A Physiologically Based Pharmacokinetic model to describe the placental transfer of the FcRn inhibitor Nipocalimab

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AGENDA

01. Background
02. Nipocalimab in MFI
03. Placental transfer PBPK model build
04. Key takeaways

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TOPIC 01

Background

FcRn receptor

Neonatal Fc receptor: IgG recycling and transport

What it is

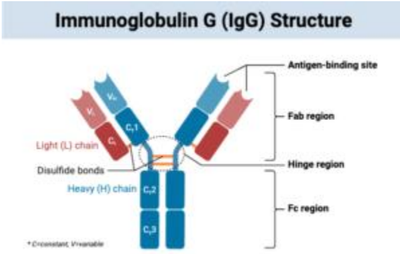
- FcRn (neonatal Fc receptor) is an MHC class I-like receptor that binds the Fc domain of IgG and albumin in a pH-dependent way
- Expressed in endothelium, myeloid cells, gut, liver, kidney and placental syncytiotrophoblast

Role in the body

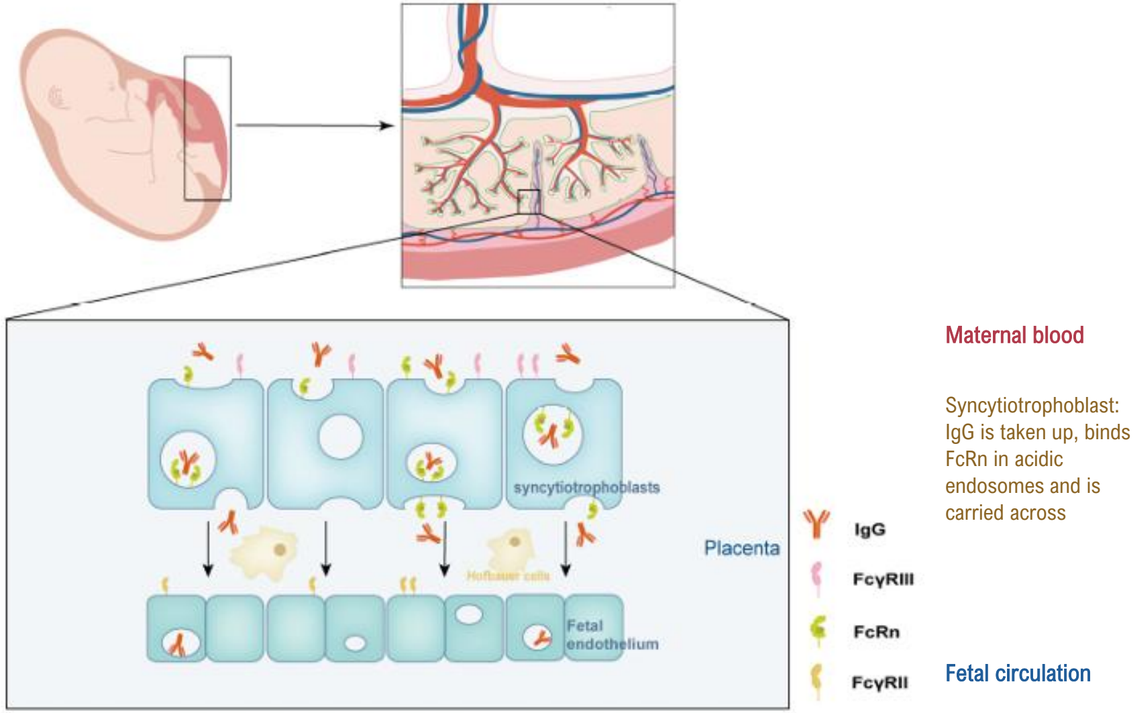
- Salvages IgG and albumin from lysosomal degradation, giving IgG its long ~3-week half-life
- Mediates transcytosis of IgG across epithelial and endothelial barriers, shaping IgG biodistribution
- Key driver of the non-linear PK of FcRn-binding therapeutics; blocking it lowers circulating IgG

Why it matters in pregnancy

- Placental FcRn actively transports maternal IgG to the fetus, rising sharply from the second trimester and providing passive immunity after birth
- The same route carries pathogenic maternal IgG, driving conditions such as HDFN and FNAIT
- FcRn blockade can reduce that transfer, making placental FcRn transport central to modeling fetal exposure

