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Modeling Motherhood III: Lactation PBPK modeling

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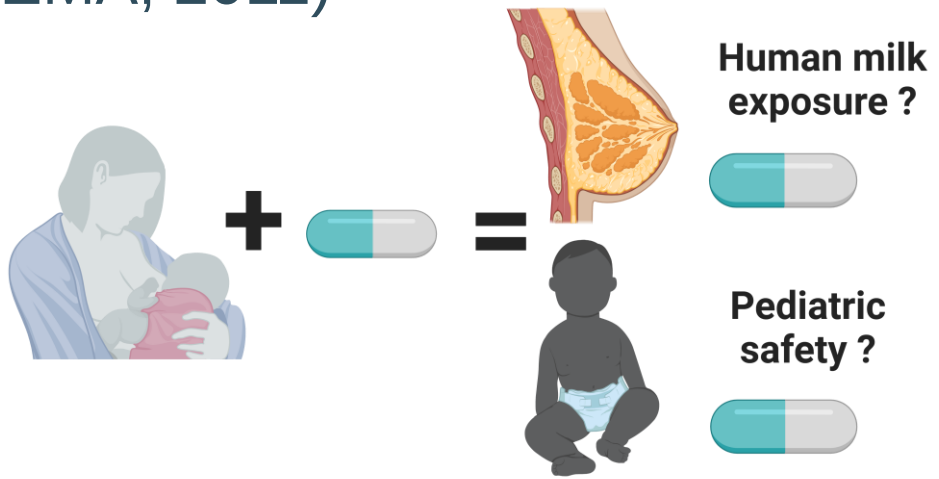
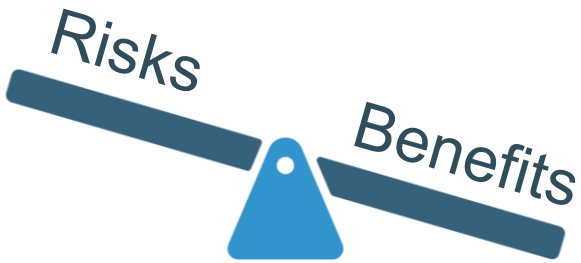
Outline

- Why develop lactation PBPK models?
- Workflow for developing lactation (and pediatrics) PBPK models
- PBPK-based simulations of concentrations in human milk for 10 model medicines
- *In vitro* permeability model across blood milk barrier
- Conclusions and future perspectives

Risk related to medication and breastfeeding

- WHO recommends exclusive breastfeeding during first 6 months of life
- 83% of medicine labels contain no information about use during lactation (EMA, 2011)

