mAb priors

Improving priors for human mAb linear PK parameters by using half-lives from pre-clinical studies

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Improving priors for human mAb linear PK parameters by using half-lives from pre-clinical studies

- Goal: Priors for linear part of mAb PK parameters for
  - First-in-man studies
  - Linear part of TMDD models to provide more robust estimation of TMDD
- But, large PK inter-drug variability (2-fold difference in half-lives)
- One can obtain improved priors by pooling information from different mAbs ($LEVEL, Covariates,...) and using half-lives from non-human-primates (NHP) for predicting human PK parameters:

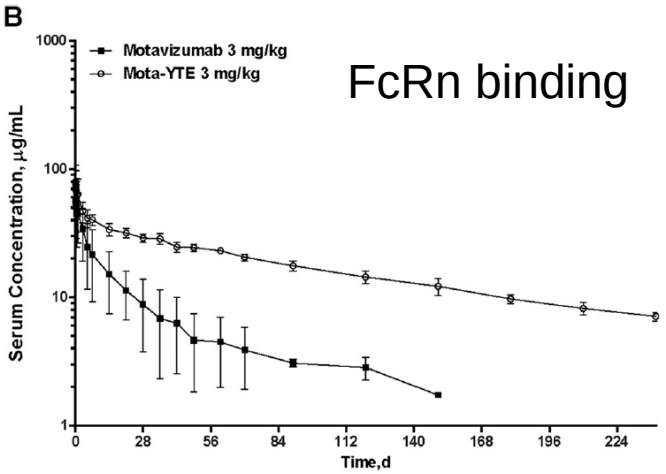
$$CL = CL^0 \left(\frac{t_{half}}{21\ \text{days}}\right)^{-1} \qquad V_t = {V_t}^0 \left(\frac{t_{half}}{21\ \text{days}}\right)^{-1}$$

t_{half} ... Extrapolated half-life in days from NHP (for 70 kg individual)

mAb PK: Properties influencing mAb PK

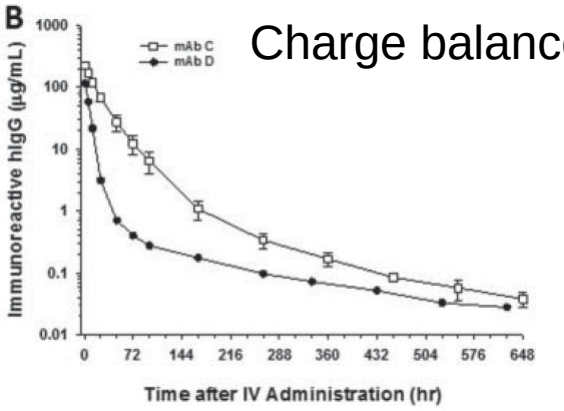
PK differences also due to target-independent properties

- Binding of Fab and Fc part
  - Fab target binding => TMDD
  - FcRn binding => Recycling (reduced elimination)



Robbie et al., Antimicrob Agens Chemother 2013

- Biochemical properties
  - Charge balance
  - Glycosylation
  - ...



Datta-Mannan et al., mAbs 2015

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mAb PK: Focus on linear 2-cmt PK

Fulfilled for total PK in saturated system with soluble target

- Linear 2-cmt PK
  - Total mAb concentrations (free + bound)
  - Soluble target
  - Saturated system (molar excess)
- Note: “linear part” includes saturated non-linear target-mediated elimination