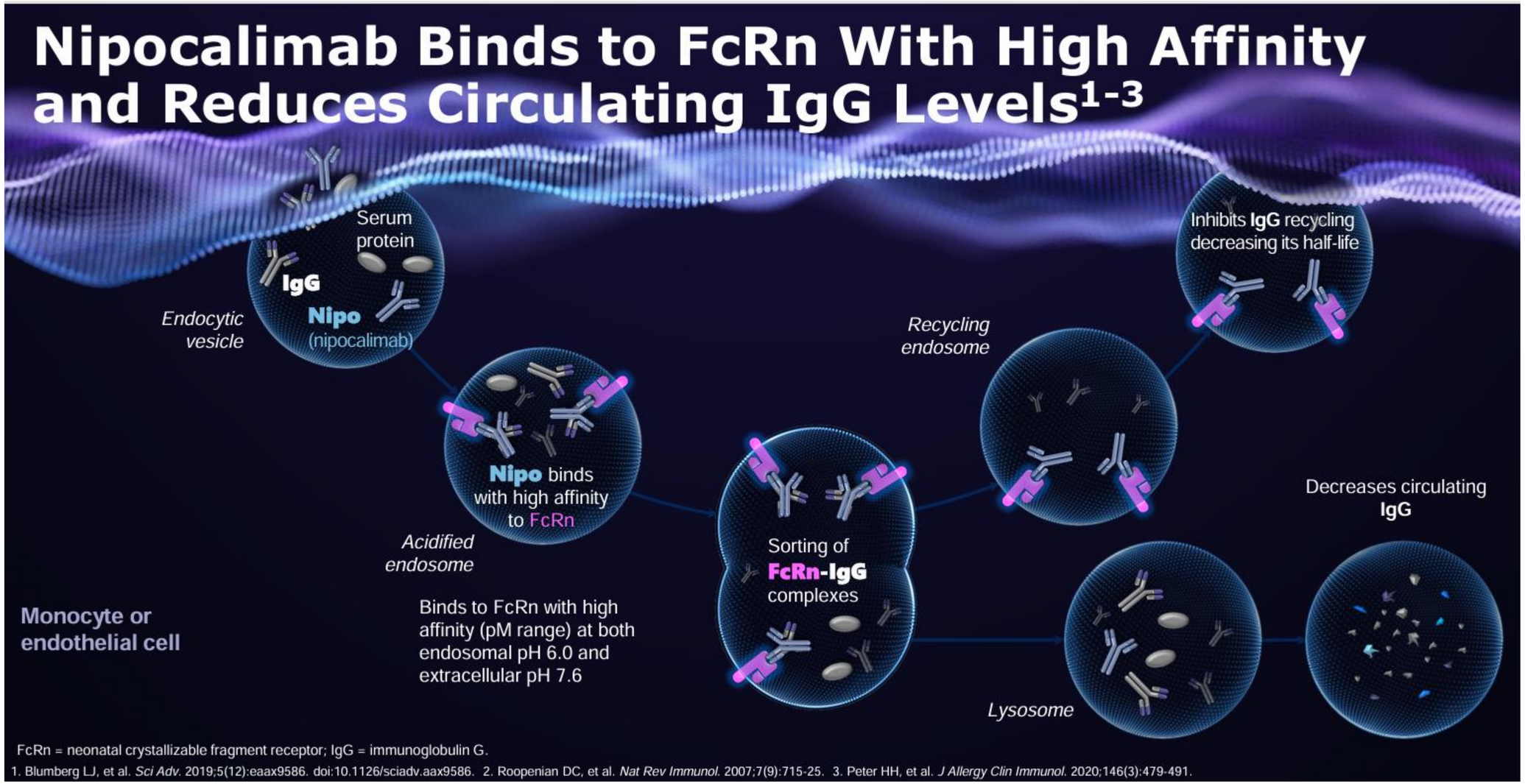


IgG transfer across the placental syncytiotrophoblast



FcRn inhibition and disease

Getting rid of IgG auto-antibodies



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TOPIC 02

Nipocalimab in MFI

Nipocalimab in maternal-fetal indications (MFI)

HDFN - FNAIT

N ENGL J MED 391;6 NEJM.ORG AUGUST 8, 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn

ABSTRACT

BACKGROUND

In early-onset severe hemolytic disease of the fetus and newborn (HDFN), transplacental transfer of maternal antierythrocyte IgG alloantibodies causes fetal anemia that leads to the use of high-risk intrauterine transfusions in order to avoid fetal hydrops and fetal death. Nipocalimab, an anti–neonatal Fc receptor blocker, inhibits transplacental IgG transfer and lowers maternal IgG levels.

METHODS

In an international, open-label, single-group, phase 2 study, we assessed treatment with intravenous nipocalimab (30 or 45 mg per kilogram of body weight per week) administered from 14 to 35 weeks' gestation in participants with pregnancies at high risk for recurrent early-onset severe HDFN. The primary end point was live birth at 32 weeks' gestation or later without intrauterine transfusions as assessed against a historical benchmark (0%; clinically meaningful difference, 10%).

ELSEVIER

Blood 144 (2024) 1193.1–1193.2



The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Design of a Phase 3, Multicenter, Randomized, Open-Label Study of Nipocalimab or IVIG in Pregnancies at Risk for Fetal and Neonatal Alloimmune Thrombocytopenia (FREESIA-3)

James B. Bussel, MD[1,2], Pamela Baker, PharmD[3], Edwin Lam[3], Paige Meizlik[3], Hein Fennema[3], Rebecca Zaha[3], Hillary Van Valkenburgh[3], Kattayoun Kordy[3]

Background: Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare, life-threatening condition with fetuses at risk of intracranial hemorrhage. Maternal immunoglobulin (IgG) alloantibodies against fetal human platelet antigens (HPAs) cross the placenta, and bind to fetal platelets, leading to platelet destruction and thrombocytopenia. Currently, there is no routine prenatal screening for HPA alloimmunization. Intravenous immunoglobulin (IVIG) is well-described as standard-of-care treatment for FNAIT in most countries. Nipocalimab is a fully human, IgG1, high-affinity, effectorless, neonatal Fc receptor (FcRn)-blocking monoclonal antibody that inhibits transplacental IgG transfer and lowers circulating maternal IgG levels. Nipocalimab showed proof-of concept efficacy in preventing or delaying fetal anemia with an acceptable safety profile in an open-label phase 2 study of hemolytic disease of the fetus and newborn (ClinicalTrials identifier: NCT03842189). Identified nipocalimab risks include hypogammaglobulinemia and infection. This suggests that nipocalimab has potential to treat other IgG alloantibody-mediated perinatal diseases (eg, FNAIT). The open-label FREESIA-3 study aims to evaluate the efficacy and safety of nipocalimab with a contemporaneous reference arm of IVIG with/without prednisone in pregnancies at risk for FNAIT (ClinicalTrials.gov identifier: NCT06533098).