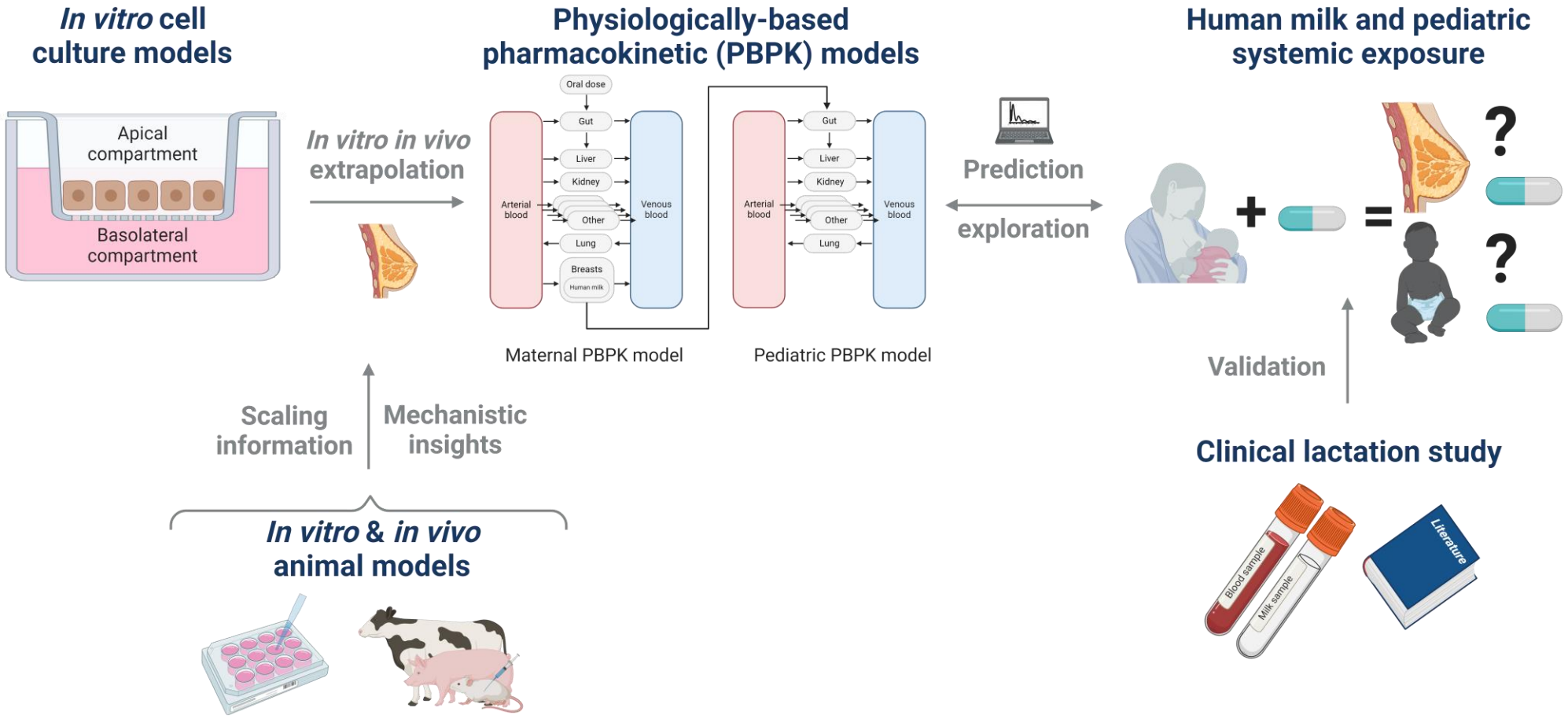




- **“No woman should have to make an uninformed decision about breastfeeding her baby” – IMI ConcePTION**

References: EMA, (2011); WHO, (2024).
Abbreviations: World Health Organization (WHO); European Medicines Agency (EMA); Innovative Medicines Initiative (IMI)

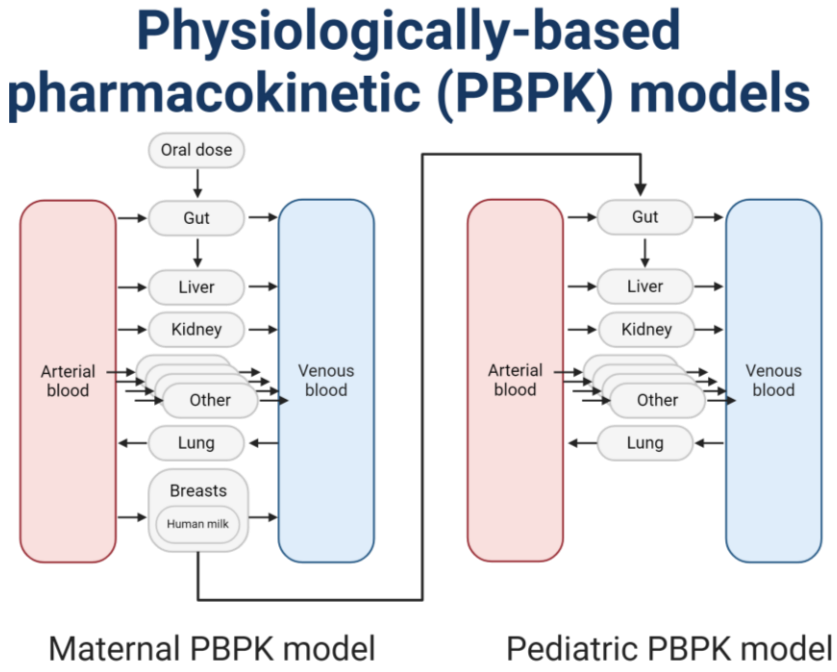
Non-clinical platform for predicting milk and infant exposure to maternal medication



Reference: https://doi.org/10.1016/j.biopha.2020.111038

The specific aims are: (i) to compile the state-of-the art of non-clinical tools for human milk medicine transfer; (ii) to develop in vitro models, enabling determination of medicine transport rates at the human blood/milk barrier; (iii) to develop PBPK models for the bottom-up prediction of in vivo human milk medicine exposure; (iv) to generate in vivo human data for the exposure of medicines in human milk; (v) to initiate regulatory acceptance for the developed non-clinical platform

Non-clinical platform for predicting milk and infant exposure to maternal medication



Development of a framework for physiologically-based pharmacokinetic (**PBPK**) predictions of **transfer of medicines into human milk**, and subsequent **infant exposure** to maternal medicines via breastfeeding.