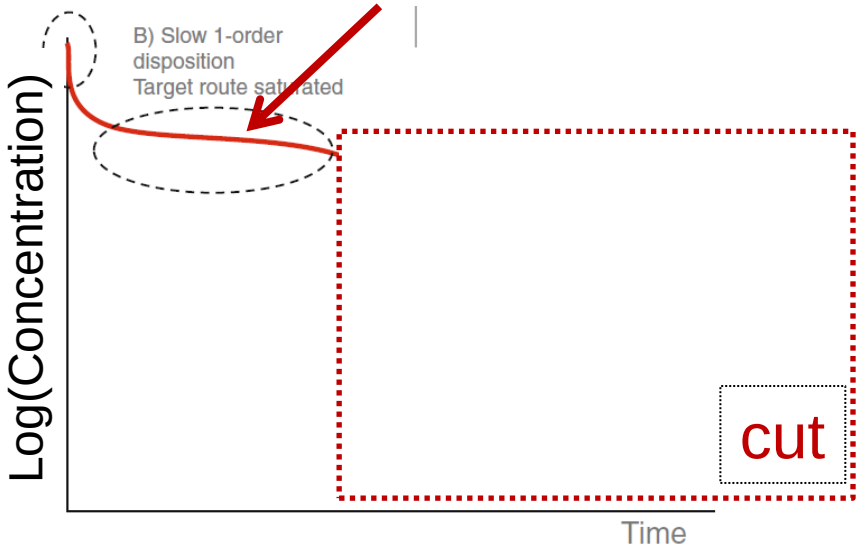
$$A_p{}' = A_t \frac{Q}{V_t} - A_p \frac{Q}{V_p} - A_p \frac{CL}{V_p}$$

$$A_t{}' = -A_t \frac{Q}{V_t} + A_p \frac{Q}{V_p}$$

A ... Amount
V ... Volume
Q ... “Intercomp. clearance”
CL ... “Clearance”

p ... Plasma
t ... Tissue

Allometric scaling by weight (exponents 1, 0.75)



Peletier & Gabrielsson, J PKPD 2012

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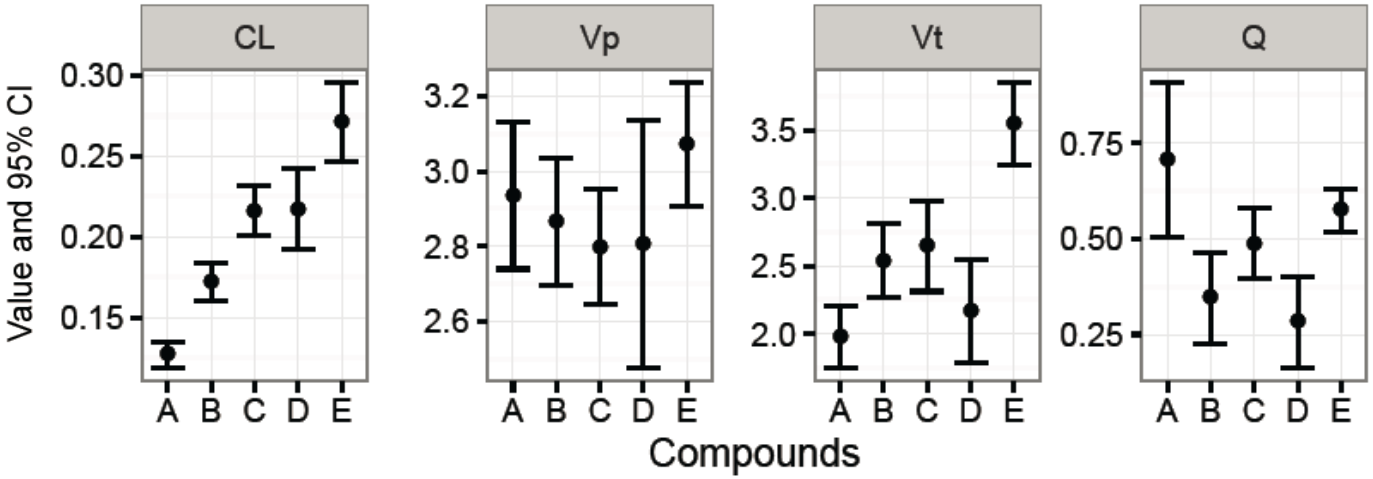
Separate fits: Differences in CL – consistency in Vp



- Substantial differences in CL & Vt
  - Correlation between CL and Vt
- Very consistent Vp (ca. 3L = plasma-volume)
  - >3L for membrane-bound mAbs
    - Rapid-binding (specific and non-specific)
    - Discussions about faster distribution into tissue?[1] Very unlikely.

