	(74)	Select a proper equation by the rule of exponent (ROE) W and BW represent body and brain weight, respectively	-
AS with MLP [1]	$CL \cdot MLP = a(W)^b$	(75)		-
AS with BW	$CL \cdot BW = a(W)^b$	(76)		[89]
Rule of exponent	If the exponent is 0.55 to 0.7, then use the simple AS, Equation (74) If the exponent is 0.71 to 1, then use the MLP, Equation (75) If the exponent is more than 1, then use the BW, Equation (76)			[90]
Two-term method	$CL = \theta(W)^a \cdot (BW)^b$	(77)	θ is a constant, which is determined by multiple regression analysis	[91]
Multiexponential	$CL_{human} = aW^b + \left[\left(\frac{1-\frac{3}{2}b}{1-\frac{1}{2}b}\right)\right] aW^{0.9}$	(78)	The unit of CL is mL/min	[92]
Normalized AS	$CL_{animal}\frac{CL_{int,human}}{CL_{int,animal}} = a(W)^b$	(79)	CL_{int} refers the unbound CL_{int} in microsomes or hepatocytes in species and humans	[93]
One species AS	$CL_{human} = CL_{animal} \cdot (\frac{W_{human}}{W_{animal}})^b$	(80)	The exponent b is a constant 0.75, which is physiologically relevant value (e.g., blood flow, filtration, etc.)	[94,95]
One species AS	$CL_{pred} = 0.152 \cdot CL_{rat} \cdot (\frac{W_{human}}{W_{rat}})$	(81)	Predict the CL of bound drug	[90]
	$CL_{pred} = 0.41 \cdot CL_{dog} \cdot (\frac{W_{human}}{W_{dog}})$	(82)		
	$CL_{pred} = 0.407 \cdot CL_{monkey} \cdot (\frac{W_{human}}{W_{monkey}})$	(83)		
Two species AS	$CL_{pred} = a_{rat-dog} \cdot W_{human}^{0.628}$	(84)	Predict the CL of bound drug	
	$CL_{pred} = a_{rat-monkey} \cdot W_{human}^{0.650}$	(85)		
Hepatic liver method	$CL_{pred} = CL_{animal} \cdot (\frac{Q_{H,human}}{Q_{H,animal}})$	(86)		[96]
FCIM [2]	$CL = 33.35 \times (\frac{a}{Rf_u})^{0.77}$	(87)	Rf_u is the f_u ratio between rats and humans and a is the coefficient form AS The unit of CL is mL/min	[97]
QSAR [3]	$LogCL_{pred} = 0.433 \cdot \log(CL_{rat}) + 1.0 \cdot \log(CL_{dog}) - 0.00627 \cdot MW + 0.189 \cdot Ha - 0.00111 \cdot \log(CL_{dog}) \cdot MW + 0.0000144 \cdot MW^2 - 0.0004 \cdot MW \cdot Ha - 0.707$	(88)	The unit of	

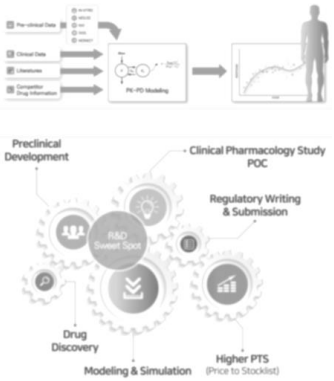


Simple allometry[5]

- $Y = a(BW)^b$
- Log-log transformation
- Dallphin's choice for Vd (exponents fixed)
- Easily done with Excel linear regression
- When a midpoint species (e.g. dog) is the source of the error, the change is primarily in the intercept rather than the slope
- Fixed exponents…

Simple allometry:
the log-log transformation





The scaling exponents

- $Y = a(BW)^b$
- Scaling exponent (b) (i.e. the slope) defines the type of scaling relationship

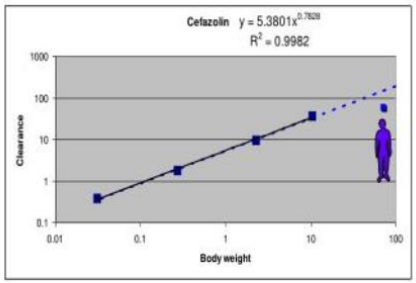
b=1.0
Y increase proportionally with BW (isometry)

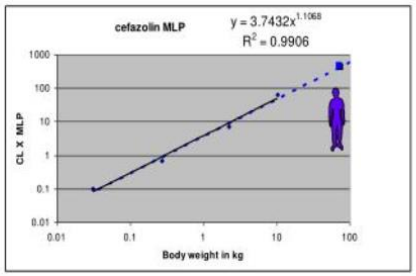
b=0.75
Y increase slower than BW
Negative allometry

