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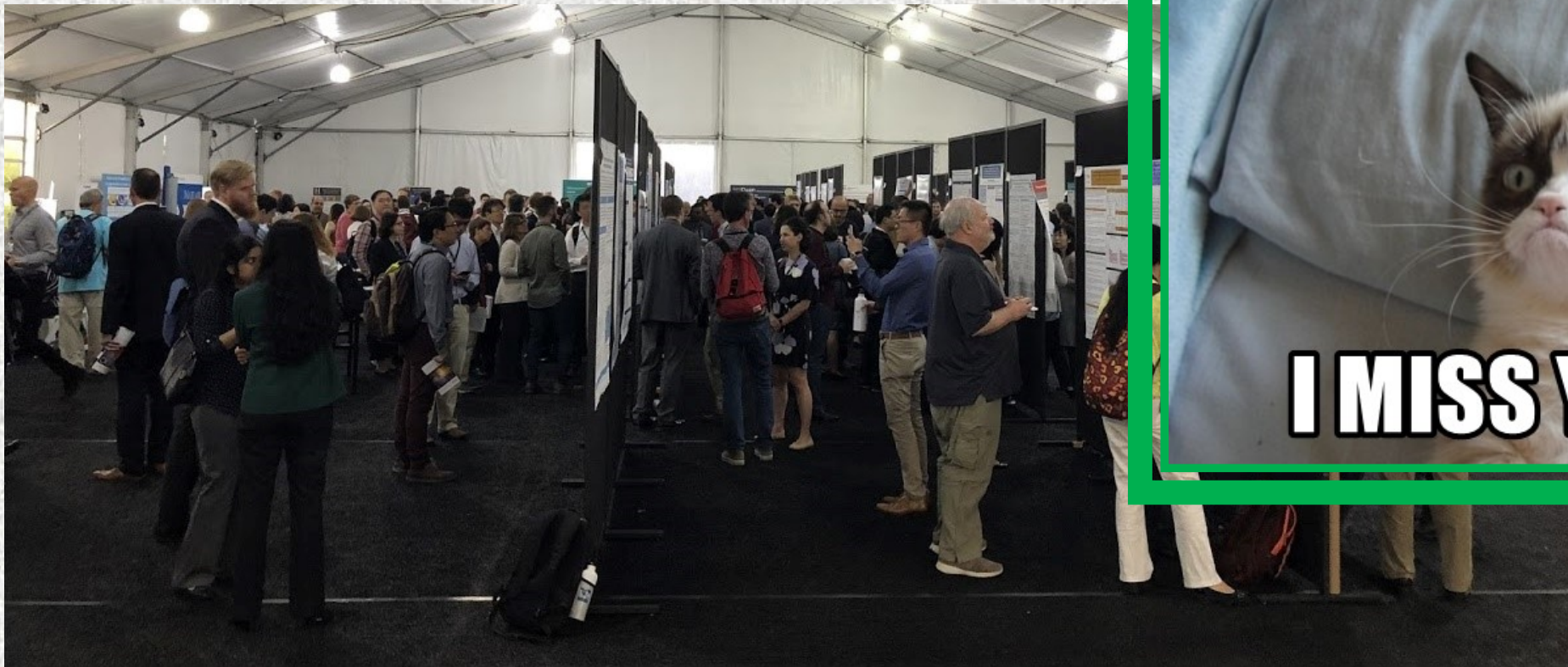
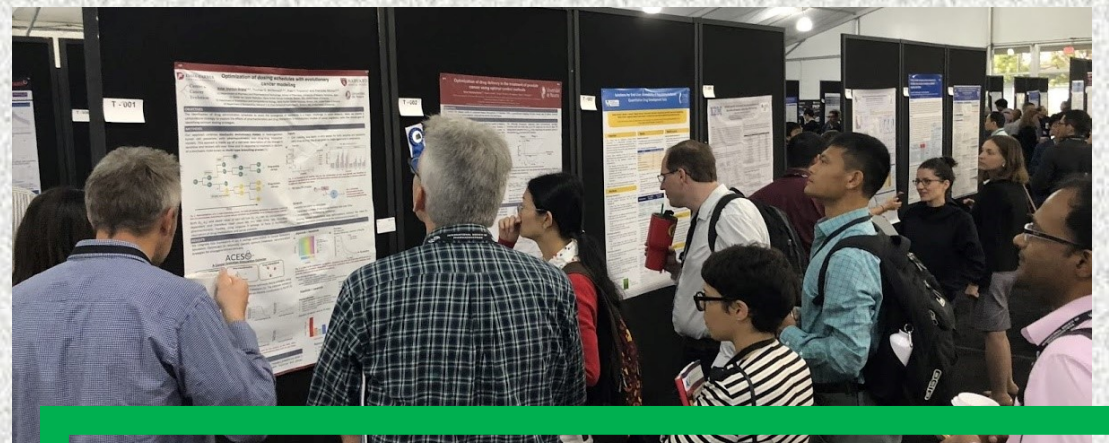
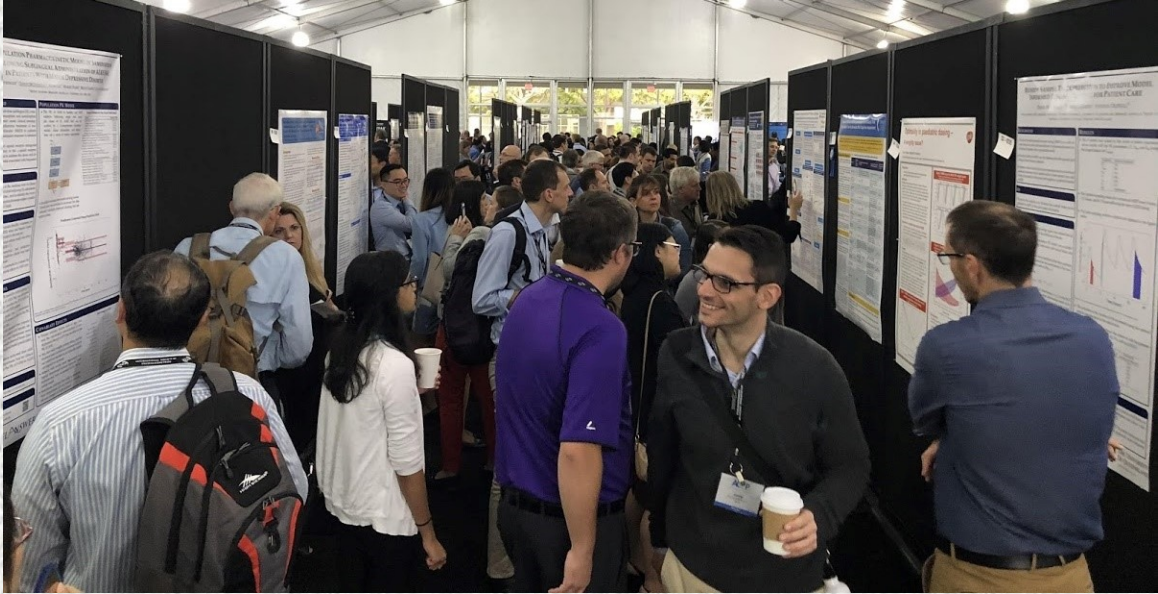
Making the 'Master' of Your Poster

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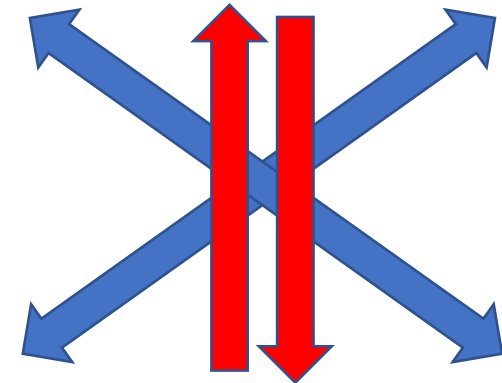
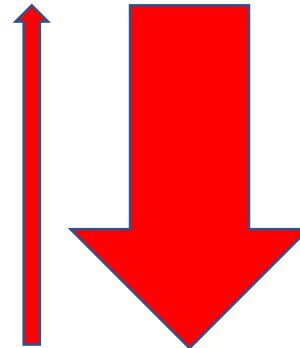
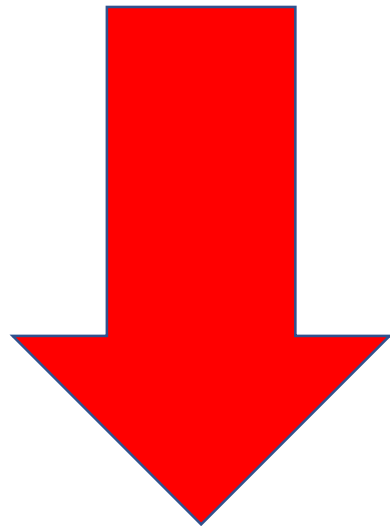
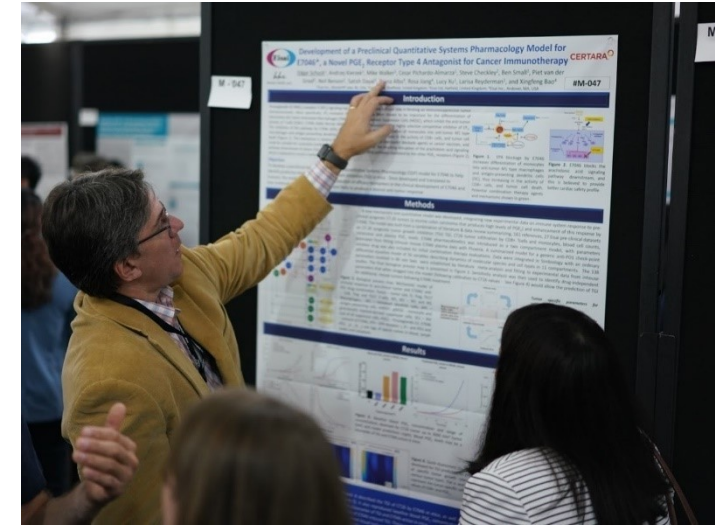
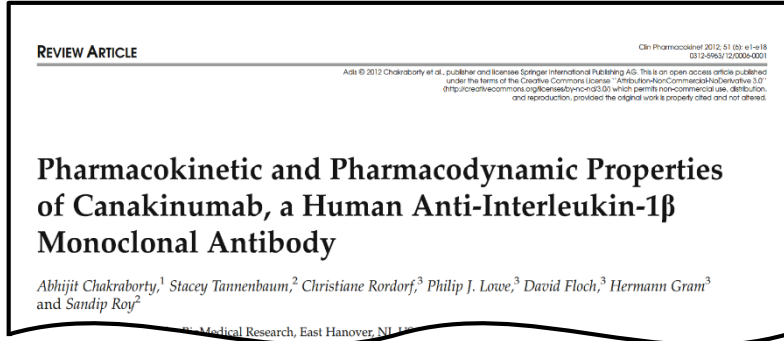


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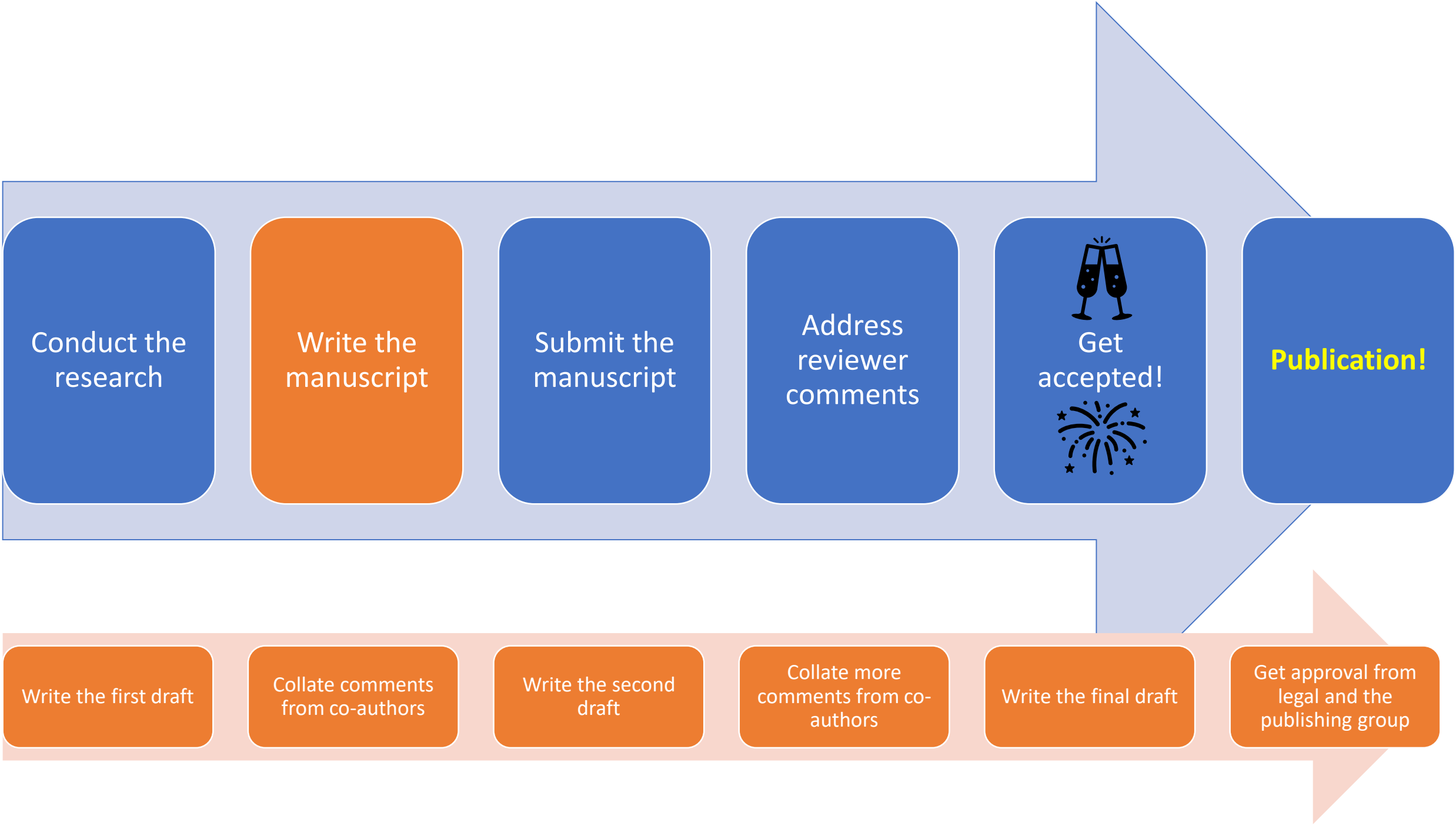
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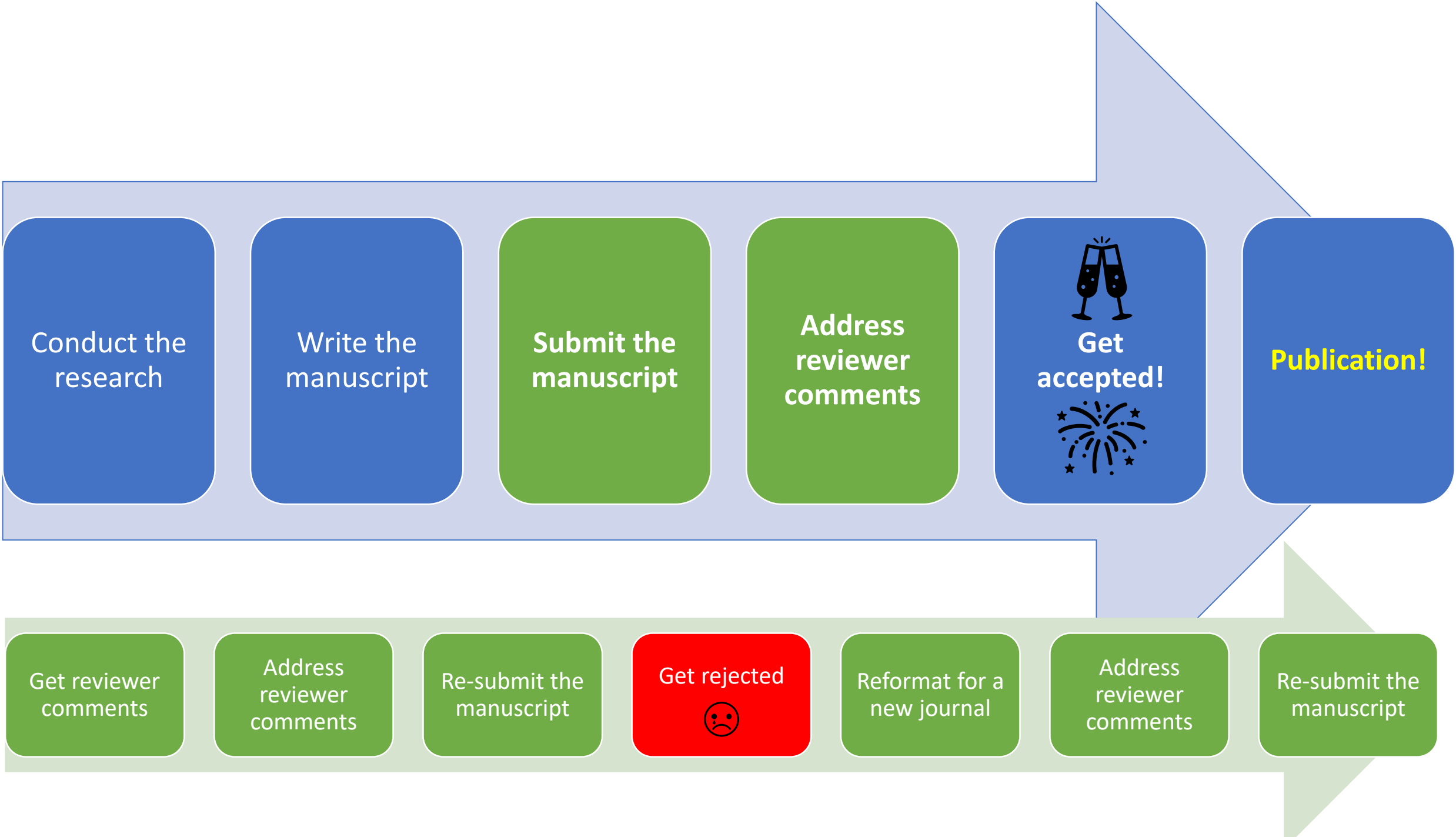
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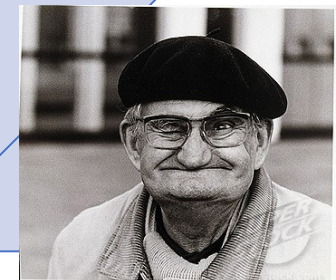
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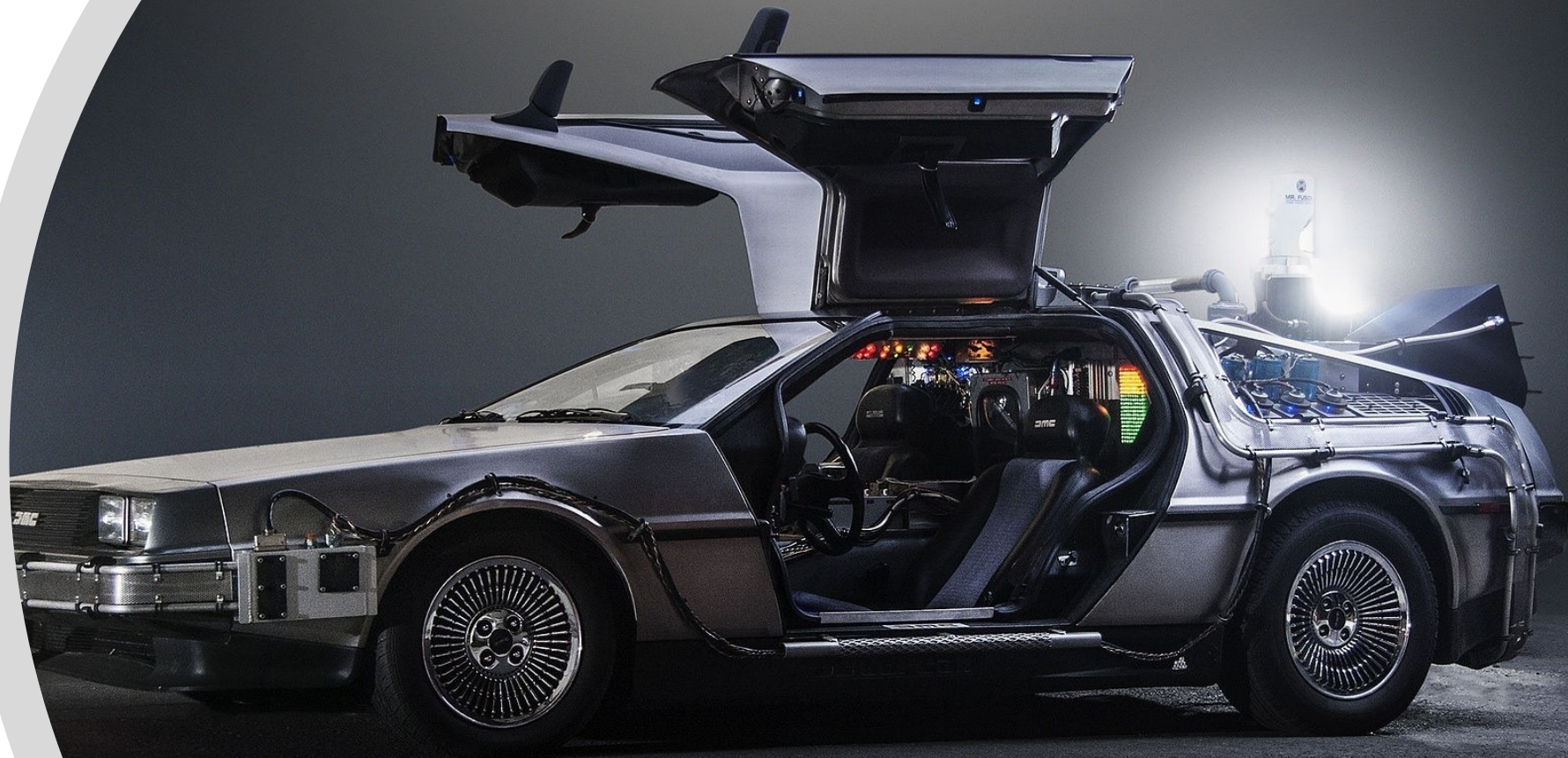
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Write the
abstract


Get
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Poster!