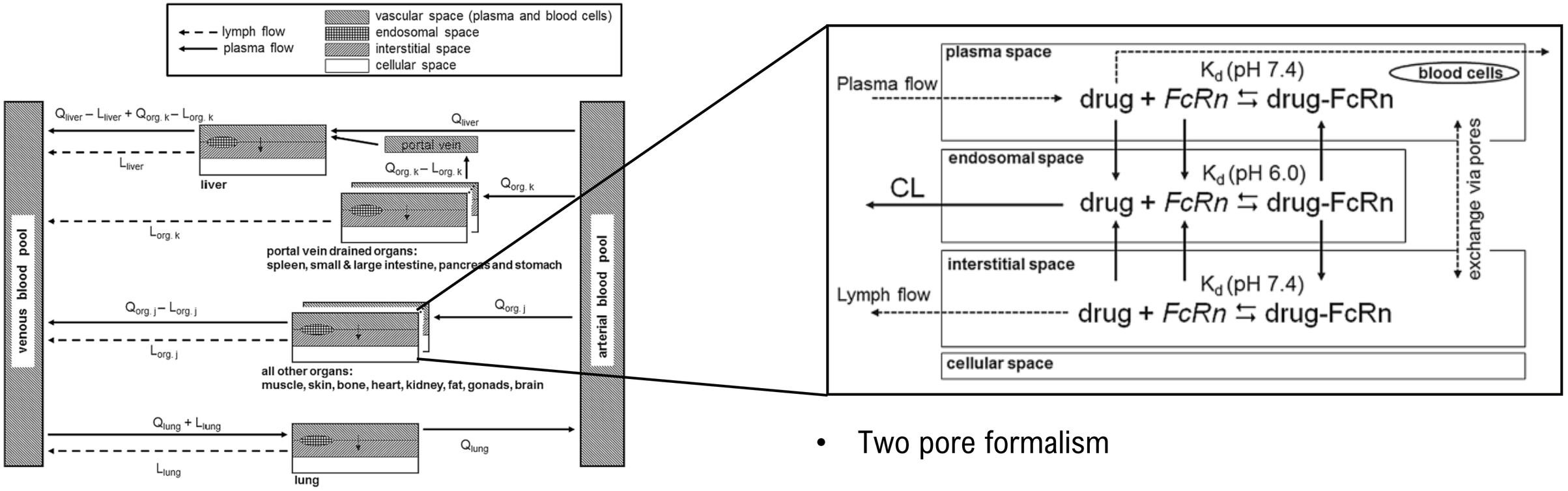
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TOPIC 03