Allometry with correction factors for CL

- Simple allometry vs. corrected allometry
- The rule of exponents provides an idea of which standard correction factor to select[7,8]

Simple vs. corrected allometry (MLP): Cefazolin clearance in man





Simple allometry
Predicted: 141 mL/min
Actual: 61 mL/min
Error: 131%

Allometry with MLP as a correcting factor
Predicted: 50.55mL/min
Actual: 61mL/min
Error:17.1%

The rule of exponents to predict human CL

1. 0.55 ≤ b <0.71 : no correction factor is necessary
2. 0.71 ≤ b <1.00 MLP should be incorporated into scaling method
3. B>1.00 Brain weight should be incorporated into the scaling method

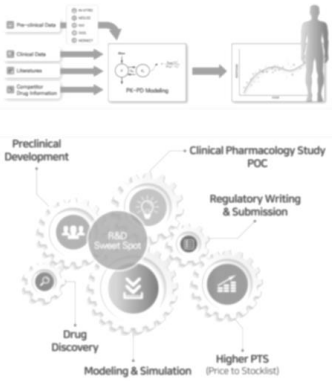
Methods	% Mean absolute error (MAE)
Simple allometry	106
CL x MLP	40
CL x brain Weight	49
Rule of exponents	**25**

How to use Dallphin allometric approach?

- 각 종별 PK modeling*을 선행적으로 수행해야함
- Model structures: 기본 1-comp or 2-compartment model
- 모든 종에서 동일한 model structure 를 사용

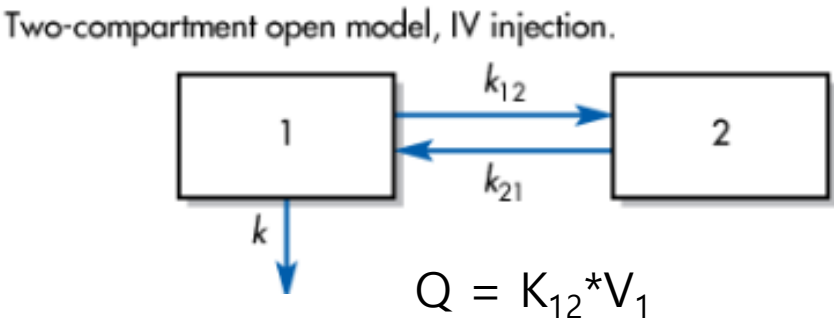
*PK modeling: General workflow

1. Model structure 정하기
2. Model optimization
3. Model diagnosis – GOF, individual plots
4. Model validation – VPC , (bootstrap for human data)
5. PK parameter estimation & extrapolation

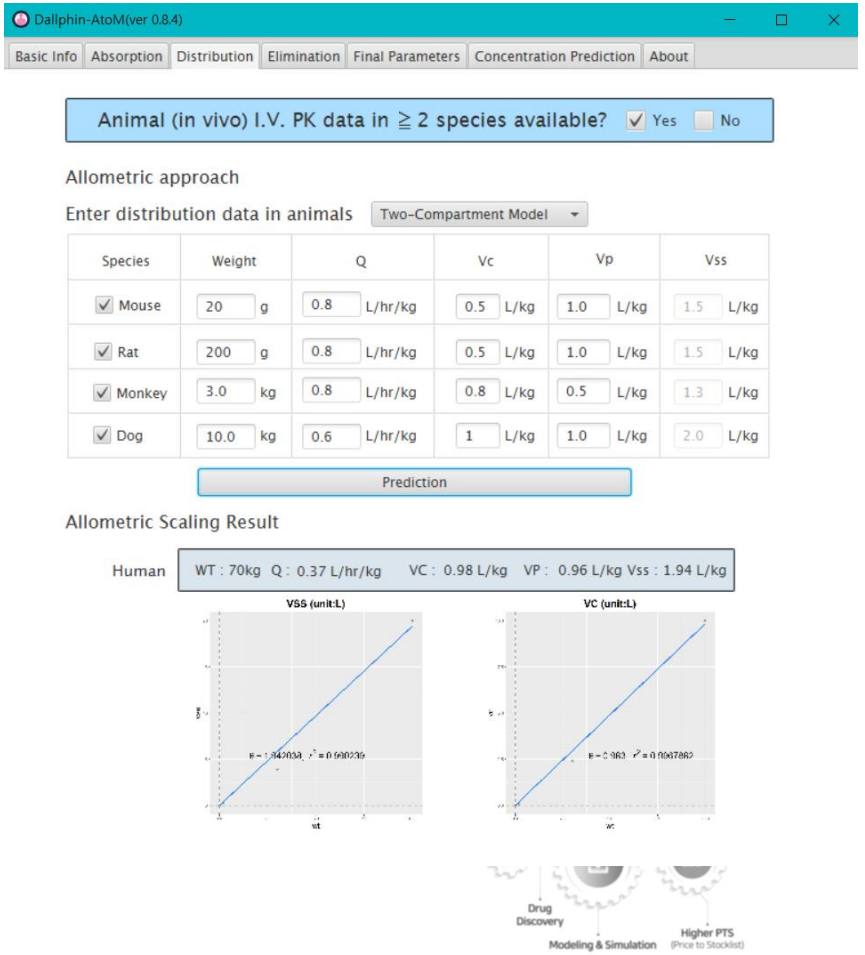


Dallphin allometric approach (Vd, Q)

