PBPK modelling of monoclonal antibodies in pediatric populations

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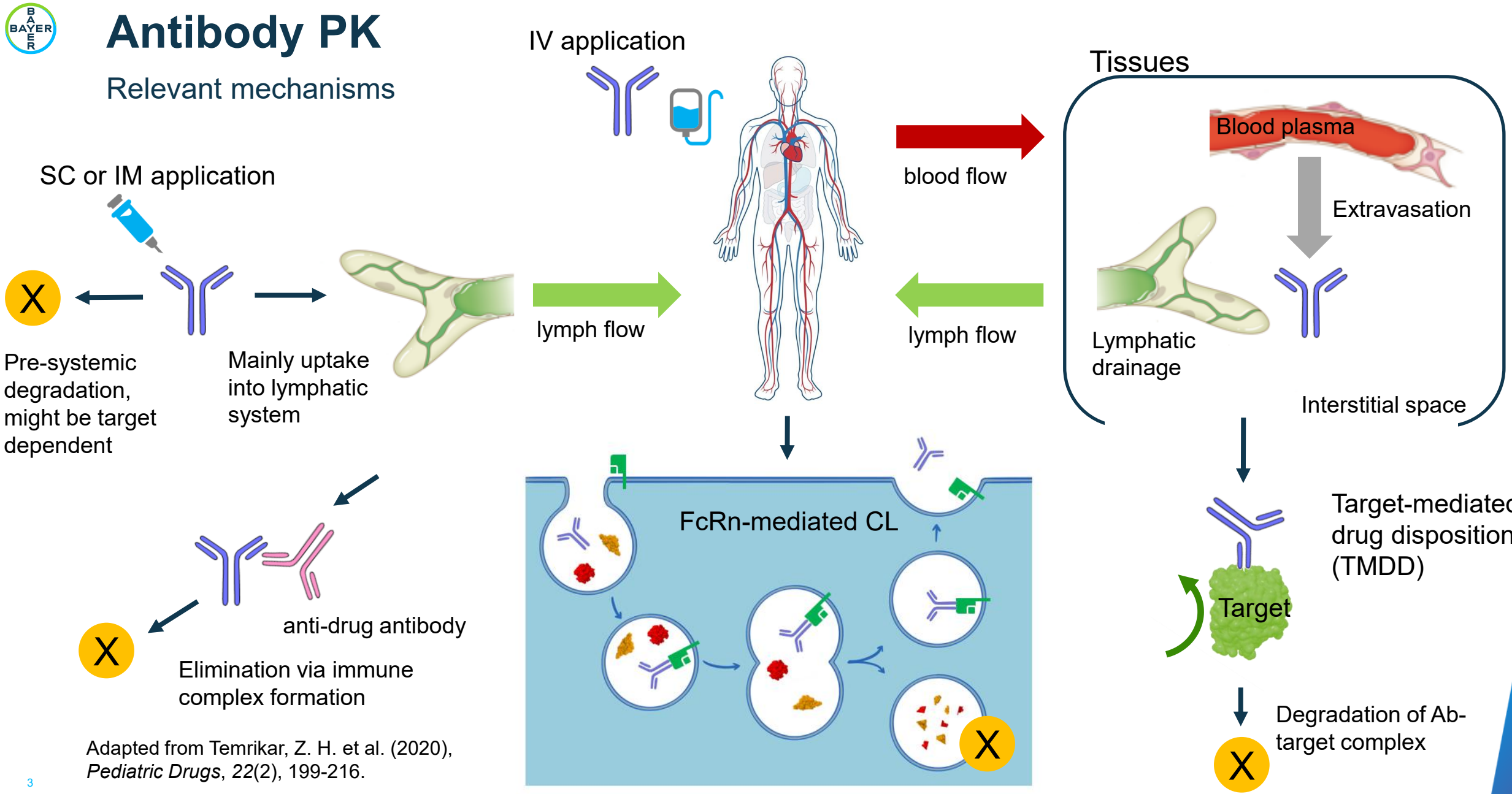


Agenda

- Physiological processes relevant for antibody PK
- Scaling the PK-Sim large-molecule model to children
  - Assumptions
  - Model behavior: examples and age trends
- Additional mAb-specific ontogenies in selected published PBPK models & further examples
- Summary

Antibody PK

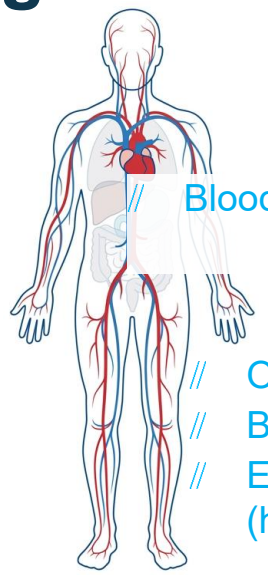
Relevant mechanisms



Adapted from Temrikar, Z. H. et al. (2020), *Pediatric Drugs*, *22*(2), 199-216.

Generic PBPK model for large molecules in PK-Sim

Mechanisms and related parameters



// Blood flow rates

// Organ volumes
// Blood volume(s)
// Extracellular volume fractions (hematocrit, fractions interstitial)

Tissues

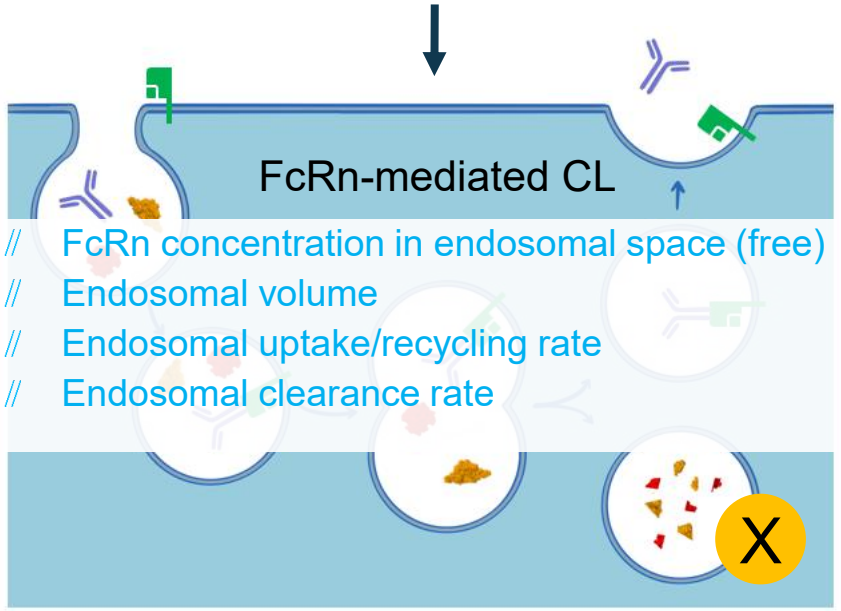


Extravasation



// Vascular wall properties
// Vascular surface area
// Lymph flow rates
// Fluid recirculation flow rate

