WEBINAR

Making the 'Moster' of Your Poster

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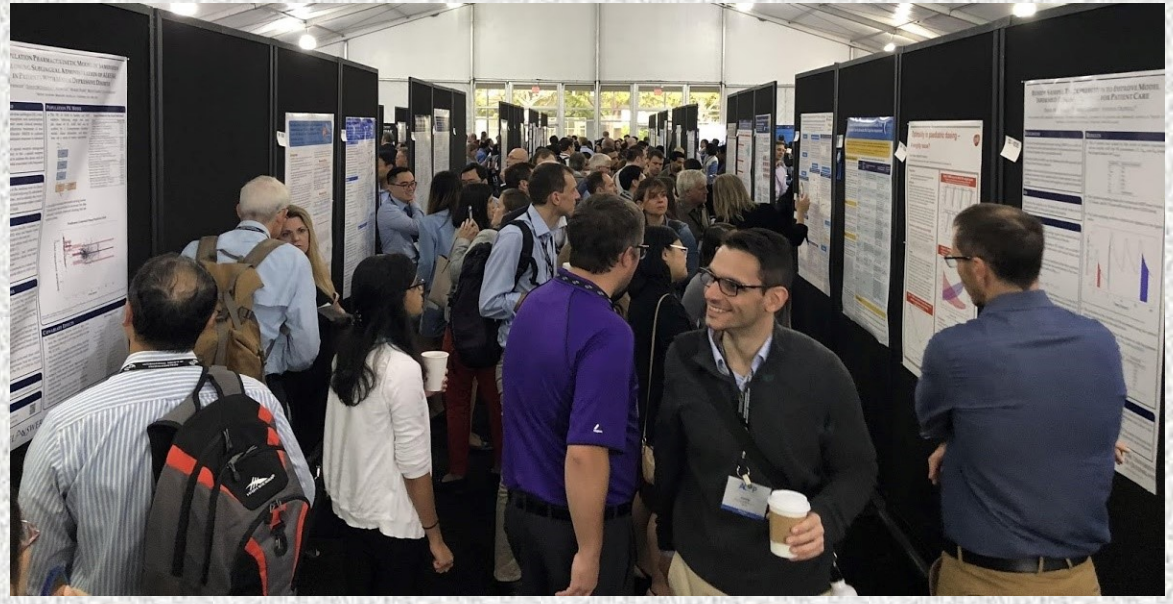

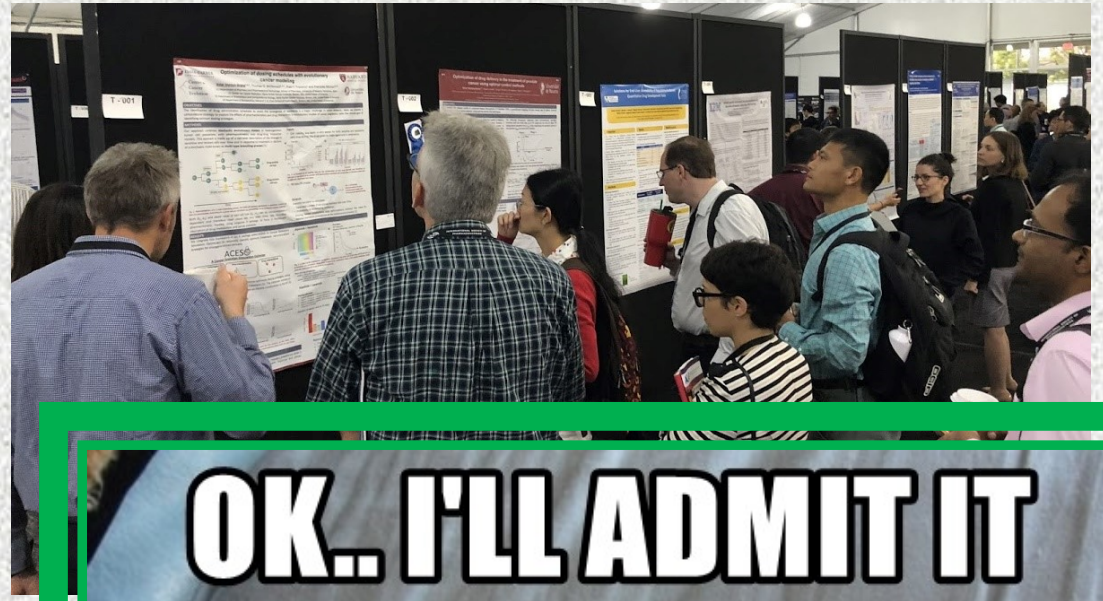

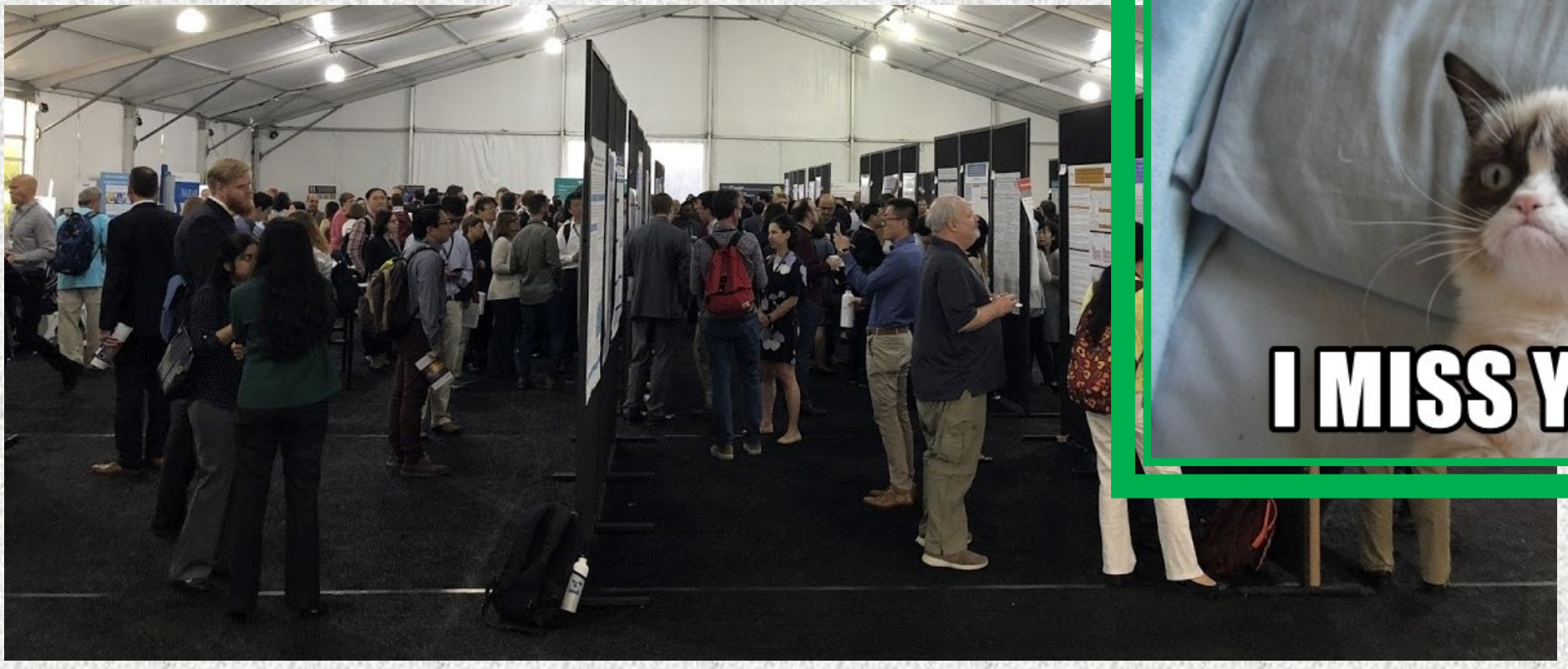

Photos by Songmao (Ben) Zheng, ACoP9 2018, Coronado, CA

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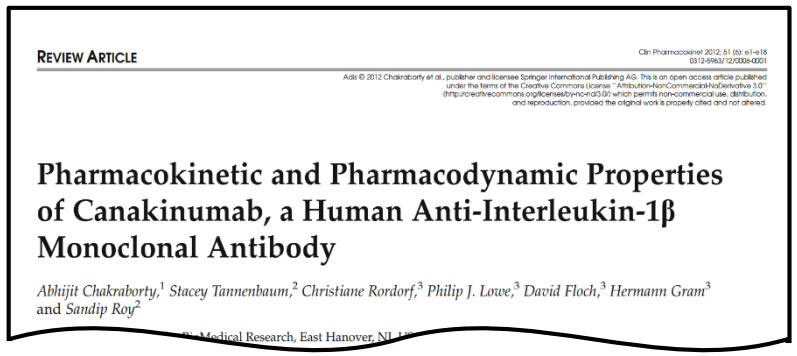
Science Producer



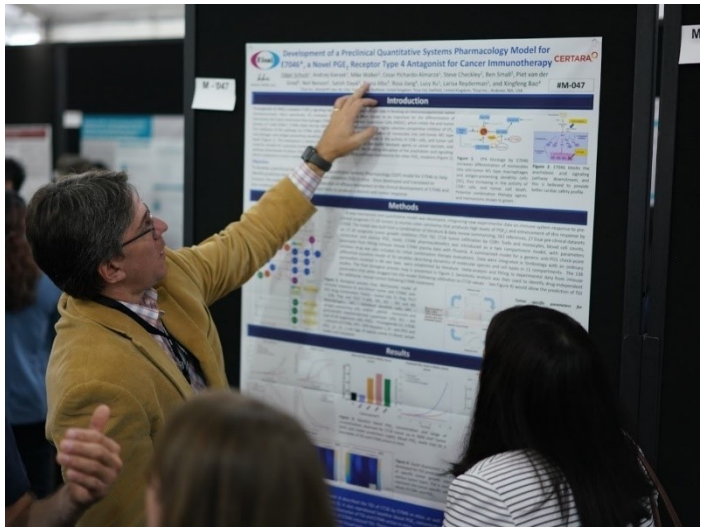
REVIEW ARTICLE

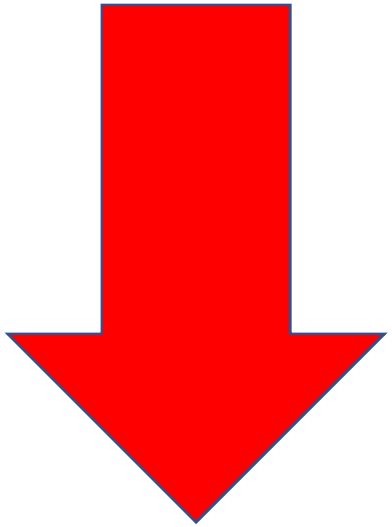
Clin Pharmacokinet 2012; 51 (5): e1–e18
0312-5963/12/0006-0001

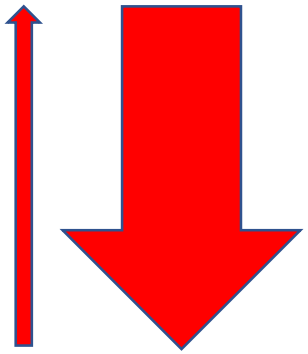
Pharmacokinetic and Pharmacodynamic Properties of Canakinumab, a Human Anti-Interleukin-1β Monoclonal Antibody

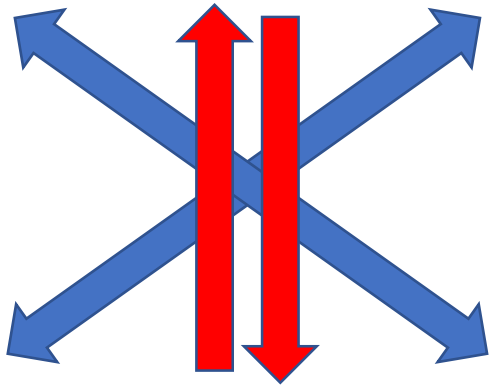
Abhijit Chakraborty,[1] *Stacey Tannenbaum,*[2] *Christiane Rordorf,*[3] *Philip J. Lowe,*[3] *David Floch,*[3] *Hermann Gram*[3] and *Sandip Roy*[2]

[1] Medical Research, East Hanover, NJ, [illegible]



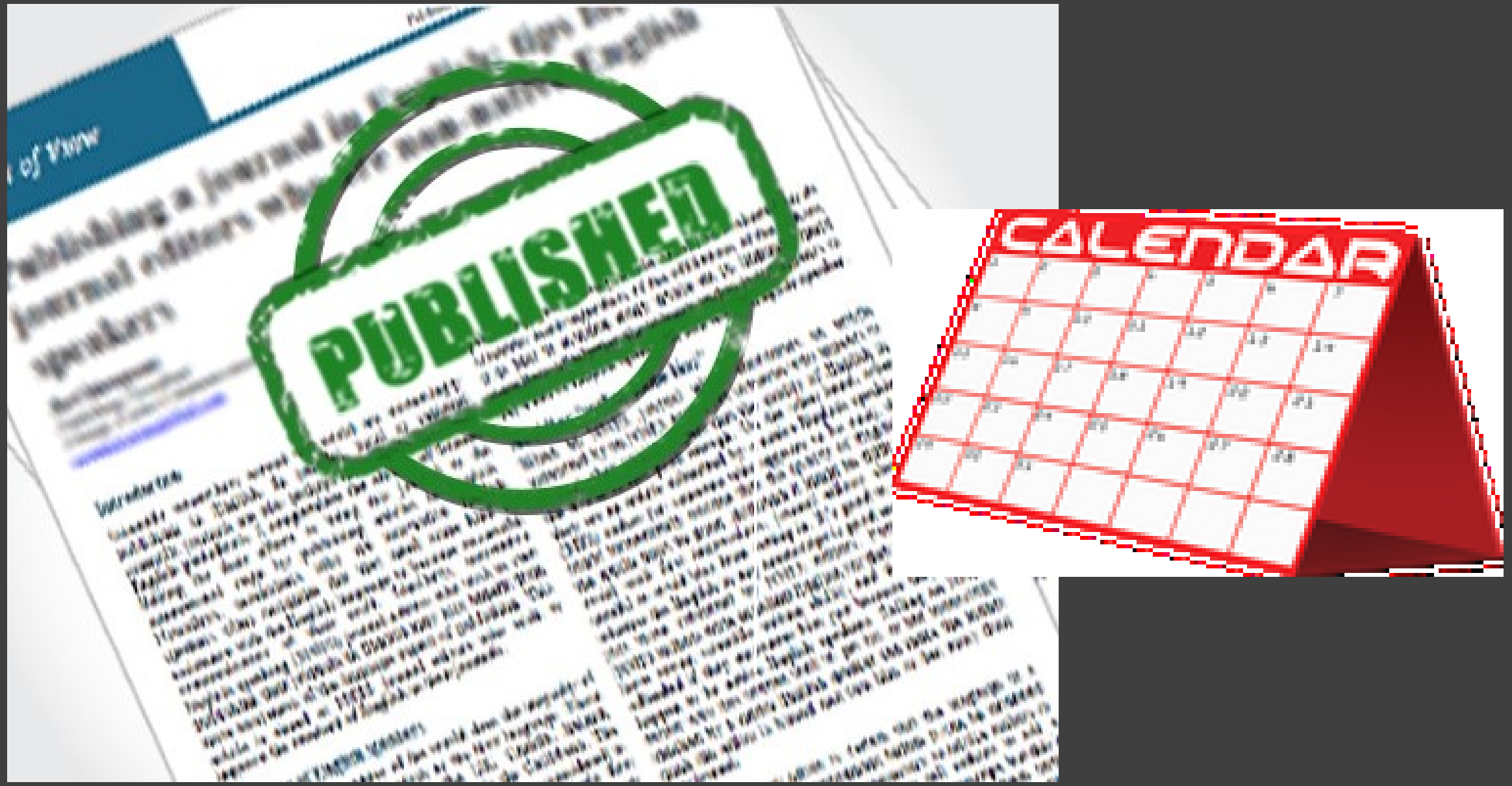






Science Consumer

Slide concept adapted from Bonate, Creating and Presenting Captivating Posters, AAPS webinar; photo credits, Ben Zheng and Brian Corrigan



