A minimal PBPK model with a nested endosome compartment to predict the enhanced target suppression of recycling antibody vs. conventional antibody

Dongfen Yuan
ACoP 2024
Phoenix, AZ

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

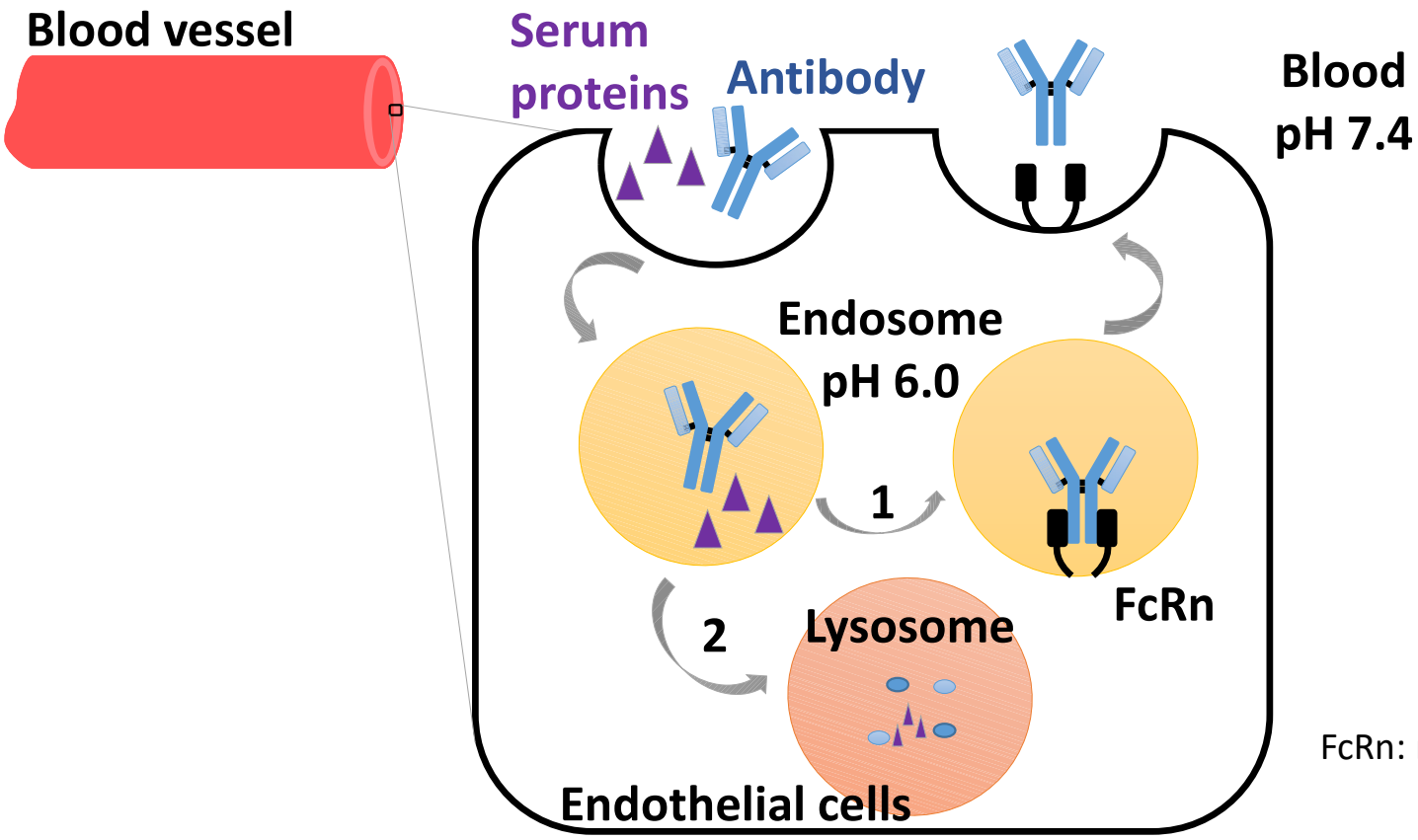
novo nordisk®

Yuan et al. AAPS J. 2018
Yuan et al. Eur J Pharm Sci. 2019

Outline

- The role of FcRn in antibody PK
- What and why of recycling antibody
- Modeling: extension of mPBPK model with a nested endosome compartment to describe the enhanced target suppression of recycling antibody vs. conventional antibody
- Shiny App demonstration

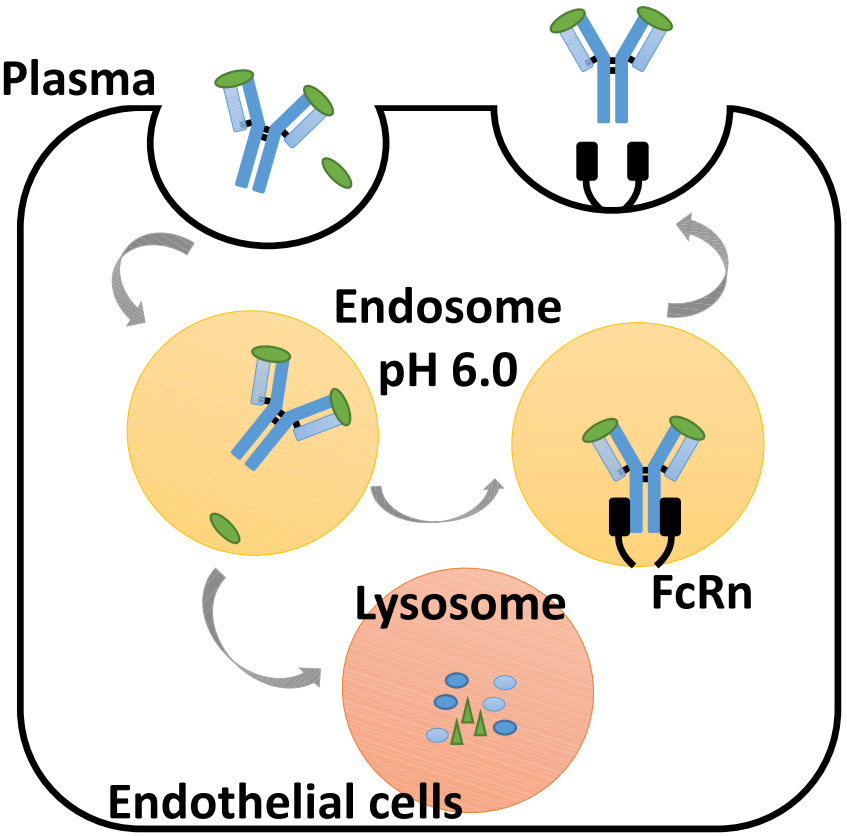
FcRn-mediated antibody recycling reduces antibody clearance