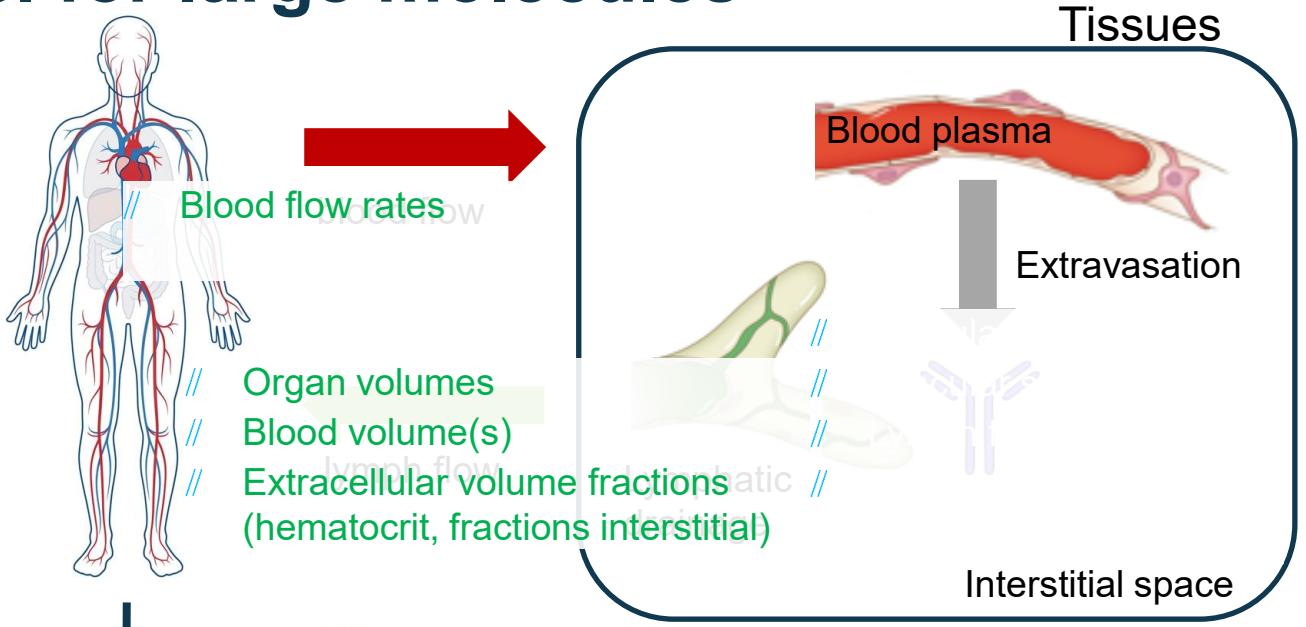
Interstitial space

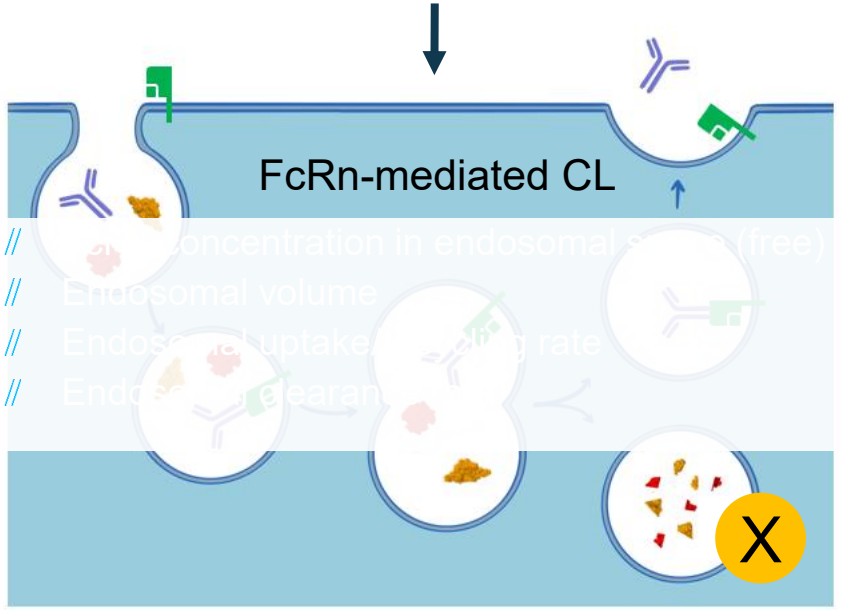


// FcRn concentration in endosomal space (free)
// Endosomal volume
// Endosomal uptake/recycling rate
// Endosomal clearance rate

Assumptions for scaling to children in the PK-Sim generic PBPK model for large molecules