Reference: https://doi.org/10.1016/j.biopha.2020.111038

The specific aims are: (i) to compile the state-of-the art of non-clinical tools for human milk medicine transfer; (ii) to develop in vitro models, enabling determination of medicine transport rates at the human blood/milk barrier; (iii) to develop PBPK models for the bottom-up prediction of in vivo human milk medicine exposure; (iv) to generate in vivo human data for the exposure of medicines in human milk; (v) to initiate regulatory acceptance for the developed non-clinical platform

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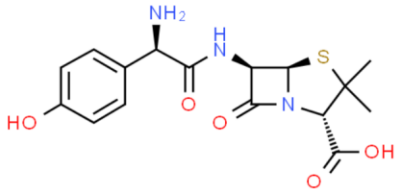
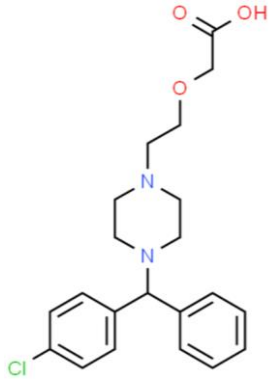
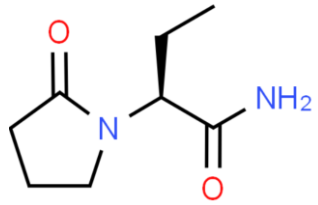
Selected model compounds



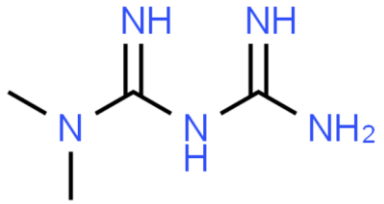
Amoxicillin
(Renal)



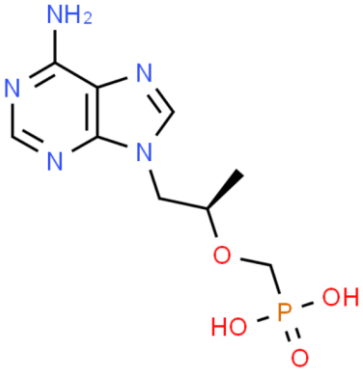
Cetirizine
(Renal)



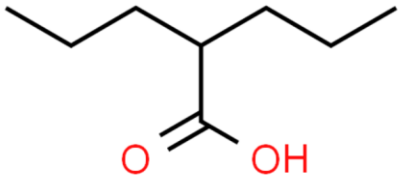
Levetiracetam
(Renal/Esterases)



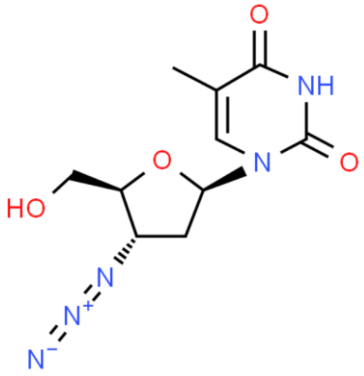
Metformin
(Renal)



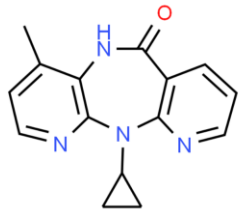
Tenofovir
(Renal)



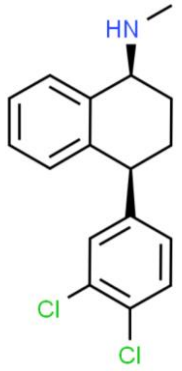
Valproic Acid
(Hepatic UGTs)



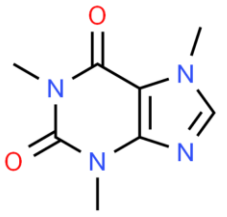
Zidovudine
(Hepatic UGT2B7)