FcRn: neonatal Fc receptor

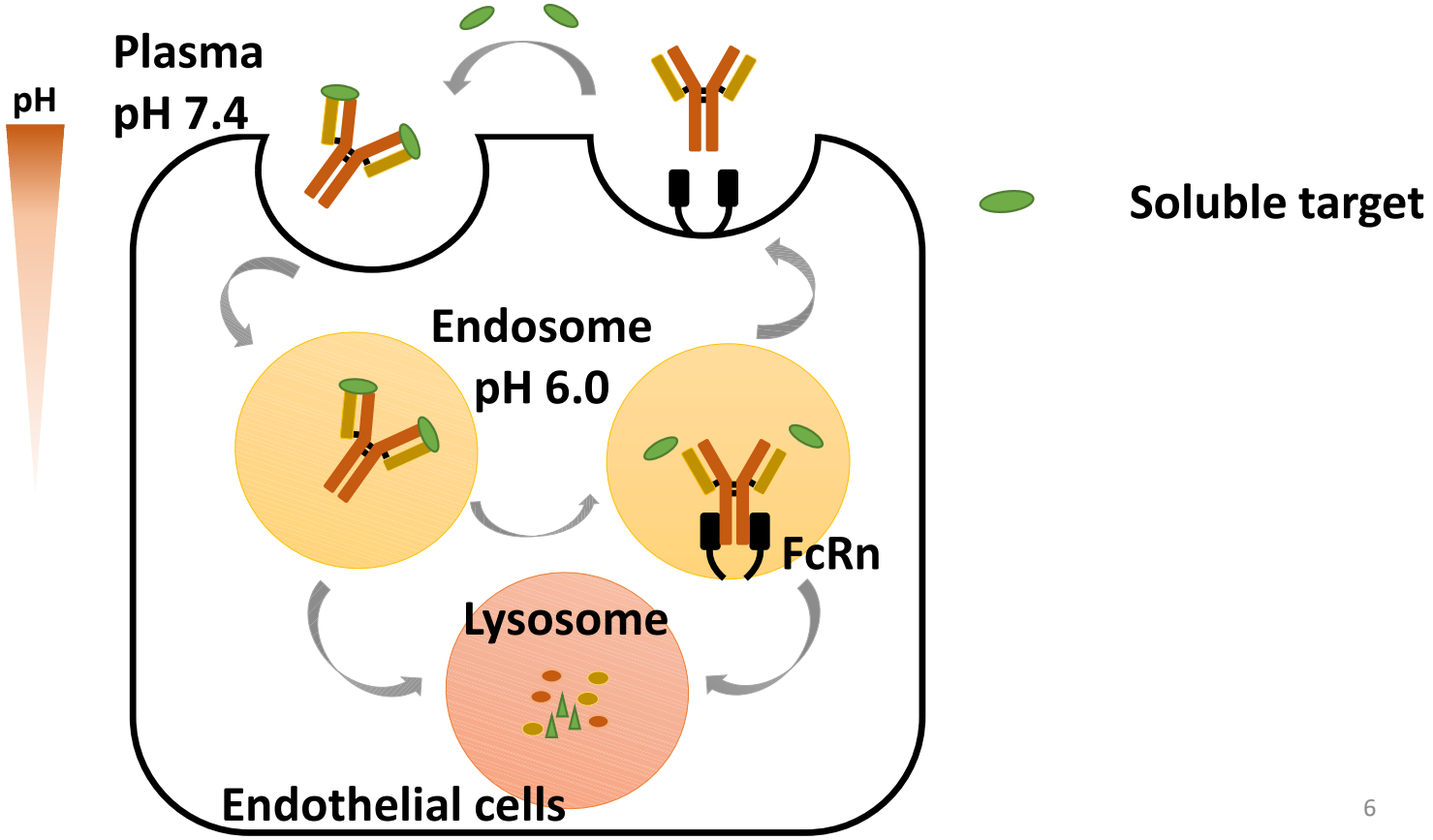
Conventional antibody against soluble target reduces antigen clearance and can bind to the target only once

Antibody-mediated target accumulation



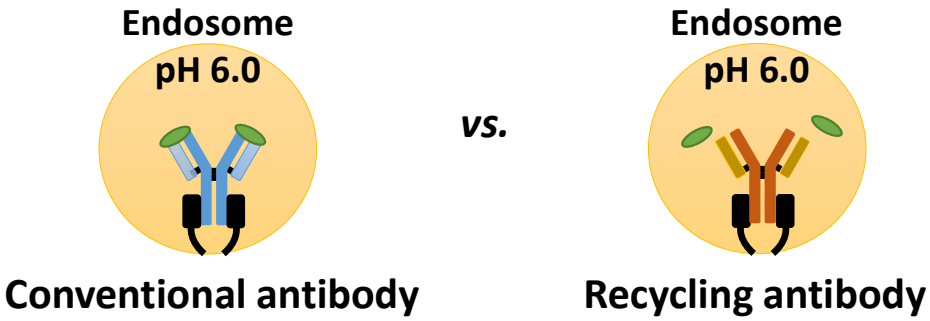
Soluble target

Recycling antibody against soluble target can bind to the antigen multiple times

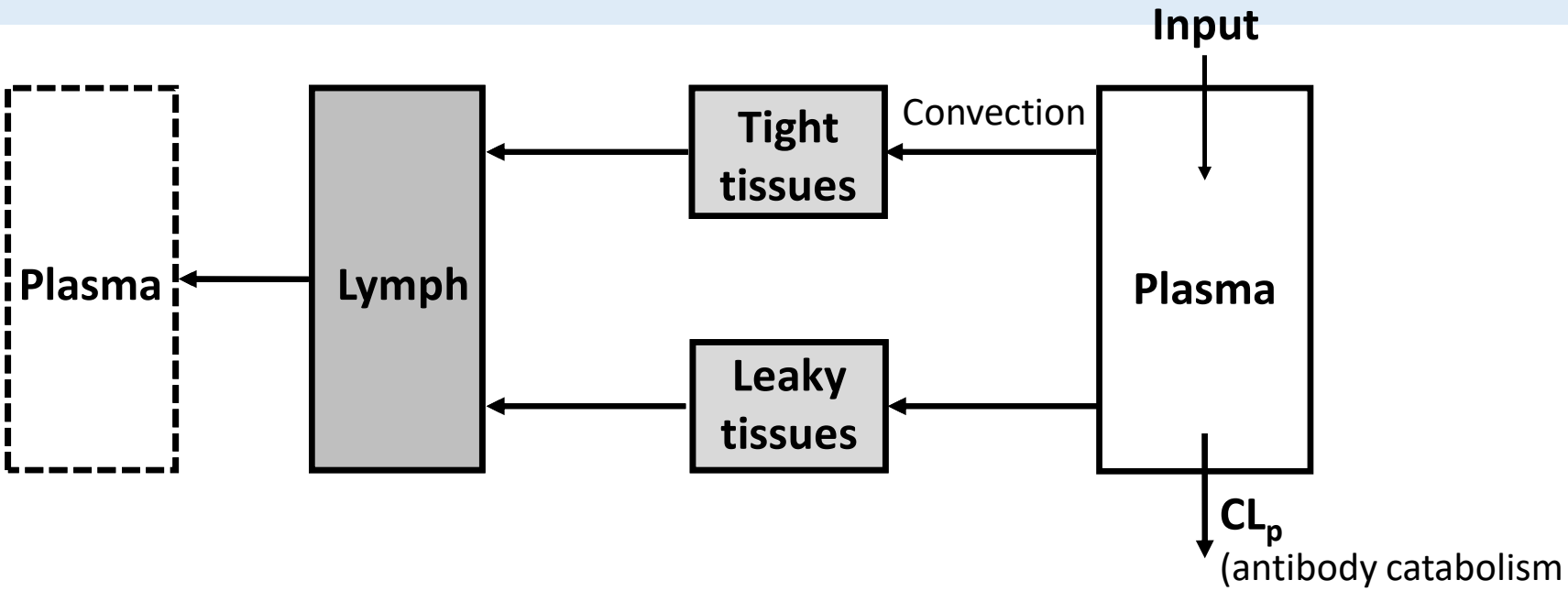


Modeling & Simulation objectives

- Predict the benefit of recycling antibodies based on *in vitro* target binding affinity
- Facilitate the interspecies translation of recycling antibodies



