

Systemic and ocular physiologically based pharmacokinetic models for protein therapeutics in rabbits

Ravi Kumar Jairam¹, Maria Franz², Anna-Kaisa Rimpelä³, Guangda Ma³, Nina Hanke², Lars Kuepfer¹

¹Institute for Systems Medicine with Focus on Organ Interaction, University Hospital RWTH Aachen, Aachen, Germany

²Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

³Drug Discovery Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Background

- Rabbits are crucial models in ocular therapeutic research.
- A physiologically based pharmacokinetic (PBPK) model tailored for rabbits has been developed to predict the pharmacokinetics of protein therapeutics after intravenous administration.
- The ocular model allows us to simulate local drug exposure in the eye.

Methods

Intravenous PBPK model development:

- Systemic PBPK models were developed for both cross-reactive (anti-VEGF) with target binding and non-cross-reactive (anti-gD) without target binding antibodies and their fragments (IgG, Fab, F(ab)₂, and Fc).¹
- A generic PBPK model in PK-Sim[®] was utilized for anti-gD, while a specific TMDD process was added using MoBi[®] for anti-VEGF proteins.²⁻³
- Model fitting, conducted through a Monte Carlo algorithm, focused on standard parameters (Table 1) for anti-gD compounds, plus kinetic constants (K_{off}, K_D), target turnover, and internal degradation of complexes, specifically tailored to anti-VEGF compounds.
- An additional renal clearance mechanism was included for lower molecular weight proteins.

Ocular PBPK model development:

- Extended ocular PBPK models were developed in R (rxode), building upon the framework proposed by Hutton-Smith et al.⁴
- These models were extended by incorporating a serum compartment and fitted (as shown in Table 2) using ocular PK data to accurately depict bevacizumab distribution across ocular compartments following intravitreal (IVT) injection.
- Strain-specific ocular anatomical and physiological values⁵⁻⁸ were utilized as initial estimates and optimized for the best fit.