2068

ALLOMETRIC ANALYSIS OF ORGAN EXTRACTION RATIOS

S Tannenbaum¹, H Boxenbaum², and M Mayersohn¹
¹College of Pharmacy and the Center for Toxicology, The University of Arizona, Tucson, AZ
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Abstract

Introduction

Methods

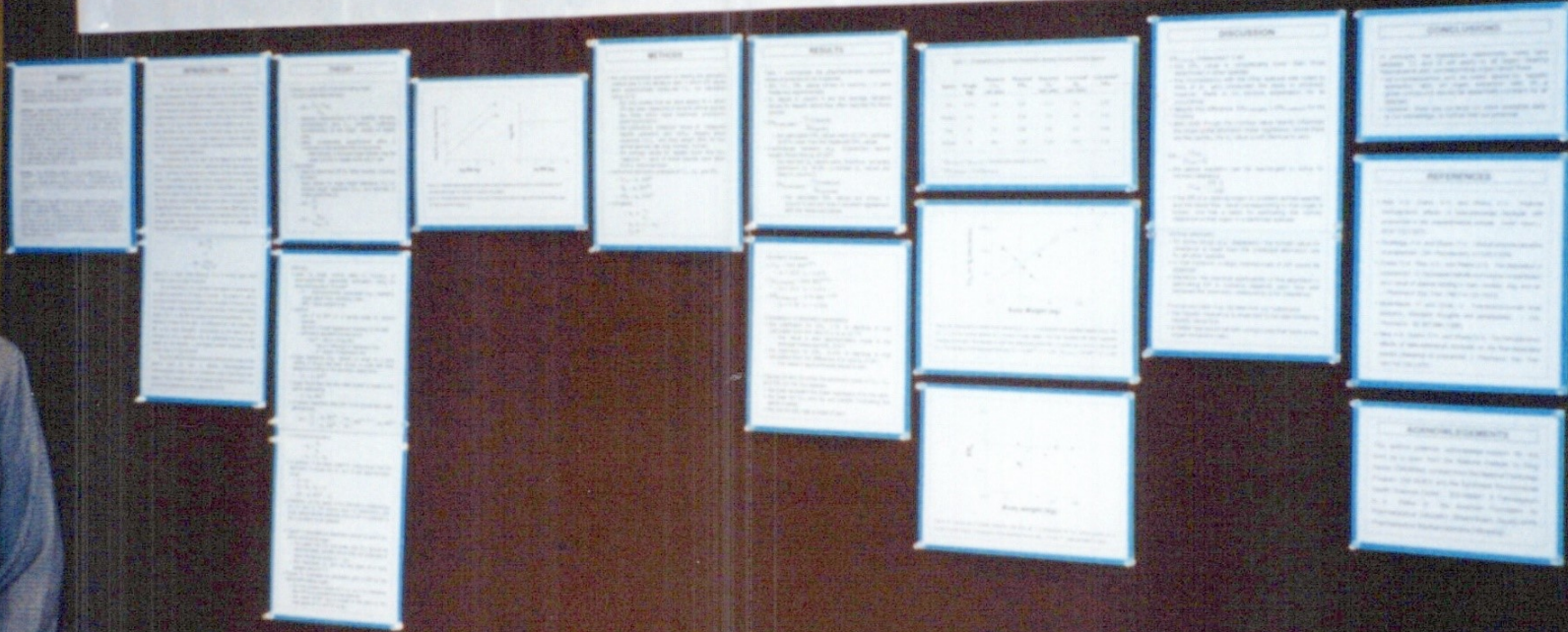
Results

Discussion

Conclusions

References

Additional Comments



1287

POTENTIAL ERRORS IN THE USE OF BODY BURDEN CALCULATION ESTIMATION OF TOXICOKINETIC PARAMETERS

S J Tannenbaum, V Sinha, and M Mayersohn
College of Pharmacy and Center for Toxicology
University of Arizona, Tucson, AZ

ABSTRACT

Abstract text describing the study's purpose and findings.

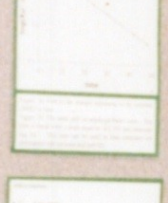
OBJECTIVES

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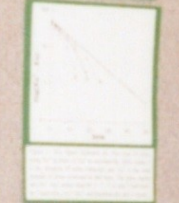
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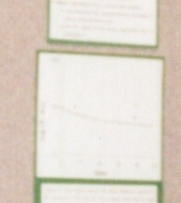
THEORY

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METHODS

Methods text.



Methods text.

RESULTS

Results text.



Results text.

Results text.

DISCUSSION

Discussion text.



Discussion text.

Discussion text.

CONCLUSIONS

Conclusions text.

ACKNOWLEDGMENTS

Acknowledgments text.

56 pieces





INTRODUCTION

Cocaine and ethanol is a widely used drug combination. It shows synergistic and synergistic effects. The "high" produced by cocaine and ethanol is thought to be the result of the synergistic effects of cocaine and ethanol. Cocaine and ethanol combination also significantly increases the maximum effect. Cocaine and ethanol combination also significantly increases the maximum effect. Cocaine and ethanol combination also significantly increases the maximum effect.

Ethanol has been shown to... Cocaine has been shown to... Cocaine and ethanol combination has been shown to have synergistic effects on cocaine, but to more potent.

The objective of this study was to investigate the pharmacological effects of an equimolar dose of cocaine and coethanol. To compare the combined effect of cocaine and ethanol and compare it to cocaine alone.

The objectives are that to building a pharmacokinetic-pharmacodynamic model for each compound and comparing the resultant parameter values.

REFERENCES

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METHODS

All data were recovered from published literature. Ethanol (E), cocaine (C), cocaine/ethanol (CE) and cocaine plus ethanol (C+E) were administered to dogs on separate occasions. E: 7.5 mg/kg IV infusion from 40 to 50 minutes. C: 7.5 mg/kg IV infusion from 40 to 50 minutes. CE: 7.5 mg/kg IV infusion from 40 to 50 minutes.

Plasma concentration and pharmacological responses were measured at several times after dosing. The left ventricular pressure was measured every 2 min using a micro-pressure transducer. Vascular conductivity (VC) measured as the maximum rate of left ventricular pressure increase. Vascular relaxation (VR) measured as the maximum fall of left ventricular pressure between.

Plasma concentration and each response (VC, VR) were averaged for all animals at each time. These mean data were plotted versus time. VC and VR were plotted as percent of baseline. The data were transferred from the literature plot using computer digitization.

The shape of the response (VC or VR) vs. plasma concentration (C or CE) curve originally suggested an inhibition model. However, upon fitting these data, the parameter values indicated that this was not an appropriate model. E_{max} values were significantly above 100% (baseline), suggesting the mechanism was not fully inhibitory. An opposing stimulatory effect at low concentrations would cause the effect to increase above baseline. This suggested the following combined inhibition-stimulation model:

$$E(\% \text{ of baseline}) = 100 - I + S$$

$$I = \frac{E_{max} C^n}{IC_{50}^n + C^n} \quad \text{and} \quad S = S_{max} \frac{B_{50} - S_{50}}{SC_{50} + C^n}$$

- E: the maximum effect (VC or VR)
- C: the plasma concentration of the drug (C or CE)
- E_{max} : the maximum inhibitory response
- IC_{50} : the concentration at 50% of E_{max}
- S_{max} : the maximum stimulatory response
- B_{50} : the maximum stimulatory response
- SC_{50} : the concentration at 50% of S_{max}
- n : a Hill-sloping parameter measurement of sigmoidality of the curve

RESULTS

The effect vs. concentration profiles were similar for both VC and VR. The VR data are in the process of being analyzed and are therefore not reported in this presentation. C, CE, and (C+E) data were fitted to the combined I+S model. Satisfactory convergence could not be attained for the (C+E) data, most likely because the effect is consistently below baseline. Inhibition appears to be the only mechanism present. Therefore, these data were fit instead to a purely inhibitory model:

$$E(\% \text{ of baseline}) = 100 - I$$

$$I = \frac{E_{max} C^n}{IC_{50}^n + C^n}$$

The resultant parameter values are shown below:

	C	CE	C+E
E_{max} (%)	320.89	212.07	106.91
IC_{50} (nmol/mL)	33.00	10.36	16.28
n	0.69	2.93	2.86
S_{max} (%)	34.70	11.61	
B_{50} (%)	66.46	166.52	
SC_{50} (nmol/mL)	5.67	10.68	
n	2.69	3.68	

Figures 1-2: Effect vs. time and vs. log plasma concentration plots for E, C, and CE (points: observed values, lines: model predictions). Administration of E caused a negative response. Administration of the other compounds led to a significant initial inhibition of response followed by a gradual return towards baseline (100%). At high concentrations of C and CE, the response surpassed and then remained above baseline for the duration of the experiment.

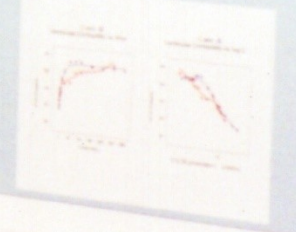


Figure 3: Simulated curves for the stimulatory (S) and inhibitory (I) components. These curves are based on the optimized parameter values for C and CE.

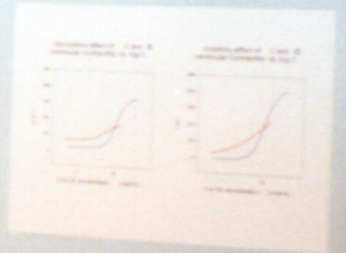
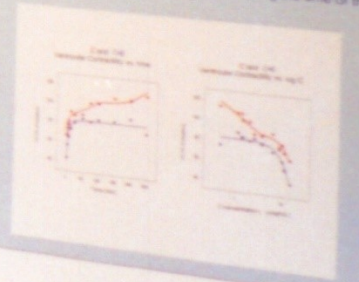


Fig 4: Effect vs. time and vs. log plasma concentration plots for C and CE. For (C+E) the response did not return to baseline during the time of the experiment.



PREDICTION OF PHARMACOKINETIC PARAMETERS IN HUMANS ON THE BASIS OF ALLOMETRIC SCALING USING A "GLOBAL" SLOPE.

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College of Pharmacy and Center for Toxicology, University of Arizona, Tucson, AZ 85721

INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: $P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^{\beta}$, where P is the parameter (clearance, volume, half-life), and BW is body weight in kg. When P vs BW data for several species are plotted on a log-log scale for a specific drug, the regression line through the data has slope β and intercept a .

It has been noted that, for a specific parameter P, the values of β tend to be similar regardless of drug. It is common practice to use slopes of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

β_{global} is defined as the average of the β -values for a parameter over all drugs. These can be used in the allometric equation to make a prediction for human P for each animal included in the publication:

$$P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^{\beta_{\text{global}}}$$

We concentrated on the most commonly used animals in allometric studies: mouse, rat, rabbit, dog, and monkey. We could then determine the predictability of the parameter based on the global slope by comparing the predictions across animals, using a number of different measurements.

Since a single animal point is used to make the human prediction, it is possible that a different slope may apply to each. For each drug and for each species, we computed the animal-to-human slope, and averaged over all drugs to find β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , and β_{monkey} . We used these β values in the above equation to make predictions, and did the same analysis as with the global slope predictions.

Our overall conclusion based on our analysis is that the animal/slope pair of rabbit/rabbit provided the most predictive estimations of the overall Phman values. However, the β_{global} values of 0.729 for CL, 0.961 for V, and 0.242 for $t_{1/2}$ support the use of 0.75, 1.0, and 0.25 to make initial estimations of human parameter values.

METHODS

DATA COLLECTION

Searched the literature for allometric/pharmacokinetic analyses of drugs/toxics that included:

- data for multiple species (must include human)
- values for body weight (BW)
- values for clearance (CL), volume of distribution (V), and/or half life ($t_{1/2}$)

Plotted log P vs log BW(kg) for each drug, where P is a pharmacokinetic parameter (CL, V, $t_{1/2}$)

Calculated the allometric parameters for P

- Allometric equation: $P = a \cdot BW^b$
- $\log P = \log a + b \log BW$
- $\log a = \text{intercept of } \log P \text{ vs } \log BW$
- $b = \text{slope of } \log P \text{ vs } \log BW$

CALCULATION OF ALLOMETRIC SLOPES

- For each parameter P (CL, V, $t_{1/2}$):
- Plot: log P vs log BW for all drugs
- (i) regression slope: determined using all animal data in plot
- (ii) animal-to-human slope: determined using one animal and the human data point
- $\beta_{\text{global}} = \frac{\sum \log P_i}{\sum \log BW_i} - \frac{\log P_{\text{human}}}{\log BW_{\text{human}}}$
- β_{animal} : average (for all drugs) of all regression slopes in (i)
- β_{animal} : average (for all drugs) of all individual animal-to-human slopes in (ii) (Mouse, Rat, Rabbit, Dog, Monkey)

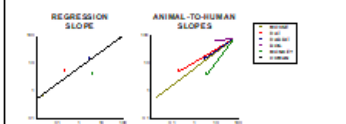


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, $t_{1/2}$. Fig A shows the regression line through all points in the plot. Fig B shows the line connecting each specific animal value to the human value. Each animal-to-human slope is calculated using the equation: $P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^{\beta}$

METHODS, cont.

CALCULATION AND EXAMINATION OF PREDICTED

For each parameter P (CL, V, $t_{1/2}$) and each species:

- Predicted human P using: $P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^{\beta}$ where $\beta = \beta_{\text{global}}$
- Compared Predicted to Observed (human P given in publication):
 - Found slope and intercept of regression line through log Ppred vs log Pobs
 - Calculated ratio = log(Pobs/Ppred) for each observed/predicted pair
 - if ratio is between -0.5 and 0.5, Ppred is between 1/3-Pobs and 3-Pobs: allowable 10-fold range
 - Repeated the above steps using $\beta = \beta_{\text{animal}}$ in the allometric equation

CHOOSING THE MOST PREDICTIVE SPECIES AND SLOPE

- For each parameter P (CL, V, $t_{1/2}$) and for each species/slope pair (e.g., mouse/ β_{mouse})
- Compared regression line through the (log Ppred vs log Pobs) pair to the line of identity
- Calculated the fraction of Pobs/Ppred values that fell within the allowable 10-fold range for each set
- Calculated the RMSE for each set
- Compared RMSEglob to β_{global} to find most predictive slope (globally)
- Compared RMSEglob across species to find most predictive species

RESULTS

Parameter	Species	β	RMSE	Fraction in Range
CL	Human	0.729	0.120	0.961
	Mouse	0.702	0.137	0.949
	Rat	0.696	0.155	0.941
	Rabbit	0.589	0.195	0.937
	Monkey	0.571	0.513	0.896
V	Human	0.961	0.136	0.242
	Mouse	0.962	0.151	0.263
	Rat	0.961	0.172	0.257
	Rabbit	0.961	0.207	0.248
	Monkey	0.829	0.252	0.154
$t_{1/2}$	Human	0.242	0.043	0.949
	Mouse	0.242	0.051	0.949
	Rat	0.242	0.057	0.949
	Rabbit	0.242	0.063	0.949
	Monkey	0.242	0.069	0.949

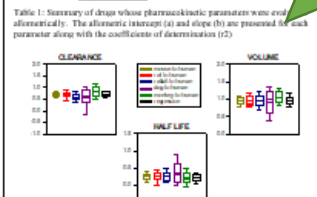


Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the β_{global} and β_{animal} values for each parameter.

RESULTS, cont.

Parameter	CL	V	$t_{1/2}$
β_{global}	0.729	0.961	0.242
β_{mouse}	0.702	0.962	0.263
β_{rat}	0.696	0.961	0.257
β_{rabbit}	0.589	0.961	0.248
β_{monkey}	0.571	0.829	0.242

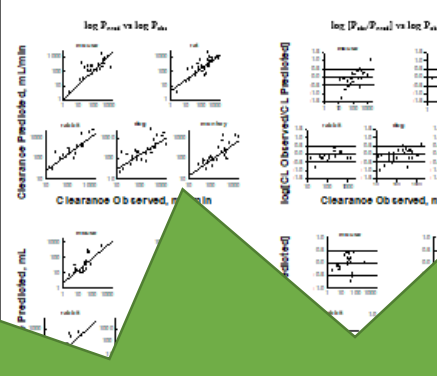


Figure 3: Log-log plots for each species/slope pair. The plots show log(P_obs/P_pred) vs log(P_obs/P_pred) for Clearance, Volume, and Half-life. The plots are arranged in a grid, with rows for parameters and columns for species. The diagonal elements represent the line of identity (y=x).

Parameter	Species	β	RMSE	Fraction in Range
CL	Human	0.729	0.120	0.961
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	Monkey	0.242	0.069	0.949

Table 2: Measures used to compare the accuracy of the human prediction based on β_{animal} (A), or based on β_{global} (B). The slope, intercept, and r^2 values are of the regression line through the log P_obs vs log P_pred plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and f_{range} is the fraction of values that fall within the allowable range on each log P_obs vs log P_pred plot (shown in Figs. 4 and 6).

RESULTS, cont.

Tables 3a and 3b list the intercepts, slopes, and r^2 values of the regression lines through the (log P_obs vs log P_pred) plots for each species/slope pair, where Ppred is based on β_{global} and the β_{animal} slopes, respectively. Global plots are shown in Figure 3 and those for rabbit/ β_{rabbit} in Figure 5.

- If $P_{\text{pred}} = P_{\text{obs}}$ (ideal), then the regression line is the line of identity
- compare slope to 1
- compare intercept to 1 (origin of log-log plot)
- compare r^2 to 1 (linear regression line perfectly fits the data)
- highlighted values in these columns show the two values that are closest to 1 for each P
- *denotes the best of the two highlighted values
- *signifies that 95% confidence interval around slope or intercept contains 1
- rabbit is highlighted 8/9 times in both Tables 3a and 3b
- 13/15 of the highlighted values are best
- after animal shows the same consistency over all three parameters

Table 3b list the RMSE values and the f_{range} values for each species/slope pair. Table 3a shows the (log (P_obs/P_pred) vs log P_obs) plots for each parameter. If P_obs (ideal), then each error would equal zero, and RMSE would equal zero. The highlighted values in this column show the two values that are closest to 0 for each parameter

- *denotes the best of the two highlighted values
- *highlighted 2/3 times in Table 3a
- *highlighted all 3 times in Table 3b
- the highlighted values are best
- after animal shows the same consistency over all three parameters
- for each species/slope pair, the highlighted values are best for each parameter
- for the set, the fringe value would be the average of the two values that are closest to 1.0 for each parameter

Table 3a shows the (log (P_obs/P_pred) vs log P_obs) plots for each parameter. If P_obs (ideal), then each error would equal zero, and RMSE would equal zero. The highlighted values in this column show the two values that are closest to 0 for each parameter

Table 3b list the RMSE values and the f_{range} values for each species/slope pair. Table 3a shows the (log (P_obs/P_pred) vs log P_obs) plots for each parameter. If P_obs (ideal), then each error would equal zero, and RMSE would equal zero. The highlighted values in this column show the two values that are closest to 0 for each parameter

Table 3b list the RMSE values and the f_{range} values for each species/slope pair. Table 3a shows the (log (P_obs/P_pred) vs log P_obs) plots for each parameter. If P_obs (ideal), then each error would equal zero, and RMSE would equal zero. The highlighted values in this column show the two values that are closest to 0 for each parameter

- future studies:
 - Clearance values may be biased due to binding and blood flow differences between species. An analysis of unbound intrinsic clearance may give more insight.
 - Variation due to the strains of each species used in different studies must be investigated.
 - 28 drugs were used in this analysis.
 - As more data becomes available, β values, and therefore the most predictive species and slope, may differ.

