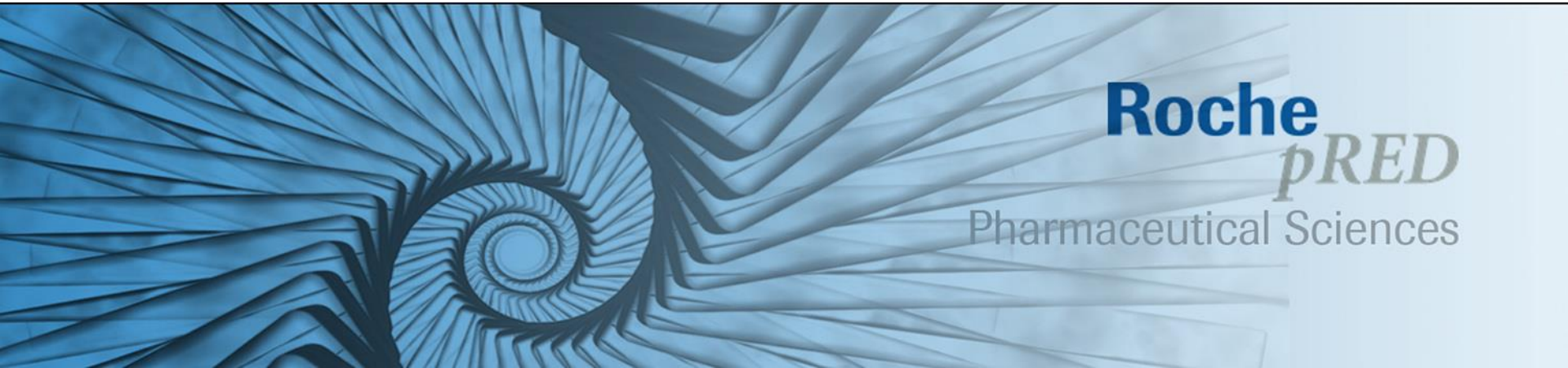
Therapeutic antibody concentrations at the biophase

Miro J. Eigenmann



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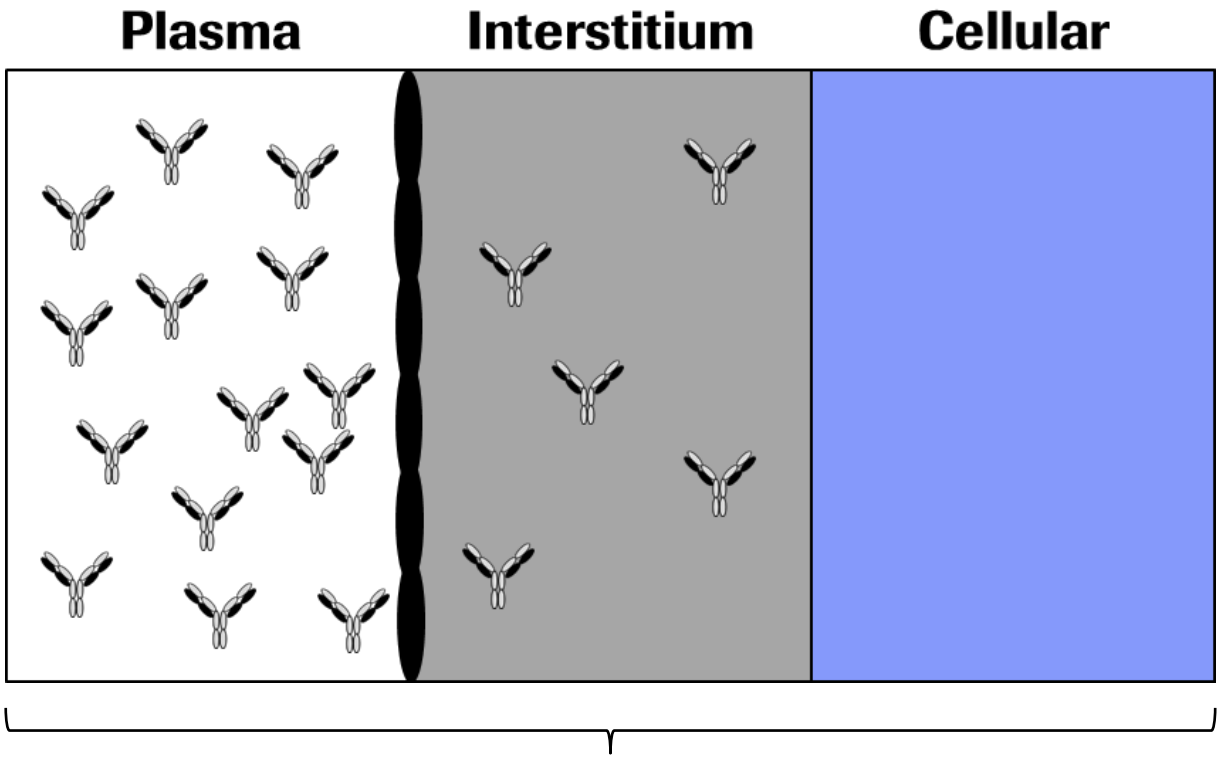
Background

