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Semi-mechanistic modelling to show the impact of structural modifications on radiolabeled-dendrimers pharmacokinetics

Jessica Ou, Béatrice Louis, Vincent Nail, Laure Balasse, Ahlem Bouhlel, Adrien Chabert, Tom Roussel, Ling Peng, Philippe Garrigue, Benjamin Guillet, et al.

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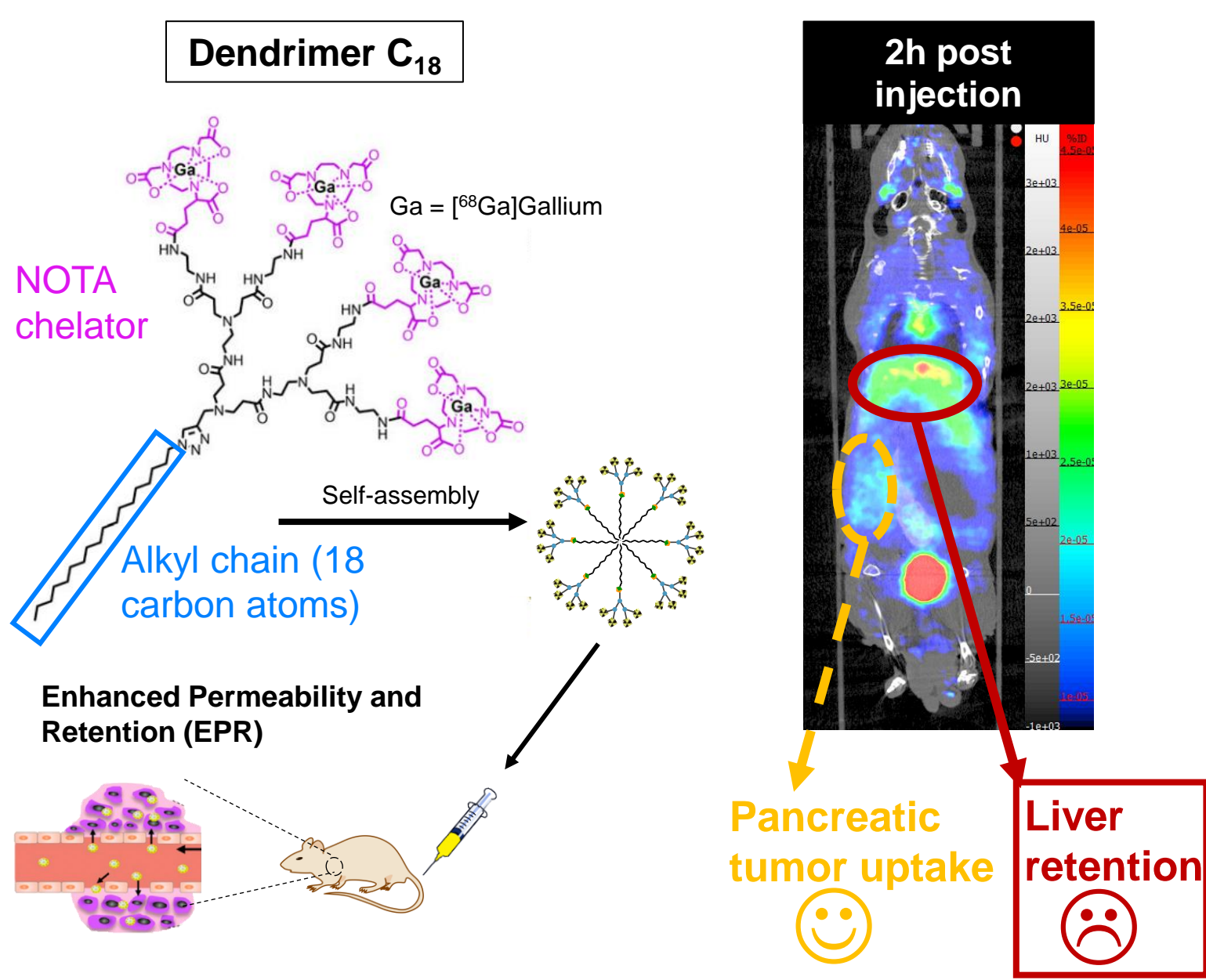
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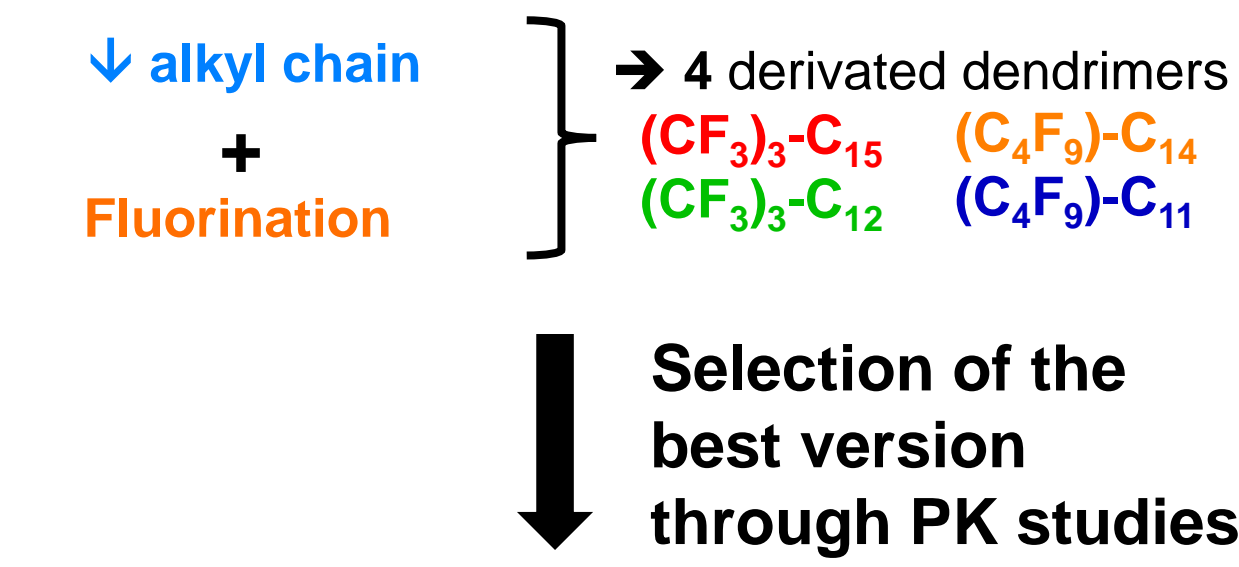
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Introduction