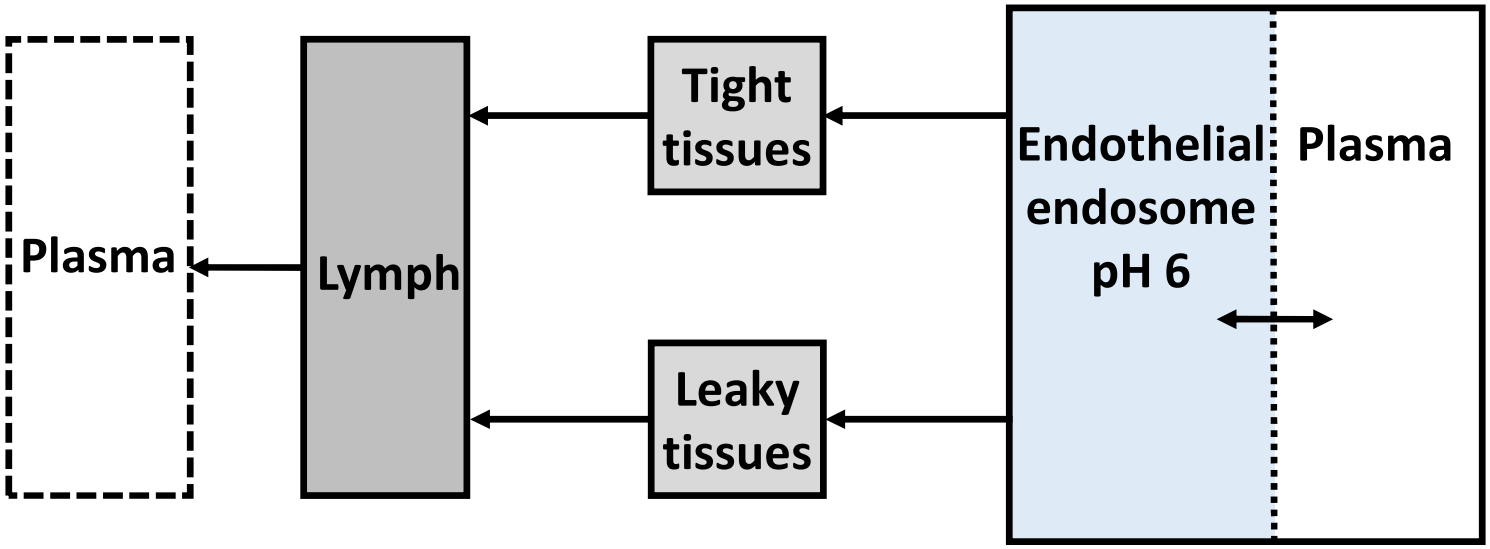
Minimal PBPK model serves as the base model to facilitate interspecies translation



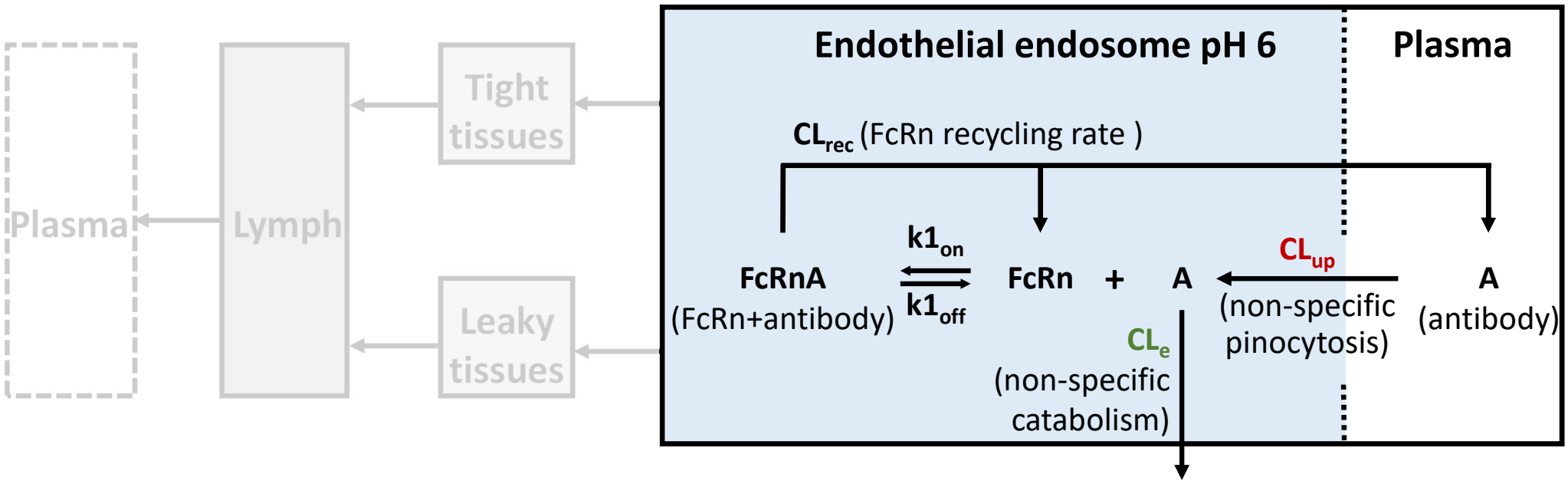
Tight tissues: muscle, skin, adipose, brain
Leaky tissues: liver, spleen, kidney, heart, etc.

Cao et al. J Pharmacokinet Pharmacodyn. 2013

An endosome compartment was nested to simulate the difference between conventional and recycling antibodies



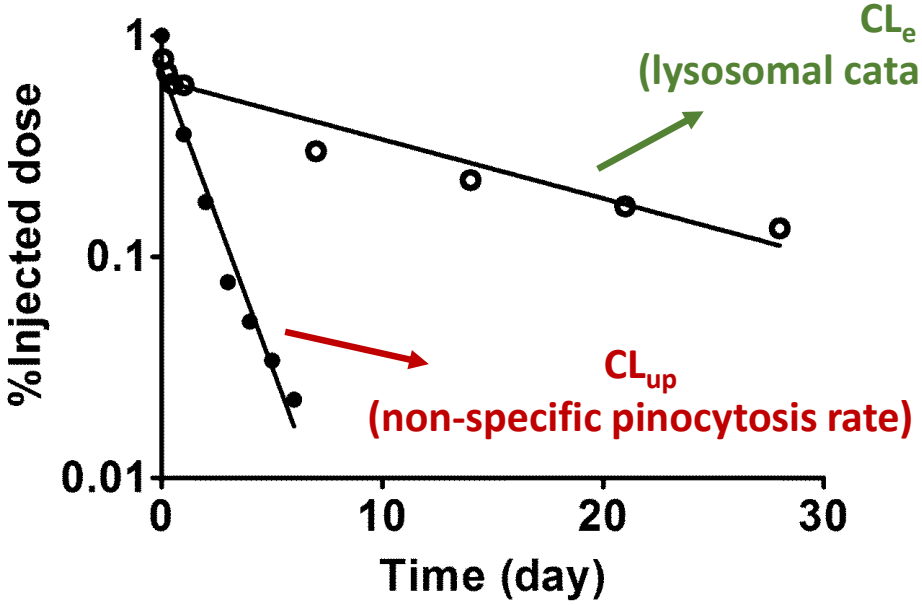
Endosome trafficking and FcRn recycling pathway were incorporated to the base model