- For 2 compartment model:
  Vss = Vc + Vp, Q
- Exponents fixed to 1 and 0.75
  $V = a(WT)^1$
  $Q = a'(WT)^{0.75}$

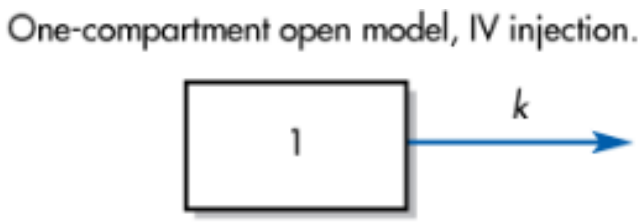


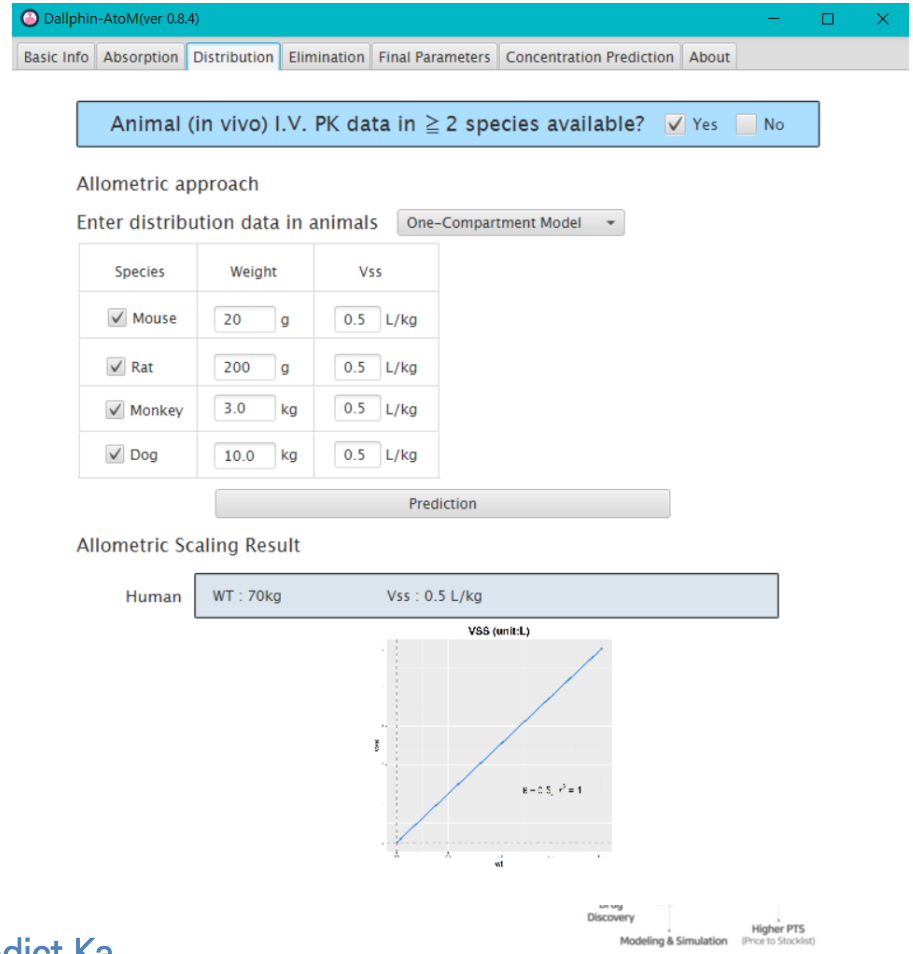
$Q = K_{12} * V_1$



Dallphin allometric approach (Vd, Q)

- For 1 compartment model:
  Vss only (~~Q, Vc, Vp~~)
- Exponents fixed to 1
  $V = a(WT)^1$
  ~~$Q = a'(WT)^{0.75}$~~