Total tissue concentration vs. concentrations in tissue subcompartments



Commonly reported total tissue concentrations represent a mixture of all three spaces!
Clinically mostly just plasma measurements available!

Aim

Refine assessment and PBPK based prediction of therapeutic antibody PK in the tissue interstitial space

- *Correction of total tissue concentrations*
- *Direct experimental assessment*
- *PBPK model based prediction*

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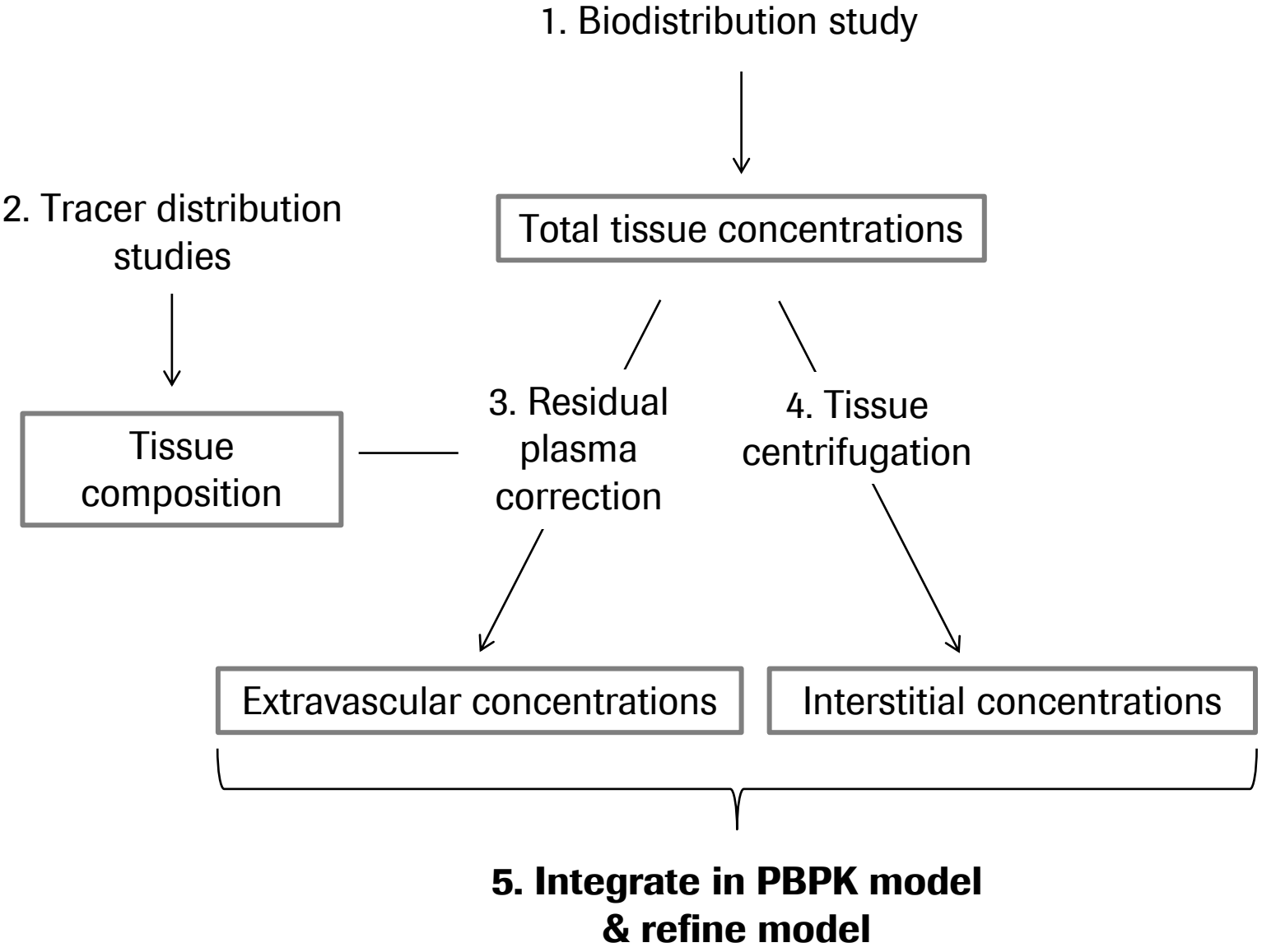

