Effects of the FcRn developmental pharmacology on the pharmacokinetics of therapeutic monoclonal IgG antibody in pediatric subjects using minimal physiologically-based pharmacokinetic modelling

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ABSTRACT
The aim of this study was to investigate neonatal Fc receptor (FcRn) concentration developmental pharmacology in adult and pediatric subjects using minimal physiologically-based pharmacokinetic (mPBPK) modelling. Three types of pharmacokinetic (PK) data for three agents (endogenous/exogenous native IgG, bevacizumab and palivizumab) were used. The adult group contained six subjects with weights from 50 to 100 kg. For pediatric subjects, seven age groups were assumed, with five subjects each having the weight of 95%, 75%, 50%, 25% and 5% percentile of the population. A first evidence-based rating system to evaluate the quality of the source data used to derive pediatric-specific mPBPK parameter model was proposed. A stepwise approach was used to examine the best combination of age/weight effect on the parameters of the mPBPK model in adult and pediatric subjects. IgG synthesis rate ($K_{syn}$), extravasation rate (ER) and FcRn were fitted simultaneously to the PK of bevacizumab and native-IgG in both adult and pediatric. All fitting showed good fits based on the graphs and the coefficient of variation of the fitted parameters (< 50%). Estimated weight-normalized $K_{syn}$ increased while weight-normalized FcRn and ER decreased with increasing age. The age and weight effect on FcRn were at least 11 TMAs approved for use in the pediatric population. Implementation of the mPBPK model enables us to analyze the relationships of age, weight, FcRn, ER and $K_{syn}$ in both adult and pediatric subject. This information may benefit the understanding of complex interaction between the FcRn developmental pharmacology and PK parameters, and improve the prediction of the antibody disposition in pediatric subjects.

Introduction
Therapeutic monoclonal IgG antibodies (TMAbs) dominate the biopharmaceutical market. TMAbs comprise more than half of total sales of all biopharmaceutical products, with market sales of USD $85.4 billion in 2015. It is anticipated about 70 TMAbs products will be on the market, with combined global sales reaching nearly USD $125 billion in 2020. Application of TMAbs in the pediatric population has substantially increased over the years. Currently, there are at least 11 TMAbs approved for use in the pediatric population. The neonatal Fc receptor (FcRn) is a MHC class I-like heterodimer protein complex that is widely expressed in endothelial cells and organs such as muscle, kidney and placenta. FcRn plays an important role in IgG homeostasis by mediating a pH-dependent endocytic salvage pathway that prevents IgG degradation, and thus contributes to the prolonged circulating half-life of IgG relative to other plasma proteins. The pharmacokinetics (PK) of IgG antibodies is affected by modulating the FcRn binding affinity at acidic and physiological pH. Correlations between the FcRn binding affinity of IgG and their clearance and terminal half-life have been reported in preclinical and clinical studies. Recently, a population analysis was conducted for palivizumab in healthy adults, preterm infants, and children <24 months of age. Body weight and age-dependent maturation were shown to be important patient-specific factors that best described the clearance of palivizumab $Cl_{pali}$ in pediatric subjects. In addition, age-related changes of endogenous IgG level have been reported in human subjects, possibly due to development maturation of IgG metabolism or synthesis. These observations suggest that age and weight-related changes in the IgG metabolism, possibly due to FcRn developmental maturation and extravasation rate, may play a role in affecting the PK of TMAbs. There is very limited information about FcRn developmental pharmacology and its effects on the PK of TMAbs in preclinical and clinical models. It has been shown that the weight normalized FcRn mRNA expression levels in the rat intestine are at maximum between 1–19 days and decrease afterward. However, the effects of this age-dependent FcRn expression on the PK of TMAbs is unknown. While age-dependent CYP-450-mediated metabolism for small molecules is well documented, development maturity of the FcRn expression and its effects on the IgG catabolism in pediatric subjects is largely unknown and has never been reported.
Several mechanism-based models have been proposed to describe the effects of FcRn-IgG interaction on the PK of TMAbs in animals and humans. Recently, full physiologically-based pharmacokinetic (PBPK) models have been increasingly used to explain the PK of TMAbs in preclinical and clinical models. It is well recognized that the full PBPK models can describe the disposition of IgG using physiological characteristics. However, the highly complicated structures of the full PBPK model, combined with very limited tissue FcRn expression and PK data used for model calibration, hinders validation of the models and justification of many assumptions used to describe the physiological processes governing the PK of IgG in human subjects. To overcome these limitations, several minimal PBPK (mPBPK) models have been proposed to provide a practical approach to estimate physiologically relevant PK parameters of IgG, especially when only plasma kinetics data is available. mPBPK modelling has been shown to have relatively similar performance compared to full PBPK modelling in predicting PK parameters, such as area under the curve (AUC) of antibodies in plasma. However, none of the full or minimal PBPK models described in the literature have been used to investigate the PK of TMAbs in pediatric subjects. Bevacizumab and palivizumab, which target vascular endothelial growth factor (VEGF) and respiratory syncytial virus, respectively, are two of the most extensively studied TMAbs in pediatric subjects. The published population PK model of these two TMAbs with detailed quantitative weight and age relationships on the important PK parameters, were derived from a large sample (> 200 subjects) with wide ranges of age and weight. In addition, the observed linear PKs of bevacizumab and palivizumab, which is due to lack of potential target-mediated drug disposition, allowed us to study the unique relationships of weight- and age-specific FcRn concentrations and inherent PK parameters of the TMAbs without interference from other potential confounding factors. Therefore, in this study, we used PK data from bevacizumab and palivizumab to develop and validate a mPBPK model describing the PK of TMAbs in pediatric subjects. Our mPBPK model was used to investigate the FcRn developmental pharmacology and its effects on the disposition of TMAbs in human subjects.