[1] *Fronton et al., JPKPD, 41:87-107 (2014)*

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Pooling: 3 approaches to obtain "prior" for next mAb

Non-linear mixed-effects methodology

- Naive pool[1]
  - This assumes that all THETAs and OMEGAs are shared between all mAbs, i.e., it assumes no differences between mAbs
- $LEVEL
  - New NONMEM function to allows additional hierarchical levels
  - Accounts for inter-drug-variation (IDV)
- Covariate(s)
  - Describing functional relationships between mAb parameters

$$CL = CL^0 \left(\frac{t_{half}}{21 \text{ days}} \right)^{-1} \qquad V_t = {V_t}^0 \left(\frac{t_{half}}{21 \text{ days}} \right)^{-1}$$

t_{half} ... Extrapolated half-life in days from NHP (for 70 kg individual)

[1] Davda et al., mAbs 2014.

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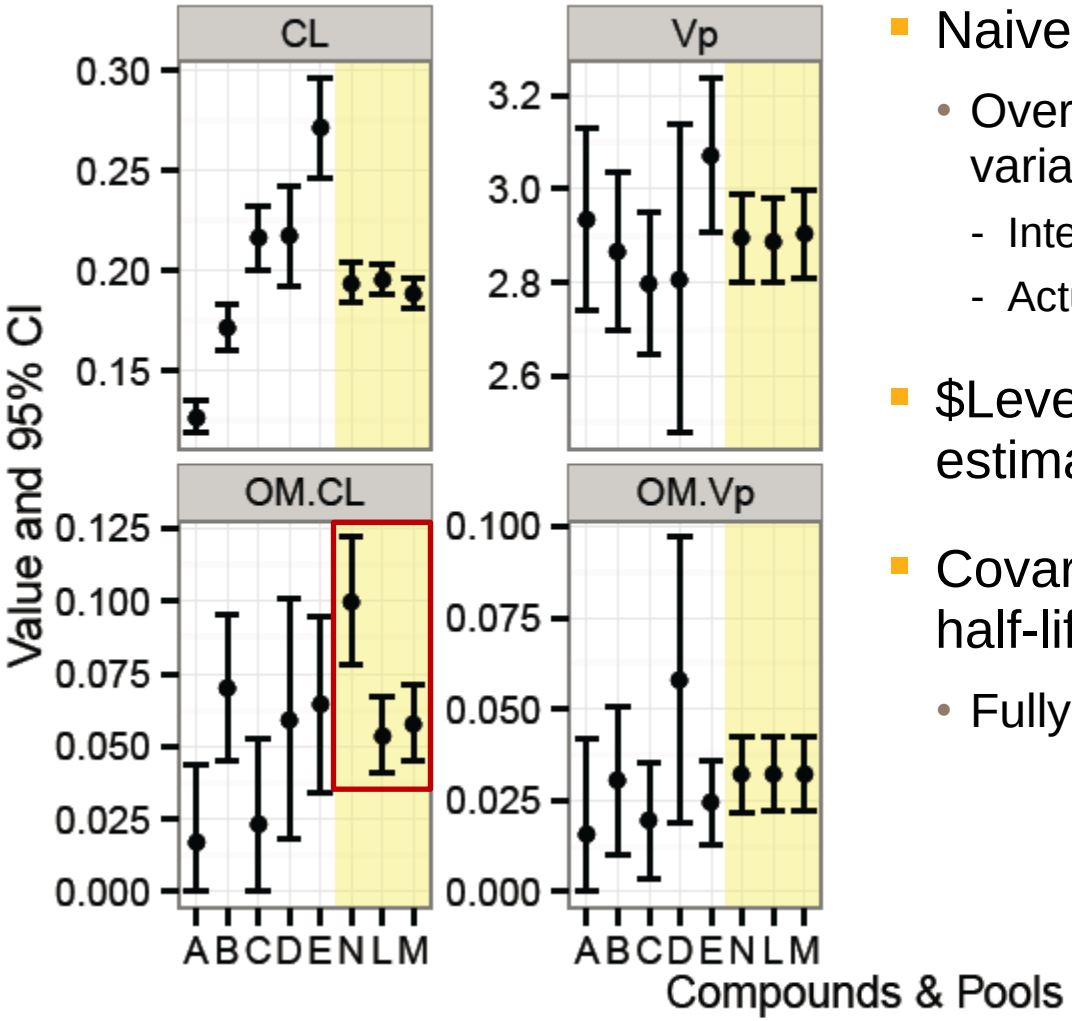
Pooling: Parameter estimates