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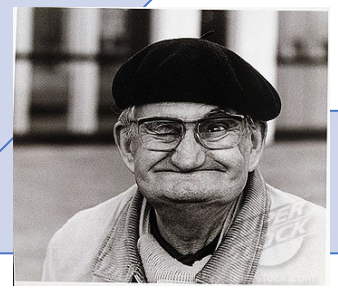

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ALLOMETRIC ANALYSIS OF ORGAN EXTRACTION RATIOS

S Tannenbaum,[1] H Boxenbaum,[2] and M Mayersohn[1]
[1]College of Pharmacy and the Center for Toxicology, The University of Arizona, Tucson, AZ
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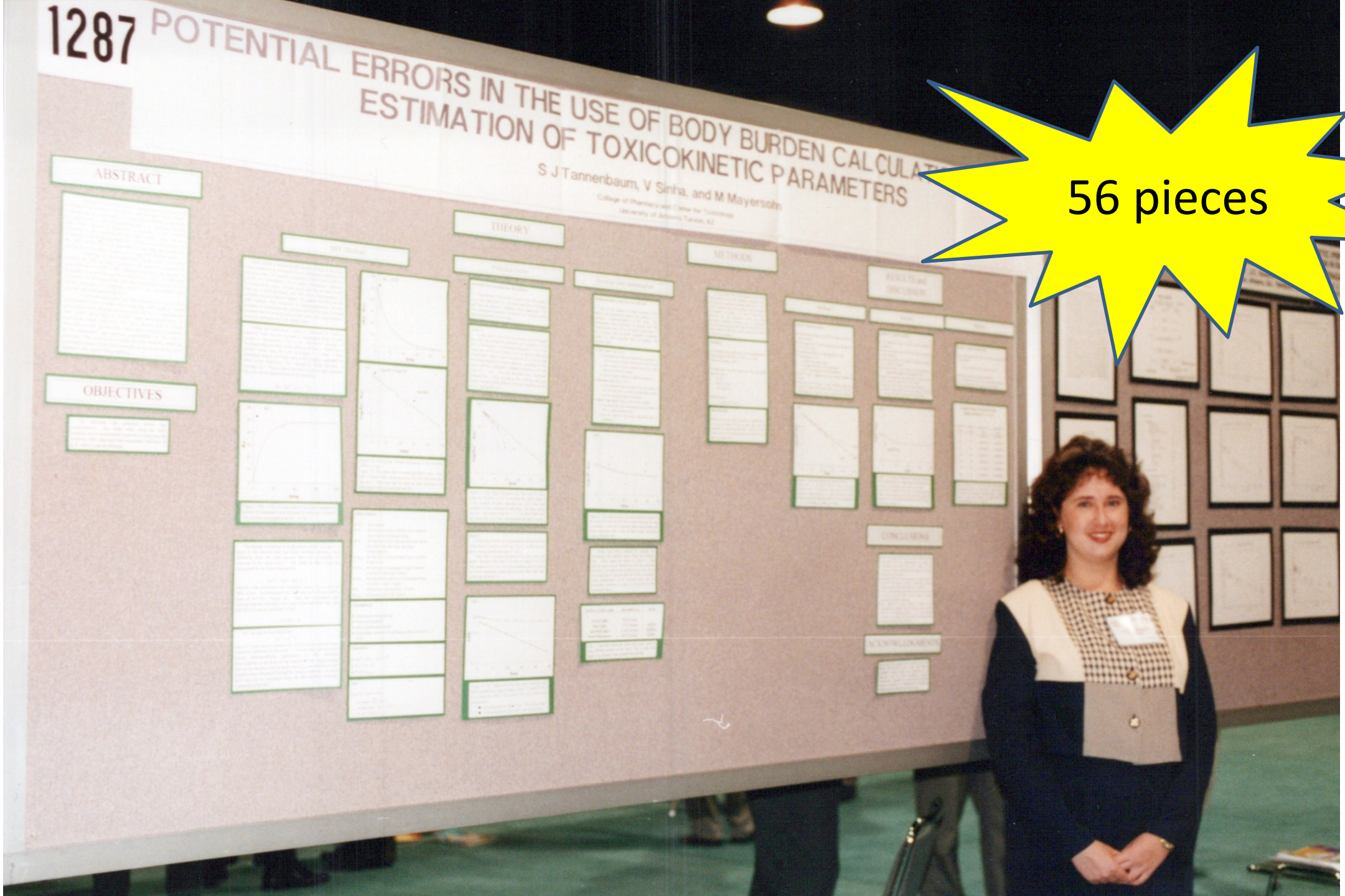
AAPS AM 1997


1287
POTENTIAL ERRORS IN THE USE OF BODY BURDEN CALCULA
ESTIMATION OF TOXICOKINETIC PARAMETERS
S J Tannenbaum, V Sinha, and M Mayersohn
ABSTRACT
OBJECTIVES
THEORY
METHODS
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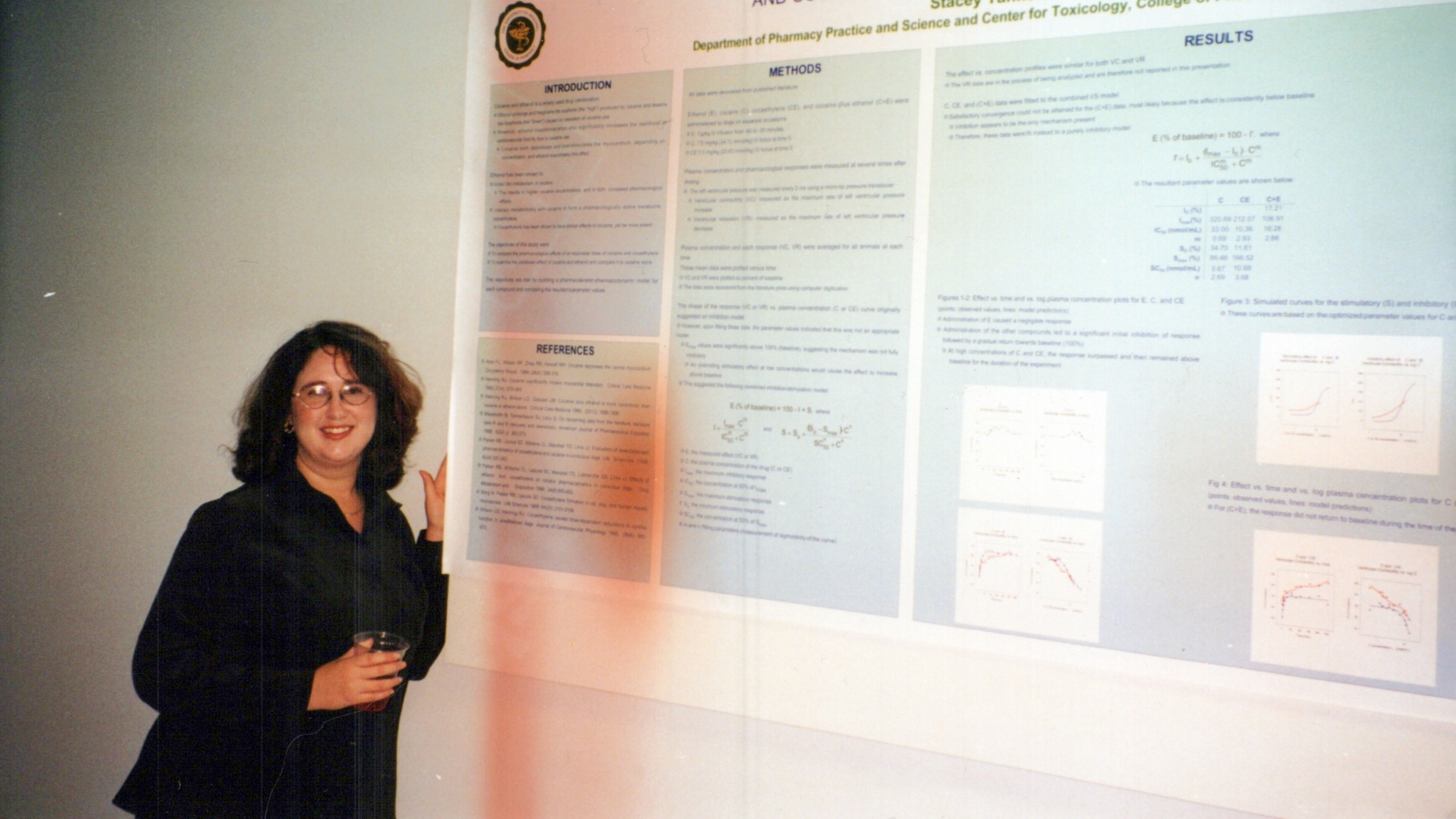
Department of Pharmacy Practice and Science and Center for Toxicology, College of
INTRODUCTION
METHODS
RESULTS
REFERENCES

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 87521

INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: P=a•BWb, 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 t1/2 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:

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

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/β_{rabbit} provided the most predictive estimations of the observed Human values. However, the β_{global} values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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 (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•BWb
  - 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, 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

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

- 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})

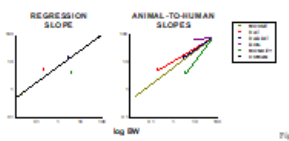

Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= β_{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 Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred 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 RMSEglobal to RMSEanimal to determine the most predictive slope (global or animal)
  - Compared RMSE across species to determine the most predictive species

RESULTS

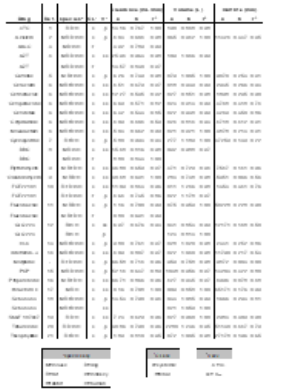

Table 1: Summary of drugs whose pharmacokinetic parameters were evaluated allometrically. The allometric intercept (a) and slope (b) are presented for each parameter along with the coefficients of determination (r^2)

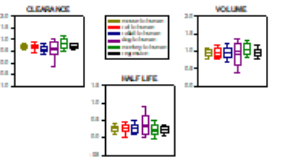

Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the β_{global} and β_{animal} values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
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	0.896	±	0.382	0.388	±	0.366
β_{monkey}	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227

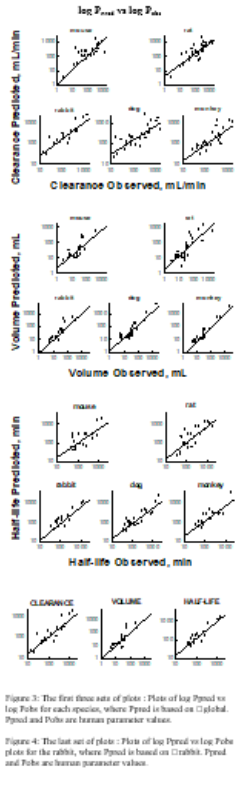

Figure 3: The first three sets of plots : Plots of log Ppred vs log Pobs for each species, where Ppred is based on □global. Ppred and Pobs are human parameter values.

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

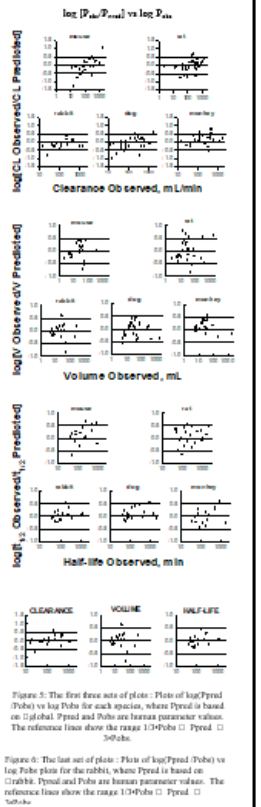

Figure 5: The first three sets of plots : Plots of log(Ppred /Pobs) vs log Pobs for each species, where Ppred is based on □global. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs □ Ppred □ 3•Pobs.

Figure 6: The last set of plots : Plots of log(Ppred /Pobs) vs log Pobs plots for the rabbit, where Ppred is based on □rabbit. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs □ Ppred □ 3•Pobs.

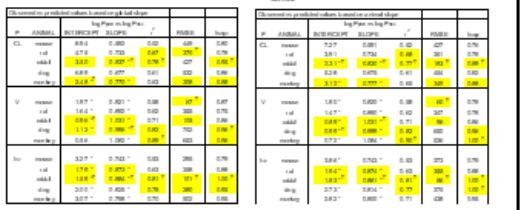

Table 2: Measures used to compare the accuracy of the human predictions based on β_{global} (A), or based on β_{animal} (B). The slope, intercept, and r^2 values are of the regression line through the log Ppred vs log Pobs plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and frange is the fraction of values that fall within the allowable range on each log Pobs/Ppred vs log Pobs 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_{pred} vs log P_{obs}] plots for each species/slope pair, where Ppred is based on β_{rabbit} and the β_{animal} slopes, respectively. Global plots are shown in Figure 3 and those for rabbit/β_{rabbit} in Figure 5.

- If $P_{pred} = P_{obs}$ (ideal), then the regression line is the line of identity
  - compare slope to 1
  - compare intercept to 1 (origin of log-log plot)
  - compare 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
    - †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
  - 13/16 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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] 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
    - †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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.

- If 1/3•Pobs ≤ Ppred ≤ 3•Pobs for every observation in the set, the frange value would equal 1.0 (100% of the data falls within the allowable range)
  - compare frange to 1.0
    - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
    - †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 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 estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{animal} 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:

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

- 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.

Supported by a grant from the National Institute on Drug Abuse (DA08094). ST is supported by an American Foundation for Pharmaceutical Education Pharmaceutics/Biopharmaceutics Fellowship.

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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 87521

INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: P=a•BWb, 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 t1/2 when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

βglobal 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:

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

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 βmouse, βrat, βrabbit, βdog, and βmonkey. 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/βrabbit provided the most predictive estimations of the observed Phuman values. However, the βglobal values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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)
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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•BWb
  - 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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

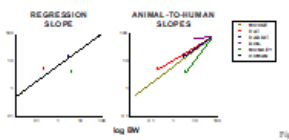

Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
  - Compared regression line through the [log Ppred vs log Pobs] to line of identity
  - Calculated the fraction of Pobs/Ppred values that fell within [illegible] range
  - Calculated [illegible] for each set

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

  - Compared RMSEglobal to RMSE of most predictive slope (global or animal)
  - Compared RMSE across species to find most predictive species

RESULTS

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 coefficients of determination (r2)

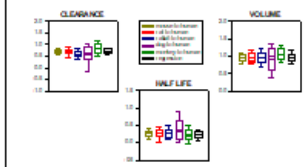

Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the βglobal and βanimal values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
βglobal	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
βmouse	0.702	±	0.137	0.949	±	0.101	0.263	±	0.104
βrat	0.696	±	0.153	0.941	±	0.172	0.257	±	0.141
βrabbit	0.589	±	0.195	0.937	±	0.229	0.282	±	0.148
βdog	0.571	±	0.513	0.896	±	0.382	0.388	±	0.366
βmonkey	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227

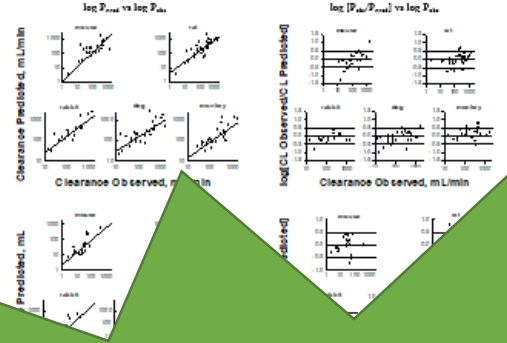

Table 2: Measures used to compare the accuracy of the human predictions based on βglobal (A), or based on βanimal (B). The slope, intercept, and r2 values are of the regression line through the log Ppred vs log Pobs plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and frange is the fraction of values that fall within the allowable range on each log Pobs/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 βrabbit and the βanimal slopes, respectively. Global plots are shown in Figure 3 and those for rabbit/βrabbit 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
    - † 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
  - 13/1[illegible] the highlighted values are best
  - [illegible] animal shows the same consistency over all three parameters

[illegible] 3b list the RMSE values and the f_{range} values for each species/slope pair.
[illegible] 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.
[illegible] Pobs (ideal), then each error would equal zero, and RMSE would equal zero
[illegible]e RMSE to 0
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[illegible] highlighted all 3 times in Table 3b
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[illegible]each species/slope pair.
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[illegible], and 0.25 for $t_{1/2}$ to compute initial
[illegible]e corresponding calculated global β
[illegible] for predicting the human
[illegible] β_{rabbit} consistently showed
[illegible] values, and high f_{range} values.
[illegible]t accurate prediction for

human parameter values is found using the

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

- 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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TMI!

