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## Physiologically-based pharmacokinetic modelling of dendrimer nanoparticles to unravel structure – PK parameters relationships

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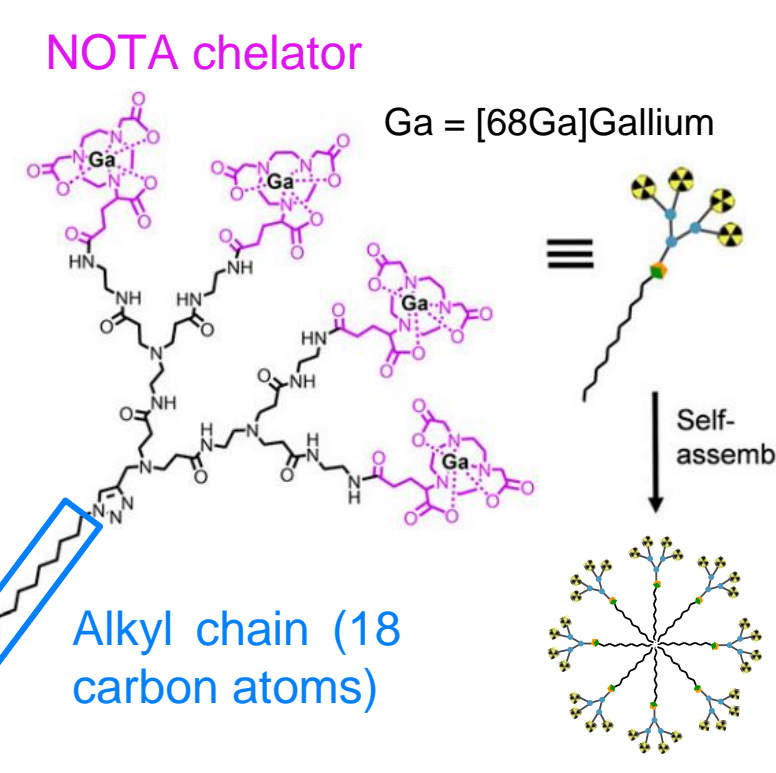
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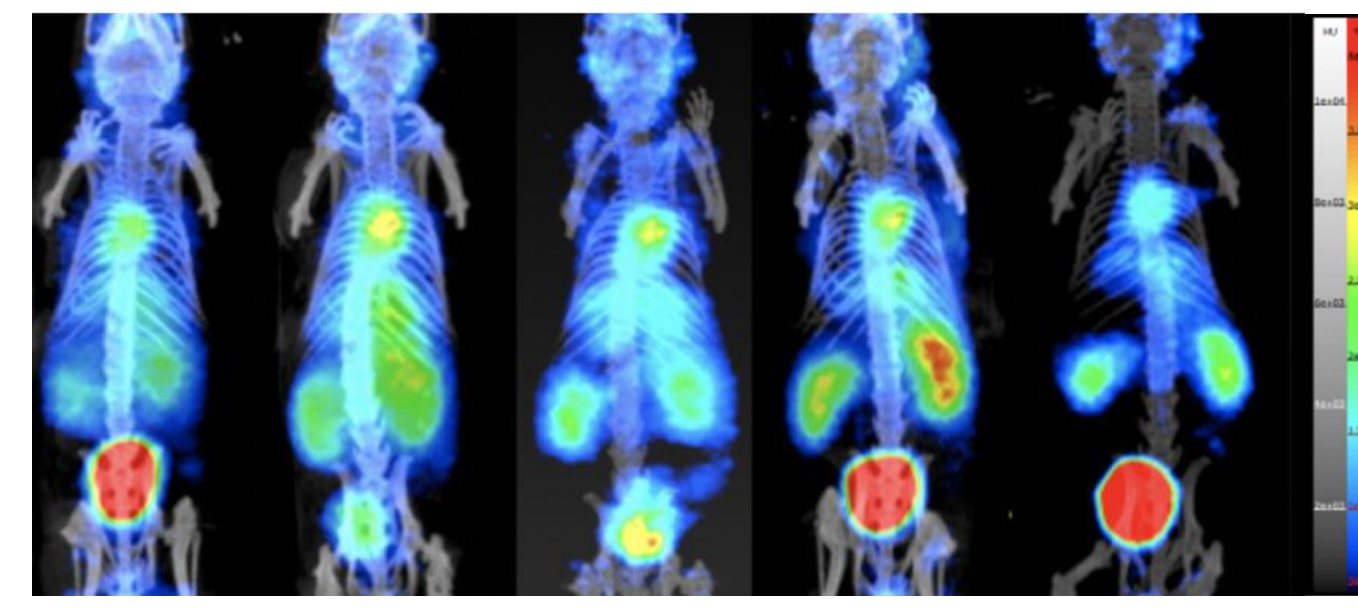
## CONTEXT & OBJECTIVES