Differences in CL; increased IIV of naive pool; unbiased IIV in $Level



- Naive pool
  - Overestimates inter-individual variability (IIV) by including both:
    - Inter-drug-variation (IDV)
    - Actual IIV (within compounds)
- $Level pool provides unbiased estimate of IIVs
- Covariate model using NHP half-life
  - Fully explains IDV in CL

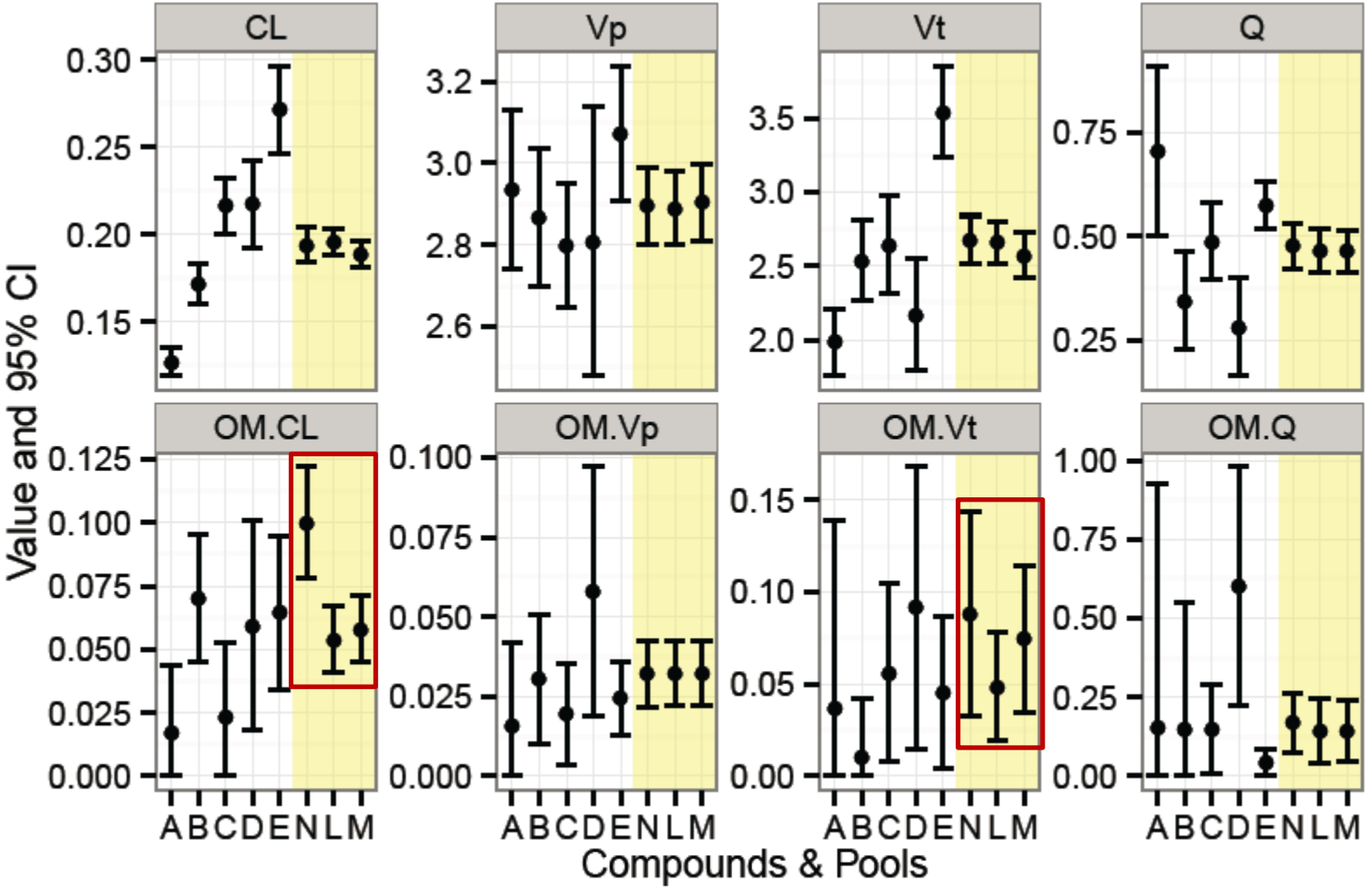
A-E: compounds, N: naive pool
L: $Level, M: covariate model