1. Development of a nanosystem for PET imaging of tumors



2. Reduce liver retention by chemical structure optimization



Dendrimers PK profiles vary due to structural modifications

3. Functionalization for a specific tumor targeting

- Addition of RGD at 2 ratios:
 - 1 dendrimer for 3 RGD (1:3)
 - 3 dendrimers for 1 RGD (3:1)
- 2 functionalized dendrimers
- 7 dendrimers studied**

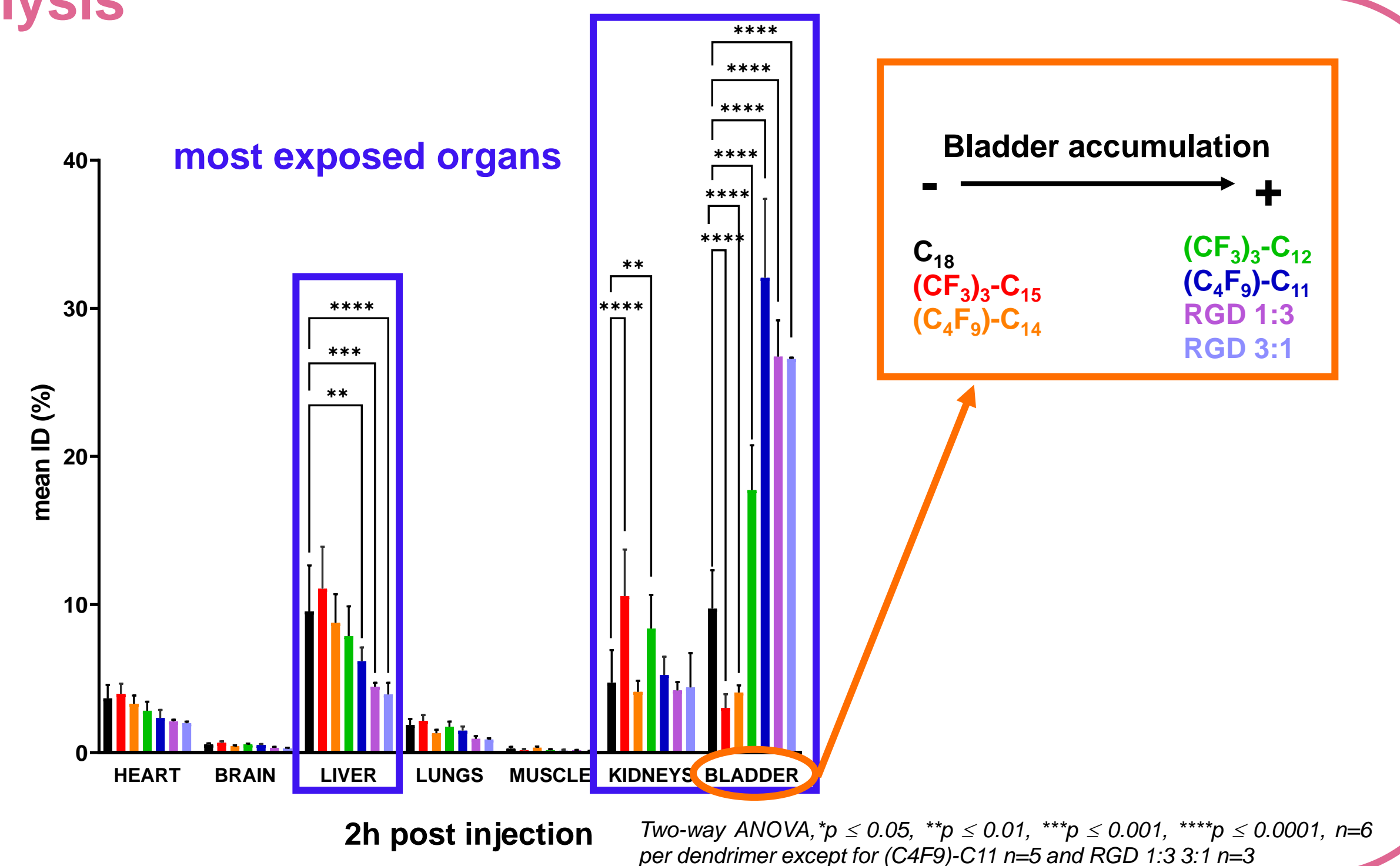
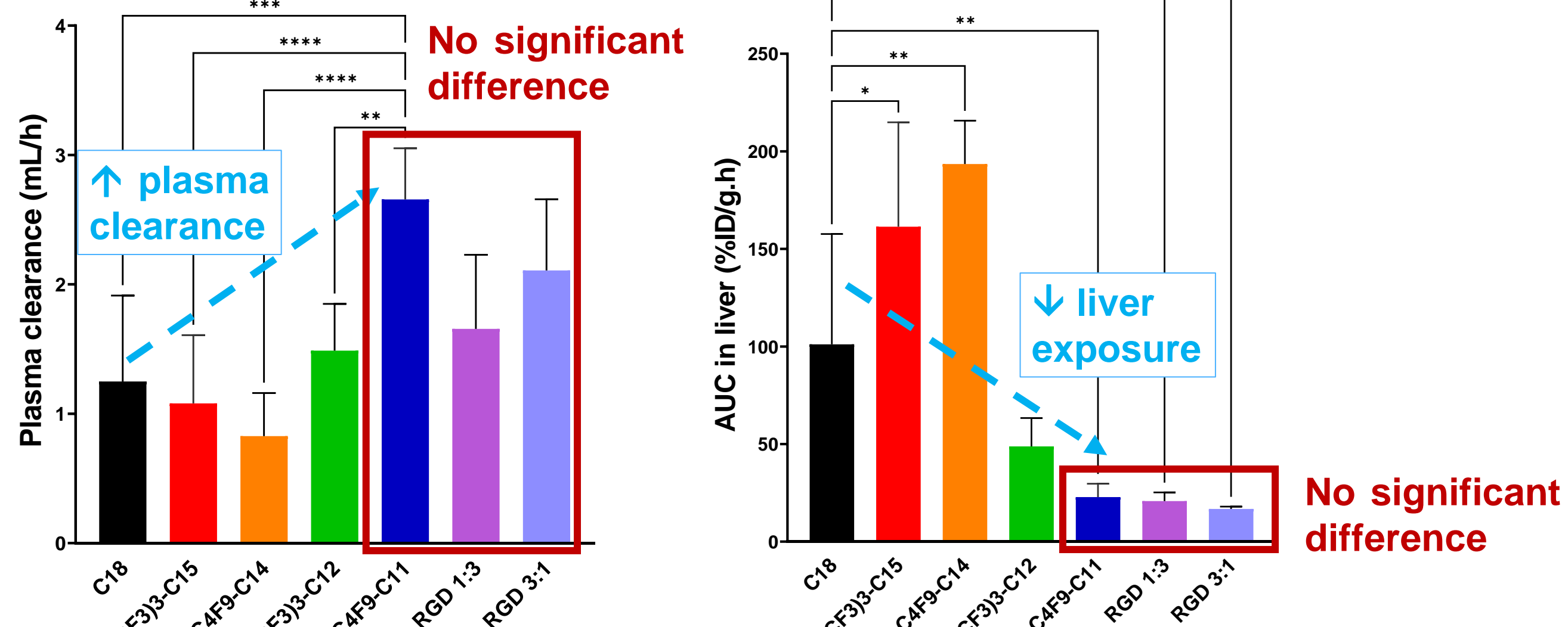
Aim of the project:
Understand the impact of structural modifications on dendrimers biodistribution with PK modelling