Nevirapine
(Hepatic CYP3A4)



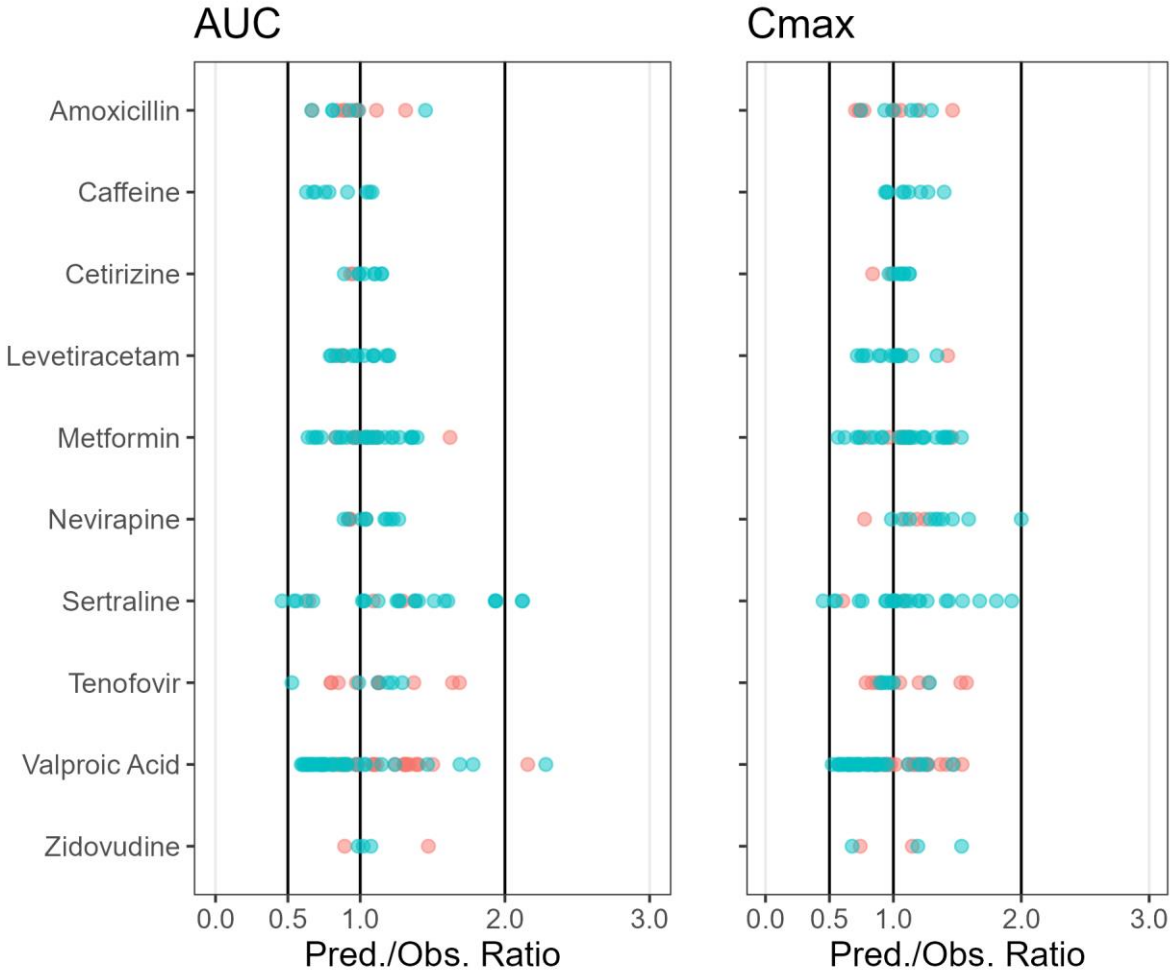
Sertraline
(Hepatic CYPs)



Caffeine
(Hepatic CYP1A2)

Red: main elimination pathway

Performance of the non-lactating adult PBPK models in PK-SIM



Across all drugs PBPK model performance for adult healthy volunteers (males and females) was within 2-fold margin for AUC and Cmax.