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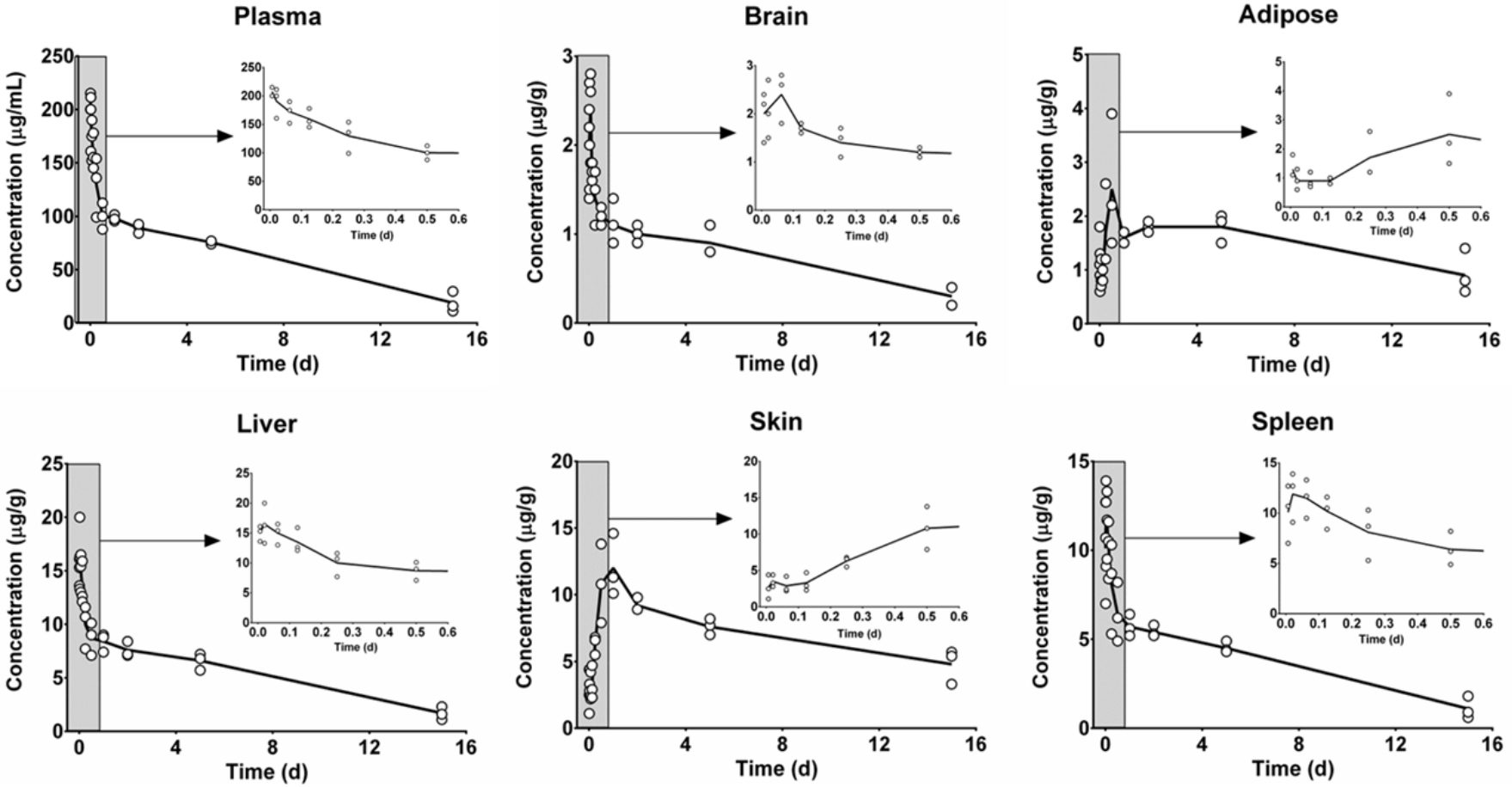
Collect biodistribution Data