**Results**

The parameters of the mPBPK model were divided into four Levels of Evidence (LOE) based on the methodological quality of the parameters collection (Table 1, Method in Supp. File). Parameters of the allometric function of LOE I and II for mPBPK model parameters were successfully estimated from the data in the literature listed in Table A and B Supp. File. The fitting showed good fits based on the visualization of the graphs (Fig. A Supp. File) and the coefficient of variations (CVs) of the estimated parameters (CV< 50%, Table 2). These allometric scaling parameters (LOE I and II) together with the parameters in LOE III and IV (Table 2) were then used for the PK study with the mPBPK model in pediatric subjects.

The two-pore mPBPK model previously developed by our group was used as the basic framework for model development (Figure 1). In general, the workflow of model development is shown in Figure 2. The final mPBPK model was able to describe the concentration-time profiles of the endogenous/exogenous native IgG and bevacizumab in both adult and pediatric subjects (e.g., Figure 3). All CV of the estimated parameters were < 50%. The model performances passed all validation criteria in the reference subject. The calculated elimination half-life from both native IgG and bevacizumab in a 77 kg adult was 23 and 18 days, respectively, which is consistent with the reported values of these antibodies. The ratio of TMAbs concentration in tissue and plasma system was 0.057 (0.058 in Ref 23). The concentration of endogenous IgG in the intersitial space was 18% of that in plasma, which is consistent with the reported values from the experimental data (≥ 17% in Refs 24,47,48).

The ability of the developed mPBPK model to predict the PK of the other TMAbs in pediatric subjects was examined using the palivizumab PK in adult/pediatric subjects as the external validation dataset. As shown in Fig. B (Supp. File), the final mPBPK model was able to describe the PK of palivizumab in adult/pediatric subjects with median body weight and age of 2, 6, 10 and 20 (adult) yr.

The estimated FcRn concentration decreased with increasing weight in all age groups (Figure 4A). There was a clear age-related weight effect on the FcRn concentrations. Increasing the weight by 3.5 kg in adults was associated with about 2% decrease of the FcRn. In pediatric subjects, increasing the weight by 3.5 kg was associated with 12% and 5% of the FcRn in the 1 and 10 yr age groups, respectively. Figure 4b showed the age-effect on the FcRn concentrations where the FcRn concentration per kg (FcRnexpression) was inversely proportional to the age. This figure was drawn for the weight of 50% percentile

| Level of evidence (LOE) | Source Data | Scaling Method to Derive the mPBPK Model Parameters in Pediatric Subject from Source Data | Parameters |
|-------------------------|-------------|---------------------------------------------------------------------------------|-------------|
| I                       | Data from both adult and pediatric human subjects | Allometric function | Vascular volume $V_p$, interstitial volume $V_i$, Blood flow $Q_p$ and Plasma volume $V_p$. |
| II                      | Data in adult human and animal subjects | Allometric function | Lymph volume $V_l$ and Endothelial volume $V_e$. |
| III                     | Data in adult human subjects or animal species used in the published PBPK model | A. Allometric function | Lymph flow $L$, Permeability surface area of IgG to the large/small pores $PS_{SS}$, Fluid recirculation rate $J_{SR}$. |
|                         |                         | B. No allometric scaling function is used. Assumed that parameters are body size-independent | Osmotic reflection coefficient of IgG to large/small pores $D_{L/S}$, Fraction of hydraulic conductivity for large/small pores $a_{L/S}$. |
| IV                      | Data in adult human subjects or animal species | No established approach is published in the PBPK literature. The model parameters in adult subject or animal species are assumed to be the same with pediatric subject. | Fraction of recycling IgG FR, Affinity profiles (KD & $k_{on}$), Lysosomal average time of ingested protein $\tau_a$ and Endothelial clearance $CL$. |

IgG endothelial recycle rate $K_{rec}$ and IgG endothelial uptake rate $K_{uptake}$. |
Table 2. List of the parameters used in the mPBPK model.

| LOE | Parameters | Value/Function for 77 kg adult human (a.) | Allometric function/ Value | Source/CV | Source/CV of the allometric exponent (h) |
|-----|------------|------------------------------------------|---------------------------|-----------|------------------------------------------|
| Ia  | Vascular volume Vv (l) | 1.52 | \( V_v = a_v \times (\frac{BW}{77})^{0.97} \) | % | %CV = 1.45 |
|     | Interstitial volume Vl (l) | 11.73 | \( V_l = a_l \times (\frac{BW}{77})^{0.80} \) | % | %CV = 2.47 |
|     | Blood Flow Q (l/h) | 250 | \( Q = a_Q \times (\frac{BW}{77})^{0.74} \) | % | %CV = 0.54 |
|     | Plasma Volume Vp (l) | 3.15 | \( V_p = a_p \times (\frac{BW}{77})^{0.97} \) | % | %CV = 4.50 |
| Ib  | Lymph volume VL (l) | 0.27 | \( V_l = a_l \times (\frac{BW}{77})^{0.94} \) | % | %CV = 0.76 |
|     | Endothelial volume Ve (l) | 0.38 | \( V_e = a_e \times (\frac{BW}{77})^{1.00} \) | % | %CV = 12.90 |
| IIIA | Lymph Flow L (l) | 0.12 | \( L = a_l \times (\frac{BW}{77})^{1} \) | 22 | 22,23,29,30 |
|     | Permeability surface area of IgG to the large pore PS_L (l/h) | 9.58 \times 10^{-6} | \( P_{S_L} = a_{PS} \times (\frac{BW}{77})^{0.75} \) | 22 | 22,29,30 |
|     | Permeability surface area of IgG to the small pore PS_S (l/h) | 2.81 \times 10^{-5} | \( P_{S_S} = a_{PS} \times (\frac{BW}{77})^{0.75} \) | 22 | 22,29,30 |
|     | Fluid recirculation rate Jiso (l/h) | 0.03 | \( J_{iso} = a_{Jiso} \times (\frac{BW}{77})^{1} \) | 32 | 22,29,30 |
| IIIB | Osmotic reflection coefficient of IgG to the large pore \( \sigma_L \) (unitless) | 0.715 | No scaling | 22 | 21-23 |
|     | Osmotic reflection coefficient of IgG to the small pore \( \sigma_S \) (unitless) | 0.74 | No scaling | 22,23 | 22 |
|     | Fraction of hydraulic conductivity for large pore \( \alpha_L \) (unitless) | 0.042 | No scaling | 21 | 21-22 |
|     | Fraction of hydraulic conductivity for small pore \( \alpha_S \) (unitless) | 0.19 | No scaling | 20 | 21-23 |
|     | Fraction of recycling IgG to vascular space FR (unitless) | 0.75 | No scaling | 34 | - |