- Many types of nanoparticles (NPs) developed but no tools to rationalize NPs development  
⇒ Need of tools for rational nanodrugs optimization
- Current work on **7 formulations** of gallium-68 radiolabeled dendrimers<sup>[1]</sup>

### Dendrimer C18



### Reduction of alkyl chain and fluorination of C18



- Addition of RGD peptide at 2 ratios:
- 1 dendrimer for 3 RGD (1:3)
  - 3 dendrimers for 1 RGD (3:1)

- PBPK modeling: **quantitative PK estimations and predictions**
- Development of a computational model describing the distribution of dendrimers in the organism depending on their characteristics

## METHODS

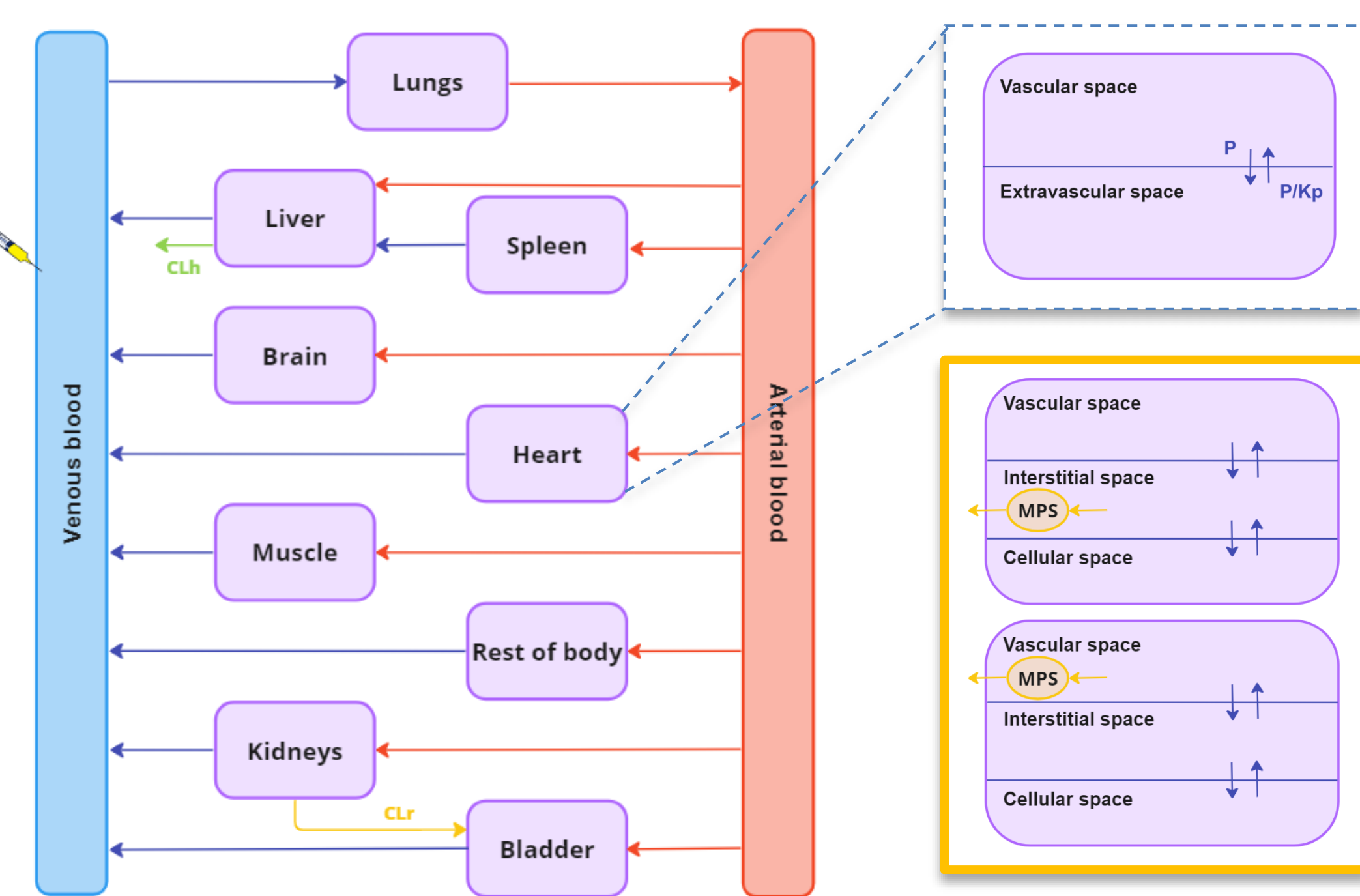
- Data:**
  - Model: healthy Swiss mice
  - Administration: intravenous
  - mPET/CT imaging for 2h (n=6, except for (C<sub>4</sub>F<sub>9</sub>)-C11 n=5, and (C<sub>4</sub>F<sub>9</sub>)-C11 with RGD n=3)
  - gamma counting (blood) for 2h (n=6, except (C<sub>4</sub>F<sub>9</sub>)-C11 with RGD n=3)
- Software:** R version 4.2.2
- Ordinary Differential Equation (ODE) solver:** deSolve
- Plots:** ggplot and GraphPad Prism 9.5