Measuring PK in plasma & total tissue PK in 11 tissues

- Untargeted IgG
- I.v. Dose: 10 mg/kg
- 3 mice / time point
- 10 sampling times



Tissue composition and volumes

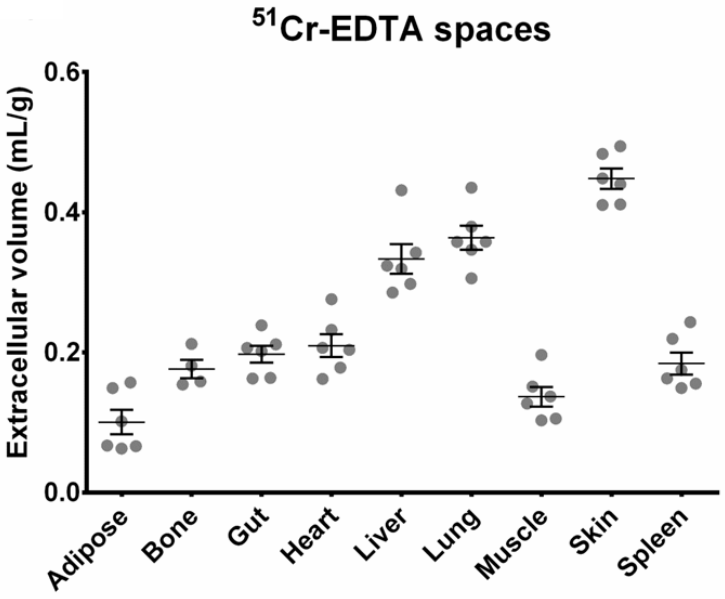
Assess residual plasma, extracellular and interstitial volumes in tissue samples

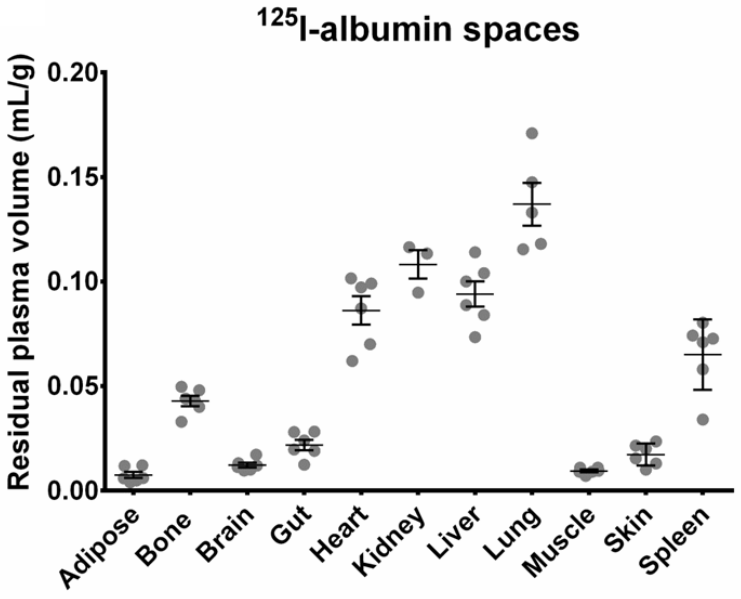
- ^{51}Cr-EDTA with 60 min distribution time for ECV