- The allometric parameters were estimated from the data listed in Table A Supp. File.
- The allometric parameters were estimated from the data listed in Table B Supp. File.
- The sensitivity analysis in our preliminary study showed that this parameter slightly affect the simulated plasma kinetic (AUC difference < 5%). Thus, the same value of \( k_{off} \) was used for native IgG, bevacizumab and palivizumab.
- Endothelial clearance represents the intrinsic catabolic clearance rate of the antibodies by lysosome in endothelial cells.

compared to the adult subjects (Figure 5a). The values of the MK were 2.57, 2.35, 2.21, 2.11, 1.89, 1.56 and 1.03 for human subjects with median body weight at each corresponding age group of 1, 2, 3, 4, 6, 10 and 20 (adult) years, respectively. IgG synthesis rate \( K_{syn} \) increased with weight in each age group (Fig. C Supp. File). The weight-normalized IgG synthesis rate decreased with increasing weight across different age groups (Figure 5b) in the pediatric subjects and remained relatively constant in the adult subjects.

**Discussion**

The use of TMAbs in the pediatric population has substantially increased over the years. Classical compartment model
and allometric scaling are usually used for PK analysis of TMAbs in pediatric subjects. However, this method may lead to an inaccurate prediction of the clearance up to two-fold of the observed value.\textsuperscript{49,50} The allometry scaling approach has been shown to over-predict the clearance at ages where the mechanism of clearance is immature, and integration of the maturation factor for important PK parameters has been proposed to overcome the limitation of conventional allometric function.\textsuperscript{51} However, age-related maturation factors for the PK parameters of TMAbs have never been quantified or reported in the published literature.

Compared to the classical compartment model, the PBPK model is more beneficial because it takes into account both system and drug-dependent parameter. By knowing these parameters, a PBPK model may be used to predict the PK of the drug outside the range of the available data,\textsuperscript{49,52} which may improve the prediction of drug behavior and optimize the outcome of the therapy. In addition, this modelling approach may offer the opportunity to incorporate multiple levels of information to estimate age-specific pharmacokinetic and integrate the maturation effect in the PK analyses of many drugs.\textsuperscript{49,53} Due to the complexity of the full PBPK model, a simpler model such as mPBPK model can be used as an alternative approach with only plasma PK data, as in the case with most of the clinical studies.\textsuperscript{25,32} Unlike small molecules,\textsuperscript{49} information about the implementation of PBPK and mPBPK models for TMAbs in pediatric subjects, and the effects of the developmental pharmacology of FcRn receptor on the TMAbs disposition is very limited. In this study, we successfully developed the first mPBPK model describing the PK of TMAbs in pediatric subjects and quantified the developmental pharmacology of FcRn and its relationships with the disposition of TMAbs in human subjects.

First, the mPBPK model (Figure 1) was calibrated with the PK data of endogenous native IgG and exogenous native IgG in a reference subject (77 kg adult) using the published parameters in the literature (Table 2) and our previous study.\textsuperscript{32} Then, the model was extended to explain the PK of bevacizumab in the reference subject with the assumption that the difference in FcRn binding affinity at acidic pH was the only factor contributed to the different PK of native IgG and bevacizumab. However, this mPBPK model was unable to explain the different PK of native IgG and bevacizumab. It is well known that many factors other than FcRn binding affinities such as surface charge, glycosylation, and aggregation can affect the PK of the TMAbs.\textsuperscript{54,55} Therefore, two modulator factors, F1 for osmotic reflection coefficient that affected the IgG distribution and F2 for endocytosis (uptake rate $K_{up}$ and recycle rate $K_{rc}$) that affected the IgG catabolism, were added to account for the different PK between native IgG and bevacizumab in the reference adult subject, as suggested in the literature.\textsuperscript{32}

The calculated osmotic reflection coefficient $\sigma$ from the estimated modulation factor F1 of bevacizumab was higher than the native IgG ($\sigma_L \text{ IgG} = 0.10$ vs $\sigma_L \text{ Beva} = 0.13$ and $\sigma_S \text{ IgG} = 0.74$ vs $\sigma_S \text{ Beva} = 0.99$), while the endocytosis rate ($K_{up}$...
and $K_{rc}$ of bevacizumab based on the estimated F2 was lower than the native IgG ($K_{up}/K_{rc\text{Beva}} = 0.2 \times K_{up}/K_{rc\text{IgG}}$). These findings were very similar to the results from our previous study for palivizumab and motavizumab-YTE in adult subjects. The simulations of the mPBPK model in 77 kg adult subjects have passed all validation criteria outlined in this study. The half-life observed from the simulated PK of native IgG and bevacizumab was 23 and 18 days, respectively, which is consistent with the reported values of these antibodies (21 d for native IgG and 20 d for bevacizumab). The ratio of bevacizumab concentration in tissue and plasma system was 0.057, which compared favorably to the reported value for the antibodies, i.e., 0.058. Concentration of endogenous IgG in the interstitial space was 18% of that in the plasma, consistent with the reported values from the experimental data, i.e., > 17%.