Parameter	Source
Partition coefficients (Kp)	In vivo data <sup>[2]</sup> Concentration in organs, tissues (%ID/g) Concentration in blood (%ID/g)
Physiology	Brown et al. <sup>[3]</sup>
Permeability (P) (mL/h)	Estimated
Renal clearance (CL <sub>r</sub> , mL/h)	In vivo data (popPK model) <sup>[2]</sup>
Hepatic clearance (CL <sub>h</sub> , mL/h)	In vivo data (popPK model) <sup>[2]</sup>

## RESULTS

### 1. Structure of the nanoPBPK model

Tissue model: permeability-limited tissue distribution



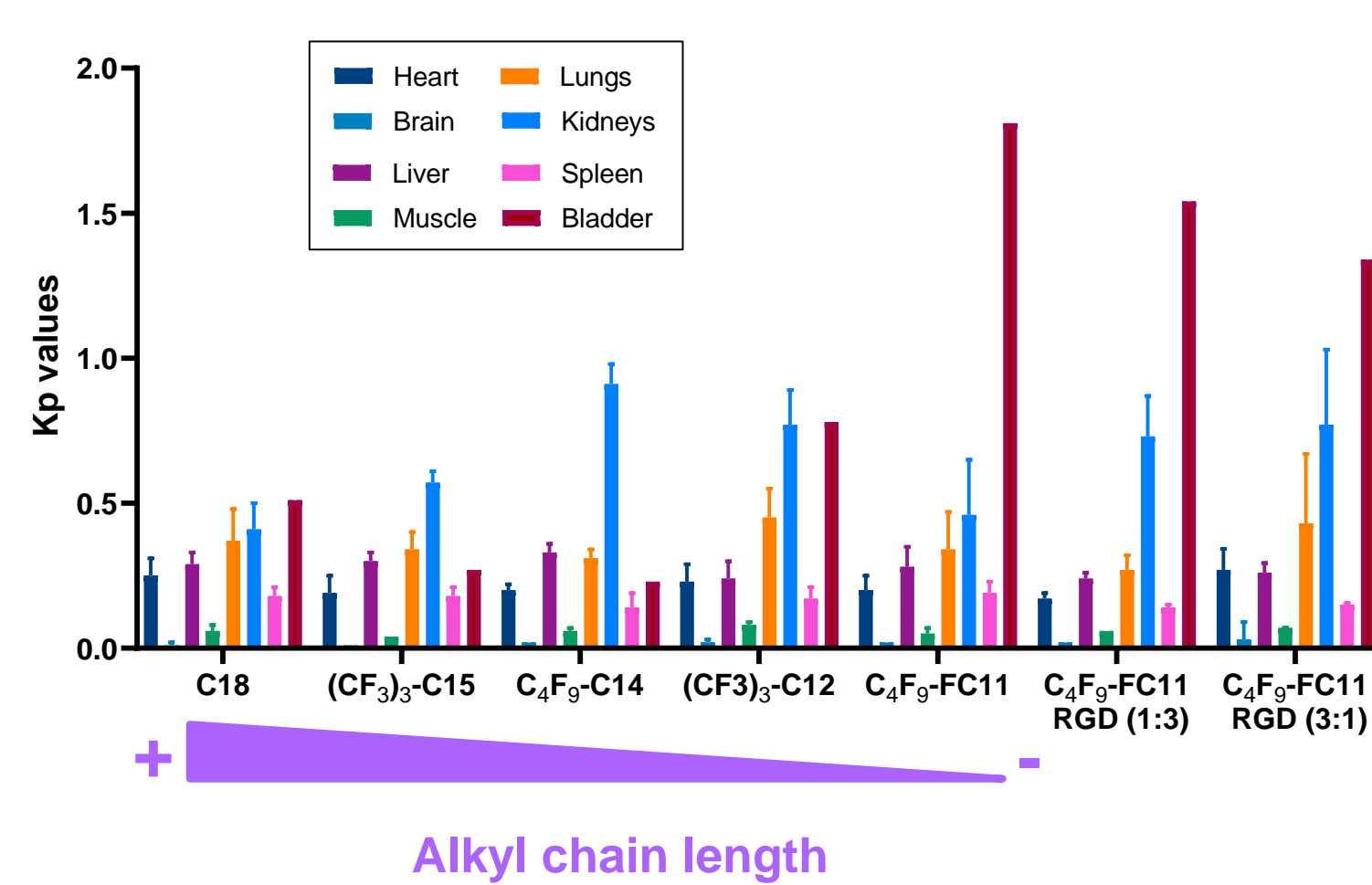
$$\frac{dA_{vascular}}{dt} = Q \cdot (CA - CV_{tissue}) - P_{tissue} \cdot CV_{tissue} + \frac{P_{tissue} \cdot C_{tissue}}{Kp}$$

$$\frac{dA_{interstitial}}{dt} = P_{tissue} \cdot CV_{tissue} - \frac{P_{tissue} \cdot C_{tissue}}{Kp}$$

