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

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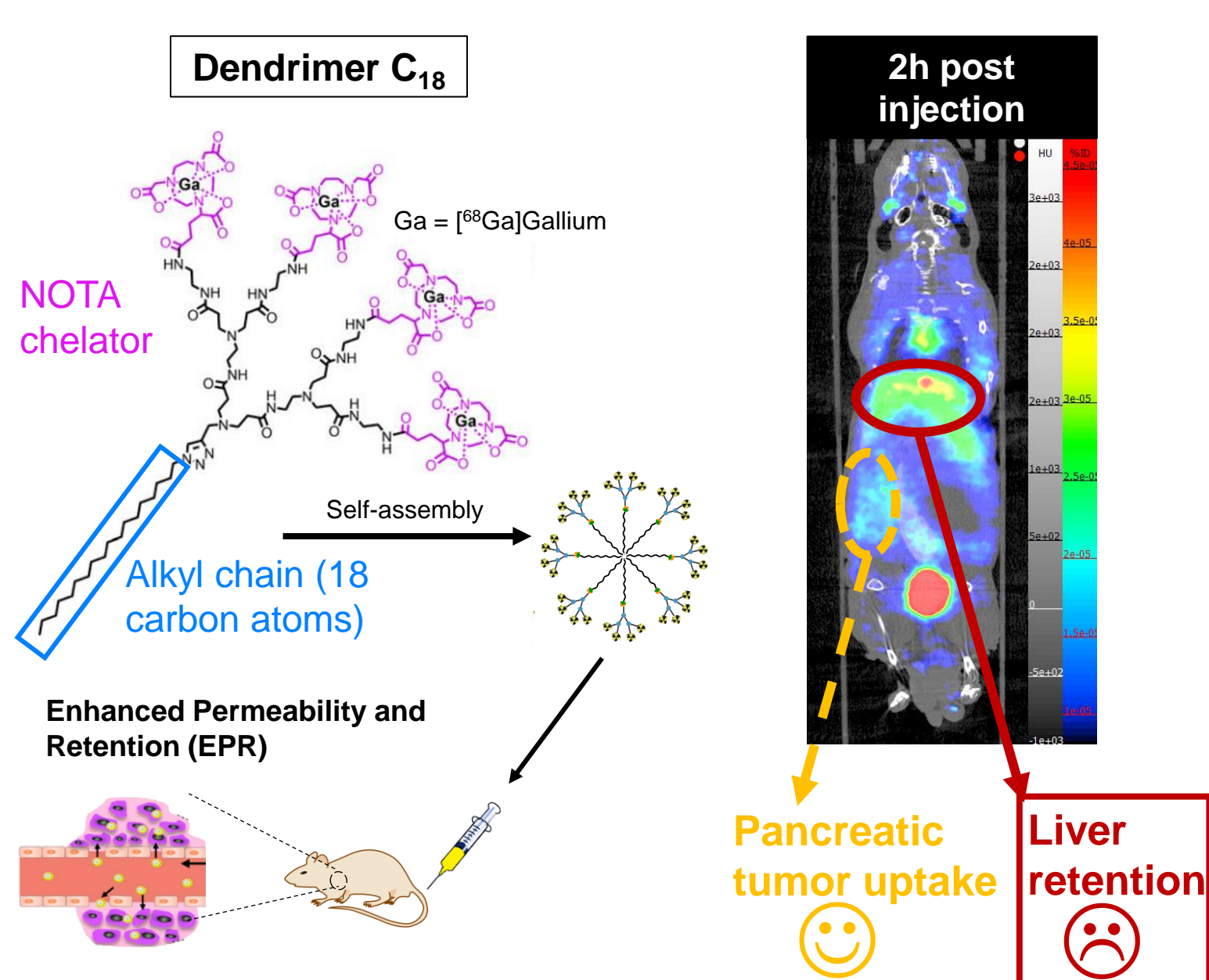
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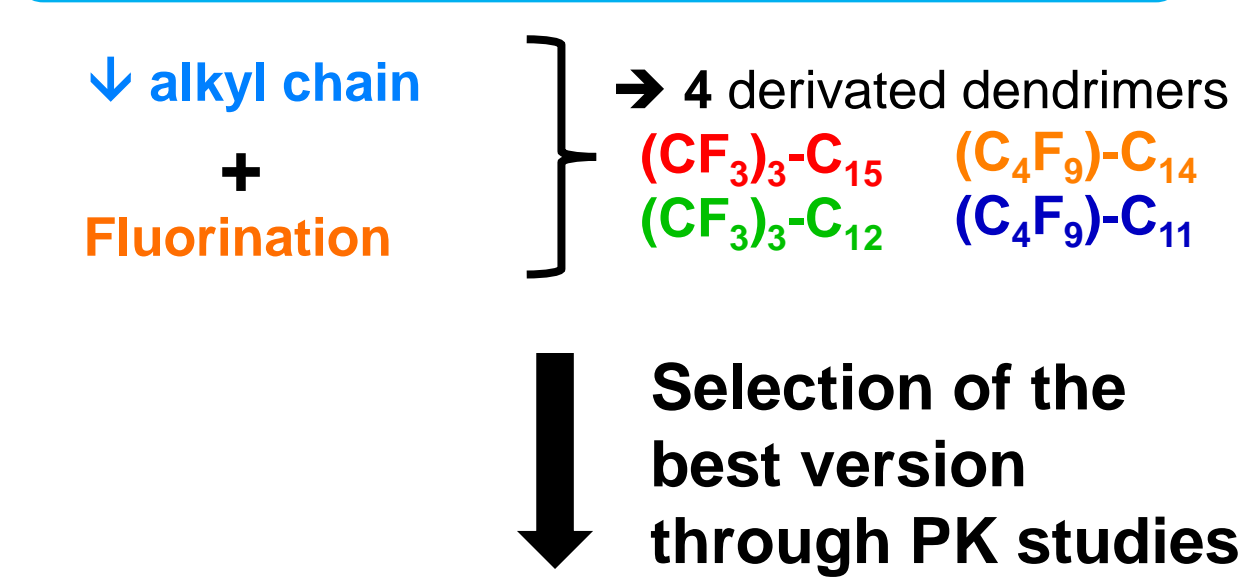
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Introduction

