

Mice with human livers improve First-in-Human prediction of pharmacokinetics



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Overview

Over the last years, a new technology allowed the creation of chimeric mice with a humanized liver consisting of human hepatocytes surrounded by phagocytic, vascular and biliary murine sourced cells. Chimeric mice with a humanized liver can be used to predict human ADME characteristics of new chemical entities such as hepatic clearance and elimination mechanisms to improve nonclinical to clinical translation. Data from such mice might be helpful especially in cases where *in vitro* to *in vivo* extrapolation (IVIVE) is challenging and classic allometric scaling with wildtype nonclinical species results in a wide prediction interval.

In a retrospective meta-analysis using in-house data from First-in-Human (FiH) studies, we compared the predicted human clearance, volume of distribution, half-life and area under the curve (AUC) as well as predicted concentration-time profiles based on data from chimeric mice with historic project-specific predictions using wildtype nonclinical species.

Methods

- // 18 Compounds included where chimeric mice and human data are available (24 data sets: 9 × IV, 15 × PO)
- // Chimeric mice: FRG® knockout mice, Yecuris Corporation
- // 1- or 2 compartment models created based on data from chimeric mice to predict human c/t-profiles
- // *Single species scaling (SSS)* with f_u correction (scaling exponents: CL = 0.75, V_{ss} = 1)
- // *Fraction unbound* from human (or chimeric mouse when available)
- // *Bioavailability*, k_a taken from original prediction
- // Clearance converted to AUC_{norm} via $AUC_{norm} = F/CL$

Results

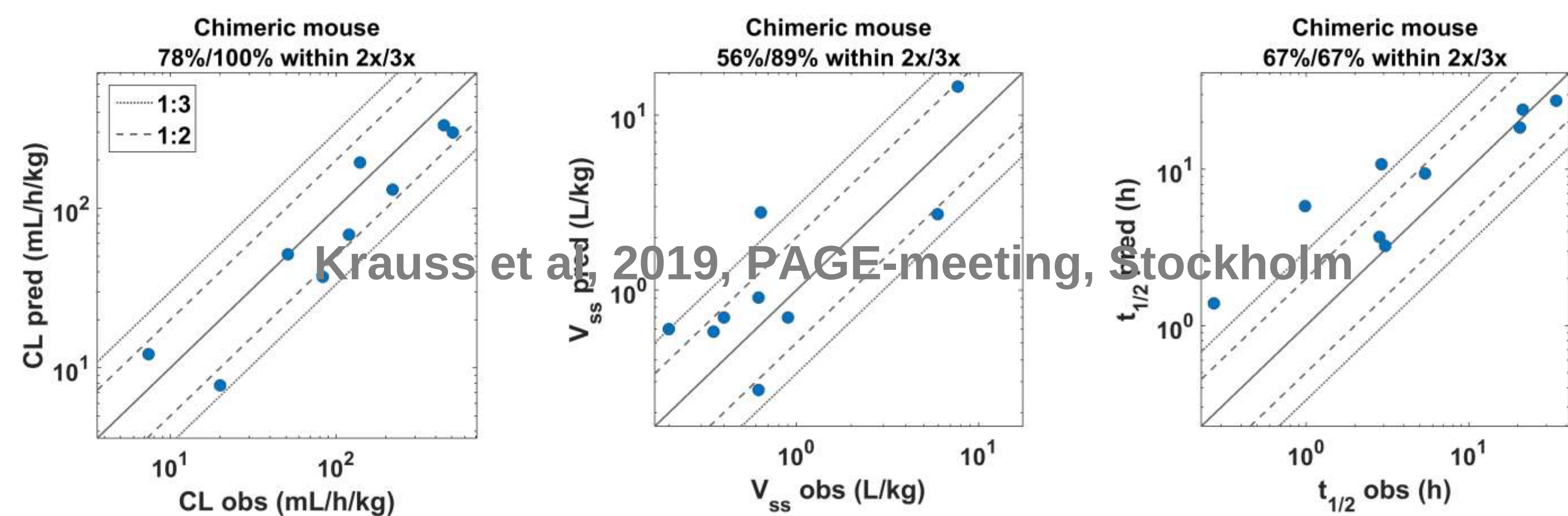


Figure 1: Comparison of predicted vs. observed clearance, volume of distribution and half-life for 9 compounds where human data following i.v. administration was available.