Age-dependent parameters according to the PK-Sim database

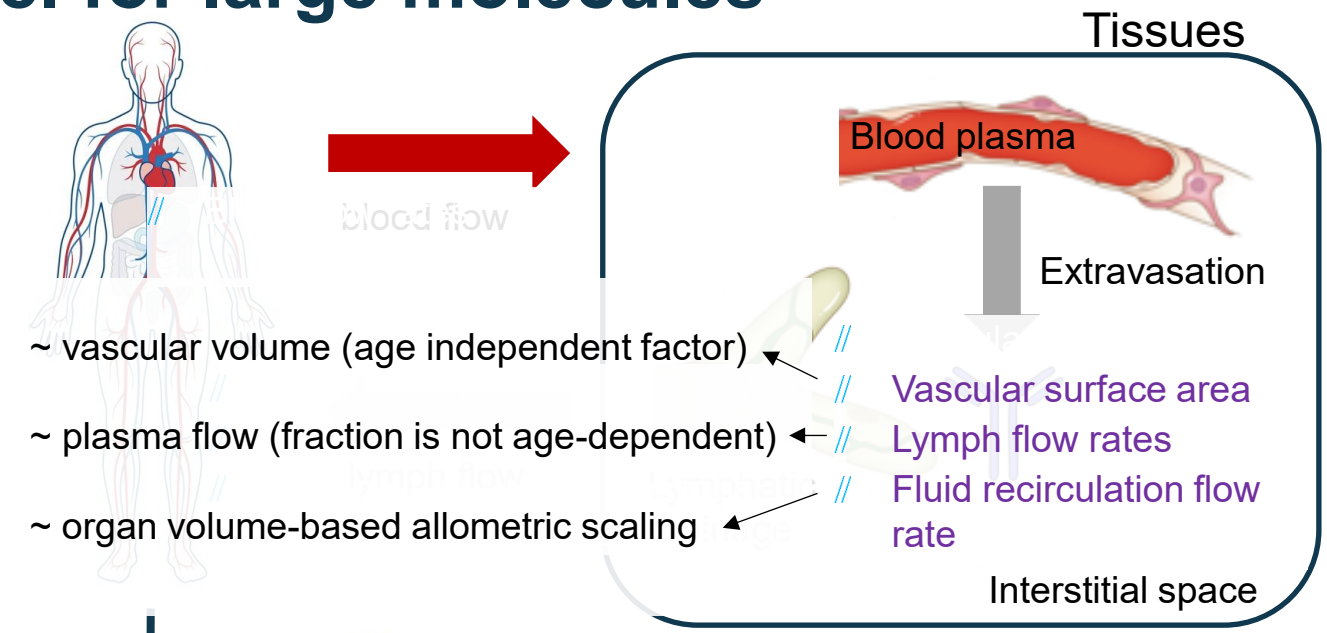


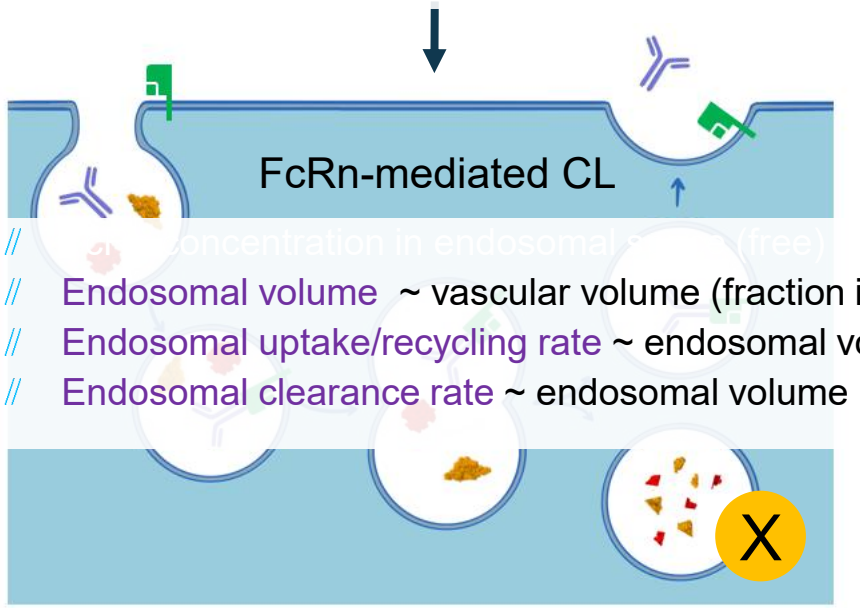


cf. Basu, S. et al. (2020),
Frontiers in pharmacology, 11, 868.

Assumptions for scaling to children in the PK-Sim generic PBPK model for large molecules

Parameters scaling indirectly with body size





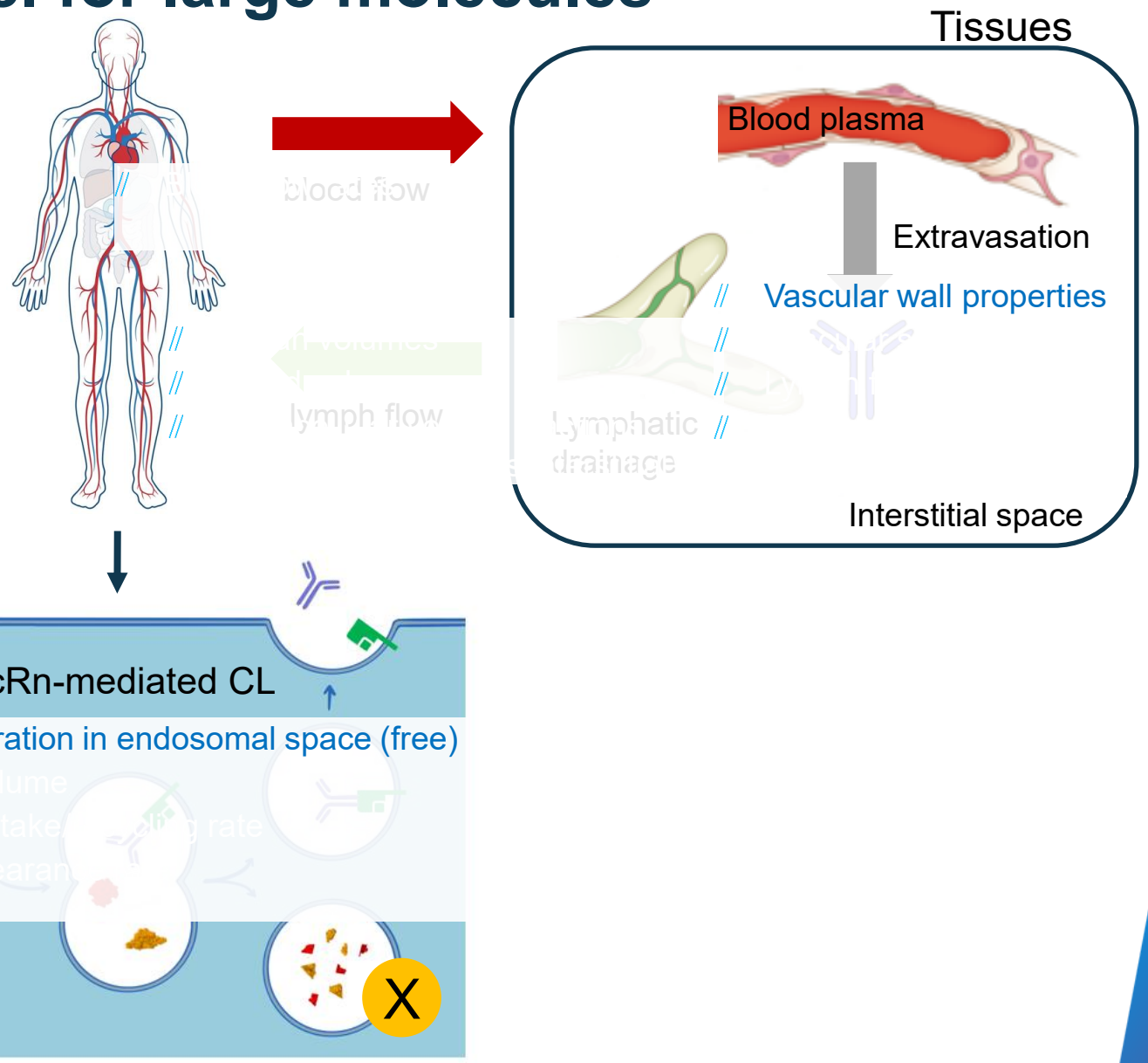
Endosomal volume ~ vascular volume (fraction is not age-dependent)
Endosomal uptake/recycling rate ~ endosomal volume
Endosomal clearance rate ~ endosomal volume

} specific rate constants are not age-dependent

cf. Basu, S. et al. (2020),
Frontiers in pharmacology, 11, 868.