The model in the reference adult subject was then extended to explain the PK of native IgG and bevacizumab in the pediatric subjects. Prediction of TMAbs PK in children based on drug physiochemistry, in vitro or preclinical data, will yield outcomes that have lower confidence than if model development incorporates adult clinical data with age/weight-specific physiological parameters. However, many age/weight-specific physiological parameters needed to develop the mPBPK model of TMAbs in pediatric subjects are not available, and therefore have to be estimated from diverse sources, including adult, preclinical species and in vitro data. In this study, we proposed a first evidence-based rating system for PBPK model development to evaluate the quality of the source data used to derive mPBPK parameters from human adult to pediatric subjects (Table 1). This evidence-based rating system provided a transparent platform and mechanism to allow us to examine and refine the mPBPK model parameters in the presence of the mPBPK model deficiency for PK prediction. The LOE I and II data were derived from weight–related allometric scaling of the high-quality human and animal experimental data, and therefore represented the most reliable parameters for mPBPK model development. In contrast, LOE III data for pediatric mPBPK model development were derived from either human or animal data with or without weight-related allometric function based on previously published PBPK studies. The assumptions used to derive LOE IV data were the least reliable because no established scaling approach was published in the previous PBPK studies and the parameters in the pediatric subject were assumed to be the same as adult subjects or animal species.

Our initial approach, which combined the developed mPBPK model in adult subjects with the weight-related

Figure 3. Example curves of plasma PK of endo/exo native IgG from mPBPK model in (a) reference adult and endo/bevacizumab in both (b) reference adult and pediatric with (c) age 1 y weight 9.6 kg, (d) age 3 y weight 14 kg, (e) age 6 y weight 20.5 kg and (f) age 10 y weight 32 kg.
scaling parameters from LOE I to IV, failed to explain the PK of the native IgG and bevacizumab in the adult and pediatric subjects with different age and weight (e.g., 8 kg 1 y pediatric and 100 kg adult) (data not shown). One possible reason was that the assumptions used to derive the LOE I to IV weight-related scaling parameters in the mPBPK model development were incomplete or incorrect. Among all the weight-related scaling parameters used to construct the mPBPK model, parameters from the LOE III and IV categories were derived from limited experimental data and/or unestablished scaling approaches, and therefore might have been the source of the model misspecification. Therefore, these LOE III-IV parameters were further examined and modified in order to improve the ability of the mPBPK model to explain different PK of native IgG and bevacizumab in adult/pediatric subjects.

Based on the sensitivity analysis, six LOE III and IV parameters were found to affect the PK of native IgG and bevacizumab in adult/pediatric subjects: FcRn concentration, two-pore extravasation rate $K_{TP}$, endosomal clearance $CL$, endocytosis rate $K_{up}/K_{rec}$, lymph flow $L$ and fraction of recycled IgG to vascular space $FR$ (data not shown). A step-wise approach was used to develop and test the mPBPK models with different combinations by adding additional modulating factors or using different weight-related allometric scaling exponents to these four parameters. There was no information on how to scale the FcRn concentration based on the weight. Therefore, four different FcRn sub-models with different allometric scaling exponents of 0 (no weight effect), 0.5, 0.75, and 1.00 were developed and examined. In addition, FcRn sub-model with the FcRn concentration fitted directly to the PK data to adult/pediatric subject without allometric scaling function was constructed and tested. A total of 46 different models was investigated in this STEP 3 model development with the PK data of bevacizumab and...
endogenous native IgG from the adult subjects with the referenced weight of 77 kg and largest weight of 100 kg, and pediatric subjects with the smallest weight of 8 kg. The model with additional age/modulating factor of the extravasation rate (MK) was found to have the lowest the akaike information criterion-corrected (AICc; data not shown) during the first stepwise selection process. Thus, a combination of MK and other modulation factor were examined and were tested in subsequent stepwise model selection processes (Table C Supp. File). Based on the AICc model selection criteria, the model with the age/modulating factor on K_{TP} (MK) and FcRn concentration (Model 9 in Table C. Supp. File) was selected as the final model. This calibrated model was then used to develop the final mPBPK model using the PK data of endogenous native IgG and bevacizumab of all subjects with various age/weight combinations. The final mPBPK model was able to describe the PK data of endogenous native IgG and bevacizumab in both adult and pediatric subjects (e.g., Figure 3).

In this study, the value of FcRn concentration from Ferl et al (Table 2), e.g., 40 µmol/l, was assumed for 77 kg adult subject. This value is in the range of the reported value by Shah et al (33 µmol/l) and Garg et al (48.9 µmol/l). The FcRn concentration has been suggested to be negatively correlated with body weight in adult subjects. However, up to now, no information about the weight- and age-related FcRn expression levels in human subjects has been available. Here, we used the PK data of bevacizumab from Han et al to develop the mPBPK model in order to explore the age and weight effect on the FcRn concentrations and the PK of IgG antibody in human subjects. To the best of our knowledge, Han and co-workers conducted one of the most comprehensive population PK study of bevacizumab to describe the disposition of TMAbs in 232 healthy adult and pediatric subjects from 0.5 y to 21 y. Furthermore, VEGF is a soluble protein and the very low expression levels of serum VEGF in human subjects resulting in insignificant serum VEGF amounts compared to bevacizumab. Therefore, target-mediated drug disposition was not expected to contribute significantly to the overall clearance of bevacizumab as a result of the observed linear PK of bevacizumab due to lack of target-mediated drug disposition allowed us to identify the unique relationships of weight- and age-specific FcRn concentration and inherent PK parameters of bevacizumab, such as clearance in human subjects.