$$fVec = \frac{^{51}Cr\ counts/1g\_Tissue}{^{51}Cr\ counts/1mL\_Plasma}$$

- ^{125}I-HSA with 5 min distribution time for residual plasma

$$fVres.pla = \frac{^{125}I\ counts/1g\_Tissue}{^{125}I\ counts/1mL\_Plasma}$$



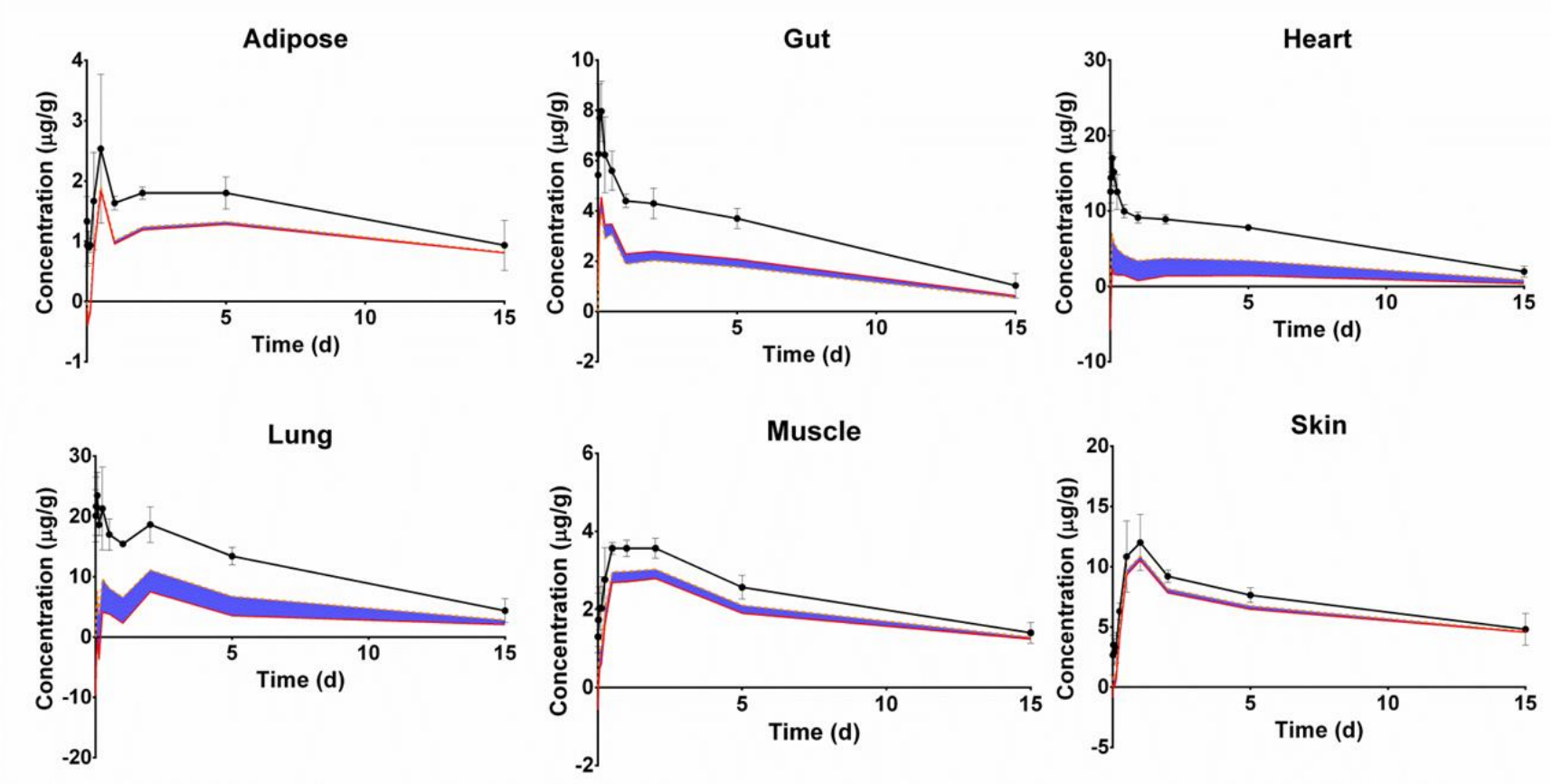


Residual plasma correction

Derive tissue extravascular concentrations

