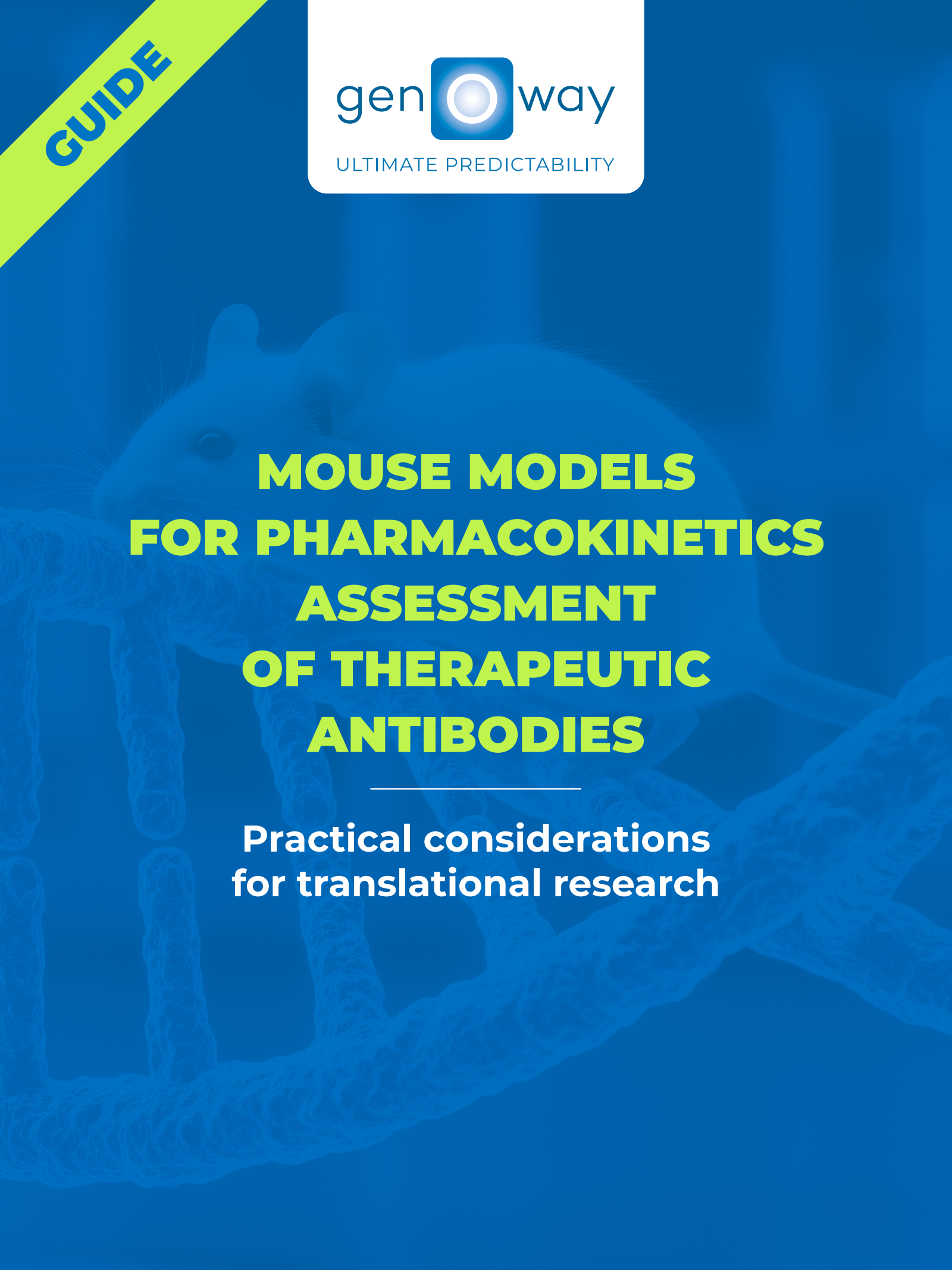
GUIDE

genOway

ULTIMATE PREDICTABILITY

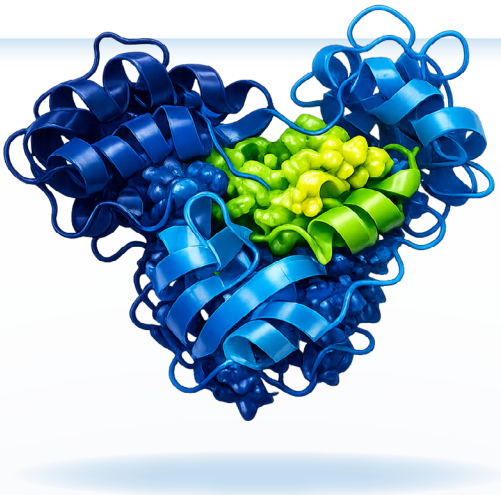


MOUSE MODELS FOR PHARMACOKINETICS ASSESSMENT OF THERAPEUTIC ANTIBODIES

Practical considerations for translational research

KEY MESSAGES

- ✓ FcRn biology is **the main driver of IgG half-life** and must be human-relevant for **translational PK**
- ✓ **Human FcRn is required** to rank human IgGs and evaluate Fc-engineered antibodies
- ✓ **Albumin recycling** is frequently underestimated but can **strongly influence antibody exposure**
- ✓ **hFcRn-only models** (e.g., Tg32) **fail for albumin-binding therapeutics** and can mis-rank candidates
- ✓ Models **expressing both human FcRn and human albumin** at physiological levels provide **the most decision-grade PK data**



INTRODUCTION / BACKGROUND

What is antibody PK assessment and why model choice matters

Pharmacokinetic (PK) assessment evaluates how long a therapeutic antibody remains in systemic circulation and determines:

• Clearance • Terminal half-life • Systemic exposure (AUC)

The role of FcRn and albumin in antibody half-life

WHAT FCRN DOES

- FcRn rescues IgG and albumin from intracellular degradation
- Binding occurs at acidic pH in endosomes and release at neutral pH
- This recycling process is the main determinant of IgG half-life

WHY SPECIES DIFFERENCES MATTER

Human and mouse FcRn differ markedly in:

- IgG binding affinity
