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

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► To cite this version:

Jessica Ou, Béatrice Louis, Laure Balasse, Tom Roussel, Ling Peng, et al.. Physiologically-based pharmacokinetic modelling of dendrimer nanoparticles to unravel structure – PK parameters relationships. GMP Symposium 2023, Oct 2023, Paris, France. hal-04344099

HAL Id: hal-04344099

<https://hal.science/hal-04344099v1>

Submitted on 20 Dec 2023

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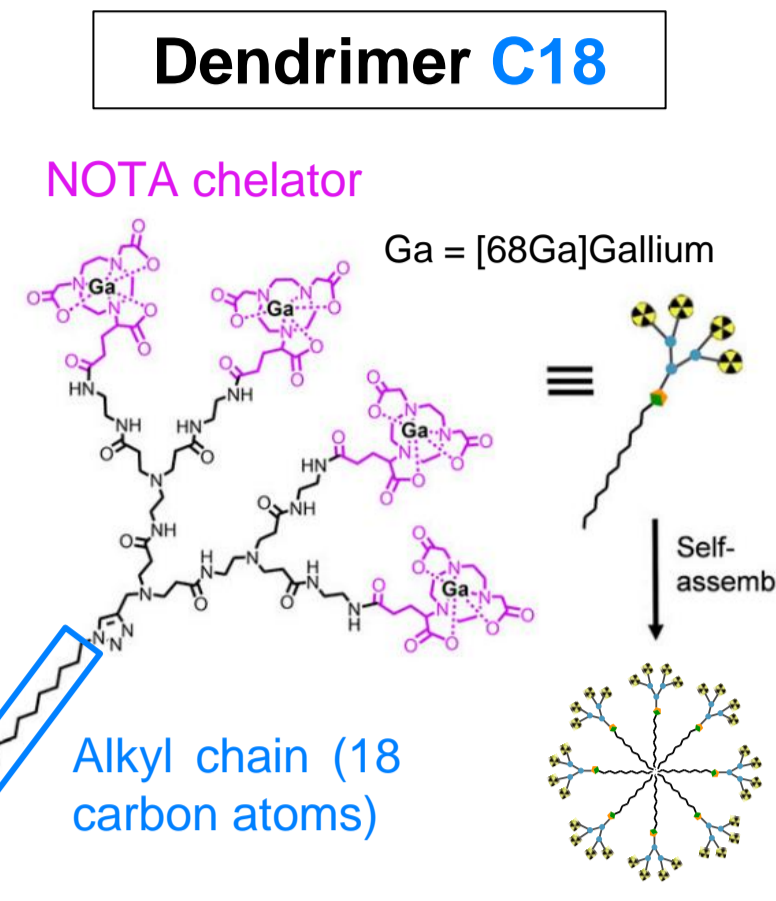
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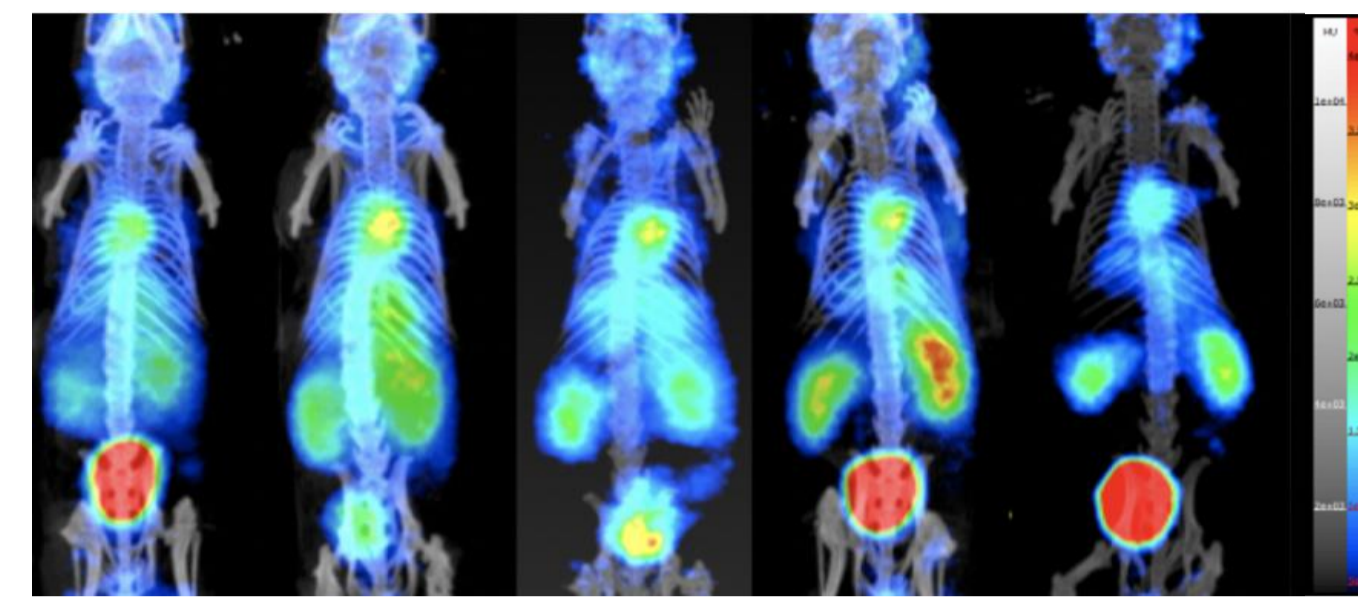
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CONTEXT & OBJECTIVES