Assumptions for scaling to children in the PK-Sim generic PBPK model for large molecules

Parameters which are not age-dependent



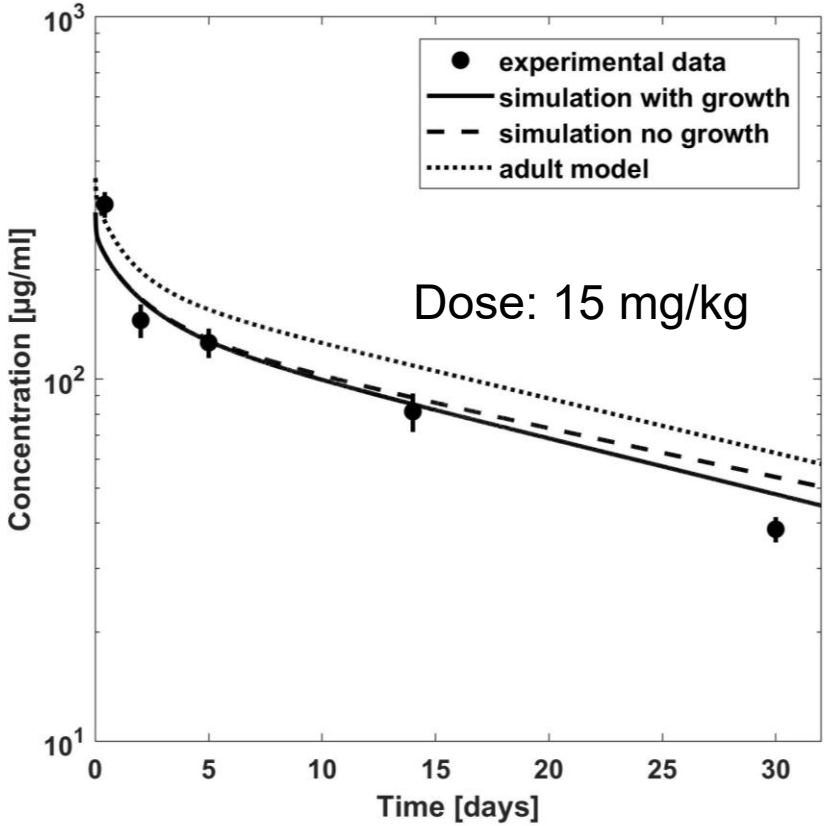
cf. Basu, S. et al. (2020),
Frontiers in pharmacology, 11, 868.

Example: Palivizumab

Anti-RSV F-protein mAb

- Assuming no TMDD
- Adult model:
  Kd(FcRn) was fitted (result: 0.863 µM) so that simulated adult CL matched the population-PK estimate from Robbie et al., 2012

Children with RSV infection, age: 5.2 ± 0.9 months



➔ Modest age-related differences predicted from PBPK model
➔ Growth during simulation time can affect predicted PK in infants

Robbie, G. J. et al. (2012),
Antimicrobial agents and chemotherapy, 56(9), 4927-4936.

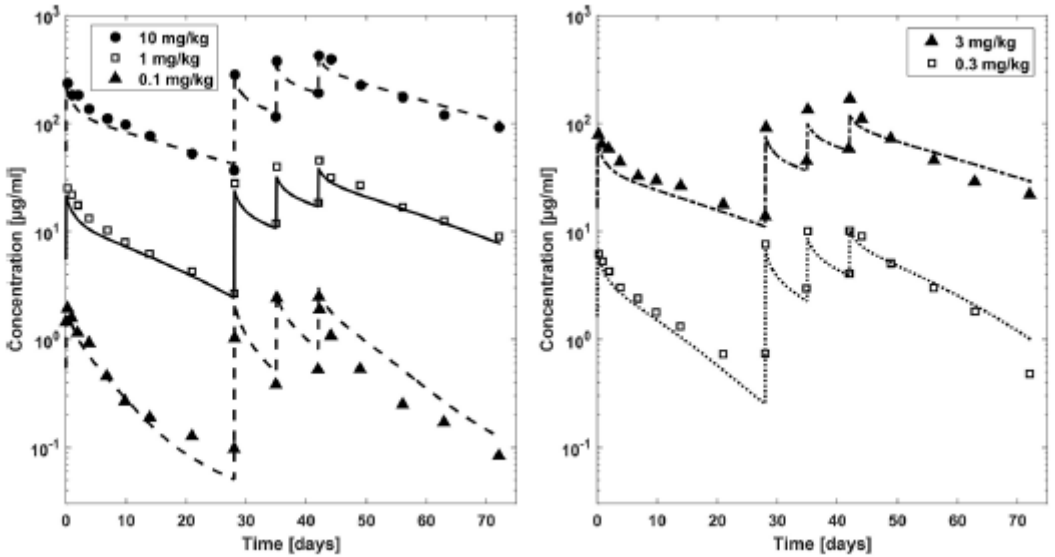
Figure from Basu, S. et al. (2020), Frontiers in pharmacology, 11, 868.
Experimental data: Sáez-Llorens, X. et al. (2004),
The Pediatric infectious disease journal, 23(8), 707-712.