The FcRn concentrations were negatively correlated with body weight across different age groups (Figure 4a and c), consistent with findings from our previous study using PK of pertuzumab in adult subjects. However, the weight difference alone was not sufficient to explain different FcRn concentrations between adults and pediatric subjects. Weight-normalized FcRn concentration for the subject with median weight (FcRn_{expression}) decreased with age (Figure 4b). This result is in agreement with the finding from a rat FcRn mRNA expression study, which showed that the weight-normalized duodenal FcRn mRNA expression level was at maximum between 1–19 days of age and decreased afterward. The clearance of bevacizumab was inversely related to the FcRn concentration in adult/pediatric subjects (Figure 6). This observation made logical and physiological sense because higher FcRn concentration was able to prevent more IgG antibody from endosomal degradation, and thus decrease the IgG catabolism. For pediatric subjects with lower body weight, the age-related weight-normalized FcRn expression had to be higher than the adult subjects in order to achieve higher FcRn concentration for lower clearance of TMAbs (Figure 6). To our best knowledge, this is the first study to suggest the complex relationships between the FcRn concentration and age/weight in human subjects. Further study is needed in order to confirm this hypothesis.

In contrast to small molecules, distribution of IgG from serum to the interstitial space is slow and mainly occurs via extravasation (K_{TP}) through vascular pores. It has been shown that, in PBPK models, the extravasation rate through vascular pores is one of the important parameters affecting the disposition of IgG antibody. Furthermore, VEGF is a soluble protein and the very low expression levels of serum VEGF in human subjects resulting in insignificant serum VEGF amounts compared to bevacizumab. Therefore, target-mediated drug disposition was not expected to contribute significantly to the overall clearance of bevacizumab as a result of the observed linear PK of bevacizumab due to lack of target-mediated drug disposition allowed us to identify the unique relationships of weight- and age-specific FcRn concentration and inherent PK parameters of bevacizumab, such as clearance in human subjects.
Supp. File). As a result, endocytosis rate ($K_{up}/K_{rec}$) and extravasation rate $K_{TP}$ were found to significantly affect the estimated FcRn expression value (Fig D Supp. File). However, the relationships between FcRn expression and age remains unchanged, i.e., FcRn expression decreases as age increases (Fig D Supp. File). These results suggested that the $K_{TP}$ and $K_{up}/K_{rec}$ affect the estimation of the FcRn expression, but not the relationships between FcRn expression and age. Our final model consisted of age-dependent $K_{TP}$, and constant $K_{up}/K_{rec}$ was selected from many tested models based on the AIC and goodness of fit test because no published experimental data about the $K_{TP}$ and $K_{up}/K_{rec}$ of TMAbs in human subjects of different ages was available. Therefore, further study is needed to confirm the finding in this study with experimentally measured endocytosis rate ($K_{up}/K_{rec}$) and extravasation rate $K_{TP}$ in human subjects.

Our results in the final model showed that the $K_{up}$ increased as weight increased (Fig. C Supp. File). However, weight-normalized $K_{up}$ decreased with increasing weight for each age group in pediatric subjects (Figure 5b). In summary, our study proposed that lower endogenous IgG levels observed in pediatric subjects with younger age compared to adult subjects may be due to the combination of both lower clearance and synthesis rate of the endogenous IgG.

Similar to the bevacizumab pediatric PK study by Han and co-worker, palivizumab population PK study conducted by Robbie et al in 1883 adult/pediatric subjects from 22 clinical studies, represented one of the most comprehensive PK study of TMAbs for pediatric subjects. Therefore, the generalizability of our developed mPBPK model in describing the PK of TMAbs in human subjects was assessed using the external experimental data of the adult subjects, but sparse data of TMAbs, including basiliximab, daclizumab, and pagibaximab, were observed in pediatric subjects with younger age compared to adult subjects for which the model under-predicted the observed PK data (Fig. B Supp. File).

The palivizumab population PK model was derived from the extensive data of the adult subjects, but sparse data of preterm infants (age < 1 y). Therefore, it was difficult to characterize the PK, especially the distribution phase of the palivizumab in younger pediatric subjects. Hence, the palivizumab population PK model could produce biased PK predictions for younger pediatric subjects, which explains the under-prediction of our model to the simulated palivizumab PK in 2 yr old pediatric subjects. The PK of several other TMAbs, including basiliximab, daclizumab, and pagibaximab, have been described in pediatric subjects. However, the data were not included in this study because only general descriptive PK parameters and not population PK parameters and quantitative covariate-parameter relationships were reported for basiliximab, daclizumab and pagibaximab. In conclusion, the mPBPK model describing the PK of TMAbs and native IgG in pediatric populations was successfully developed. This mPBPK model provided important physiological insights of FcRn developmental pharmacology and its effects on the disposition of IgG antibody in human subjects. However, further study is needed to assess the generalizability of our approach for the PK analyses of antibody therapeutics in pediatric subjects.