Placental transfer
PBPK model build

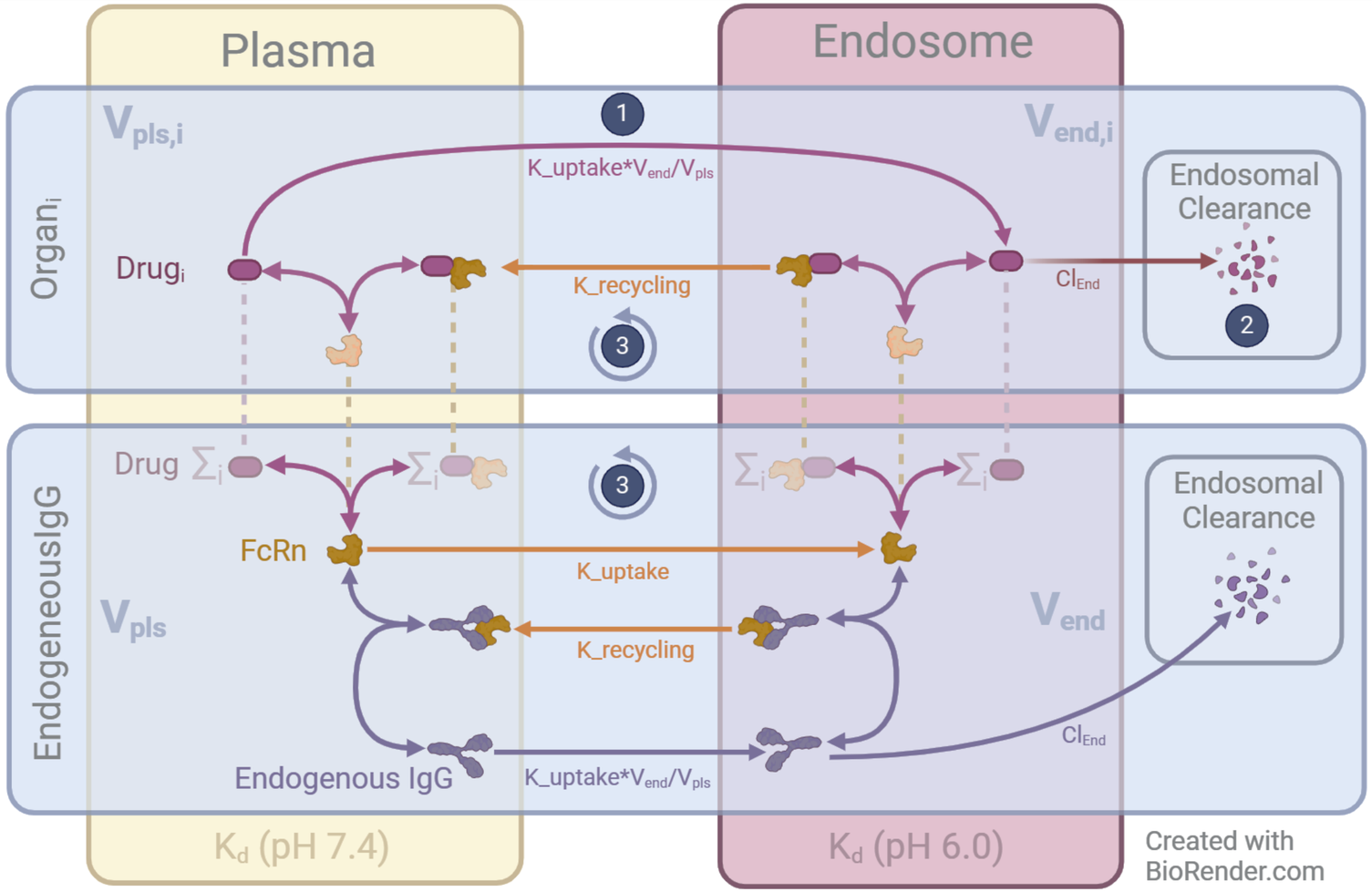
Starting point: PBPK model previously developed for large molecules



- Two pore formalism
- FcRn-mediated recycling
- Lymph flow

Niederalt, Christoph, et al. "A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim." *Journal of pharmacokinetics and pharmacodynamics* 45 (2018): 235-257.