Example: Bevacizumab

Anti-VEGF mAb

- Adult model includes TMDD;
  for pediatric extrapolation, TMDD parameters are kept at adult values (no ontogeny assumed)
- TMDD is however negligible at therapeutic doses

Adult model: PBPK model (lines) versus experimental data (symbols)

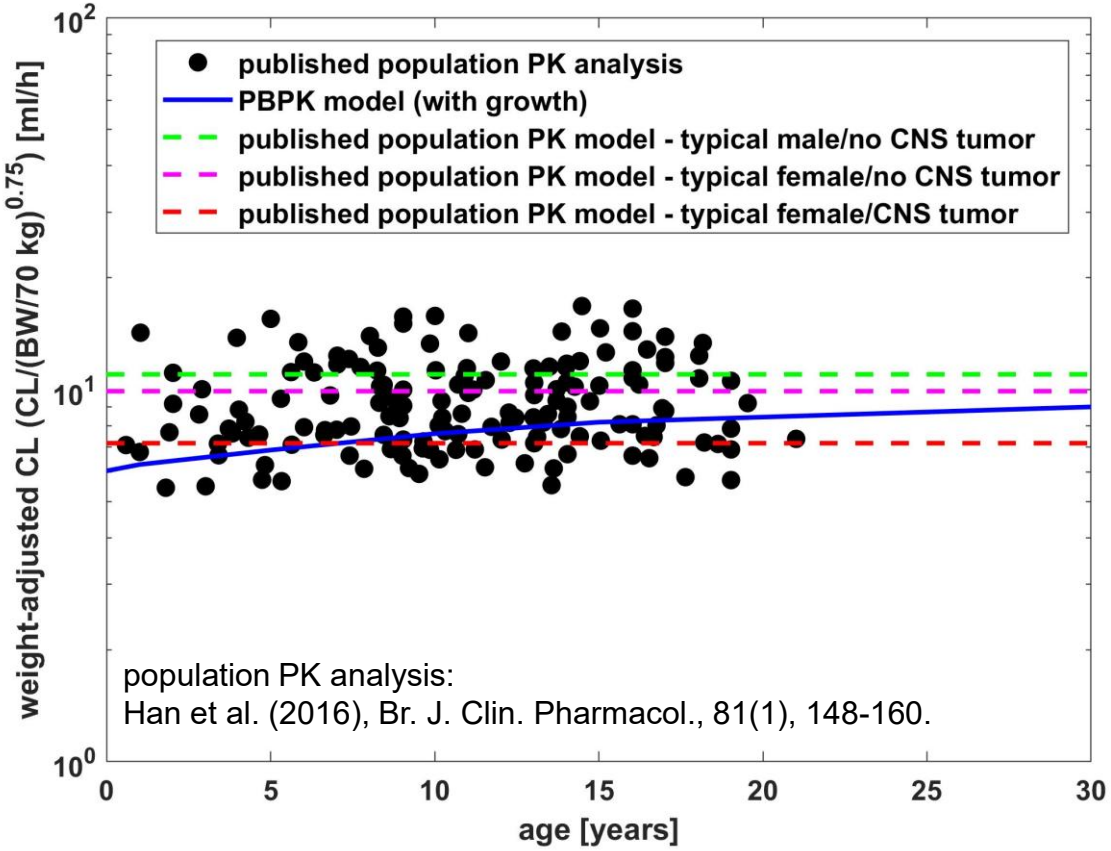


Phase 1 data
in cancer patients

Figure from Basu et al. (2020), Frontiers in pharmacology, 11, 868.
Experimental adult data: Gordon, M.S. et al. (2001), Journal of Clinical Oncology, 19(3), 843-850.