### Material and methods

#### Data

The plasma PK data of exogenous native IgG in normal volunteers after administration of iodide-labelled IgG were obtained from Waldmann et al using the software WebPlotDigitizer (version 3.8, http://arohatgi.info/WebPlotDigitizer). The simulated PK data from published adult/pediatric population PK analysis of two TMAbs were used in this study: bevacizumab for mPBPK model development and palivizumab for external validation of the developed mPBPK model. Plasma concentration-time profiles of bevacizumab for adults and pediatric subjects with different weight were simulated using two-compartment linear PK model with the following covariate-parameter relationships for both pediatric and adult subjects:}

\[
\begin{align*}
CL_{Beva,i} &= \theta_{Beva,CL} \times \left( \frac{BW_i}{70} \right)^{0.75} \\
Vc_{Beva,i} &= \theta_{Beva, Vc} \times \left( \frac{BW_i}{70} \right)^{0.701} \\
Vp_{Beva,i} &= \theta_{Beva,Q} \times \left( \frac{BW_i}{70} \right)^{0.766} \\
Q_{Beva,i} &= \theta_{Beva,Vp} \times \left( \frac{BW_i}{70} \right)^{0.75}
\end{align*}
\]

where $CL_{Beva,i}$, $Vc_{Beva,i}$, $Q_{Beva,i}$ and $Vp_{Beva,i}$ represent the typical values of clearance, distribution volume at central compartment, inter-compartment flow, and distribution volume at peripheral compartment for subjects with weight $BW_i$ for bevacizumab, respectively. $\theta_{Beva,CL}$, $\theta_{Beva, Vc}$, $\theta_{Beva,Q}$ and $\theta_{Beva,Vp}$ represent typical population values of clearance ($9.90 \times 10^{-3} \, \text{l/h}$), distribution volume at central compartment (2.85 l), inter-compartment flow (0.28 l/h), and distribution volume at peripheral compartment (2.56 l) for subjects with reference weight of 70 kg.

Plasma concentration-time profiles of palivizumab for adults and pediatric subjects with different weight and age were simulated using reported two-compartment linear PK model with the following covariate-parameter relationships:}

\[
\begin{align*}
CL_{Pali,i} &= \theta_{Pali,CL} \times \left( \frac{BW_i}{70} \right)^{0.75} \\
& \quad \times \left( 1 - \beta \times e^{-\frac{\text{AGE} \times \text{BMI}}{450}} \times \left( \frac{h_{BMI}}{1.6} \right) \right) \\
Vc_{Pali,i} &= \theta_{Pali,Vc} \times \left( \frac{BW_i}{70} \right)^{1.0}
\end{align*}
\]
where $CL_{Pali,i}$, $V_{Pali,i}$, $Q_{Pali,i}$, and $V_{Pali,i}$ represent the typical values of clearance, distribution volume at central compartment, inter-compartment flow, and distribution volume at peripheral compartment for subjects with weight $BW_i$, for palivizumab, respectively. $	heta_{Pali,CL}$, $\theta_{Pali,VC}$, $\theta_{Pali,Q}$, and $\theta_{Pali, VP}$ represent typical population values of clearance (8.20 × 10⁻³ l/h), distribution volume at central compartment (4.09 l), inter-compartment flow (3.66 × 10⁻³ l/h), and distribution volume at peripheral compartment (2.23 l) for subjects with reference weight of 70 kg. Parameter $\beta$ is the fractional change in $CL$ for a typical full-term infant with 40-week of postnatal age $PAGe$ ($\beta=0.411$), and $T_{CL}$ is the maturation half-life for CL ($T_{CL}=249.2$ weeks). Postnatal age $PAGe$ was calculated as $(AGE$ (months) + $(GA$ (weeks)/4.35 (weeks/months)) with gestational age GA was set to 40-week.

Plasma drug concentrations of both bevacizumab and palivizumab were collected after a single intravenous bolus injection of 10 mg/kg of the antibodies at 1, 2, 6, 8, 12, 24, 48, 96, 168, 336, 504, 672, 840, 1008, and 1176 h post injection. In adult subjects, body weights of 50, 70, 80, 90 and 100 kg were used for simulation and fitting. For the pediatric subjects, six age groups were used, i.e., 1, 2, 3, 4, 6, and 10 yr. In each age group, the weight of 5%, 25%, 50%, 75%, and 95% percentile corresponding to age group from the CDC standard growth chart was used. Ten steady-state baselines of the mean endogenous IgG concentrations data were simulated using the reported reference values in adult (80.70 µM) and pediatric (45.26–67.13 µM) subjects. The baseline was implemented before administrations of single intravenous bolus dose of 10 mg/kg of exogenous IgG or TMAbs (bevacizumab/palivizumab) in order to assess the interaction between the endogenous IgG and exogenous IgG or TMAbs (bevacizumab/palivizumab).

**Model development**

The two-pore mPBPK model previously developed by our group was used as the basic framework for the model development (Figure 1). This model was divided into three major compartments of the plasma, tissue and lymph node. All body tissues were merged into a single biological compartment consisting of vascular space, endothelial space and interstitial space. The endogenous native IgG and exogenous IgG or TMAbs entered the tissue vascular space from the plasma by the arterial blood flow (Q) and exited the tissue vascular space to the plasma by venous blood flow (Q-L). In the tissue vascular space, antibodies moved directly to the interstitial space via paracellular pathway (two-pore extravasation rate, $K_{TP}$). The antibodies moved from both vascular and interstitial space to the endothelial space by endocytosis rate ($K_{up}$). In the endothelial space, endogenous native IgG and exogenous native IgG or TMAbs competitively interacted with the FcRn receptor to form bound and unbound components. The unbound antibodies were then cleared from the endothelial space (CL). The bound antibodies were recycled back from endothelial space to either vascular or interstitial space with a rate constant of $K_c$. FR and (1-FR) represented the fraction of bound antibodies recycled back to vascular and interstitial space, respectively. In the interstitial space, antibodies moved to the lymph node and then back to the plasma with lymph flow, L.