Expanding the model to FcRn inhibitors



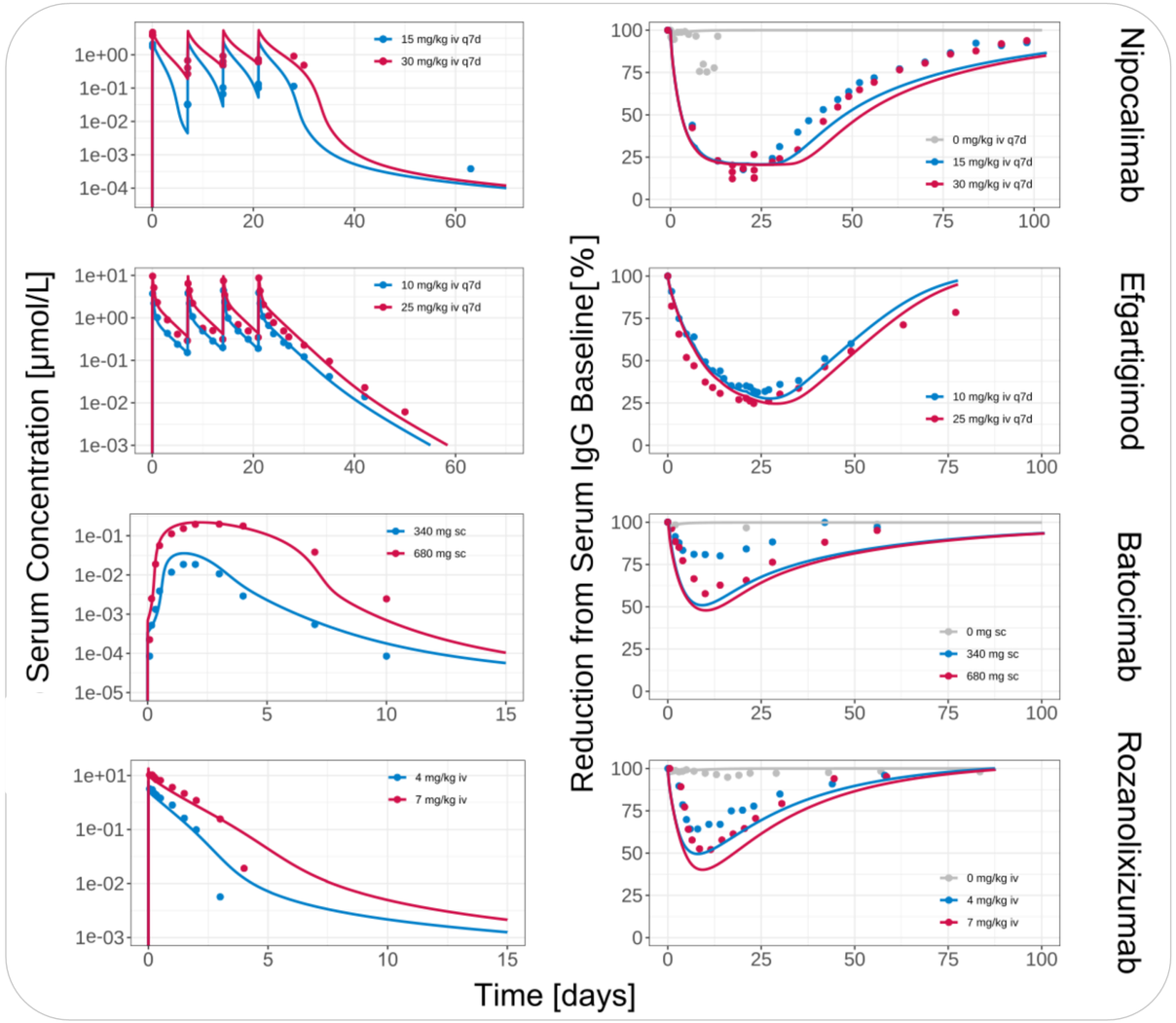
Mechanisms

1. Drug uptake by endosome
2. Endosomal degradation
3. FcRn mediated drug conservation

Legend

- Endogenous IgG
- $FcRn_{EndogeniousIgG}$ (Variable & Value)
- $FcRn_{EndogeniousIgG}$ (Value)
- Drug (Organ)
- $\sum_i$ Drug (Organism Sum)
- FcRn-Drug Complex (Organ)
- $\sum_i$ FcRn-Drug Complex (Organism Sum)
- Catabolite

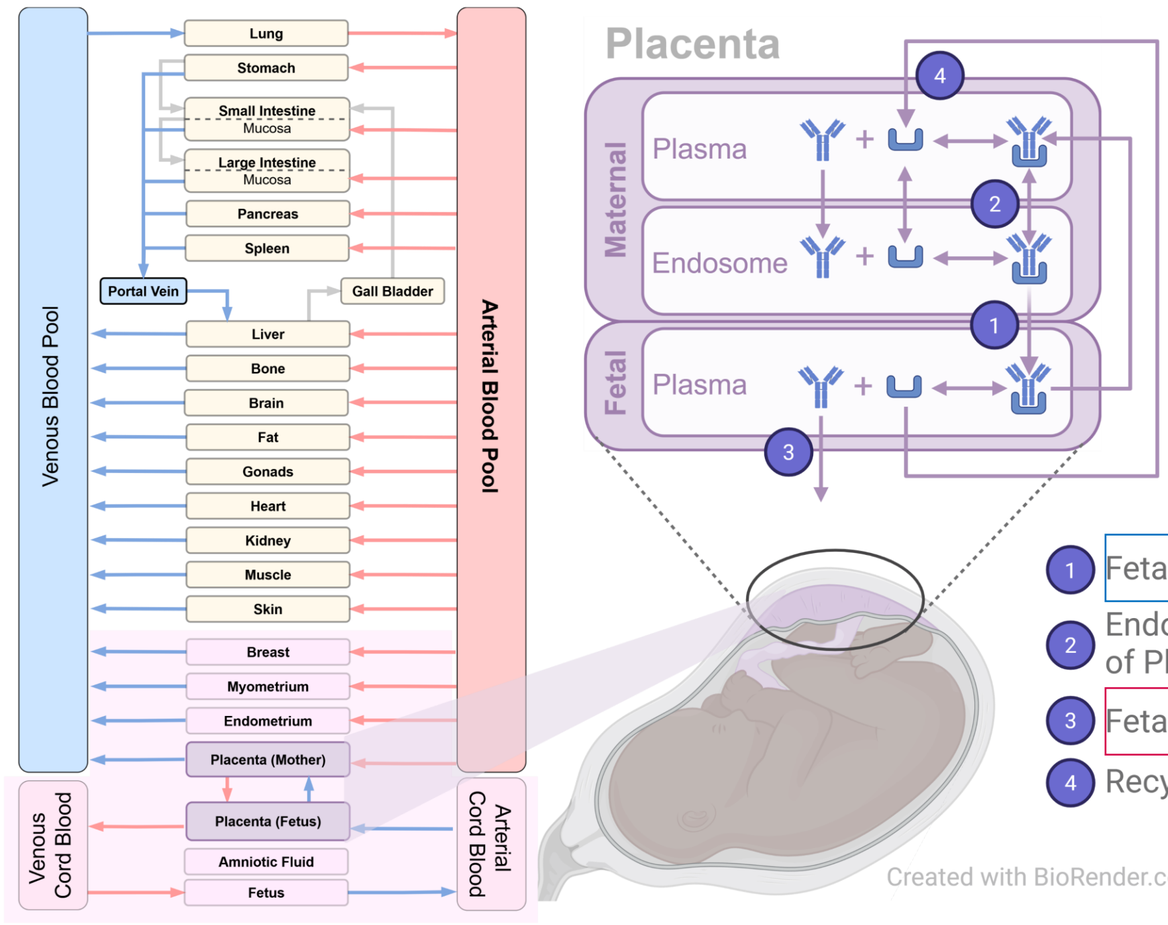
Healthy normal volunteers' model for FcRn inhibitors validated with FIH studies



- Data published – all publicly available[1-4]
- Nipocalimab data from the FIH study were used