This qualified as base model for lactation PBPK model

Individual predicted/observed ratios are shown for model building (**red circles**) and model verification (**blue circles**) data. Black lines represent the 0.5- and two-fold prediction error ratio

References: Nauwelaerts et al. (2023)

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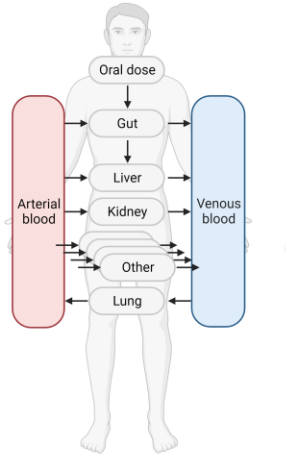
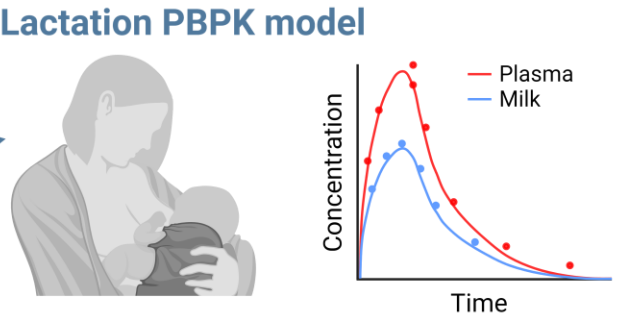
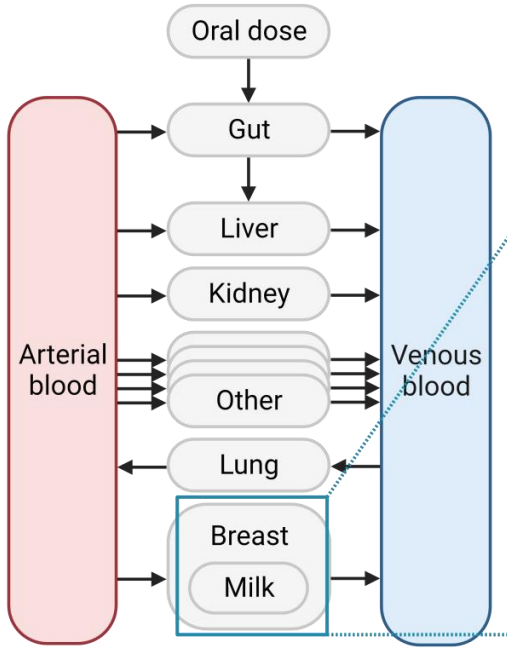
Workflow for lactation PBPK model development