A non-equilibrium binding (association rate $k_{on}$ and dissociation rate $k_{off}$) was used to describe the IgG-FcRn interaction, and implementation of two pores model for the extravasation of the IgG antibodies from vascular to interstitial space $K_{TP}$. The amounts of the antibodies (native endogenous/exogenous IgG and TMAbs) are governed by the following set of equations:

$$\frac{dX_{\text{e}}}{dt} = \frac{D_{exo} + K_{syn} + \left(\frac{Q}{V_L} + L \times X_L \times J_{IgG} \times \frac{1}{V_L} \times X_L \times J_{IgG}\right)}{Q \times X_p}$$

$$\frac{dX_V}{dt} = \frac{Q \times X_p - \left(\frac{(Q - L)}{V_L} + K_{up} + K_{TP}\right) \times X_V}{FR \times K_{rec} \times X_e^{bo}} + K_{off} \times X_e^{bo}$$

$$\frac{dX_{bo}}{dt} = - \left(\frac{FR \times K_{rec} + K_{off} + (1 - FR) \times K_{rec}}{V_e} \times X_e^{bo}\right) + \frac{k_{on} \times FcRn_{Free} \times X^{bo}}{V_e}$$

$$\frac{dX_i}{dt} = - \frac{L \times X_i + K_{TP} \times X_V + (1 - FR) \times K_{rec} \times X_e^{bo} \times X_i}{V_L} + K_{up} \times (X_i)$$

$$\frac{dX_L}{dt} = - \frac{L \times X_L + L \times X_L}{V_L} + X_i$$

Where $X_u$ is the amount of the antibodies in compartment $u$ and $V_u$ is the volume of compartment $u$; $u$ refers to $p$ = plasma, $v$ = vascular space, $i$ = interstitial space, and $L$ = lymph node. $X_e^{bo}$ and $X_e^{bo}$ are the amount of unbound and bound antibodies in the endothelial cells, respectively. $D_{exo}$ is the dose (intravenous bolus injection) for exogenous native IgG/ TMAbs, i.e., intravenous bolus injection of 10 mg/kg. $K_{syn}$ is the synthesis rate of endogenous IgG. The transport of the IgG antibody from the vascular to interstitial space is modelled using two pores theory $K_{TP}$ (Eq. (15)).

$$K_{TP} = \left[\frac{J_L \times (1 - \alpha_l)}{V_e} + PS_e \times \left(\frac{1}{V_e} - \frac{1}{V_i} \times X_i \times \frac{1}{V_e} \times X_i \times \frac{1}{V_L} \times X_L \times \frac{1}{V_L} \times X_L \times \frac{1}{Pe_l}\right)^{(ex Pe_l - 1)}\right]$$

$$+ J_3 \times (1 - \alpha_3) \times PS_3 \times \left(\frac{1}{V_e} - \frac{1}{V_i} \times X_i \times \frac{1}{V_e} \times X_i \times \frac{1}{V_L} \times X_L \times \frac{1}{V_L} \times X_L \times \frac{1}{Pe_l}\right)^{(ex Pe_l - 1)}$$

The convective term was described by the fluid flow rates ($J_L$ for large pore $J_L = J_{iso}(\alpha_1) \times L$ and $J_3$ for small pore $J_3 = 1 - J_{iso} + (1 - \alpha_3) \times L$, and the osmotic reflection coefficient ($\sigma_1$ for
large pore and $\sigma_S$ for small pore). The diffusion term was described by the permeability surface area product ($PS$), and the Peclet number ($Pe$). The two equal physiological systems (endogenous IgG-exogenous IgG or endogenous IgG-TMAbs) are connected by the competition to the same FcRn receptor at pH 6.

Model parameters

The mPBPK model parameters were obtained from diverse sources with different quality. In this study, we developed an evidence-based rating system to evaluate the quality of the data used to scale the mPBPK parameters from human adult to pediatric subjects for the IgG antibody. The data were divided into four different LOE based on the methodological quality of the parameters collection (Table 1, Method in Supp. File). The first level (LOE I) represented the highest rank of scientific evidence and mainly consisted of data from human subjects (Table A Supp. File). This level represented a high level of comfort that the data were highly relevant and reliable to be used for scaling of the mPBPK parameters in human subjects. In the absence of the LOE I data, the LOE II data, which contained data from both human adult subjects and animal species (Table B Supp. File), were used to derive the mPBPK model parameters in pediatric subjects with allometric scaling method. If both LOE I and II data were not available, then the established approaches for PBPK model development in the literature were used to scale the data from either human or animal species (LOE III) to model parameters in pediatric subjects. An assumption of the same parameter value for both adult and pediatric subjects was used to generate the LOE IV parameters in pediatric subjects in the absence of any published approaches for parameters scaling in the literature.

The production of endogenous IgG ($K_{syn}$) was assumed to be a zero-order rate process in the plasma compartment. The dissociation constant $K_D$ and dissociation rate $k_{off}$ values of the FcRn-IgG binding at acidic pH were obtained from the literature (Table 2) and $k_{on}$ was calculated using the equation $k_{on} = k_{off}/K_D$. An earlier sensitivity study showed that changing $k_{off}$ by a factor of ± 50% lead to a small effect on the calculated AUCs, i.e., AUC difference < 5% (data not shown). Thus, $k_{off}$ of native IgG was used for TMAbs (Table 2) and the different FcRn binding affinity profiles of native IgG and TMAbs in this study were affected only by the values of KD.

