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# Interspecies scaling and prediction of human clearance: comparison of small- and macro-molecule drugs

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## Abstract

1. Human clearance prediction for small- and macro-molecule drugs was evaluated and compared using various scaling methods and statistical analysis.
2. Human clearance is generally well predicted using single or multiple species simple allometry for macro- and small-molecule drugs excreted renally.
3. The prediction error is higher for hepatically eliminated small-molecules using single or multiple species simple allometry scaling, and it appears that the prediction error is mainly associated with drugs with low hepatic extraction ratio (Eh). The error in human clearance prediction for hepatically eliminated small-molecules was reduced using scaling methods with a correction of maximum life span (MLP) or brain weight (BRW).
4. Human clearance of both small- and macro-molecule drugs is well predicted using the monkey liver blood flow method. Predictions using liver blood flow from other species did not work as well, especially for the small-molecule drugs.

### Keywords

Interspecies scaling; human clearance prediction; small-molecule; macro-molecule; liver blood flow

## Introduction

Allometric scaling is an empirical approach developed based on cross species similarities in anatomy, physiology, and biochemistry with a power function correlating physiological parameters with body size ($Y = aW^b$, where Y is the parameter of interest, W is the body weight, and a and b are the coefficient and exponent of the allometric equation, respectively). This method has been applied to the projection of human pharmacokinetics for small-molecule drugs as well as therapeutic proteins and is widely used in the pharmaceutical industry for early decision making at several stages in drug discovery and development (e.g., lead compound selection and optimization, first dose in human, etc).



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It is known that allometric projections generally work well for drugs mainly renally eliminated. However, for some small-molecule drugs with high cross-species variability in hepatic metabolism, this method may not work well in the extrapolation of hepatic metabolic CL from laboratory animals to humans. To improve the predictability of metabolic CL in humans, several modified scaling methods have been suggested and examined. Because longevity is frequently inversely correlated with hepatic cytochrome P450 drug oxidation rates, maximum life-span potential (MLP) and brain weight (BRW) were proposed as correction factors in allometric scaling by Boxenbaum (Boxenbaum, 1982). His work was later supported by other scientists, and their work also demonstrated that MLP and BRW corrections improved the accuracy of human CL prediction when the allometry power exponent b was higher than 0.80–0.90 (Feng et al., 2000, Mahmood and Balian, 1996). Recently, Nagilla and Ward suggested using liver blood flow (LBF) as a correction factor for the scaling of small-molecule drugs (Nagilla and Ward, 2004). Based on their analysis of 103 compounds comparing simple allometry with LBF or MLP/BRW correction, they concluded that scaling with monkey liver blood flow was the best approach among the methods tested (68% success rate). These modified approaches have improved the accuracy of prediction to some extent.

While many studies have demonstrated the use of allometric scaling in the prediction of human CL for small-molecule drugs, only a few articles reported the application of this method to macro-molecule drugs. Currently, the market of biotherapeutics, including peptide, protein and oligonucleotide drugs have been growing rapidly. The annual growth rate of biotherapeutics sales was approximately 20% from 2001 and 2006, which is much higher compared to a growth rate of only 6–8% for small-molecule drugs (Aggarwal, 2007). Although the general principles of pharmacokinetics and pharmacodynamics are applicable to biotherapeutics, their disposition in the body is known to be unique and different from conventional small-molecules (Tang et al., 2004, Lin, 2009). The binding process of biotherapeutics with receptors or other targets in the body may be species- specific and saturable exhibiting non-linear kinetics. In addition, protein drugs derived from human sources may be recognized as a foreign compound in animal species and thereby induce immune system mediated reaction, known as immunogenicity. Therefore, differences are expected in interspecies scaling from animals to humans when comparing small- versus macro-molecule drugs. Since clearance is an important pharmacokinetic parameter critical for the design of first-time-in-human study and the selection of dose regimen, it is important to understand differences and the mechanism associated with the human clearance prediction between small and macro-molecule drugs.

Positive results from human clearance prediction of macro-molecule drugs using allometric scaling have already been reported by several groups (Mordenti et al., 1991, Mahmood, 2004, Mahmood, 2009b, Ling et al., 2009, Wang and Prueksaritanont, 2010). Mordenti et al demonstrated reasonable accuracy in predicting human clearance and volume of distribution using interspecies scaling for five protein drugs with molecular weights ranging from 6 to 98 kDa (Mordenti et al., 1991). Mahmood expanded the data set to 15 therapeutic proteins and reported a low prediction error of human clearance (Mahmood, 2004, Mahmood, 2009b). He also suggested the use of at least three animal species for interspecies scaling. However, acceptable prediction of human clearance using single animal species for macro-molecule

drugs has also been reported later by Ling and Wang (Ling et al., 2009, Wang and Prueksaritanont, 2010). Ling et al suggested using a fixed exponent of '0.85' or '0.90' for human CL prediction of monoclonal antibody drugs, and '0.80' was suggested by Wang and Prueksaritanont not only for monoclonal antibodies, but also for other protein drugs.

In this study, literature data for small- and macro-molecule drugs were collected and analyzed by various allometry methods using single or multiple species scaling, and the accuracy of human clearance prediction was compared. For macro-molecule drugs, almost all the peptide and protein drugs previously reported in the literature with molecular weights ranging from 1 to 340 kDa were included in our data set, along with several oligonucleotide drugs. As a result, this study provides very useful information of the potential application of allometric scaling in human clearance prediction for both small- and macro-molecule drugs.

## Methods

### Data collection

Clearance data of 675 small-molecule drugs and 80 macro-molecule drugs following intravenous administration were obtained from the literature. The criteria that divide the drugs into small versus macro-molecule is 1000 Da. Drugs having molecular weights greater than 1000 Da are regarded as macro-molecule and the others as small-molecule. Based on these criteria, all biotherapeutics including protein, peptide and oligonucleotide drugs were classified as macro-molecule drugs. The clearance of 81 of the small-molecule drugs in animals and humans were collected and used for the analysis of interspecies scaling and compared with 53 of macro-molecule drugs in human clearance prediction (Tables 1 and 2).

### Allometric scaling using single species

Human clearance was predicted using single species with the allometry exponent fixed at 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, or 0.90. The following equation was used to calculate human clearance:

$$Clearance_{human} = Clearance_{animal} \times (BW_{human}/BW_{animal})^{b} \quad (1)$$

where BW is the body weight and b is the allometry exponent. Based on the availability of literature data, 36, 78, 78, and 63 small-, and 25, 40, 19, and 43 macro-molecule drugs were used in single species scaling for mouse, rat, dog, and monkey, respectively.

### Single species scaling using liver blood flow

Human clearance was estimated using liver blood flow (LBF) with the following equation as proposed by Ward and Smith (Ward and Smith, 2004):

$$Clearance_{human} = Clearance_{animal} \times (LBF_{human}/LBF_{animal}) \quad (2)$$

LBF values used for mouse, rat, dog, monkey and human were 90.0, 55.2, 30.9, 43.6 and 20.7 mL/min/kg, respectively (Davies and Morris, 1993). To be used in this equation, each

LBF value was multiplied by the corresponding body weight. For example, for a mouse weighting 0.02 kg, the $LBF_{mouse}$ became 1.8 mL/min.

## Allometric scaling using multiple species

Several methods (i.e. simple allometry, exponent rule-corrected allometry, multiexponential allometry and exponent rule-corrected multiexponential allometry) were evaluated. At least three animal species were used for the scaling and the prediction of human clearance for each compound. Based on the availability of literature data, 81 small- and 36 macro-molecule drugs were used in multiple species scaling. Small-molecule drugs were divided by 3 groups based on elimination mechanism: (1) “hepatic”– if the drugs are mainly eliminated via metabolism or biliary excretion ($n$ = 50), (2) “renal”– if most of drug molecules are eliminated renally as unchanged ($n$ = 19), (3) “mixed” - if both renal and hepatic routes contribute to the elimination ($n$ = 12).