- Albumin binding affinity
- Ligand competition dynamics

As a result: Wild-type mice poorly predict human IgG PK; and human FcRn expression is required for translational relevance.

ALBUMIN IS A CRITICAL FCRN LIGAND

- FcRn recycles both IgG and albumin
- Mouse and human albumin bind human FcRn differently
- Albumin competes for FcRn recycling capacity

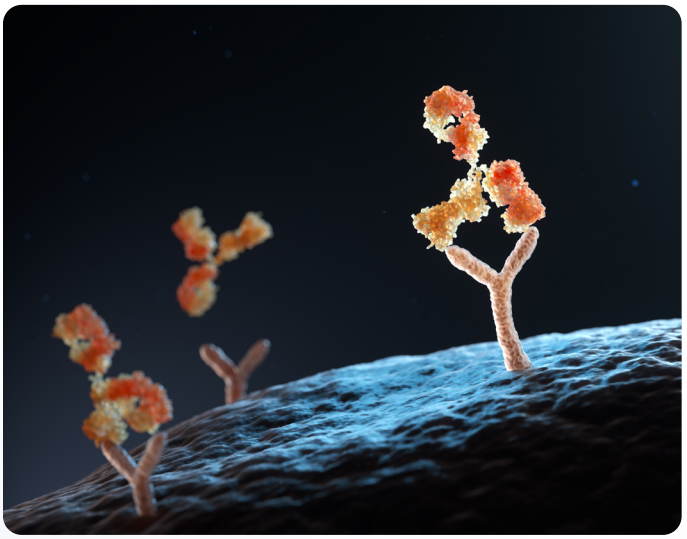
As a result: Ignoring albumin biology can distort clearance, half-life and candidate ranking.

Therapeutic modalities commonly assessed in FcRn models

HUMANIZED FCRN MOUSE MODELS ARE USED TO ASSESS PK OF:

- Conventional IgG antibodies
- Fc-engineered antibodies (altered FcRn affinity)
- Bispecific and multivalent antibodies
- Fc fusion proteins
- Albumin-binding antibodies or domains
- Albumin based half-life extension strategies

Critical distinction: Albumin centric modalities require human albumin expression, not just human FcRn.



genOway | ULTIMATE PREDICTABILITY

GUIDE: MOUSE MODELS FOR PHARMACOKINETICS ASSESSMENT OF THERAPEUTIC ANTIBODIES

Featuring the genO-hSA/hFcRn (scan or click)

HOW TO CHOOSE THE CORRECT MODEL FOR A STUDY

Ask yourself these questions first:

1. Is my molecule a human IgG?
2. Does my molecule entail Fc engineering?
3. Does my molecule bind albumin or use albumin for half-life extension?
4. Do I need ranking between closely related candidates?
5. Is this data used for go/no go decision making?