Model fitting

The model was implemented using simulation analysis and modelling compartment software SAAMII v.2.3 (The Epsilon group, Charlottesville, Vancouver, USA). The stepwise approach was used to develop and calibrate the final mPBPK model and the workflow for the final mPBPK model development (Figure 2). First, the model was calibrated using the PK data of endogenous and exogenous native IgG in 77 kg adult subjects (STEP 1). The parameters obtained from the literature (Table 2) and our previous study were used for the calibration. This calibrated mPBPK model was then used to include the PK of bevacizumab in 77 kg adult subjects in STEP 2. The mPBPK model developed in STEP 2 was validated to the published experimental data to determine if the implementation of $K_D$ is sufficient to explain the PK of native IgG and bevacizumab in adult subjects. The following criteria were used to validate the mPBPK model in the adult subject: a mean half-life of ~ 21 of native IgG and 20 days of bevacizumab, a ratio of 0.058 between TMAbs (bevacizumab) concentration in tissue and plasma and a concentration of endogenous IgG in the interstitial space ≥ 17% of that in plasma. In the case where the $K_D$ was not sufficient (validation failed) to explain the PK different between native IgG and bevacizumab, a factor other than the FcRn binding affinity profile at acidic pH was then added to the model. Two modulation factors on two important model parameters were added to the model to explain the inter-antibody differences, as suggested in our previous study. The first modulator factor $F_1$ was for osmotic reflection coefficient that governed the IgG distribution from plasma to interstitial space, and the second factor $F_2$ was for endocytosis rate ($K_{up}$ and $K_{rc}$) that affected the IgG catabolism.

Due to the many age/weight combinations that needed to be tested for the final mPBPK model, the mPBPK model developed using the adult subjects with reference weight of 77 kg in STEP 2 was calibrated using the adult/pediatric subjects with extreme age/weight values (100 kg for adult subject and 8 kg for one year old child) in STEP 3. The mPBPK model scaled based on the model parameters using weight-related allometric scaling method (LOE listed on Table 2) were not sufficient to describe the PK of the native IgG and bevacizumab in subjects with different age and weight. Therefore, mPBPK models with a different combination of weight- and age-related effects on FcRn concentration, two-pore extravasation rate $K_{TP}$, endosomal clearance CL, endocytosis rate $K_{up}/K_{rc}$, lymph flow L and fraction of recycled IgG to vascular space FR were developed and examined. The calibrated model that best described the PK data of bevacizumab and native IgG in adult subjects with the referenced weight of 77 kg and largest weight of 100 kg, and pediatric subjects with the smallest weight of 8 kg, was selected based on the AICc. This calibrated mPBPK model was then used to develop the final mPBPK model in describing the endogenous IgG and bevacizumab PK for all adult and pediatric subjects included in this analysis (STEP 4). In the final mPBPK model, the following equation was used to explore the effects of age and weight on the FcRn concentration in adult/pediatric subjects with different age and weight:

$$F_{cRn_i} = F_{cRn_{ref}} \times \left( \frac{BW_i}{77} \right)^{\theta_{BW}} \times \left( \frac{Age_i}{20} \right)^{\theta_{Age}} \quad (16)$$

Where $F_{cRn_i}$ is the FcRn concentration in subject $i$ with weight of $BW_i$ and age of $Age_i$. $F_{cRn_{ref}}$ is the reference value of FcRn concentration for a 77 kg 20 yr old (adult) subject. $\theta_{BW}$ is the exponent of the weight scaling term. $\theta_{Age}$ is the exponent of the age scaling term. The parameters of Eq. (16) were simultaneously fitted to the FcRn concentration data (estimated using mPBPK model) using MATLAB version R2017a. The performance of the final developed mPBPK model using the endogenous/exogenous IgG and bevacizumab was then examined with the external validation data set that
consisted of palivizumab PK in 70 kg adult, 10 y (32 kg), 6 y (20.5 kg) and 1 y (12.1 kg) pediatric subjects. The computational settings were described elsewhere. Supplemental data for this article can be accessed here.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| AICc | Akaike Information Criterion-corrected |
| CDC | Centers for Disease Control and Prevention |
| CL | Antibody clearance in endothelial space |
| CL_pali/beva | Two-compartment clearance of palivizumab/bevacizumab |
| CV | Coefficient of variations |
| FCN_expression | FcRn concentration per kg |
| FR | Recycling fraction of IgG to vascular space |
| F1 | Modulation factor of TMAbs osmotic reflection coefficient |
| F2 | Modulation factor of TMAbs endocytosis rate (endothelial \( K_u \) and \( K_e \)) |
| GA | Gestational age |
| IV | Intravenous |
| \( J_{iso} \) | Fluid recirculation rate |
| \( J_L/J_S \) | Fluid flow rates for large/small pore |
| \( K_D \) | Dissociation constant |
| \( K_{iff} \) | Dissociation rate constant |
| \( K_{in} \) | Association rate constant |
| \( K_e \) | Endocytosis recycle rate |
| \( K_{syn}/K_{synw} \) | Endogenous IgG synthesis rate/Ksyn per kg |
| \( K_{TP} \) | Two-pore extravasation rate |
| \( K_{up} \) | Endocytosis uptake rate |
| L | Lymph flow |
| LOE | Levels of Evidence |
| MK | Age/modulation factor of \( K_{TP} \) |
| mPBPK | Minimal physiologically based pharmacokinetic |
| PAGE | Post-natal age |
| PBPK | Physiologically based pharmacokinetic |
| Pe | Peclet number |
| PK | Pharmacokinetics |
| PS | Permeability surface area |
| Q | Two-compartment flow |
| TMAbs | Therapeutic monoclonal IgG antibodies |
| \( V_e \) | Two-compartment volume of distribution |
| VEGF | Vascular endothelial growth factor |
| \( V_p \) | two-compartment volume of peripheral tissue |
| \( a_l \) | Fraction of hydraulic conductivity for large pore |
| \( \sigma_l/\sigma_s \) | Osmotic reflection coefficient for large/small pore |
| \( \theta_{BW}/\theta_{Age} \) | Exponent of the weight/age effect to FcRn |

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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