Example: Bevacizumab

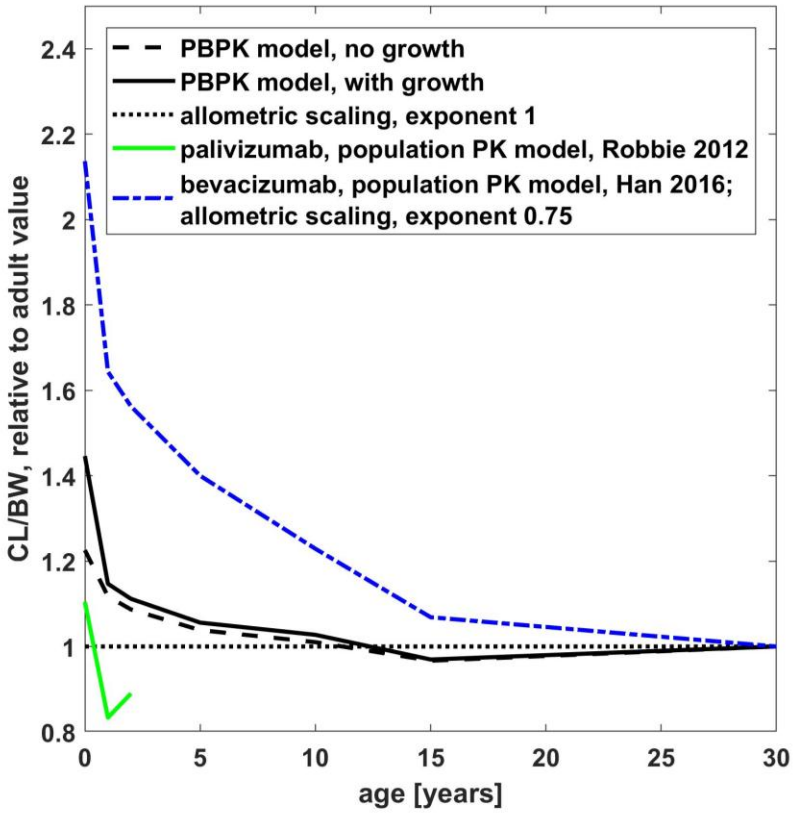
Anti-VEGF mAb

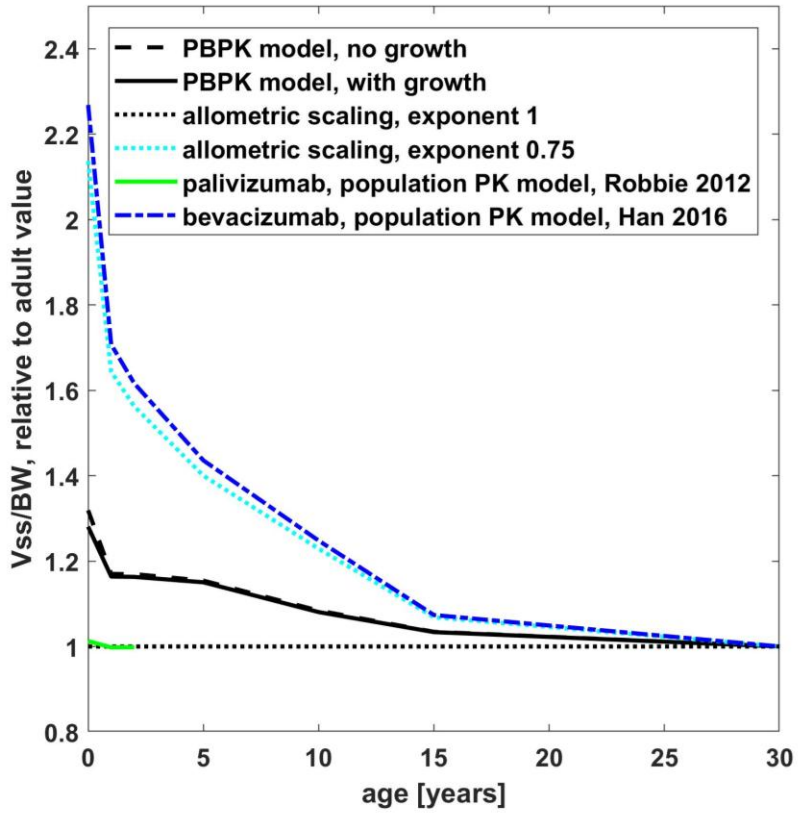


➔ PBPK predicts slightly lower weight-normalized CL in younger children than the published population-PK model
➔ Disease/indication related factors may also contribute

Figure taken from Basu, S. et al. (2020), Frontiers in pharmacology, 11, 868.

Age dependency of CL and Vss with PK-Sim (without additional ontogeny)





➔ PK-Sim predicts modest age-related changes in CL/BW and Vss/BW
➔ Increase in CL/BW reflects age-related vascular/endosomal volume per body weight
➔ Increase in Vss/BW reflects changes in body composition (extracellular volume) and lymph flow

Figures taken from Basu, S. et al. (2020), Frontiers in pharmacology, 11, 868.

Additional mAb-specific ontogeny: Selected published PBPK approaches

Illustrative examples

- Malik 2020: PBPK model adding ontogeny to generic PK-Sim model for
  - lymph flow rate (data from newborn lambs)
  - capillary surface area / density
  - hematopoietic cell concentration (endosomal clearance)
- Application to preterm neonates and ex-preterm infants for pagibaximab, palivizumab, nirsevimab, and IVIG
- Contribution of hematopoietic cells to high clearance in young children was later considered to be mechanistically unlikely (Malik 2022)

- Pan 2020: PBPK model (Simcyp) adding mAb-PK related ontogeny for
  - vascular, interstitial and endothelial volumes
  - lymph flow (scaled allometrically)
  - endogenous IgG ontogeny
  - typical FcRn conc. not age dependent, individual FcRn conc. linked to IgG by an assumed correlation
  - allometric scaling for CL_{cat} & $CL_{additional}$
- Application to neonates to adolescents for 6 biologics including infliximab and basiliximab (additional ontogeny for e.g., GFR relevant for smaller proteins)

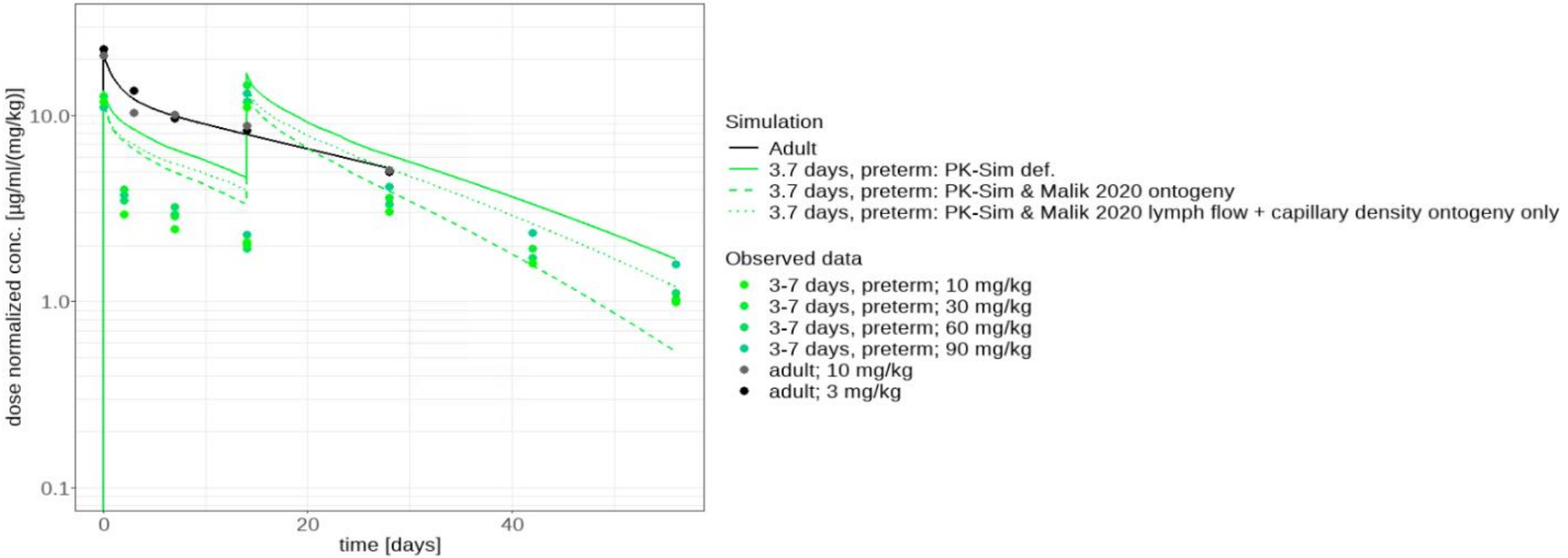
➔ No consensus representation of mAb-specific ontogeny has yet emerged

Malik 2020: Malik, P. R. et al. (2020), The Journal of Clinical Pharmacology, 60(4), 466-476.
Malik 2022: Malik, P. R. et al. (2022), Pharmaceutical Research, 39(2), 239-250.
Pan2020: Pan, X. et al. (2020), The AAPS journal, 22(4), 76.

For reviews regarding ontogeny of physiology relevant for Ab PBPK cf. e.g.
→ Malik, P., & Edginton, A. (2018), Expert opinion on drug metabolism & toxicology, 14(6), 585-599.
→ Lim, A. et al. (2023), Pharmaceutics, 15(5), 1552.