Methods

- Data: two-hour long μ PET/CT imaging (5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120 min) and gamma counting biodistribution (5, 15, 30, 45, 60, 75, 90, 105, 120 min) from healthy mice (n=6) after IV administration for each dendrimer
 - Non-compartmental analysis: PKanalix[®]
 - Population PK analysis: Monolix[®]
Several models tested: \neq number of compartments per organ (1 or 2), \neq elimination pathways (liver, kidneys, bladder, central compartment)
- Covariates:** $\theta_{TV,i} = \theta_{REF} * \exp(\beta * x_i)$
- θ_{REF} = value of θ_{TV} in the reference category (rc)
 β = parameter quantifying the effect of the i^{th} category on the typical value θ_{TV}
 x_i = indicator variable value equal to 0 (rc) or 1 (i^{th} category)

Results

Non-compartmental analysis

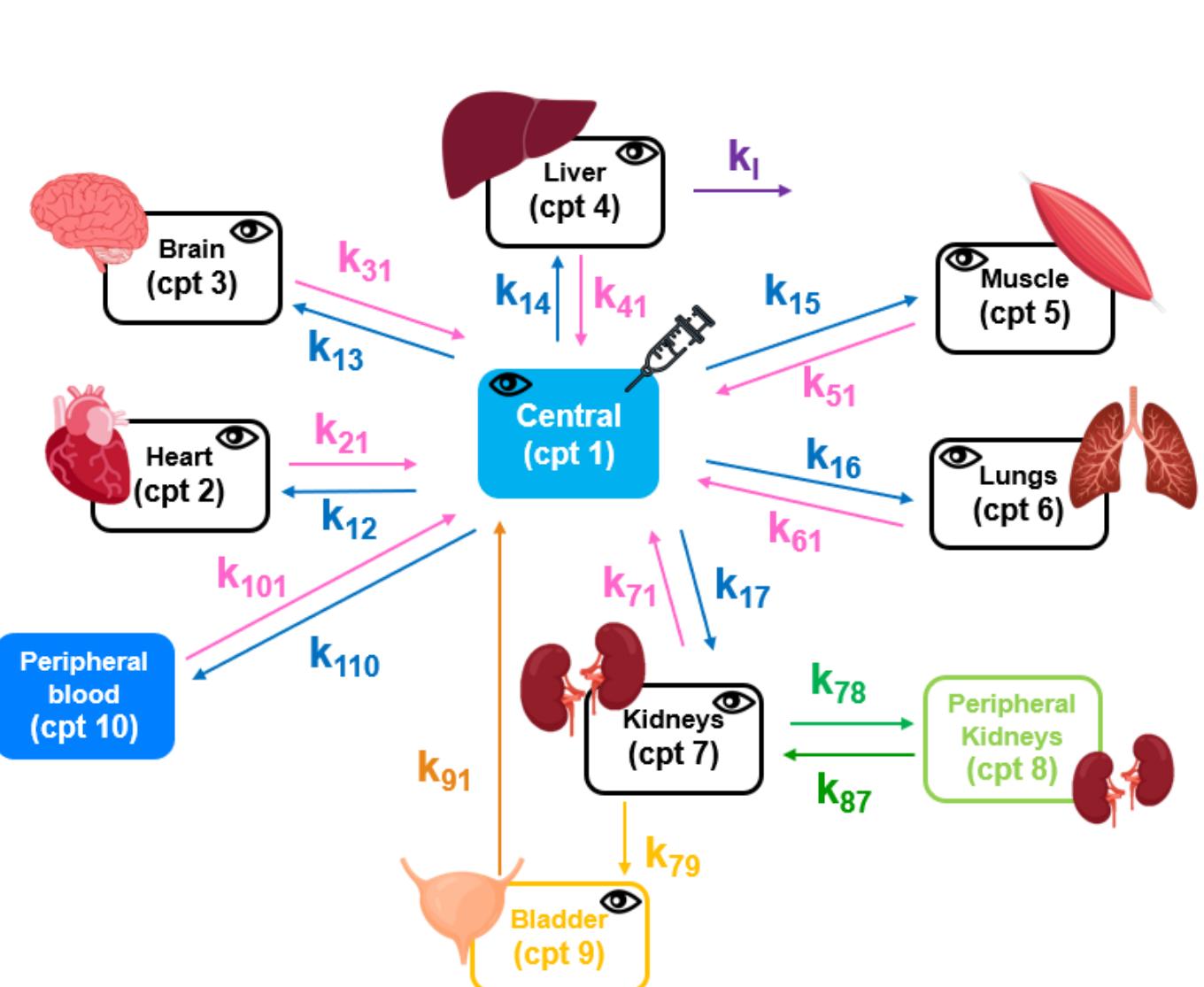


1. Selection of C₄F₉-C11 for functionalization
2. Similar PK parameters between C₄F₉-C11 +/- RGD

One-way ANOVA post-hoc Tukey's test, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, n=6 except RGD 1:3 3:1 n=3