- 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^[1]



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

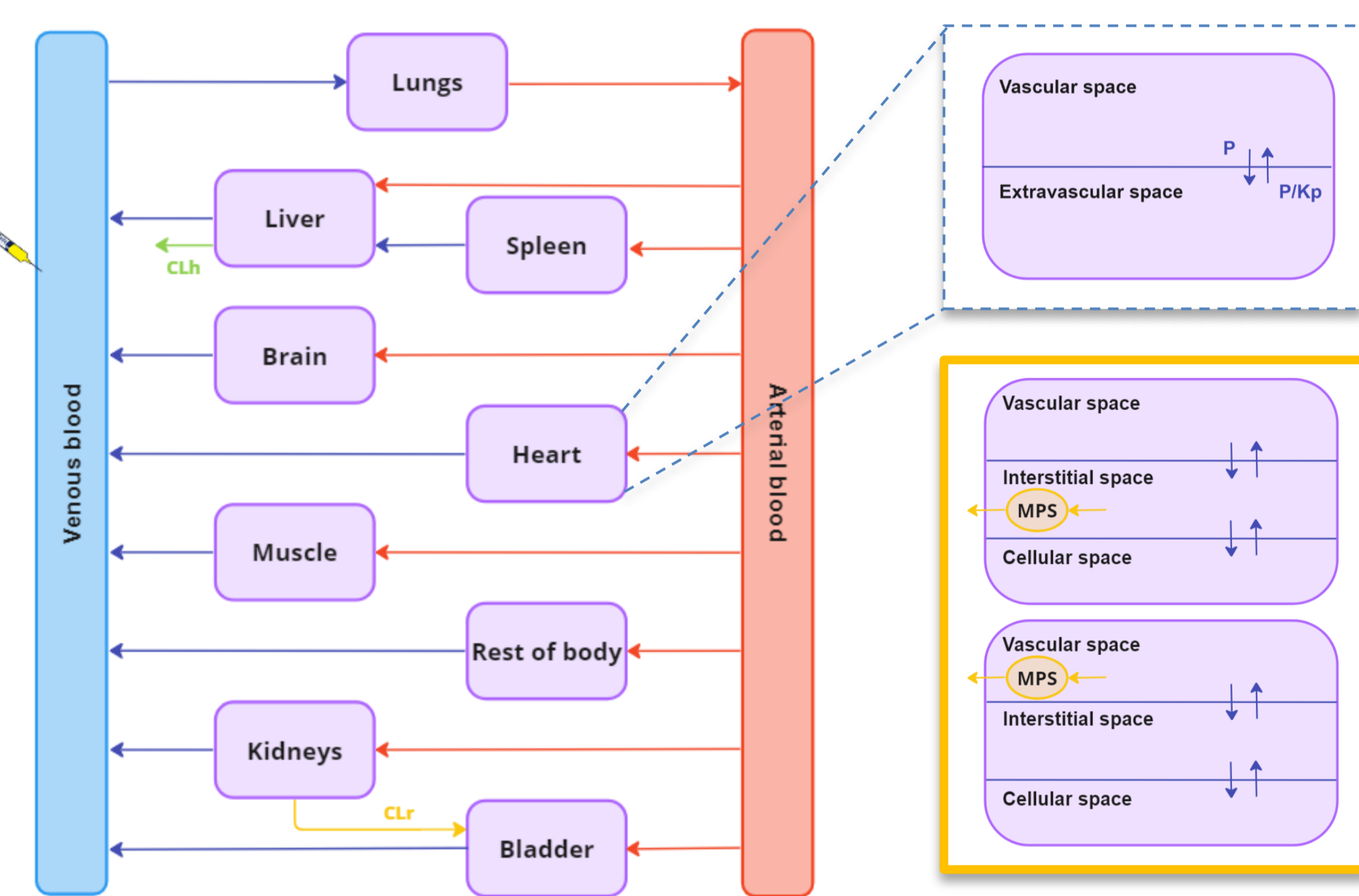
- Data:**
 - Model: healthy Swiss mice
 - Administration: intravenous
 - mPET/CT imaging for 2h (n=6, except for (C₄F₉)-C11 n=5, and (C₄F₉)-C11 with RGD n=3)
 - gamma counting (blood) for 2h (n=6, except (C₄F₉)-C11 with RGD n=3)
- Software:** R version 4.2.2
- Ordinary Differential Equation (ODE) solver:** deSolve
- Plots:** ggplot and GraphPad Prism 9.5