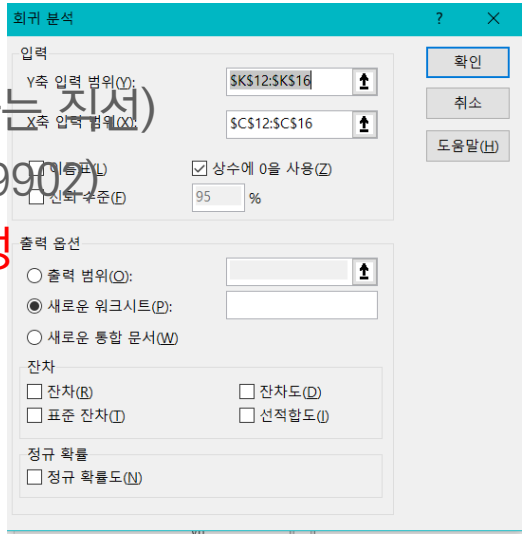


*Note: when using 1-compartment model, in order to predict Ka, Vss was used instead of Vc (as in 2-compartment model)[13], which may provide potential discrepancy in predicting human Ka.

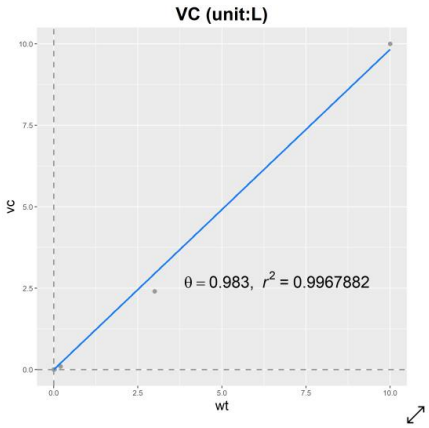
$$k_{a,eq} = \frac{P_m S}{V_c}$$

Dallphin's allometric approach example (Vd)

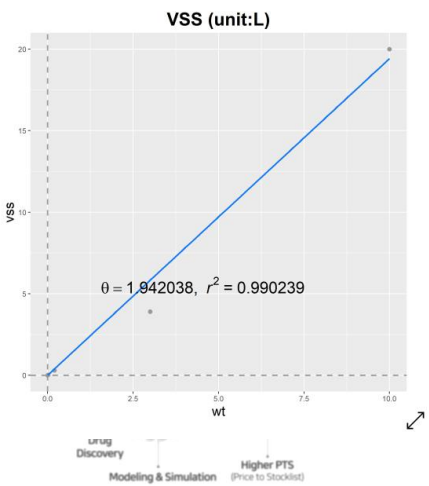
- Excel 데이터분석의 "회귀분석"과 같은 결과
- Natural scale 그래프로 제시, 상수는 0 을 사용 ((0,0) 을 지나가는 직선)
- Vc = 0.9833(WT) (R^2 = 0.9967), Vss = 1.9420(WT) (R^2 = 0.9902)
- 다음 버전에는 scaling exponent 를 예측하도록 update 될 예정



	A	B	C	D	E	F	G	H	I
1	요약 출력		Vc						
2									
3	회귀분석 통계량								
4	다중 상관계수	0.998393							
5	결정계수	0.996788	R2						
6	조정된 결정계수	0.746788							
7	표준 오차	0.291426							
8	관측수	5							
9									
10	분산 분석								
11		자유도	제곱합	제곱 평균	F 비	유의한 F			
12	회귀	1	105.4304	105.4304	1241.396	5.03E-05			
13	잔차	4	0.339716	0.084929					
14	계	5	105.7701						
15									
16		계수	표준 오차	t 통계량	P-값	하위 95%	상위 95%	하위 95.0%	상위 95.0%
17	Y 절편	0	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
18	X 1	0.983307	0.027908	35.23345	3.87E-06	0.905821	1.060793	0.905821	1.060793
19		theta							

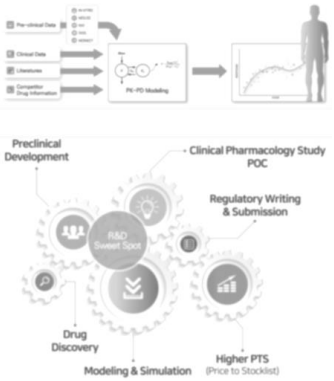


	A	B	C	D	E	F	G	H	I
1	요약 출력		Vss						
2									
3	회귀분석 통계량								
4	다중 상관계수	0.995108							
5	결정계수	0.990239	R2						
6	조정된 결정계수	0.740239							
7	표준 오차	1.006699							
8	관측수	5							
9									
10	분산 분석								
11		자유도	제곱합	제곱 평균	F 비	유의한 F			
12	회귀	1	411.2471	411.2471	405.7924	0.000267			
13	잔차	4	4.053769	1.013442					
14	계	5	415.3009						
15									
16		계수	표준 오차	t 통계량	P-값	하위 95%	상위 95%	하위 95.0%	상위 95.0%
17	Y 절편	0	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
18	X 1	1.942038	0.096406	20.14429	3.58E-05	1.674371	2.209705	1.674371	2.209705
19		theta							