- Subtract drug in residual plasma from totally measured amount of drug

$$C_{ev} = \frac{A_{tis} - A_{respla_{tis}}}{V_{tis} - V_{respla_{tis}}}$$



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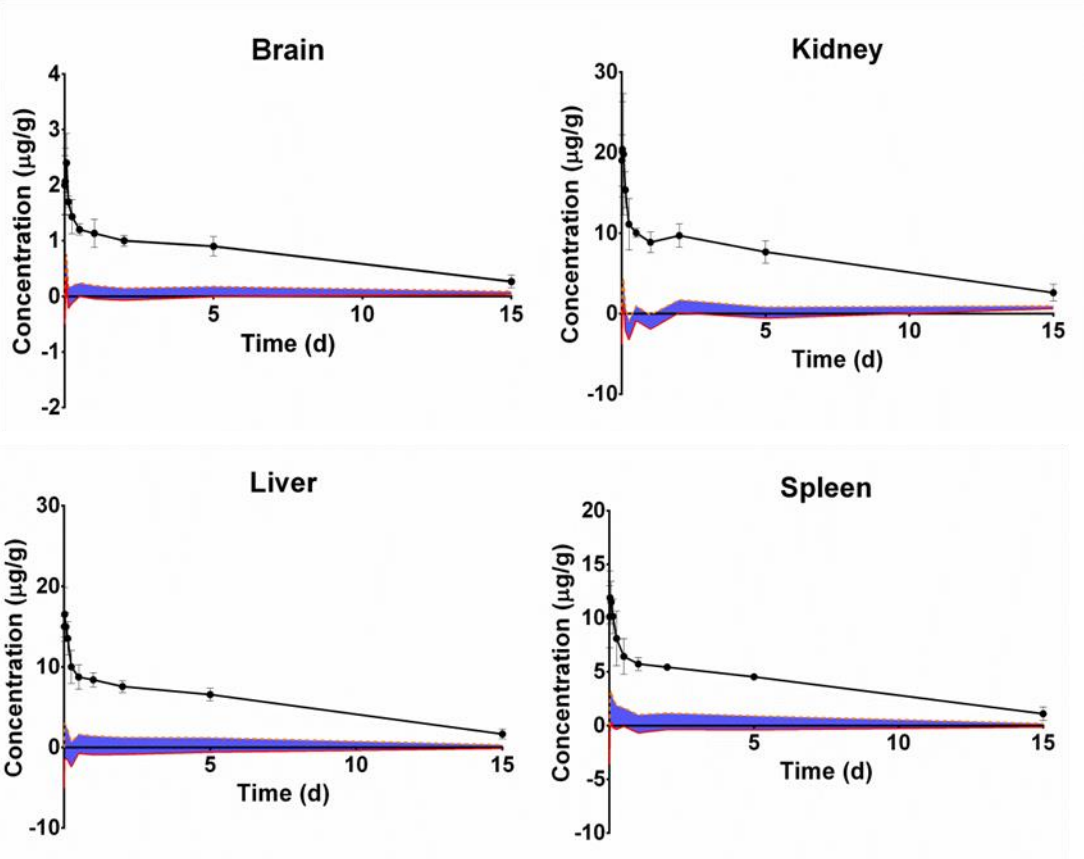
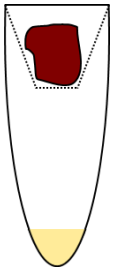
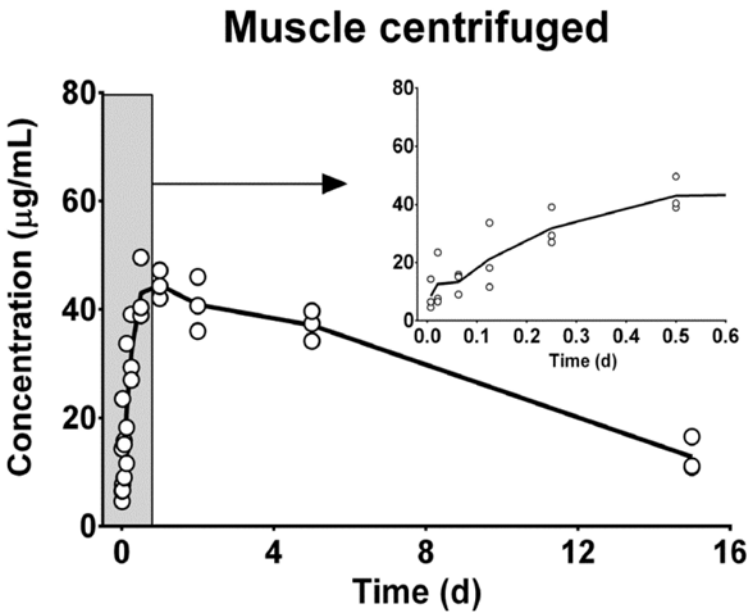