AAPS
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1996

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.

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!

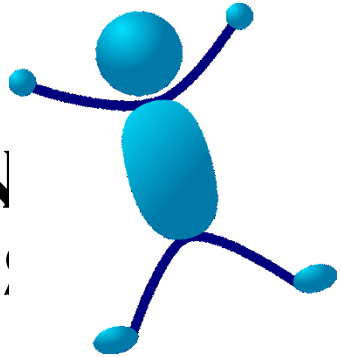
OMG!

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

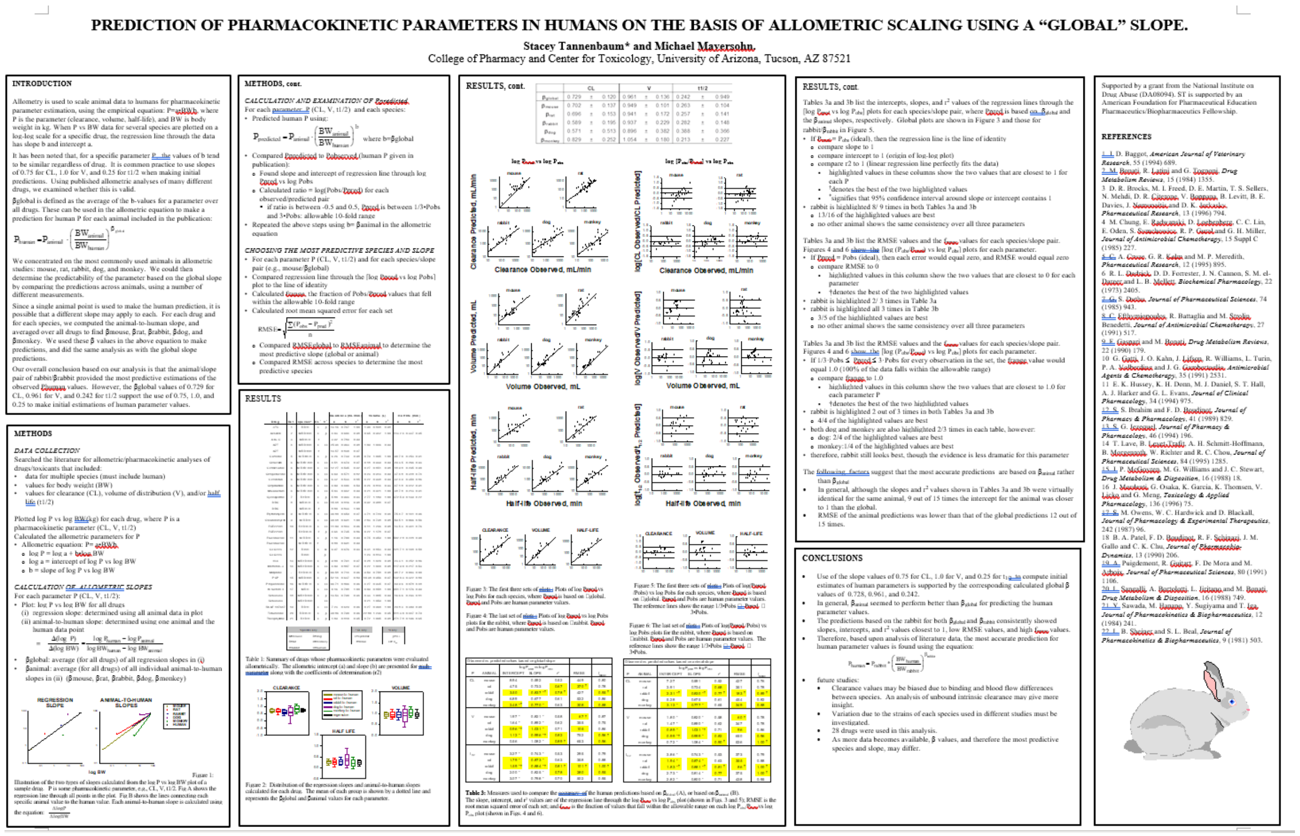
CONCLUSION: The rabbit/β_{rabbit} pairing provided the most predictive estimates. However, the β_{global} values (.729, 0.961, and 0.242 for CL, V, and t1/2) also support the use of the common slope values to make initial estimations of human parameter values

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 Mayersohn,
College of Pharmacy and Center for Toxicology, University of Arizona, Tucson, AZ 87521

INTRODUCTION

METHODS

METHODS, cont.

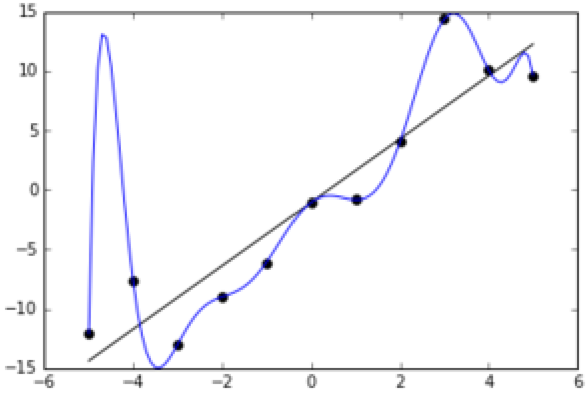
RESULTS

RESULTS, cont.

RESULTS, cont.

CONCLUSIONS

REFERENCES



Sensitivity Analysis FTW!

https://en.wikipedia.org/wiki/Overfitting

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

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INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: $P = a \cdot BW^b$, 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 t1/2 when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

βglobal 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:

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

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 βmouse, βrat, βrabbit, βdog, and βmonkey. 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/βrabbit provided the most predictive estimations of the observed Phuman values. However, the βglobal values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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 (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·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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

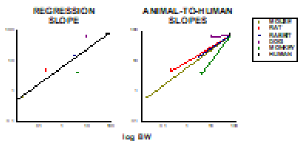

Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
- Compared regression line through the [log Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred 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 RMSEglobal to RMSEanimal to determine the most predictive slope (global or animal)
  - Compared RMSE across species to determine the most predictive species

RESULTS

[illegible]

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 coefficients of determination (r2)

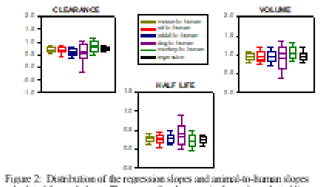

Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the βglobal and βanimal values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
β_{mouse}	0.702	±	0.137	[illegible]	±	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	0.262	±	0.148
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

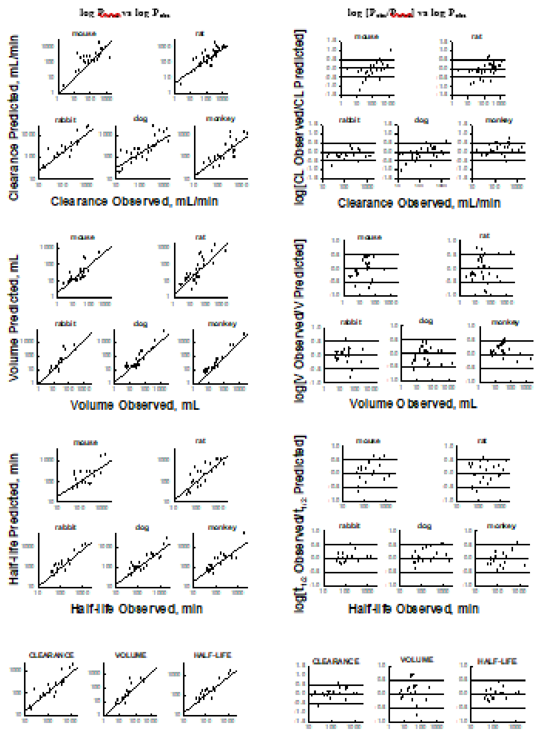

Figure 3: The first three sets of plots: Plots of log Ppred vs log Pobs for each species, where Ppred is based on βglobal. Ppred and Pobs are human parameter values.

Figure 4: The last set of plots: Plots of log Ppred vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. 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 βglobal. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

Figure 6: The last set of plots: Plots of log(Ppred/Pobs) vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

[illegible]

Table 3: Measures used to compare the accuracy of the human predictions 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); RMSE is the root mean squared error of each set; and frange is the fraction of values that fall within the allowable range on each log Pobs/Ppred vs log Pobs plot (shown in Figs. 4 and 6).

Tables 3a and 3b list the intercepts, slopes, and r² values of the regression lines through the [log P_{pred} vs log P_{obs}] 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 $P_{pred} = P_{obs}$ (ideal), then the regression line is the line of identity
  - compare slope to 1
  - compare intercept to 1 (origin of log-log plot)
  - compare 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
    - †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
  - 13/16 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 frange values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] 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
    - †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 frange values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.

- If 1/3·Pobs ≤ Ppred ≤ 3·Pobs for every observation in the set, the frange value would equal 1.0 (100% of the data falls within the allowable range)
  - compare frange to 1.0
    - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
    - †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_{animal} 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_{animal} 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 r² values closest to 1, low RMSE values, and high frange values.
- Therefore, based upon analysis of literature data, the most accurate prediction for human parameter values is found using the equation:

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

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

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INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: P=a•BWb, 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 t1/2 when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

βglobal 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:

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

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 βmouse, βrat, βrabbit, βdog, and βmonkey. 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/βrabbit provided the most predictive estimations of the observed Phuman values. However, the βglobal values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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 (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•BWb
  - 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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

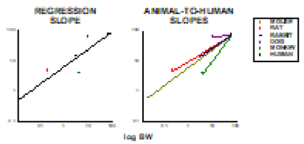


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted
For each parameter P (CL, V, t1/2) and each species:
- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
- Compared regression line through the [log Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred 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 RMSEglobal to RMSEanimal to determine the most predictive slope (global or animal)
  - Compared RMSE across species to determine the most predictive species

RESULTS

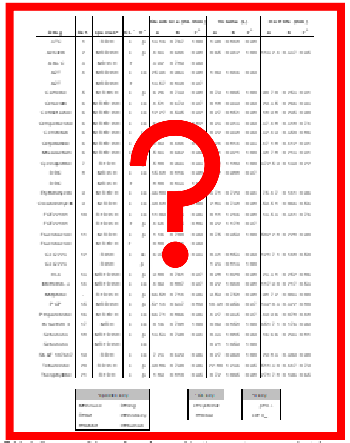


Table 1: Summary of drugs whose pharmacokinetic parameters were evaluated allometrically. The allometric intercept (a) and slope (b) are presented for each compound along with the coefficients of determination (r2)

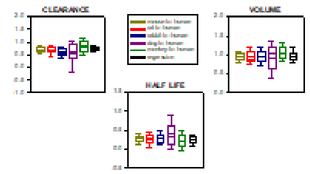
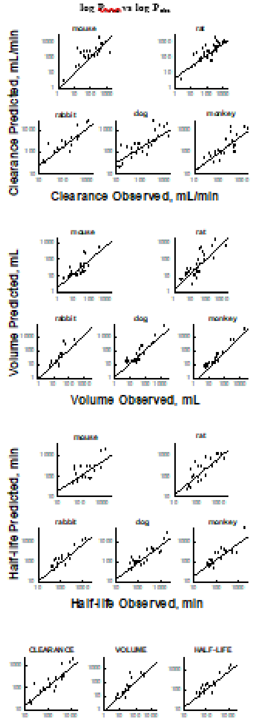


Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the βglobal and βanimal values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
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	0.896	±	0.382	0.388	±	0.366
β_{monkey}	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227



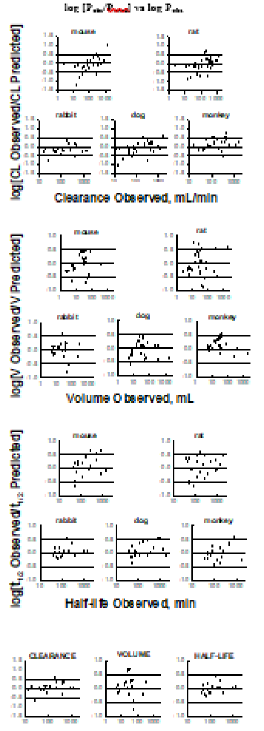


Figure 3: The first three sets of plots: Plots of log Ppred vs log Pobs for each species, where Ppred is based on βglobal. Ppred and Pobs are human parameter values.

Figure 4: The last set of plots: Plots of log Ppred vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. 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 βglobal. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

Figure 6: The last set of plots: Plots of log(Ppred/Pobs) vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

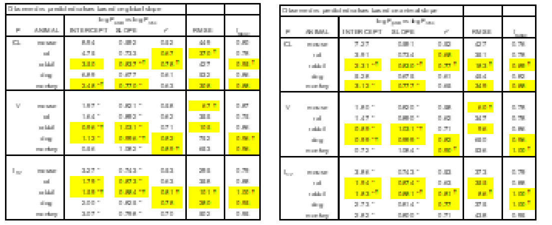


Table 3: Measures used to compare the accuracy of the human predictions based on β_{global} (A), or based on β_{animal} (B). The slope, intercept, and r² values are of the regression line through the log P_{pred} vs log P_{obs} plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and f_{range} is the fraction of values that fall within the allowable range on each log P_{obs}/P_{pred} 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_{pred} vs log P_{obs}] 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_{pred} = 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 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
    - †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
  - 13/16 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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] 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
    - †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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.
- If 1/3·Pobs ≤ Ppred ≤ 3·Pobs for every observation in the set, the frange value would equal 1.0 (100% of the data falls within the allowable range)
  - compare frange to 1.0
    - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
    - †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_{animal} 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 estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{animal} 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:

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

- 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.

Supported by a grant from the National Institute on Drug Abuse (DA08094). ST is supported by an American Foundation for Pharmaceutical Education Pharmaceutics/Biopharmaceutics Fellowship.