Supported by a grant from the National Institute on Drug Abuse (DA08894). ST is supported by an American Foundation for Pharmaceutical Education Pharmaceutics/Biopharmaceutics Fellowship.

REFERENCES

1. J. D. Baggett, *American Journal of Veterinary Research*, 55 (1994) 689.
2. M. Bonati, R. Latini and G. Topponi, *Drug Metabolism Reviews*, 15 (1984) 1355.
3. D. R. Brooks, M. J. Freed, D. E. Martin, T. S. Sellers, N. Mehdi, D. R. Cimen, V. Boppina, B. Levitt, B. E. Davies, J. Nemunaitis and D. K. Jorkasky, *Pharmaceutical Research*, 13 (1986) 794.
4. M. Clume, E. Radwanski, D. Loebenberg, C. C. Lin, E. Oden, S. Szymchowicz, R. P. Gural and G. H. Miller, *Journal of Antimicrobial Chemotherapy*, 15 Suppl C (1985) 227.
5. C. A. Crane, G. R. Kelm and M. P. Meredith, *Pharmaceutical Research*, 12 (1995) 895.
6. B. L. Dedrick, D. D. Forrester, J. M. Cannon, S. M. ed-Desser and L. B. Mellett, *Biochemical Pharmacology*, 22 (1973) 2405.
7. G. S. Dulha, *Journal of Pharmaceutical Sciences*, 74 (1985) 943.
8. C. Efthymiopoulos, R. Battaglia and M. Strolin Benedetti, *Journal of Antimicrobial Chemotherapy*, 27 (1991) 517.
9. F. Gaspari and M. Bonati, *Drug Metabolism Reviews*, 22 (1990) 179.
10. G. Gatti, J. O. Kahn, J. Lifson, R. Williams, L. Turin, P. A. Volberding and J. G. Gamberoglio, *Antimicrobial Agents & Chemotherapy*, 35 (1991) 2531.
11. E. K. Hussey, K. H. Doan, M. J. Daniel, S. T. Hall, A. J. Harker and G. L. Evans, *Journal of Clinical Pharmacology*, 34 (1994) 975.
12. S. S. Ibrahim and F. D. Boudinot, *Journal of Clinical Pharmacy & Therapeutics*, 41 (1989) 829.
13. S. G. Jesequel, *Journal of Pharmacy & Pharmacology*, 46 (1994) 196.
14. T. Lave, B. Levet-Traff, A. H. Schmitt-Hoffmann, B. Mergenthaler, W. Richter and R. C. Chou, *Journal of Pharmaceutical Sciences*, 84 (1995) 1285.
15. J. P. McGovern, M. G. Williams and J. C. Stewart, *Drug Metabolism & Dispensation*, 16 (1988) 18.
16. J. Mondeni, G. Osaka, K. Garcia, K. Thomsen, V. Licko and G. Meng, *Toxicology & Applied Pharmacology*, 136 (1996) 75.
17. S. M. Owens, W. C. Hanbwick and D. Blackall, *Journal of Pharmacology & Experimental Therapeutics*, 242 (1987) 96.
18. A. Patel, F. D. Boudinot, R. F. Schinazi, J. M. Chou, *Journal of Pharmacokinetics and Biopharmaceutics*, 13 (1990) 206.
19. A. Puigdemont, R. Guitari, F. De Mora and M. Arboix, *Journal of Pharmaceutical Sciences*, 80 (1991) 1106.
20. L. Sangalli, A. Bertolotti, L. Jiriano and M. Bonati, *Drug Metabolism & Dispensation*, 16 (1988) 749.
21. Y. Sawada, M. Hanano, Y. Sugiyama and T. Iga, *Journal of Pharmacokinetics & Biopharmaceutics*, 12 (1984) 241.
22. L. B. Sheiner and S. L. Beal, *Journal of Pharmacokinetics & Biopharmaceutics*, 9 (1981) 503.





PROBLEM STATEMENT

Allometry scales animal pharmacokinetic data to humans using the equation: $P = a \cdot BW^b$, where P is the parameter (clearance, volume, half-life), BW is body weight in kg, and a and b are the slope and intercept of the log-log plot, respectively.

Fixed slopes (0.75, 1.0 and 0.25 for CL, V, and $t_{1/2}$) are commonly used for initial human predictions. Using published allometric analyses of 28 drugs, we examined whether this is a valid practice, and explored whether any particular species is more predictive.

Two slope values were used in the allometric equation to make a prediction for human PK parameters from animal data:

- β_{global} = the average of the b -values for a parameter over all drugs.
- β_{animal} = animal-to-human slope for each drug and parameter computed for mouse, rat, rabbit, dog, and monkey, averaged over all drugs

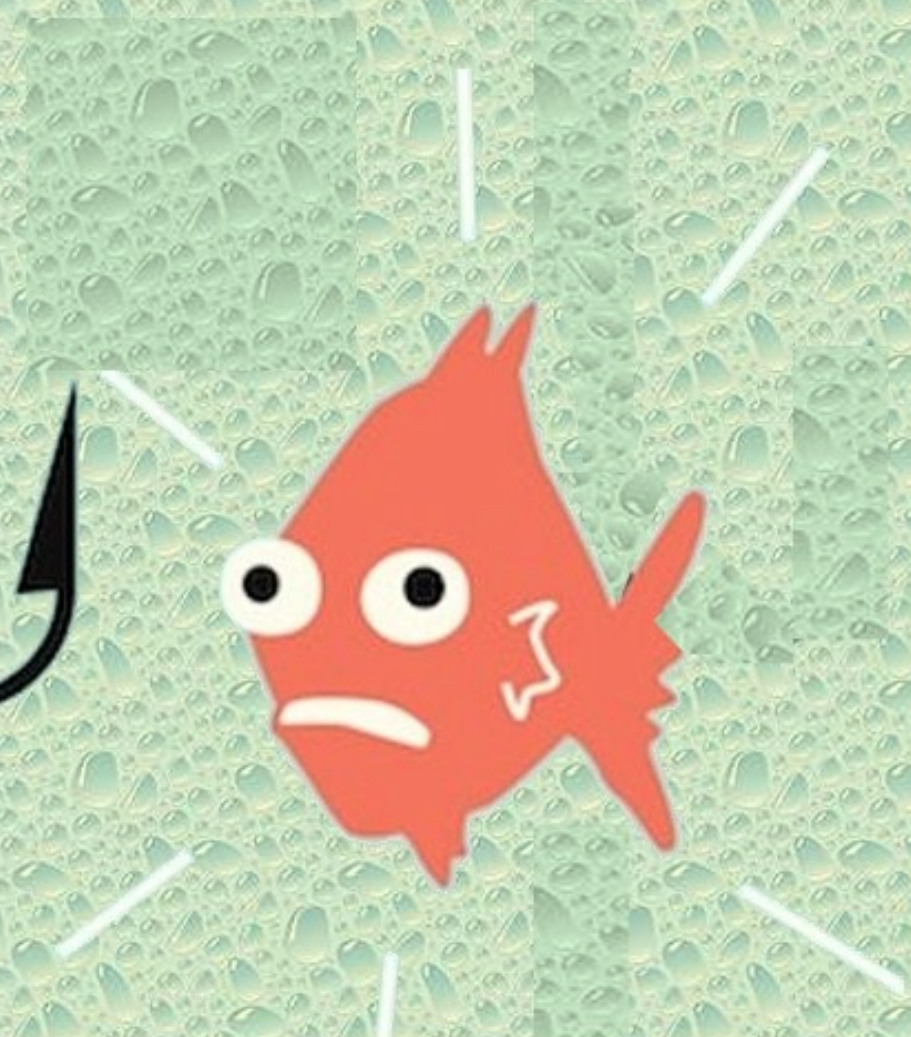
The predictions of human PK were compared across animals for both slopes, using a number of different metrics.

CONCLUSION

The rabbit/ β_{rabbit} pairing provided the most predictive estimates. However, the β_{global} values (.729, 0.961, and 0.242 for CL, V, and $t_{1/2}$) also support the use of the common slope values to make initial estimations of human parameter values.



Your Poster TITLE



Your Poster TITLE



WOW!

**You WON'T BELIEVE the
impact that WEIGHT has on the
pharmacokinetics of drug X!!**

**REVEALED!! The two
MOST IMPACTFUL
covariates on drug X!**

**What you don't know
MIGHT KILL YOU!**

**Learn the SHOCKING truth
about the PK of drug X!!**

**5 facts about the PK of drug X:
#3 will BLOW...YOUR... MIND!**



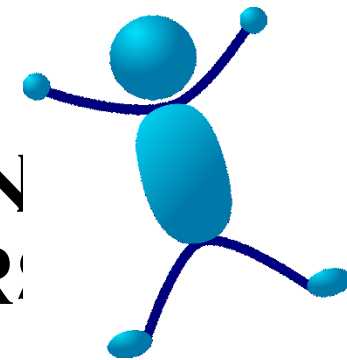
OMG!

PREDICTION OF PHARMACOKINETIC PARAMETERS IN HUMANS ON THE BASIS OF ALLOMETRIC SCALING USING A “GLOBAL” SLOPE



CONCLUSION: The rabbit/ β_{rabbit} pairing provided the most predictive estimates. However, the β_{global} values (.729, 0.961, and 0.242 for CL, V, and t1/2) also support the use of the common slope values to make initial estimations of human parameter values

NICK HOLFORD IS RIGHT!
FIXED ALLOMETRIC SLOPES CAN PREDICT HUMAN PK PARAMETERS!



IN THE RACE FOR PREDICTING HUMAN PK PARAMETERS, THE HARE WINS!



PREDICTION OF PHARMACOKINETIC PARAMETERS IN HUMANS ON THE BASIS OF ALLOMETRIC SCALING USING A "GLOBAL" SLOPE.

Stacey Tannenbaum* and Michael Mayerzohn.

College of Pharmacy and Center for Toxicology, University of Arizona, Tucson, AZ 85721

INTRODUCTION
Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation, $P = aBW^b$, where P is the parameter (clearance, volume, half-life), and BW is body weight in kg. When P vs BW data for several species are plotted on a log-log scale for a specific drug, the regression line through the data has slope b and intercept a .

It has been noted that, for a specific parameter, b values of 0 tend to be similar regardless of drug. It is common practice to use slopes of 0.75 for CL , 1.0 for V , and 0.25 for $t_{1/2}$ when making initial predictions. Using published allometric analysis of many different drugs, we examined whether this is valid.

Global defined as the average of the b -values for a parameter over all drugs. These can be used in the allometric equation to make a prediction for human P for each animal included in the publication:

$$P_{human} = P_{animal} \left(\frac{BW_{human}}{BW_{animal}} \right)^b$$

We concentrated on the most commonly used animals in allometric studies: mouse, rat, rabbit, dog, and monkey. We could then determine the probability of the parameter based on the global slope by comparing the predictions across animals, using a number of different measurements.

Since a single animal point is used to make the human prediction, it is possible that a different slope may apply to each. For each drug and for each species, we compared the animal-to-human slope, and averaged over all drugs to find B_{mouse} , B_{rat} , B_{rabbit} , B_{dog} , and B_{monkey} . We used these B values in the above equation to make predictions, and did the same analysis as with the global slope predictions.

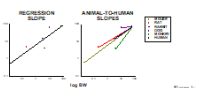
Our overall conclusion based on our analysis is that the animal slope of rabbit-to-human provided the most predictive estimation of the observed B_{human} values. However, the global values of 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$ support the use of 0.75, 1.0, and 0.25 to make initial estimations of human parameter values.

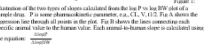
METHODS
DATA COLLECTION
Searched the literature for allometric pharmacokinetic analyses of drugs/parameters that included:
• data for multiple species (must include human)
• values for body weight (BW)
• values for clearance (CL), volume of distribution (V), and/or half-life ($t_{1/2}$)

Plotted $\log P$ vs $\log BW$ for each drug, where P is a pharmacokinetic parameter (CL, V, $t_{1/2}$).
Calculated the allometric parameters for P
• Allometric equation: $P = aBW^b$
• $\log P = \log a + b \log BW$
• $\log a =$ intercept of $\log P$ vs $\log BW$
• $b =$ slope of $\log P$ vs $\log BW$

CALCULATION OF ALLOMETRIC SLOPES
For each parameter (CL, V, $t_{1/2}$):
• Plot $\log P$ vs $\log BW$ for all drugs
• (a) regression slope, determined using all animal data in plot
• (b) animal-to-human slope, determined using one animal and the human data point:
$$b = \frac{\log(P_{human}) - \log(P_{animal})}{\log(BW_{human}) - \log(BW_{animal})}$$

• Global average (for all drugs) of all regression slopes in (a)
• Animal average (for all drugs) of all individual animal-to-human slopes in (b) (B_{mouse} , B_{rat} , B_{rabbit} , B_{dog} , B_{monkey})

REGRESSION


ANIMAL-HUMAN


METHODS, cont.
CALCULATION AND EXAMINATION OF OBSERVED
For each parameter (CL, V, $t_{1/2}$) and each species:
• Predicted human P using:
$$P_{predicted} = P_{animal} \left(\frac{BW_{human}}{BW_{animal}} \right)^b$$
 where b = global
• Compared $P_{predicted}$ to $P_{observed}$ (human P given in publication)
• Found slope and intercept of regression line through log P_{obs} vs log P_{pred}
• Calculated ratio = $\log(P_{obs}/P_{pred})$ for each observed/predicted pair
• If ratio is between -0.5 and 0.5, P_{obs} is within 1.5-fold and 0.7-fold, allowable 10-fold range
• Repeated the above steps using b from the allometric equation

CHOOSING THE MOST PREDICTIVE SPECIES AND SLOPE
• For each parameter (CL, V, $t_{1/2}$) and each species, chose pair (e.g., mouse/Rabbit)
• Compared regression line through the log P_{obs} vs log P_{pred} plot to the line of identity
• Calculated $RMSD$, the fraction of log P_{obs} vs log P_{pred} values that fell within the allowable 10-fold range
• Calculated root mean squared error for each pair

RMSD
$$RMSD = \frac{\sum (P_{obs} - P_{pred})^2}{n}$$

• Compared $RMSD$ values to $RMSD_{global}$ to determine the most predictive slope (closest to animal)
• Compared $RMSD$ across species to determine the most predictive species

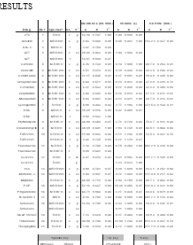
RESULTS


Table 1: Summary of drug observations. Parameters were evaluated individually. The observed animal (a) and age (b) are reported in **bold** letters, along with the coefficients of determination (R^2)

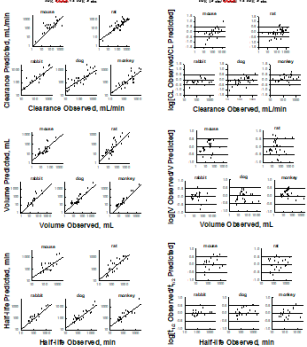
RESULTS, cont.


Figure 3: The first three rows of data: Plot of log P_{obs} vs log P_{pred} for each species. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{animal} for each species.

Figure 4: The last row of data: Plot of log P_{obs} vs log P_{pred} for the global. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{global} for each parameter.

Table 2: Human values versus the observed values for each parameter. The observed animal and B values are the regression line through the log P_{obs} vs log P_{pred} plot, as shown in Fig. 3 and 4. $RMSD$ is the root mean squared error for each drug. B_{global} is the slope of the line that best fits when the predicted values are scaled by the B_{global} value (shown in Fig. 4 and 5).

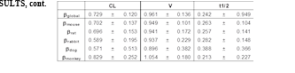
RESULTS, cont.


Table 3: The first three rows of data: Plot of log P_{obs} vs log P_{pred} for each species. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{animal} for each species.

Table 4: The last row of data: Plot of log P_{obs} vs log P_{pred} for the global. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{global} for each parameter.

Table 5: Human values versus the observed values for each parameter. The observed animal and B values are the regression line through the log P_{obs} vs log P_{pred} plot, as shown in Fig. 3 and 4. $RMSD$ is the root mean squared error for each drug. B_{global} is the slope of the line that best fits when the predicted values are scaled by the B_{global} value (shown in Fig. 4 and 5).

RESULTS, cont.
Tables 3a and 3b list the intercepts, slopes, and r^2 values of the regression lines through the log P_{obs} vs log P_{pred} plots for each species/slope pair. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{animal} for each species.

Tables 4a and 4b list the $RMSD$ values and the B_{global} values for each species/slope pair. Figures 4 and 5 show the log P_{obs} vs log P_{pred} plots for each parameter.

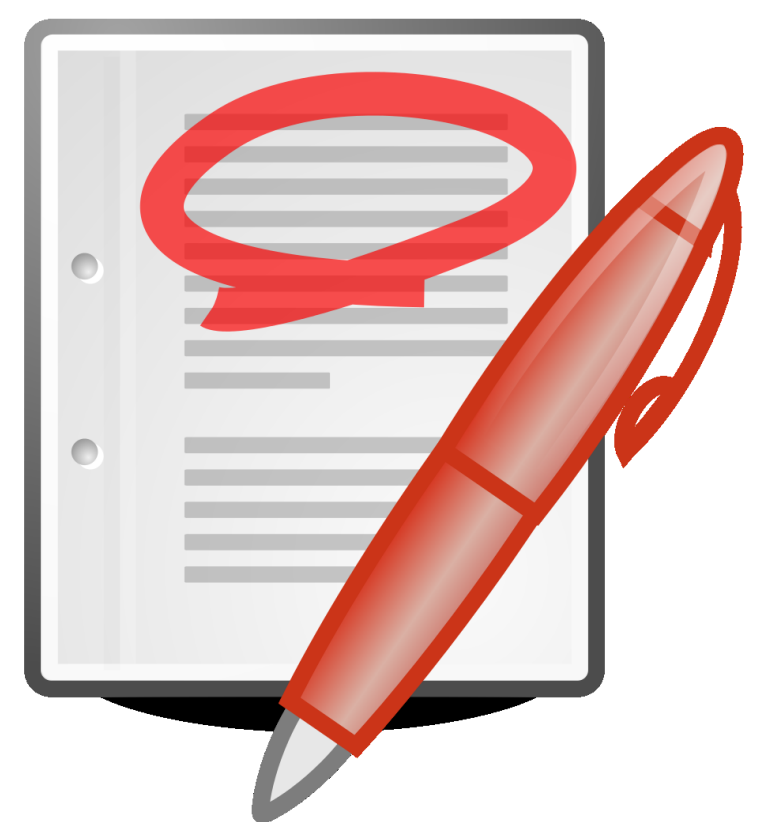
Figure 4: The last row of data: Plot of log P_{obs} vs log P_{pred} for the global. When P_{obs} and P_{pred} are the same, the global B value is 0.75 for CL , 0.961 for V , and 0.242 for $t_{1/2}$. The observed lines show the slope B_{global} for each parameter.

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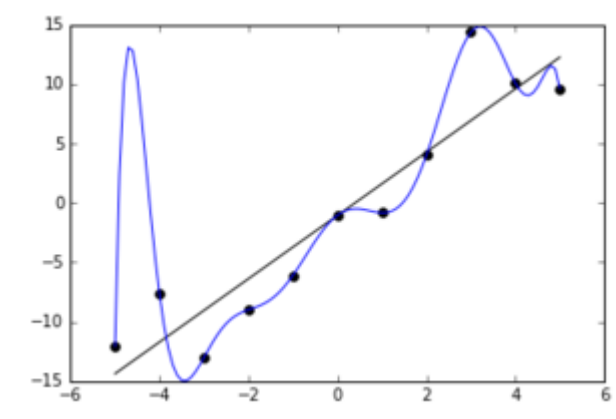
CONCLUSIONS
• Use of the slope values of 0.75 for CL , 1.0 for V , and 0.25 for $t_{1/2}$ compute initial estimates of human parameters is supported by the corresponding calculated global B values of 0.75, 0.961, and 0.242.
• In general, B_{rabbit} seemed to perform better than B_{global} for predicting the human parameter values.
• The predictions based on the rabbit for both B_{mouse} and B_{dog} consistently showed slopes, intercepts, and r^2 values closest to 1.0, low $RMSD$ values, and high B_{global} values.
• Therefore, based upon analysis of literature data, the most accurate prediction for human parameter values is found using the equation:
$$P_{human} = P_{rabbit} \left(\frac{BW_{human}}{BW_{rabbit}} \right)^b$$

• Future studies:
• Clearance values may be biased due to binding and blood flow differences between species. An analysis of subrenal clearance may give more insight.
• Variations due to the strains of each species used in different studies must be investigated.
• 28 drugs were used in this analysis.
• As more data becomes available, B values, and therefore the most predictive species and slope, may differ.