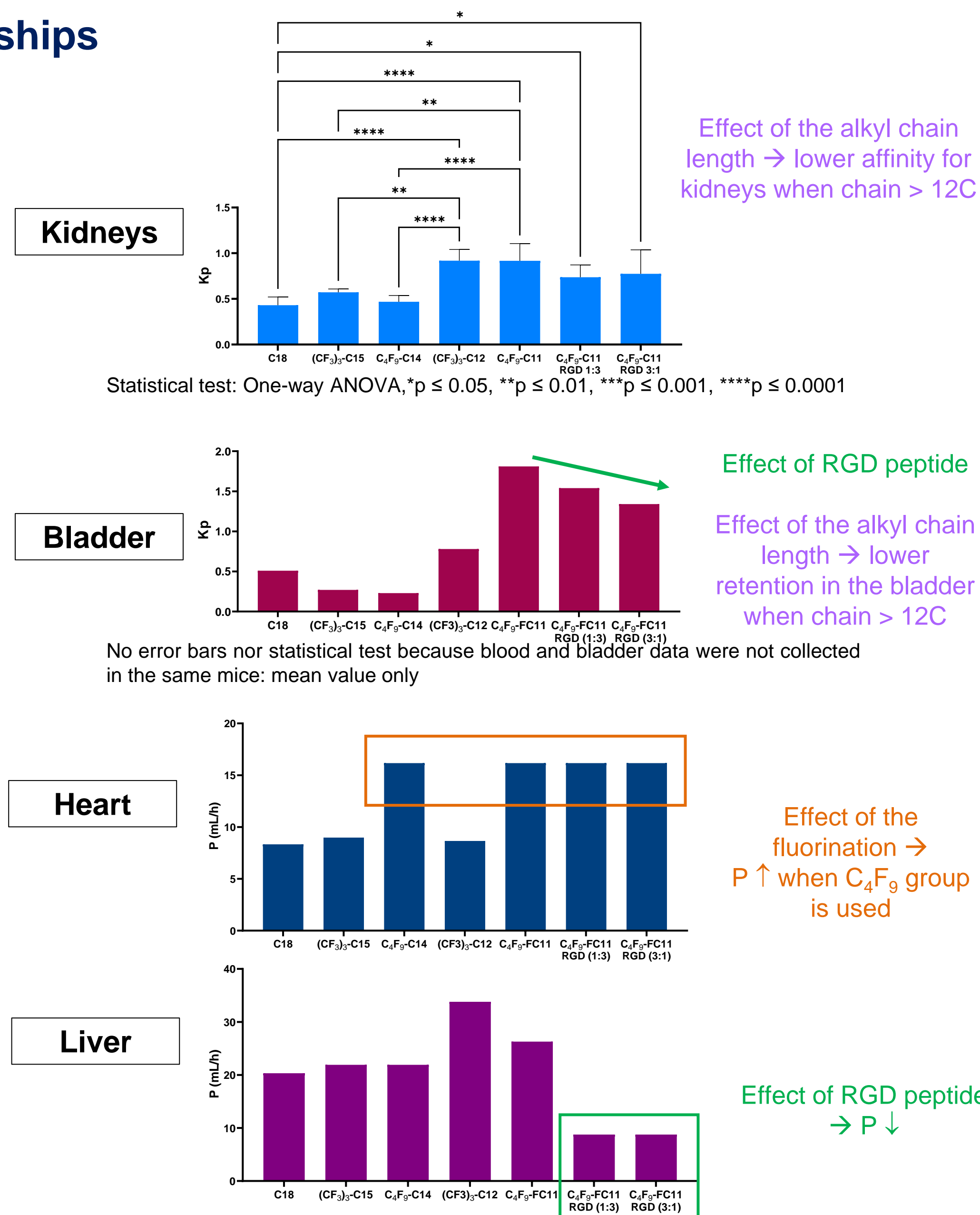
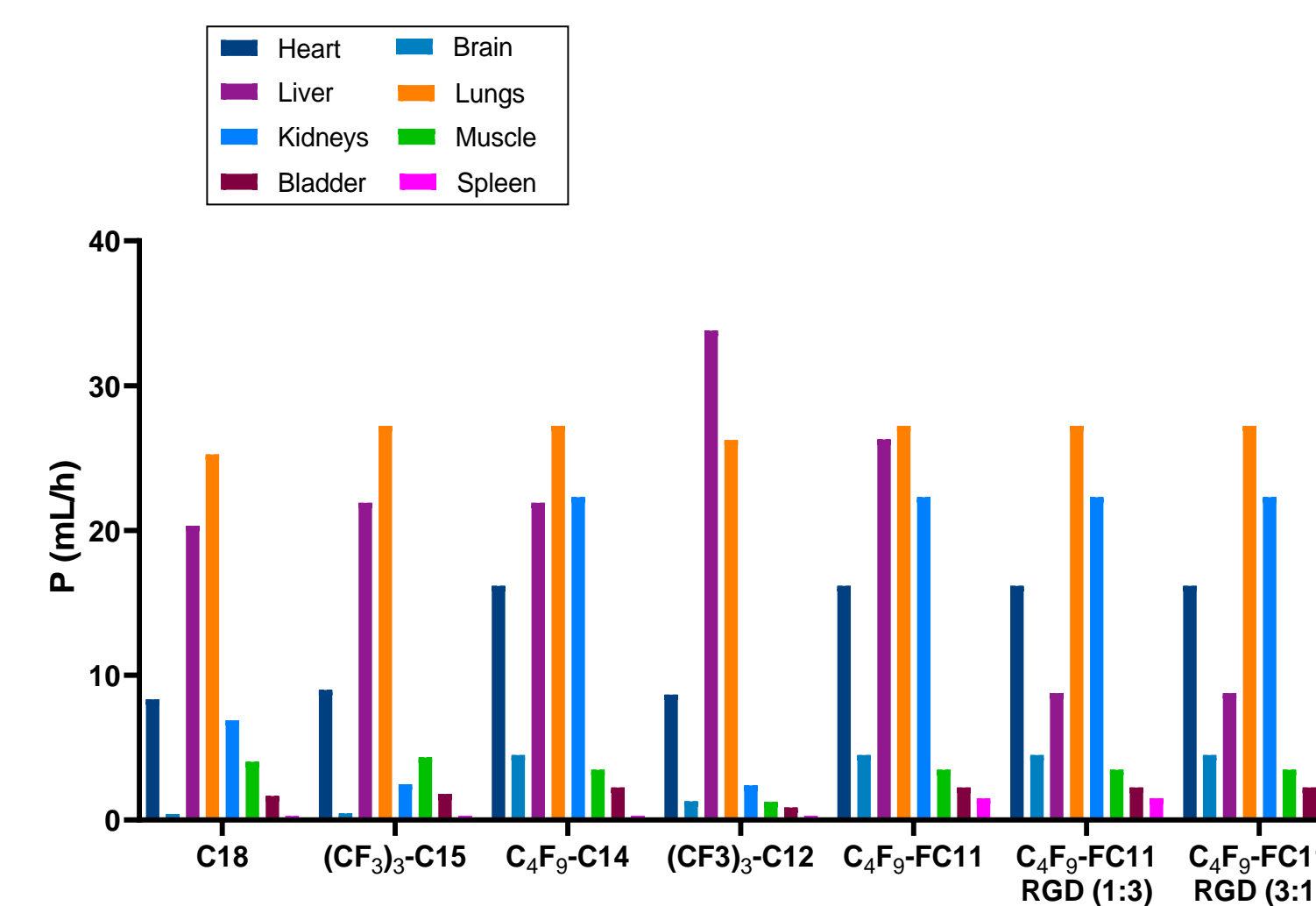
C: concentration (%ID/g)  
CA: arterial concentration (%ID/mL)  
CV: venous concentration (%ID/mL)  
Q: Blood flow (mL/h)