Example: Pagibaximab

Anti-LTA (*Staphylococcus epidermidis*) mAb in preterm infants (gestational age: 25 – 33 weeks)

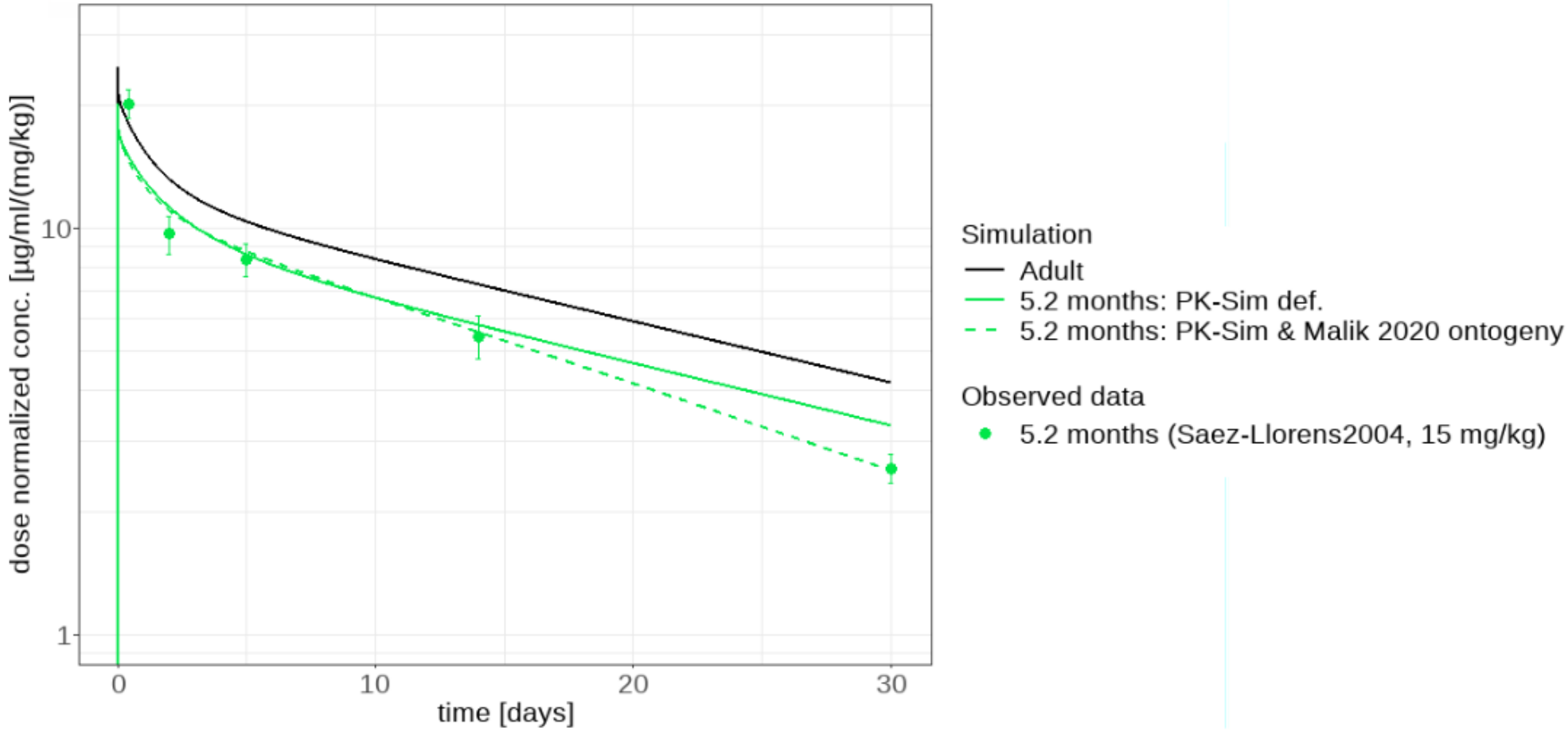


➔ Adding ontogeny improves prediction for pagibaximab in preterm infants
➔ Candidates for missing ontogeny: vascular leakiness, endosomal volume (not hematopoietic), endosomal uptake rate

Experimental data: Weisman, L. E. et al. (2009), International immunopharmacology, 9(5), 639-644.
Weisman, L. E. et al. (2009), Antimicrobial agents and chemotherapy, 53(7), 2879-2886.

Example: Palivizumab

Same simulations as above (with growth) compared to simulation including Malik2020 ontogeny