REFERENCES
1. D. D. Bagley, *Journal of Veterinary Research*, 33 (1984) 685.
2. J. L. Brouha, P. L. Lott, and G. L. Gossard, *Drug Metabolism and Pharmacokinetics*, 14 (1984) 150.
3. D. R. Brock, M. L. Frost, D. B. Martin, T. S. Sellers, N. M. Smith, D. R. Gossard, V. S. Srinivasan, R. E. Davis, J. S. Srinivasan, D. R. Gossard, *Pharmacokinetics Research*, 13 (1986) 794.
4. M. Chang, S. Srinivasan, D. Gossard, C. C. Liu, R. G. Srinivasan, R. P. Srinivasan, G. H. Miller, *Journal of Pharmaceutical Sciences*, 13 Suppl C (1987) 22.
5. J. A. Conner, G. R. Kaba, and M. P. Mendell, *Pharmacokinetics Research*, 12 (1985) 895.
6. R. L. DeBella, D. S. Inoué, J. N. Cannon, S. M. de Groot, L. T. Srinivasan, *Biopharmaceutics Research*, 11 (1977) 2405.
7. J. A. Conner, G. R. Kaba, and M. P. Mendell, *Pharmacokinetics Research*, 12 (1985) 895.
8. R. L. DeBella, D. S. Inoué, J. N. Cannon, S. M. de Groot, L. T. Srinivasan, *Biopharmaceutics Research*, 11 (1977) 2405.
9. S. Srinivasan and M. Srinivasan, *Drug Metabolism Research*, 22 (1986) 179.
10. P. G. Gali, P. G. Kohn, G. L. Gossard, W. Williams, L. Fierth, P. A. Heston, and J. G. Gossard, *Antimicrobial Agents & Chemotherapy*, 33 (1991) 2251.
11. R. K. Heston, K. H. Donn, M. J. Daniel, S. Y. Hall, A. J. Heston, C. L. Jones, *Journal of Clinical Pharmacology*, 34 (1994) 973.
12. S. Srinivasan and J. D. Srinivasan, *Journal of Pharmacy & Pharmacology*, 41 (1989) 125.
13. J. L. Brouha, P. L. Lott, A. H. Schmitt-Hoffmann, R. Srinivasan, W. Richter, and R. C. Chen, *Journal of Pharmaceutical Sciences*, 84 (1995) 1285.
14. J. P. Maddipati, M. C. Williams, and C. Stewart, *Drug Metabolism and Disposition*, 10 (1981) 18.
15. J. Maddipati, G. V. Subramanian, K. Thomsen, V. Srinivasan, G. V. Subramanian, *Pharmazie & Applied Pharmacology*, 36 (1991) 100.
16. M. Owen, W. C. Heston, and D. Blackall, *Pharmacology & Experimental Therapeutics*, 242 (1987) 96.
17. H. A. Patel, F. D. Srinivasan, P. Srinivasan, J. M. Gossard, and C. A. Chen, *Journal of Pharmaceutical Sciences*, 71 (1982) 206.
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20. J. Maddipati, M. Srinivasan, V. Srinivasan, and T. A. Srinivasan, *Journal of Pharmaceutical Sciences*, 72 (1983) 241.
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SENSITIVITY ANALYSIS FTW!



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INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: $P = aBW^b$, where P is the parameter (clearance, volume, half-life), and BW is body weight in kg. When P vs BW data for several species are plotted on a log-log scale for a specific drug, the regression line through the data has slope b and intercept a.

It has been noted that, for a specific parameter P , the values of b tend to be similar regardless of drug. It is common practice to use slopes of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

β_{global} is defined as the average of the b-values for a parameter over all drugs. These can be used in the allometric equation to make a prediction for human P for each animal included in the publication:

$$P_{human} = P_{animal} \left(\frac{BW_{human}}{BW_{animal}} \right)^{\beta_{global}}$$

We concentrated on the most commonly used animals in allometric studies: mouse, rat, rabbit, dog, and monkey. We could then determine the predictability of the parameter based on the global slope by comparing the predictions across animals, using a number of different measurements.

Since a single animal point is used to make the human prediction, it is possible that a different slope may apply to each. For each drug and for each species, we computed the animal-to-human slope, and averaged over all drugs to find β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , and β_{monkey} . We used these β values in the above equation to make predictions, and did the same analysis as with the global slope predictions.

Our overall conclusion based on our analysis is that the animal/slope pair of rabbit/rabbit provide the most predictive estimations of the observed P_{human} values. However, the β_{global} values of 0.729 for CL, 0.961 for V, and 0.242 for $t_{1/2}$ support the use of 0.75, 1.0, and 0.25 to make initial estimations of human parameter values.

METHODS

DATA COLLECTION

Searched the literature for allometric/pharmacokinetic analyses of drugs/toxicants that included:

- data for multiple species (must include human)
- values for body weight (BW)
- values for clearance (CL), volume of distribution (V), and/or half-life ($t_{1/2}$)

Plotted log P vs log BW (kg) for each drug, where P is a pharmacokinetic parameter (CL, V, $t_{1/2}$)

Calculated the allometric parameters for P

- Allometric equation: $P = aBW^b$
- $\log P = \log a + b \log BW$
- $\log a =$ intercept of log P vs log BW
- $b =$ slope of log P vs log BW

CALCULATION OF ALLOMETRIC SLOPES

For each parameter P (CL, V, $t_{1/2}$):

- Plot: log P vs log BW for all drugs
- (i) regression slope: determined using all animal data in plot
- (ii) animal-to-human slope: determined using one animal and the human data point

$$\beta_{animal} = \frac{\Delta \log P}{\Delta \log BW} = \frac{\log P_{human} - \log P_{animal}}{\log BW_{human} - \log BW_{animal}}$$

- β_{global} : average (for all drugs) of all regression slopes in (i)
- β_{animal} : average (for all drugs) of all individual animal-to-human slopes in (ii) (β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , β_{monkey})

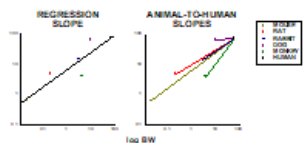


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, $t_{1/2}$. Fig A shows the regression line through all points in the plot. Fig B shows the line connecting each specific animal value to the human value. Each animal-to-human slope is calculated using the equation: $\beta_{animal} = \frac{\log P_{human} - \log P_{animal}}{\log BW_{human} - \log BW_{animal}}$

METHODS, cont.

CALCULATION AND EXAMINATION OF $\beta_{observed}$

For each parameter P (CL, V, $t_{1/2}$) and each species:

- Predicted human P using:

$$P_{predicted} = P_{animal} \left(\frac{BW_{human}}{BW_{animal}} \right)^b \quad \text{where } b = \beta_{global}$$

- Compared $\beta_{observed}$ to $\beta_{observed}$ (human P given in publication):
 - Found slope and intercept of regression line through log $\beta_{observed}$ vs log Pobs
 - Calculated ratio = log Pobs/ $\beta_{observed}$ for each observed/predicted pair
 - if ratio is between -0.5 and 0.5, $\beta_{observed}$ is between 1/3-Pobs and 3-Pobs: allowable 10-fold range
- Repeated the above steps using β_{animal} in the allometric equation

CHOOSING THE MOST PREDICTIVE SPECIES AND SLOPE

- For each parameter P (CL, V, $t_{1/2}$) and for each species/slope pair (e.g., mouse/ β_{global})
 - Compared regression line through the $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plot to the line of identity
 - Calculated $\beta_{observed}$, the fraction of Pobs/ $\beta_{observed}$ values that fell within the allowable 10-fold range
 - Calculated root mean squared error for each set
- $$RMSE = \sqrt{\frac{\sum (P_{obs} - P_{pred})^2}{n}}$$
- Compared $RMSE_{global}$ to $RMSE_{animal}$ to determine the most predictive slope (global or animal)
 - Compared $RMSE_{observed}$ across species to determine the most predictive species

RESULTS

Drug	Species	Parameter	Human P	Animal P	Animal BW	Human BW	$\beta_{observed}$	β_{animal}	R^2
Amphetamine	Human	CL	1.45						
	Human	V	1.45						
	Human	$t_{1/2}$	1.45						
	Human	CL	1.45						
	Human	V	1.45						
	Human	$t_{1/2}$	1.45						
Diazepam	Human	CL	1.45						
	Human	V	1.45						
	Human	$t_{1/2}$	1.45						
	Human	CL	1.45						
	Human	V	1.45						
	Human	$t_{1/2}$	1.45						

Table 1: Summary of drugs whose pharmacokinetic parameters were evaluated allometrically. The allometric intercept (a) and slope (b) are presented for $\beta_{observed}$ along with the coefficients of determination (R^2)

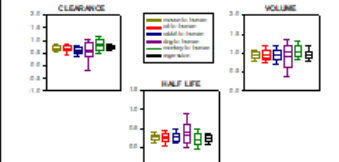


Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the β_{global} and β_{animal} values for each parameter.

RESULTS, cont.

Parameter	CL	V	$t_{1/2}$
β_{global}	0.729 ± 0.120	0.961 ± 0.136	0.242 ± 0.049
β_{mouse}	0.702 ± 0.137	0.949 ± 0.101	0.263 ± 0.104
β_{rat}	0.696 ± 0.153	0.941 ± 0.172	0.257 ± 0.141
β_{rabbit}	0.589 ± 0.195	0.937 ± 0.229	0.282 ± 0.148
β_{dog}	0.571 ± 0.513	0.890 ± 0.382	0.388 ± 0.366
β_{monkey}	0.829 ± 0.252	1.054 ± 0.180	0.213 ± 0.227

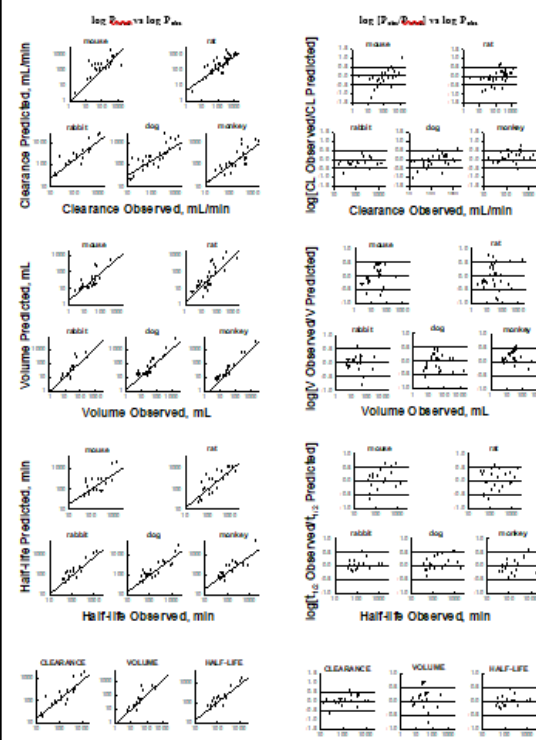


Figure 3: The first three sets of $\beta_{observed}$ plots of $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ for each species, where $\beta_{observed}$ is based on (global, β_{mouse} , β_{rat} , and β_{dog}) and Pobs are human parameter values.

Figure 4: The last set of $\beta_{observed}$ plots of $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ for the rabbit, where $\beta_{observed}$ is based on (rabbit, β_{global} , and Pobs are human parameter values).

Parameter	Global	β_{mouse}	β_{rat}	β_{rabbit}	β_{dog}	β_{monkey}
CL	0.729	0.702	0.696	0.589	0.571	0.829
V	0.961	0.949	0.941	0.937	0.890	1.054
$t_{1/2}$	0.242	0.263	0.257	0.282	0.388	0.213

Table 3: Measures used to compare the accuracy of the human predictions based on $\beta_{observed}$ (A), or based on β_{animal} (B). The slope, intercept, and R^2 values are of the regression line through the $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and $\beta_{observed}$ is the fraction of values that fall within the allowable range on each $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plot (shown in Figs. 4 and 6).

RESULTS, cont.

- Tables 3a and 3b list the intercepts, slopes, and R^2 values of the regression lines through the $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plots for each species/slope pair, where $\beta_{observed}$ is based on β_{global} and the β_{animal} slopes, respectively. Global plots are shown in Figure 3 and those for rabbit/ β_{rabbit} in Figure 5.
- If $\beta_{observed} = P_{obs}$ (ideal), then the regression line is the line of identity
 - compare slope to 1
 - compare intercept to 1 (origin of log-log plot)
 - compare R^2 to 1 (linear regression line perfectly fits the data)
 - highlighted values in these columns show the two values that are closest to 1 for each P
 - \dagger denotes the best of the two highlighted values
 - $\dagger\dagger$ signifies that 95% confidence interval around slope or intercept contains 1
- rabbit is highlighted 8/9 times in both Tables 3a and 3b
- 13/16 of the highlighted values are best
- no other animal shows the same consistency over all three parameters

- Tables 3a and 3b list the RMSE values and the $\beta_{observed}$ values for each species/slope pair. Figures 4 and 6 show the $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plots for each parameter.
- If $\beta_{observed} = P_{obs}$ (ideal), then each error would equal zero, and RMSE would equal zero
 - compare RMSE to 0
 - highlighted values in this column show the two values that are closest to 0 for each parameter
 - \dagger denotes the best of the two highlighted values
 - rabbit is highlighted 2/3 times in Table 3a
 - rabbit is highlighted all 3 times in Table 3b
 - 3/5 of the highlighted values are best
 - no other animal shows the same consistency over all three parameters

- Tables 3a and 3b list the RMSE values and the $\beta_{observed}$ values for each species/slope pair. Figures 4 and 6 show the $\log(P_{obs}/\beta_{observed})$ vs $\log P_{obs}$ plots for each parameter.
 - If 1/3-Pobs \leq $\beta_{observed}$ \leq 3-Pobs for every observation in the set, the $\beta_{observed}$ value would equal 1.0 (100% of the data falls within the allowable range)
 - compare $\beta_{observed}$ to 1.0
 - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
 - \dagger denotes the best of the two highlighted values
 - rabbit is highlighted 2 out of 3 times in both Tables 3a and 3b
 - 4/4 of the highlighted values are best
 - both dog and monkey are also highlighted 2/3 times in each table, however:
 - dog: 3/4 of the highlighted values are best
 - monkey: 1/4 of the highlighted values are best
 - therefore, rabbit still looks best, though the evidence is less dramatic for this parameter
- The following factors suggest that the most accurate predictions are based on β_{rabbit} rather than β_{global}
- In general, although the slopes and R^2 values shown in Tables 3a and 3b were virtually identical for the same animal, 9 out of 15 times the intercept for the animal was closer to 1 than the global.
 - RMSE of the animal predictions was lower than that of the global predictions 12 out of 15 times.

CONCLUSIONS

- Use of the slope values of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ to compute initial estimations of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{rabbit} seemed to perform better than β_{global} for predicting the human parameter values.
- The predictions based on the rabbit for both $\beta_{observed}$ and β_{animal} consistently showed slopes, intercepts, and R^2 values closest to 1, low RMSE values, and high $\beta_{observed}$ values.
- Therefore, based upon analysis of literature data, the most accurate prediction for human parameter values is found using the equation:

$$P_{human} = P_{rabbit} \left(\frac{BW_{human}}{BW_{rabbit}} \right)^{\beta_{rabbit}}$$
- future studies:
 - Clearance values may be biased due to binding and blood flow differences between species. An analysis of unbound intrinsic clearance may give more insight.
 - Variation due to the strains of each species used in different studies must be investigated.
 - 28 drugs were used in this analysis.
 - As more data becomes available, β values, and therefore the most predictive species and slope, may differ.

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REFERENCES

1. D. Baggot. *American Journal of Veterinary Research*, 55 (1994) 689.
2. M. Bhatti, R. Lajtha and G. Jaganmohan. *Drug Metabolism Reviews*, 15 (1984) 1355.
3. D. R. Brocks, M. I. Freed, D. E. Martin, T. S. Sellers, N. Mehd, D. R. Claxton, V. Bopanna, B. Levitt, B. E. Davies, J. Nussbaum and D. K. Jelliffe. *Pharmaceutical Research*, 13 (1996) 794.
4. M. Chung, E. Reddy, D. Leobon, C. C. Lin, E. Oden, S. Suman, R. P. Gupta and G. H. Miller. *Journal of Antimicrobial Chemotherapy*, 15 Suppl C (1985) 227.
5. A. G. G. R. G. and M. P. Meredith. *Pharmaceutical Research*, 12 (1995) 895.
6. R. L. Bhatti, D. D. Forester, J. N. Cannon, S. M. el-Deeb, and L. B. Jelliffe. *Biochemical Pharmacology*, 22 (1973) 2405.
7. S. S. Datta. *Journal of Pharmaceutical Sciences*, 74 (1985) 943.
8. C. E. Fildes, R. Battaglia and M. Scrocco. *Benedetti, Journal of Antimicrobial Chemotherapy*, 27 (1991) 517.
9. E. G. G. and M. Bhatti. *Drug Metabolism Reviews*, 22 (1990) 179.
10. G. G. J. O. Kahn, J. L. R. Williams, L. Turin, P. A. V. and J. G. *Antimicrobial Agents & Chemotherapy*, 35 (1991) 2531.
11. E. K. Hussey, K. H. Donn, M. J. Daniel, S. T. Hall, A. J. Harker and G. L. Evans. *Journal of Clinical Pharmacology*, 34 (1994) 975.
12. S. S. Ibrahim and F. D. Boudreau. *Journal of Pharmacy & Pharmacology*, 41 (1989) 829.
13. S. G. Jaganmohan. *Journal of Pharmacy & Pharmacology*, 46 (1994) 196.
14. T. Lave, B. L. A. H. Schmitt-Hoffmann, B. W. Richter and R. C. Chou. *Journal of Pharmaceutical Sciences*, 84 (1995) 1285.
15. P. M. G. M. G. Williams and J. C. Stewart. *Drug Metabolism & Disposition*, 16 (1988) 18.
16. J. G. G. O. Osaka, K. Garcia, K. Thomsen, V. L. and G. Meng. *Toxicology & Applied Pharmacology*, 136 (1996) 75.
17. M. Owens, W. C. Hardwick and D. Blackall. *Journal of Pharmacology & Experimental Therapeutics*, 242 (1987) 96.
18. B. A. Patel, F. D. Boudreau, R. F. Schmitt, J. M. Gallo and C. K. Chu. *Journal of Pharmacokinetics & Dynamics*, 13 (1990) 206.
19. A. Puigdemont, R. G. De Mora and M. J. *Journal of Pharmaceutical Sciences*, 80 (1991) 1106.
20. L. S. A. B. I. L. and M. B. *Drug Metabolism & Disposition*, 16 (1988) 749.
21. Y. Sawada, M. Y. Sugiyama and T. I. *Journal of Pharmacokinetics & Biopharmaceutics*, 12 (1984) 241.
22. L. B. S. and S. L. Beal. *Journal of Pharmacokinetics & Biopharmaceutics*, 9 (1981) 503.