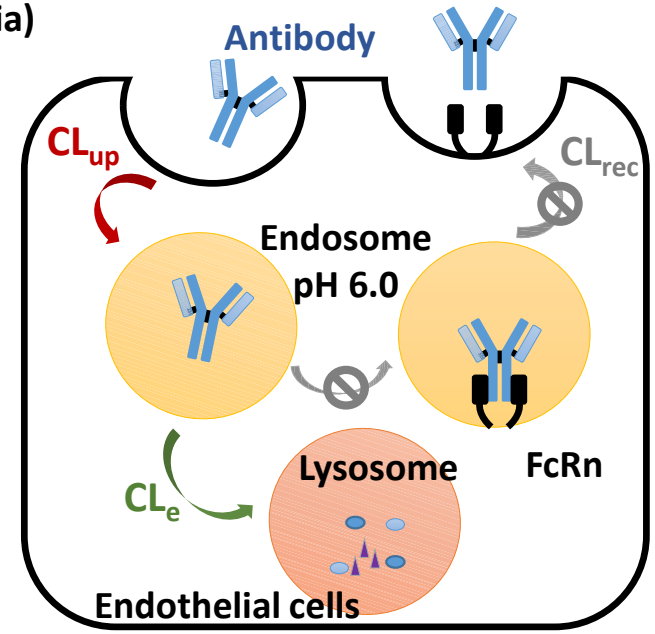


$k1_{on}/k1_{off}$: antibody-FcRn association/dissociation rate constants

Non-specific pinocytosis rate and lysosomal catabolism rate were estimated from human data

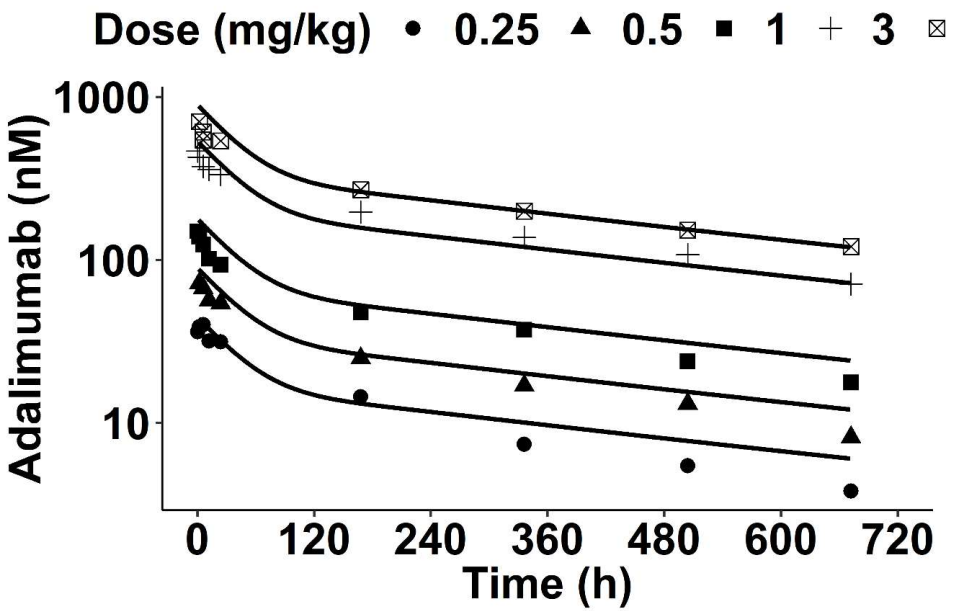
- FcRn functional human
- FcRn mutant human (familial hypercatabolic hypoproteinemia)



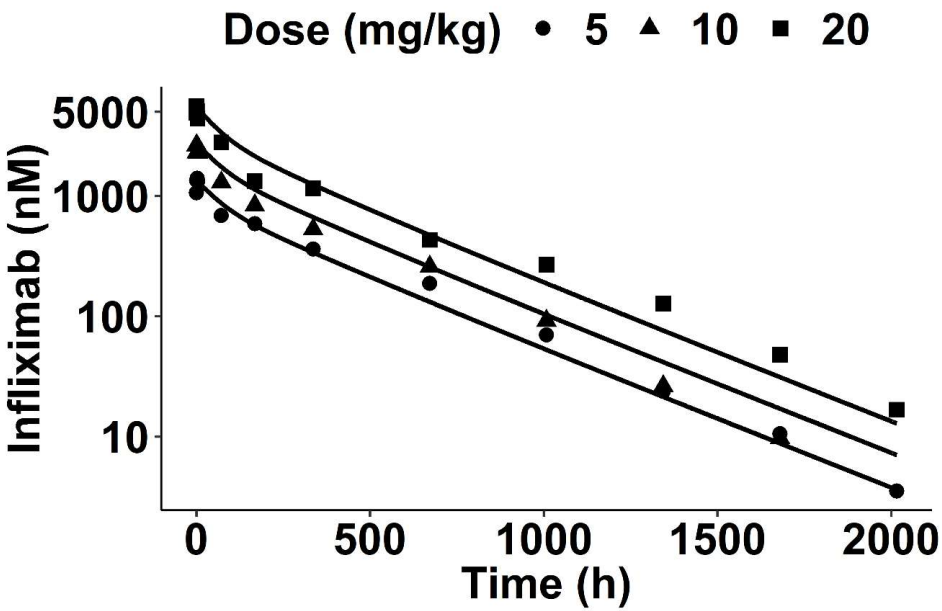


The model can predict the PK of mAbs with different FcRn binding affinities in human

Adalimumab (672 nM)

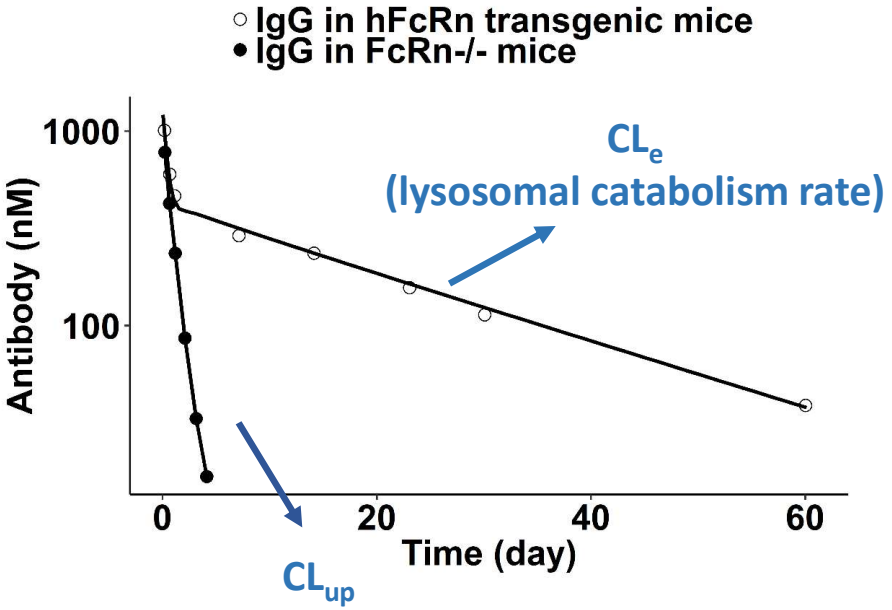


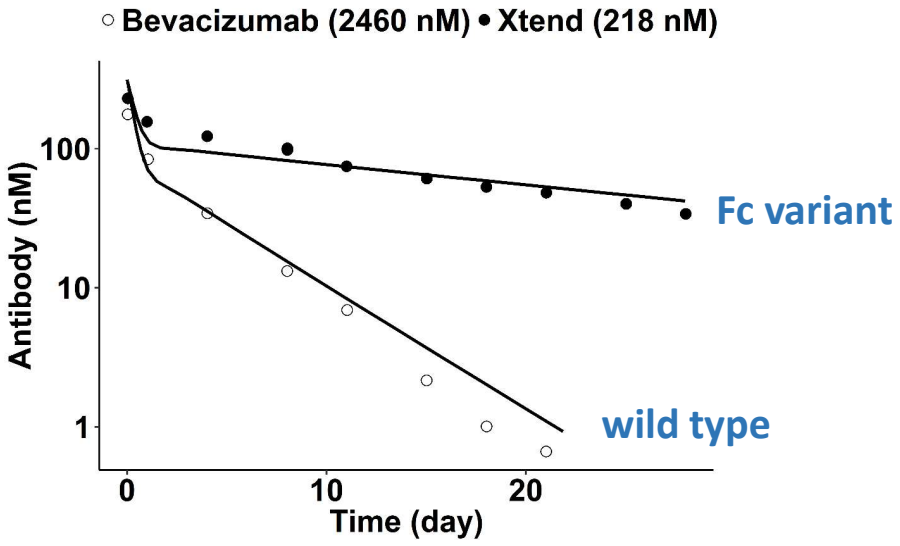
Infliximab (727 nM)



