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A Physiologically Based Pharmacokinetic Model of ^{89}Zr -adalimumab in Healthy and Uveitis Diseased Rats



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INTRODUCTION AND OBJECTIVES

As the incidence of eye diseases is expected to increase, the **development of new treatments and drug delivery systems becomes a critical necessity**. The **aim** of the present work was to develop a **physiologically-based pharmacokinetic model** of ^{89}Zr -adalimumab after **intravitreal (IVT) administration** in **healthy** and **endotoxin-induced uveitis (EIU)** diseased rats to assess the **effect of dose on TNF- α reduction** in the anterior chamber of the eye.

MATERIAL AND METHODS

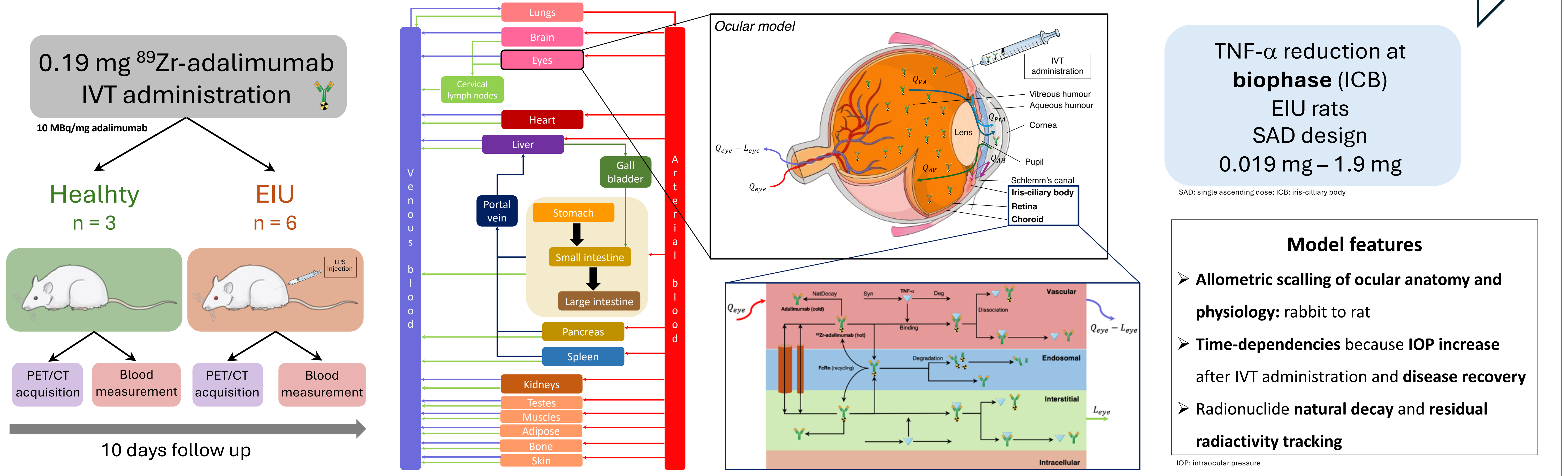
Experimental dataset



Data modelling



“What if...?” testing



RESULTS

Table 1. Drug- and system-related model parameters.