Comparison of mouse models for antibody PK assessment

MOUSE MODEL	USE WHEN	AVOID WHEN	ADVANTAGES	KEY LIMITATIONS
Wild-type mice	• Very early PK exploration • Basic exposure checks	• Human PK prediction • Fc engineering	Simple, fast, low cost	Murine FcRn is not human
Humanized FcRn (e.g. Tg32)	• Standard human IgG PK ranking • Fc-engineered antibody	Albumin-binding or albumin-fused modalities	• Improved human IgG clearance • Captures FcRn engineering well established	Murine albumin distorts fcRn ligand competition
hFcRn + human albumin (general)	Albumin-influenced PK mechanisms	Decision-grade studies on low volumes	More relevant FcRn ligand dynamics than hFcRn alone	Human albumin / FcRn often non-physiologic
genO-HSA/hFcRn (genOway)	• Albumin-binding or albumin-extended antibodies • Standard human IgG PK ranking • Fc-engineered antibodies • Decision-grade PK ranking	Low-value exploratory screening	• Physiological hFcRn + human albumin expression • Human-like PK interpretation • Elevated translational package	Higher complexity and cost

PRACTICAL EXAMPLES

What happens if I test an albumin-binding antibody in the Tg32 mouse model?

Due to the recycling of albumin through the neonatal Fc receptor (FcRn), albumin-binding therapeutic antibodies are designed to have a longer half-life. However, when analyzing the half-life of an albumin-binding antibody in the Tg32 model, the pharmacokinetics (PK) analysis may be misleading due to the lack of human albumin expression and murine albumin expression instead. Consequently, the antibody will not bind correctly to albumin, resulting in inefficient antibody recycling and a shorter half-life than predicted.

KEY PROBLEMS IN TG32 MODEL:

- Antibody cannot correctly bind to albumin
- Murine albumin competes for human FcRn
- FcRn recycling dynamics are distorted
- PK differences may be exaggerated, masked or reversed

Outcome: Wrong candidate can be selected due to model artifact, not true human biology.

What happens when testing an hFcRn or HSA-binding antibody in WT mice?

Although WT mice might be useful for initial screening of PK profiles, they do not express human FcRn or human serum albumin. Consequently, when testing therapeutic antibodies designed to bind hFcRn or HSA for extended half-life, WT mouse models will generate inaccurate PK profiles, likely underestimating the half-life of the antibody. This is exemplified in a study by Crescendo Therapeutics, whereby an albumin-binding T cell engager (CB307) tested in WT mice (NCG) has a considerably lower half-life than when testing the TCE in **genO-hSA/hFcRn mice** (Figure 1) (Archer et al., 2024).

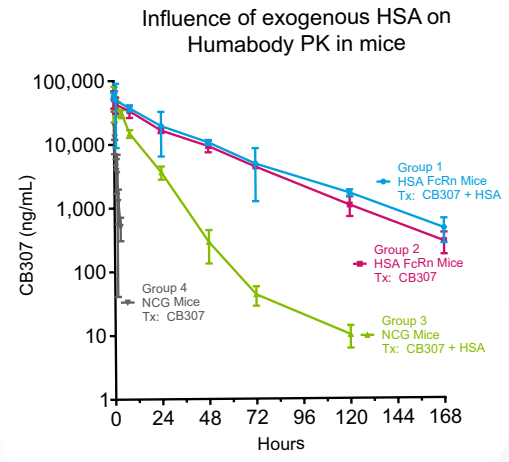


Figure 1 - Comparison of PK profiles between WT and genO-hSA/hFcRn mice. Adapted from Archer et al.; 2024

KEY PROBLEMS IN WT MODEL:

- Antibody cannot correctly bind to albumin
- Antibodies do not get recycled due to reduced binding of human antibodies to murine FcRn
- FcRn recycling dynamics are distorted
- PK profile is underestimated

Outcome: Antibody might be discarded due to misleading reduced half-life.