Changes in population physiology

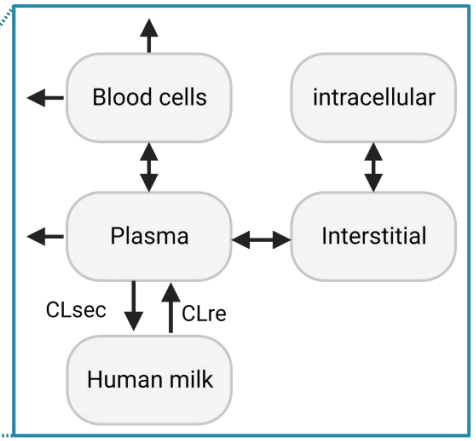


$$M/P\ ratio = \frac{AUC_{human\ milk}}{AUC_{plasma}}$$



$$\frac{dN_{milk}}{dt} = C_{plasma} * fu_{plasma} * CL_{sec}$$

$$\frac{dN_{plasma}}{dt} = C_{milk} * fu_{milk,total} * CL_{re}$$



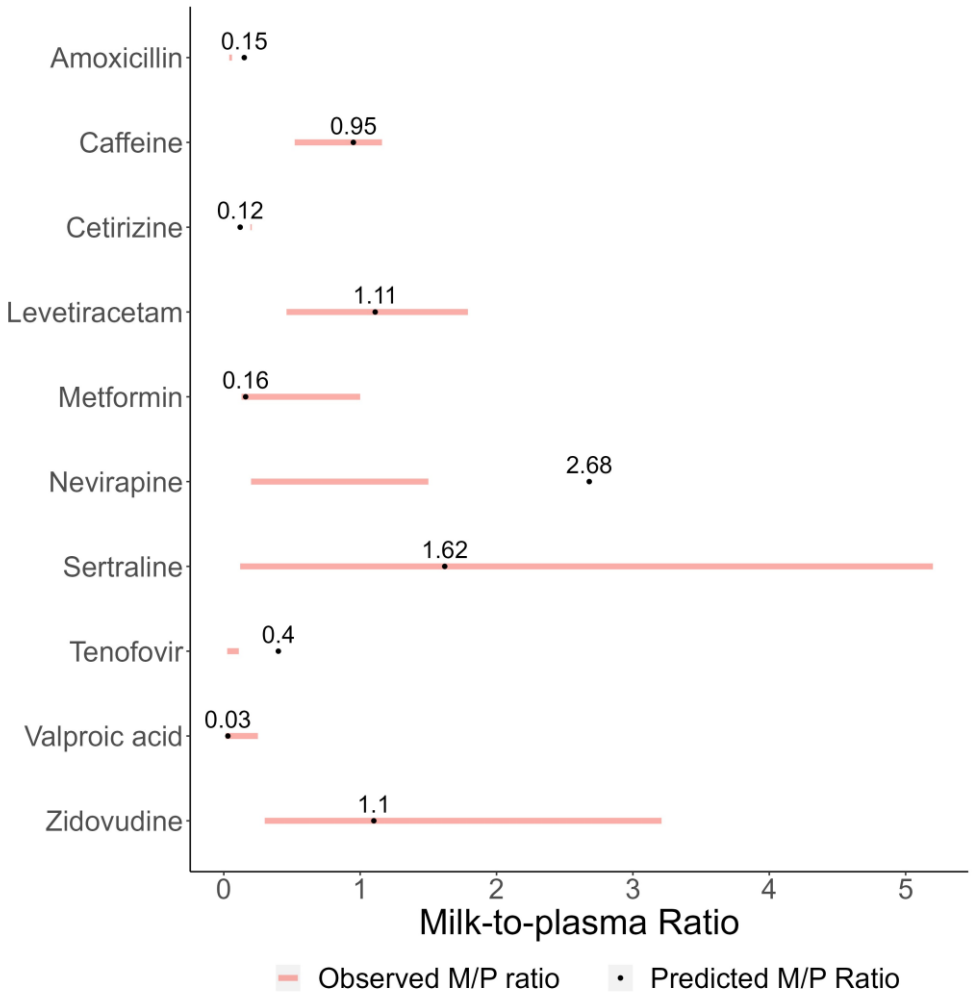
$$\mathrm{Log}(CL_{sec}) = -3.912 - 0.015\ PSA + 3.367\ \mathrm{Log}(MW) - 0.164\ \mathrm{Log}\left(\frac{P}{D_{7.4}}\right)$$