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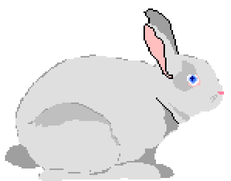

Drug	Ref.	species*	CL†	V‡	Clearance (mL/min) a	Clearance (mL/min) b	Clearance (mL/min) r^2	Volume (L) a	Volume (L) b	Volume (L) r^2	Half life (min) a	Half life (min) b	Half life (min) r^2
3TC	1	RDH	s	β	13.16	0.767	1.00	1.90	0.848	0.98			
Acivicin	2	MRDmH	s	β	4.03	0.604	0.98	0.65	0.942	1.00	113.24	0.337	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	MRrmH	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	s					4	0.814	0.93	47.18	0.412	0.91
Moxalactam	6	MRrDmH	s					1	0.921	1.00	38.78	0.213	0.91
Cyclosporine	7	RrDH	s					7	1.189	1.00	372.59	0.139	0.22
DDC	8	MRmH	s					2	0.988	0.97			
DDC		MRmH	r										
Erythromycin	9	MRrDH	s					1	0.729	0.94	75.47	0.141	0.96
Oleandomycin	9	MRDH	s					3	0.738	0.98	59.51	0.066	0.56
FCE22101	10	RrDmH	s					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			

Drug	Ref.	species*	CL†	V‡	Clearance (mL/min) a	b	r^2	Volume (L) a	b	r^2	Half life (min) a	b	r^2
3TC													
Acivici											4	0.337	0.95
Ara-C													
AZT													
AZT													
Caffein											0	0.253	0.91
Cefazol											5	0.266	0.93
Cefmetaz											3	0.295	0.90
Cefoperaz											3	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	s					4	0.814	0.93	47.18	0.412	0.91
Moxalactam	6	MRrDmH	s					1	0.921	1.00	38.78	0.213	0.91
Cyclosporine	7	RrDH	s					7	1.189	1.00	372.59	0.139	0.22
DDC	8	MRmH	s					2	0.988	0.97			
DDC		MRmH	r										
Erythromycin	9	MRrDH	s					1	0.729	0.94	75.47	0.141	0.96
Oleandomycin	9	MRDH	s					3	0.738	0.98	59.51	0.066	0.56
FCE22101	10	RrDmH	s					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			

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

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

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INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: P=a•BWb, 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 t1/2 when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

βglobal 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:

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

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 βmouse, βrat, βrabbit, βdog, and βmonkey. 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/βrabbit provided the most predictive estimations of the observed Phuman values. However, the βglobal values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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 (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•BWb
  - 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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

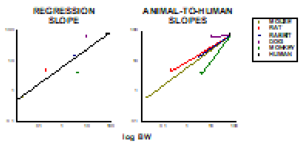

Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
- Compared regression line through the [log Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred 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 RMSEglobal to RMSEanimal to determine the most predictive slope (global or animal)
  - Compared RMSE across species to determine the most predictive species

RESULTS

Drug	[illegible]	[illegible]	[illegible]	Clearance (mL/min)	Volume (L)	Half-life (min)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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 coefficients of determination (r2)

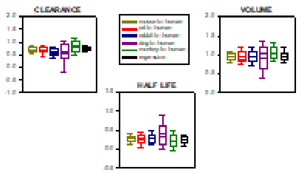

Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the βglobal and βanimal values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
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	0.896	±	0.382	0.388	±	0.366
β_{monkey}	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227

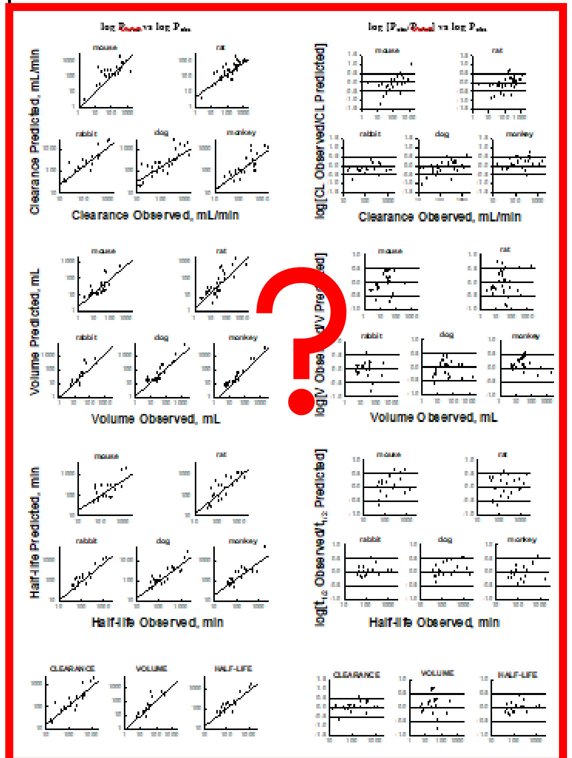

Figure 3: The first three sets of plots: Plots of log Ppred vs log Pobs for each species, where Ppred is based on βglobal. Ppred and Pobs are human parameter values.

Figure 4: The last set of plots: Plots of log Ppred vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. 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 βglobal. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

Figure 6: The last set of plots: Plots of log(Ppred/Pobs) vs log Pobs plots for the rabbit, where Ppred is based on βrabbit. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs ≤ Ppred ≤ 3•Pobs.

(A) Observed vs. predicted values based on global slope

P	ANIMAL	INTERCEPT	SLOPE	r^2	RMSE	f_{range}
CL	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
V	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$t_{1/2}$	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

(B) Observed vs. predicted values based on animal slope

P	ANIMAL	INTERCEPT	SLOPE	r^2	RMSE	f_{range}
CL	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
V	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$t_{1/2}$	mouse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rat	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	rabbit	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	dog	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	monkey	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 3: Measures used to compare the accuracy of the human predictions based on β_{global} (A), or based on β_{animal} (B). The slope, intercept, and r^2 values are of the regression line through the log P_{pred} vs log P_{obs} 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}/P_{pred} 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_{pred} vs log P_{obs}] 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_{pred} = 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 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
    - †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
  - 13/16 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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] 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
    - †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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.

- If 1/3·Pobs ≤ Ppred ≤ 3·Pobs for every observation in the set, the frange value would equal 1.0 (100% of the data falls within the allowable range)
  - compare frange to 1.0
    - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
    - †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_{animal} 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 estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{animal} 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:

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

- 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.

Supported by a grant from the National Institute on Drug Abuse (DA08094). ST is supported by an American Foundation for Pharmaceutical Education Pharmaceutics/Biopharmaceutics Fellowship.

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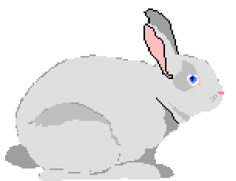
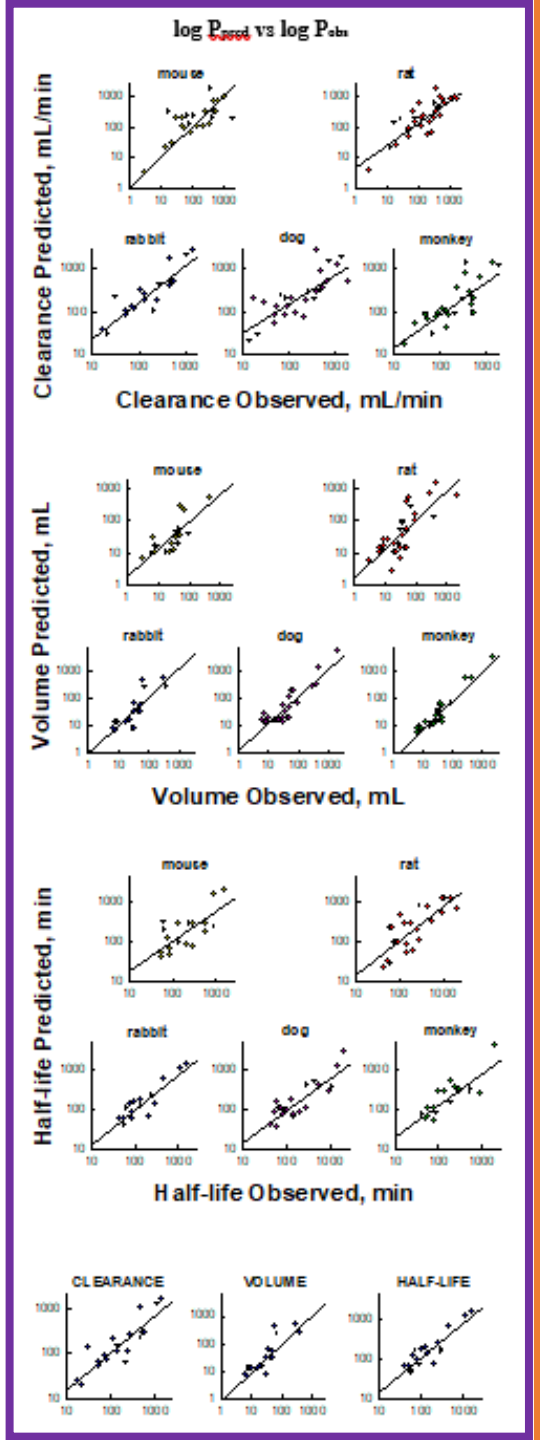
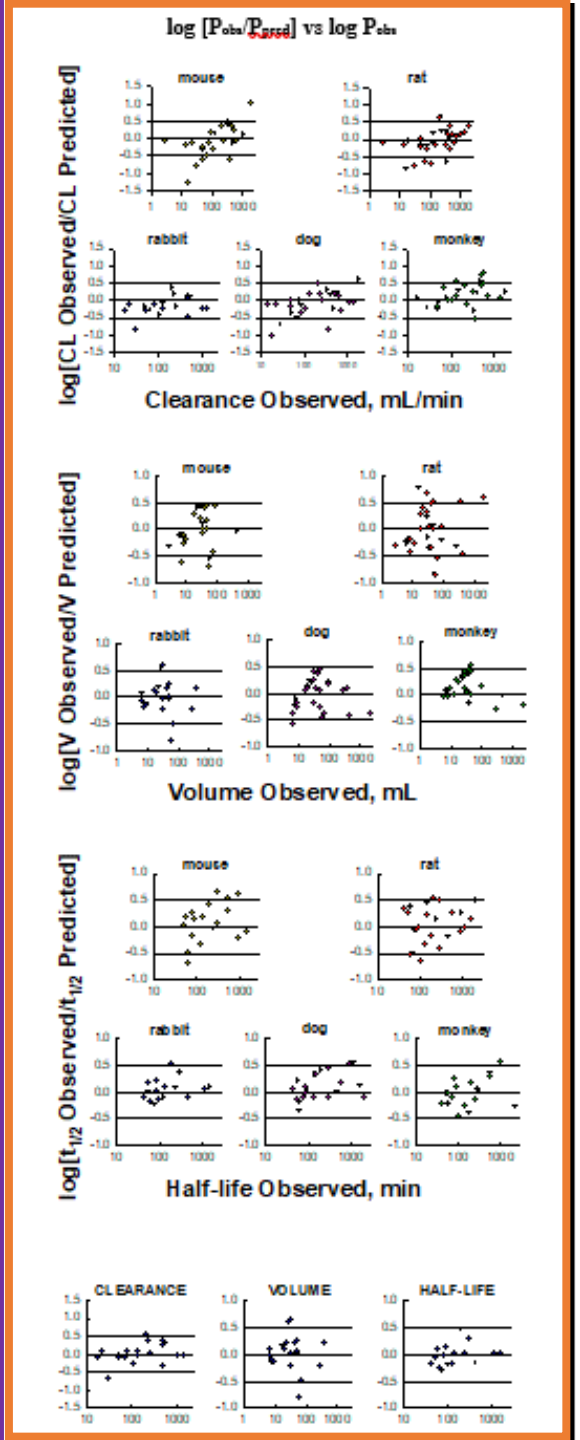
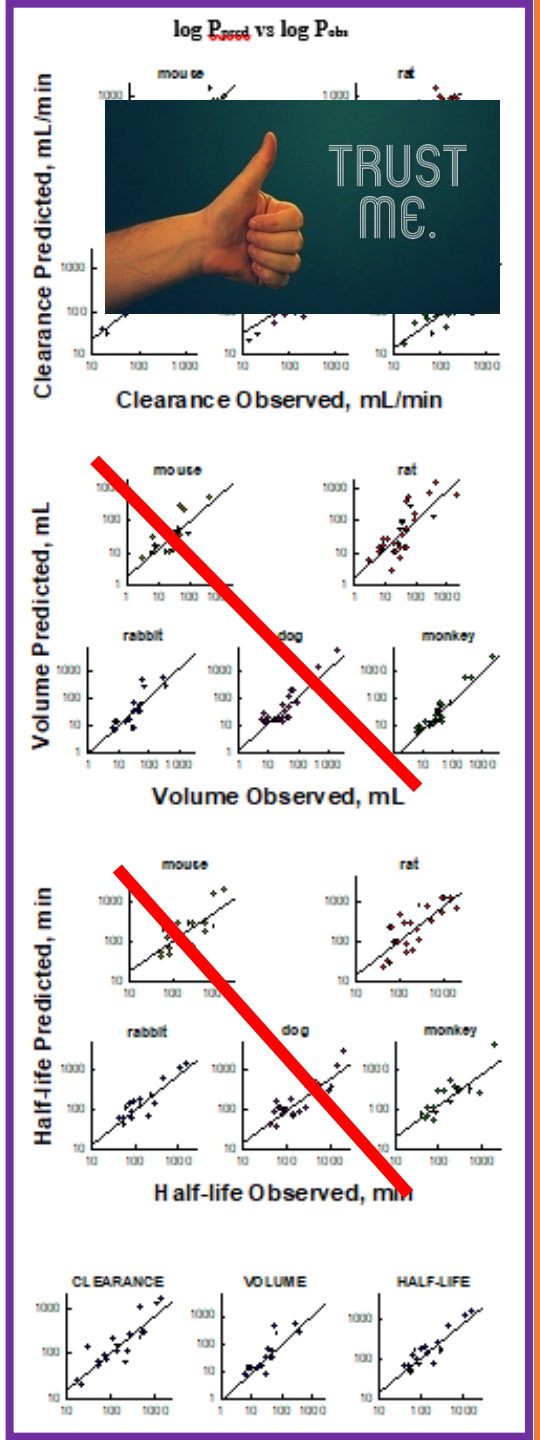
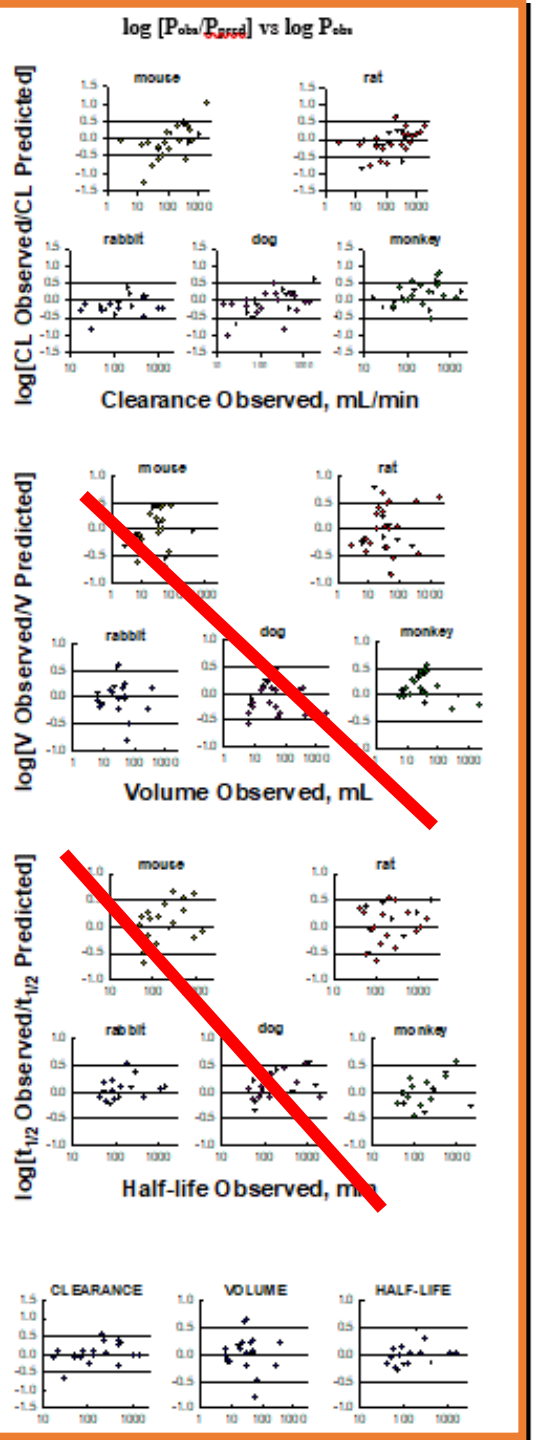
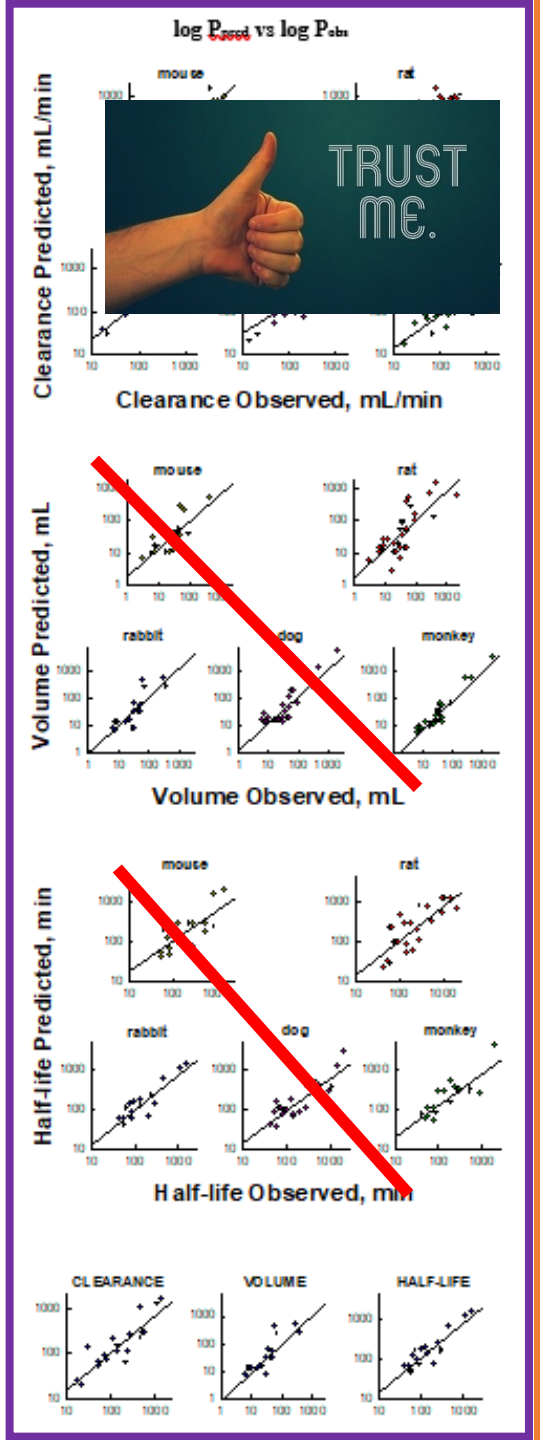