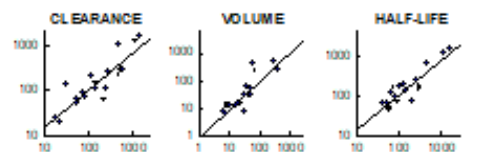
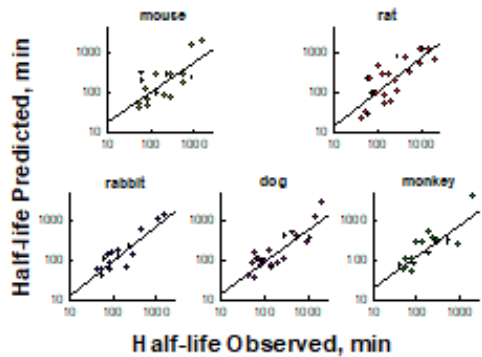
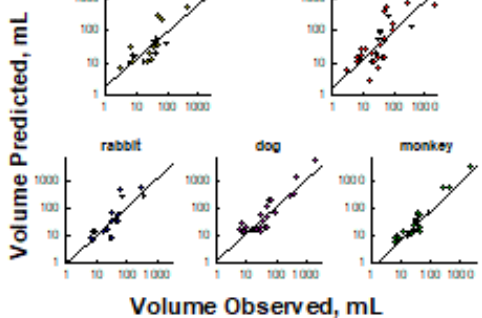
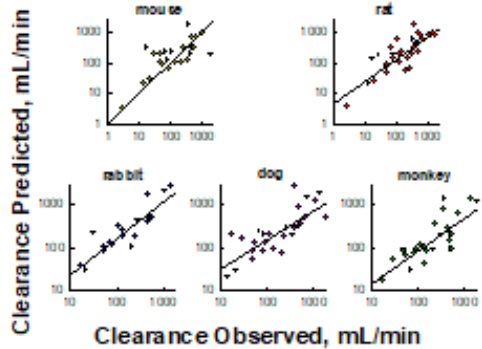
Drug	Ref.	species*	CL [†]	V [‡]	Clearance (mL/min)			Volume (L)			Half life (min)		
					a	b	r ²	a	b	r ²	a	b	r ²
3TC	1	RDH	s	β	13.16	0.767	1.00	1.90	0.848	0.98			
Acivicin	2	MRDmH	s	β	4.03	0.604	0.98	0.65	0.942	1.00	113.24	0.337	0.95
Ara-C	3	MDmH	r		3.92	0.789	0.99						
AZT	4	MRDmH	s	ss	25.94	0.963	0.98	1.09	1.046	0.99			
AZT		MRDmH	r		13.57	0.830	0.97						
Caffeine	5	MRmH	s	β	6.26	0.739	0.98	0.79	1.005	1.00	90.70	0.253	0.91
Cefazolin	6	MRrDmH	s	ss	4.51	0.679	0.97	0.18	0.939	0.99	29.35	0.266	0.93
Cefmetazole	6	MRrDmH	s	ss	12.27	0.595	0.92	0.27	0.851	0.98	18.98	0.295	0.90
Cefoperazone	6	MRrDmH	s	ss	6.69	0.571	0.82	0.23	0.913	0.99	37.48	0.318	0.74
Cefotetan	6	MRrDmH	s	ss	6.32	0.533	0.85	0.22	0.938	0.99	32.49	0.350	0.86
Cefpiramide	6	MRrDmH	ε					1	0.814	0.93	47.18	0.412	0.91
Moxalactam	6	MRrDmH	ε					1	0.921	1.00	38.78	0.213	0.91
Cyclosporine	7	RrDH	ε					7	1.189	1.00	372.59	0.139	0.22
DDC	8	MRmH	ε					2	0.988	0.97			
DDC		MRmH	r										
Erythromycin	9	MRrDH	ε					1	0.729	0.94	75.47	0.141	0.96
Oleandomycin	9	MRDH	ε					3	0.738	0.98	59.51	0.066	0.56
FCE22101	10	RrDmH	ε					1	1.246	0.98	13.53	0.341	0.76
FCE22101		RrDmH	r	β	4.64	0.735	0.86	0.22	1.178	0.97			
Fluconazole	11	MRDH	s	β	1.16	0.700	0.99	0.75	0.959	1.00	502.28	0.228	0.90
Fluconazole		MRrDH	r		0.80	0.691	0.99						
GLQ223	12	RmH	s	ss	6.97	0.676	0.93	0.31	0.853	0.99	121.71	0.148	0.50
GLQ223		RmH		β				1.23	0.813	1.00			



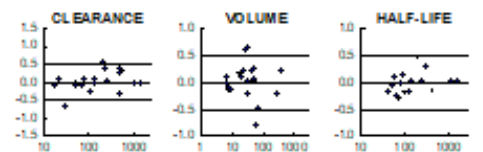
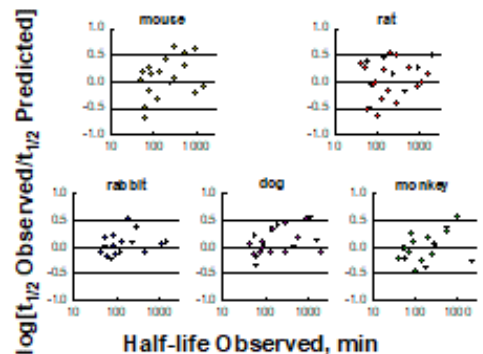
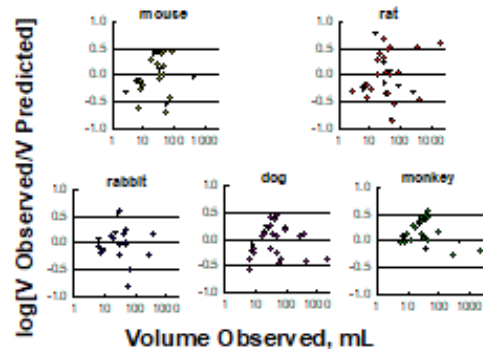
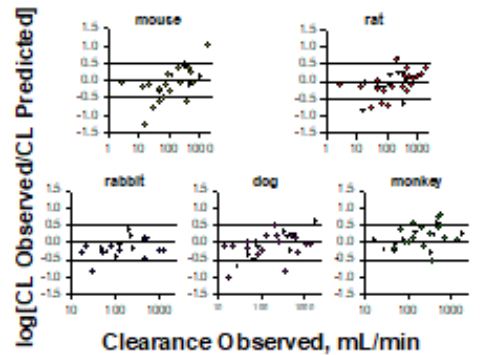


TRUST
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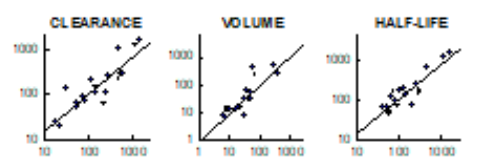
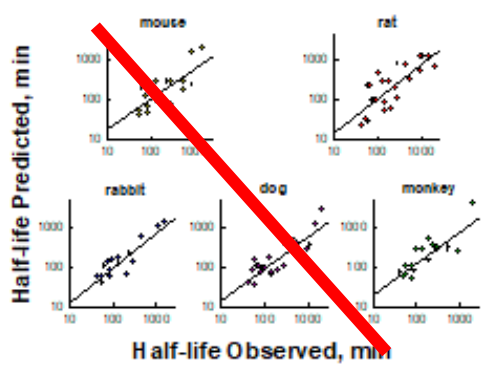
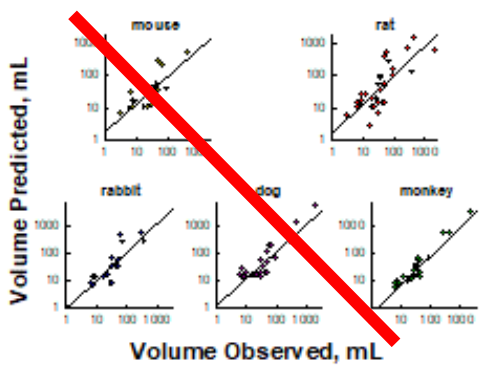
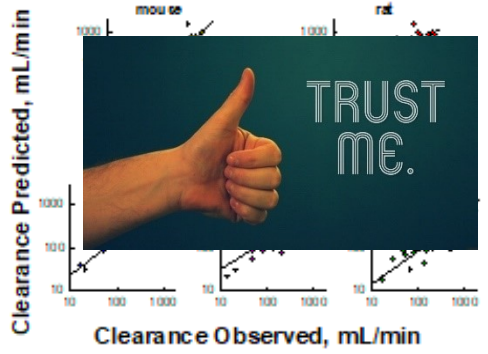
$\log P_{pred}$ vs $\log P_{obs}$



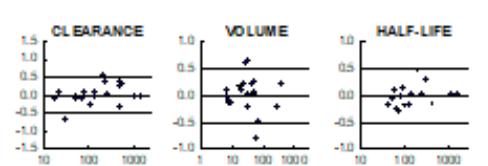
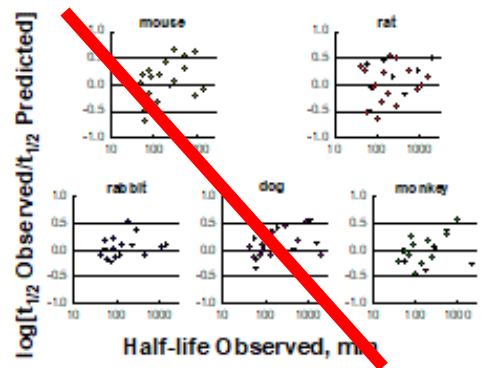
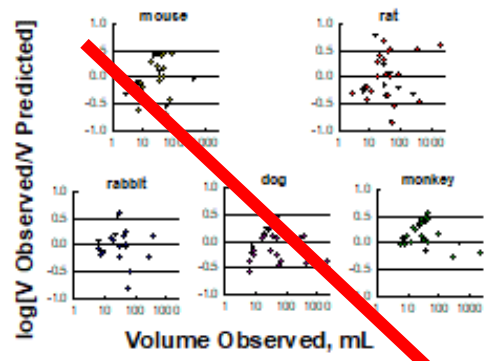
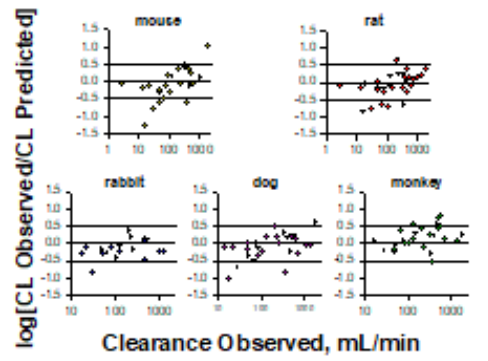
$\log [P_{obs}/P_{pred}]$ vs $\log P_{obs}$

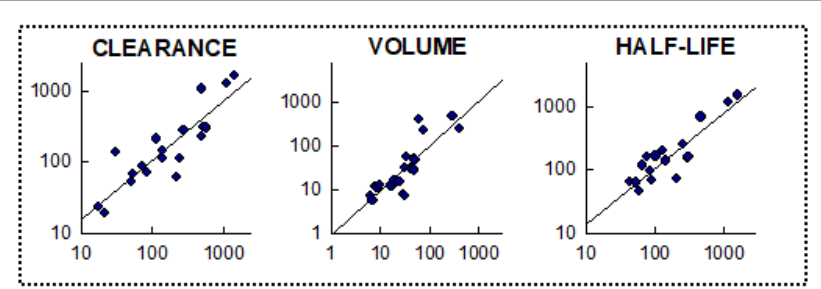
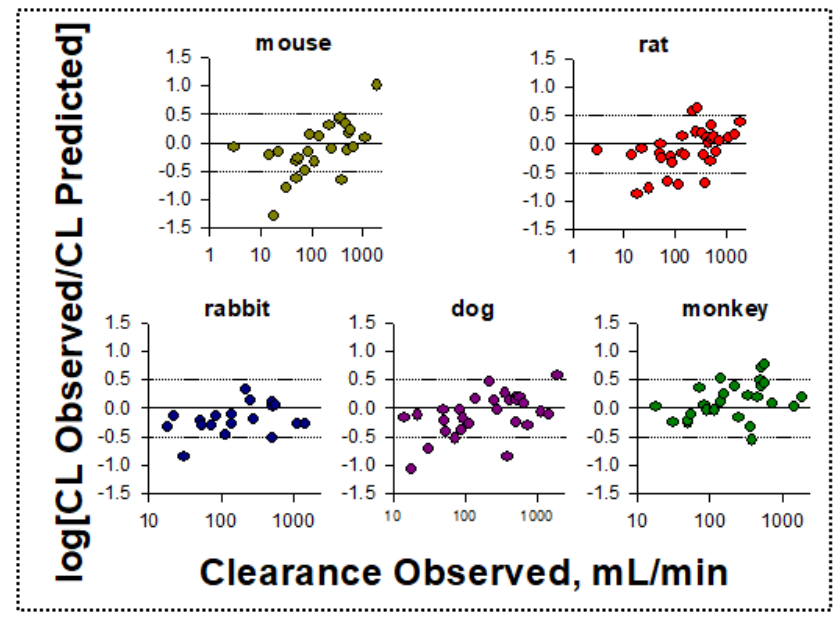
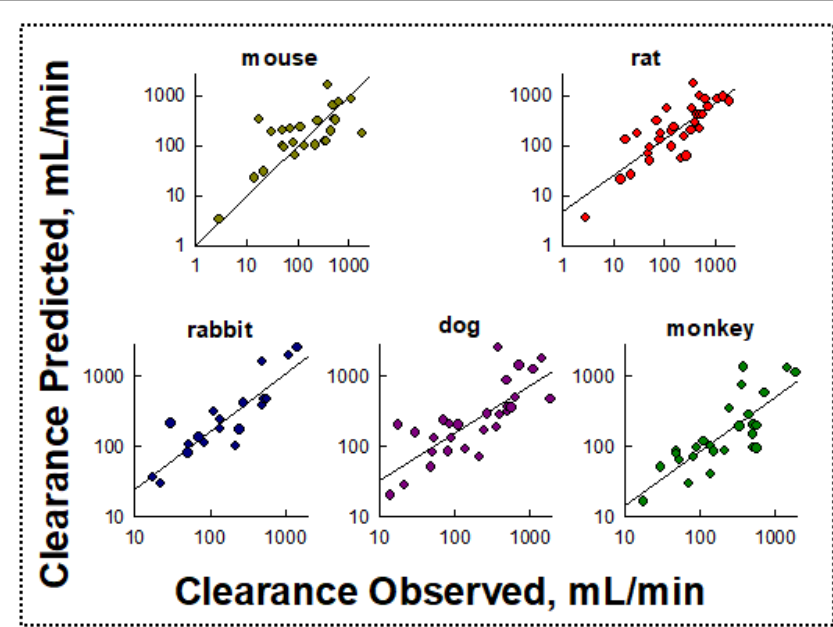
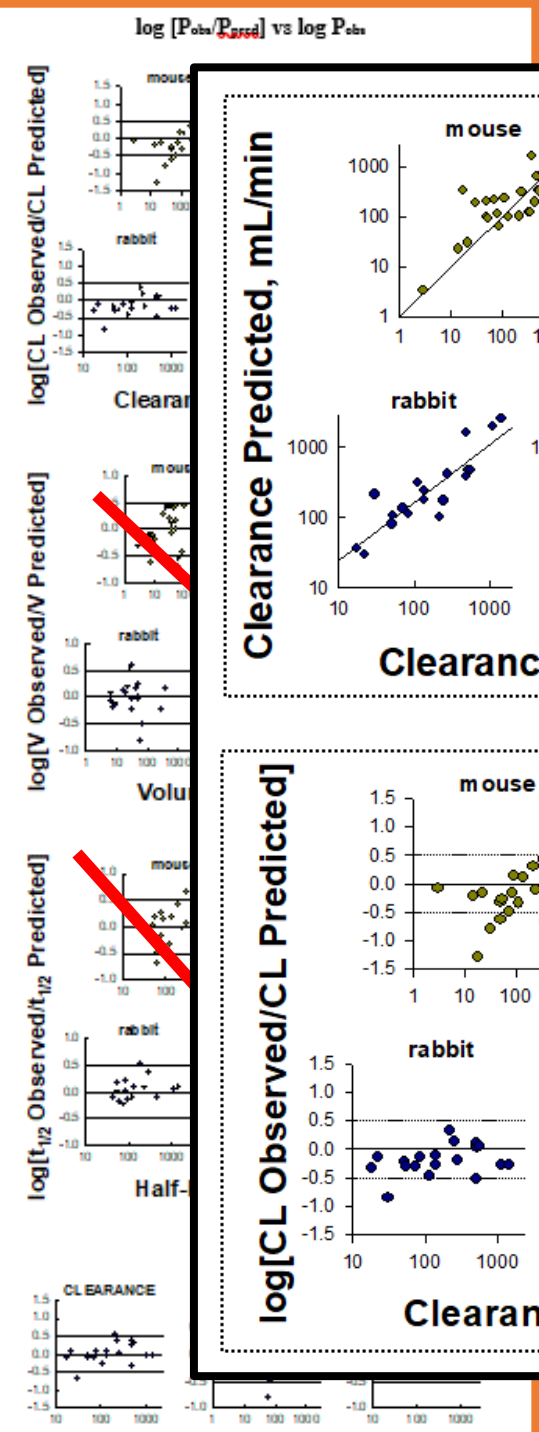
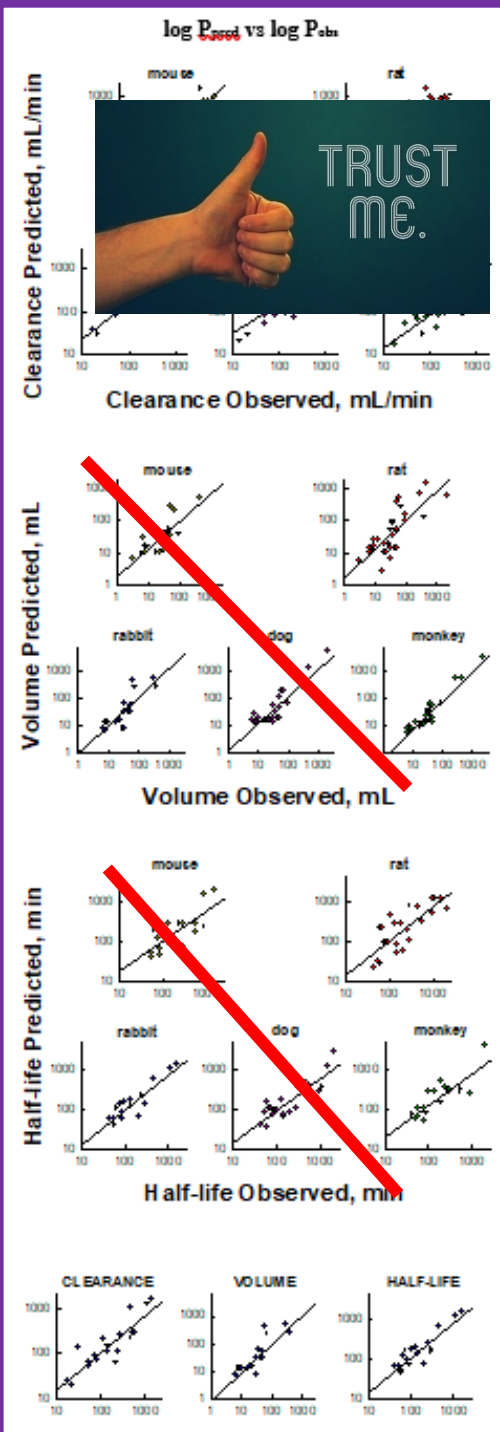


$\log P_{pred}$ vs $\log P_{obs}$



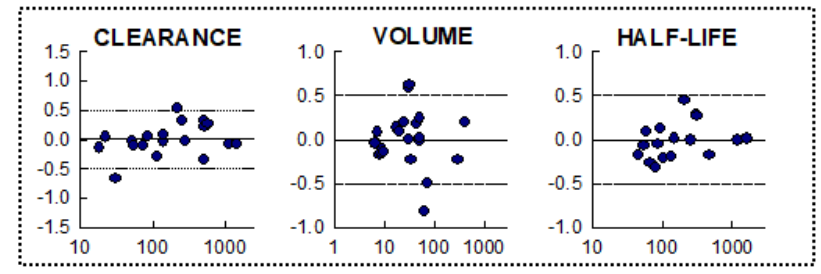
$\log [P_{obs}/P_{pred}]$ vs $\log P_{obs}$





Left: Log-log plot of human predicted clearance ($CL_{pred,global}$) vs observed (CL_{obs}), split by species; *other parameter plots available on request*

Right: Log-log plot of $P_{pred,rabbit}$ vs P_{obs} , where P is clearance, volume, and half-life, respectively; *other species plots available on request*



Left: Log-log plot of ($CL_{obs}/CL_{pred,global}$) vs CL_{obs} , split by species; *other parameter plots available on request*

Right: Log-log plot of ($P_{obs}/P_{pred,rabbit}$) vs CL_{obs} , where P is clearance, volume, and half-life, respectively; *other species plots available on request*

Reference lines are 10-fold range (1/3 – 3 fold CL_{obs})

METHODS

DATA COLLECTION

Searched the literature for allometric/pharmacokinetic analyses of drugs/toxicants that included:

- data for multiple species (must include human)
- values for body weight (BW)
- values for clearance (CL), volume of distribution (V), and/or half life (t1/2)

Plotted log P vs log BW(kg) for each drug, where P is a pharmacokinetic parameter (CL, V, t1/2)

Calculated the allometric parameters for P

- Allometric equation: $P = a \cdot BW^b$
- $\log P = \log a + b \cdot \log BW$
 - $\log a = \text{intercept of } \log P \text{ vs } \log BW$
 - $b = \text{slope of } \log P \text{ vs } \log BW$

CALCULATION OF ALLOMETRIC SLOPES

For each parameter P (CL, V, t1/2):

- Plot: log P vs log BW for all drugs
- (i) regression slope: determined using all animal data in plot
- (ii) animal-to-human slope: determined using one animal and the human data point

$$= \frac{\Delta(\log P)}{\Delta(\log BW)} = \frac{\log P_{\text{human}} - \log P_{\text{animal}}}{\log BW_{\text{human}} - \log BW_{\text{animal}}}$$

- β_{global} : average (for all drugs) of all regression slopes in (i)
- β_{animal} : average (for all drugs) of all individual animal-to-human slopes in (ii) (β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , β_{monkey})

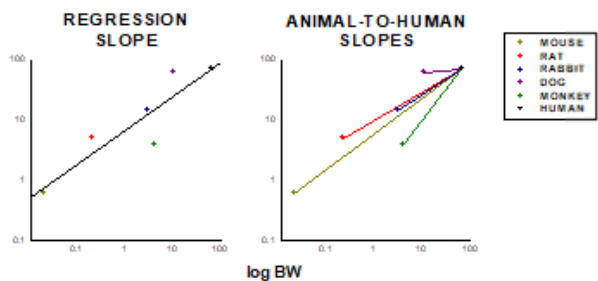


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human value. Each animal-to-human slope is calculated using the equation

$$\frac{\Delta \log P}{\Delta \log BW}$$

METHODS, cont.

