

Development of a physiologically-based pharmacokinetic (PBPK) model to understand and predict the disposition of gallium-68 radiolabeled dendrimers *in vivo*

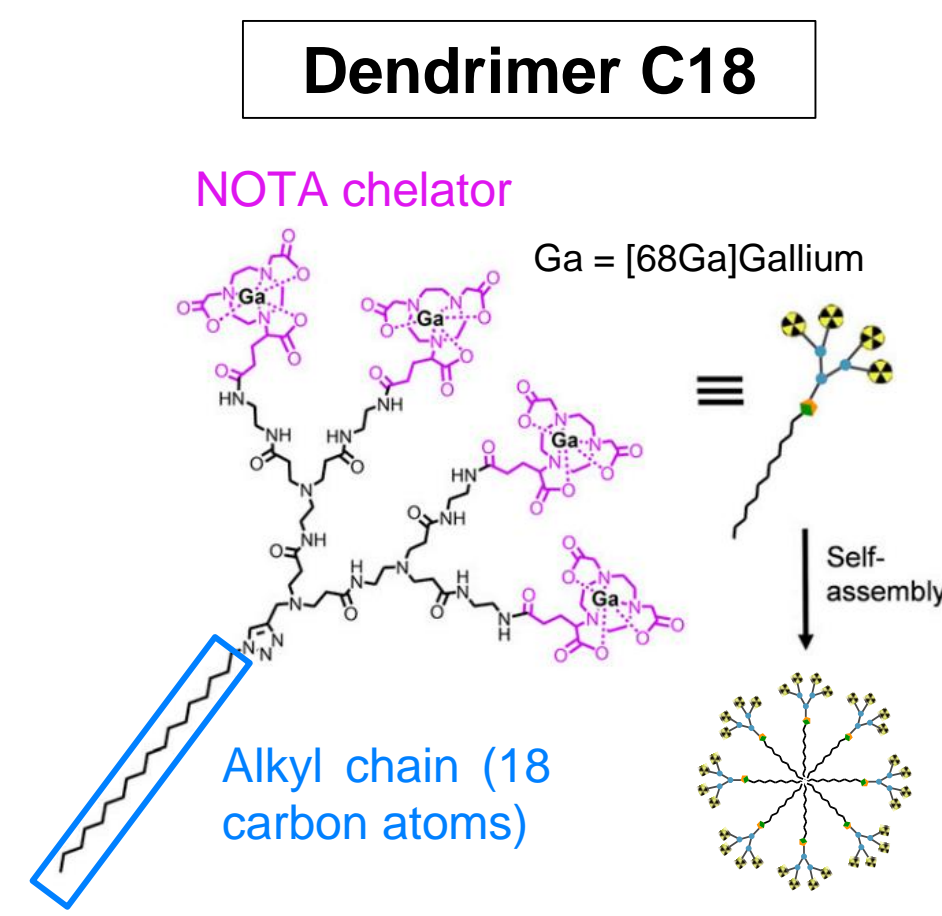
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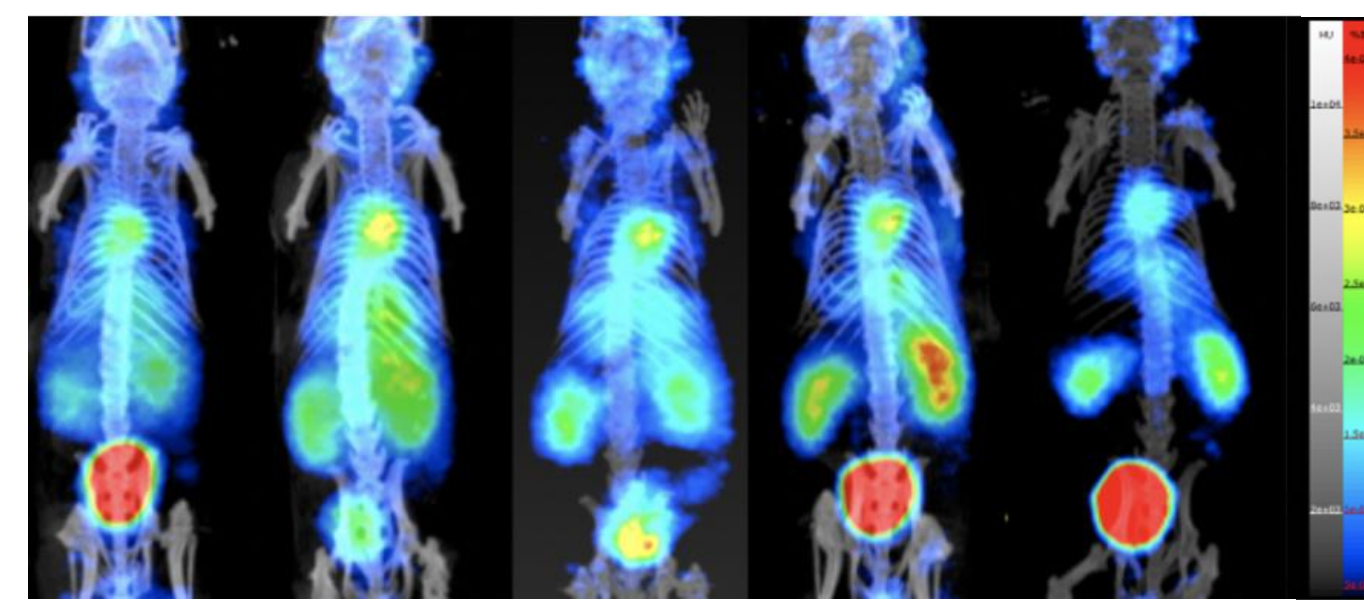
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CONTEXT & OBJECTIVES