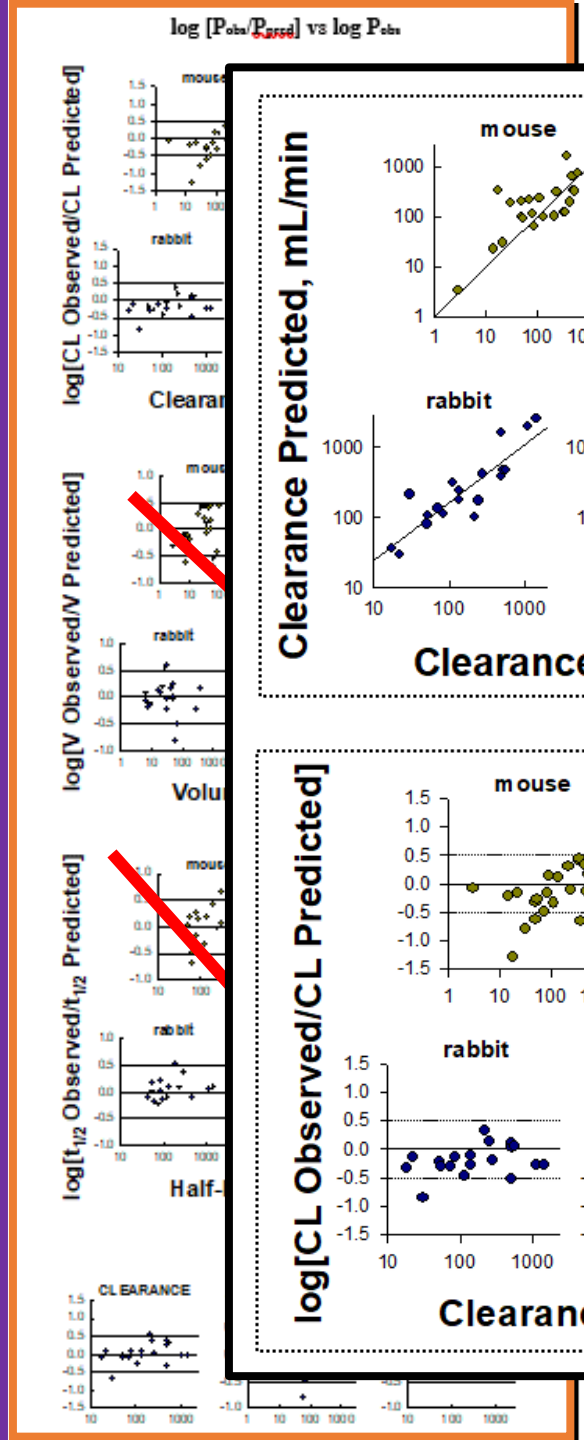

log Ppred vs log Pobs
mouse
rat
rabbit
dog
monkey
Clearance Predicted, mL/min
Clearance Observed, mL/min
Volume Predicted, mL
Volume Observed, mL
Half-life Predicted, min
Half-life Observed, min
CLEARANCE
VOLUME
HALF-LIFE

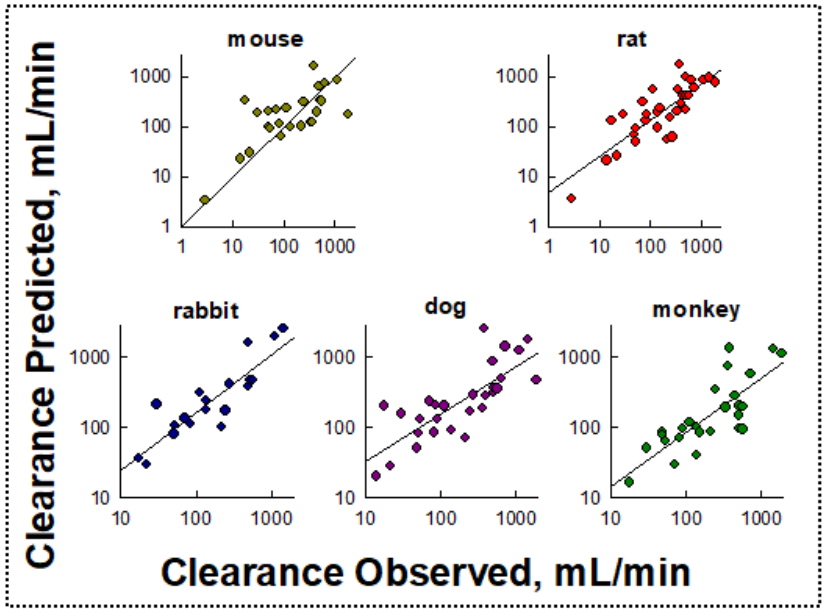

log [Pobs/Ppred] vs log Pobs
mouse
rat
rabbit
dog
monkey
log[CL Observed/CL Predicted]
Clearance Observed, mL/min
log[V Observed/V Predicted]
Volume Observed, mL
log[t1/2 Observed/t1/2 Predicted]
Half-life Observed, min
CLEARANCE
VOLUME
HALF-LIFE

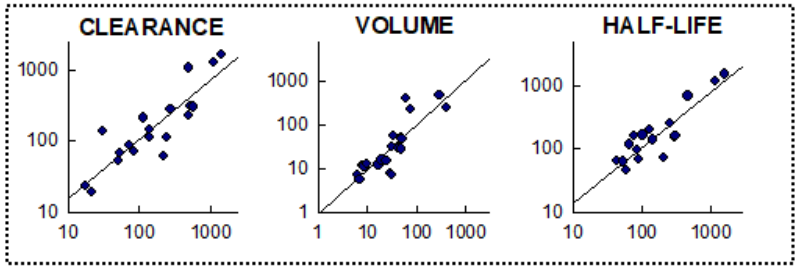

log P_{pred} vs log P_{obs}
mouse
rat
TRUST ME.
Clearance Predicted, mL/min
Clearance Observed, mL/min
rabbit
dog
monkey
Volume Predicted, mL
Volume Observed, mL
Half-life Predicted, min
Half-life Observed, min
CLEARANCE
VOLUME
HALF-LIFE


log [P_{obs}/P_{pred}] vs log P_{obs}
mouse
rat
log[CL Observed/CL Predicted]
Clearance Observed, mL/min
rabbit
dog
monkey
log[V Observed/V Predicted]
Volume Observed, mL
log[$t_{1/2}$ Observed/$t_{1/2}$ Predicted]
Half-life Observed, min
CLEARANCE
VOLUME
HALF-LIFE



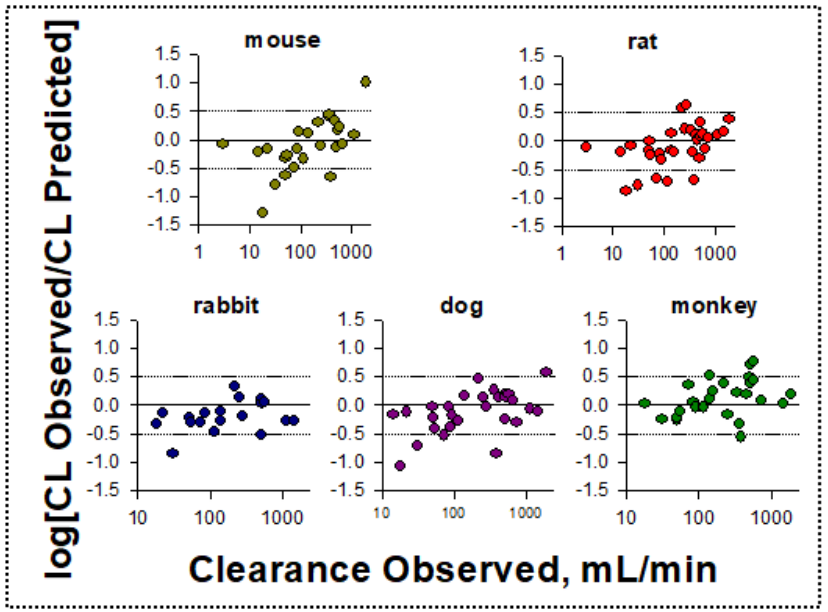


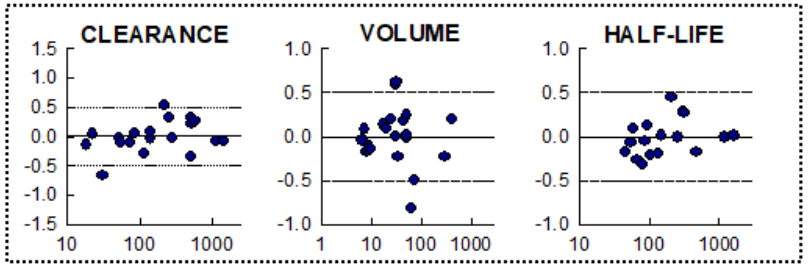




Left: Log-log plot of human predicted clearance ($CL_{pred,global}$) vs observed (CL_{obs}), split by species; *other parameter plots available on request*

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 reauest*





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: $P = a \cdot BW^b$

- $\log P = \log a + b \cdot \log BW$
- $\log a$ = 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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

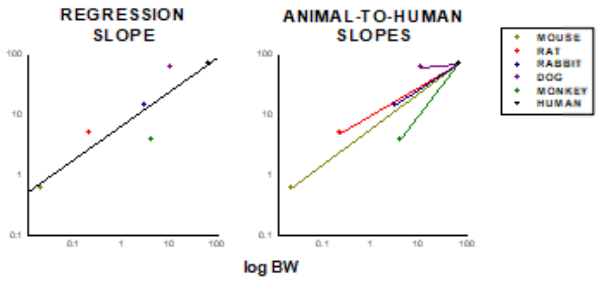


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
- Compared regression line through the [log Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred values that fell within the allowable 10-fold range
- Calculated root mean squared error for each set

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

  - Compared RMSEglobal to RMSEanimal 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 87521

INTRODUCTION

Allometry is used to scale animal data to humans for pharmacokinetic parameter estimation, using the empirical equation: P=a•BWb, 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 t1/2 when making initial predictions. Using published allometric analyses of many different drugs, we examined whether this is valid.

βglobal 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:

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

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 βmouse, βrat, βrabbit, βdog, and βmonkey. 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/βrabbit provided the most predictive estimations of the observed Human values. However, the βglobal values of 0.729 for CL, 0.961 for V, and 0.242 for t1/2 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 (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•BWb
  - 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, 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

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

- βglobal: average (for all drugs) of all regression slopes in (i)
- βanimal: average (for all drugs) of all individual animal-to-human slopes in (ii) (βmouse, βrat, βrabbit, βdog, βmonkey)

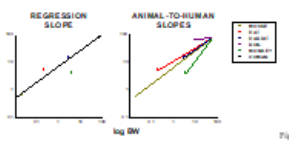


Figure 1: Illustration of the two types of slopes calculated from the log P vs log BW plot of a sample drug. P is some pharmacokinetic parameter, e.g., CL, V, t1/2. Fig A shows the regression line through all points in the plot. Fig B shows the lines connecting each specific animal value to the human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

METHODS, cont.

CALCULATION AND EXAMINATION OF Ppredicted

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

- Predicted human P using:

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

- Compared Ppredicted to Pobserved (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= βanimal 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/βglobal)
- Compared regression line through the [log Ppred vs log Pobs] plot to the line of identity
- Calculated frange, the fraction of Pobs/Ppred 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 RMSEglobal to RMSEanimal to determine the most predictive slope (global or animal)
  - Compared RMSE across species to determine the most predictive species

RESULTS

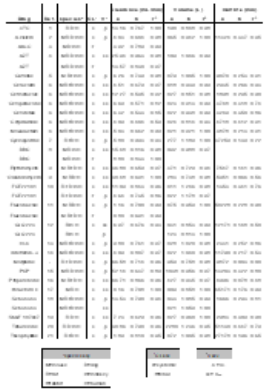


Table 1: Summary of drugs whose pharmacokinetic parameters were evaluated allometrically. The allometric intercept (a) and slope (b) are presented for each parameter along with the coefficients of determination (r^2)

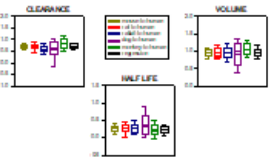


Figure 2: Distribution of the regression slopes and animal-to-human slopes calculated for each drug. The mean of each group is shown by a dotted line and represents the βglobal and βanimal values for each parameter.

RESULTS, cont.

	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	0.949
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	0.896	±	0.382	0.388	±	0.366
β_{monkey}	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227

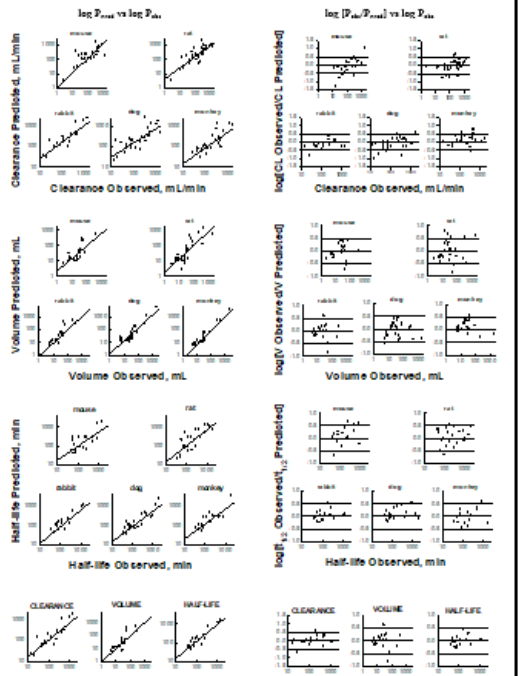


Figure 3: The first three sets of plots : Plots of log Ppred vs log Pobs for each species, where Ppred is based on □global. Ppred and Pobs are human parameter values.

Figure 4: The last set of plots : Plots of log Ppred vs log Pobs plots for the rabbit, where Ppred is based on □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 □global. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs □ Ppred □ 3•Pobs.

Figure 6: The last set of plots : Plots of log(Ppred /Pobs) vs log Pobs plots for the rabbit, where Ppred is based on □rabbit. Ppred and Pobs are human parameter values. The reference lines show the range 1/3•Pobs □ Ppred □ 3•Pobs

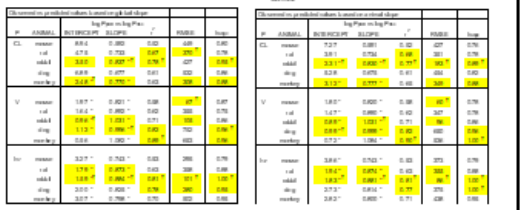


Table 2: Measures used to compare the accuracy of the human predictions based on β_{global} (A), or based on β_{animal} (B). The slope, intercept, and r^2 values are of the regression line through the log Ppred vs log Pobs plot (shown in Figs. 3 and 5); RMSE is the root mean squared error of each set; and frange is the fraction of values that fall within the allowable range on each log Pobs/Ppred vs log Pobs 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_{pred} vs log P_{obs}] 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 $P_{pred} = P_{obs}$ (ideal), then the regression line is the line of identity
  - compare slope to 1
  - compare intercept to 1 (origin of log-log plot)
  - compare 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
    - †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
  - 13/16 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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] 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
    - †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_{range} values for each species/slope pair. Figures 4 and 6 show the [log (P_{obs}/P_{pred}) vs log P_{obs}] plots for each parameter.