Parameter	Value	Source/Comments
Adalimumab		
MW (kDa)	144.19	DrugBank
Radius (nm)	5.60	[1]
K_d FcRn (μM)	1.18	[2]
K_d TNF- α (μM)	1.52	[1]
k_{off} TNF- α (h^{-1})	0.18	[3]
TNF-α		
MW (kDa)	52	Novusbio
Baseline (pM)	1	Assumed
k_{deg} (h^{-1})	0.223	[3]
Synthesis Factor		
1 (healthy)	Assumed	
7 (EIU)	In house determination	
Ocular anatomy and physiology		
V_{cornea} (mL)	4.93	Scaled from rabbits
V_{AH} (mL)	13.6	[4]
V_{VH} (mL)	52	[5]
Q_{eye} (L/h)	$5.53 \cdot 10^{-3}$	Scaled from rabbits
L_{eye} (L/h)	$1.11 \cdot 10^{-5}$	Calculated (0.2% of Q_{eye})
Q_{AV} (L/h)	$3.43 \cdot 10^{-6}$	Scaled from rabbits
Q_{VA} (L/h)	$9.15 \cdot 10^{-7}$	Scaled from rabbits
Q_{AH} (L/h)	$2.43 \cdot 10^{-5}$	Scaled from rabbits
$f_{Schlemm}$	0.95	[4]
Q_{PIA} (L/h)	Calculated	$Q_{AH} + Q_{AV} - Q_{VA}$
PS_{cornea} (L/h)	$1.36 \cdot 10^{-9}$	Scaled from rabbits
PS_{ret} (L/h)	$3.02 \cdot 10^{-7}$	Scaled from rabbits
PS_{chor} (L/h)	$3.29 \cdot 10^{-7}$	Scaled from rabbits
σ_{AH} (σ_{PIA})	0.95 (0.1)	[6] (Assumed)
σ_{ret}	0.99	[6]
σ_{chor}	0.99	[6]
$t_{1/2}$ recovery (days)	2	[7]
Iris-ciliary body (ICB)		
Q_{ICB} (l/min)	$1.21 \cdot 10^{-5}$	Calculated (13.1% of Q_{eye})
V_{ICB} (mL)	4.88	Scaled from rabbits
V_{plasma} (mL)	1.12	Calculated (23% of V_{ICB})
V_{bc} (mL)	0.56	Calculated (11.5% of V_{ICB})
V_{int} (mL)	1.95	Calculated (40% of V_{ICB})
V_{end} (mL)	0.02	Calculated (0.5% of V_{ICB})
V_{cell} (mL)	1.22	Calculated (25% of V_{ICB})
Choroid		
Q_{chor} (l/min)	$7.92 \cdot 10^{-5}$	Calculated (86% of Q_{eye})
V_{chor} (mL)	1.58	Scaled from rabbits
V_{plasma} (mL)	0.36	Calculated (23% of V_{chor})
V_{bc} (mL)	0.18	Calculated (11.5% of V_{chor})
V_{int} (mL)	0.63	Calculated (40% of V_{chor})
V_{end} (mL)	0.01	Calculated (0.5% of V_{chor})
V_{cell} (mL)	0.39	Calculated (25% of V_{chor})
Retina		
Q_{ret} (l/min)	$8.39 \cdot 10^{-7}$	Calculated (0.9% of Q_{eye})
V_{ret} (mL)	2.33	Scaled from rabbits
V_{plasma} (mL)	0.67	Calculated (28.7% of V_{ret})
V_{bc} (mL)	0.33	Calculated (14.35% of V_{ret})
V_{int} (mL)	0.75	Calculated (32% of V_{ret})
V_{end} (mL)	0.01	Calculated (0.5% of V_{ret})
V_{cell} (mL)	0.57	Calculated (24.5% of V_{ret})