- Many nanoparticles (NPs) developed
- No tools to rationalize NPs development
- ⇒ Need of tools for rational nanodrugs optimization
- Current work on gallium-68 radiolabeled dendrimers^[1]
- ⇒ *In vivo* data used in a previous population pharmacokinetic (popPK) analysis^[2]



Reduction of alkyl chain and fluorination of C18



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

Total: 7 dendrimers

- 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:** two-hour long mPET/CT imaging and gamma counting biodistribution from healthy mice (n=6) after IV administration for each dendrimer
- Software:** R version 4.2.2
- Structure of the PBPK model based on published work from Cheng *et al.*^[3] and Kumar *et al.*^[4]
- Endocytosis parameters:**

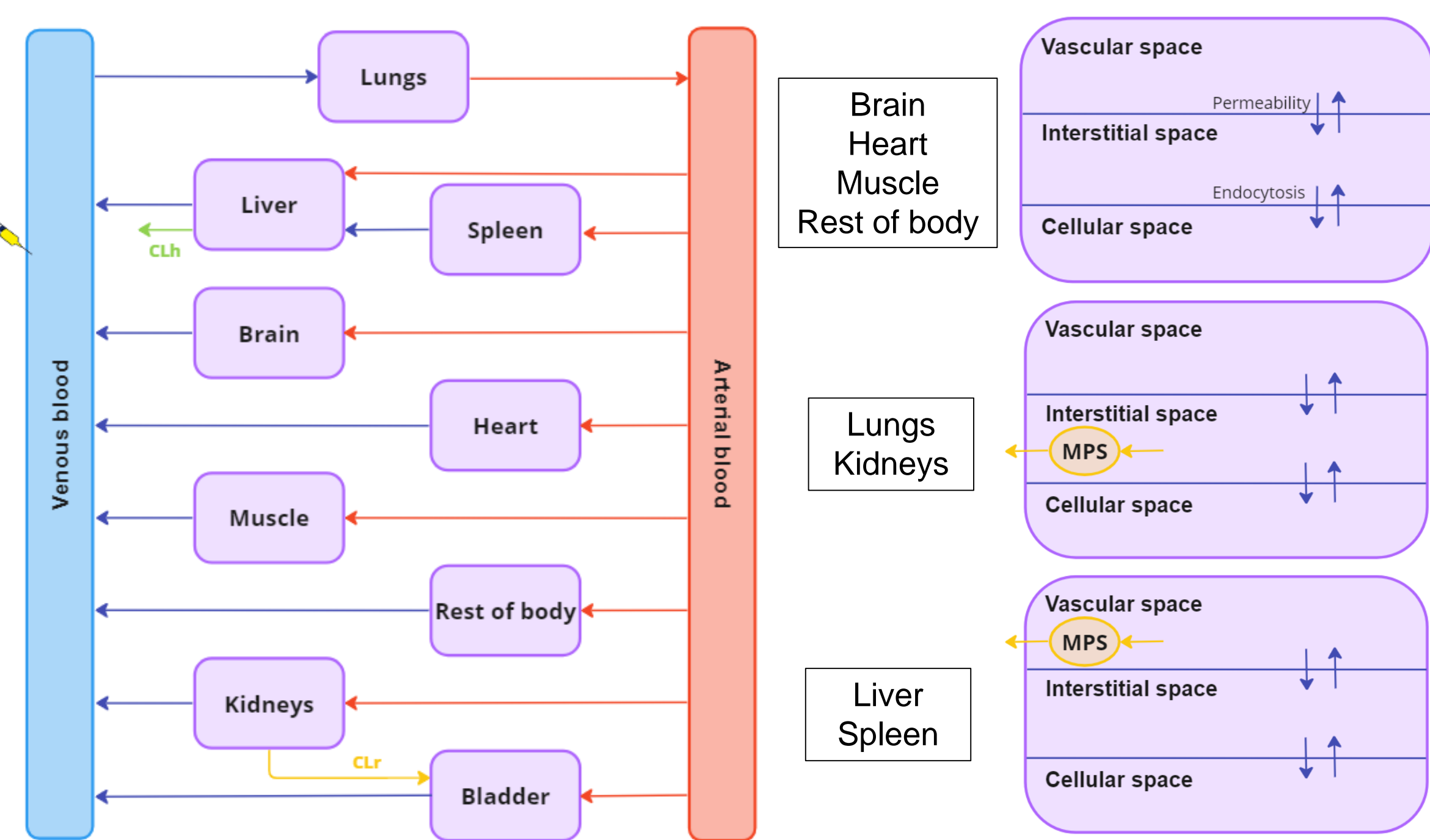
Parameter	Obtention
Partition coefficients (Kp)	$Kp = \frac{AUC_{mean\ organ}}{AUC_{mean\ blood}}$ <i>In vivo</i> data ^[2]
Physiology	Brown <i>et al.</i> ^[5]
Permeability (P) (mL/h)	Fitted
Renal clearance (CLr, mL/h)	<i>In vivo</i> data (popPK model) ^[2]
Hepatic clearance (CLh, mL/h)	<i>In vivo</i> data (popPK model) ^[2]

$$KUP_{tissue} = \frac{K_{max} * Time^n}{K_{50} + Time^n}$$

K_{max} : Maximum uptake rate constant of cells (h⁻¹)
 K_{50} : Time reaching half maximum uptake rate (h)
 n : Hill coefficient (unitless)

RESULTS

1. Structure of the nanoPBPK model



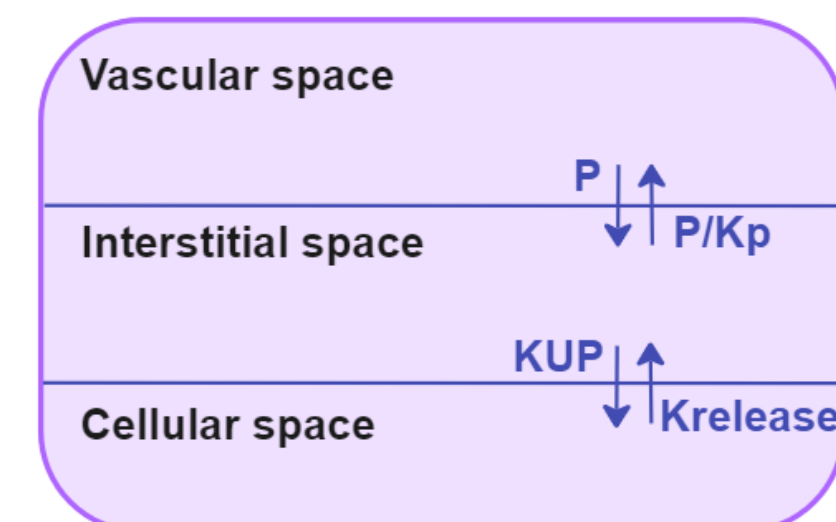
Tissue model: permeability-limited tissue distribution