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

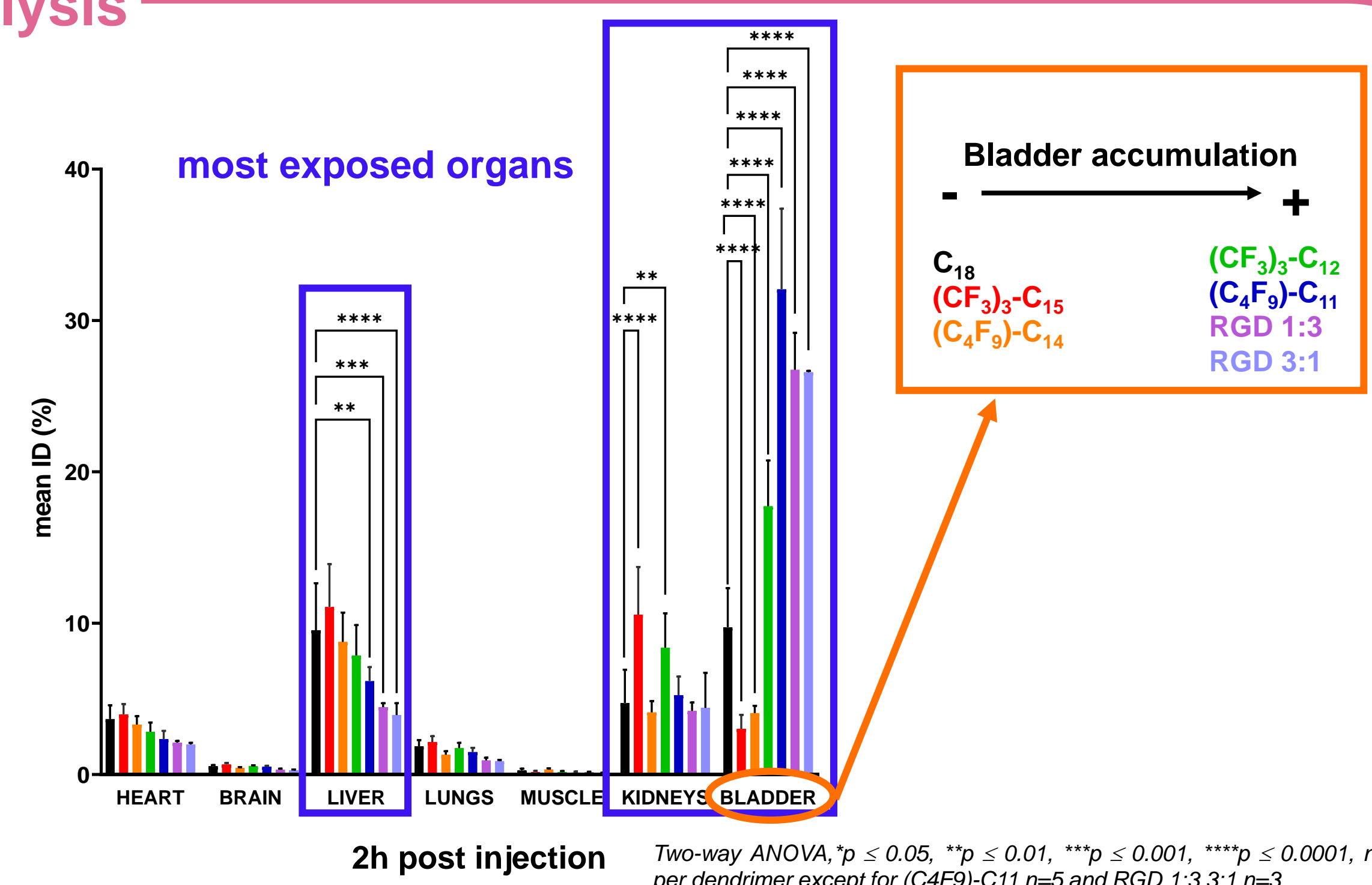
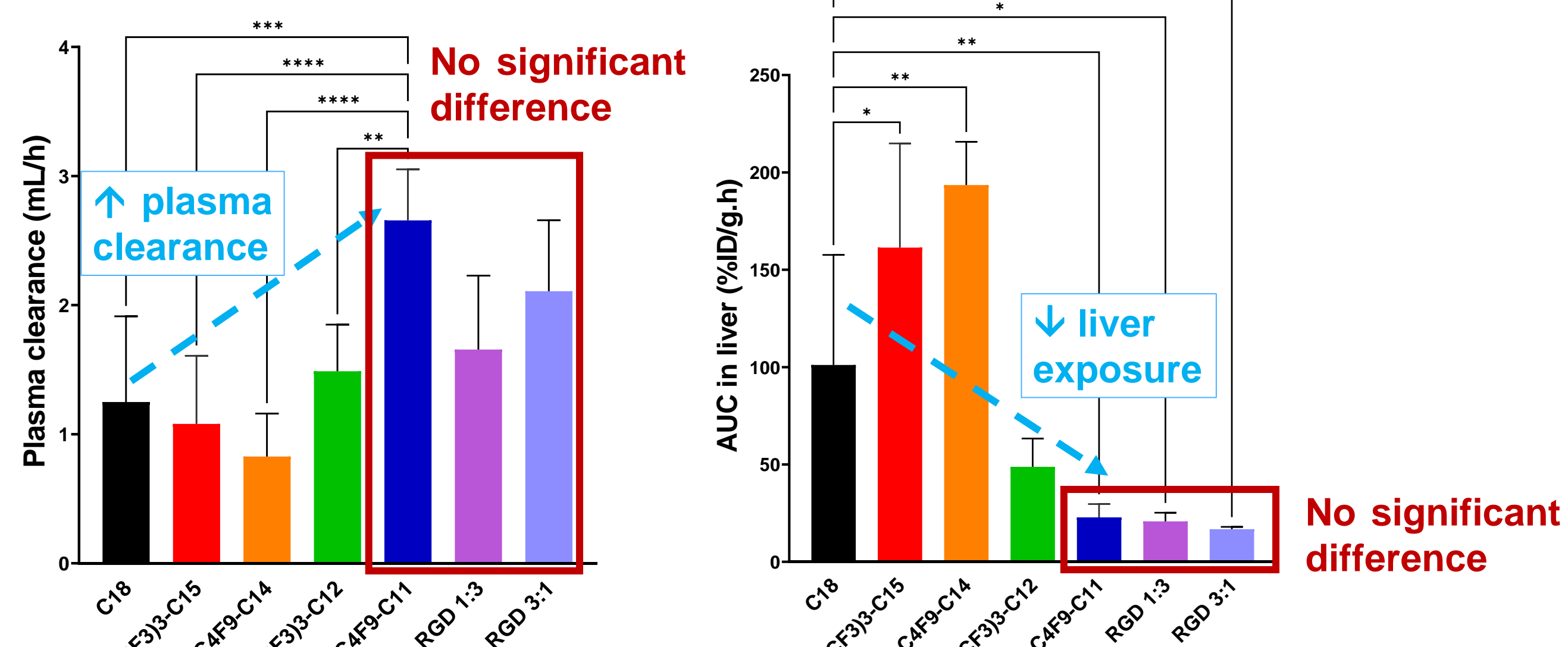
- Non-compartmental analysis: PKanalix[®]
- Population PK analysis: Monolix[®]
Several models tested: \neq number of compartments per organ (1 or 2), \neq elimination pathways (liver, kidneys, bladder, central compartment)