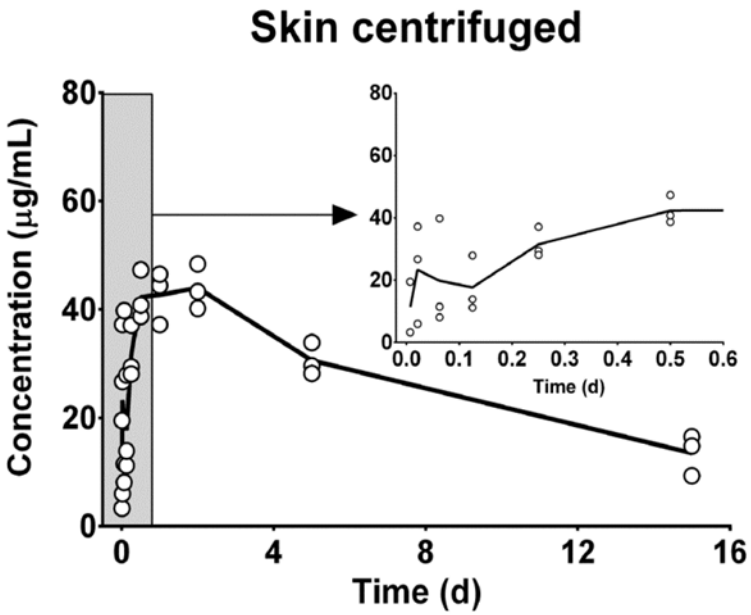
Tissue centrifugation – Interstitial PK

Direct experimental assessment of interstitial concentrations

- Centrifuge tissue sample in tube at low speed
- Collect fluid sample at the bottom of the tube[1]







[1]Wiig, H. et al. *Isolation of interstitial fluid from rat mammary tumors by a centrifugation method.* American journal of physiology. Heart and circulatory physiology, 2003.

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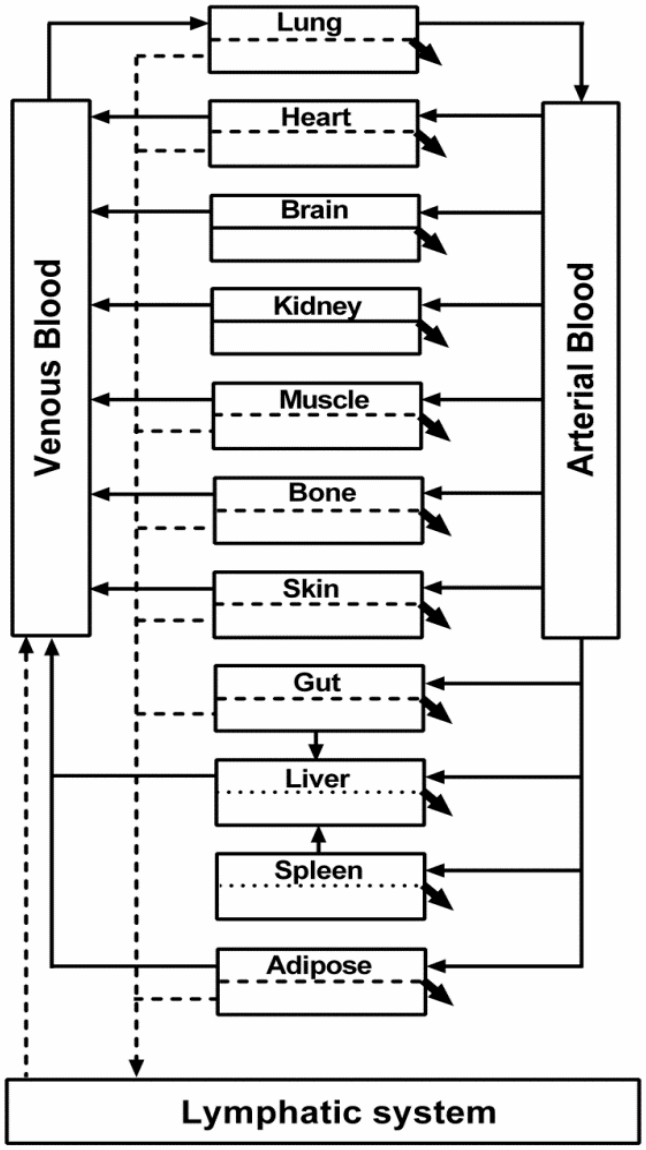
Impact on PBPK model