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

$$\frac{dA_{interstitial}}{dt} = P_{tissue} * CV_{tissue} - \frac{P_{tissue} * C_{tissue}}{Kp} - KUP_{tissue} * A_{interstitial} + Krelease_{tissue} * A_{cellular}$$

$$\frac{dA_{cellular}}{dt} = KUP_{tissue} * A_{interstitial} - Krelease_{tissue} * A_{cellular}$$

$$\frac{dA_{MPS}}{dt} = KUP_{tissue} * A_{interstitial\ or\ vascular} - Krelease_{tissue} * A_{MPS}$$

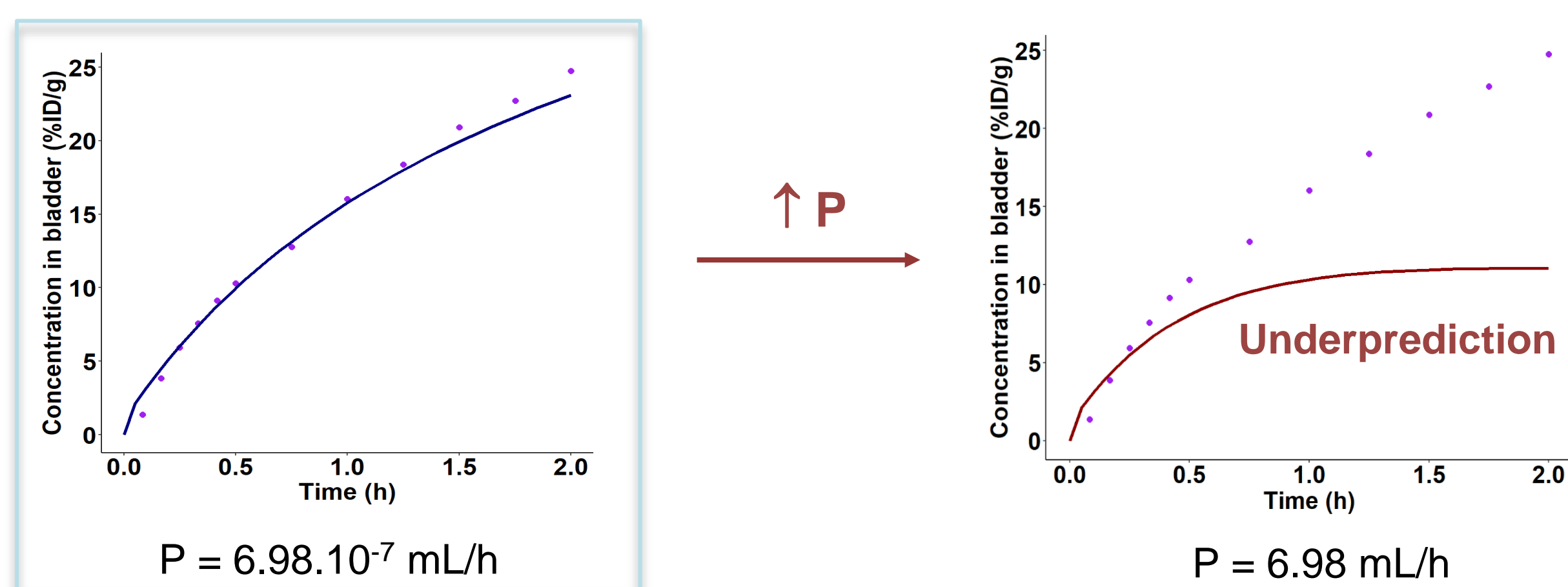


KUP: Uptake rate constant of tissue cells or phagocytes (h⁻¹)
Krelease: Release rate constant of tissue cells or phagocytes (h⁻¹)