4. Examples

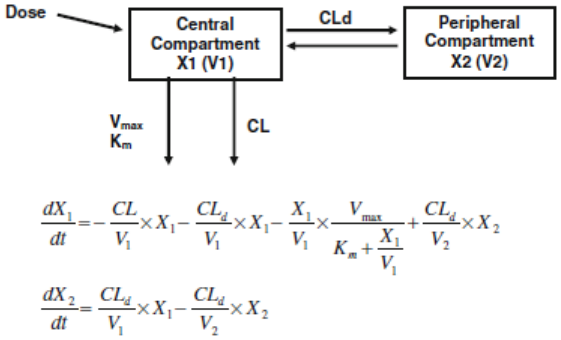
1. Simple allometry using monkey data
2. Simple allometry using 4 species data (mouse, rat, monkey, dog)
3. Allometry with correction factor (brain weight)
4. Modified allometry with correction factor



Simple allometry example (1)

- 실제 수행된 모델링 프로젝트에서의 simple allometry
- Scaling 3-kg monkey to 70-kg human for mAb[9]
- Scaling CL (non-specific CL), Vc, Vp, Q, and Vmax, Km (target-specific CL)

	monkey	Unit	x 3 kg monkey	Unit	Human	allometry
CL		L/h/kg		l/h		•CLh = CLm*(WTh/WTm)^0.85
V1		l/kg		l		•V1 = V1m*(WTh/WTm)^1
V2		l/kg		l		•V2 = V2m*(WTh/WTm)^1
Q		l/h/kg		l/h		•Q h = CLm*(WTh/WTm)^0.85
Vmax		mg/h/kg		mg/h		•Vmax = Vmaxmm*(WTh/WTm)^0.85
Km		mg/l		mg/l		•Km 그대로



$$\frac{dX_1}{dt} = -\frac{CL}{V_1} \times X_1 - \frac{CL_d}{V_1} \times X_1 - \frac{X_1}{V_1} \times \frac{V_{max}}{K_m + \frac{X_1}{V_1}} + \frac{CL_d}{V_2} \times X_2$$

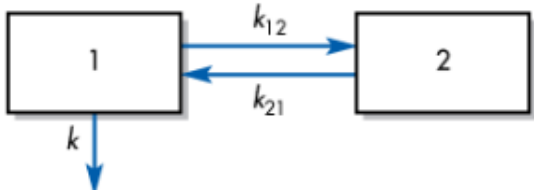
$$\frac{dX_2}{dt} = \frac{CL_d}{V_1} \times X_1 - \frac{CL_d}{V_2} \times X_2$$

Fig. 1 Two-compartment nonlinear PK model

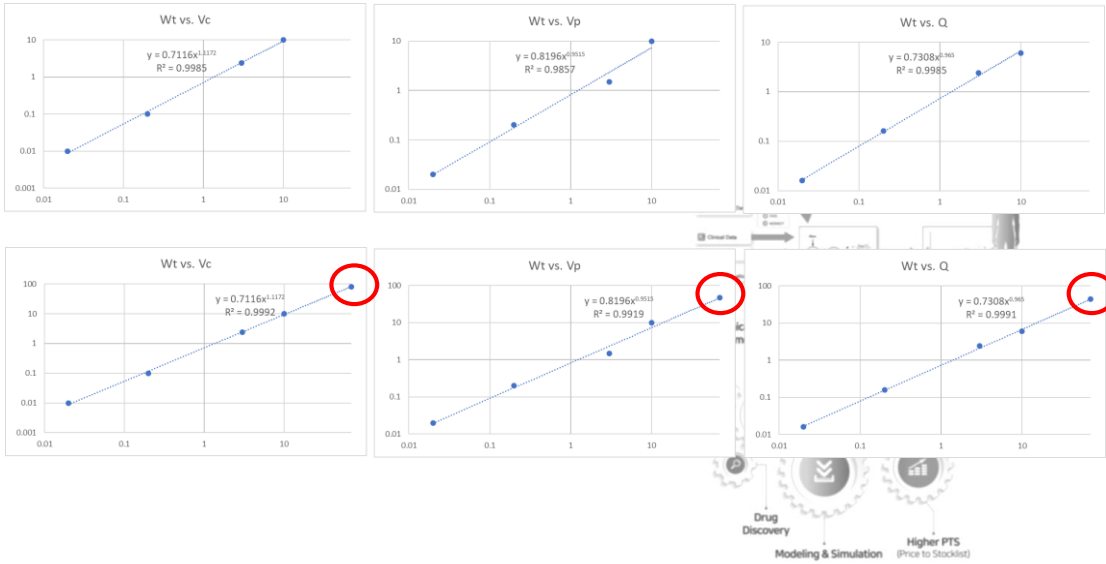
Simple allometry example (2)