Integrate data into PBPK model & refine model

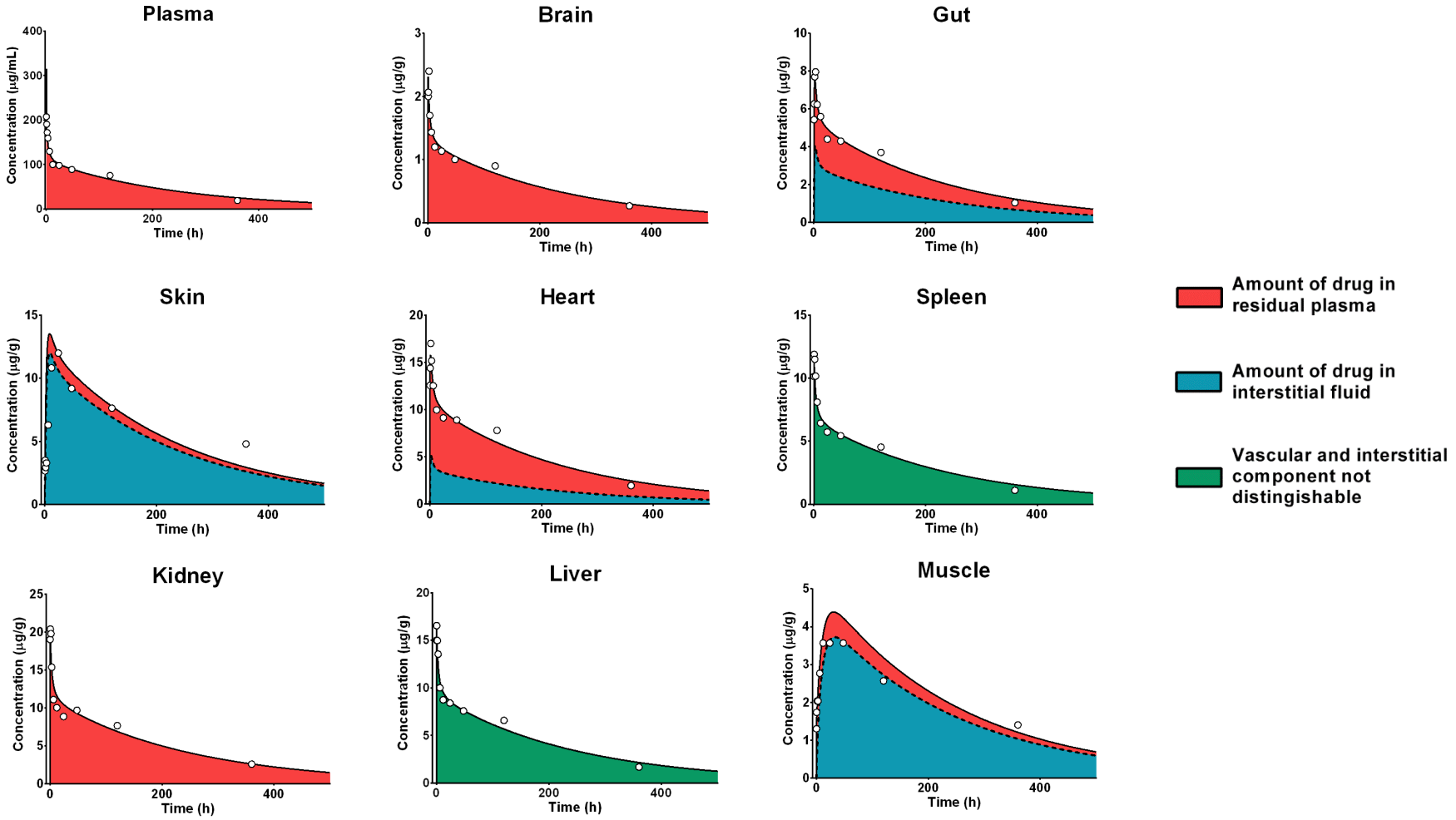
Tissues modeled based on underlying capillary types:

- Continuous (- - -)
  - *Distinct interstitial & vascular space*
  - *Uptake & lymph flow estimated*
- Discontinuous (·····)
  - *Interstitial & vascular space equilibrated, not distinguishable based on data*
  - *Uptake & lymph flow not identifiable*
- Tight (——)
  - *Antibodies largely restricted to vascular space*
  - *Negligible uptake & lymph flow not identifiable*



Model based analysis

Describe biodistribution data and predict drug amount in tissue subcompartments



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- Interstitial antibody concentrations are highly tissue specific:
  - Depend on underlying capillary structure
    - *Continuous capillaries: ~50-60% of plasma concentration*
    - *Discontinuous capillaries: reflected by plasma concentrations*
    - *Tight capillaries: restricted to vasculature → negligible interstitial concentrations*
- More tissue specific implementation into PBPK model
- Allows more realistic model based predictions of the PK in the interstitial space

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Thank you!

Questions?

Doing now what patients need next