3. Influence of permeability coefficient (P)

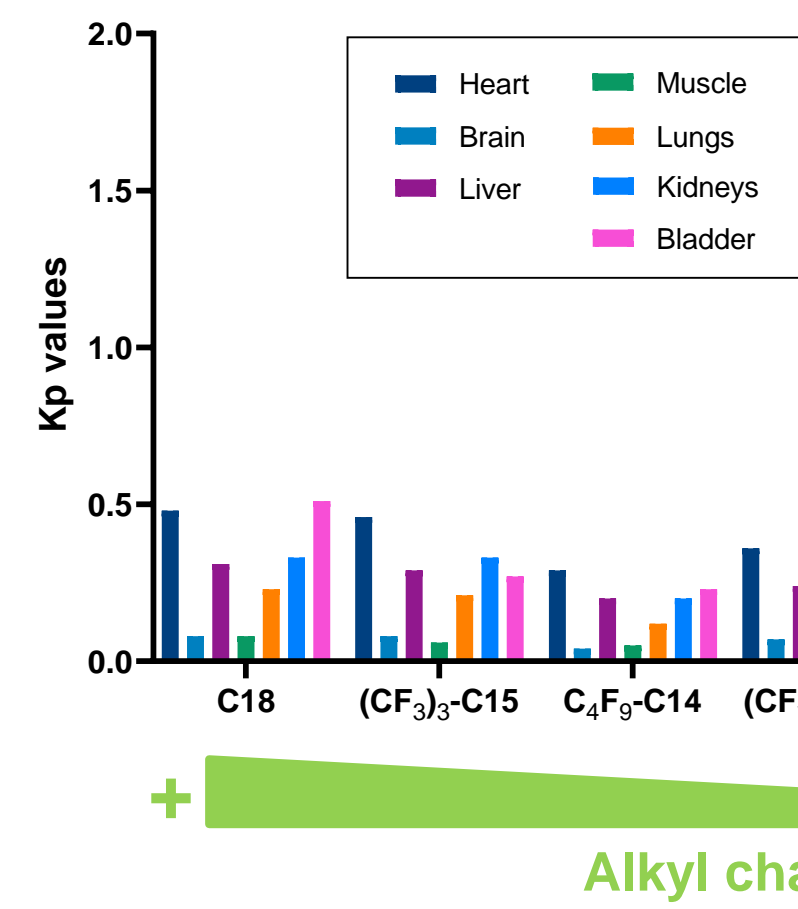
Permeability coefficient mainly influenced the shape of the simulation curve for all organs and dendrimers

Example of bladder for C₄F₉-C11 dendrimer



- Highly influential parameter
- Bladder ++
- Strongly dependent on dendrimer type