OM are IIV (σ^2)

Median EBE/compound
Predictions for compounds

Pooling: Parameter estimates

Differences in CL; increased IIV of naive pool; unbiased IIV in $Level



A-E: compounds, N: naive pool
L: $Level, M: covariate model

OM are IIV (σ^2)

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Pooling: Summary of results

$Level provides robust estimates – Covariate model suitable for prediction

- $LEVEL provides estimates for IDV
  - CL 23%CV, Vt 12%CV, Q 10%CV
  - But cannot be used for prediction
- Covariate model using NHP half-life
  - Fully explains IDV in CL – only partially for Vt
  - Can be used for predicting mAb parameters
- Combine the two
  - Use unbiased estimates of IIV from $LEVEL
  - Use the adjustment of CL and Vt based on NHP thalf

Parameters for mAb linear PK

With full covariance matrix

	THETA	IIV (σ)	IDV (σ)	ETA-Shrinkage
CL^0 (L/d)	0.189 (21d t_{half})	0.23	0.23	6%
Vp (L)	2.91	0.16	-	10%
Vt^0 (L)	2.57 (21d t_{half})	0.24	0.12	19%
Q (L/d)	0.452	0.38	0.10	28%

$$CL = CL^0 \left(\frac{t_{half}}{21\ \text{days}}\right)^{-1} \qquad V_t = {V_t}^0 \left(\frac{t_{half}}{21\ \text{days}}\right)^{-1}$$

t_{half}: Extrapolated half-life in days from NHP (to 70 kg)

Correlation	OM.CL(σ)	OM.Vp(σ)	OM.Vt(σ)	OM.Q(σ)
OM.CL(σ)	0.233			
OM.Vp(σ)	0.379	0.158		
OM.Vt(σ)	0.155	0.723	0.237	
OM.Q(σ)	0.004	0.566	0.349	0.382