### 2. Structure-PK parameters relationships

#### Partition coefficients (Kp)



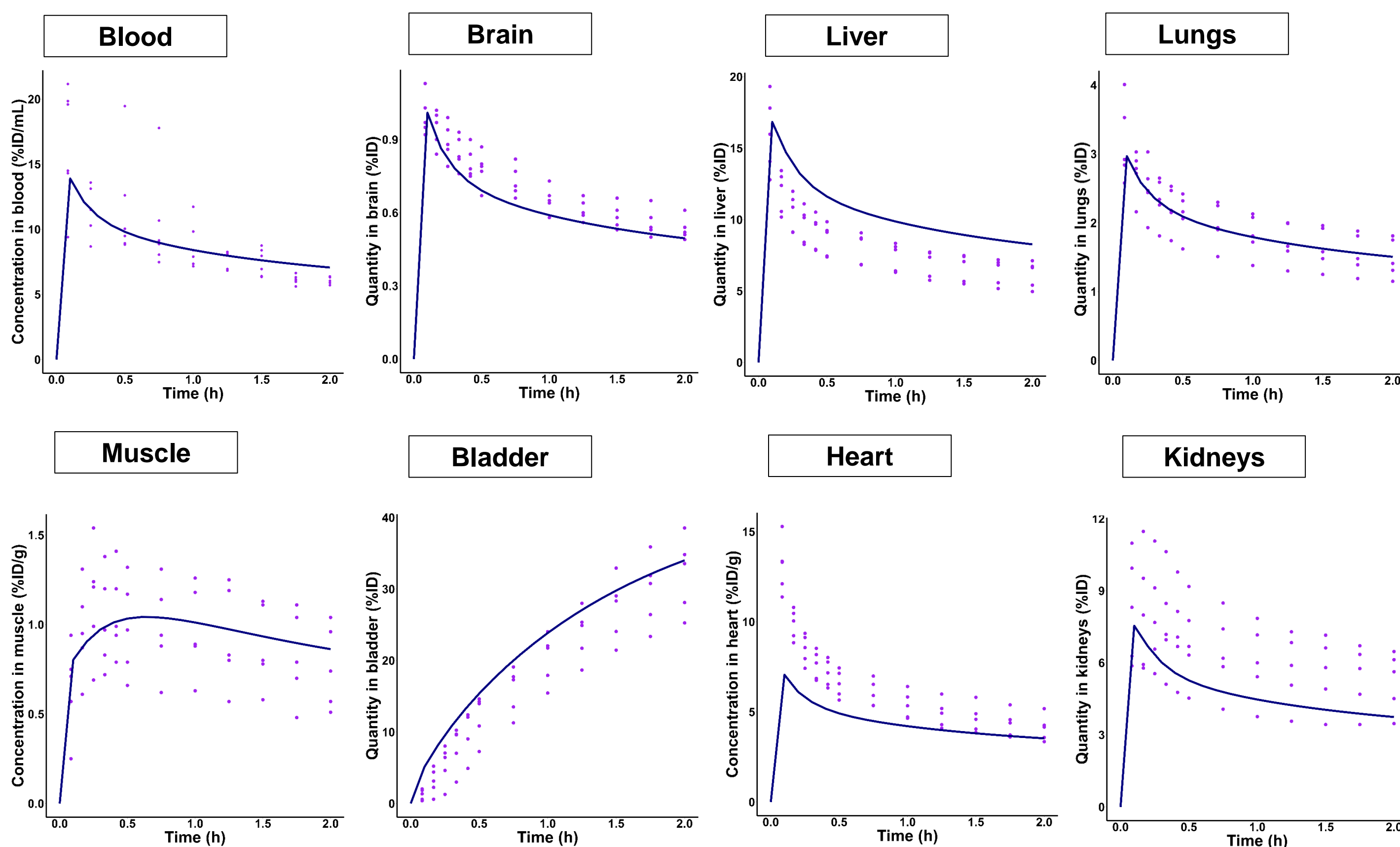
#### Permeability (P)