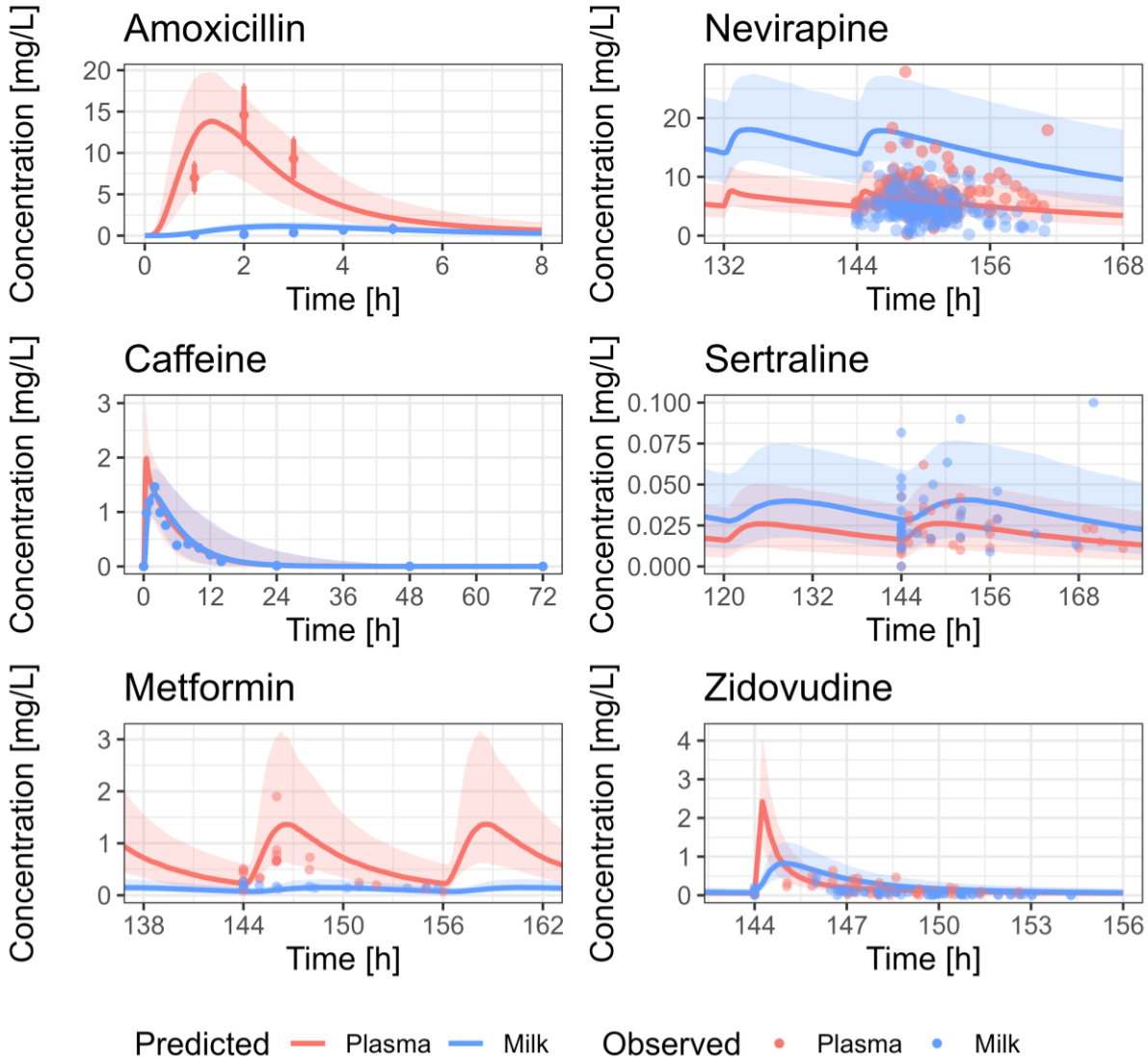
$$\mathrm{Log}(CL_{re}) = 2.793 + 0.179\ LogP - 0.132\ HBD$$

References: Nauwelaerts et al. (2023)

Abbreviations: Physiologically-based pharmacokinetic modelling (PBPK modelling); Milk-to-plasma ratio (M/P ratio); area-under-the-curve (AUC); plasma concentration (C_{plasma}); fraction unbound in plasma (fu_{plasma}); secretion clearance (CL_{sec}); human milk concentration (C_{milk}); total unbound fraction in milk ($fu_{milk,\ total}$); reuptake clearance (Cl_{re}); polar surface area (PSA); molecular weight (MW); octanol water partition coefficient (LogP); octanol:buffer (pH 7.4) distribution coefficient (LogD7.4); hydrogen bound donors (HBD)

Lactation PBPK model predictions were comparable with literature for 80% of the selected (model) compounds





References: Nauwelaerts et al. (2023)

For amoxicillin, the M/P ratio was calculated using the peak concentration in plasma and the highest measured concentration in human milk. Alternatively, non-compartmental analysis was applied to estimate the area-under-the-curve (AUC) based M/P ratio, assuming that the elimination slope in human milk is identical to plasma. For cetirizine, the M/P ratio was calculated using the observed steady-state AUC in human milk (0.50 mg*h/L), and the observed plasma AUC in non-lactating adults receiving the same dosing regimen (2.50 mg*h/L). Some studies report human milk concentrations below the limit of quantitation for sertraline and valproic acid.