CALCULATION AND EXAMINATION OF $P_{\text{predicted}}$

For each parameter P (CL, V, t1/2) and each species:

- Predicted human P using:

$$P_{\text{predicted}} = P_{\text{animal}} \cdot \left(\frac{BW_{\text{animal}}}{BW_{\text{human}}} \right)^b \quad \text{where } b = \beta_{\text{global}}$$

- Compared $P_{\text{predicted}}$ to P_{observed} (human P given in publication):
 - Found slope and intercept of regression line through log P_{pred} vs log P_{obs}
 - Calculated ratio = $\log(P_{\text{obs}}/P_{\text{pred}})$ for each observed/predicted pair
 - if ratio is between -0.5 and 0.5, P_{pred} is between $1/3 \cdot P_{\text{obs}}$ and $3 \cdot P_{\text{obs}}$: allowable 10-fold range
- Repeated the above steps using $b = \beta_{\text{animal}}$ in the allometric equation

CHOOSING THE MOST PREDICTIVE SPECIES AND SLOPE

- For each parameter P (CL, V, t1/2) and for each species/slope pair (e.g., mouse/ β_{global})
- Compared regression line through the [log P_{pred} vs log P_{obs}] plot to the line of identity
- Calculated fringe, the fraction of $P_{\text{obs}}/P_{\text{pred}}$ values that fell within the allowable 10-fold range
- Calculated root mean squared error for each set

$$RMSE = \sqrt{\frac{\sum (P_{\text{obs}} - P_{\text{pred}})^2}{n}}$$

- Compared $RMSE_{\text{global}}$ to $RMSE_{\text{animal}}$ to determine the most predictive slope (global or animal)
- Compared RMSE across species to determine the most predictive species

- Assume basic knowledge
- Limit repetition
- SLASH as much text as you can!



BTW...this guy's name is SLASH. He is the guitarist for the band Guns-n-Roses.

PREDICTION OF PHARMACOKINETIC PARAMETERS IN HUMANS ON THE BASIS OF ALLOMETRIC SCALING USING A "GLOBAL" SLOPE.

Stacey Tannenbaum* and Michael Mayersohn.

College of Pharmacy and Center for Toxicology, University of Arizona, Tucson, AZ 85721

INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: $P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^b$, where P is the parameter (clearance, volume, half-life), and BW is body weight in kg. When P vs BW data for several species are plotted on a log-log scale for a specific drug, the regression line through the data has slope b and intercept a.

It has been noted that, for a specific parameter P, the values of b tend to be similar regardless of drug. It is common practice to use slopes of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

Global b is defined as the average of the b-values for a parameter over all drugs. These can be used in the allometric equation to make a prediction for human P for each animal included in the publication:

$$P_{\text{human}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^{b_{\text{global}}}$$

We concentrated on the most commonly used animals in allometric studies: mouse, rat, rabbit, dog, and monkey. We could then determine the predictability of the parameter based on the global slope by comparing the predictions across animals, using a number of different measurements.

Since a single animal point is used to make the human prediction, it is possible that a different slope may apply to each. For each drug and for each species, we computed the animal-to-human slope, and averaged over all drugs to find β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , and β_{monkey} . We used these β values in the above equation to make predictions, and did the same analysis as with the global slope predictions.

Our overall conclusion based on our analysis is that the animal/slope pair of rabbit/rabbit provided the most predictive estimations of the observed human values. However, the global values of 0.729 for CL, 0.961 for V, and 0.242 for $t_{1/2}$ support the use of 0.75, 1.0, and 0.25 to make initial estimations of human parameter values.

METHODS

DATA COLLECTION

Searched the literature for allometric/pharmacokinetic analyses of drugs/toxins that included:

- data for multiple species (must include human)
- values for body weight (BW)
- values for clearance (CL), volume of distribution (V), and/or half life ($t_{1/2}$)

Plotted log P vs log BW(kg) for each drug, where P is a pharmacokinetic parameter (CL, V, $t_{1/2}$)

- Allometric equation: $P = a + b \log BW$
- $\log P = \log a + b \log BW$
- $\log a =$ intercept of log P vs log BW
- $b =$ slope of log P vs log BW

CALCULATION OF ALLOMETRIC SLOPES

- For each parameter P (CL, V, $t_{1/2}$):
- Plot: log P vs log BW for all drugs
- (i) regression slope: determined using all animal data in plot
- (ii) animal-to-human slope: determined using one animal and the human data point
- $b_{\text{global}} = \frac{\Delta \log P}{\Delta \log BW} = \frac{\log P_{\text{human}} - \log P_{\text{animal}}}{\log BW_{\text{human}} - \log BW_{\text{animal}}}$
- β_{global} : average (for all drugs) of all regression slopes in (i)
- β_{animal} : average (for all drugs) of all individual animal-to-human slopes in (ii) (β_{mouse} , β_{rat} , β_{rabbit} , β_{dog} , β_{monkey})

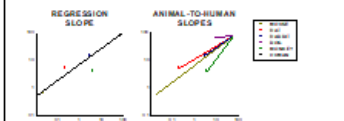


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, $t_{1/2}$. Fig A shows the regression line through all points in the plot. Fig B shows the line connecting each specific animal value to the human value. Each animal-to-human slope is calculated using the equation:

METHODS, cont.

CALCULATION AND EXAMINATION OF PREDICTED

For each parameter P (CL, V, $t_{1/2}$) and each species:

- Predicted human P using: $P_{\text{predicted}} = P_{\text{animal}} \left(\frac{BW_{\text{human}}}{BW_{\text{animal}}} \right)^b$ where $b = \beta_{\text{global}}$
- Compared Predicted to Observed (human P given in publication):
- Found slope and intercept of regression line through log Ppred vs log Pobs
- Calculated ratio = log(Pobs/Ppred) for each observed/predicted pair
 - if ratio is between -0.5 and 0.5, Ppred is between 1/3-Pobs and 3-Pobs: allowable 10-fold range
- Repeated the above steps using $b = \beta_{\text{animal}}$ in the allometric equation

CHOOSING THE MOST PREDICTIVE SPECIES AND SLOPE

- For each parameter P (CL, V, $t_{1/2}$) and for each species/slope pair (e.g., mouse/ β_{mouse})
- Compared regression line through the (log Ppred vs log Pobs) plot to the line of identity
- Calculated fringe, i.e. the fraction of Pobs/Ppred values that fell within the allowable 10-fold range
- Calculated root mean squared error for each set
- $RMSSE = \sqrt{\frac{\sum (P_{\text{obs}} - P_{\text{pred}})^2}{n}}$
- Compared RMSSEglobal to RMSSEanimal to determine the most predictive slope (global or animal)
- Compared RMSSE across species to determine the most predictive species

RESULTS

Drug	Species	CL (mL/min)	V (L)	$t_{1/2}$ (min)
Amoxicillin	Human	1000	100	100
Amoxicillin	Mouse	100	10	10
Amoxicillin	Rat	200	20	20
Amoxicillin	Rabbit	300	30	30
Amoxicillin	Dog	400	40	40
Amoxicillin	Monkey	500	50	50
...

Table 1: Summary of drugs whose pharmacokinetic parameters were evaluated allometrically. The allometric intercept (a) and slope (b) are presented for each parameter along with the coefficient of determination (r²)

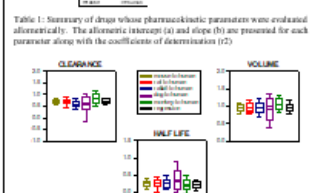


Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the β_{global} and β_{animal} values for each parameter.

RESULTS, cont.

Parameter	CL	V	$t_{1/2}$
β_{global}	0.729 ± 0.120	0.961 ± 0.136	0.242 ± 0.040
β_{mouse}	0.702 ± 0.137	0.949 ± 0.101	0.263 ± 0.104
β_{rat}	0.696 ± 0.153	0.941 ± 0.172	0.261 ± 0.141
β_{rabbit}	0.589 ± 0.190	0.937 ± 0.229	0.282 ± 0.148
β_{dog}	0.571 ± 0.513	0.896 ± 0.382	0.368 ± 0.366
β_{monkey}	0.829 ± 0.252	1.054 ± 0.180	0.213 ± 0.227

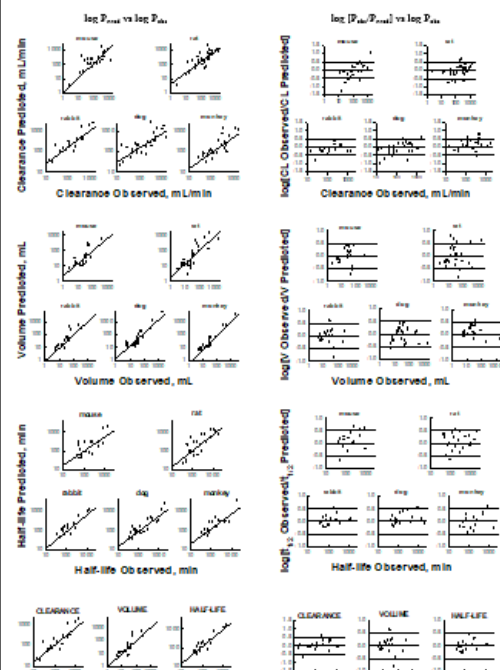


Figure 3: The first three sets of plots: Plots of log Ppred vs log Pobs for each species, where Ppred is based on β_{global} . Ppred and Pobs are human parameter values.

Figure 4: The last set of plots: Plots of log Ppred vs log Pobs for the rabbit, where Ppred is based on β_{rabbit} . Ppred and Pobs are human parameter values.

Figure 5: The first three sets of plots: Plots of log Ppred (Pobs) vs log Pobs for each species, where Ppred is based on log Pobs. Ppred and Pobs are human parameter values. The reference line shows the range 1/3-Pobs to 3-Pobs.

Figure 6: The last set of plots: Plots of log Ppred (Pobs) vs log Pobs for the rabbit, where Ppred is based on β_{rabbit} . Ppred and Pobs are human parameter values. The reference line shows the range 1/3-Pobs to 3-Pobs.

Parameter	Species	β_{global}	β_{animal}	r ²	Fringe	RMSSE
CL	Human	0.729	0.729	0.961	100%	0.100
	Mouse	0.729	0.702	0.949	95%	0.100
	Rat	0.729	0.696	0.941	92%	0.100
	Rabbit	0.729	0.589	0.937	85%	0.100
	Dog	0.729	0.571	0.896	70%	0.100
V	Human	0.961	0.961	0.961	100%	0.050
	Mouse	0.961	0.949	0.949	95%	0.050
	Rat	0.961	0.941	0.941	92%	0.050
	Rabbit	0.961	0.937	0.937	90%	0.050
	Dog	0.961	0.937	0.937	90%	0.050
$t_{1/2}$	Human	0.242	0.242	0.961	100%	0.010
	Mouse	0.242	0.263	0.949	95%	0.010
	Rat	0.242	0.261	0.941	92%	0.010
	Rabbit	0.242	0.282	0.937	90%	0.010
	Dog	0.242	0.368	0.896	70%	0.010

Table 2: Measures used to compare the accuracy of the human prediction based on β_{global} (A), or based on β_{animal} (B). The slope, intercept, and r² values are of the regression line through the log Ppred vs log Pobs plot (shown in Figs. 3 and 5); RMSSE is the root mean squared error of each set; and Fringe is the fraction of values that fall within the allowable range on each log Ppred vs log Pobs plot (shown in Figs. 4 and 6).

RESULTS, cont.

Tables 3a and 3b list the intercepts, slopes, and r² values of the regression lines through the log Ppred vs log Pobs plots for each species/slope pair, where Ppred is based on β_{global} and the β_{animal} slopes, respectively. Global plots are shown in Figure 3 and those for rabbit/ β_{rabbit} in Figure 5.

- If Ppred = Pobs (ideal), then the regression line is the line of identity
- compare slope to 1
- compare intercept to 1 (origin of log-log plot)
- compare r² to 1 (linear regression line perfectly fits the data)
- highlighted values in these columns show the two values that are closest to 1 for each P
 - β_{rabbit} denotes the best of the two highlighted values
 - β_{rabbit} highlights that 95% confidence interval around slope or intercept contains 1
- rabbit is highlighted 8/9 times in both Tables 3a and 3b
- 13/16 of the highlighted values are best
- no other animal shows the same consistency over all three parameters

Tables 3a and 3b list the RMSE values and the f_{allow} values for each species/slope pair. Figures 4 and 6 show the (log (Pobs/Ppred) vs log Pobs) plots for each parameter.

- If Ppred = Pobs (ideal), then each error would equal zero, and RMSE would equal zero
- compare RMSE to 0
 - highlighted values in this column show the two values that are closest to 0 for each parameter
 - β_{rabbit} denotes the best of the two highlighted values
- rabbit is highlighted 2/3 times in Table 3a
- rabbit is highlighted all 3 times in Table 3b
- 3/5 of the highlighted values are best
- no other animal shows the same consistency over all three parameters

Tables 3a and 3b list the RMSE values and the f_{allow} values for each species/slope pair. Figures 4 and 6 show the (log (Pobs/Ppred) vs log Pobs) plots for each parameter.

- If 1/3-Pobs \leq Ppred \leq 3-Pobs for every observation in the set, the fringe value would equal 1.0 (100% of the data falls within the allowable range)
- compare fringe to 1.0
 - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
 - β_{rabbit} denotes the best of the two highlighted values
 - rabbit is highlighted 2 out of 3 times in both Tables 3a and 3b
 - 4/4 of the highlighted values are best
- both dog and monkey are also highlighted 2/3 times in each table, however:
 - dog: 2/4 of the highlighted values are best
 - monkey: 1/4 of the highlighted values are best
- therefore, rabbit still looks best, though the evidence is less dramatic for this parameter

The following factors suggest that the most accurate predictions are based on β_{rabbit} rather than β_{global} .

- In general, although the slopes and r² values shown in Tables 3a and 3b were virtually identical for the same animal, 9 out of 15 times the intercept for the animal was closer to 1 than the global.
- RMSE of the animal predictions was lower than that of the global predictions 12 out of 15 times.

CONCLUSIONS

- Use of the slope values of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ to compute initial estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{rabbit} seemed to perform better than β_{global} for predicting the human parameter values.
- The predictions based on the rabbit for both β_{rabbit} and β_{global} , consistently showed slopes, intercepts, and r² values closest to 1, low RMSE values, and high f_{allow} values.
- Therefore, based upon analysis of literature data, the most accurate prediction for human parameter values is found using the equation:

$$P_{\text{human}} = P_{\text{rabbit}} \left(\frac{BW_{\text{human}}}{BW_{\text{rabbit}}} \right)^{\beta_{\text{rabbit}}}$$

- future studies:
 - Clearance values may be biased due to binding and blood flow differences between species. An analysis of unbound intrinsic clearance may give more insight.
 - Variation due to the strains of each species used in different studies must be investigated.
 - 28 drugs were used in this analysis.
 - As more data becomes available, β values, and therefore the most predictive species and slope, may differ.

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REFERENCES

1. J. D. Baggett, *American Journal of Veterinary Research*, 55 (1994) 689.
2. M. Bonati, R. Latini and G. Topponi, *Drug Metabolism Reviews*, 15 (1984) 1355.
3. D. R. Brooks, M. J. Freed, D. E. Martin, T. S. Sellers, N. Mehdi, D. R. Cimen, V. Boppina, B. Levitt, B. E. Davies, J. Nemunaitis and D. K. Jorkasky, *Pharmaceutical Research*, 13 (1996) 794.
4. M. Clume, E. Radwanski, D. Loebenberg, C. S. Lin, E. Oden, S. Szymchowicz, R. P. Gural and G. H. Miller, *Journal of Antimicrobial Chemotherapy*, 15 Suppl C (1985) 227.
5. C. A. Cruz, G. R. Kelm and M. P. Meredith, *Pharmaceutical Research*, 12 (1995) 895.
6. B. L. Dedrick, D. D. Forrester, J. M. Cannon, S. M. ed-Desser and L. B. Mellett, *Biochemical Pharmacology*, 22 (1973) 2405.
7. G. S. Dulha, *Journal of Pharmaceutical Sciences*, 74 (1985) 943.
8. C. E. Fythiopoulos, R. Battaglia and M. Strolin Benedetti, *Journal of Antimicrobial Chemotherapy*, 27 (1991) 517.
9. F. Gaspari and M. Bonati, *Drug Metabolism Reviews*, 22 (1990) 179.
10. G. Gatti, J. O. Kahn, J. Lifson, R. Williams, L. Turin, P. A. Volberding and J. G. Gamberoglio, *Antimicrobial Agents & Chemotherapy*, 35 (1991) 2531.
11. E. K. Hussey, K. H. Deon, M. J. Daniel, S. T. Hall, A. J. Harker and G. L. Evans, *Journal of Clinical Pharmacology*, 34 (1994) 975.
12. S. S. Ibrahim and F. D. Boudinot, *Journal of Pharmacy & Pharmacology*, 41 (1989) 829.
13. S. G. Jezequel, *Journal of Pharmacy & Pharmacology*, 46 (1994) 196.
14. T. Lave, B. Levet-Traff, A. H. Schmitt-Hoffmann, B. Mergemuth, W. Richter and R. C. Chou, *Journal of Pharmaceutical Sciences*, 84 (1995) 1285.
15. J. P. McGovern, M. G. Williams and J. C. Stewart, *Drug Metabolism & Dispensation*, 16 (1988) 18.
16. J. Mondeni, G. Osaka, K. Garcia, K. Thomsen, V. Licko and G. Meng, *Toxicology & Applied Pharmacology*, 136 (1996) 75.
17. S. M. Owens, W. C. Hanwick and D. Blackall, *Journal of Pharmacology & Experimental Therapeutics*, 242 (1987) 96.
18. B. A. Patel, F. D. Boudinot, R. F. Schinazi, J. M. Gallo and C. K. Chu, *Journal of Pharmacokinetics & Dynamics*, 13 (1990) 206.
19. A. Puigdemont, R. Guitari, F. De Mora and M. Arboix, *Journal of Pharmaceutical Sciences*, 80 (1991) 1106.
20. L. Sangalli, A. Bertolotti, L. Jiriano and M. Bonati, *Drug Metabolism & Dispensation*, 16 (1988) 749.
21. Y. Sawada, M. Hanano, Y. Sugiyama and T. Iga, *Journal of Pharmacokinetics & Biopharmaceutics*, 12 (1984) 241.
22. L. B. Sheiner and S. L. Beal, *Journal of Pharmacokinetics & Biopharmaceutics*, 9 (1981) 503.



The summary

NICK HOLFORD IS RIGHT! FIXED ALLOMETRIC SLOPES CAN PREDICT HUMAN PK PARAMETERS

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BRIEF SUMMARY

ometry scales animal pharmacokinetic data to humans using the equation: $P_{human} = a \cdot BW^b$, where P is the parameter (clearance, volume, half-life), and BW is body weight (kg), and a and b are the slope and intercept of the log-log plot, respectively. Fixed slopes (0.75, 1.0 and 0.25 for CL, V, and t_{1/2}) are commonly used for initial human predictions. Using published allometric analyses of 28 drugs, we examined whether this is a valid practice, and explored whether any particular species is more predictive.

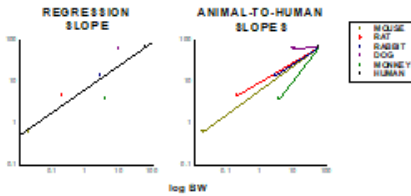
Two slope values were used in the allometric equation to make a prediction for human PK parameters from animal data:

- β_{global} = the average of the b-values for a parameter over all drugs.
- $\beta_{species}$ = animal-to-human slope for each drug and parameter computed for mouse, rat, rabbit, dog, and monkey, averaged over all drugs

The predictions of human PK were compared across animals for both slopes, using a number of different metrics. The rabbit/ β_{rabbit} pair provided the most predictive estimates. However, the β_{global} values (0.729, 0.961, and 0.242 for CL, V, and t_{1/2}) also support the use of the common slope values to make initial estimations of human parameter values.