**Simple allometry (SA)—**Human clearance was predicted with the following allometric equation as previously described (Boxenbaum and DiLea, 1995):

$$Clearance = a(BW)^b \quad (3)$$

where a is the coefficient and b is the allometry exponent.

**Exponent rule-corrected allometry (ROE)—**As mentioned previously, Boxenbaum (1982) proposed using maximum life-span potential (MLP) and brain weight (BRW) as correction factors in allometric scaling since longevity is frequently inversely correlated with hepatic cytochrome P450 drug oxidation rates. The application of MLP and BRW were also assessed and supported by other scientists including Feng (Feng et al., 2000), and Mahmood and Balian (Mahmood and Balian, 1996). In this study, the exponent rule-corrected method previously suggested by Mahmood and Balian was adopted: If $b < 0.71$ in simple allometry, no correction factor was applied; if $0.71 \leq b < 1$, MLP was used as a correction factor; if $1 \leq b$, BRW was used as an correction factor. Human clearance was predicted using the following equations:

$$Clearance \times MLP = a(BW)^b \quad (4)$$

$$Clearance \times BRW = a(BW)^b \quad (5)$$

BRW values were 1.65, 0.57, 0.78, 1.56, and 2% of body weight, and the MLP values 2.7, 4.7, 22.0, 20.0, and 93.4 for mouse, rat, dog, monkey, and human, respectively (Brown et al., 1997, Sacher, 2008).

**Multiexponential allometry (MA)—**Multiexponential allometry method was used to predict human clearance as suggested by Goteti et al using the following equation (Goteti et al., 2008):

$$CL = aBW^b + \left[\frac{(1-\frac{3}{2}b)}{(1-\frac{1}{2}b)}\right] aBW^{0.9} \quad (6)$$

where a and b are the coefficient and the allometry exponent determined from the simple allometry analysis.

**Exponent rule-corrected multiexponential allometry (SA+MA)—**Human clearance was predicted using simple allometry method if the exponent b is < 0.71 with no correction factor applied. If the exponent b is ≥ 0.71, the multiexponential allometry equation listed above was used for human clearance prediction.

### Relationship between CL and molecular size

Literature data of 675 small- and 80 macro-molecule drugs were collected and the correlation between total clearance and molecular weight (MW) was assessed.

### Statistical analysis

Average-fold error (AFE) for human CL prediction was calculated based on equation 7 (Bolton, 1997) and used to compare the various prediction methods,

$$AFE = 10^{\sum |\log(predicted/actual)|/N} \quad (7)$$

By using this equation, under-estimations can have the same magnitude of error as over-estimations. For example, a 2-fold over-prediction and under-prediction would have the same value of 2 for AFE.

Student's *t*-test was used to determine the statistical differences in AFE values between two groups and $p < 0.05$ was considered statistically significant. For multiple-group comparison in AFE values, analysis of variance (ANOVA) was performed followed by Tukey or Student's *t*-test.

## Results

### Scaling using single species

The results from single species scaling with a fixed allometry exponent are summarized in Figures 1–3. For macro-molecule drugs, human clearance is generally well predicted with average-fold error < 2 using a fixed allometry exponent of 0.75–0.80. Increase or decrease of the exponent "b" only results in a small fluctuation of the AFE (Figure 1b). It appears that human clearance of macro- molecules is best predicted using monkey as a single species with the AFE value of 1.45, which is statistically lower ($p < 0.05$) than the AFEs of 1.89, 1.94, 1.72 using mouse, rat or dog for single species scaling with optimal allometry exponent fixed at 0.80 (Figure 3). For the small-molecule drugs, human clearance is best predicted using a fixed allometry exponent of 0.65–0.70. The AFEs for small-molecule drugs increased significantly when the exponent "b" value was higher than 0.80 (Figure 1a). The AFEs are 2.67, 2.31, 2.50, and 2.00, respectively, using mouse, rat, dog, or monkey as a

single species with an optimal allometry exponent fixed at 0.65. Those AFE values are not statistically different across the species, although human clearance appears better predicted using monkey data. As shown in Figure 1c, when the small-molecule drugs are divided by 3 groups based on elimination mechanism: “hepatic”, “renal” and “mixed”, similar trend is observed with human clearance best predicted using a fixed allometry exponent of 0.65–0.70 and the AFEs increased significantly when the exponent “b” value was higher than 0.80. The correlation between the prediction accuracy [ratio of predicted/observed (Pred/Obs)] and the actual value of human clearance for small-molecule drugs using single species allometric scaling with fixed exponent of 0.65 is presented in Figure 2 and the plots suggest the prediction error is mainly associated with drugs with low extraction ratio.

Prediction of human clearance using single species liver blood flow is also examined in this study for macro- and hepatically eliminated small-molecule drugs, and the results suggest that human clearance is well predicted with AFE ≤ 2.0 for all drugs using monkey liver blood flow (Table 3). However, the liver blood flow method did not work as well using other species especially for the small-molecule drugs with high AFE values of 4.04, 3.47, and 2.83 in mouse, rat, and dog, respectively.

## Scaling using multiple species

The multiple species scaling methods, SA, ROE, MA and exponent rule-corrected MA (SA+MA), are evaluated in this study. Although several studies have reported the scaling of 2 animal species for the prediction of human clearance, we used three or more species in our analysis and the results are summarized in Table 4a and 4b. The results indicated that the SA method delivered a high accuracy in human clearance prediction for macro-molecule drugs with an AFE of 1.67, and no additional correction using MLP or BRW seems needed. This may be explained by their elimination mechanism. The therapeutic proteins are mainly eliminated by non-specific proteolysis that is very different compared to the complicated oxidative metabolic pathways for small-molecule drugs. Therefore, the use of ROE, MA, and SA+MA did not improve the prediction of human clearance for macromolecule drugs and resulted in a higher AFE of 2.06, 1.87, and 1.95, respectively. As mentioned previously, the small-molecule drugs were grouped by mechanism of elimination to assess if the elimination mechanism may affect the prediction accuracy of human clearance. As listed in Table 4a, for drugs in the “renal” group, the human clearance is generally well predicted using simple allometry with AFE of 1.84 and it appears that no MLP or BRW correction is needed for those drugs. The AFEs from ROE, MA, and SA+MA methods are 1.95, 1.73, 1.66, respectively and not statistically different from the AFE of the SA method. The AFE of human clearance prediction is 3.14 using the SA method for drugs in the “hepatic” group, which is statistically significantly higher than the values in other groups ($p < 0.05$). Results from additional analysis presented in Table 4b indicated that the prediction error for hepatically eliminated small-molecules is mainly associated with drugs with low hepatic extraction ratio (Eh) with AFE of 4.51. The AFE is 2.46 and 1.35 for drugs with medium and high Eh, respectively, and the AFE in the high Eh group is significantly lower ($p < 0.05$) than the corresponding values in the other two groups, which is consistent with the outcome from single species scaling (Figure 2) and the literature information as the elimination process of drugs with high Eh is mainly controlled by liver blood flow, a physiological

parameter extrapolated very well from animals to humans (Feng et al 1998a and 1998b). Correction with MLP or BRW did help to reduce the prediction error for hepatically eliminated drugs with low and medium Eh. The AFE is 2.25 for small-molecule drugs in the mixed group and the correction with MLP or BRW also reduced the error of prediction (Table 4a).

### Relationship between CL and molecular size

The relationship between human clearance and molecular weight is presented in Figure 4. The small-molecule drugs were divided into 3 groups with MW < 300 Da in group 1 ($n$ = 233), 300 ≤ MW < 400 Da in group 2 ($n$ = 221); and 400 ≤ MW < 500 Da in group 3 ($n$ = 221). Based on one-way ANOVA analysis, the clearance values in the 3 groups are not statistically different ($p > 0.05$). The macro-molecule drugs were also divided into 2 groups with MW < 69 kDa in group 1 ($n$ = 49) and MW ≥ 69 kDa in group 2 ($n$ = 29). The clearance values in group 2 are significantly lower and statistically different compared to those in group 1 based on $t$-test ($p < 0.01$).