$$\text{Covariates: } \theta_{TV,i} = \theta_{REF} * \exp(\beta * x_i)$$

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

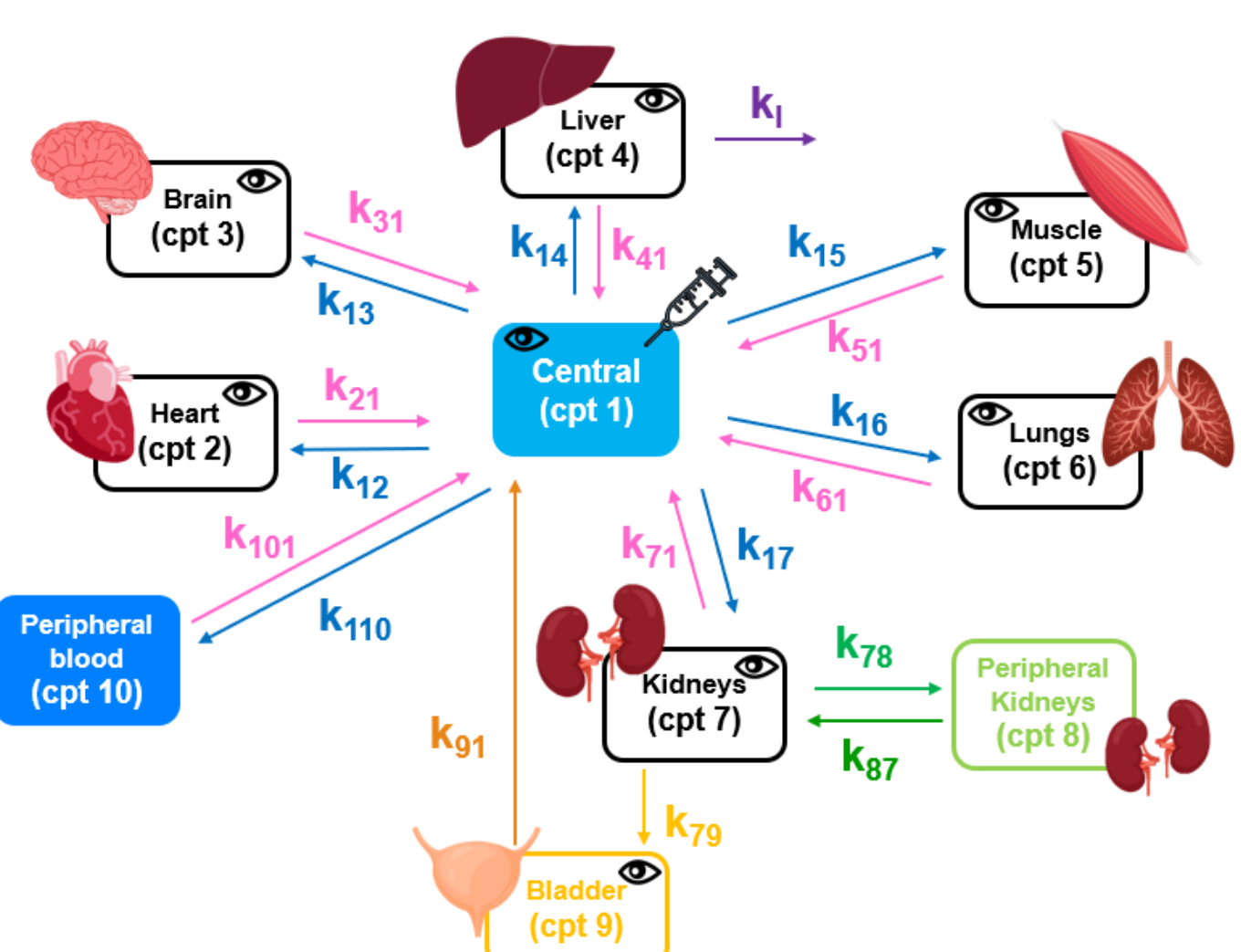


1. Selection of C₄F₉-C11 for functionalization
2. Similar PK parameters between C₄F₉-C11 +/- RGD

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

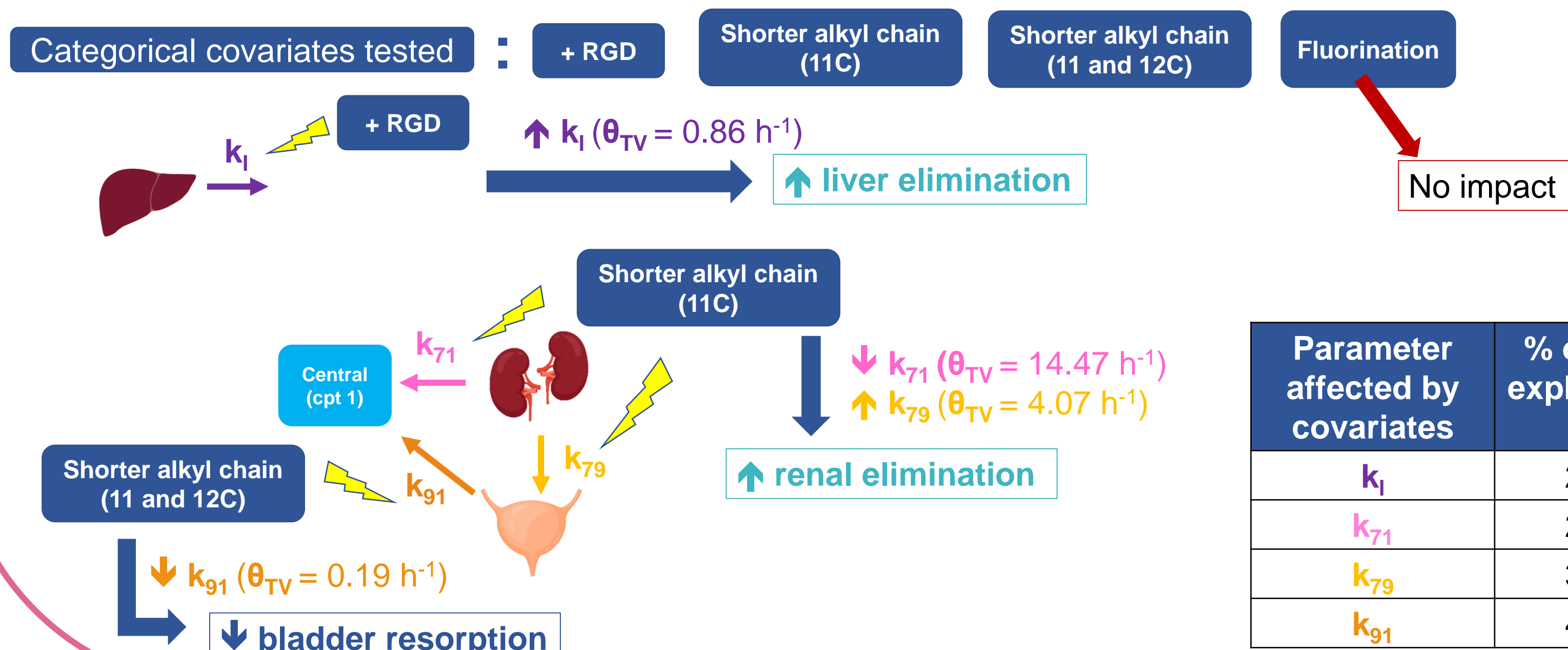
1. Final model



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