FAQ

Which mouse models are used to predict the half-life of therapeutic antibodies / are used for antibody pharmacokinetic studies?

Antibody pharmacokinetic and half-life studies are often initiated in wild-type mice, but translational assessment increasingly relies on human FcRn mouse models, including human FcRn transgenic mice such as the Tg32 model and mice expressing both humanized FcRn and human serum albumin, such as the **genO-hSA/hFcRn** mouse model. These models enable more accurate evaluation of FcRn dependent clearance and improved prediction of human IgG pharmacokinetics (Viuff et al., 2016; Roopenian and Akilesh, 2007; Fuchs et al., 2022).

How do FcRn mouse models compare (e.g. vs Tg32)?

Among FcRn mouse models, Tg32 mice expressing human FcRn on a mouse FcRn null background have long served as a reference model for antibody pharmacokinetics; however, their reliance on murine albumin limits the physiological relevance of FcRn occupancy and ligand competition. In contrast, genOway's **genO-hSA/hFcRn** model, which co-expresses human FcRn and human serum albumin, more faithfully reproduces human FcRn biology by capturing the competitive recycling of IgG and albumin and by normalizing FcRn engagement across both ligands, thereby improving prediction of human antibody half-life and clearance compared with Tg32 and other single humanized models (Viuff et al., 2016; Christianson et al., 2026; Lee et al., 2025).

What are the advantages of humanized FcRn mouse models compared with wild-type mice?

Humanized FcRn mouse models allow monoclonal antibodies to engage human FcRn *in vivo*, enabling accurate assessment of Fc-mediated recycling and clearance mechanisms that are not faithfully captured in wild-type mice due to species-specific FcRn binding differences (Roopenian and Akilesh, 2007; Pyzik et al., 2023).

What are the limitations of traditional mouse models for antibody PK studies?

Traditional wild-type mouse models are limited by the fact that murine FcRn binds human IgG with different affinity and kinetics than human FcRn, leading to systematic overestimation of antibody half-life and poor translational accuracy for human pharmacokinetic prediction (Roopenian and Akilesh, 2007).

How does a human FcRn mouse model improve prediction of antibody half-life?

Human FcRn mouse models improve antibody half-life prediction by reproducing the pH-dependent interaction between the human IgG Fc domain and human FcRn, allowing *in vivo* clearance rates to more closely reflect those observed in clinical studies (Fuchs et al., 2022; Mackness et al., 2019).

What is the function of the neonatal Fc receptor (FcRn) in antibody recycling?

FcRn functions as an intracellular salvage receptor that binds IgG in acidic endosomes after nonspecific uptake, protects it from lysosomal degradation, and returns it to the circulation where IgG is released at neutral pH (Roopenian and Akilesh, 2007).

How does FcRn regulate the half-life of IgG antibodies / how does FcRn binding affinity influence antibody clearance?

FcRn regulates IgG half-life through the efficiency of pH-selective binding, such that increased affinity at acidic pH enhances recycling and prolongs serum persistence, whereas reduced or improperly tuned binding accelerates lysosomal degradation and clearance (Roopenian and Akilesh, 2007; Mackness et al., 2019).

Why is FcRn important for therapeutic antibody pharmacokinetics?

FcRn is central to therapeutic antibody pharmacokinetics because it governs systemic exposure, dosing interval, and the success of Fc engineering strategies designed to extend antibody half-life in cancer, autoimmune, and inflammatory diseases (Pyzik et al., 2023).

What biological differences between mouse FcRn and human FcRn affect antibody half-life?

Amino acid differences at the FcRn–Fc interface and subclass-specific binding disparities between mouse and human FcRn result in altered recycling efficiencies, explaining why human IgG half-life is misrepresented in wild-type mice (Roopenian and Akilesh, 2007).

Why is albumin recycling important when studying FcRn biology?

Albumin recycling is important because FcRn also rescues albumin from intracellular degradation, and competition between albumin and IgG for FcRn binding influences receptor occupancy, antibody clearance, and the pharmacokinetics of Fc fusion and albumin binding therapeutics (Pyzik et al., 2023).

genOway | ULTIMATE PREDICTABILITY

GUIDE: MOUSE MODELS FOR PHARMACOKINETICS ASSESSMENT OF THERAPEUTIC ANTIBODIES

Featuring the genO-hSA/hFcRn (scan or click)

How are Fc-engineered antibodies tested *in vivo*?