		kg	Vss (L/kg)	vc (L/kg)	vc (L)	vp (L/kg)	vp (L)	Q (L/h/kg)	Q(L/h)
		0			0		0		0
	mouse	0.02	1.5	0.5	0.01	1	0.02	0.8	0.016
	rat	0.2	1.5	0.5	0.1	1	0.2	0.8	0.16
	monkey	3	1.3	0.8	2.4	0.5	1.5	0.8	2.4
	dog	10	2	1	10	1	10	0.6	6
exp		70	1.84	1.17	81.96	0.67	46.69	0.63	44.09
dallphine			1.94	0.98		0.96		0.37	

Two-compartment open model, IV injection.



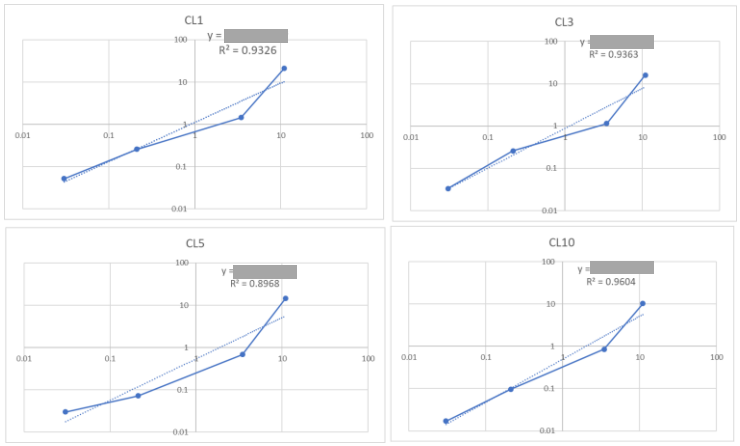
- 4 Species PK data
- Each species PK parameters estimated **from 2-compartment model**
- $Vd = a(WT)^b$, $Q = a(WT)^b$
- a, b estimated from regression line
- Extrapolation to predict PK in a 70-kg human

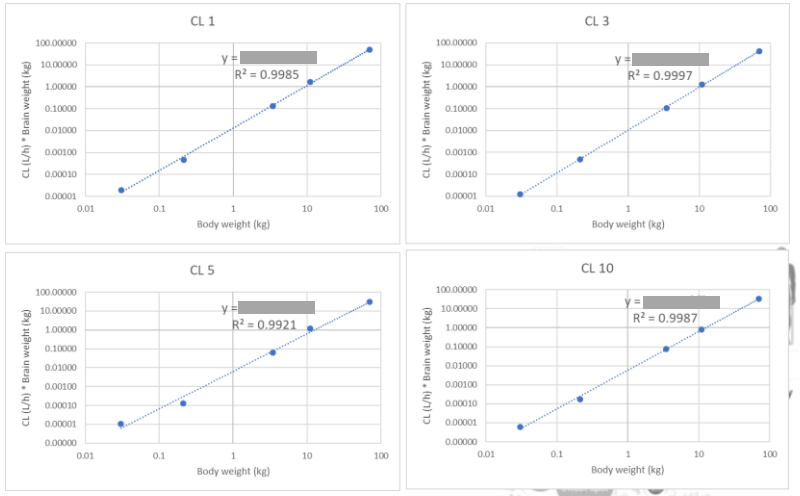


Allometry with correction factor example (3)

L/h	CL1	CL3	CL5	CL10
mouse				
rat				
monkey				
dog				
human				

BRAIN WT*					
KG	L/h	CL1*Br WT	CL3*Br WT	CL5*Br WT	CL10*Br W
0.00036	mouse				
0.0018	rat				
0.09	monkey				
0.08	dog				
1.4	human				





- $CL = a(BW)^b$ vs. $CL \times Brain\ Weight = a(BW)^b$

Modified allometry with correction factor example (4)

- 실제 수행된 모델링 프로젝트에서의 modified allometry
- Brain weight 를 correction factor 로 사용하여 human CL 예측 후, 용량에 따른 CL 변화를 수식으로 설명함