1. Ling, Leona E, et al. “M281, an Anti-FcRn Antibody: Pharmacodynamics, Pharmacokinetics, and Safety Across the Full Range of IgG Reduction in a First-in-Human Study.” Clinical pharmacology and therapeutics vol. 105,4 (2019): 1031-1039.
2. Ulrichts, Peter, et al. “Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans”. The Journal of clinical investigation, 128(10), 4372–4386.
3. Yap, Desmond Y H, et al. “Safety, tolerability, pharmacokinetics, and pharmacodynamics of HBM9161, a novel FcRn inhibitor, in a phase I study for healthy Chinese volunteers.” Clinical and translational science vol. 14,5 (2021): 1769-1779.
4. Kiessling, Peter et al. “The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study.” Science translational medicine vol. 9,414 (2017): eaan1208.

Pregnancy PBPK model structure for FcRn-mediated placental transfer



mAb/IgG

FcRn

Complex

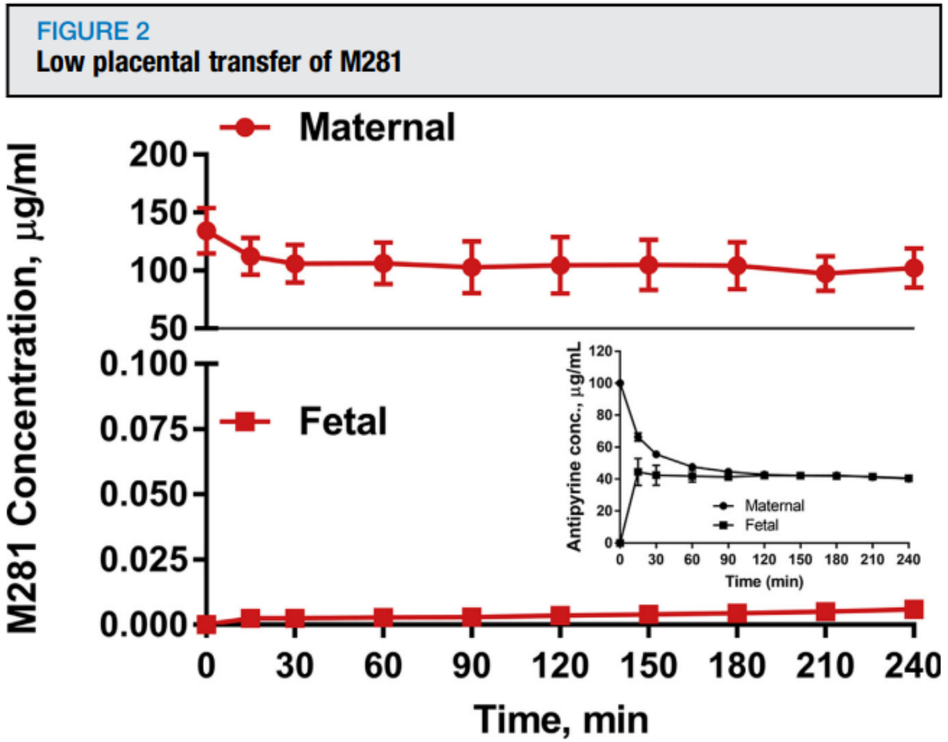
1. Fetal Uptake of IgG/mAb:FcRn
2. Endosomal Uptake & Recycling of Placental Endosomes
3. Fetal Clearance of IgG/mAb
4. Recycling of FcRn