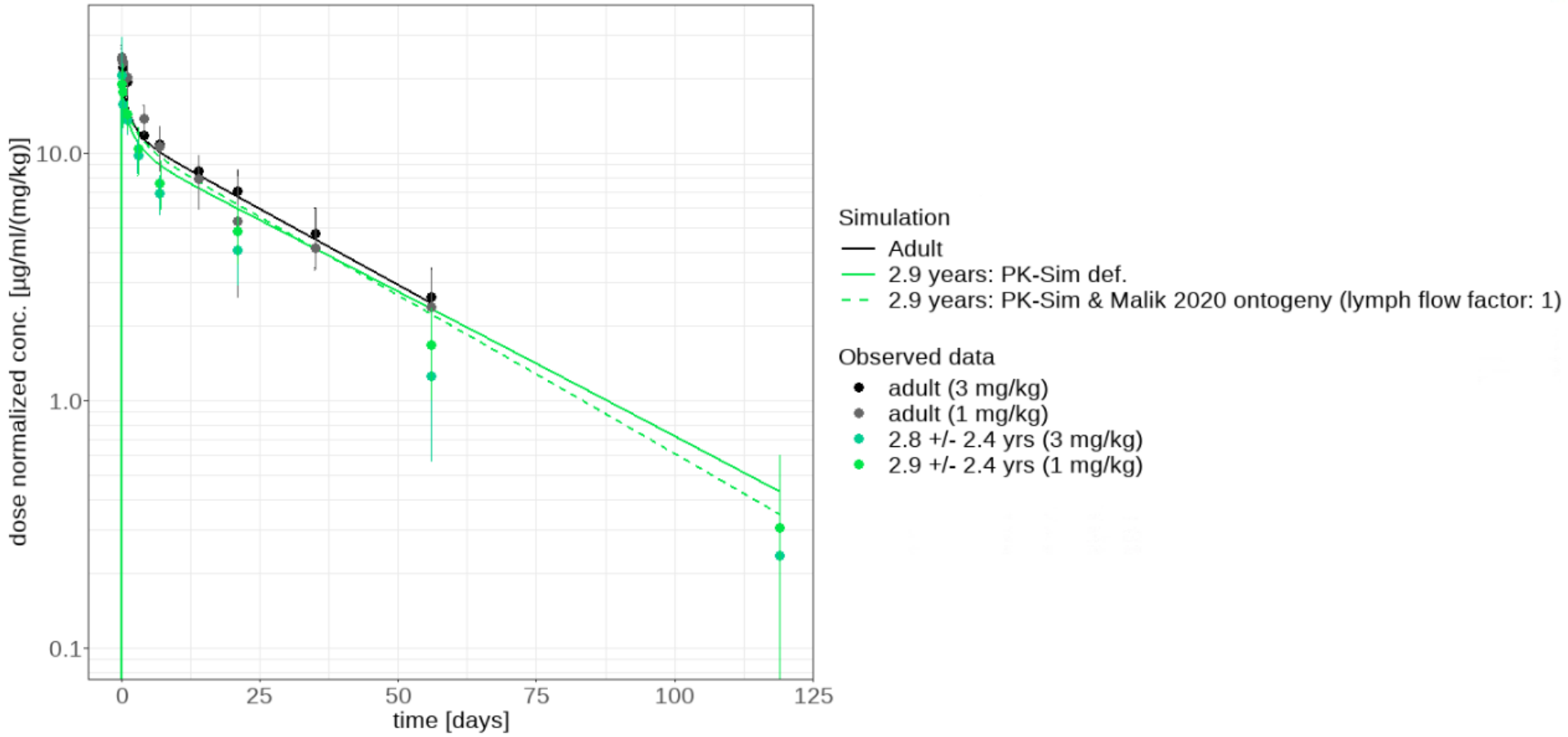


➔ Adding ontogeny improves prediction also for infants

Experimental data: Sáez-Llorens, X. et al. (2004),
The Pediatric infectious disease journal, 23(8), 707-712.

Example: Urtoxazumab

Anti-Shiga toxin 2 (*Escherichia coli*) mAb

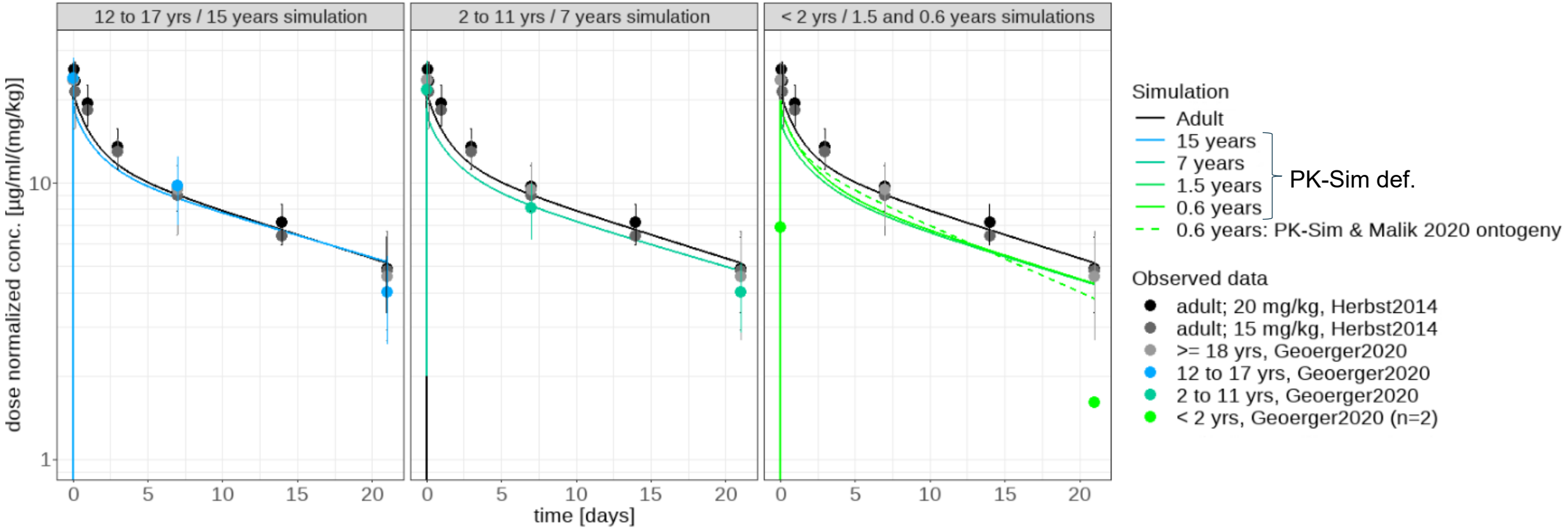


➔ Effect of additional Malik 2020 ontogeny is less pronounced in older children ~ 3 years

Experimental data: López, E. L. et al. (2010), Antimicrobial agents and chemotherapy, 54(1), 239-243.

Example: Atezolizumab

Anti-PD-L1 mAb



➔ For older children, PBPK predictions describe the experimental profiles reasonably well

➔ Reasons for discrepancies in infants not known (n=2)

Experimental data:
Herbst, R. S. et al. (2014), Nature, 515(7528), 563-567.
Geoerger, B. et al. (2020), The Lancet Oncology, 21(1), 134-144.

A recent platform pediatric PBPK model for multiple mAbs

Kumar et al. (2026)

- PBPK model of 11 antibodies showing linear PK for IV and SC administration (based on University at Buffalo PBPK platform)
- Comparison of pediatric vs adult PK for 20 antibodies(*)
- Representation of ontogeny
  - age-, weight- and sex-dependent anatomy and body composition
  - lymph flow scales as plasma flow
  - no ontogeny for lymph flow fraction, vascular properties or FcRn-mediated endosomal clearance
- Key findings
  - Pediatric initial concentration 20-40% lower (correspondingly higher V_c) compared to adults
  - For many linear-PK mAbs, adult and pediatric body weight-normalized CL were similar after age 2 years
  - Faster clearance in very young children suggests missing mAb-specific ontogeny
  - For nonlinear-PK mAbs, pediatric vs adult differences may be dominated by target biology and TMDD

Kumar, M., Lanke, S., & Shah, D. K. (2026). The AAPS Journal, 28(1), 44.
(*) 21 antibodies in Fig. 3 & 4, no adult data for naxitamab

Summary

- Age-dependent anatomy and body composition are relatively well established and are represented similarly across published pediatric mAb PBPK models
- Published models differ in their representation of mAb-specific ontogeny related to FcRn-mediated clearance and extravasation. Quantitative understanding of the ontogeny of related parameters remains less mature than for many small-molecule processes
- This uncertainty is especially relevant for preterm neonates, neonates and infants
- TMDD can dominate age-related differences when target-mediated elimination is relevant, and target expression itself may be age- and disease-dependent
- Beyond ontogeny, disease and indication differences between adult and pediatric populations may be relevant for pediatric extrapolation

Health for all, Hunger for none

Thank you!

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