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

RESULTS

1. Structure of the nanoPBPK model

Tissue model: permeability-limited tissue distribution



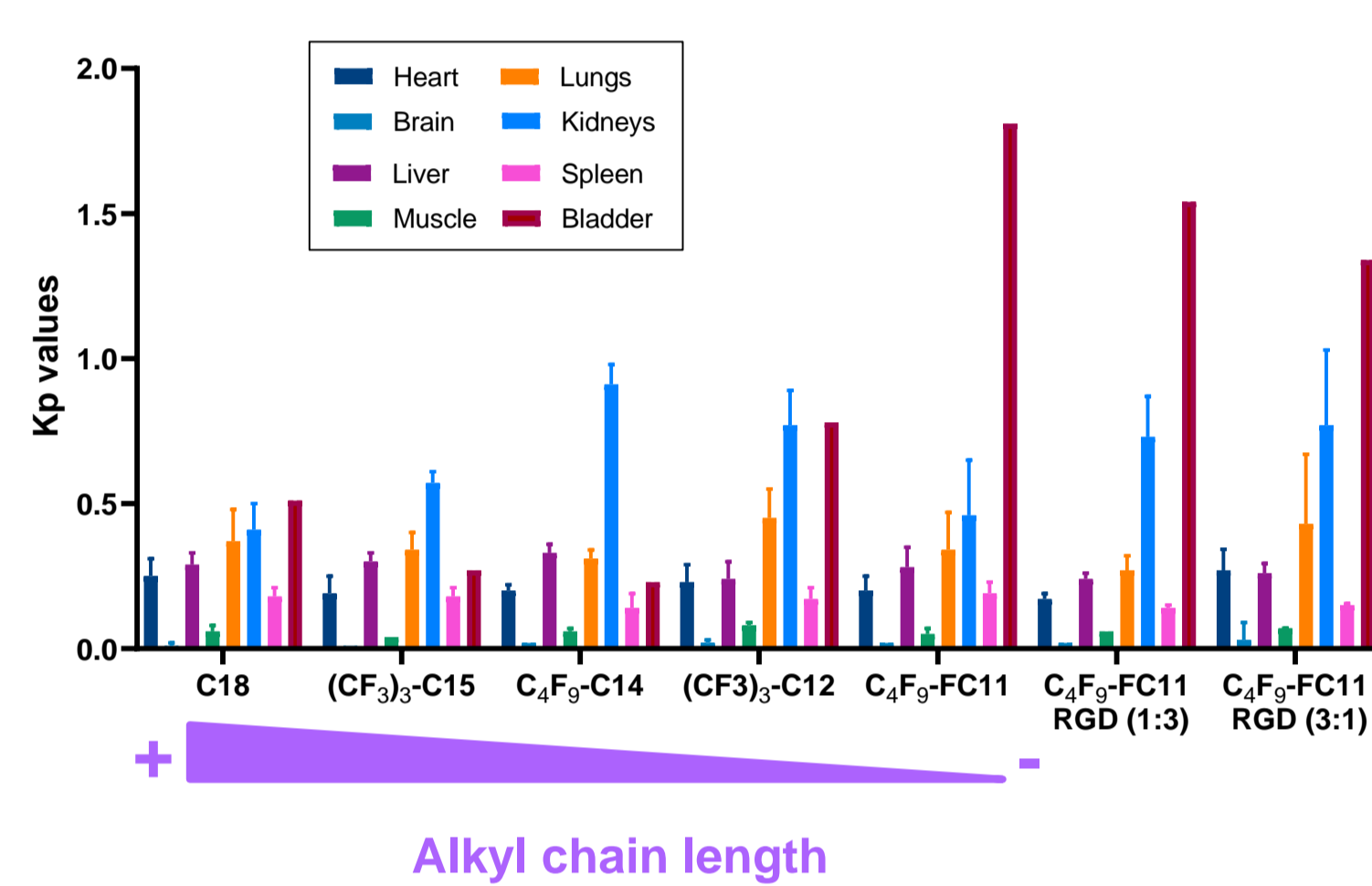
$$\frac{dA_{vascular}}{dt} = Q*(CA - CV_{tissue}) - P_{tissue} * CV_{tissue} + \frac{P_{tissue} * C_{tissue}}{Kp}$$