Scales with placental surface

Replaced with endosomal clearance as in adult model

Created with BioRender.com

Ex-vivo placenta perfusion experiments helped inform FcRn placental transport



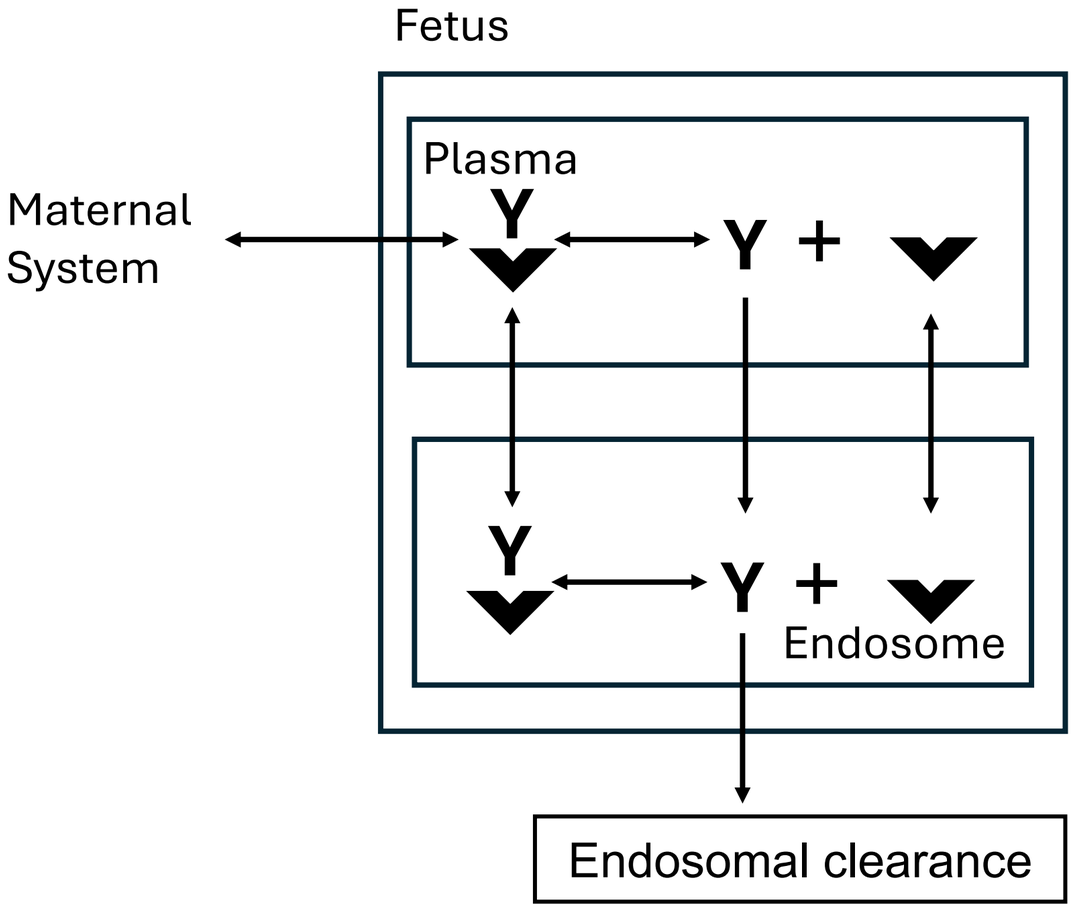
- Roy, Sucharita, et al. (2019) showed minimal transfer of M281/nipo using the dually perfused human placental lobule model
- Placental transfer in the PBPK model optimized first without fetal clearance, **ensuring minimal transfer** as observed
- Process that controls nipo concentration on the fetal side in the model:

dN/dt = kass_FcRn * drug * FcRn - Kd_FcRn_drug * kass_FcRn * drug_FcRn

- Via model optimization association rate constant (k_{ass}) was adjusted to the right ballpark based on UNITY data

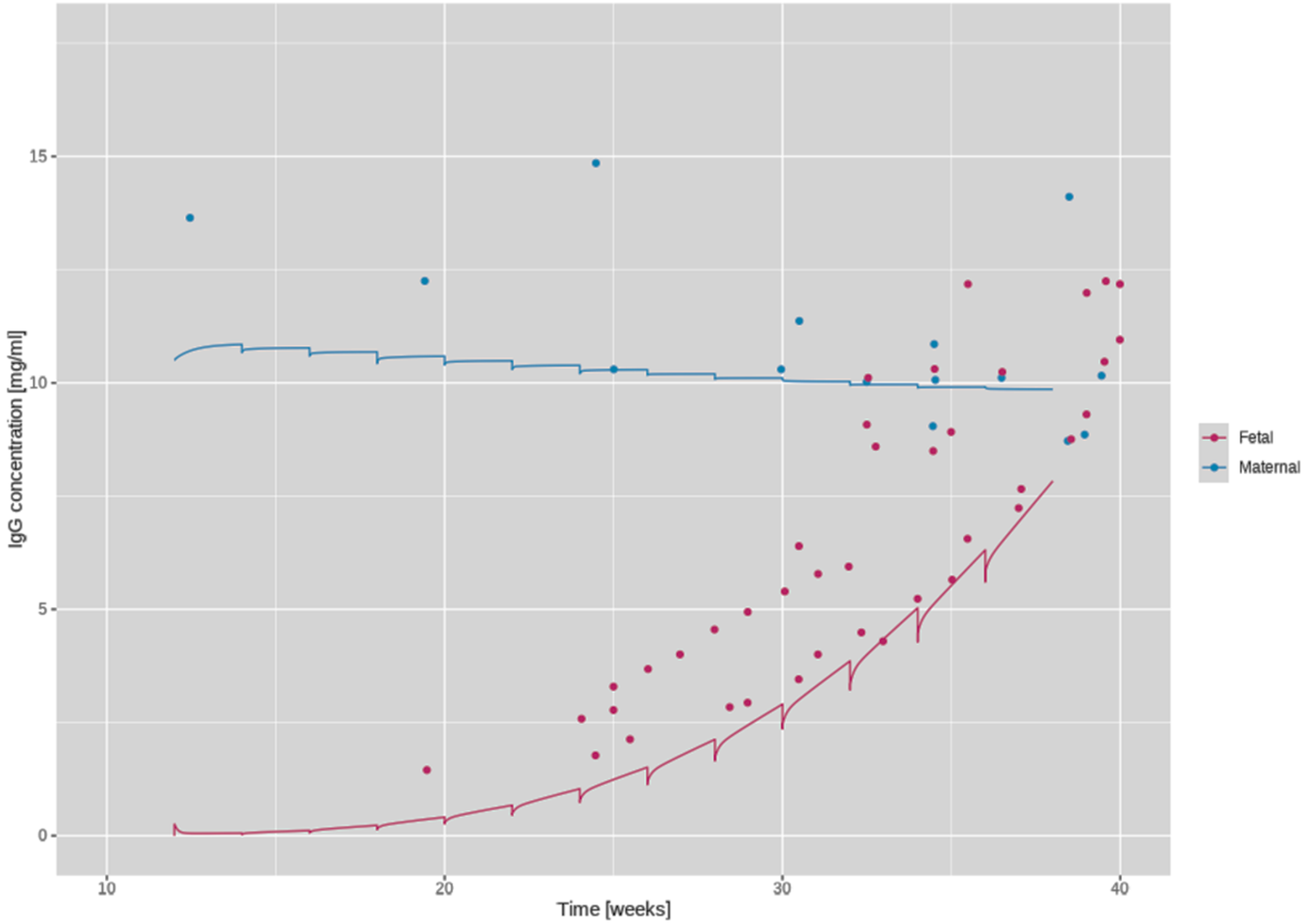
Roy, Sucharita, et al. "M281, an anti-FcRn antibody, inhibits IgG transfer in a human ex vivo placental perfusion model." *American journal of obstetrics and gynecology* 220.5 (2019): 498-e1