## Discussion

### Scaling using single species

Single species scaling with a fixed allometry exponent or using LBF was evaluated in the current study. Although there are different opinions regarding the use of single species scaling (Mahmood, 2009a, Mahmood, 2005), the method does have advantages in the respect of cost-effectiveness. Finding an optimal value for the allometry exponent in single species scaling is always a challenge. Although previous studies have suggested there could be a universal exponent value across animal species, the reported results are still controversial (Hu and Chiu, 2009, Hu and Hayton, 2001). In our study, optimal allometry exponent values of ‘0.65–0.70’ with AFE of 2.40–2.49 were identified that generally worked best for human clearance predictions for small-molecules, while for the macro-molecules, optimal exponent value of ‘0.75–0.80’ with AFE of 1.75–1.77 were selected. These values are close to the historically recommended standard exponent value of ‘0.75’ in interspecies scaling derived from the observation that basal metabolic rates across species could be scaled by body weight with an exponent of ‘0.75’ (Kleiber, 1947, Feldman and McMahon, 1983). For the macro-molecules, the prediction error from single species scaling is generally within 2-fold for majority of the drugs in our analysis (Figure 3), which is consistent with other results in the literature (Ling et al., 2009, Wang and Prueksaritanont, 2010). Most macro-molecule drugs are peptides or proteins that are eliminated from the body via non-specific proteolysis, a process very different from the complicated oxidative metabolic pathways for small-molecule drugs. It is known that ubiquitously expressed proteolytic enzymes responsible for the elimination of macro-molecules are universal across animal species, which could help to explain the successful extrapolation from animals to humans for macro-molecule drugs. As mentioned previously, several antisense oligonucleotide drugs (e.g., ISIS compounds) were included in the macro-molecule category. Oligonucleotide drugs are mainly eliminated from the body by metabolic pathways via nucleases (Levin, 1999, Levin et al., 2001). Nucleases are also ubiquitously expressed throughout the body and could be scaled across animal species. Interestingly, it

has been shown that the plasma clearance values of ISIS compounds are quite similar in rat, rabbit, dog and monkey ranging from 1 to 3 mL/min/kg (Geary et al., 2001). Several outliers (infliximab, IFNβ and EGFr3) with relatively high prediction errors (6- or 7-fold) were, however, observed in our analysis of macro-molecules (Figure 3), which may be the result of species-specific differences in binding activity and non-linear pharmacokinetics. While human IFNs bind to receptors in monkey, they lack binding activity in rodents (Kagan et al., 2010). This may help to explain why the prediction error of IFNβ was high when mouse or rat was used in single species scaling. Non-linear pharmacokinetics can be a potential explanation for the high prediction error of EGFr3 in dog, since a relatively low dose was used for the pharmacokinetic study of EGFr3 in dogs compared to other preclinical studies as previous study has shown (Wang and Prueksaritanont, 2010). For small-molecule drugs, the plots in Figure 1 and 2 suggest that human clearance is better predicted using monkey data although the cross-species comparison of AFEs does not indicate statistical differences.

The LBF method appears useful in human clearance prediction for both small and macro-molecule drugs when monkey data are available. If data from other animal species were used, the prediction accuracy may be acceptable for most of the macro-molecule drugs (within 2-fold), but the error appears high for small-molecule drugs.

### Scaling using multiple species

Interspecies scaling using 3 or more animal species was also evaluated in this study. The results suggest that the SA method delivered a high accuracy prediction of human clearance for macro-molecule drugs (AFE = 1.67, Table 4a), which is consistent with the phenomena that the clearance mechanism of macro-molecule drugs is evolutionally well conserved compared to the species-specific metabolism of small-molecule drugs. Only EGFr3 is a notable outlier in the SA method and it may be associated with nonlinear pharmacokinetics as previously discussed.

In general, the SA method also worked well with AFEs < 2.0 for small-molecule drugs excreted renally (Table 4a). The AFE from the SA method is higher for drugs mainly eliminated hepatically, and a correction with MLP or BRW (using the ROE, MA, or SA +MA methods) helped to reduce the prediction error for those drugs (Table 4a and 4b). The correction with MLP was proposed in 1982 by Boxenbaum based on the observation that longevity was frequently inversely correlated with hepatic cytochrome P450 drug oxidation rates (Boxenbaum, 1982, Boxenbaum and Ronfeld, 1983). The MLP Clearance product represents the volume from which drug would be cleared per person's maximum life-span potential assuming constant drug exposure. Using antipyrine as an example, Boxenbaum demonstrated that the regression of volume cleared per MLP is approximately proportional to body weight. With respect to humans, it would appear that the relatively low intrinsic unbound clearance (with respect to liver weight) is synchronized to his (or hers) longevity; i.e. the low activity is conserved over the relatively longer chronological MLP. Boxenbaum also explored the possibility of using brain weight (BRW) as a correction factor since MLP is closely correlated to BRW $MLP$=185.4 ($BRW^{0.636}$) ($W^{(-0.225)}$). Boxenbaum's work was later supported by the results of other scientists. Results from our previous work also demonstrated that the MLP and BRW correction improved the accuracy of human clearance

predictions when the allometry power exponent b was higher than 0.80–0.90 (Feng et al., 1998a, Feng et al., 1998b, Feng et al., 2000, Mahmood and Balian, 1996). The results from our current study indicated that multiple species scaling generally worked better than single species allometry for small-molecule drugs, and the ROE, MA and SA+MA methods using a correction with MLP or BRW could help to increase the accuracy of prediction for small-molecule drugs mainly hepatically eliminated. However, there were a few notable outliers with high prediction error even after using MLP or BRW as a correction factor. All these drugs are mainly hepatically eliminated either by metabolism or by biliary excretion and have relatively low clearance.

### Relationship between CL and molecular size

The results of this study also indicated that the pharmacokinetic properties of small- and macro-molecule drugs are quite different when the relationship between clearance and molecular weight was examined. A trend for macro-molecules is observed (Figure 4), in which the CL values of those drugs in group 2 (MW ≥ 69 kDa) are significantly lower than those in group 1 (MW < 69 kDa). It is generally known that a molecule with MW < 10 kDa is readily excreted by glomerular filtration in the kidney, while a molecule with MW ≥ 69 kDa (MW of albumin ≈ 69 kDa) is highly restricted at the glomerulus (Braeckman, 2000, Lin, 2009). Therefore, glomerular filtration could limit the renal excretion of group 2 drugs, and this may help us to understand the differences in clearance between group 1 and 2. However, one needs to be cautious in directly relating clearance with molecular weight, since MW does not necessarily represent the effective molecular size and the effective molecular radius may be a better way to determine the degree of glomerular filtration. Drug molecules in group 2 may be eliminated mainly by non-specific proteolysis or receptor mediated degradation. Other physicochemical properties such as lipophilicity, charge and functional groups may further influence the distribution and elimination mechanisms (Braeckman, 2000).

## Conclusion

In summary, human clearance of macro-molecule drugs may be predicted using single-species allometric scaling with an optimal component value of “0.80” or using multiple-species simple allometry scaling. No correction by MLP or BRW seems needed for the scaling of macro-molecules probably due to their elimination mechanism. The therapeutic proteins are mainly eliminated by non-specific proteolysis that is very different compared to the complicated oxidative metabolic pathways of the small-molecules. In general, human clearance of small-molecule drugs may be predicted (AFE value of 2.0) using monkey body weight scaling and an optimal allometry exponent value of “0.65”. However, the prediction appears less accurate when mouse, rat or dog data are used for single species allometric scaling. Human clearance is also well predicted using SA method with AFE < 2.0 for small-molecules renally excreted. The prediction error is higher for small-molecules hepatically excreted, and correction using MLP or BRW (ROE, MA and SA+MA methods) could help to reduce the prediction error. Human clearance of both small- and macro-molecule drugs could also be predicted using the monkey liver blood flow method, but the prediction using liver blood flow from other species did not work as well especially for the small molecules.