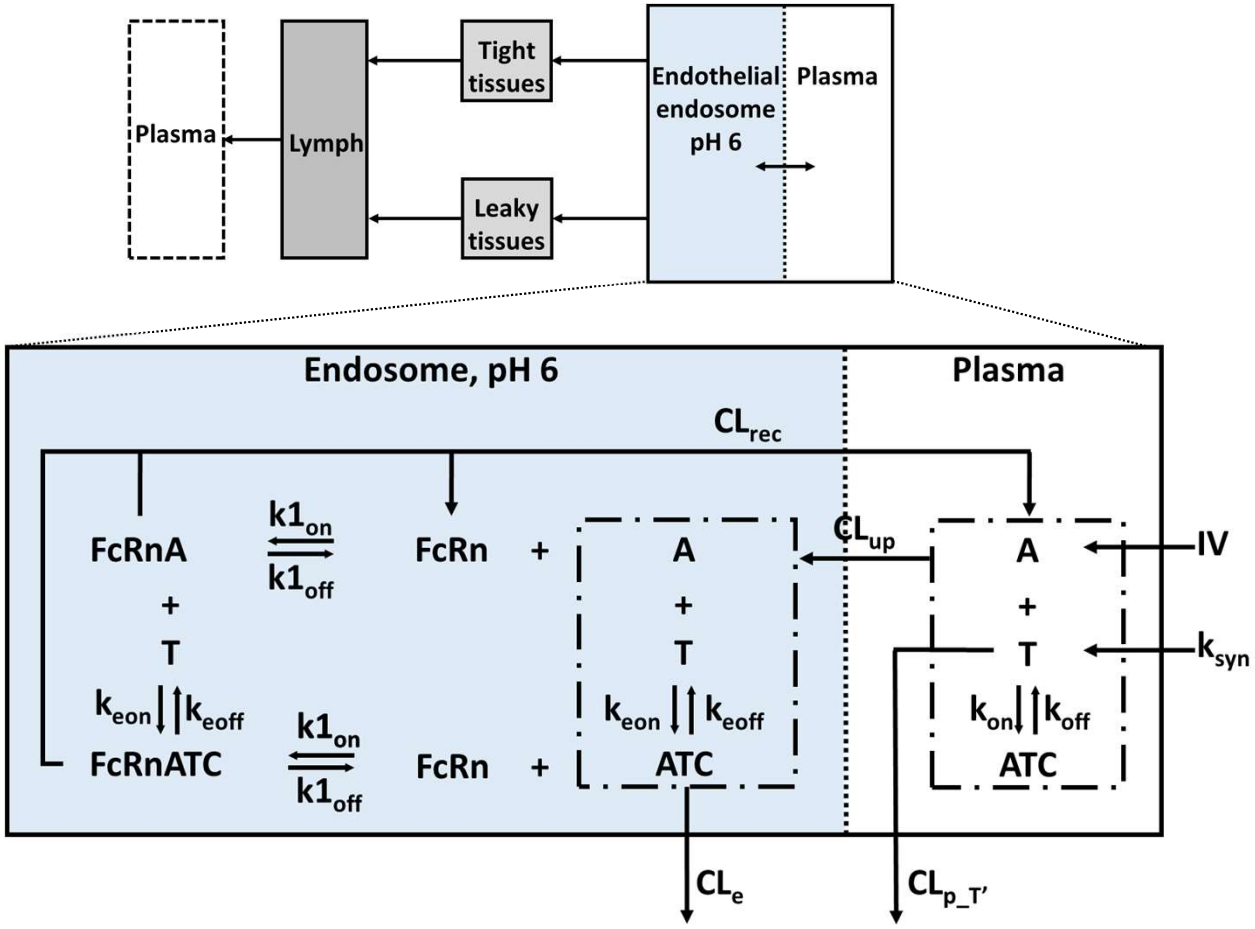
A complementary mouse model can predict the extended circulation of Fc-engineered antibody in mice

Estimation of CL_{up} and CL_e in mice



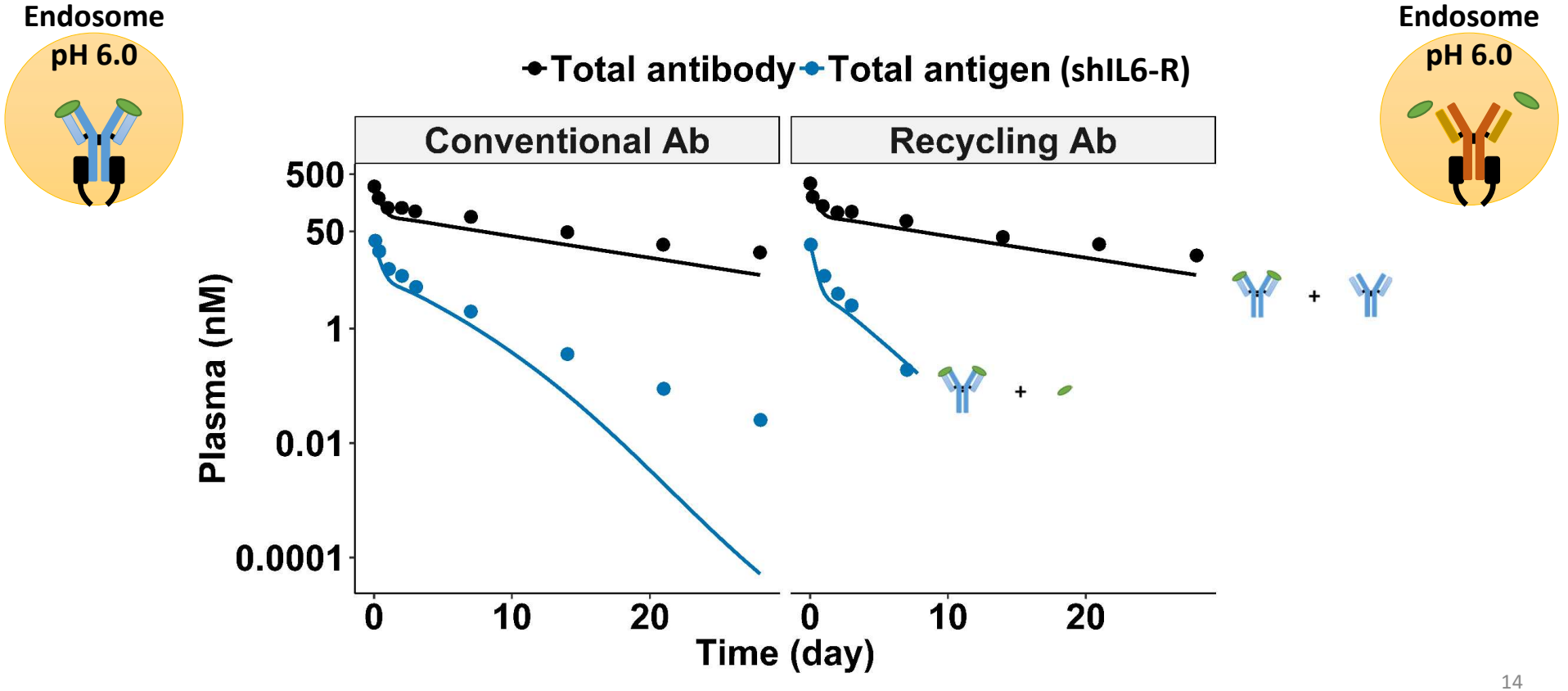


Target binding kinetics in plasma and endosomes were added to describe the difference between recycling and conventional antibodies