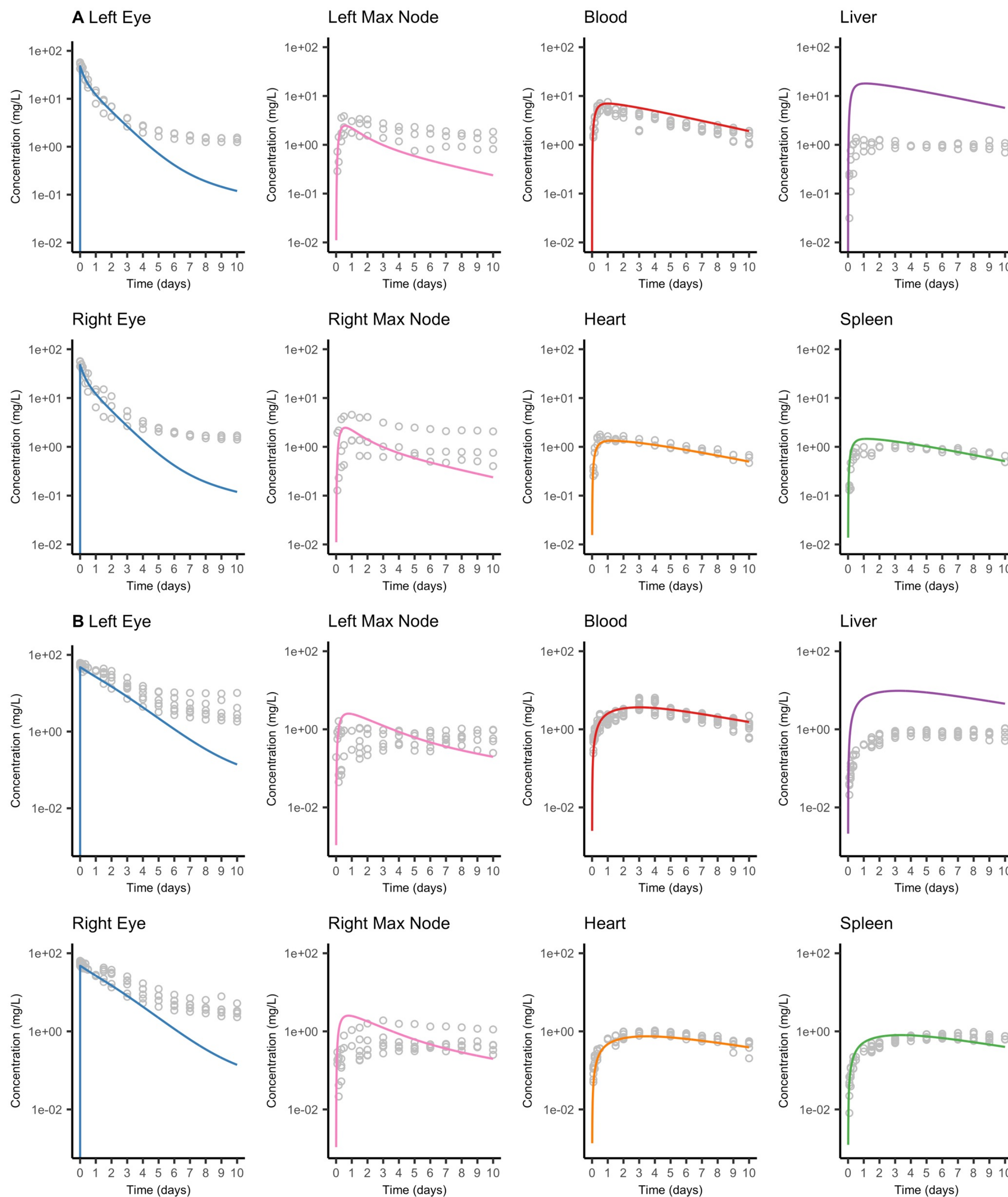


Figure 1. Graphical evaluation of model performance. Observed (grey circles) versus predicted (solid line) ^{89}Zr -adalimumab specific activity. A: healthy group; B: endotoxin-induced uveitis group.

Table 2. Numerical evaluation of model performance.

Group	Prediction Error	Right eye	Left eye	Right cervical node	Left cervical node	Blood	Heart	Liver	Spleen
Healthy	AUC	0.72	0.72	0.92	0.45	1.43	0.92	12.61	1.19
	C_{max}	0.86	0.89	1.80	0.81	1.10	0.80	14.60	1.38
EIU	AUC	0.54	0.57	2.47	1.88	0.66	0.84	10.35	1.09
	C_{max}	0.91	0.90	5.29	2.58	0.65	0.76	10.21	1.01

EIU: endotoxin-induced uveitis

Table 3. TNF- α kinetics in aqueous humour, systemic bloodstream and ICB after single dose intravitreal administration of adalimumab.