For small molecule drugs with complicated oxidative metabolic pathway and significant cross-species differences in hepatic metabolism, the simple allometry power equation may not work well for the estimation of human clearance, and in addition to MLP and BRW, other correction factors (e.g. liver blood blow, *in vitro* metabolic clearance, free fraction in blood, binding affinity to receptors or subcellular components, etc.) have been proposed to enhance the accuracy of prediction. Each of these techniques mentioned above has its own merits and drawbacks, and some of them have had only partial success in predicting human clearance. Research work using *in vitro*, *in vivo*, and in silico models are still ongoing to further improve the estimation accuracy of human pharmacokinetic profiles to help reducing the risk and the tremendous financial costs associated with failed clinical trials.

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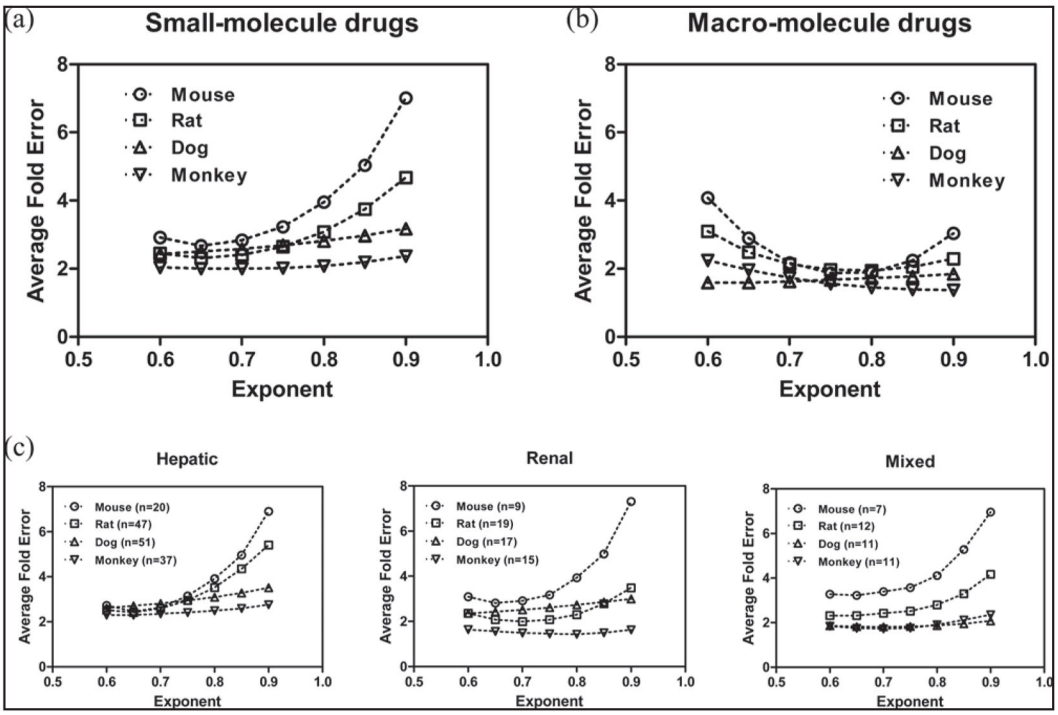


**Figure 1.**

Average fold-error (AFE) for human clearance predictions using single animal species with allometry exponent fixed in the range of 0.6–0.9.

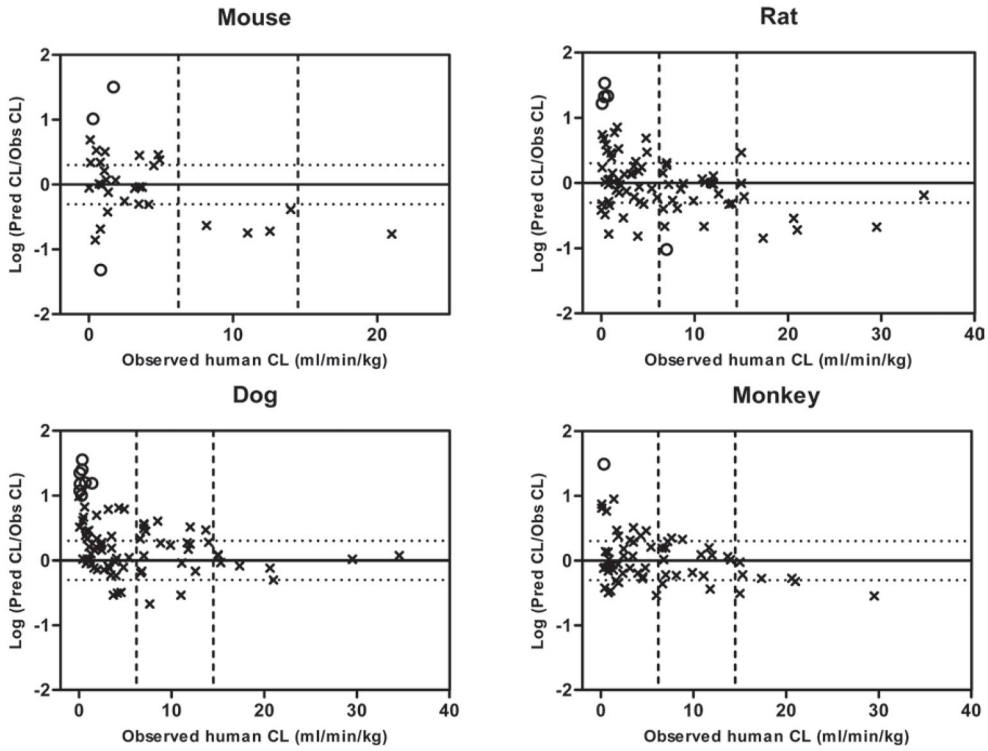


**Figure 2.**

Correlation between the prediction accuracy [ratio of predicted/observed (Pred/Obs)] and the observed value of human clearance (CL) for small-molecule drugs using single species allometric scaling with fixed exponent of 0.65 (the average optimal value from Figure 1). The solid horizontal line represents the identity with Pred/Obs ratio = 1 and the upper and lower dotted horizontal lines represent 2-fold above and 2-fold below the identity, respectively. Several outliers with prediction error of greater than 10 were denoted as open circles. The two dotted vertical lines represent the criteria dividing small-molecules with low (hepatic extraction ratio < 0.3), medium, and high (hepatic extraction ratio > 0.7) clearance drugs.