Semi-mechanistic modelling

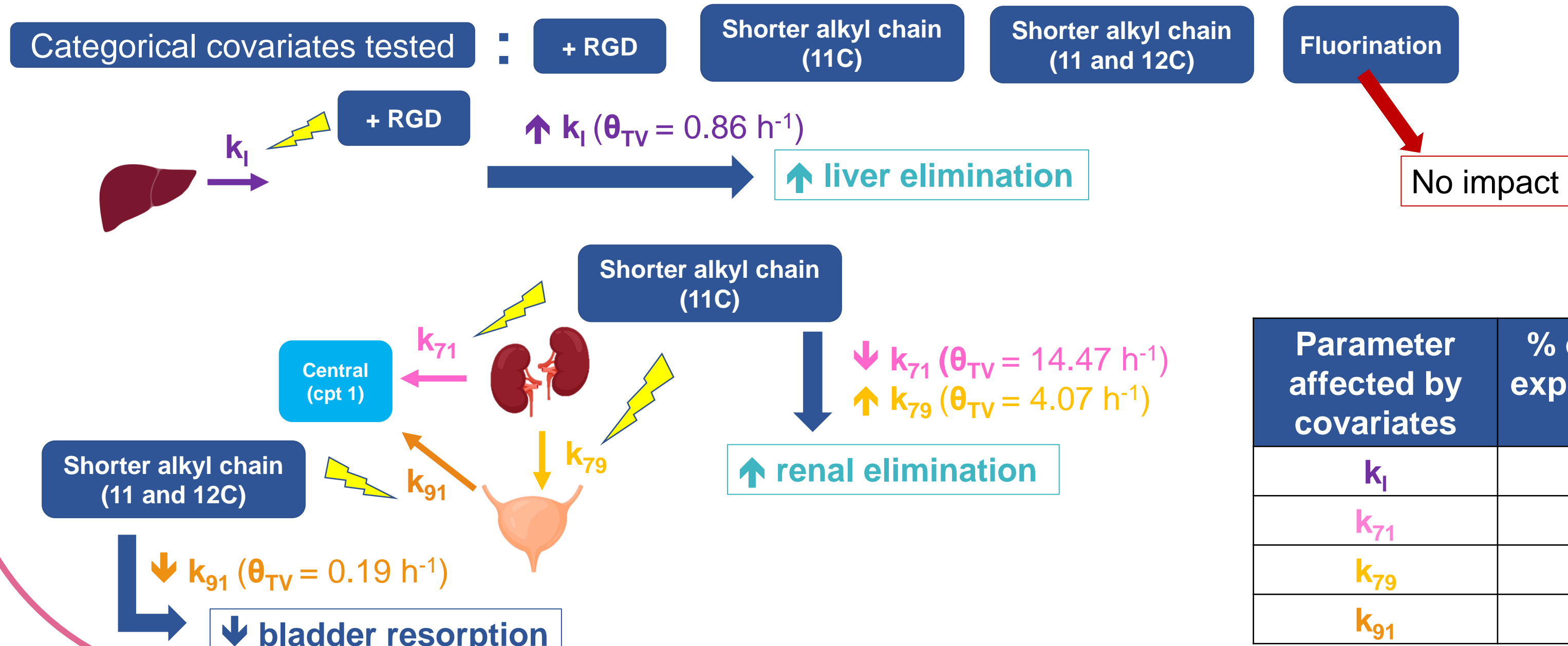
1. Final model