2. Correlation between partition coefficients (Kp) and dendrimer type

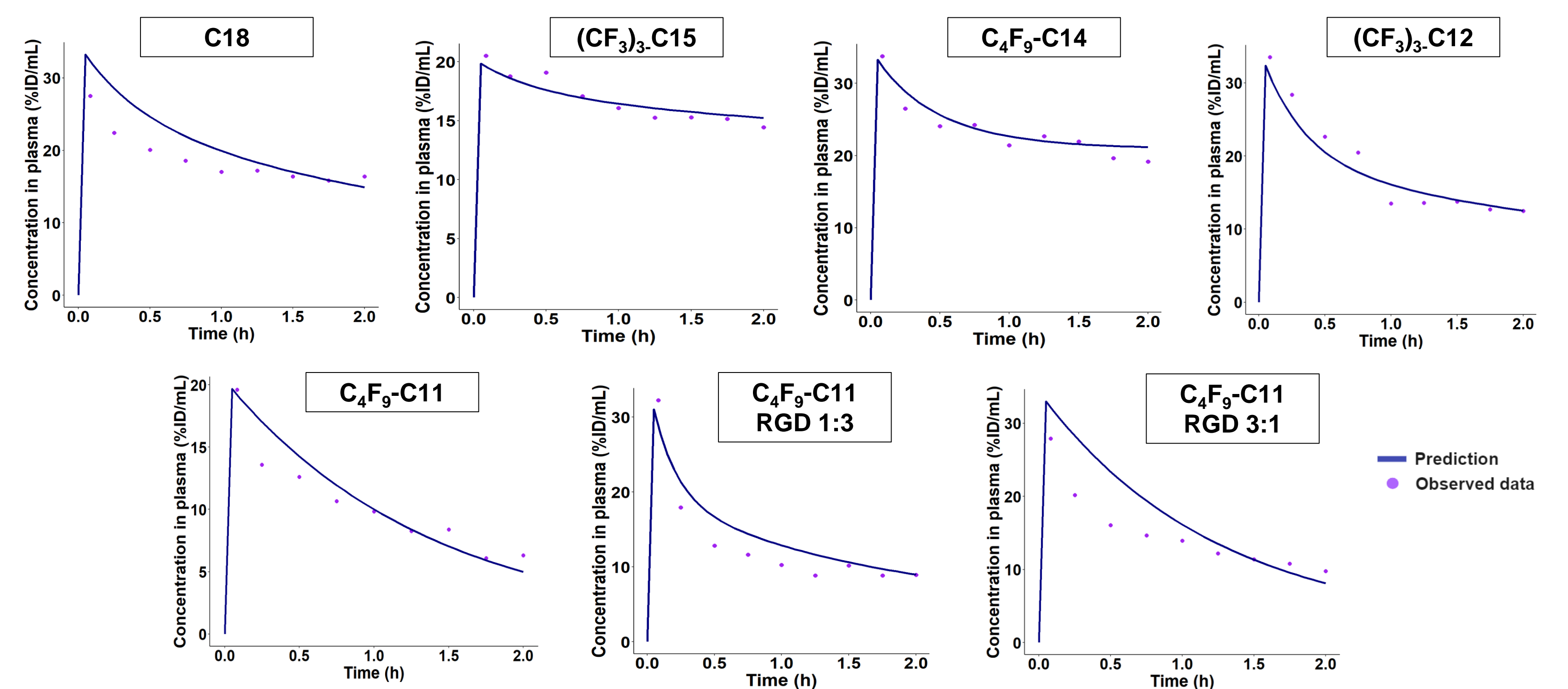


- No correlation between Kp and alkyl chain length
- Addition of RGD ↓ Kp for all organs

No error bars because blood and organ data were not collected in the same mice

4. Predictions of dendrimers disposition *in vivo*

Individual plasmatic profiles after permeability fitting



Good description of the observed data in plasma and other organs (data not shown)

Validation

Dendrimer	AUC _{observed 0-2h} (%ID/g.h)	AUC _{predicted 0-2h} (%ID/g.h)	Fold error
C18	37.68	42.64	1.13
(CF ₃) ₃ -C15	33.66	33.63	1.00
C ₄ F ₉ -C14	47.23	47.98	1.02
(CF ₃) ₃ -C12	37.33	36.04	0.97
C ₄ F ₉ -C11	21.01	21.76	1.04
C ₄ F ₉ -C11 RGD 1:3	26.35	30.58	1.16
C ₄ F ₉ -C11 RGD 3:1	30.05	35.61	1.19

Fold error < 2

CONCLUSION

- Permeability-limited model accurately simulated the distribution of dendrimers
- Permeability parameter was found to be the most influential parameters on dendrimer exposure
- Correlation between Kp and dendrimer physicochemical characteristics
- Results consistent with our previous PK study^[5]

PERSPECTIVES

- Get rid of arbitrary or adjusted parameters
- Collection of *in vitro* parameters
- Development of *in silico* models } Oponization and permeability
- 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] Cheng YH. *et al.*, ACS Nano. 14(3):3075-3095 (2020)
[4] Kumar M. *et al.*, Adv Drug Deliv Rev. 194:114708 (2023)
[5] Brown RP *et al.*, Toxicol Ind Health. 13: 407 (1997)
[6] Yuan D. *et al.*, J. Pharm. Sci. 10(7), 1267 (2019)
[7] Kutumova E *et al.*, Int. J. Mol. Sci. 23(20), 12560 (2022)

Abbreviations

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

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