### 4. Predictions of dendrimers disposition in vivo

#### Individual plasmatic profiles after permeability fitting in organs

Example of dendrimer C<sub>4</sub>F<sub>9</sub>-C11 (n=5)



Predictions of the PBPK model satisfactory for C<sub>4</sub>F<sub>9</sub>-C11 and other dendrimers (results not shown)  
Space for improvement (overprediction in liver, underprediction in heart for C<sub>4</sub>F<sub>9</sub>-C11)

#### Internal evaluation of the model

Comparison of blood PK parameters (C<sub>max</sub> and AUC) calculated from observed data (obs) and predicted (pred) from the PBPK model for each dendrimer

Dendrimer	C <sub>max</sub> <sub>obs</sub> (%ID/g)	C <sub>max</sub> <sub>pred</sub> (%ID/g)	C <sub>max</sub> Fold error	AUC <sub>obs</sub> 0-2h (%ID/g.h)	AUC <sub>pred</sub> 0-2h (%ID/g.h)	AUC Fold error
C18	22.29	27.87	1.25	30.19	39.87	1.32
(CF <sub>3</sub> ) <sub>3</sub> -C15	24.57	26.19	1.07	32.84	37.03	1.13
C <sub>4</sub> F <sub>9</sub> -C14	30.42	24.39	0.80	42.09	33.69	0.80
(CF <sub>3</sub> ) <sub>3</sub> -C12	30.98	27.66	0.89	35.99	32.55	0.90
C <sub>4</sub> F <sub>9</sub> -C11	16.47	13.9	0.84	19.10	17.39	0.91
C <sub>4</sub> F <sub>9</sub> -C11 RGD 1:3	24.91	24.04	0.97	23.35	29.79	1.28
C <sub>4</sub> F <sub>9</sub> -C11 RGD 3:1	25.67	22.67	0.88	28.05	26.84	0.96

Fold error < 2

## CONCLUSION

- PBPK model accurately predicted the distribution of dendrimers
- Relationships between dendrimer structure and PK parameters established  
→ tool to guide the development of dendrimers

## PERSPECTIVES

- Collection of in vitro parameters to add NP-specific processes in the model (cellular uptake (endocytosis), opsonization)
- Expand the PBPK model to other types of NPs
- Apply this approach to design new optimal NPs

[1] Garrigue P. et al., Proc. Natl. Acad. Sci. 115, 11454–11459 (2018)  
[2] Ou J. et al., hal-03930671 (2022)  
[3] Brown RP et al., Toxicol Ind Health. 13: 407 (1997)

**Abbreviations**  
AUC: Area under the curve  
C: carbon  
ID: injected dose  
MPS: Mononuclear Phagocyte System  
RGD: Arginyl-glycyl-aspartic acid

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