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

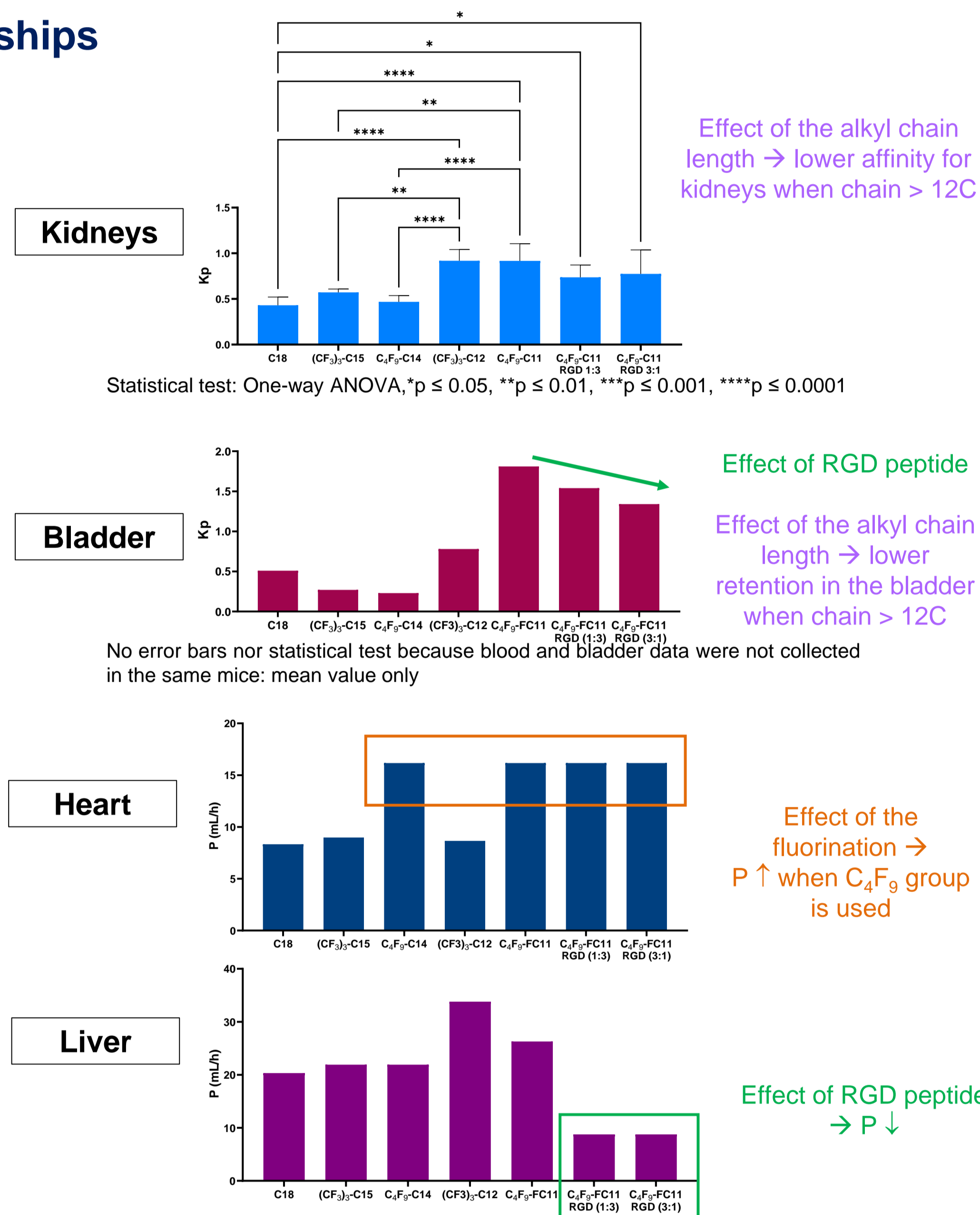
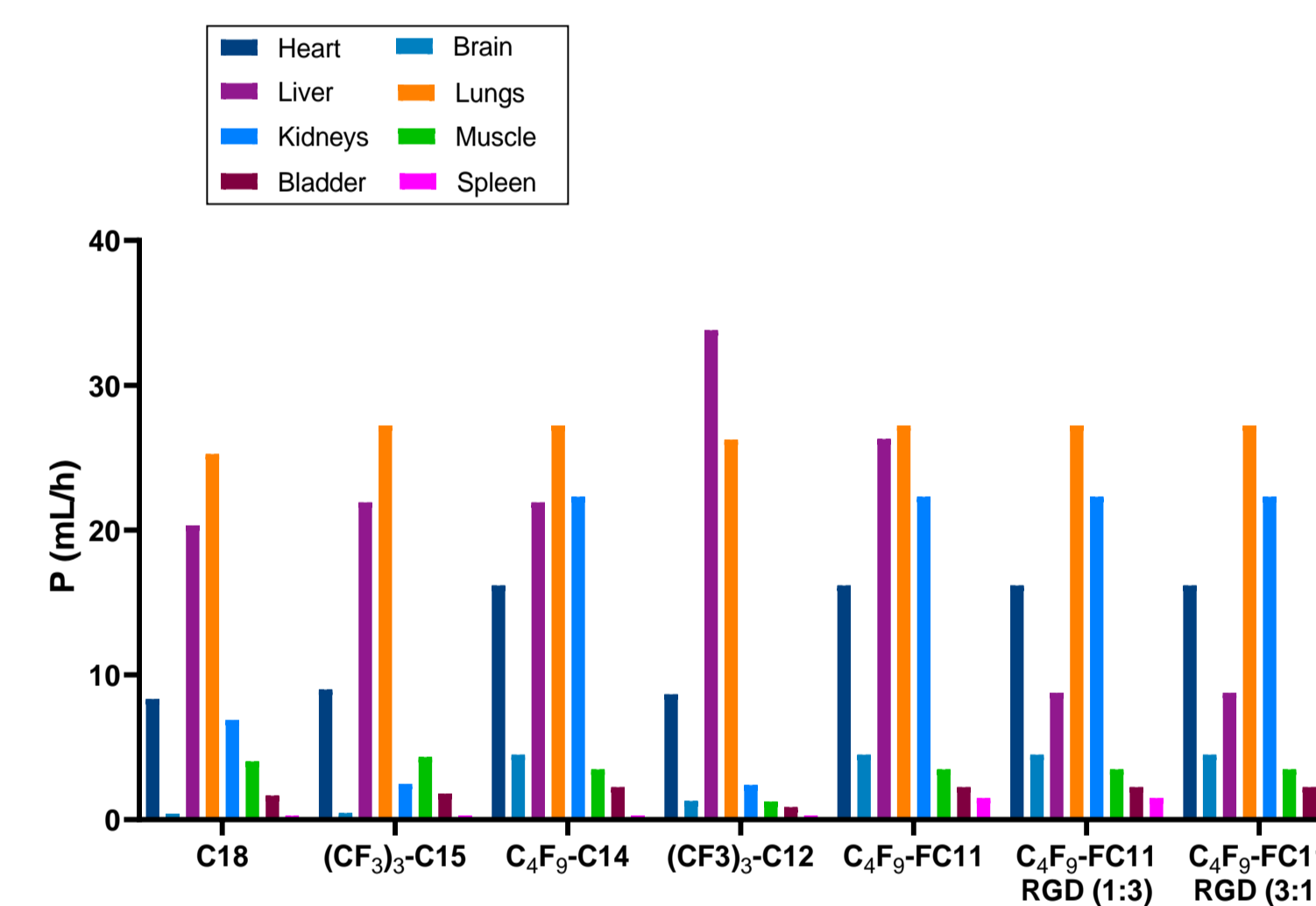
C: concentration (%ID/g)
CA: arterial concentration (%ID/mL)
CV: venous concentration (%ID/mL)
Q: Blood flow (mL/h)

2. Structure-PK parameters relationships

Partition coefficients (Kp)