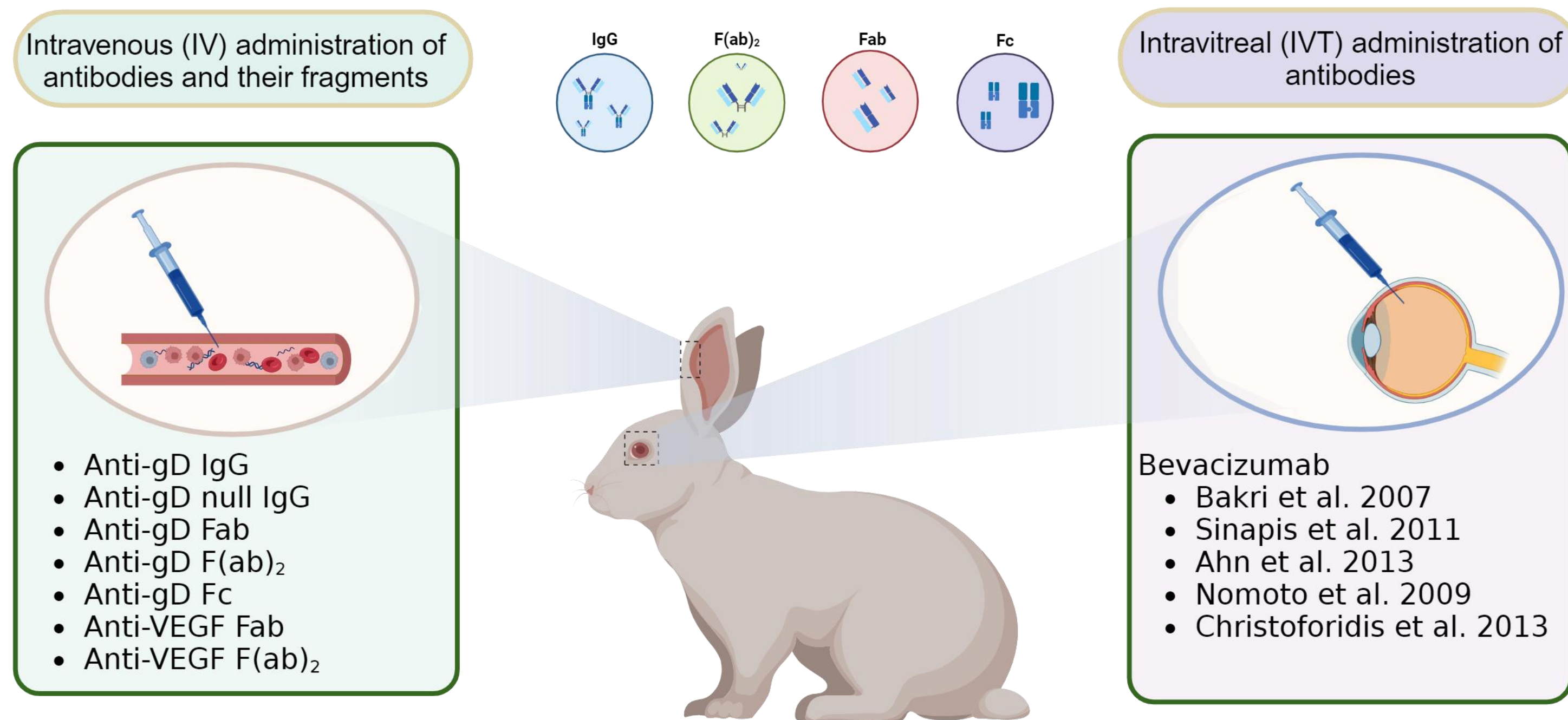


Fig. 1. Strategy for intravenous and ocular PBPK model building in rabbits

Results

Intravenous PBPK models:

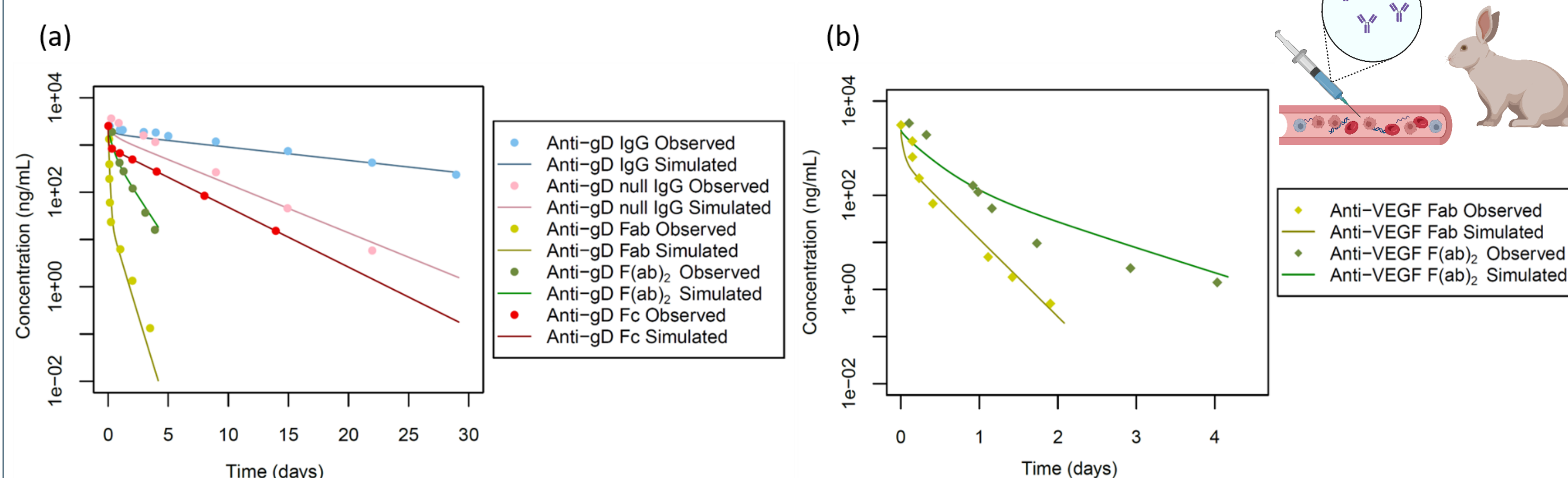


Fig. 2. Simulated and observed¹ profiles of monoclonal antibodies (mAbs) and their fragments in rabbit: (a) non-cross-reactive anti-gD protein therapeutics and (b) cross-reactive anti-VEGF protein therapeutics

Table 1. Standard parameters derived from our intravenous PBPK models for various mAbs and their fragments in rabbit. mAbs; monoclonal antibodies, MW; molecular weight, FcRn; neonatal fragment crystallizable receptor, KD-FcRn; equilibrium dissociation constant of IgG with FcRn in rabbits, R_{CL}; renal clearance

mAbs	MW (kDa)	FcRn binding in rabbit	Target binding in rabbit	Solute radius (nm)	KD-FcRn (μmol/L)	R _{CL} (mL/min/kg)
Anti-gD IgG	150	Yes	No	4.13	2.52	-
Anti-gD null IgG	150	Yes	No	4.13	13.3	-
Anti-gD Fab	50	No	No	3.30	-	0.70
Anti-gD F(ab) ₂	100	No	No	3.07	-	0.05
Anti-gD Fc	50	Yes	No	2.40	1.30	0.04
Anti-VEGF Fab	50	No	Yes	2.40	-	0.56
Anti-VEGF F(ab) ₂	100	No	Yes	3.70	-	0.10

Ocular PBPK models:

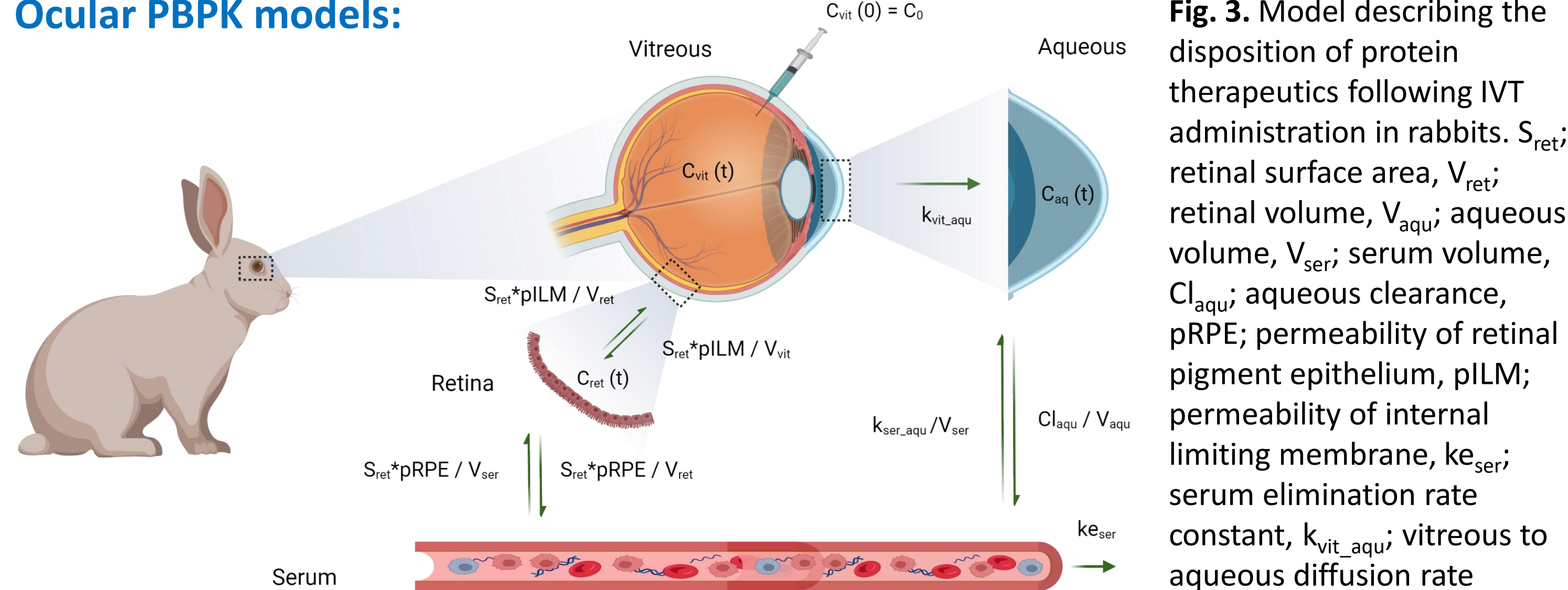


Fig. 3. Model describing the disposition of protein therapeutics following IVT administration in rabbits. S_{ret}; retinal surface area, V_{ret}; retinal volume, V_{aq}; aqueous volume, V_{ser}; serum volume, Cl_{aq}; aqueous clearance, pRPE; permeability of retinal pigment epithelium, pILM; permeability of internal limiting membrane, k_{e_ser}; serum elimination rate constant, k_{vit_aqu}; vitreous to aqueous diffusion rate

- Computational PK analysis was conducted to explore distribution patterns across eye compartments following IVT administration of bevacizumab utilizing Bakri et al. data.
- Utilized strain-specific parameters, including vitreal volume, retinal thickness, and aqueous clearance, to differentiate between NZW and DB rabbits.
- Accommodated dataset diversity through dose adjustments.

Parameter estimation (Table 2):

- Dose: The intravitreal dose of bevacizumab was adjusted.
- Vitreal t_{1/2}: Fell within a narrow range, within 2-fold of reported values.
- Serum t_{1/2}: Was closely aligned with reported values.