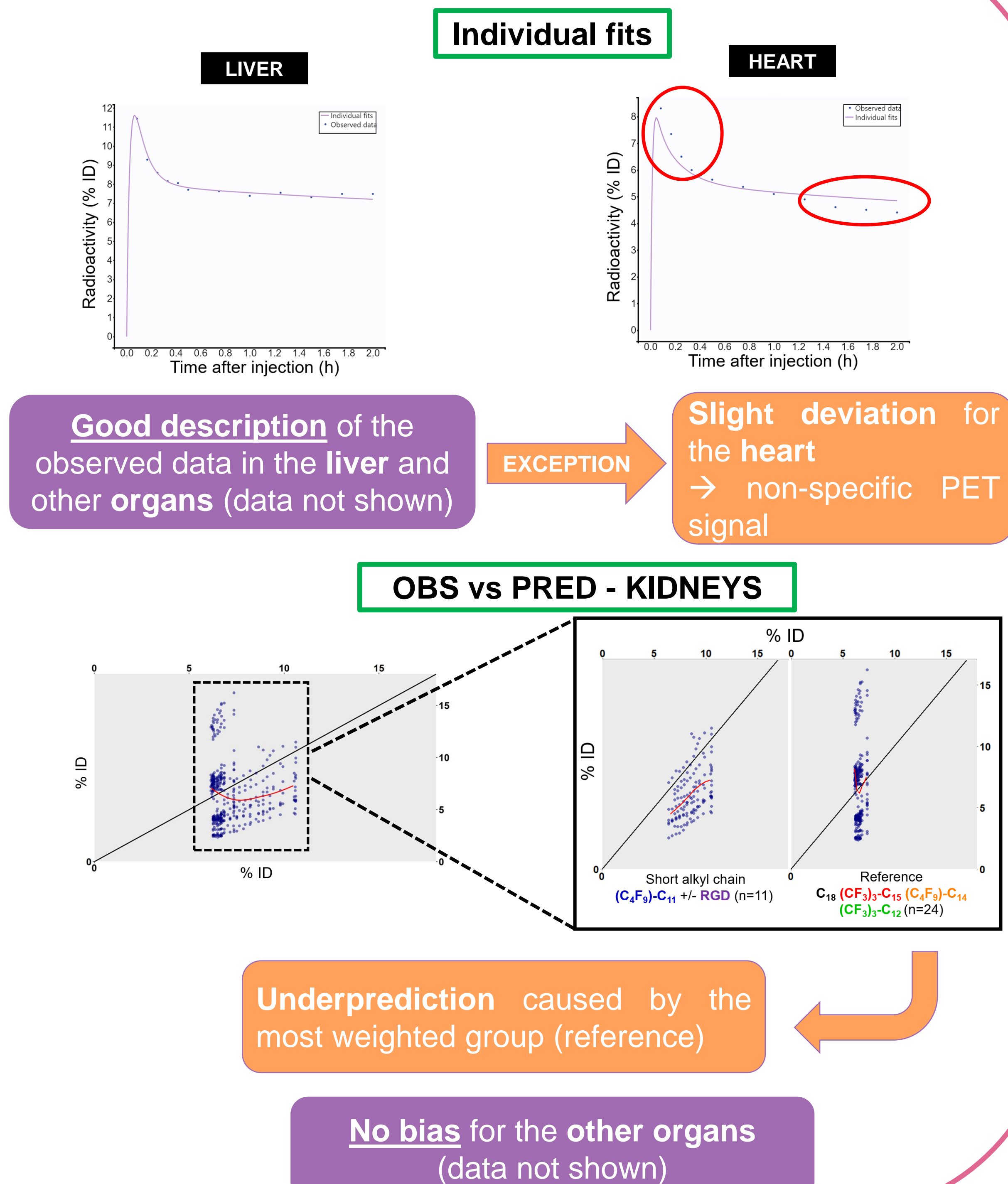
Parameter (unit)	Tissue	Value	IIV value (%)	Covariate value (β)
k12 (h ⁻¹)	Heart	6.55	45	
k21 (h ⁻¹)	Heart	54.56	50	
k13 (h ⁻¹)	Brain	0.33	55	
k31 (h ⁻¹)	Brain	18.14	34	
k14 (h ⁻¹)	Liver	13.39	58	
k41 (h ⁻¹)	Liver	42.04	53	
k1 (h ⁻¹)	Liver	0.39	69	0.79
k15 (h ⁻¹)	Muscle	0.032	59	
k51 (h ⁻¹)	Muscle	5.5	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



Parameter affected by covariates	% of IIV explained
k ₁	22
k ₇₁	21
k ₇₉	31
k ₉₁	42

3. Model validation



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

Slight deviation for the heart → non-specific PET signal

Underprediction caused by the most weighted group (reference)

No bias for the other organs (data not shown)

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

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