- If 1/3•Pobs ≤ Ppred ≤ 3•Pobs for every observation in the set, the frange value would equal 1.0 (100% of the data falls within the allowable range)
  - compare frange to 1.0
    - highlighted values in this column show the two values that are closest to 1.0 for each parameter P
    - †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_{animal} 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 estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{animal} 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:

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

- 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.

Supported by a grant from the National Institute on Drug Abuse (DA08094). ST is supported by an American Foundation for Pharmaceutical Education Pharmaceutics/Biopharmaceutics Fellowship.

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The summary

Larger font

Consistent color coding

No more boxed in text

QR code (it works!)

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

Stacey Tannenbaum* and Michael Mayersohn
College of Pharmacy and Center for Toxicology, University of Arizona, Tucson, AZ 87521

VE SUMMARY

metry scales animal pharmacokinetic data to humans using the equation: W^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 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.**

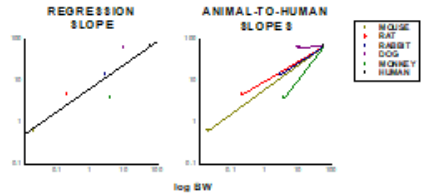
Two slope values were used in the allometric equation to make a prediction for human PK parameters from animal data:

- 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. **The rabbit/β_{rabbit} pair 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.**

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 (t1/2)
- For each drug and parameter P (CL, V, t1/2). 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:

$$P_{pred} = P_{animal} \cdot \left(\frac{BW_{animal}}{BW_{human}}\right)^{b}$$, where b is:

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

ed P_{pred} to P_{obs} (from publication) using the following metrics:
- ression line through log P_{pred} vs log P_{obs} for all drugs
- compare slope and intercept to line of identify (=1 for log-log plot)
- compare r^2 to 1 (perfect correspondence)
- culated 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 Pobs/Ppred values that fell within the range

Calculated root mean squared error (RMSE) for each set:

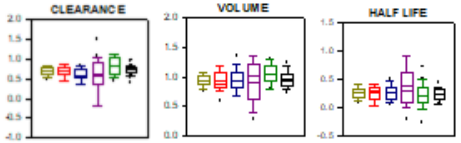
$$RMSE = \sqrt{\frac{\sum (P_{obs} - P_{pred})^2}{n}}$$

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

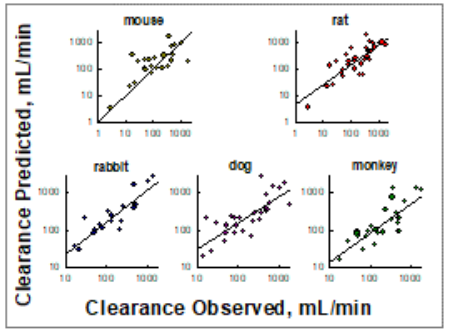
RESULTS

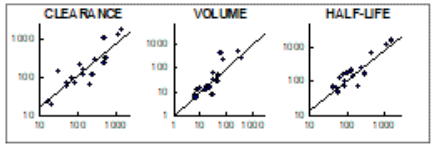
Relevant data from 28 compounds was identified in the literature search *(references available upon request)*

- 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 βglobal and βanimal values for each parameter, shown also in the table below



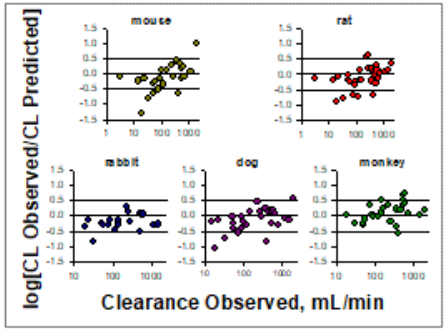
	CL			V			t1/2		
β_{global}	0.729	±	0.120	0.961	±	0.136	0.242	±	[illegible]
β_{animal}	0.702	±	0.137	0.949	±	0.101	0.263	±	[illegible]
β_{rat}	0.696	±	0.153	0.941	±	0.172	[illegible]	±	0.141
β_{rabbit}	0.589	±	0.195	0.937	±	0.229	0.282	±	0.148
β_{dog}	0.571	±	0.513	0.896	±	0.382	0.388	±	0.366
β_{monkey}	0.829	±	0.252	1.054	±	0.180	0.213	±	0.227

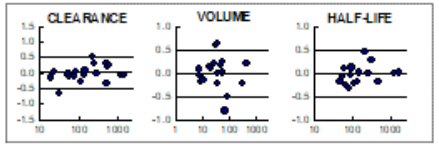




Left: Log-log plot of human predicted clearance ($Cl_{predicted}$) vs observed (Cl_{obs}), split by species; *other parameter plots available on request*

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 (Cl_{obs}/$Cl_{predicted}$) vs Cl_{obs}, split by species; *other parameter plots available on request*

Right: Log-log plot of (P_{obs}/$P_{predicted}$) 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})

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_{animal}				
	log P_{pred} vs log P_{obs}					log P_{pred} vs log P_{obs}				
	INT.	SLOPE	r^2	f_{range}	RMSE	INT.	SLOPE	r^2	f_{range}	RMSE
mouse	8.94	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	351
rabbit	3.50	0.837*	0.78*	0.95†	427	2.31*†	0.830*†	0.77*	0.89†	183†
dog	6.89	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

vs the number of highlighted values for each animal acro
number of those values that were the closest to the id
and r^2 of log-log plot for P_{pred} vs P_{obs}: ideal value = 1 (compared
): 9 possible "best values" (3 per metric)
se=0 (no error): 3 possible best values
=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		frange	
	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_{animal} rather than β_{global}

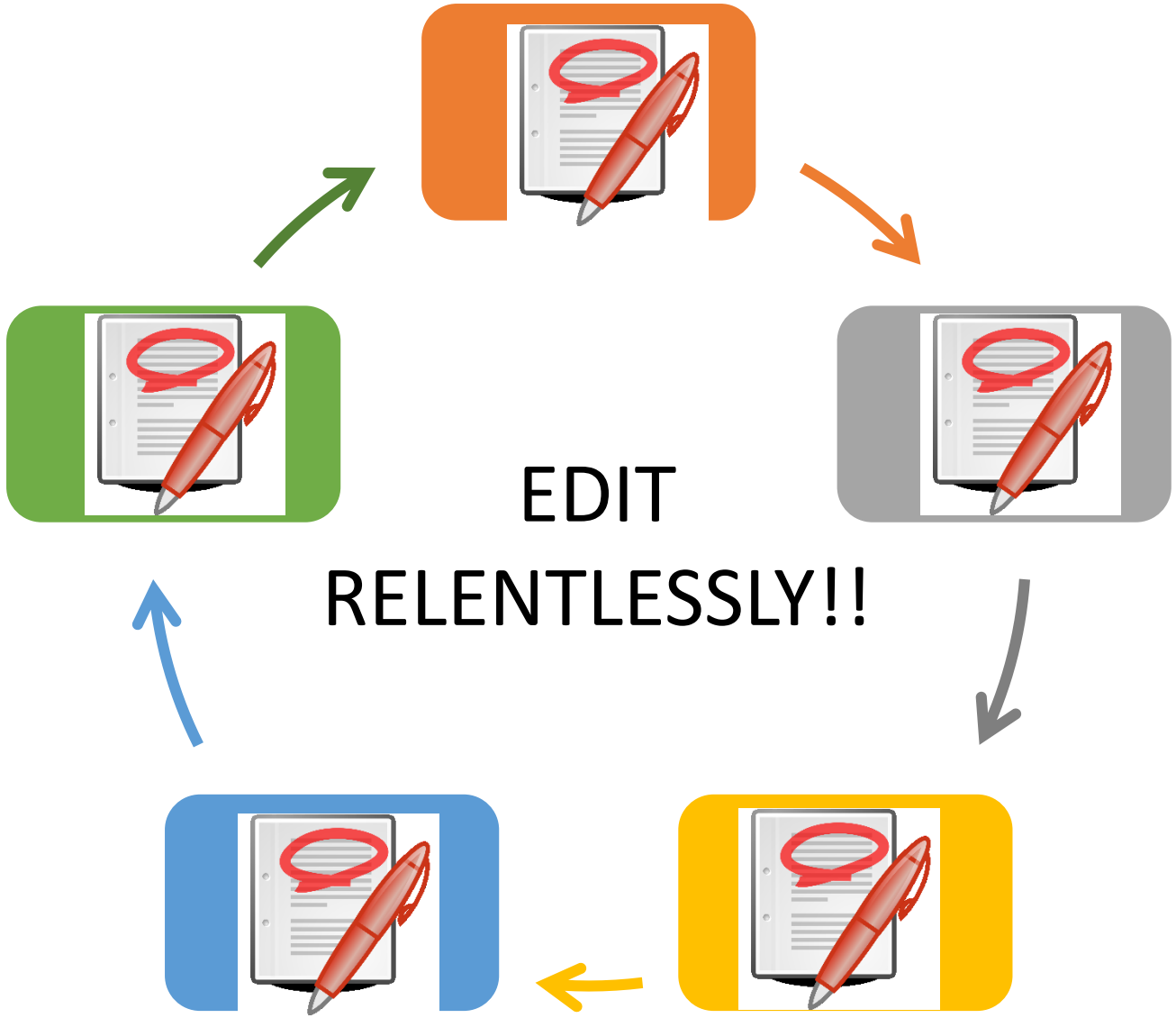
- 9 of 15 times the intercept for the animal was closer to 1 than the global.
- RMSE of the animal predictions were lower than that of the global predictions 12 of 15 times

CONCLUSIONS

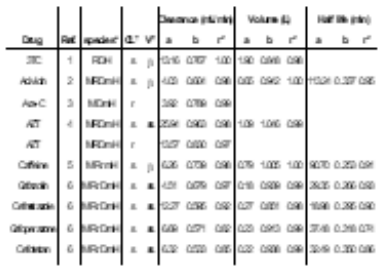
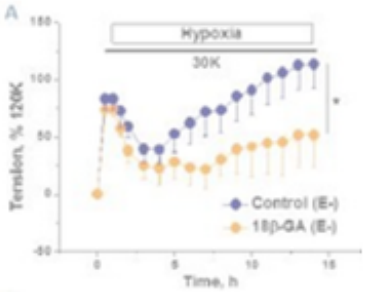
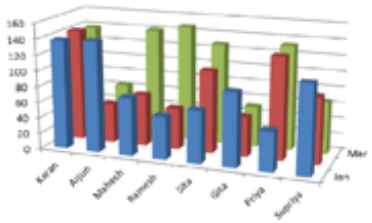
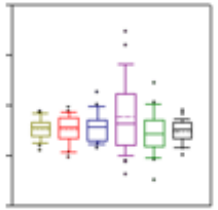
- Use of the slope values of 0.75 for CL, 1.0 for V, and 0.25 for $t_{1/2}$ to compute initial estimates of human parameters is supported by the corresponding calculated global β values of 0.728, 0.961, and 0.242.
- In general, β_{animal} seemed to perform better than β_{global} for predicting the human 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:

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

**Supported by a grant from the National Institute on Drug Ab
is supported by an American Foundation for Pharmaceutica
Pharmaceutics/Biopharmaceutics Fellowship**

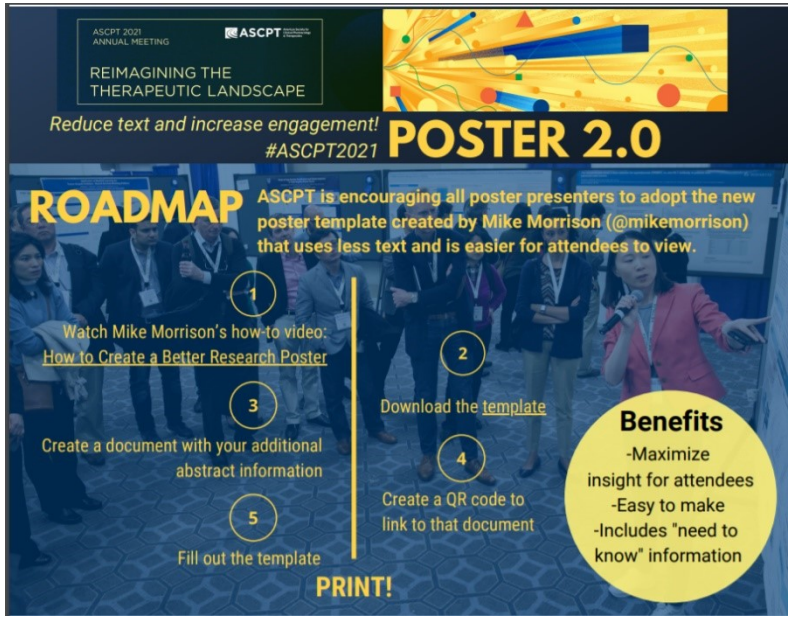


- Spelling
- Grammar
- Formatting
- Color consistency
- Equations
- Legibility
- Clarity
- Figure and table annotation, legends
- Spacing
- Clutter/filler
- Repetition

P	OS	T	E	R
 Poster layout doesn't line up	Boxes Within Boxes	Horizontal letters	More than three fonts	VERY LONG AND COMPLICATED TITLES THAT DON'T INCLUDE A CONCLUSION OR DRAW YOU IN
Gratuitously patterned background	 The wall of numbers	 Fuzzy pictures	 Bad 3D plots	 Figures without legends, axis labels
Over use of color	*Unreadable fonts*	Mispelings and grammer errors	**ALL CAPITALS**	Font too small to read
Lots and lots and lots and lots of dense text crammed together so it's basically unreadable	Too many ***emphasis*** formats	Comic sans	Tmax t_{max} T_{max} tmax Inconsistency	No links, or QR code to get more info

Concept adapted from Bonate, Creating and Presenting Captivating Posters, AAPS webinar

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



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).

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.

QR Code

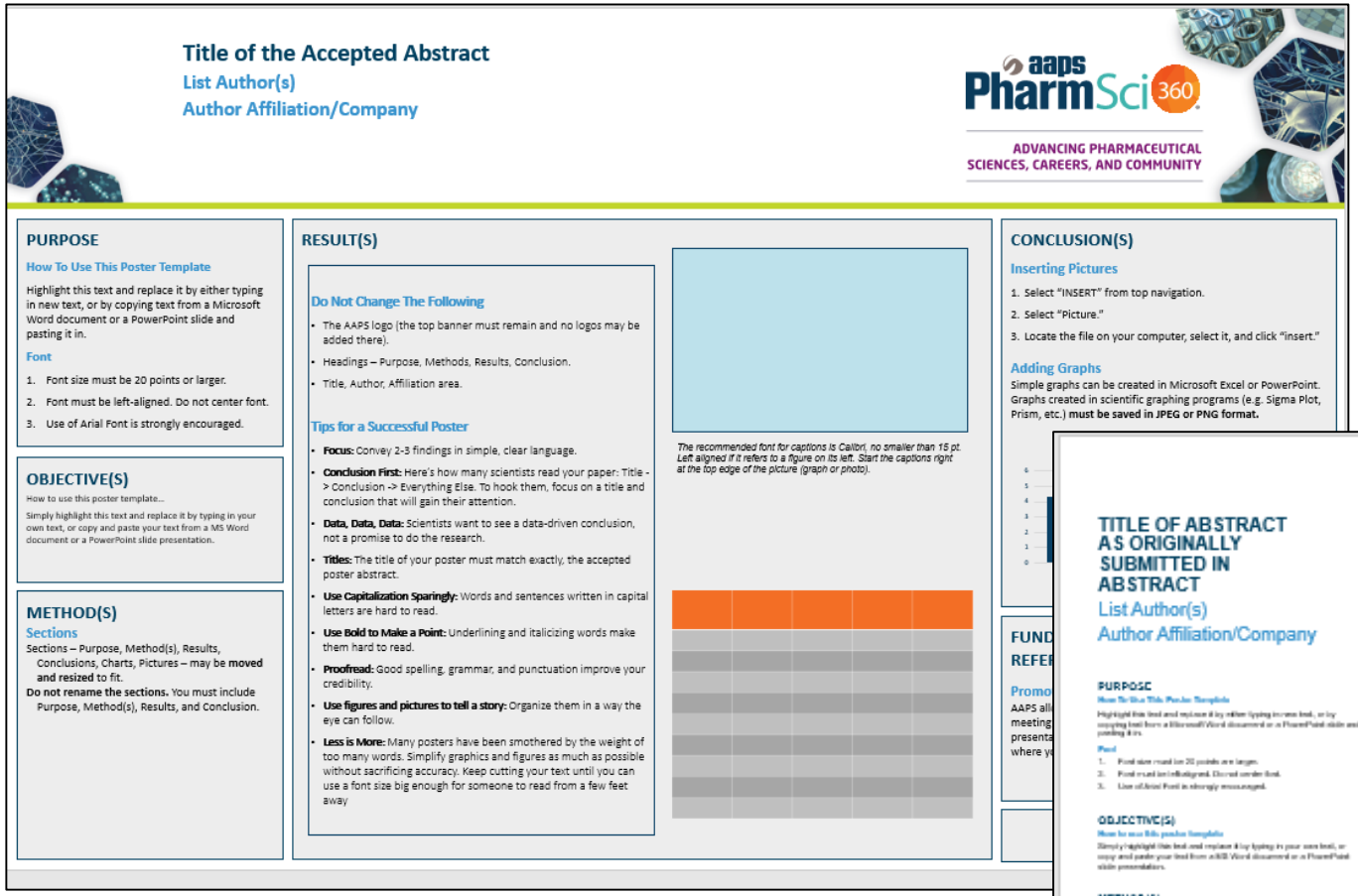
Point your phone camera at this and instantly download the full paper, a copy of the poster, the presenter's details... and/or even the data set powering the study.