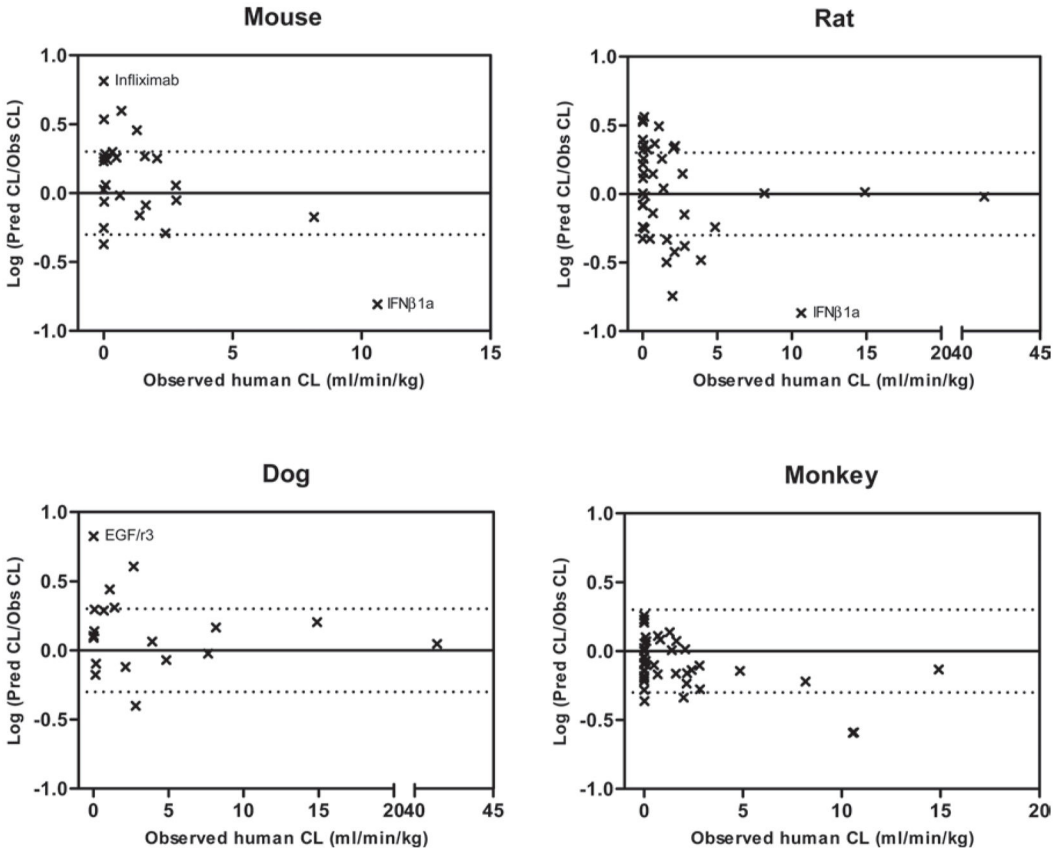


**Figure 3.**

Correlation between the prediction accuracy [ratio of predicted/observed (Pred/Obs)] and the observed value of human clearance (CL) for macro-molecule drugs using single species allometric scaling with fixed exponent of 0.80 (the average optimal value from Figure 1). The solid horizontal line represents the identity with Pred/Obs ratio = 1 and the upper and lower dotted horizontal lines represent 2-fold above and 2-fold below the identity, respectively.

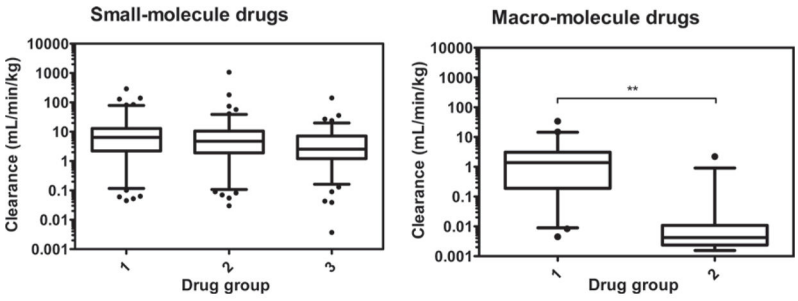


**Figure 4.**

Relationship between human clearance and molecular weight for small- and macro-molecule drugs. Whiskers of box and whiskers plots represent the 5–95th percentile of data. For small-molecules: group1, MW < 300 Da ($n$ = 233); group 2, 300 ≤ MW < 400 Da ($n$ = 221); group 3, 400 ≤ MW ($n$ = 221). For macro-molecules: group 1, MW < 69 kDa ($n$ = 49) and group 2 ($n$ = 29), MW ≥ 69 kDa (**$p$ < 0.01 as determined by t-test).

**Table 1**

Compound list for all macro-molecule drugs.

| | Compounds | MW (kDa) | Observed CL (Mean (CV%), ml/hr/kg) in human | a | b | Reference | Group |
|---|---|---|---|---|---|---|---|
| 1 | Abciximab | 47.6 | 288 (59) | | | (Abernethy et al., 2002) | 1 |
| 2 | Alefacept | 51.8 | 0.25 | | | (Tang et al., 2004) | |
| 3 | Alteplase[a] | 67.5 | 894 (14) | 34.8 | 0.863 | (Martin et al., 1991, Martin et al., 1992) | |
| 4 | ANF[a] | 67.5 | 2229 (11) | 112 | 0.847 | (Yandle et al., 1986, Cernacek et al., 1988, Krieter and Trapani, 1989, Marleau et al., 1989) | |
| 5 | BM06.022[a] | 39.0 | 239 (13) | 6.98 | 0.893 | (Martin et al., 1991) | |
| 6 | Cetrorelix | 1.49 | 72 | | | (Obach et al., 2008) | |
| 7 | Cyclosporin[a] | 1.20 | 321 (38) | 5.51 | 1.15 | (Sangalli et al., 1988) | |
| 8 | Dalbavancin | 1.82 | 0.61 (3.6) | | | (Obach et al., 2008) | |
| 9 | Daptomycin | 1.62 | 9.0 (10) | | | (Obach et al., 2008) | |
| 10 | Darbepoetin alfa | 37.1 | 2.3 (35) | | | (Egrie Jc Fau - Dwyer et al., 2003) | |
| 11 | Denileukin diftitox | 57.6 | 105 (20) | | | (Tang et al., 2004) | |
| 12 | Desmopressin | 1.07 | 143 (34) | | | (Agerso H Fau - Seiding Larsen et al.) | |
| 13 | Digoxin-Fab[a] | 45.5 | 19 (32) | 1.017 | 0.667 | (Grene-Lerouge Na Fau - Bazin-Redureau et al., 1996, Ujhelyi and Robert, 1995) | |
| 14 | Drotrecogin-α | 55.0 | 314 (31) | | | (Olsen and Martin, 2002) | |
| 15 | EPO-α | 30.4 | 8.1 (12) | | | (Halstenson et al., 1991) | |
| 16 | EPO-β[a] | 36.0 | 7.9 (15) | 0.234 | 0.660 | (Bleuel et al., 1996, Halstenson et al., 1991) | |
| 17 | Factor IX[a] | 56.5 | 9.1 (16) | 0.288 | 0.715 | (Keith et al., 1995, McCarthy et al., 2002, White et al., 1998) | |
| 18 | Filgrastim | 18.8 | 36 (24) | | | (Tang et al., 2004) | |
| 19 | GLQ223[b] | 27.0 | 130 (54) | | | (Gatti et al., 1991) | |
| 20 | Glucagon | 3.50 | 810 | | | (Tang et al., 2004) | |
| 21 | IFNβ1a[a] | 22.5 | 573 (47) | 4.98 | 0.907 | (Kagan et al., 2010) | |
| 22 | IFNβ1b[b] | 18.5 | 760 (37) | | | (Kagan et al., 2010) | |
| 23 | ISIS 2503[a] | NA | 144 | 2.41 | 0.879 | (Geary et al., 2001) | |
| 24 | ISIS 3521[a] | 6.72 | 67 (2.7) | 2.12 | 0.599 | (Geary et al., 2001) | |
| 25 | ISIS 5132[a] | 6.63 | 76 (32) | 3.23 | 0.873 | (Geary et al., 2001) | |