Adalimumab Dose (mg)	TNF- α in aqueous humour				TNF- α in ICB (interstitial)			
	Reduction (%)	Time to baseline (days)	Rebound (%)	Time to rebound (days)	Reduction (%)	Time to baseline (days)	Rebound (%)	Time to rebound (days)
0.019	39.0	0.82	602	10.3	47.7	4.66	16	8.1
0.038	67.8	3.93	582	11.8	70.2	5.56	21	9.32
0.095	86.6	6.19	502	14	86.2	6.83	27	11.7
0.19	93.2	7.81	401	15.8	92.5	8.40	28	15.5
0.38	96.6	9.56	284	18	95.9	11.5	30	28.4
0.95	98.6	12.4	153	25.8	98.2	22.1	45	48.0
1.9	99.3	15.8	131	49.3	99.1	33	59	63.7
TNF-α in ICB (plasma)								
0.019	-	-	-	-	-	-	-	-
0.038	-	-	-	-	-	-	-	-
0.095	-	-	-	-	-	-	-	-
0.19	-	-	-	-	-	-	-	-
0.38	25.3	6.69	40	28.4	28.2	6.96	39	28.3
0.95	64.2	20.01	55	48	65.7	20.05	54	48
1.9	80.1	30.92	71	63.8	81	30.92	70	63.7

ICB: iris-ciliary body

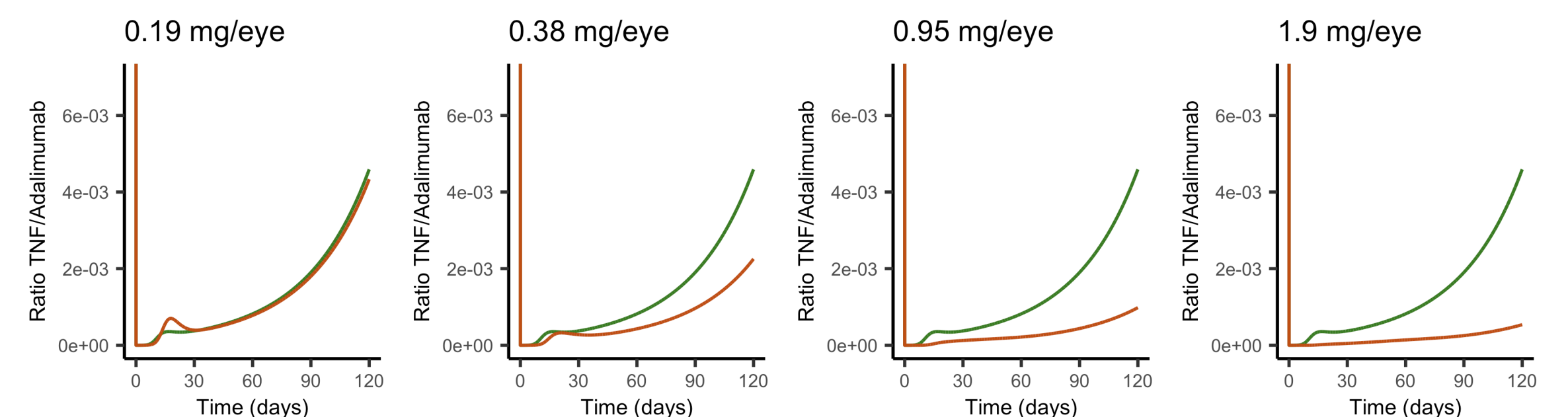


Figure 3. TNF- α /adalimumab free concentration ratios over time at higher dose levels. Green profile: healthy rats; brown profile: EIU diseased rats.

CONCLUSIONS

- ✓ The PBPK model here reported represents a **consistent basis to mechanistically explore radiolabeled biologic drugs disposition** after IVT administration, allowing to perform **translational modelling between species**. The model considers the interaction with FcRn and TNF- α simultaneously, the intraocular pressure increase due to IVT administration and disease recovery.
- ✓ The incorporation of radioactivity-related processes allows the use of observed data coming from **non-invasive (images) preclinical experiments**.
- ✓ IVT administration of **adalimumab in early-stage ocular inflammatory disorders** would be a **suitable therapeutic strategy**, but **high doses** would be needed to achieve the desired therapeutic effect, what poses a **formulation challenge** due to the requirements of this route of administration.



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References

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