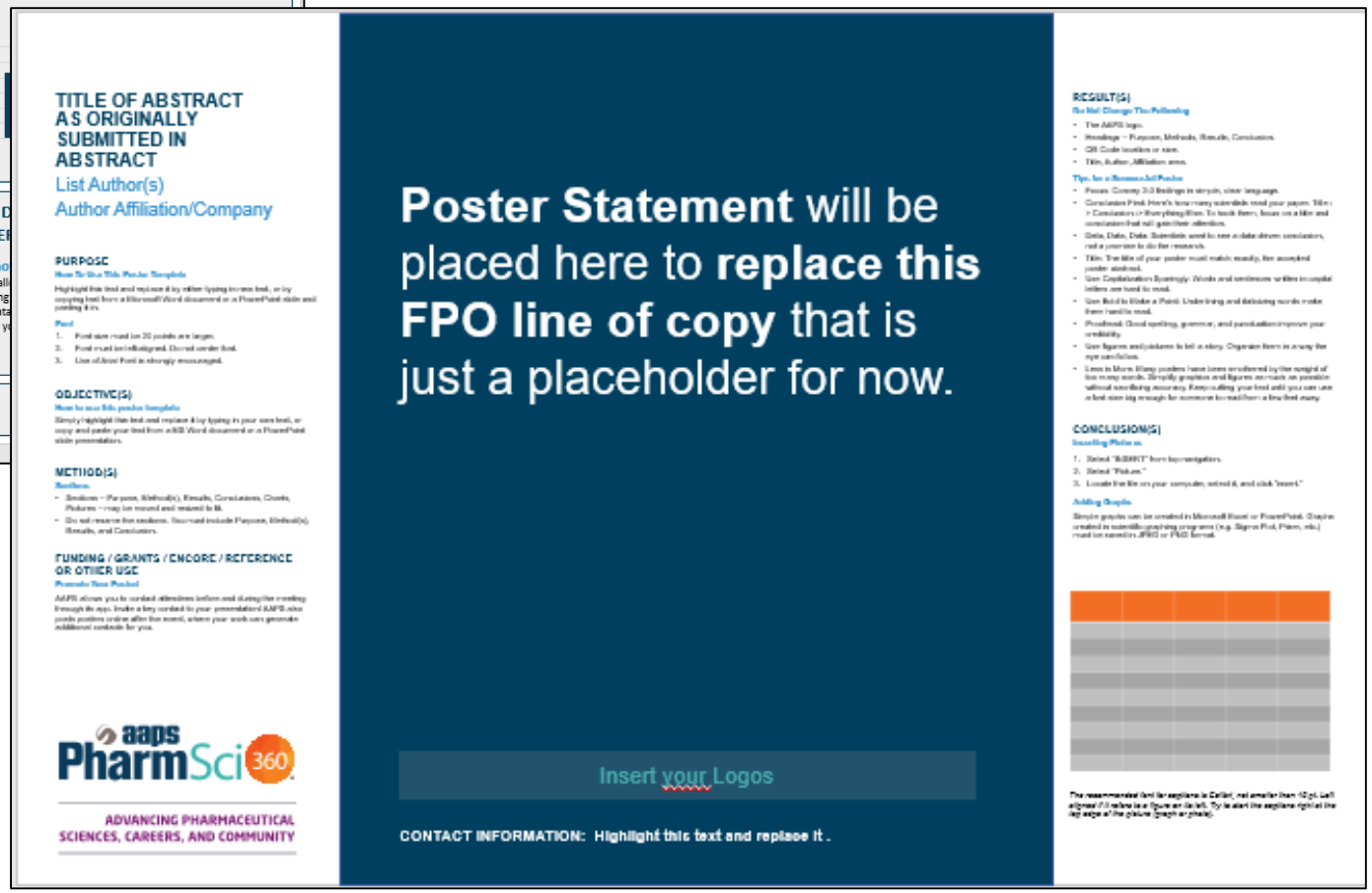
Main Finding

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.

https://www.ascpt.org/Portals/28/docs/Annual%20Meetings/2021%20Annual%20Meeting/Call%20for%20submissions/ASCPT%202021%20Poster%202.0%20v%202.pdf?ver=2020-07-15-100341-613





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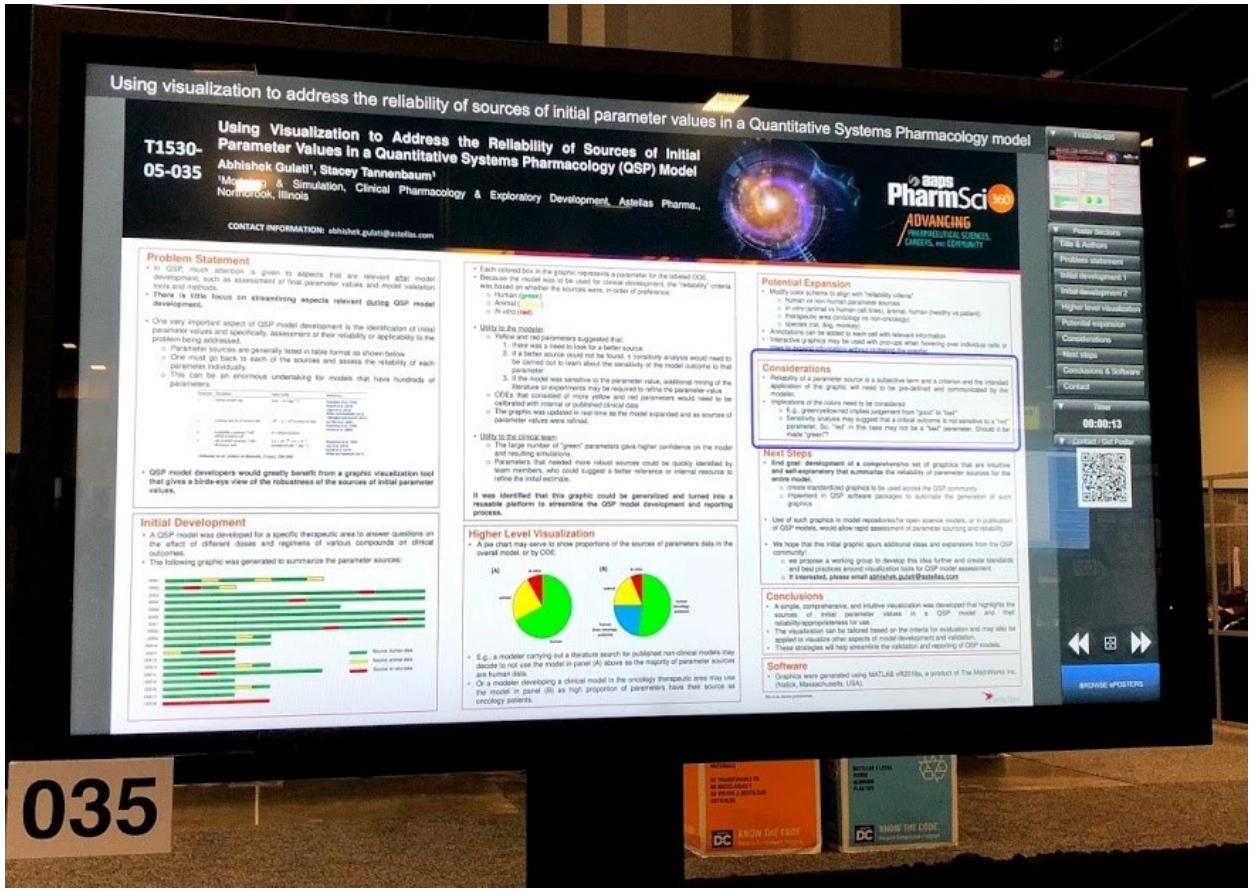
AAPS: American Association of Pharmaceutical Scientists

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



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

ePoster With Audio Narration

aaps PharmSci 360

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 Orlowski, Professor**
Department of Physiology, McGill University, Montreal, QC, Canada

MULTILEARNING

ABSTRACT

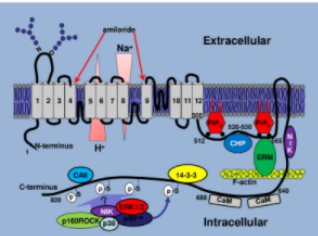
Restoration of cardiac intracellular pH (pHi) following acidification is of crucial importance for the maintenance of myocardial contractility. The primary mechanism responsible for this is the function of the sodium/proton exchanger isoform 1 (NHE1). NHE1 is localized predominantly at the intercalated 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 HOMOLGOUS PROTEIN 3

CHP3, CALCIUM & MYRISTOYLATION

N-myristoylation and Ca^{2+}-binding are crucial for cell surface

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+

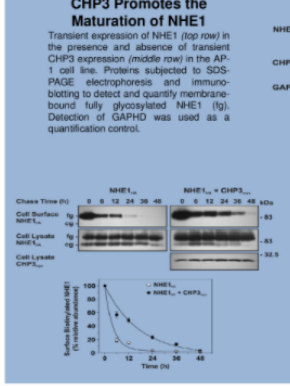
FUNCTION

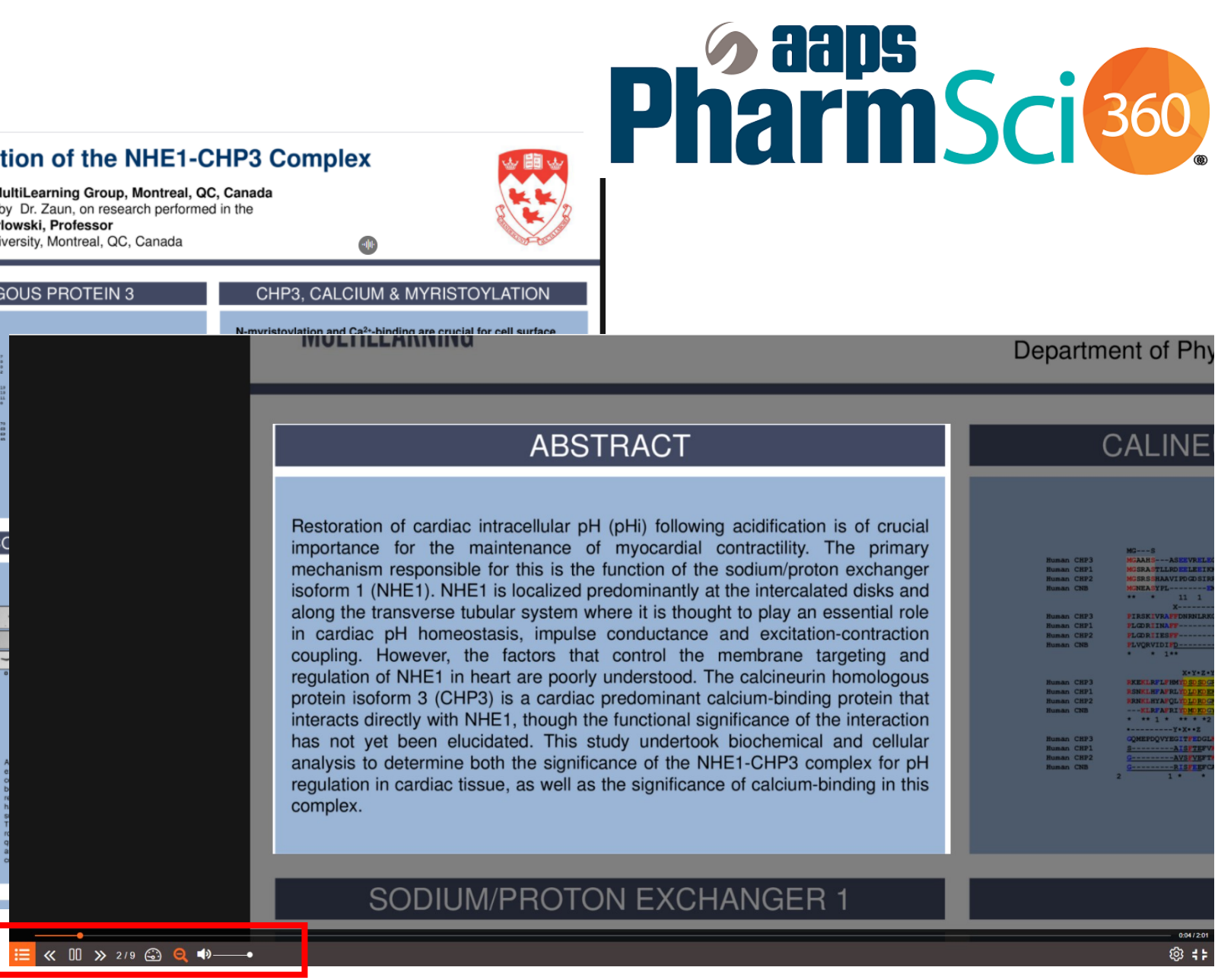
- pH homeostasis (cytoplasmic and organellar)
- Cell volume regulation
- Cell Proliferation, shape, and migration.

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 immuno-blotting to detect and quantify membrane-bound fully glycosylated NHE1 (fg). Detection of GAPHD was used as a quantification control.





ePoster With Audio Narration

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CALINEURIN HOMOLGOUS PROTEIN 3

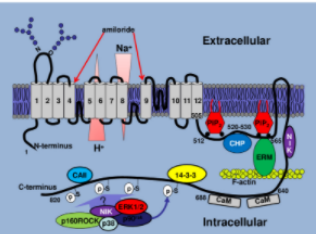
- Specifically interacts with the cytosolic tail of NHE1.
- Novel N-myristoylated regulatory protein containing a putative EF-Hand Ca^{2+}-binding motif.
- Potential role in regulation of NHE1 in cardiac tissues.