| | Compounds | MW (kDa) | Observed CL (Mean (CV%), ml/hr/kg) in human | a | b | Reference | Group |
|---|---|---|---|---|---|---|---|
| 26 | ISIS 104838[a] | 7.41 | 41 (12) | 155 | 0.709 | (Sewell et al., 2002, Geary et al., 2003) | |
| 27 | ISIS 301012[b] | 7.39 | 41 (12) | 96.8 | 0.487 | (Yu et al., 2007) | |
| 28 | Leuprolide | 1.21 | 114 (7.4) | | | (Obach et al., 2008) | |
| 29 | Nartograstim[a] | 19 | 29 (11) | 49.2 | 0.655 | (Kuwabara et al., 1994, Ohdo et al., 1998) | |
| 30 | Octreotide | 1.00 | 121 (25) | | | (Tang et al., 2004) | |
| 31 | Pamiteplase[a] | 37.0 | 130 (7.7) | 2.06 | 0.913 | (Oikawa et al., 2000, Oikawa et al., 2001) | |
| 32 | PEG-EPO[a] | 60.0 | 0.50 (6.0) | 1.95 | 0.674 | (Macdougall et al., 2006) | |
| 33 | PEG-IL2[a] | 22.0 | 6.0 | 0.179 | 0.750 | (Braeckman, 2000) | |
| 34 | rCD4[a] | 50.0 | 49 (43) | 3.36 | 0.577 | (Mordenti et al., 1991) | |
| 35 | Relaxin[a] | 6.00 | 139 (37) | 5.83 | 0.776 | (Mordenti et al., 1991) | |
| 36 | rEPO[a] | 36.0 | 10.1 (35) | 0.221 | 0.921 | (Flaharty et al., 1990, Woo and Jusko, 2007) | |
| 37 | Reteplase | 39.6 | 300 (40) | | | (Tang et al., 2004) | |
| 38 | rhGH[a] | 20.0 | 124 | 6.47 | 0.688 | (Mordenti et al., 1991) | |
| 39 | rhIL-2[a] | 15.0 | 165 (54) | 4.79 | 0.650 | (Braeckman, 2000) | |
| 40 | rHirudin[a] | 6.91 | 168 | 8.48 | 1.01 | (Nowak, 1991) | |
| 41 | rHuIFN-αA[a] | 19.0 | 169 (38) | 3.68 | 0.710 | (Lave et al., 1995) | |
| 42 | rHuIL-10 | 18.0 | 65 (11) | | | (Radwanski et al., 1998) | |
| 43 | rt-PA[a] | 63.0 | 490 | 16.2 | 0.862 | (Mordenti et al., 1991, Collen et al., 1991) | |
| 44 | SK&F 107647 | 1.17 | 65 (28) | | | (Brocks et al., 1996) | |
| 45 | SR 90107A[a] | 1.11 | 6.3 (16) | 41.2 | 0.506 | (Herault et al., 1997) | |
| 46 | Teicoplanin A2-1 | 1.88 | 12 (5.0) | | | (Obach et al., 2008) | |
| 47 | Telavancin | 1.76 | 12 (12) | | | (Obach et al., 2008) | |
| 48 | Tenecteplase[a] | 59.0 | 83 (14) | 3.35 | 0.903 | (Tanswell et al., 2002) | |
| 49 | Valspodar | 1.22 | 156 | | | (Obach et al., 2008) | |
| 50 | Vancomycin | 1.45 | 112 (5.4) | | | (Obach et al., 2008) | |
| 51 | Abatacept[a] | 92.0 | 0.23 | 0.563 | 0.647 | (Srinivas et al., 1997, Srinivas et al., 1996a, Srinivas et al., 1996b) | 2 |
| 52 | Adalimumab[b] | 148 | 0.13 (31) | | | (Lobo et al., 2004, Weisman et al., 2003) | |
| 53 | Basiliximab | 144 | 0.59 (46) | | | (Tang et al., 2004) | |

| | Compounds | MW (kDa) | Observed CL (Mean (CV%), ml/hr/kg) in human | a | b | Reference | Group |
|---|---|---|---|---|---|---|---|
| 54 | Bevacizumab[a] | 149 | 0.12 (42) | 0.0046 | 0.684 | (Lin et al., 1999, Gordon et al., 2001) | |
| 55 | CD4-IgG[a] | 98.0 | 1.9 | 0.102 | 0.740 | (Mordenti et al., 1991) | |
| 56 | Cetuximab[b] | 146 | 0.50 (37) | | | (Lobo et al., 2004) | |
| 57 | CNTO136[b] | NA | 0.19 (32) | | | (Ling et al., 2009) | |
| 58 | CNTO328[b] | 145 | 0.47 (34) | | | (Ling et al., 2009, Puchalski et al.) | |
| 59 | CNTO95[b] | 180 | 0.28 (13) | | | (Ling et al., 2009, Mullamitha et al., 2007) | |
| 60 | Daclizumab[b] | 143 | 0.19 | | | (Tang et al., 2004, Ling et al., 2009) | |
| 61 | Eculizumab | 148 | 0.29 (12) | | | # | |
| 62 | Efalizumab[b] | 150 | 0.65 (32) | | | (Ling et al., 2009, Bauer et al., 1999) | |
| 63 | EGFr3[a] | 150 | 0.98 (18) | 0.0865 | 1.02 | (Crombet et al., 2001) | |
| 64 | Factor VIII[a] | 340 | 3.0 | 0.182 | 0.744 | (Mordenti et al., 1996, Stokol et al., 1997) | |
| 65 | Gemtuzumab | 152 | 3.3 (85) | | | (Dowell et al., 2001) | |
| 66 | Golimumab[b] | 147 | 0.28 (79) | | | (Ling et al., 2009) | |
| 67 | Horse F(ab′)2[a] | 100 | 0.93 (84) | 0.0328 | 0.534 | (Bazin-Redureau et al., 1998, Ho et al., 1990) | |
| 68 | Infliximab[a] | 144 | 0.14 (20) | 0.0075 | 0.540 | (Tang et al., 2004, Palframan R Fau - Airey et al., 2009, Rojas et al., 2005) | |
| 69 | Laronidase | 83.0 | 132 (32) | | | (Tang et al., 2004) | |
| 70 | Lenercept[a] | 120 | 0.30 | 0.008 | 1.06 | (Richter Wf Fau - Gallati et al., 1999) | |
| 71 | Natalizumab[b] | 149 | 0.27 (1.5) | | | (Ling et al., 2009, Sheremata et al., 1999) | |
| 72 | Panitumumab[b] | 147 | 0.20 (10) | | | (Ling et al., 2009, Cohenuram and Saif, 2007) | |
| 73 | Pertuzumab[a] | 150 | 0.14 (36) | 0.259 | 0.926 | (Agus et al., 2005, Adams et al., 2006) | |
| 74 | Rituximab | 145 | 0.13 | | | (Cartron et al., 2007) | |
| 75 | RSHZ19[a] | 146 | 0.122 (15) | 0.0035 | 0.731 | (Davis et al., 1995, Everitt et al., 1996) | |
| 76 | Tanezumab[b] | 145 | 0.11 | | | # | |
| 77 | Tositumomab | 144 | 0.97 | | | (Lobo et al., 2004) | |
| 78 | Trastuzumab[b] | 146 | 0.41 (61) | | | (Tang et al., 2004, Ling et al., 2009) | |
| 79 | Ustekinumab[b] | 146 | 0.093 (28) | | | (Ling et al., 2009) | |
| 80 | Veltuzumab | 145 | 0.093 (39) | | | (Morschhauser et al., 2009, Goldenberg et al., 2009) | |

[a] PK data available in ≥ 3 animal species and in human.

[b] PK data available in monkey and human.

[#] Eculizumab; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_PharmacometricsR.pdf Tanezumab; http://www.aapsj.org/abstracts/NBC_2009/NBC09-000419.PDF

**Table 2**

Compound list of small-molecule drugs used for interspecies scaling.