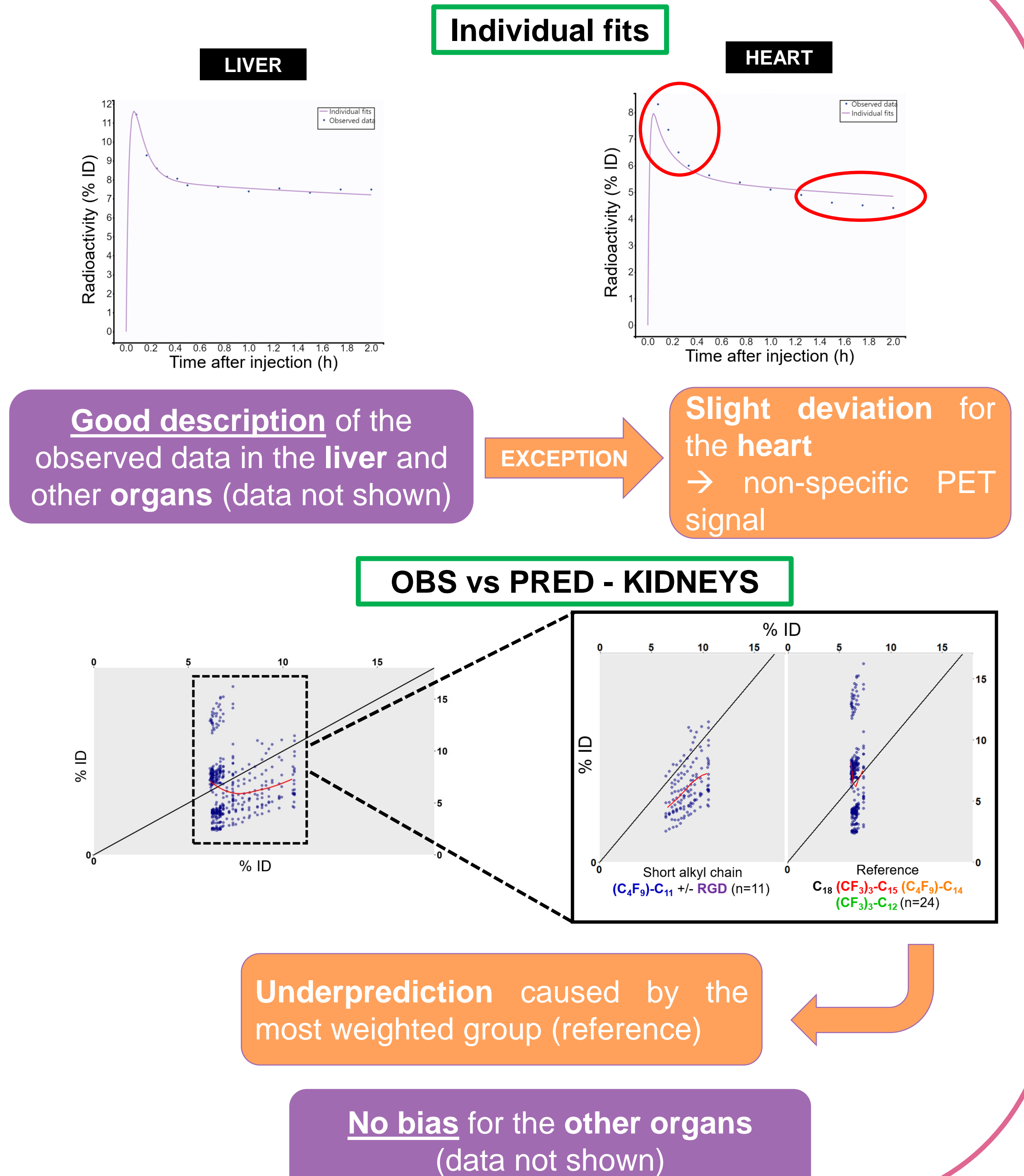
RSE < 30% except for β_{k_1} RSE = 41.7%