Fc-engineered antibodies are tested *in vivo* by comparing their pharmacokinetic profiles to wild-type Fc antibodies in human FcRn transgenic mice, where improved or impaired half-life directly reflects changes in FcRn binding properties (Mackness et al., 2019; Ko et al., 2022).

How can researchers measure antibody recycling in mouse models?

Antibody recycling in mouse models is measured through longitudinal serum pharmacokinetic analysis, comparison with FcRn knockout mice, tissue distribution studies, and tracer based approaches that assess FcRn dependent intracellular rescue (Bryniarski et al., 2024).

How do FcRn mouse models help predict human pharmacokinetics of biologics?

FcRn mouse models aid human pharmacokinetic prediction by enabling quantitative scaling of clearance and half-life based on human relevant FcRn interactions, often achieving predictive accuracy comparable to that of non human primates (Haraya et al., 2025; Christianson et al., 2026).

What preclinical models are used to study FcRn mediated drug recycling?

Preclinical models used to study FcRn mediated drug recycling include human FcRn transgenic mice such as Tg32, human FcRn knock-in mice, FcRn-deficient mice for mechanistic validation, and complementary *in vitro* FcRn binding and recycling assays (Roopenian and Akilesh, 2007; Pyzik et al., 2023).

Do albumin and IgGs compete for FcRn binding?

FcRn engages albumin and IgG through separate, non-overlapping binding interfaces, and interaction with either ligand occurs in a pH-dependent manner, being restricted to acidic conditions below pH 6.5 and absent at neutral pH (Chaudhury et al., 2006; Andersen et al., 2006).

REFERENCES

1. *Bryniarski, M. A., Haque Tuhin, M. T., Acker, T. M., et al. (2024). Cellular neonatal Fc receptor recycling efficiencies can differentiate target independent clearance mechanisms of monoclonal antibodies. Journal of Pharmaceutical Sciences, 113(9), 2879–2894.*
2. *Christianson, G. J., Howard, Z. M., Kenney, S., et al. (2026). Optimizing human FcRn mouse models to improve pharmacokinetic evaluation of antibody drug candidates. mAbs, 18(1), 2649990.*
3. *Fuchs, A., Afroz, T., Ollier, R., et al. (2022). Human FcRn transgenic mice (Tg32) as a model for early assessment and prediction of human pharmacokinetics of monoclonal antibodies. Pharmaceutical Research, 39, 1197–1211.*
4. *Haraya, K., Ichikawa, T., Murao, N., et al. (2025). Prediction of human pharmacokinetics of Fc engineered therapeutic monoclonal antibodies using human FcRn transgenic mice. mAbs, 17(1), 2484443.*
5. *Ko, S., Park, S., Sohn, M. H., et al. (2022). An Fc variant with two mutations confers prolonged serum half-life and enhanced effector functions on IgG antibodies. Experimental & Molecular Medicine, 54, 1850–1861.*
6. *Lee, S. B., Kyung, M., Park, M., et al. (2025). Advanced human FcRn knock in mice for pharmacokinetic profiling of therapeutic antibodies. Scientific Reports, 15, 27186.*
7. *Mackness, B. C., Jaworski, J. A., Boudanova, E., et al. (2019). Antibody Fc engineering for enhanced neonatal Fc receptor binding and prolonged circulation half-life. mAbs, 11(7), 1276–1288.*
8. *Pyzik, M., Kozicky, L. K., Gandhi, A. K., & Blumberg, R. S. (2023). The therapeutic age of the neonatal Fc receptor. Nature Reviews Immunology, 23, 415–432.*
9. *Roopenian, D. C., & Akilesh, S. (2007). FcRn: the neonatal Fc receptor comes of age. Nature Reviews Immunology, 7(9), 715–725.*
10. *Viuff, D., Antunes, F., Evans, L., et al. (2016). Generation of a double transgenic humanized neonatal Fc receptor (FcRn)/albumin mouse to study the pharmacokinetics of albumin linked drugs. Journal of Controlled Release, 223, 22–30.*

Click to access genO-hSA/hFcRn model page

Or scan this QR code

genoway

ULTIMATE PREDICTABILITY

www.genoway.com

AN-1509-EN-2611 **Rev A**