| | Compounds | MW | Observed CL (Mean (CV%), ml/min/kg) in human | Character | Elimination | Fu% | a | b | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Acivicin | 178.6 | 0.78 (27) | Acid | Mixed | 100 | 4.10 | 0.558 | (Mahmood and Balian, 1996) |
| 2 | Actisomide | 369.6 | 6.8 (16) | Base | Mixed | NA | 10.9 | 1.04 | (Mahmood and Balian, 1996) |
| 3 | Amethopterin | 454.4 | 3.5 | Acid | Renal | 50 | 10.4 | 0.724 | (Dedrick et al., 1970) |
| 4 | Amiodarone | 645.3 | 1.9 | Base | Hepatic | 4.4 | 13.5 | 0.979 | (Evans et al., 2006) |
| 5 | Amphotericin B | 924.1 | 0.34 (75) | Zwitt | Hepatic | 5.2 | 0.967 | 0.847 | (Hutchaleelaha et al., 1997, Robbie and Chiou, 1998) |
| 6 | Antipyrine | 188.2 | 0.78 (21) | Base | Hepatic | 100 | 11.7 | 0.843 | (Lave et al., 1997) |
| 7 | Ara-C | 243.2 | 1.3 | Base | Hepatic | 98 | 4.21 | 0.830 | (Dedrick et al., 1973) |
| 8 | Betamipron | 193.2 | 6.6 (12) | Acid | Renal | 48 | 13.7 | 0.782 | (Mahmood, 1998) |
| 9 | Biperiden | 311.5 | 15 | Base | Hepatic | 40 | 44.6 | 0.719 | (Evans et al., 2006) |
| 10 | Bosentan | 569.6 | 1.9 (26) | Acid | Hepatic | 2 | 24.9 | 0.562 | (Lave et al., 1997) |
| 11 | Caffeine | 194.2 | 2.0 (11) | Neutral | Hepatic | 96 | 8.07 | 0.584 | (Lave et al., 1997) |
| 12 | Cefmetazole | 471.5 | 1.7 (26) | Base | Renal | 15 | 12.8 | 0.633 | (Feng et al., 2000) |
| 13 | Cefotetan | 619.6 | 0.60 (15) | Acid | Renal | 12 | 7.15 | 0.641 | (Mahmood and Balian, 1996) |
| 14 | Cefazolin | 454.5 | 0.88 | Base | Renal | 13 | 4.79 | 0.733 | (Mahmood and Balian, 1996) |
| 15 | Cefodizime | 584.7 | 0.74 (24) | Acid | Renal | 12 | 1.51 | 1.00 | (Matsushita et al., 1990) |
| 16 | Cefoperazone | 645.7 | 1.4 (14) | Base | Hepatic | 18 | 6.75 | 0.578 | (Lave et al., 1997) |
| 17 | Cefpiramide | 612.6 | 0.48 (42) | Base | Renal | 3.7 | 4.27 | 0.443 | (Nakagawa et al., 1984) |
| 18 | Ceftizoxime | 405.4 | 2.4 (21) | Base | Renal | 72 | 10.3 | 0.544 | (Mahmood and Balian, 1996) |
| 19 | Chlorpromazine | 318.9 | 4.3 | Base | Hepatic | 10 | 47.1 | 0.889 | (Evans et al., 2006) |
| 20 | CI-1007 | 329.5 | 21 | Base | Hepatic | 2 | 35.0 | 0.905 | (Feng et al., 1998) |
| 21 | Ciprofloxacin | 331.4 | 6.0 | Acid | Renal | 60 | 14.5 | 0.939 | (Siefert et al., 1986, Nouws et al., 1988) |
| 22 | Coumarin | 206.2 | 16 (24) | Acid | Hepatic | 14 | 21.2 | 1.10 | (Ritschel et al., 1991) |
| 23 | Cytoxan | 279.1 | 2.25 (79) | Acid | Hepatic | 100 | 21.0 | 0.843 | (Mellett, 1969) |
| 24 | DA-1131 | 445.6 | 5.0 | Acid | Mixed | 90 | 11.6 | 0.825 | (Kim et al., 1998) |
| 25 | Diazepam | 284.8 | 0.32 (31) | Neutral | Hepatic | 3.2 | 37.4 | 0.735 | (Mahmood and Balian, 1996) |
| 26 | Diltiazem | 414.5 | 16 (35) | Base | Hepatic | 25 | 62.8 | 0.888 | (Evans et al., 2006) |
| 27 | Doxorubicin | 543.5 | 13 | Base | Hepatic | 25 | 40.8 | 0.887 | (Harris and Gross, 1975, Tranum et al., 1975) |

| | Compounds | MW | Observed CL (Mean (CV%), ml/min/kg) in human | Character | Elimination | Fu% | a | b | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 28 | Enoxacin | 320.3 | 9.3 (14) | Acid | Mixed | 69 | 0.353 | 1.51 | (Nakamura et al., 1983, Chang et al., 1988) |
| 29 | Enprofylline | 194.2 | 3.6 (24) | Base | Renal | 49 | 6.34 | 0.526 | (Tsunekawa et al., 1992) |
| 30 | Epiroprim | 353.4 | 3.5 (17) | Acid | Mixed | 12.5 | 34.4 | 0.609 | (Evans et al., 2006) |
| 31 | Felodipine | 384.3 | 11 (19) | Neutral | Hepatic | 1 | 43.8 | 0.575 | (Evans et al., 2006) |
| 32 | Fentanyl | 336.5 | 11 (33) | Base | Hepatic | 17 | 15.6 | 0.805 | (Bjorkman and Redke, 2000, Valverde et al., 2000) |
| 33 | Flindokalner | 359.7 | 7.6 | Acid | Hepatic | 0.38 | 21.9 | 0.629 | (Evans et al., 2006) |
| 34 | Furosemide | 330.7 | 2.3 (47) | Acid | Renal | 5 | 3.78 | 1.11 | (Doyle et al., 1982, Prandota and Pruitt, 1991, Hirai et al., 1992) |
| 35 | Garenoxacin | 426.4 | 1.2 | Acid | Mixed | 13 | 5.78 | 0.605 | (Evans et al., 2006) |
| 36 | GV150526 | 360.2 | 0.086 (24) | Acid | Hepatic | 0.002 | 1.99 | 1.20 | (Iavarone et al., 1999) |
| 37 | Haloperidol | 375.9 | 12 | Base | Hepatic | 10 | 46.1 | 0.573 | (Evans et al., 2006) |
| 38 | Imatinib | 493.6 | 3.2 (34) | Base | Hepatic | 5.9 | 29.6 | 0.866 | (Neville et al., 2004, Peng et al., 2004, Ishizuka et al., 2007, Oostendorp et al., 2009) |
| 39 | Inogatran | 439.0 | 5.8 (8.6) | Base | Renal | 0.2 | 24.7 | 0.748 | (Eriksson et al., 1998, Hauptmann, 2002) |
| 40 | ITF296 | 238.2 | 30 (20) | Acid | Hepatic | NA | 40.8 | 1.05 | (Monzani et al., 1995, Sardina et al., 1995, Giachetti et al., 1998, Monzani et al., 1999) |
| 41 | Ketoprofen | 254.3 | 1.2 (68) | Acid | Hepatic | 1 | 0.930 | 1.31 | (Lepist and Jusko, 2004) |
| 42 | Ketorolac | 376.4 | 0.80 (11) | Acid | Mixed | 0.8 | 1.28 | 0.989 | (Mroszczak et al., 1987) |
| 43 | Lamifiban | 468.5 | 1.9 | Zwitt | Renal | 94 | 6.14 | 0.884 | (Lave et al., 1996) |
| 44 | Meropenem | 383.5 | 3.2 (16) | Acid | Mixed | 98 | 17.7 | 0.418 | (Harrison et al., 1989) |
| 45 | Methadone | 429.6 | 1.4 | Base | Mixed | 20 | 43.5 | 0.775 | (Evans et al., 2006) |
| 46 | Metoprolol | 267.4 | 16 (53) | Base | Hepatic | 88 | 137 | 0.426 | (Rane et al., 1984, Belpaire et al., 1990, Bortolotti et al., 1989, Murthy et al., 1991) |
| 47 | Mibefradil | 495.6 | 7.0 | Acid | Hepatic | 1 | 66.9 | 0.804 | (Lave et al., 1997) |
| 48 | Midazolam | 309.5 | 7.6 (5.9) | Neutral | Hepatic | 4.0 | 42.4 | 0.737 | (Evans et al., 2006) |
| 49 | Mifepristone | 325.8 | 0.33 | Base | Hepatic | 2 | 34.7 | 0.720 | (Evans et al., 2006, Kenny and Grime, 2006) |
| 50 | Mofarotene | 433.6 | 11 | Base | Hepatic | 0.1 | 11.5 | 0.733 | (Mahmood and Balian, 1996) |
| 51 | Moxalactam | 520.5 | 1.6 (26) | Acid | Renal | 40 | 4.97 | 0.651 | (Mahmood and Balian, 1996) |
| 52 | Nicardipine | 479.5 | 7.0 | Base | Hepatic | 1.5 | 63.1 | 0.727 | (Higuchi and Shiobara, 1980) |
| 53 | Nifedipine | 346.3 | 7.0 | Neutral | Hepatic | 5 | 6.12 | 1.24 | (Evans et al., 2006) |
| 54 | Ofloxacin | 361.4 | 4.5 (15) | Zwitt | Renal | 75 | 9.44 | 0.569 | (Evans et al., 2006) |
| 55 | Panipenem | 339.4 | 3.1 (12) | Acid | Mixed | 92.6 | 14.8 | 0.492 | (Kurihara et al., 1992) |