| Parameter (unit) | Tissue | Value | IIV value (%) | Covariate value (β) |
|-------------------------|--------------------|-------|---------------|-----------------------------|
| k12 (h ⁻¹) | Heart | 6.55 | 45 | |
| k21 (h ⁻¹) | Heart | 54.56 | 50 | |
| k13 (h ⁻¹) | Brain | 0.33 | 55 | |
| k31 (h ⁻¹) | Brain | 18.14 | 34 | |
| k14 (h ⁻¹) | Liver | 13.39 | 58 | |
| k41 (h ⁻¹) | Liver | 42.04 | 53 | |
| k1 (h ⁻¹) | Liver | 0.39 | 69 | 0.79 |
| k15 (h ⁻¹) | Muscle | 0.032 | 59 | |
| k51 (h ⁻¹) | Muscle | 5.5 | 22 | |
| k16 (h ⁻¹) | Lungs | 2.19 | 72 | |
| k61 (h ⁻¹) | Lungs | 38.17 | 51 | |
| k17 (h ⁻¹) | Kidneys | 4.64 | 62 | |
| k71 (h ⁻¹) | Kidneys | 29.72 | 54 | -0.72 |
| k78 (h ⁻¹) | Peripheral kidneys | 0.51 | 113 | |
| k87 (h ⁻¹) | Peripheral kidneys | 0.92 | 124 | |
| k79 (h ⁻¹) | Bladder | 1.94 | 38 | 0.74 |
| k91 (h ⁻¹) | Bladder | 1.15 | 82 | -1.82 |
| k101 (h ⁻¹) | Peripheral blood | 4.31 | 43 | |
| k10 (h ⁻¹) | Peripheral blood | 4.30 | 16 | |
| V (mL) | Central | 1.71 | 9.3 | |

2. Covariates



3. Model validation



Conclusion

- Selection of C₄F₉-C11 for functionalization
- Description of dendrimers biodistribution with the semi-mechanistic model
- Functionalization (RGD) → Higher liver elimination
- Shorter carbon chain → Higher renal elimination
- No impact of fluorination on dendrimers PK

Perspective

PBPK model tailored to nanoparticles (NPs) to predict PK profiles *in vivo* based on NP structural characteristics → NP optimization

References
Garrigue P. *et al.*, Proc. Natl. Acad. Sci. 115, 11454–11459 (2018)

Acknowledgments

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Abbreviations

C: carbon
ID: injected dose
IIV: interindividual variability
RGD: Arginyl-glycyl-aspartic acid
RSE: relative standard error

Correspondence

Jessica OU, PhD student
COMPO Inria-Inserm
Aix-Marseille University
jessica.ou@etu.univ-amu.fr

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