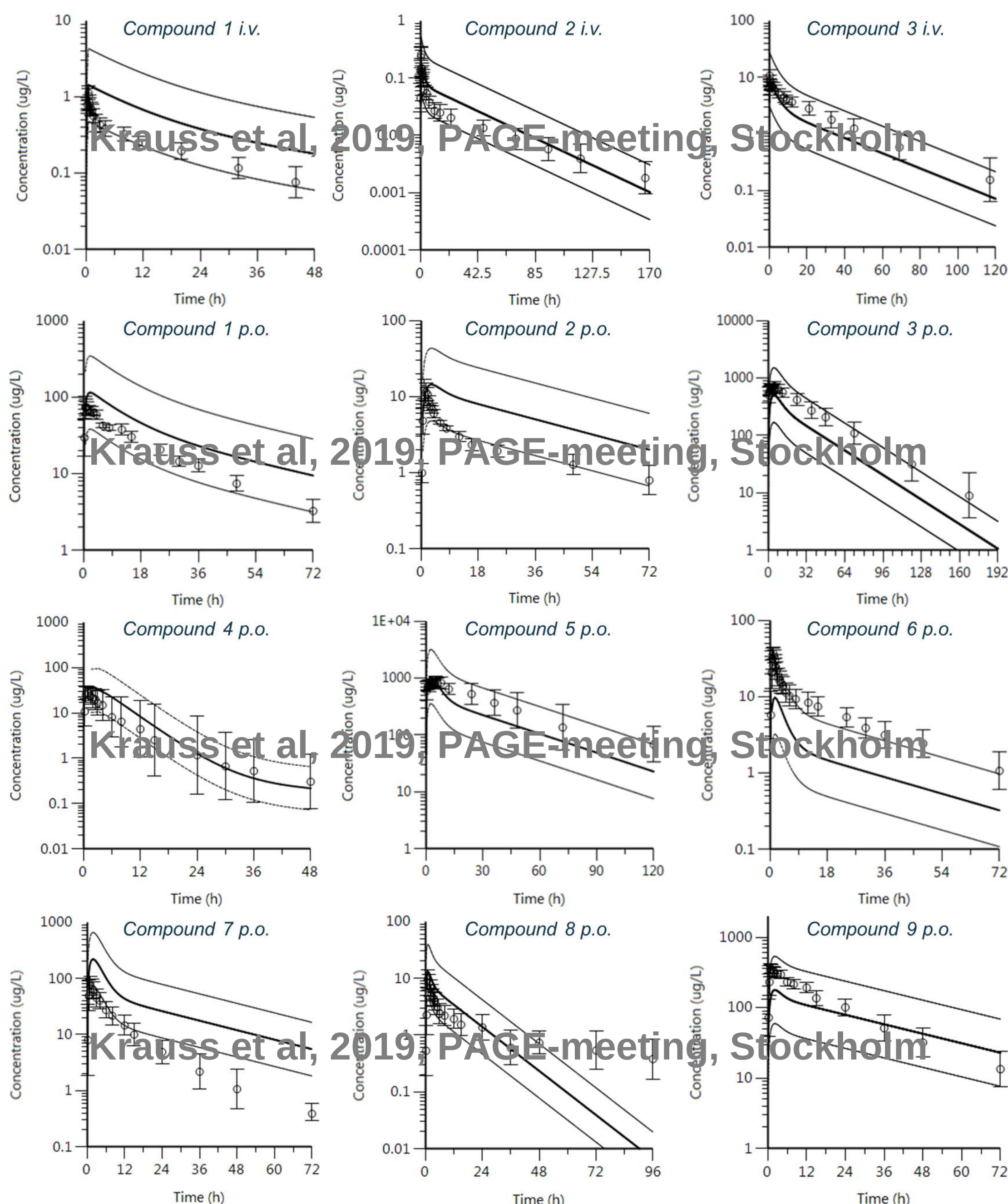


Figure 2: Prediction of human concentration time profiles following i.v. administration (3 exemplary compounds) as well as following p.o. administration (9 exemplary compounds). Bold line: prediction, dashed lines: 3-fold prediction range, circles with error bars: exp. data from human studies.