METHODS

- Searched the literature for allometric pharmacokinetic analyses of drugs/toxicants including data from animals and humans:
 - body weight (BW)
 - clearance (CL), volume of distribution (V), and/or half-life (t_{1/2})
- For each drug and parameter P (CL, V, t_{1/2}), calculated the intercept (a) and up to 6 different slopes (b) of the allometric relationship: $P = a \cdot BW^b$
 - regression slope: using all animal data in plot (left figure)
 - animal-to-human slope: using single animal and human values (right figure)



- Human values for each parameter P were predicted for each drug and applicable species:

$$P_{pred} = P_{animal} \left(\frac{BW_{human}}{BW_{animal}} \right)^b$$

where b is:

β_{global} = average regression slope across all drugs for each parameter P
 $\beta_{species}$ = average animal-to-human slope across all drugs for each parameter P each individual species (mouse, rat, rabbit, dog, monkey)

Used P_{obs} vs P_{pred} (from publication) using the following metrics:
 Regression line through $\log P_{obs}$ vs $\log P_{pred}$ for all drugs
 compare slope and intercept to line of identity (=1 for log-log plot)
 compare r^2 to 1 (perfect correspondence)
 Calculated ratio = $\log(P_{obs}/P_{pred})$ for each observed/predicted pair
 -0.5 to 0.5 log scale = 1/3- P_{obs} to 3- P_{obs} (allowable 10-fold range)
 f_{range} = fraction of P_{obs}/P_{pred} values that fell within the range
 Calculated root mean squared error (RMSE) for each set:

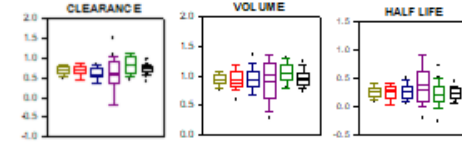
$$RMSE = \sqrt{\frac{\sum (P_{obs} - P_{pred})^2}{n}}$$

- Target value = 0
- Compared RMSE to RMSE_{global} for most predictive slope (global vs animal)
- Compared RMSE across species for the most predictive species

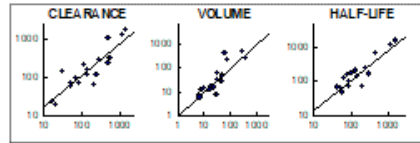
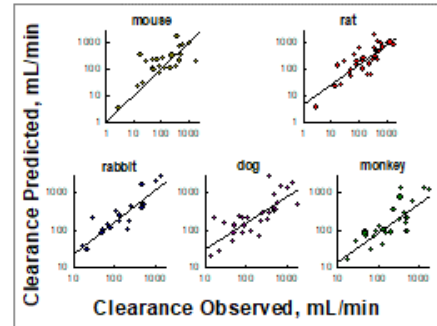
RESULTS

Relevant data from 28 compounds was identified in the literature search (references available upon request)

- Distribution of the regression slopes and animal-to-human slopes are shown below
- The mean of each group is shown by a dotted line and represents the global and animal values for each parameter, shown also in the table below

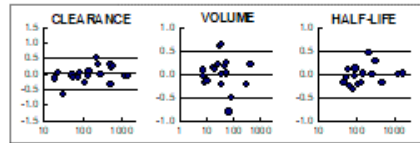
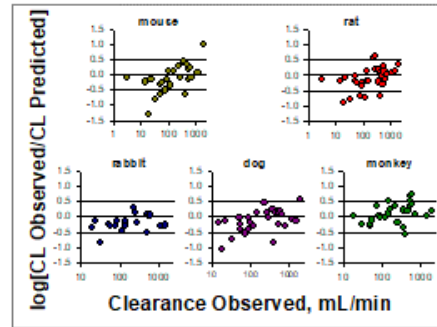


	CL	V	t _{1/2}
β_{global}	0.729 ± 0.120	0.961 ± 0.136	0.242 ± 0.067
β_{mouse}	0.702 ± 0.137	0.949 ± 0.101	0.263 ± 0.071
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β_{dog}	0.571 ± 0.513	0.896 ± 0.382	0.388 ± 0.366
β_{monkey}	0.829 ± 0.252	1.054 ± 0.180	0.213 ± 0.227



Left: Log-log plot of human predicted clearance ($CL_{predicted}$) vs observed (CL_{obs}), split by species; other parameter plots available on request

Right: Log-log plot of $P_{predicted}$ vs P_{obs} , where P is clearance, volume, and half-life, respectively; other species plots available on request



Left: Log-log plot of $(\frac{CL_{obs}}{CL_{pred}})$ vs CL_{obs} split by species; other parameter plots available on request

Right: Log-log plot of $(\frac{P_{obs}}{P_{pred}})$ vs CL_{obs} , where P is clearance, volume, and half-life, respectively; other species plots available on request

Reference lines are 10-fold range (1/3 - 3-fold)

Metrics for determination of "best" slope and species are shown below for clearance; other parameter results available upon request

- The two values closest to ideal across the 5 species identified for each P and metric as shown below

	β_{global}					β_{rabbit}					
	log P_{pred} vs log P_{obs}	INT.	SLOPE	r^2	f_{range}	RMSE	log P_{pred} vs log P_{obs}	INT.	SLOPE	r^2	f_{range}
mouse	0.94	0.592	0.52	0.80	449	7.27	0.591	0.52	0.76	427	
rat	4.75	0.733	0.67	0.78	370 [†]	3.91	0.734	0.68	0.78	381	
rabbit	3.50	0.837 [†]	0.76	0.85 [†]	427	2.31 [†]	0.830 [†]	0.77	0.89 [†]	183 [†]	
dog	8.89	0.677	0.61	0.86	532	5.28	0.675	0.61	0.82	454	
monkey	2.48 [†]	0.770 [†]	0.63	0.88	308	3.12 [†]	0.777 [†]	0.65	0.88	349	

Highlight: two best values across species for each metric (targets: 1 for intercept, slope, r^2 , f_{range} ; 0 for RMSE)

[†] best of the two highlighted values for a given metric and parameter

* 95% confidence interval around slope or intercept contains 1

Consistent color coding

...vs the number of highlighted values for each animal across...
 ...number of those values that were the closest to the id...
 ...and r^2 of log-log plot for P_{obs} vs P_{pred} ; ideal values = 1 (compared...
 ...); 9 possible "best values" (3 per metric)
 ... $f_{range}=0$ (no error); 3 possible best values
 ... $f_{range}=1$ (100% of values in allowable range); 3 possible best values

Overall, the rabbit shows the strongest results across all metrics

	Regression P_{pred} vs P_{obs}		RMSE		f _{range}	
	global	animal	global	animal	global	animal
Mouse	0(0)	0(0)	1(1)	1(1)	0(0)	0(0)
Rat	3(0)	3(0)	1(1)	1(0)	0(0)	0(0)
Rabbit	8(6)	8(7)	2(1)	3(2)	2(2)	2(2)
Dog	4(1)	4(1)	1(0)	0(0)	2(1)	2(1)
Monkey	3(2)	3(1)	1(0)	1(0)	2(0)	2(1)

* 100% of values in range

Metrics also suggest that the most accurate predictions are based on β_{rabbit} rather than β_{global}

- 9 of 15 times the intercept for the animal was closer to 1 than the global.
- RMSE of the animal predictions were lower than that of the global predictions 12 of 15 times

CONCLUSIONS

- Use of the slope values of 0.75 for CL, 1.0 for V, and 0.25 for t_{1/2} to compute initial estimates of human parameters is supported by the corresponding calculated global β values of 0.729, 0.961, and 0.242.
- In general, β_{rabbit} seemed to perform better than β_{global} for predicting the human parameter values.
- The predictions based on the rabbit for both β_{global} and β_{rabbit} consistently showed slopes, intercepts, and r^2 values closest to 1, low RMSE values, and high f_{range} values.
- Therefore, based upon analysis of literature data, the most accurate prediction for human parameter values is found using the equation:

$$P_{human} = P_{rabbit} \left(\frac{BW_{human}}{BW_{rabbit}} \right)^{\beta_{rabbit}}$$



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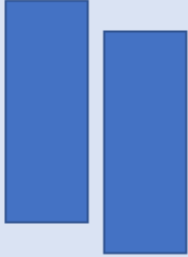
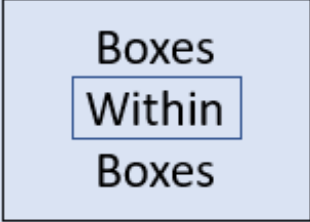
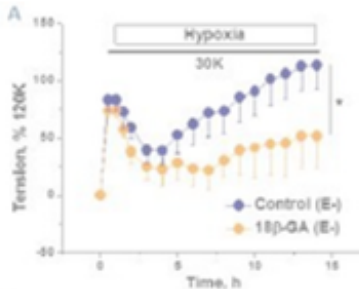
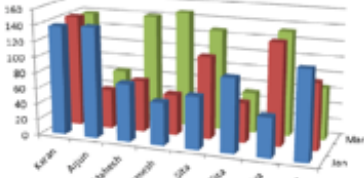
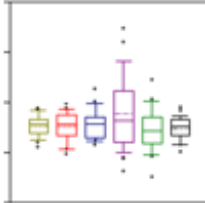



QR code (it works!)

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- Spelling
- Grammar
- Formatting
- Color consistency
- Equations
- Legibility
- Clarity
- Figure and table annotation, legends
- Spacing
- Clutter/filler
- Repetition

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<p>Gratuitously patterned background</p>	<table border="1" data-bbox="677 568 1052 815"> <thead> <tr> <th rowspan="2">Drug</th> <th rowspan="2">Ref</th> <th rowspan="2">Species</th> <th rowspan="2">E²</th> <th rowspan="2">V²</th> <th colspan="3">Distance (µm/s)</th> <th colspan="3">Volume (µ)</th> <th colspan="3">Half life (min)</th> </tr> <tr> <th>a</th> <th>b</th> <th>r²</th> <th>a</th> <th>b</th> <th>r²</th> <th>a</th> <th>b</th> <th>r²</th> </tr> </thead> <tbody> <tr> <td>3BC</td> <td>1</td> <td>RDJ</td> <td>s</td> <td>β</td> <td>0.16</td> <td>0.07</td> <td>1.00</td> <td>1.90</td> <td>0.98</td> <td>0.98</td> <td></td> <td></td> <td></td> </tr> <tr> <td>AcAc</td> <td>2</td> <td>SDRch</td> <td>s</td> <td>β</td> <td>1.03</td> <td>0.09</td> <td>0.98</td> <td>0.05</td> <td>0.90</td> <td>1.00</td> <td>10.24</td> <td>0.20</td> <td>0.95</td> </tr> <tr> <td>Ac-C</td> <td>3</td> <td>SDRch</td> <td>r</td> <td>β</td> <td>0.50</td> <td>0.06</td> <td>0.98</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>AT</td> <td>4</td> <td>SDRch</td> <td>s</td> <td>α</td> <td>2.54</td> <td>0.92</td> <td>0.98</td> <td>1.08</td> <td>1.06</td> <td>0.98</td> <td></td> <td></td> <td></td> </tr> <tr> <td>AT</td> <td>5</td> <td>SDRch</td> <td>r</td> <td>β</td> <td>0.57</td> <td>0.00</td> <td>0.97</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Caffeine</td> <td>5</td> <td>SDRch</td> <td>s</td> <td>β</td> <td>0.26</td> <td>0.06</td> <td>0.98</td> <td>0.76</td> <td>1.00</td> <td>1.00</td> <td>9.07</td> <td>0.20</td> <td>0.98</td> </tr> <tr> <td>Clonidine</td> <td>6</td> <td>SDRch</td> <td>s</td> <td>α</td> <td>1.01</td> <td>0.05</td> <td>0.97</td> <td>0.16</td> <td>0.99</td> <td>0.98</td> <td>26.05</td> <td>0.20</td> <td>0.98</td> </tr> <tr> <td>Clozapine</td> <td>6</td> <td>SDRch</td> <td>s</td> <td>α</td> <td>0.27</td> <td>0.06</td> <td>0.92</td> <td>0.27</td> <td>0.91</td> <td>0.98</td> <td>18.98</td> <td>0.20</td> <td>0.98</td> </tr> <tr> <td>Clonidine</td> <td>6</td> <td>SDRch</td> <td>s</td> <td>α</td> <td>0.69</td> <td>0.01</td> <td>0.92</td> <td>0.23</td> <td>0.95</td> <td>0.98</td> <td>21.68</td> <td>0.20</td> <td>0.91</td> </tr> <tr> <td>Clozapine</td> <td>6</td> <td>SDRch</td> <td>s</td> <td>α</td> <td>0.12</td> <td>0.03</td> <td>0.95</td> <td>0.23</td> <td>0.98</td> <td>0.98</td> <td>20.49</td> <td>0.20</td> <td>0.98</td> </tr> </tbody> </table> <p>The wall of numbers</p>	Drug	Ref	Species	E ²	V ²	Distance (µm/s)			Volume (µ)			Half life (min)			a	b	r ²	a	b	r ²	a	b	r ²	3BC	1	RDJ	s	β	0.16	0.07	1.00	1.90	0.98	0.98				AcAc	2	SDRch	s	β	1.03	0.09	0.98	0.05	0.90	1.00	10.24	0.20	0.95	Ac-C	3	SDRch	r	β	0.50	0.06	0.98							AT	4	SDRch	s	α	2.54	0.92	0.98	1.08	1.06	0.98				AT	5	SDRch	r	β	0.57	0.00	0.97							Caffeine	5	SDRch	s	β	0.26	0.06	0.98	0.76	1.00	1.00	9.07	0.20	0.98	Clonidine	6	SDRch	s	α	1.01	0.05	0.97	0.16	0.99	0.98	26.05	0.20	0.98	Clozapine	6	SDRch	s	α	0.27	0.06	0.92	0.27	0.91	0.98	18.98	0.20	0.98	Clonidine	6	SDRch	s	α	0.69	0.01	0.92	0.23	0.95	0.98	21.68	0.20	0.91	Clozapine	6	SDRch	s	α	0.12	0.03	0.95	0.23	0.98	0.98	20.49	0.20	0.98	 <p>Fuzzy pictures</p>	 <p>Bad 3D plots</p>	 <p>Figures without legends, axis labels</p>
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How to create a better research poster in less time (including templates) — #betterposter PART 1



Non-Cognitive
Predictors
5

International students,
perseverance and a sense of
responsibility are extra
important for predicting
year GPA.



15:40 / 19:31

Scroll for details
↓



Video: https://www.youtube.com/watch?v=1RwJbhkCA58&ab_channel=MikeMorrison

ASCP 2021 ANNUAL MEETING

REIMAGINING THE THERAPEUTIC LANDSCAPE

Reduce text and increase engagement!
#ASCP2021 **POSTER 2.0**

ROADMAP ASCPT is encouraging all poster presenters to adopt the new poster template created by Mike Morrison (@mikemorrison) that uses less text and is easier for attendees to view.

- 1 Watch Mike Morrison's how-to video: [How to Create a Better Research Poster](#)
- 2 Download the [template](#)
- 3 Create a document with your additional abstract information
- 4 Create a QR code to link to that document
- 5 Fill out the template

Benefits

- Maximize insight for attendees
- Easy to make
- Includes "need to know" information

PRINT!

BEST PRACTICES

Font Spacing

- Main finding = 72 to 150-point font,
- All other text = 36-point font
- Use Helvetica, Arial, or Verdana
- Use font colors that contrast with the background
- 1.2 to 2.0 line-spacing

Images and Graphics

- Include captions
- Do not place text over images
- Image resolution = 300 dots per inch, avoid images below 250Kb

Skeptical?
See [trending posts from actual presenters who have used the Poster 2.0 Format](#).

QR code

- Link to a full study, full abstract, presenter's contact details, or even the data set
- Link to a Google Doc with sharing set to view-only (you can keep editing the document until you present)
- 5x5 inches, 13x13 centimeters
- QR Code Creator Websites:
 - <http://www.mobile-barcodes.com/>
 - <https://www.qr-code-generator.com/>

ANATOMY OF A POSTER

Silent Presenter Bar

Concentrated summary of your intro, methods, and results that can be skimmed in 1-5 minutes. Located intentionally far away from the presenter's personal space. For when an attendee wants more detail but the presenter is busy (or they just don't feel like interacting).

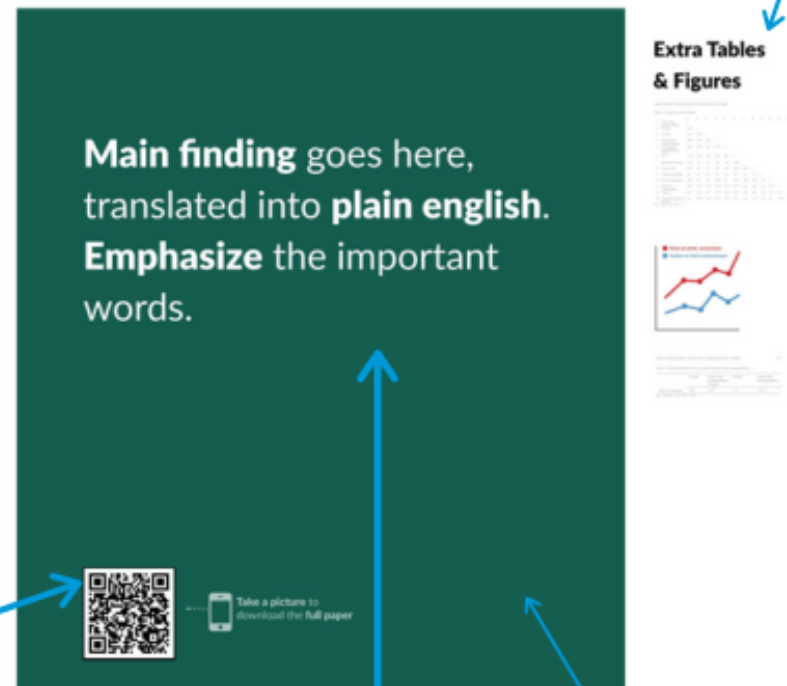


QR Code

Point your phone camera at this and instantly download the full paper, a copy of the poster, the presenter's details... and/or even the data set powering the study.

Ammo Bar

For all the figures and tables that you feel like you need to be able to point to if somebody asks you a hard question. Leave it messy! It's just for your reference.



Main Finding

The key "takeaway" of the study is central, translated into plain english. Research on usability writing suggests that casual language is interpreted faster than formal language.

Hardly "wasted" negative space maximizes signal-to-noise ratio and helps attendees quickly find the takeaway.

Title of the Accepted Abstract
List Author(s)
Author Affiliation/Company

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

How To Use This Poster Template

Highlight this text and replace it by either typing in new text, or by copying text from a Microsoft Word document or a PowerPoint slide and pasting it in.

Font

1. Font size must be 20 points or larger.
2. Font must be left-aligned. Do not center font.
3. Use of Arial Font is strongly encouraged.

OBJECTIVE(S)

How to use this poster template.

Simply highlight this text and replace it by typing in your own text, or copy and paste your text from a MS Word document or a PowerPoint slide presentation.

METHOD(S)

Sections

Sections – Purpose, Method(s), Results, Conclusions, Charts, Pictures – may be moved and resized to fit.

Do not rename the sections. You must include Purpose, Method(s), Results, and Conclusion.

RESULT(S)

Do Not Change The Following

- The AAPS logo (the top banner must remain and no logos may be added there).
- Headings – Purpose, Methods, Results, Conclusion.
- Title, Author, Affiliation area.

Tips for a Successful Poster

- **Focus:** Convey 2-3 findings in simple, clear language.
- **Conclusion First:** Here's how many scientists read your paper: Title -> Conclusion -> Everything Else. To hook them, focus on a title and conclusion that will gain their attention.
- **Data, Data, Data:** Scientists want to see a data-driven conclusion, not a promise to do the research.
- **Titles:** The title of your poster must match exactly the accepted poster abstract.
- **Use Capitalization Sparingly:** Words and sentences written in capital letters are hard to read.
- **Use Bold to Make a Point:** Underlining and italicizing words make them hard to read.
- **Proofread:** Good spelling, grammar, and punctuation improve your credibility.
- **Use figures and pictures to tell a story:** Organize them in a way the eye can follow.
- **Less is More:** Many posters have been smothered by the weight of too many words. Simplify graphics and figures as much as possible without sacrificing accuracy. Keep cutting your text until you can use a font size big enough for someone to read from a few feet away.



The recommended font for captions is Calibri, no smaller than 18 pt. Left aligned if it refers to a figure on its left. Top aligned if the picture (graph or photo).