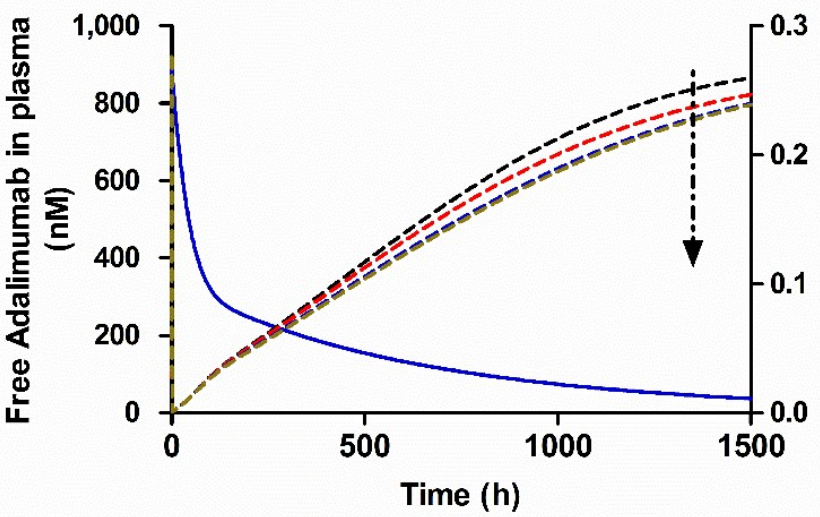
A: antibody
T: soluble target
ATC: antibody-target complex

Model predicts reduced antigen accumulation for a recycling antibody in mice

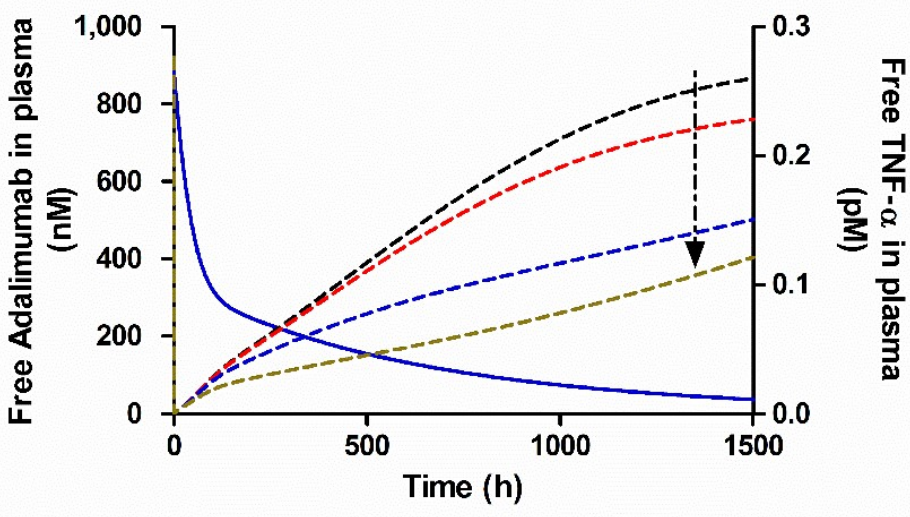


Increasing target dissociation rate constant at pH 6 can efficiently enhance target suppression