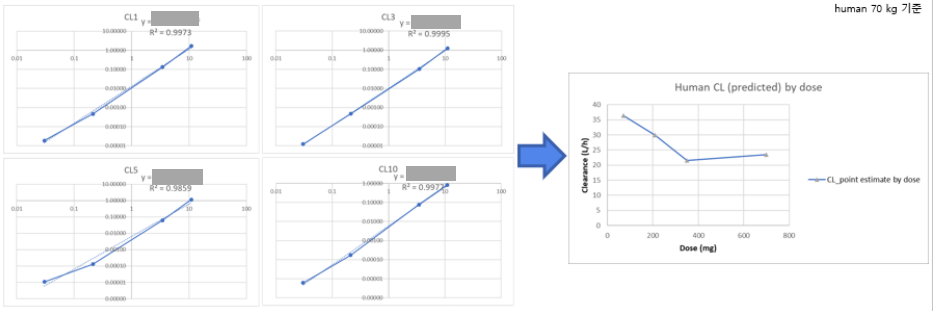
$$CL \times Brain\ weight = a \cdot f(Dose) \cdot (BW)^b$$

CL: allometry with standard correction factor (brain weight) (1)

BRAIN WT[1]					
KG	L/h	CL1*Br WT	CL3*Br WT	CL5*Br WT	CL10*Br WT
0.00036	mouse				
0.0018	rat				
0.09	monkey				
0.08	dog				
1.4	human				

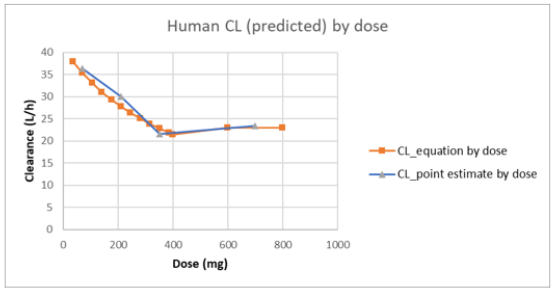
L/h	CL1	CL3	CL5	CL10
mouse				
rat				
monkey				
dog				
human				

human 70 kg 기준



- Brain weight 을 standard correction factor로 사용하여 CL 에 대해 각각의 용량 (1, 3, 5, 10 mg/kg)에 따른 interspecies scaling (모든 용량군의 R^2~0.99) 을 수행하여 CL 를 구함 (CL_point estimate by dose)
- Clearance x BrainWeight = aBW^b

CL: allometry with standard correction factor (brain weight) (2)



- 앞서 Mouse 에서 얻은 용량에 따른 CL 수식을 기반으로 이를 interspecies scaling 에 적용함, 400 mg 이하에서 수식을 적용하였으며, 400 mg 초과시 CL 는 일정하다고 가정함 --400 mg 이하: CL*BrainWeight = a*(CLmax*(1-DOSE/(DOSE+CL50)))*BW^b
  (CLmax= [redacted] CL50=[redacted], a= [redacted] b = 1 *상수 a 와 b 는 모델링을 통해 산출한 값임)
  -400 mg 초과: CL 는 용량에 따라 일정하다고 가정함
- 따라서, 용량에 따른 CL 변화를 BW 에 따라 나타낼 수 있으며, 용량과 BW 정보가 있다면 이젠 CL 산출이 가능해짐
- 이를 기반으로 70kg 사람에서의 CL 를 산출한 결과는 위와 같음(CL_equation by dose), 이를 앞의 각각 용량별 interspecies scaling 결과(CL_point estimate by dose)와 비교하였음

Modeling & Simulation Higher PTS (Price to Stocklist)

CL prediction: Allometry vs. in vitro data[11]

- Allometry vs. IVIVE methods

- Allometry: fu intercept method and two-species-based allometry (rat-dog) were best
- IVIVE: Using microsomes (incorporating both plasma and microsomal binding) and hepatocytes (not incorporating binding) resulted in better prediction

⇒ Allometry slightly more accurate than predictions based on in vitro data

⇒ Dallphin uses only in vitro data for CL prediction

- 다음 버전에는 allometry(in vivo data)를 통해 CL 예측이 가능하도록 update 될 예정

Final parameters

- Hepatic CL: CLh_fromRativivc
- Renal CL:

–CLr (Rat to human prediction)

–CLr (Dog to human prediction)