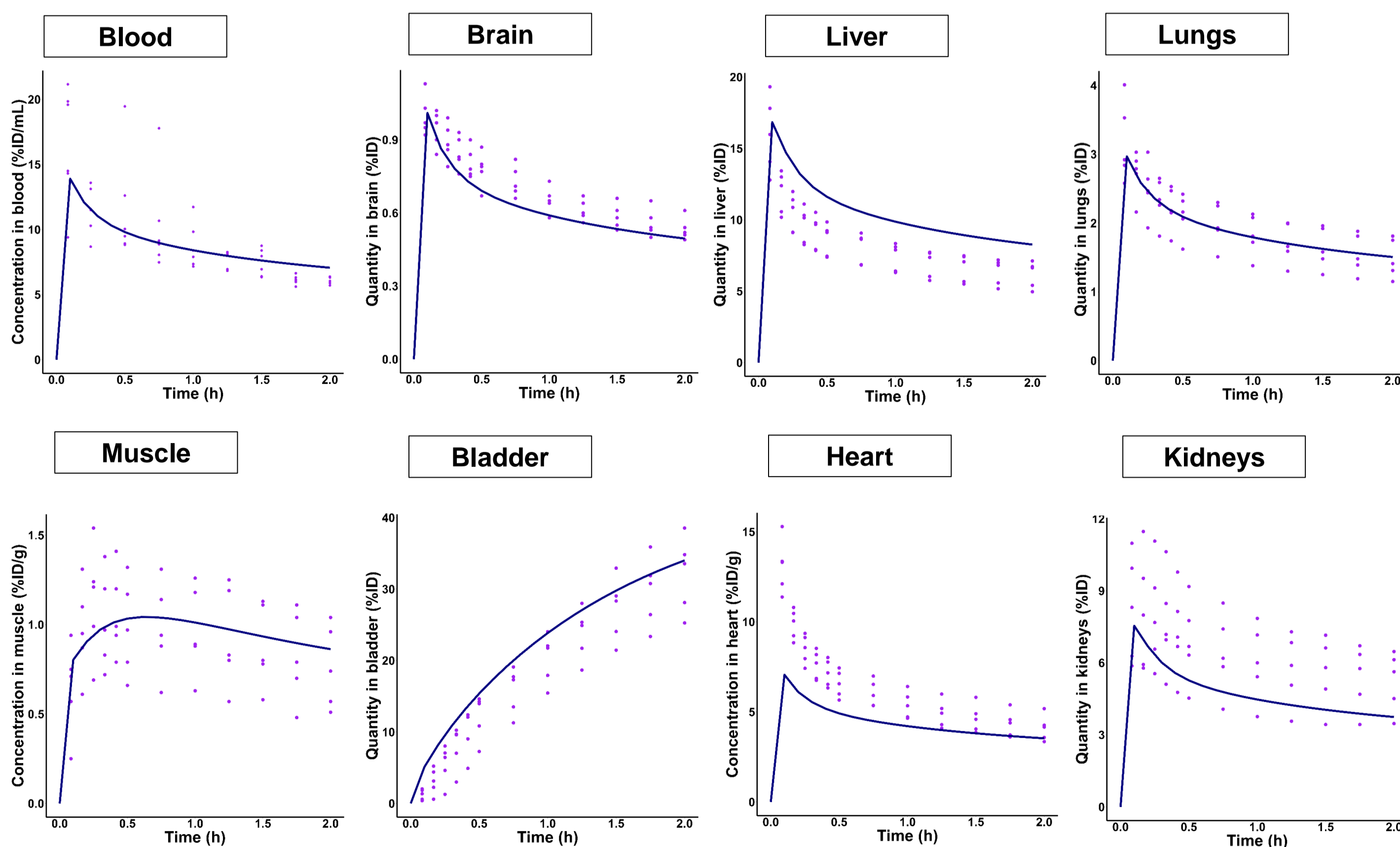
Permeability (P)



4. Predictions of dendrimers disposition in vivo

Individual plasmatic profiles after permeability fitting in organs

Example of dendrimer C₄F₉-C11 (n=5)



Predictions of the PBPK model satisfactory for C₄F₉-C11 and other dendrimers (results not shown)
Space for improvement (overprediction in liver, underprediction in heart for C₄F₉-C11)

Internal evaluation of the model

Comparison of blood PK parameters (C_{max} and AUC) calculated from observed data (obs) and predicted (pred) from the PBPK model for each dendrimer

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

Acknowledgments
J. Ou's PhD is financed by a grant from Ecole Doctorale 62 – Sciences de la vie, Aix-Marseille University. The authors thank PACA Cancerop le, Conseil R gional PACA and Institut National du Cancer for financial support.

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