10x stepwise decrease of K_{eon} at pH 6

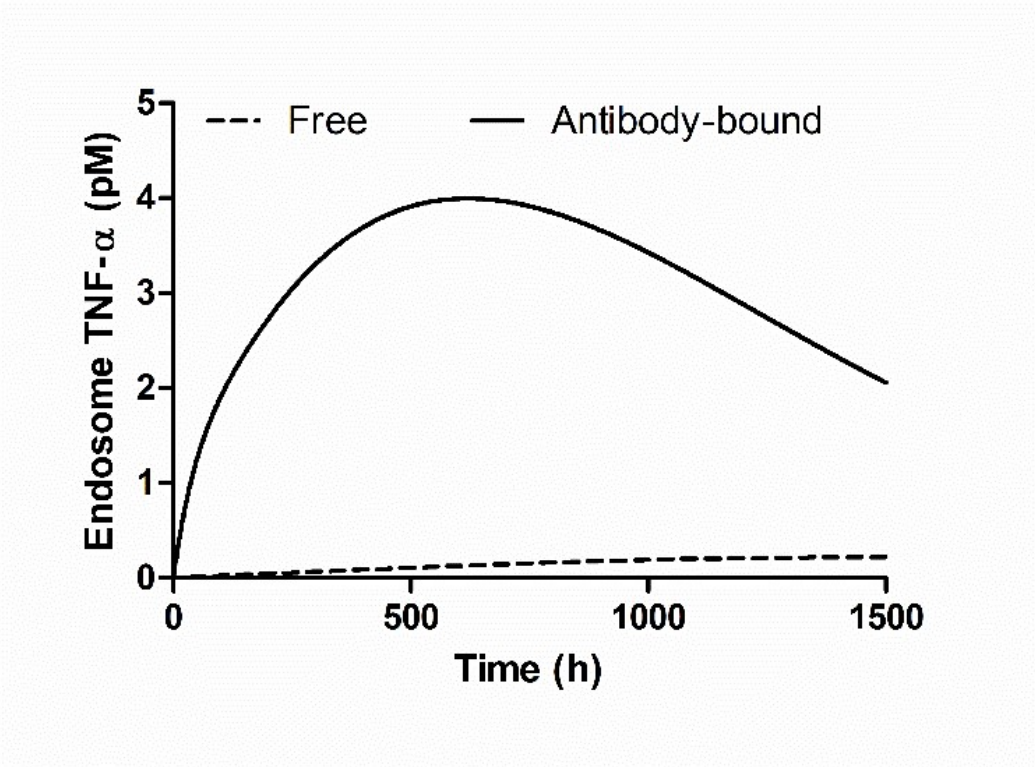


10x stepwise increase of K_{eoff} at pH 6

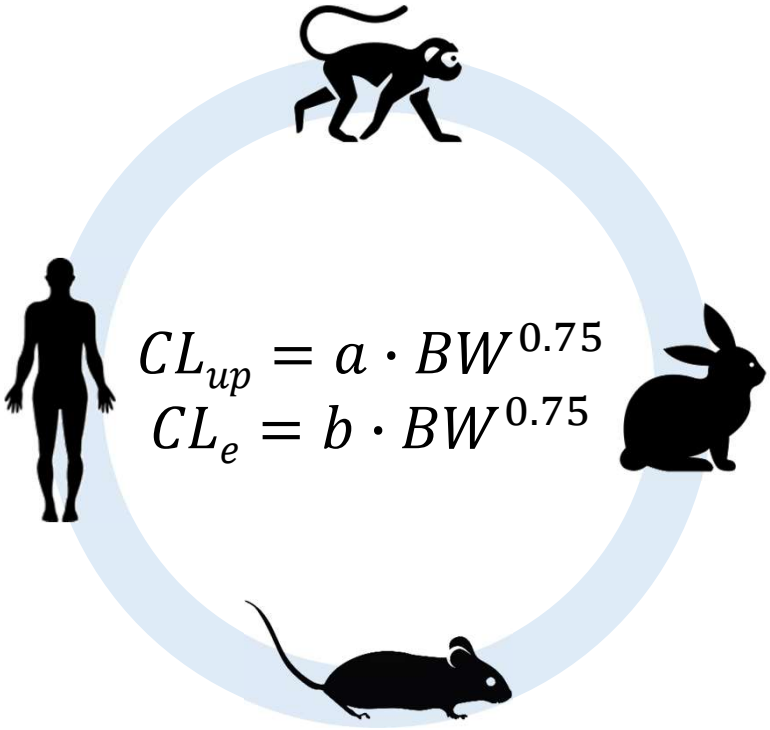


Solid lines: antibody
Dashed lines: target

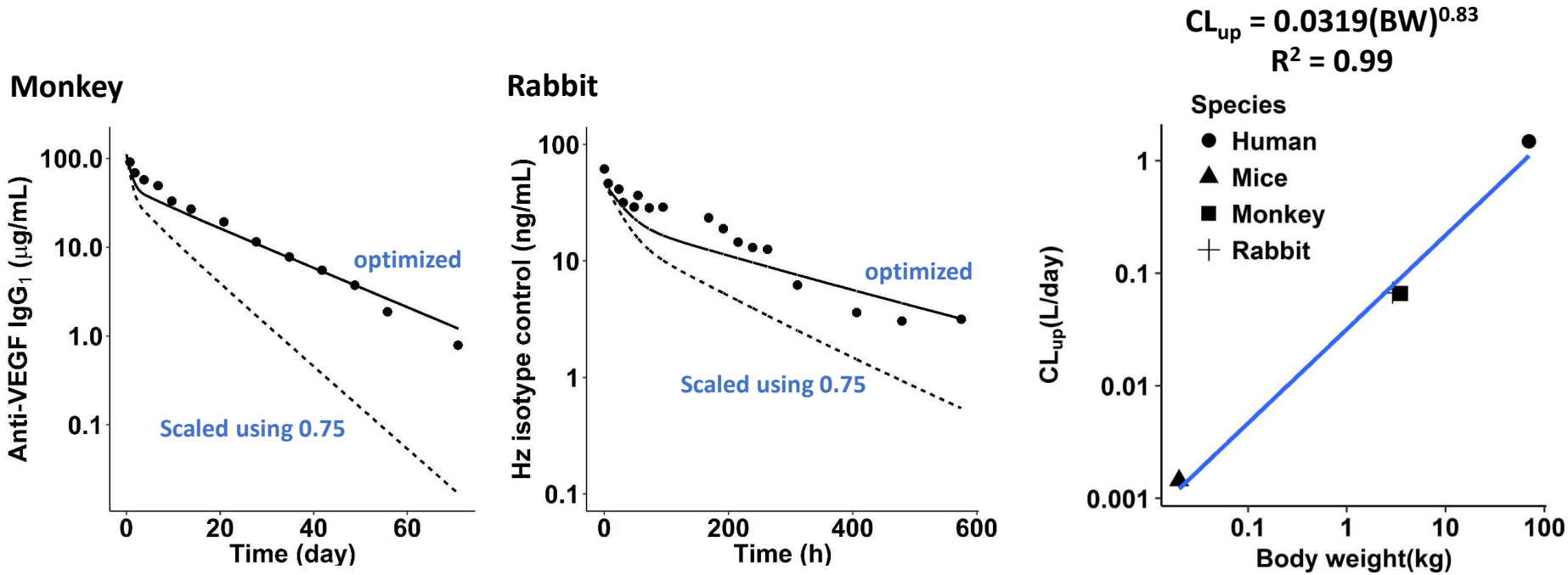
Most targets were bound to antibodies in endosomes, thus increasing target dissociation rate constant is more efficient in releasing the targets