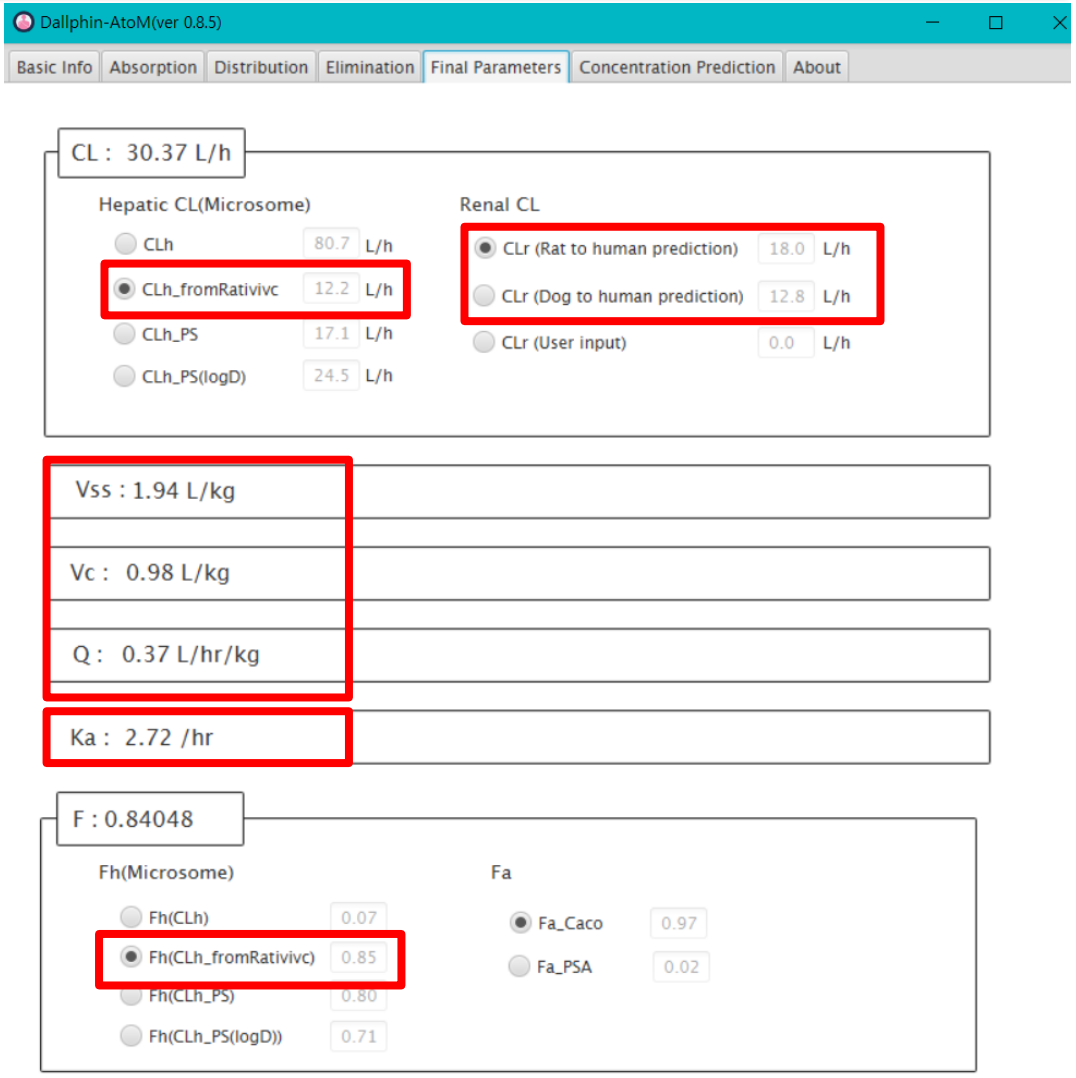
- Vss
- Vc ➡ Ka
- Q

- Fh (CL h_fromRativivc)

$$k_{a,eq} = \frac{P_m S}{V_c}$$

$$Fh = 1 - \frac{CL_{hepatic}}{Q_H}$$

P_m : drug permeability across intestinal mucosa (Caco-2 Papp)
S : absorptive surface area



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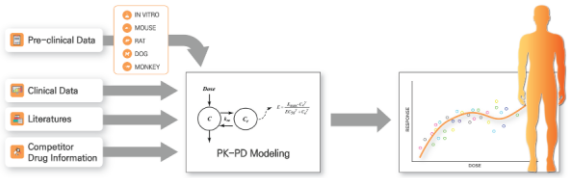
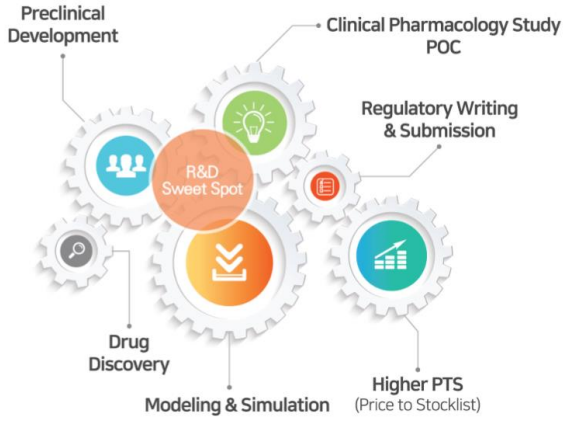
경청해 주셔서 감사합니다.

주요 *in vivo* 정보와
이를 활용한 인간 약동학 예측 이론





분당서울대병원 헬스케어 혁신파크 2019.04.25