| | Compounds | MW | Observed CL (Mean (CV%), ml/min/kg) in human | Character | Elimination | Fu% | a | b | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 56 | PD1 | 364.8 | 0.0043 | Base | Hepatic | 49 | 0.0276 | 0.966 | (Feng et al., 2000) |
| 57 | PD8 | 245.3 | 1.6 | Base | Renal | 16 | 5.06 | 0.629 | (Feng et al., 2000) |
| 58 | Phencyclidine | 243.4 | 5.1 (22) | Base | Hepatic | 35 | 76.3 | 0.763 | (Bachmann, 1989) |
| 59 | PNU-96391 | 281.4 | 7.2 (38) | Base | Hepatic | 0.73 | 41.7 | 0.923 | (Evans et al., 2006) |
| 60 | PNU-288034 | 403.4 | 7.3 | Base | Renal | NA | 10.7 | 0.699 | (Lai et al.) |
| 61 | Propafenone | 341.5 | 18 (19) | Base | Hepatic | 3 | 50.9 | 0.841 | (Evans et al., 2006) |
| 62 | Propranolol | 259.3 | 12 (7.7) | Base | Hepatic | 8.4 | 47.7 | 0.652 | (Mahmood and Balian, 1996) |
| 63 | Quinidine | 324.4 | 3.8 (47) | Base | Hepatic | 17.5 | 30.0 | 0.539 | (Ueda et al., 1977, Guentert et al., 1982, Iven, 1977) |
| 64 | Remoxipride | 371.3 | 1.7 (29) | Base | Hepatic | 6.5 | 91.2 | 0.506 | (Evans et al., 2006) |
| 65 | RO 24–6173 | 349.3 | 12 | NA | Hepatic | 10 | 68.8 | 0.716 | (Lave et al., 1997) |
| 66 | RO 25–6833 | 560.5 | 0.39 (29) | Acid | Mixed | 4.3 | 1.06 | 1.18 | (Richter et al., 1998) |
| 67 | Salicylic acid | 138.1 | 0.56 | Acid | Hepatic | 15 | 0.0554 | 1.63 | (Davis and Westfall, 1972) |
| 68 | Sematilide | 313.4 | 4.1 (14) | Base | Renal | 96 | 19.7 | 0.727 | (Hinderling et al., 1993) |
| 69 | Semaxanib | 238.3 | 14 (50) | Base | Mixed | 0.8 | 48.8 | 0.857 | (Evans et al., 2006) |
| 70 | Stavudine | 242.2 | 9.8 (39) | Base | Renal | 100 | 20.8 | 0.909 | (Kaul et al., 1999) |
| 71 | Susalimod | 408.0 | 0.090 | Acid | Hepatic | 23.5 | 9.32 | 0.957 | (Feng et al., 2000) |
| 72 | Tamsulosin | 408.5 | 0.69 | Base | Hepatic | 1.0 | 61.1 | 0.594 | (Bolton, 1997) |
| 73 | Tebufelone | 300.4 | 9.9 | Acid | Hepatic | 0.001 | 31.1 | 0.878 | (Cruze et al., 1995) |
| 74 | Theophylline | 180.2 | 0.86 (28) | Acid | Hepatic | 58 | 2.68 | 0.906 | (Mahmood and Balian, 1996) |
| 75 | Tolcapone | 273.2 | 1.5 (22) | Base | Hepatic | 0.1 | 12.4 | 0.654 | (Lave et al., 1997) |
| 76 | Trimethadione | 143.1 | 0.70 (14) | Neutral | Hepatic | 0.1 | 3.78 | 0.743 | (Tanaka et al., 1999) |
| 77 | Troglitazone | 441.5 | 2.5 (20) | Acid | Hepatic | 1 | 12.5 | 0.795 | (Izumi et al., 1996) |
| 78 | Valproate | 144.2 | 0.11 (18) | Acid | Hepatic | 5.2 | 3.61 | 0.947 | (Bolton, 1997) |
| 79 | Verapamil | 454.6 | 13 (31) | Base | Hepatic | 10 | 40.7 | 1.08 | (Evans et al., 2006) |
| 80 | Vinorelbine | 778.9 | 19 (19) | Acid | Hepatic | 9–21 | 25.8 | 0.915 | (Evans et al., 2006) |
| 81 | Warfarin | 308.3 | 0.058 (19) | Acid | Hepatic | 1 | 0.382 | 1.20 | (Bachmann, 1989) |

Zwitt, zwitterion; NA, information not avaliable.

**Table 3**

Average-fold error (AFE) of human CL prediction using liver blood flow method.

| | Mouse | | Rat | | Dog | | Monkey | |
|---|---|---|---|---|---|---|---|---|
| **Drugs** | **Small** | **Macro** | **Small** | **Macro** | **Small** | **Macro** | **Small** | **Macro** |
| # of drugs | 36 | 25 | 78 | 40 | 78 | 19 | 63 | 43 |
| AFE | 4.04 | 2.38 | 3.47 | 1.98 | 2.83 | 2.06 | 2.02 | 1.63 |

**Table 4a**

Average-fold error (AFE) of human CL predictions using multiple species scaling: comparison of small- versus macro-molecule drugs.

| | | SA | ROE | MA | SA+MA |
|---|---|---|---|---|---|
| Small-molecule | Hepatic (*n* = 50) | 3.14 | 2.18 | 2.37 | 2.16 |
| | Renal (*n* = 19) | 1.84 | 1.95 | 1.73 | 1.66 |
| | Mixed (*n* = 12) | 2.25 | 1.99 | 2.09 | 1.97 |
| | All (*n* = 81) | 2.64 | 2.10 | 2.16 | 2.00 |
| Macro-molecule | (*n* = 36) | 1.67 | 2.06 | 1.87 | 1.95 |

SA, simple allometry; ROE, exponent rule-corrected SA (exponent≥1, corrected by BRW; 0.71≤exponent<1, corrected by MLP; exponent<0.71, SA); MA, multiexponential allometry; SA+MA, exponent rule-corrected MA (exponent≥0.71, MA; exponent<0.71, SA). Hepatic: drug molecules are mainly eliminated hepatically; Renal: drug molecules are mainly eliminated renally; Mixed: drug molecules are eliminated by both hepatic and renal routes.

**Table 4b**

Average-fold error (AFE) of human clearance predictions using multiple species scaling for small-molecule drugs mainly hepatically eliminated with low (< 0.3), medium (0.3–0.7), and high (> 0.7) extraction ratio.

| | | SA | ROE | MA | SA+MA |
|---|---|---|---|---|---|
| Small-molecule | Low (*n* = 27) | 4.51 | 2.81 | 3.31 | 2.79 |
| | Medium (*n* = 16) | 2.46 | 1.59 | 1.47 | 1.55 |
| | High (*n* = 7) | 1.35 | 1.71 | 1.99 | 1.74 |
| | All (*n* = 50) | 3.14 | 2.18 | 2.37 | 2.16 |

SA, simple allometry; ROE, exponent rule-corrected SA (exponent≥1, corrected by BRW; 0.71≤exponent<1, corrected by MLP; exponent<0.71, SA); MA, multiexponential allometry; SA+MA, exponent rule-corrected MA (exponent≥0.71, MA; exponent<0.71, SA).