The model was scaled to monkey and rabbit to facilitate interspecies translation

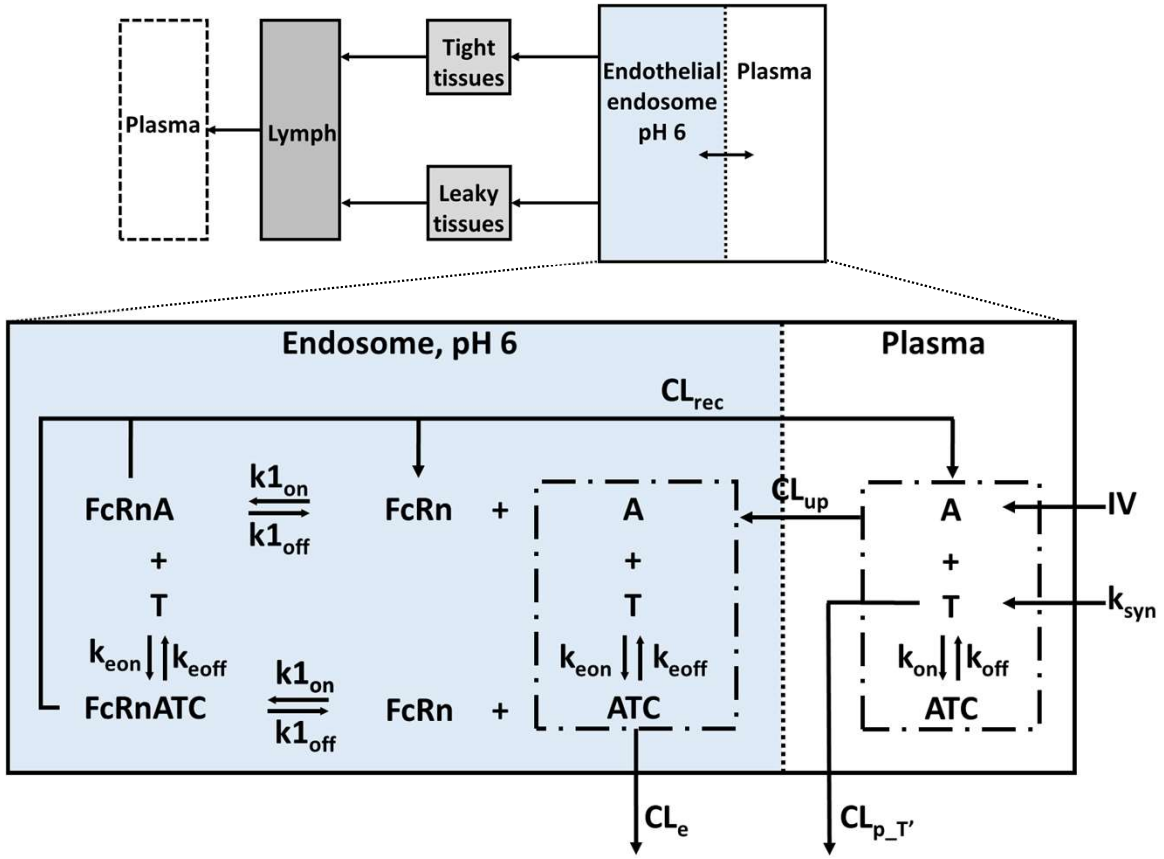


Interspecies scaling of non-specific pinocytosis CL_{up} using exponent of 0.83



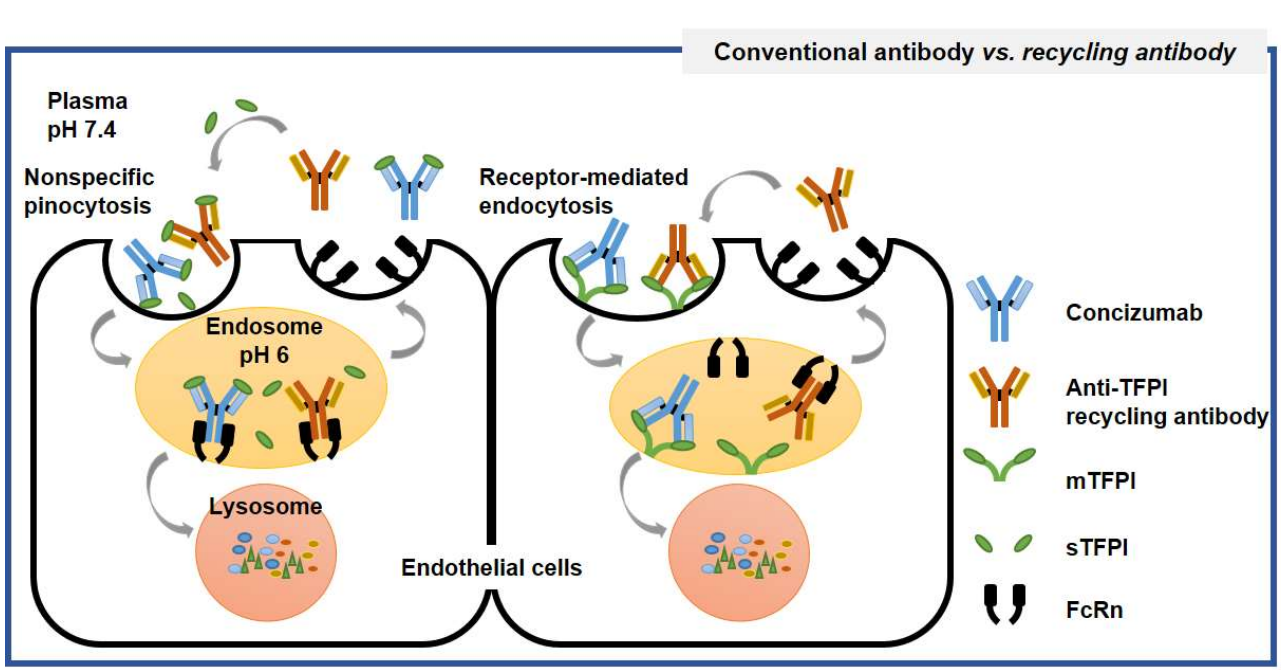
Yuan et al. Eur J Pharm Sci. 2019

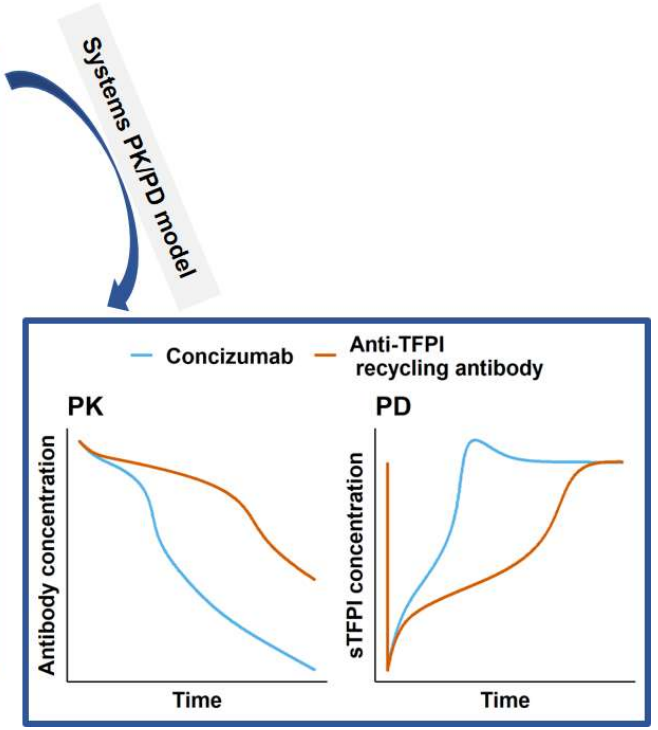
A generic model for recycling antibodies against soluble target in human, mouse, monkey, and rabbit



A: antibody
T: soluble target
ATC: antibody-target complex

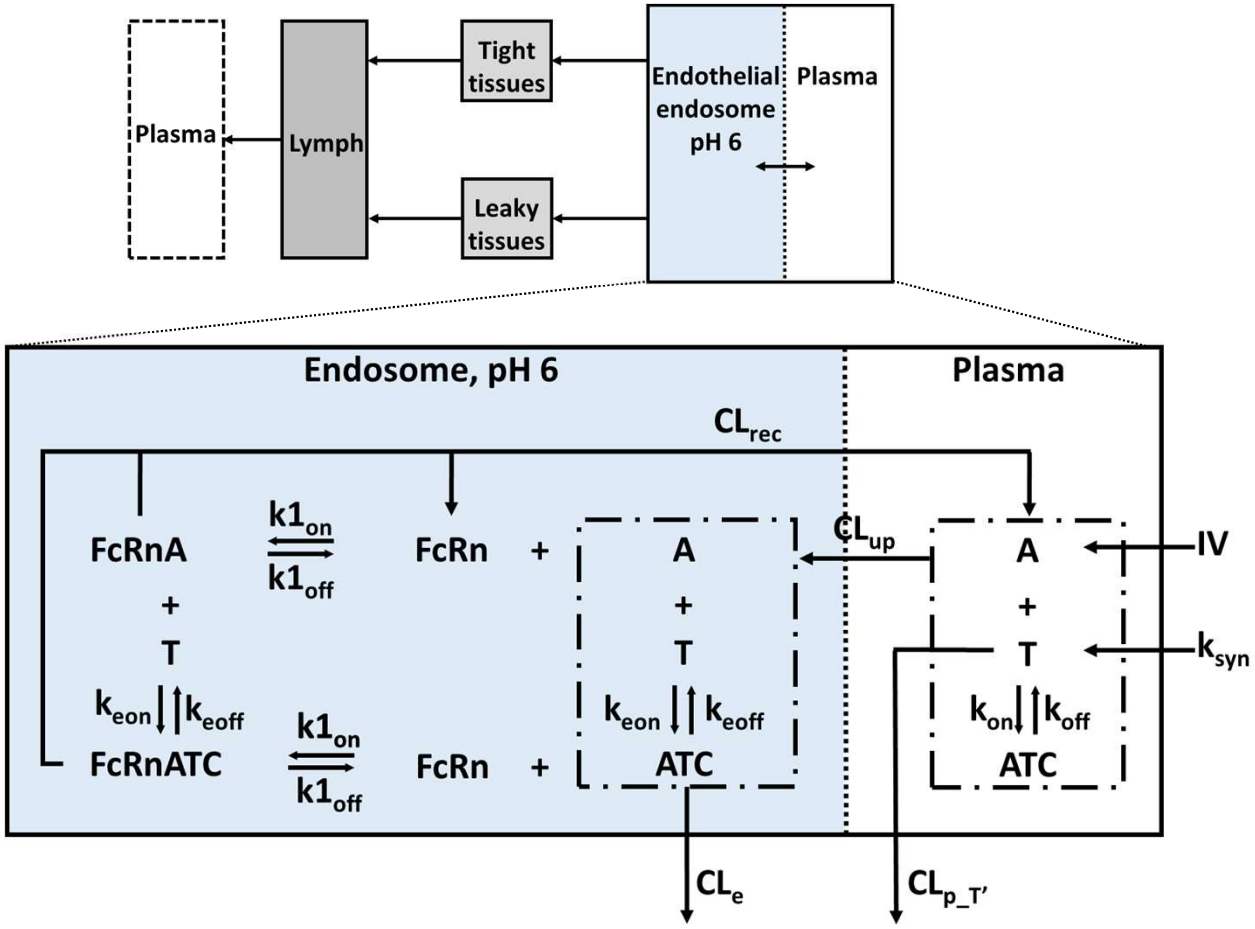
Recycling antibody can prolong the suppression of soluble target by reducing membrane target-mediated antibody clearance





Yuan et al. Eur J Pharm Sci. 2019

Shiny App Demonstration



A: antibody
T: soluble target
ATC: antibody-target complex