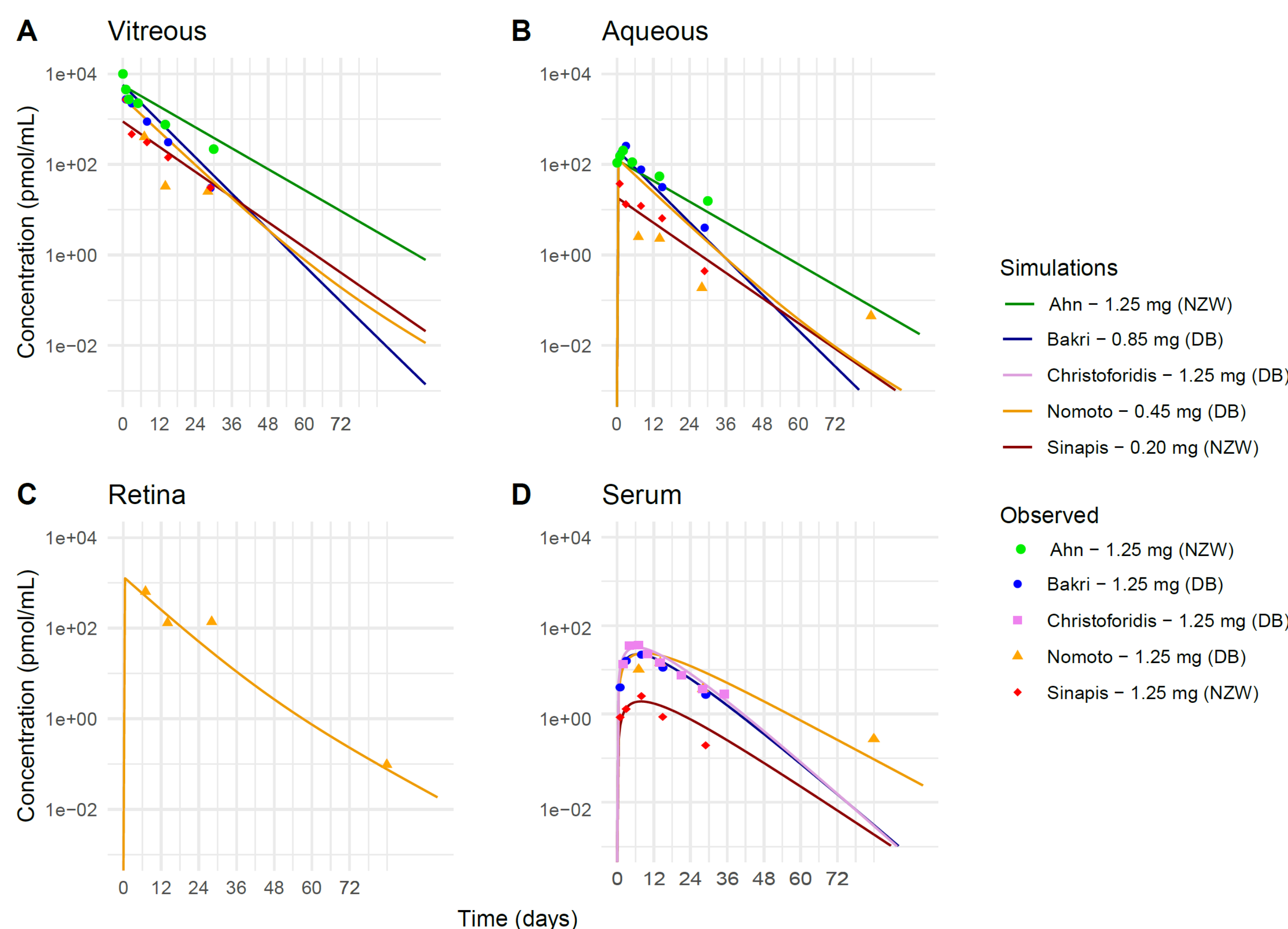


Fig. 4. Simulated and observed concentration-time profiles from various publications for bevacizumab in rabbit ocular compartments and serum following intravitreal (IVT) administration. NZW; New Zealand White, DB; Dutch Belted

Table 2. Parameters estimated from our ocular PBPK models for bevacizumab in rabbits

Literature source	Strain	Vitreous volume (mL)	Retinal thickness (cm)	Estimated model parameters			
				Dose (mg/eye)	Vitreal t _{1/2} (days)	Serum t _{1/2} (days)	Aqueous clearance (mL/day)
Ahn et al. 2013 ⁹	NZW	1.5 ^{5,8}	0.01 ³	1.25	7.8	-	4.32
Bakri et al. 2007 ¹⁰	DB	1.0 ⁸	0.023 ⁷	0.85	4.5	4.8	3.80
Christoforidis et al. 2013 ¹¹	DB	1.0 ⁸	0.023 ⁷	1.25	-	4.5	-
Nomoto et al. 2009 ¹²	DB	1.0 ⁸	0.023 ⁷	0.45	4.8	8.0	4.03
Sinapis et al. 2011 ¹³	NZW	1.5 ^{5,8}	0.01 ³	0.20	6.5	4.5	4.32

Conclusions

- A tailored PBPK platform for rabbits was developed, and our models effectively characterized the systemic disposition of protein therapeutics following intravenous administration.
- Our intravenous PBPK models have been fitted across various antibodies and their fragments, enabling an accurate description of antibody pharmacokinetics.
- Bevacizumab's ocular disposition after IVT administration across multiple literature datasets was successfully modeled.
- These PBPK models enhance preclinical pharmacokinetic research, aiding in translation of findings from preclinical to clinical settings and streamlining drug development processes for ocular indications.

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