CHP3, CALCIUM & MYRISTOYLATION

N-myristoylation and Ca^{2+}-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-mysitoylation-deficient CHP3, or calcium-binding deficient CHP3 were subject to cell surface labelling. 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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NHE1-CHP3 COMPLEX

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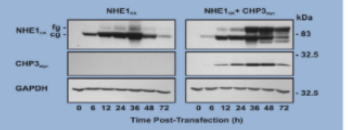
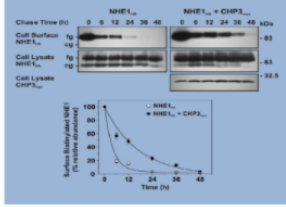
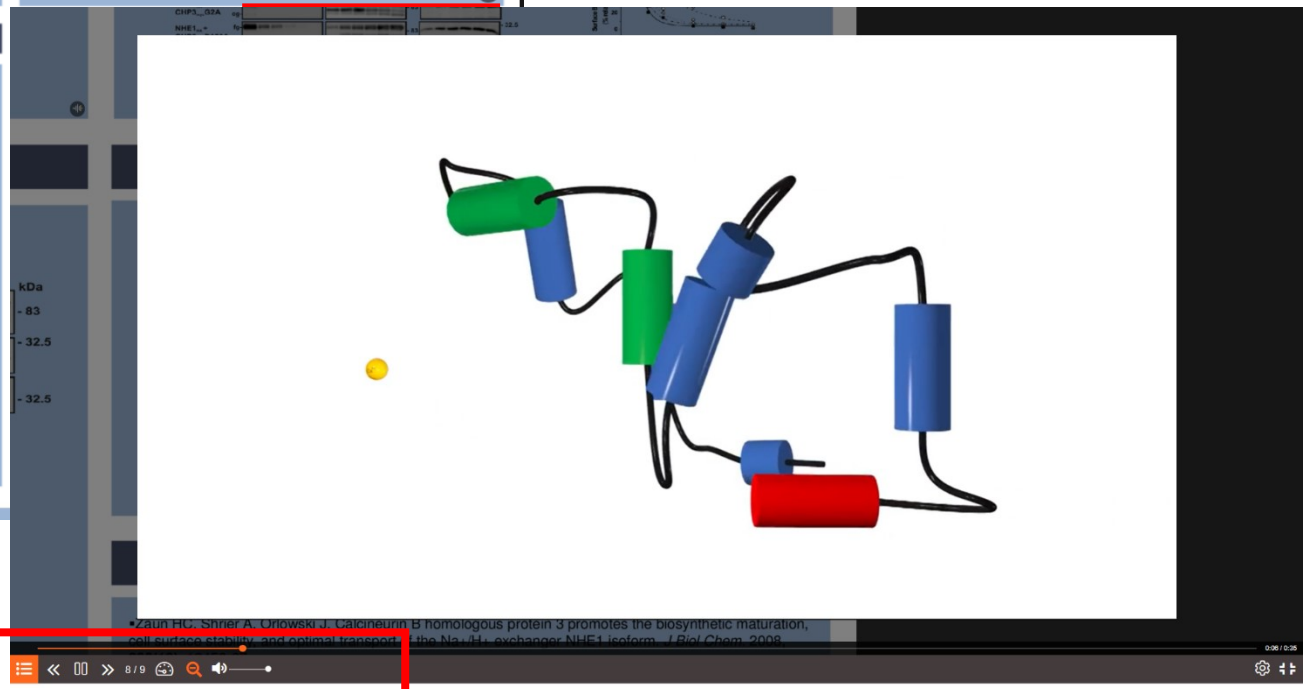
Transient expression of NHE1 *(top row)* in the presence and absence of transient CHP3 expression *(middle row)* in the AP-1 cell line. Proteins subjected to SDS-PAGE electrophoresis and immuno-blotting to detect and quantify membrane-bound fully glycosylated NHE1 (fg). Detection of GAPHD was used as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



CHP3 Promotes the Cell Surface Stability of NHE1

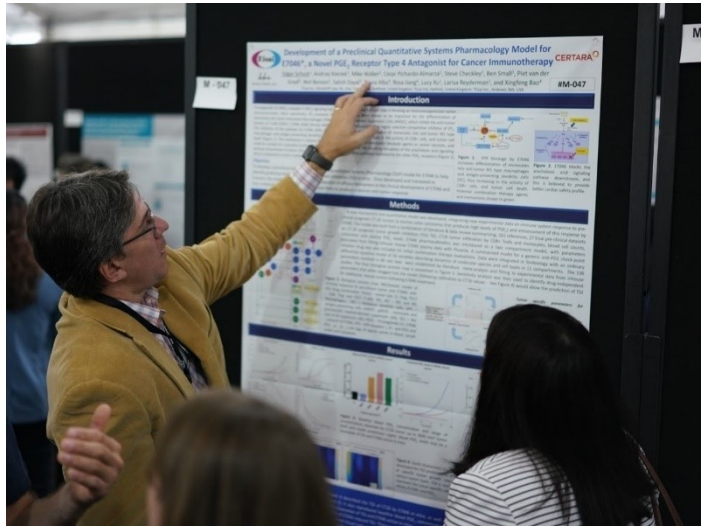
AP-1 cells stably expressing NHE1 alone or co-expressing NHE1 and CHP3 were subject to cell surface biotinylation to label membrane-bound fully-glycosylated NHE1 (fg). Cells were returned to growth media and the protein was harvested at varying time points. Proteins were subject to SDS-PAGE and immuno-blotting. 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.





Songmao (Ben) Zheng
ACoP9 2018

Science Producer



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  - 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

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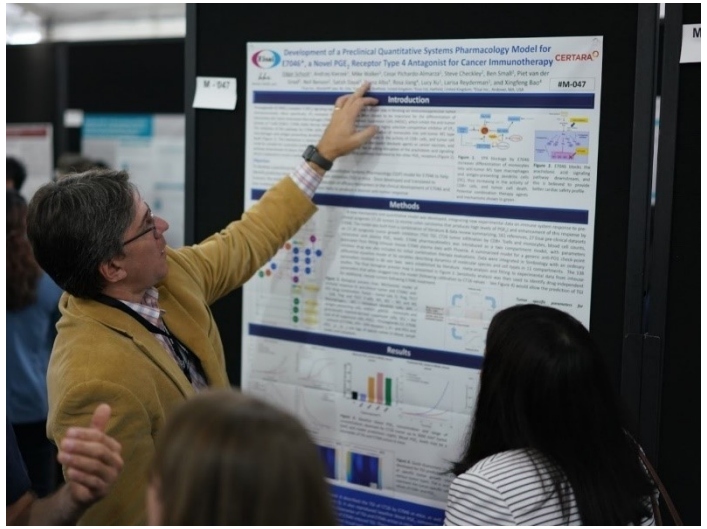
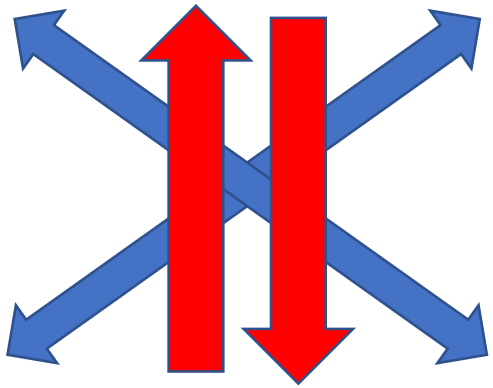
Science Producer





- 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

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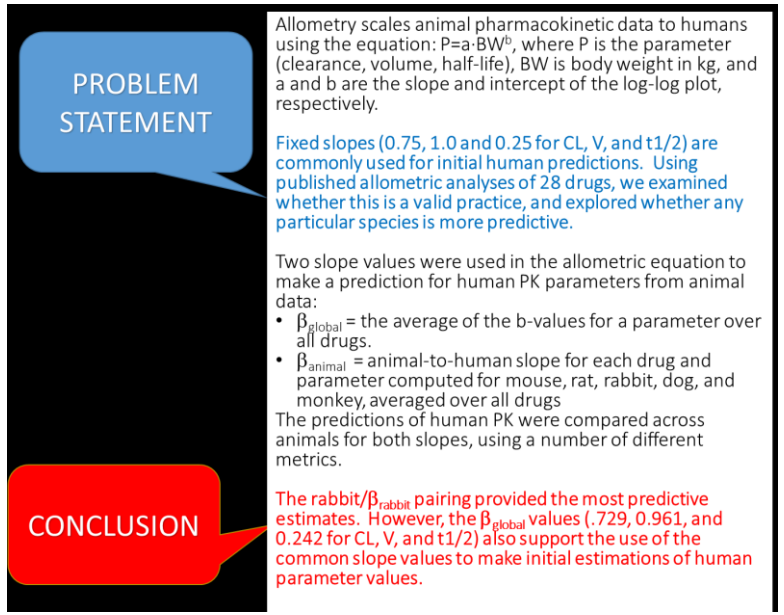
- Confirm the time and format (live, audio, video, screen capture) and adjust your content to fit
  - 30 second basic intro/advertisement vs full poster walk through (3-5 minutes max)
  - Stick to your allotted time- shows respect for the listener
- Your summary is a great starting point
  - Problem statement/conclusion at a minimum
  - Then fill in gaps for time allotted

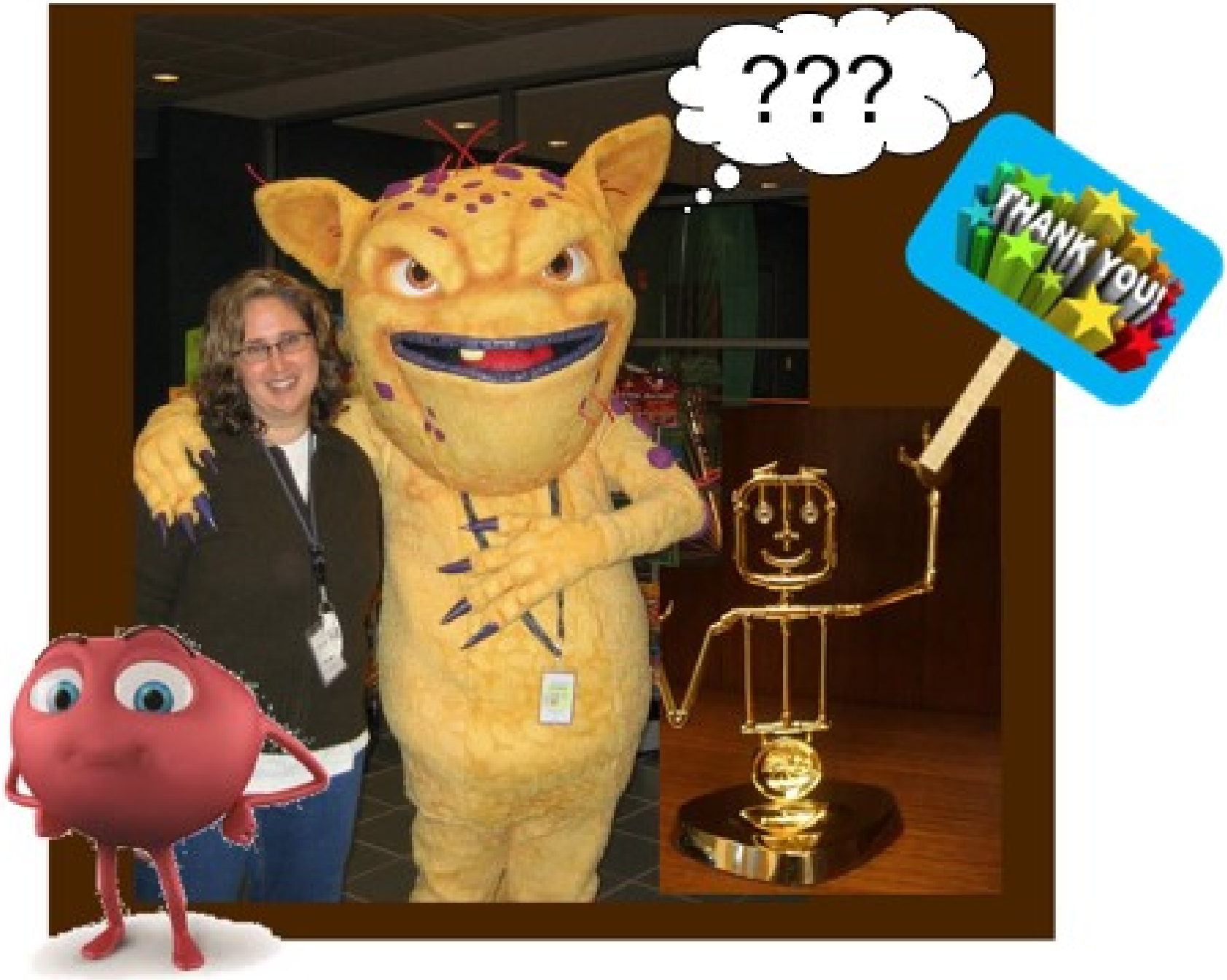
- Tell people why they should care about your research
- Pique their interest with a hook
  - Hit the highlights- don't give everything away!
  - Give them a reason to visit your poster
- Maybe leave them with an assignment (a question, a discussion point, etc) to bring to the Q&A

- ***PRACTICE PRACTICE PRACTICE***



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

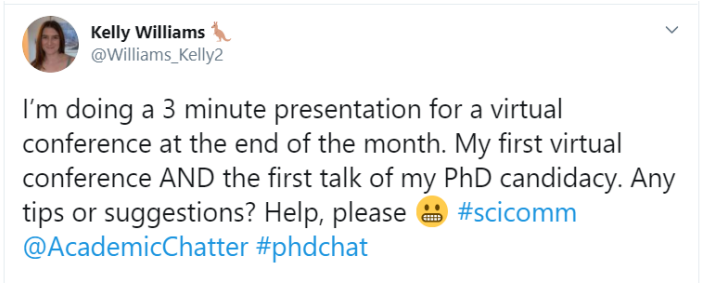
- Good science does not necessarily make a good poster!
  - A poorly prepared or presented poster is a lost opportunity to engage with science consumers
- Poster prep is not a trivial activity
  - Skills you develop will help you throughout your career
- **Put forth the time, effort, and energy to make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

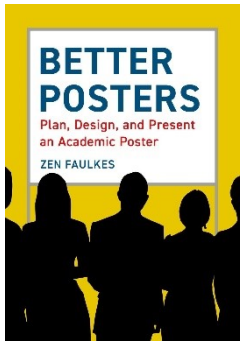


- Rebecca Baillie
- Peter Bonate
- Bill Williams
- Joy Davis
- Stefanie Hennig
- Matt Riggs
- Peiying Zuo
- Eric Jordie
- Poster presenters everywhere ☺

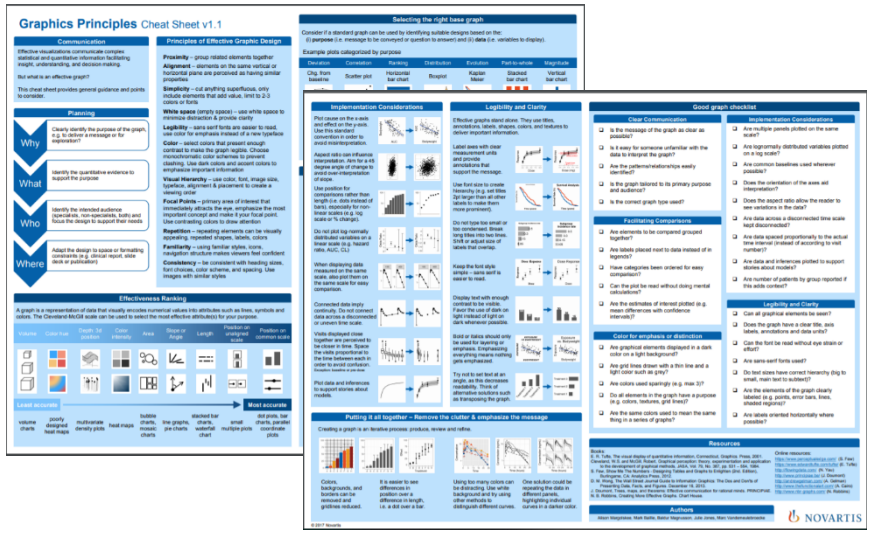
References

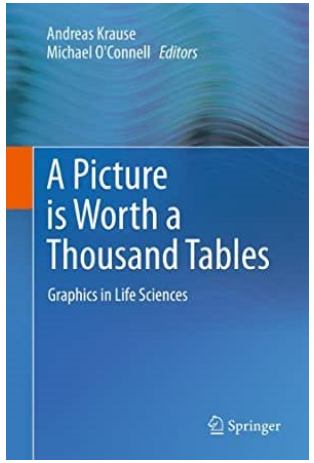
- [Mike Morrison (#betterposter) You Tube Channel]
- [Better Posters blog]
- [http://mkweb.bcgsc.ca/poster.design/]
- [3 minute thesis (3MT)]
- [1 minute poster pitch]
- [THIS ↓TWEET]





- [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 'Moster' of Your Poster

Stacey Tannenbaum

Astellas Pharma

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ROSA