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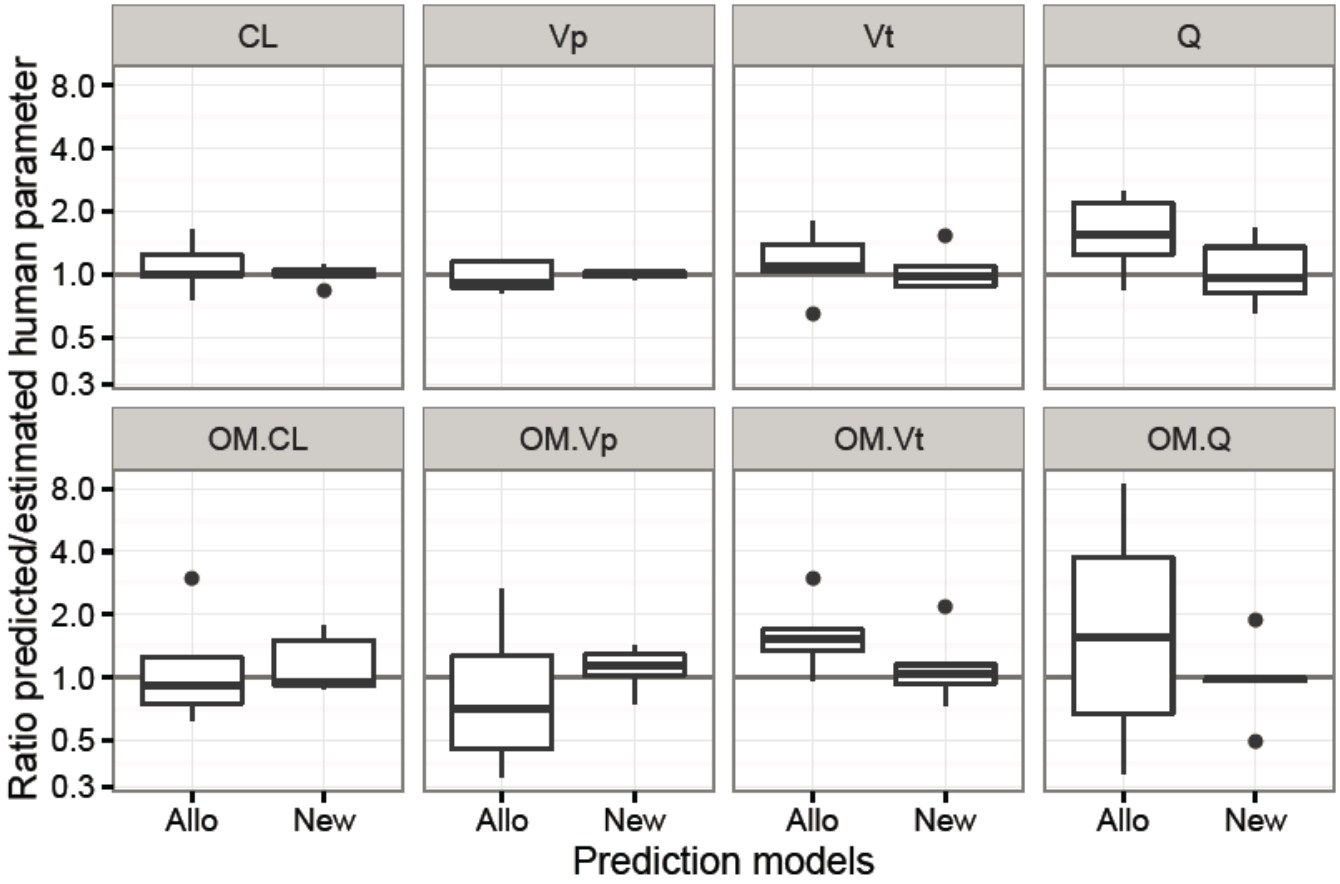
Prediction: Priors vs. pure allometric scaling

Internal validation favors the new approach

- Relative error predicted/estimated parameter for the two methods (1 data point per compound A-E)



OM are IIV (σ^2)

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Conclusions & Next steps

- Using the terminal half-life estimates from NHP data one can account for most of the inter-drug variability in human and thus provide non-inflated priors for the linear PK parameters of mAbs
  - This approach uses unbiased priors for IIV (compared to the naive pool)
  - It also showed slightly better performance than predictions from the naive pool or was pure allometric scaling