CONCLUSION(S)

Inserting Pictures

1. Select "INSERT" from top navigation.
2. Select "Picture."
3. Locate the file on your computer, select it, and click "insert."

Adding Graphs

Simple graphs can be created in Microsoft Excel or PowerPoint. Graphs created in scientific graphing programs (e.g. Sigma Plot, Prism, etc.) must be saved in JPEG or PNG format.

- 1
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- 8
- 9
- 0

FUND REFERENCE

Promo AAPS all meeting present where you

TITLE OF ABSTRACT AS ORIGINALLY SUBMITTED IN ABSTRACT
List Author(s)
Author Affiliation/Company

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FUNDING / GRANTS / ENDORSE / REFERENCE OR OTHER USE
Promo: How to Use
 AAPS allows you to contact attendees before and during the meeting through the app. In order to be contacted by your promotional AAPS, you must post your name on the app event, where your work area provides additional contacts for you.

Poster Statement will be placed here to replace this FPO line of copy that is just a placeholder for now.

Insert your Logos

CONTACT INFORMATION: Highlight this text and replace it.

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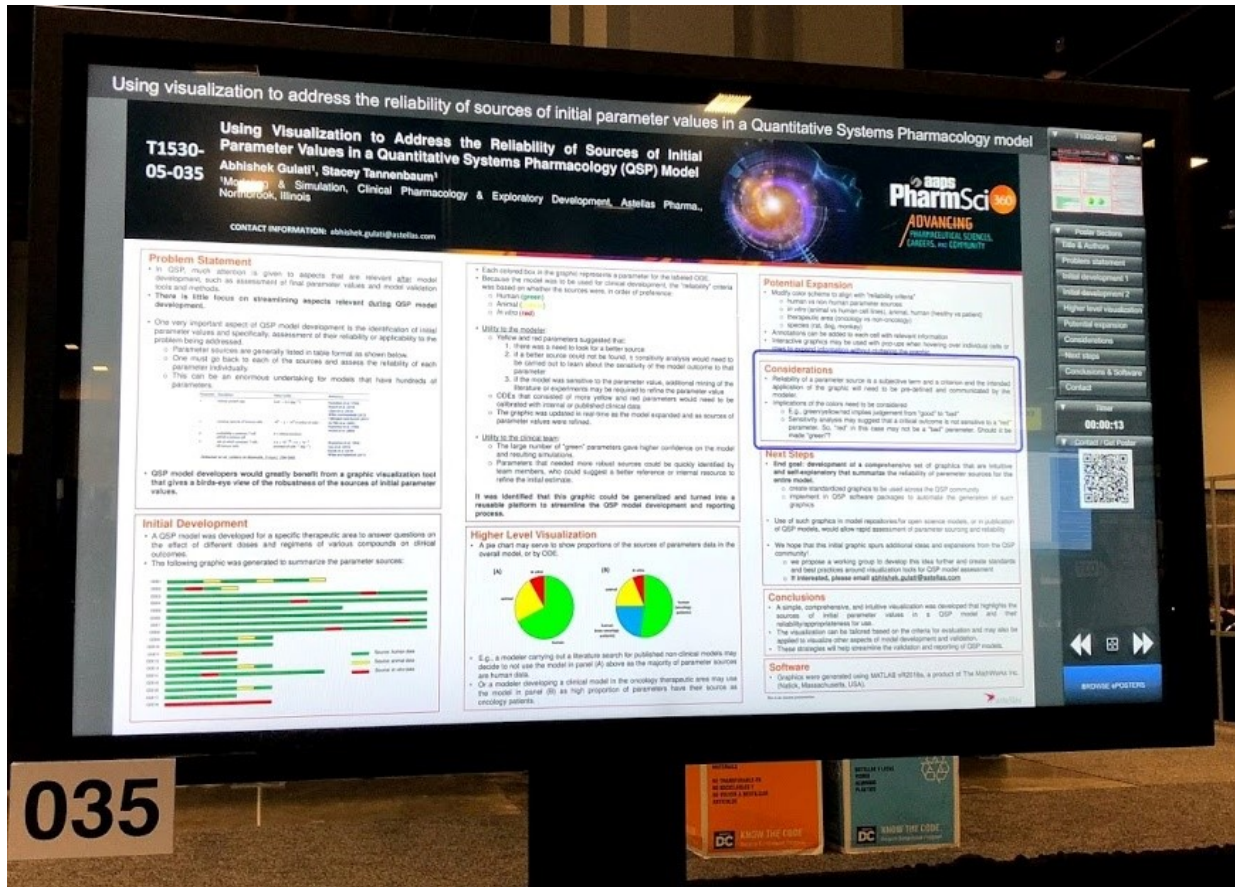
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AAPS: American Association of Pharmaceutical Scientists

<https://www.aaps.org/pharmsci/posters>



035





The Role of Calcium in the Stabilization of the NHE1-CHP3 Complex

Hans-Christian Zaun, Ph. D. Scientific Advisor, MultiLearning Group, Montreal, QC, Canada

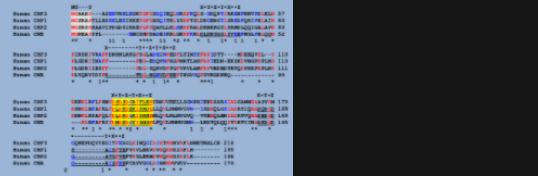
This poster is adapted for promotional purposes by Dr. Zaun, on research performed in the laboratory of Dr. John Orłowski, Professor
Department of Physiology, McGill University, Montreal, QC, Canada



ABSTRACT

Restoration of cardiac intracellular pH (pHi) following acidification is of crucial importance for the maintenance of myocardial contractility. The primary mechanism responsible for this is the function of the sodium/proton exchanger isoform 1 (NHE1). NHE1 is localized predominantly at the intercalated disks and along the transverse tubular system where it is thought to play an essential role in cardiac pH homeostasis, impulse conductance and excitation-contraction coupling. However, the factors that control the membrane targeting and regulation of NHE1 in heart are poorly understood. The calcineurin homologous protein isoform 3 (CHP3) is a cardiac predominant calcium-binding protein that interacts directly with NHE1, though the functional significance of the interaction has not yet been elucidated. This study undertook biochemical and cellular analysis to determine both the significance of the NHE1-CHP3 complex for pH regulation in cardiac tissue, as well as the significance of calcium-binding in this complex.

CALINEURIN HOMOLOGOUS PROTEIN 3



CHP3, CALCIUM & MYRISTOYLATION

N-myristoylation and Ca²⁺-binding are crucial for cell surface

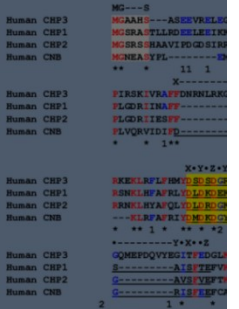
MULTILEARNING

ABSTRACT

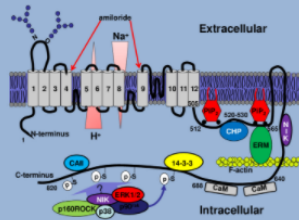
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Department of Phy

CALINE



SODIUM/PROTON EXCHANGER 1



- Highly regulated (glyco)phosphoprotein
- Present in virtually all mammalian cells, tissues and species to date
- Catalyzes electroneutral exchange between Na⁺ and H⁺

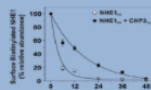
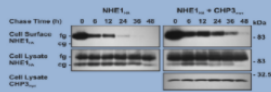
FUNCTION

- pH homeostasis (cytoplasmic and organellar)
- Cell volume regulation
- Cell Proliferation, shape, and migration.

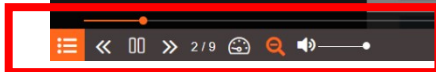
NHE1-CHP3 CO

CHP3 Promotes the Maturation of NHE1

Transient expression of NHE1 (top row) in the presence and absence of transient CHP3 expression (middle row) in the AP-1 cell line. Proteins subjected to SDS-PAGE electrophoresis and immunoblotting to detect and quantify membrane-bound fully glycosylated NHE1 (fg). Detection of GAPDH was used as a quantification control.



SODIUM/PROTON EXCHANGER 1





The Role of Calcium in the Stabilization of the NHE1-CHP3 Complex

Hans-Christian Zaun, Ph. D. Scientific Advisor, MultiLearning Group, Montreal, QC, Canada

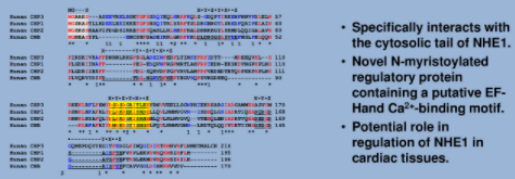
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CALINEURIN HOMOLOGOUS PROTEIN 3

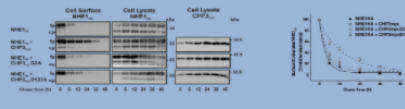


- Specifically interacts with the cytosolic tail of NHE1.
- Novel N-myristoylated regulatory protein containing a putative EF-Hand Ca²⁺-binding motif.
- Potential role in regulation of NHE1 in cardiac tissues.

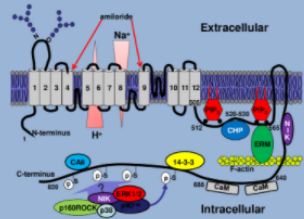
CHP3, CALCIUM & MYRISTOYLATION

N-myristoylation and Ca²⁺-binding are crucial for cell surface stability of the NHE1/CHP3 complex

Cells expressing NHE1 alone or co-expressing NHE1 with wild type CHP3, N-myristoylation-deficient CHP3, or calcium-binding deficient CHP3 were subject to cell surface labeling. Cells returned to growth media and proteins were harvested in varying time points. Proteins were subjected to SDS-PAGE and immunoblotting. The remaining cell surface NHE1 was detected and quantified in relation to the initial quantity (t=0) (graph). Cell lysate NHE1 and CHP3 were detected as quantification controls.



SODIUM/PROTON EXCHANGER 1



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- Present in virtually all mammalian cells, tissues and species to date
- Catalyzes electroneutral exchange between Na⁺ and H⁺

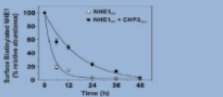
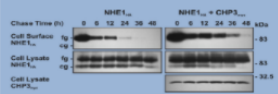
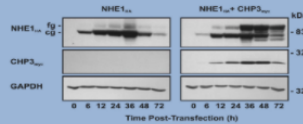
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NHE1-CHP3 COMPLEX

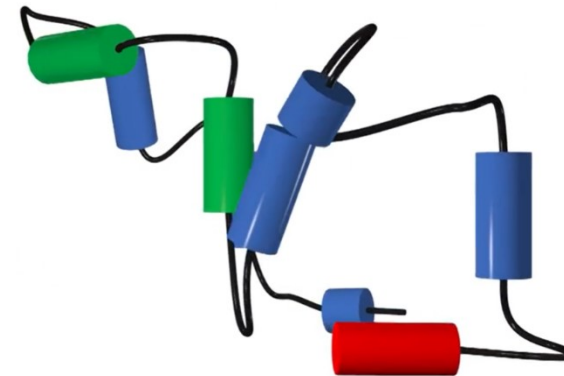
CHP3 Promotes the Maturation of NHE1

Transient expression of NHE1 (top row) in the presence and absence of transient CHP3 expression (middle row) in the AP-1 cell line. Proteins subjected to SDS-PAGE electrophoresis and immunoblotting to detect and quantify membrane-bound fully glycosylated NHE1 (fg). Detection of GAPDH was used as a quantification control.



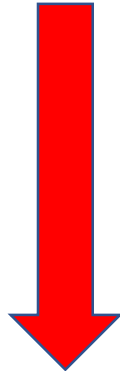
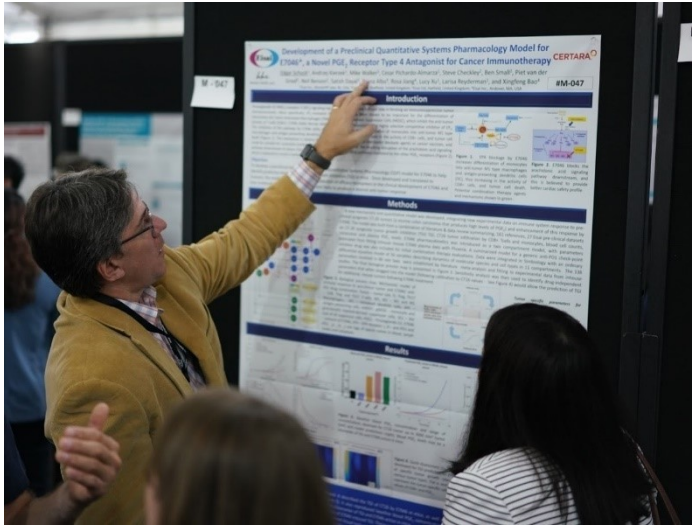
CHP3 Promotes the Cell Surface Stability of NHE1

AP-1 cells stably expressing NHE1 alone or co-expressing NHE1 and CHP3 were subject to cell surface biotinylation to label membrane-bound fully-glycosylated NHE1 (fg). Cells were returned to growth media and the protein was harvested at varying time points. Proteins were subject to SDS-PAGE and immunoblotting. The remaining fully-glycosylated NHE1 (top row) was quantified as a factor of the initial quantity at t=0 (lower graph). Cell lysate NHE1 and CHP3 were detected as a quantification control.





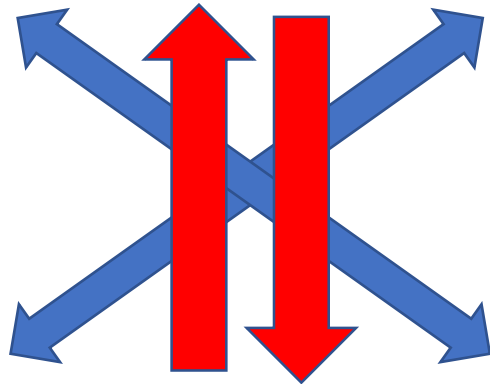
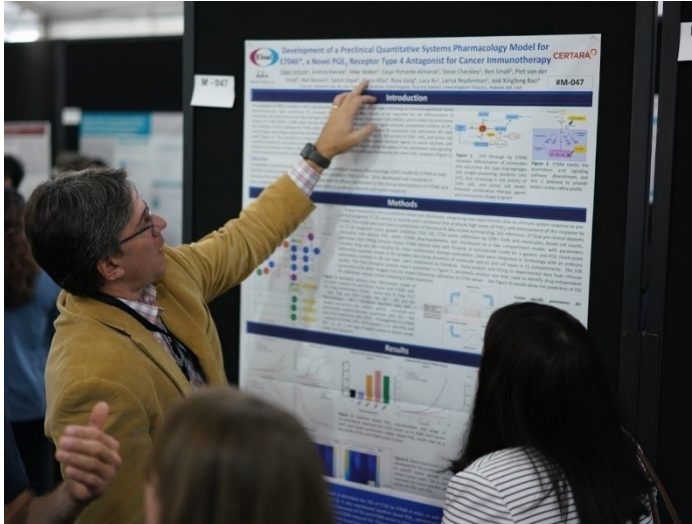
Science Producer



- Downloadable text-only poster content
 - Full poster reprint
 - Split into PPT slides or word/PDF outline, summary
 - E-poster: static or interactive (to zoom)
- E-poster with added AV
 - Audio recording of poster pitch (summary)
 - Audio recording of individual sections (commentary)
 - Video recording with screen capture
- Supplementary materials
 - Any removed material from poster
 - Link to publication and other resources, if available
 - **Code sharing! DDMore, Github, web download**

Science Consumers

Science Producer



- Email (between producer/consumer)
- 1-1 discussion (set up by producer/consumer)
- Live discussions by topic area (online or Zoom)
 - During the meeting (scheduled poster sessions)
 - After the meeting
- Conference app
- Social media (LinkedIn, Twitter, YouTube)
 - Add #hashtag
- Discussion forums
 - Slack, Discord, discussion board/email forum, AAPS Community

Science Consumers



- Confirm the time and format (live, audio, video, screen capture) and adjust your content to fit
 - 30 second basic intro/advertisement vs full poster walk through (3-5 minutes max)
 - Stick to your allotted time- shows respect for the listener
- Your summary is a great starting point
 - Problem statement/conclusion at a minimum
 - Then fill in gaps for time allotted
- Tell people why they should care about your research
- Pique their interest with a hook
 - Hit the highlights- don't give everything away!
 - Give them a reason to visit your poster
- Maybe leave them with an assignment (a question, a discussion point, etc) to bring to the Q&A
- **PRACTICE PRACTICE PRACTICE**

PROBLEM STATEMENT

Allometry scales animal pharmacokinetic data to humans using the equation: $P=a \cdot BW^b$, where P is the parameter (clearance, volume, half-life), BW is body weight in kg, and a and b are the slope and intercept of the log-log plot, respectively.

Fixed slopes (0.75, 1.0 and 0.25 for CL, V, and t1/2) are commonly used for initial human predictions. Using published allometric analyses of 28 drugs, we examined whether this is a valid practice, and explored whether any particular species is more predictive.

Two slope values were used in the allometric equation to make a prediction for human PK parameters from animal data:

- β_{global} = the average of the b-values for a parameter over all drugs.
- β_{animal} = animal-to-human slope for each drug and parameter computed for mouse, rat, rabbit, dog, and monkey, averaged over all drugs

The predictions of human PK were compared across animals for both slopes, using a number of different metrics.

CONCLUSION

The rabbit/ β_{rabbit} pairing provided the most predictive estimates. However, the β_{global} values (.729, 0.961, and 0.242 for CL, V, and t1/2) also support the use of the common slope values to make initial estimations of human parameter values.

If no one reads your poster, does it have an impact?

- Good science does not necessarily make a good poster!
 - A poorly prepared or presented poster is a lost opportunity to engage with science consumers
- Poster prep is not a trivial activity
 - Skills you develop will help you throughout your career
- **Put forth the time, effort, and energy to make the MOSTER of your POSTER!**







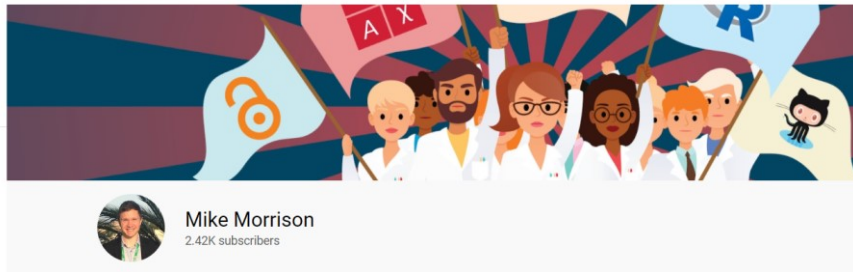
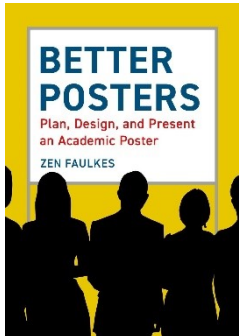
- Rebecca Baillie
- Peter Bonate
- Bill Williams
- Joy Davis
- Stefanie Hennig
- Matt Riggs
- Peiyong Zuo
- Eric Jordie
- **Poster presenters everywhere 😊**

References

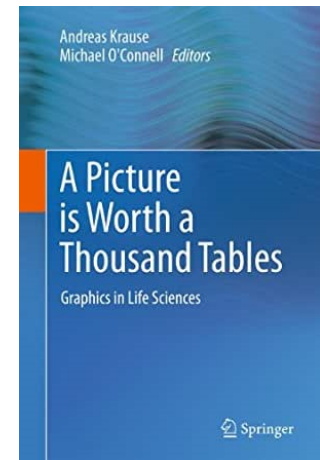
- [Mike Morrison \(#betterposter\) You Tube Channel](#)
- [Better Posters blog](#)
- <http://mkweb.bcgsc.ca/poster.design/>
- [3 minute thesis \(3MT\)](#)
- [1 minute poster pitch](#)
- [THIS ↓ TWEET](#)

 **Kelly Williams** 
@Williams_Kelly2

I'm doing a 3 minute presentation for a virtual conference at the end of the month. My first virtual conference AND the first talk of my PhD candidacy. Any tips or suggestions? Help, please 🙏 #scicomm @AcademicChatter #phdchat



- [Graphics Principles Cheat Sheet](#)
 - [Effective Visual Communication for the Quantitative Scientist \(pub\)](#)
 - [How can we make better graphs? An initiative to increase the graphical expertise and productivity of quantitative scientists \(pub\)](#)
 - [Effective Visualizations for Data Driven Decisions \(webinar\)](#)
- <https://www.amazon.com/Picture-Worth-Thousand-Tables-Graphics/dp/1461453283>



WEBINAR

Making the 'Master' of Your Poster

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