Implementation of fetal endosomal clearance



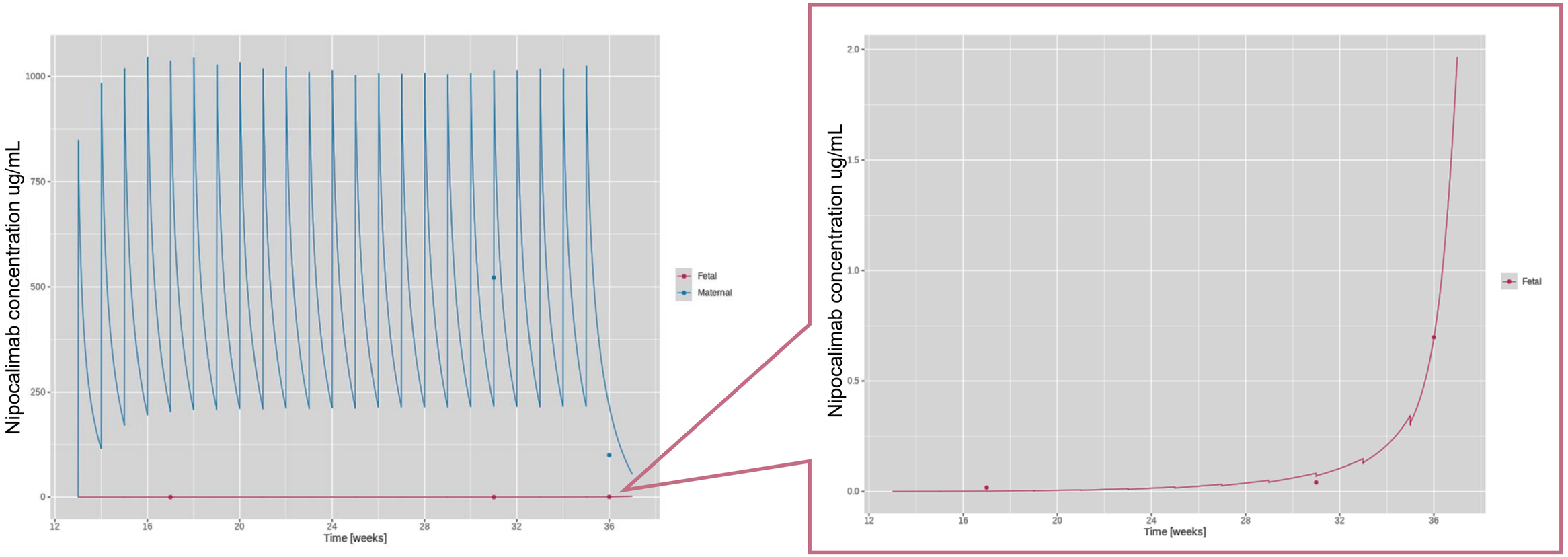
- For IgG and nipocalimab that are full monoclonal antibodies, endosomal clearance is the only clearance pathway
- This process accounts for the non-linear pharmacokinetics observed for nipocalimab due to target mediated drug distribution (TMDD)

The current model adequately described the natural course of IgG placental transfer during pregnancy



Data digitized from Gill and Jones 2022

Combining fetal endosomal clearance with recalibration of k_{ass} led to improved fittings for nipocalimab based on UNITY data



Dose simulated: 45 mg/kg QW

Solid lines represent the model predicted concentrations, the bullets represent the observed concentrations from UNITY

Blue represents maternal and red represents fetal concentrations

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TOPIC 04

Key takeaways

Key Takeaways

1

The HNV PBPK model describes the IgG reduction and nipocalimab concentrations based on observed FIH data well

2

The pregnancy model including placental transfer describes well:

- The natural course of IgG placental transfer during pregnancy
- The UNITY data collected for nipocalimab concentrations both in maternal volunteers and in cord blood

3

The pregnancy model including placental transfer predicts that nipocalimab's fetal exposure is limited

Acknowledgements

JnJ

Jocelyn Leu

Eleni Caratzas

Yaowei Zhu

Edwin Lam (early stages of the model, now at Biogen)

EQSLabs

Sophie Fischer-Holzhausen

Wilbert de Witte

Stephan Schaller

THANK YOU



Photo: Grote Markt, Antwerp, Belgium

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Global Head Pharmacometrics

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