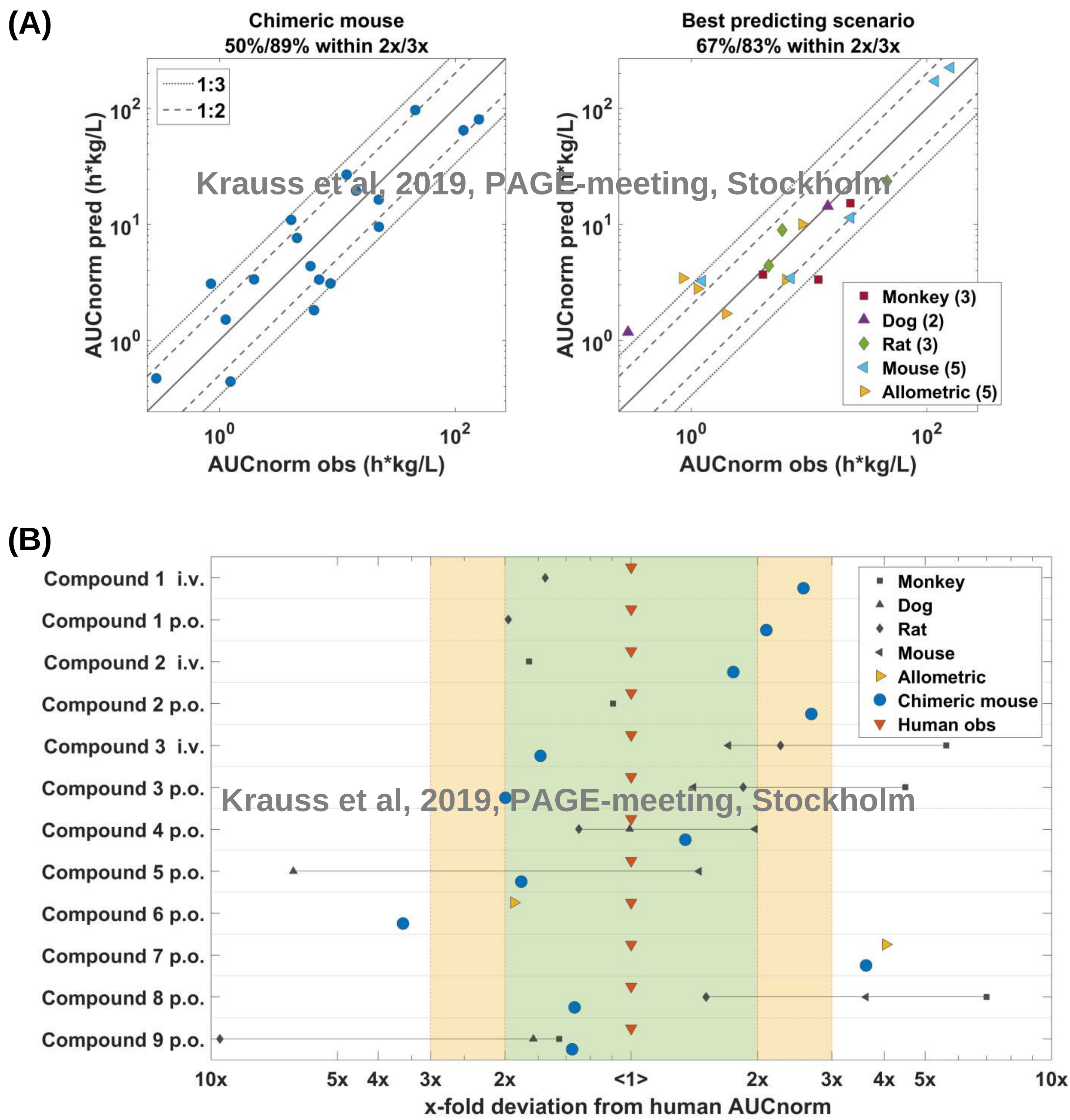


Figure 3: Comparison of predicted vs. observed AUC. (A) Predicted vs. observed AUC of chimeric mouse and best predicting scenario (single-species scaling or allometric scaling) for all 18 compounds. (B) Fold deviation of 9 compounds (same as in Figure 2) from observed human AUC: comparison of prediction using chimeric mice with applied scaling approaches within the projects (line between different SSS-approaches indicates a multiple-species scenario).

Species (N)	Comparison to human AUC				Deviation from human prediction					
	Species	CM	Species	CM	Species	CM	Species	CM	Species	CM
	within 2x [% (N)]		within 3x [% (N)]		Geomean (x-fold)	CV (%)	Min (x-fold)		Max (x-fold)	
Best wildtype species (18)	67 (12)	50 (9)	83 (15)	89 (16)	1.8	2	48	33	1	1.3
Monkey (10)	70 (7)	60 (6)	70 (7)	90 (9)	2.1	2	75	35	1.04	1.3
Dog (13)	31 (4)	38 (5)	46 (6)	85 (11)	3.1	2.1	69	35	1.01	1.3
Rat (18)	61 (11)	50 (9)	78 (14)	89 (16)	2.3	2	96	33	1.04	1.3
Mouse (13)	46 (6)	54 (7)	69 (9)	92 (12)	2.5	2	51	32	1.41	1.3
Allometric (5)	60 (3)	40 (2)	80 (4)	60 (3)	1.9	2.4	57	47	1.14	1.3

Table 1: Quantitative evaluation of human AUC prediction. AUC predictions of chimeric mice (CM) were compared regarding accuracy and precision with each species available for SSS within the projects as well as allometric scaling.

Conclusions

The results presented demonstrate that SSS from chimeric mice with humanized livers accurately predicts human clearance and leads to valuable predictions of human pharmacokinetics in general. In comparison to current scaling approaches used for in-house compounds, predictions from chimeric mice are as good as the retrospectively derived best prediction from wildtype species. Already identified caveats are e.g. large differences in fraction unbound between mice and humans or relevant extrahepatic metabolism of compounds. Overall, especially for compounds where a broad range of human CL was predicted based on wildtype nonclinical species and when IVIVE is challenging, chimeric mice clearly strengthen human ADME and PK prediction. Therefore, chimeric mice with a humanized liver can expand the toolbox to improve prediction of human ADME properties, especially by further derivation of mass balance data and information about potential human metabolites. Such data can then be incorporated into mechanistic modeling approaches to further improve predictivity of human PK in future drug development programs.