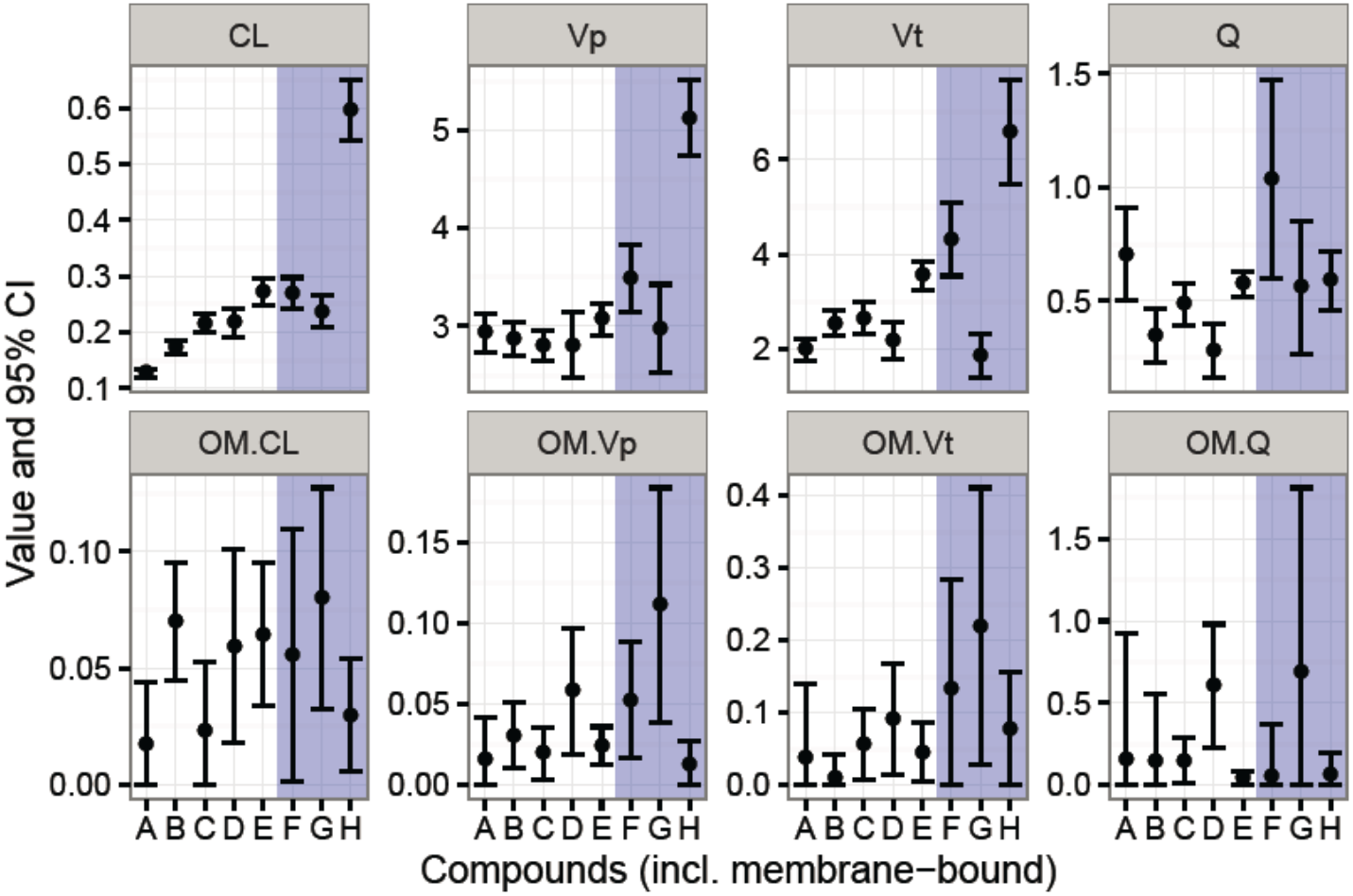
- Next, we want to use the priors derived here to non-linear mAbs to obtain more robust TMDD parameters

Thank you!

Questions?

Non-linear mAbs in human

Rapid membrane bound – or just dose-dependent PK parameters



White bckgrd:
5 linear mAbs

Blue bckgrd:
3 non-linear mAbs

OM are IIV (σ^2)

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