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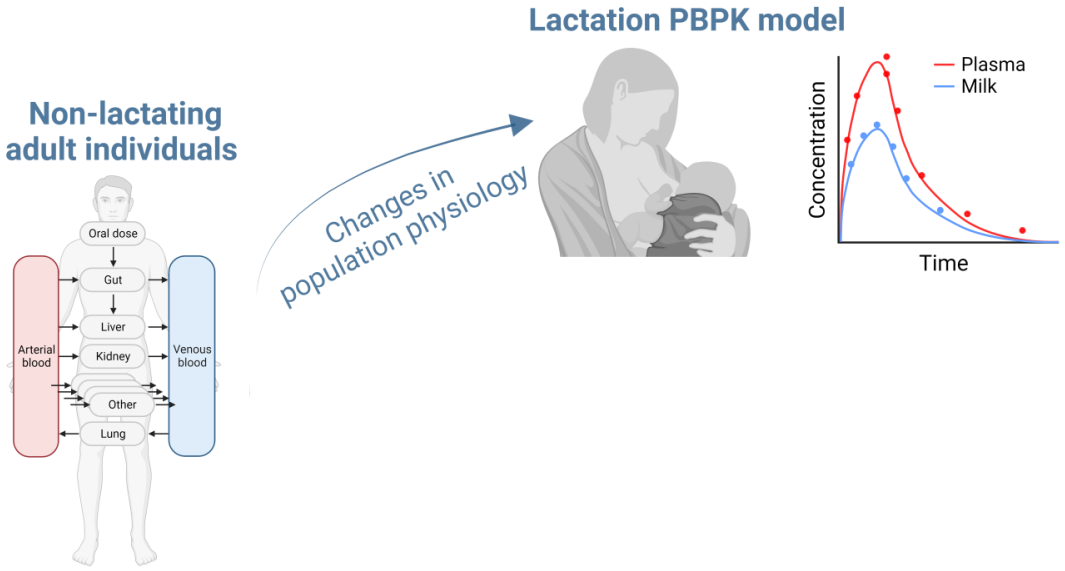
Infant exposure



$$\text{Daily infant dosage (DID, } mg/kg/day) = Concentration_{\text{human milk}}(mg/mL) * Volume_{\text{human milk}}\ (mL/kg/day)$$

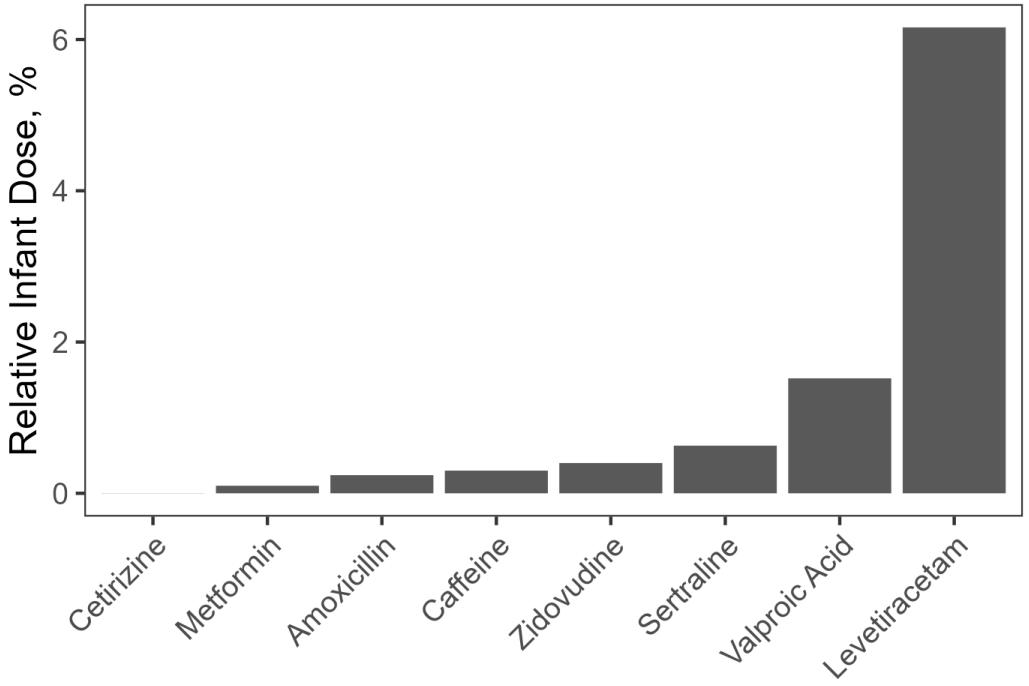
$$\text{Relative infant dose (RID, \%)} = \frac{Daily\ infant\ dosage}{Daily\ maternal\ dosage} * 100\ \%$$

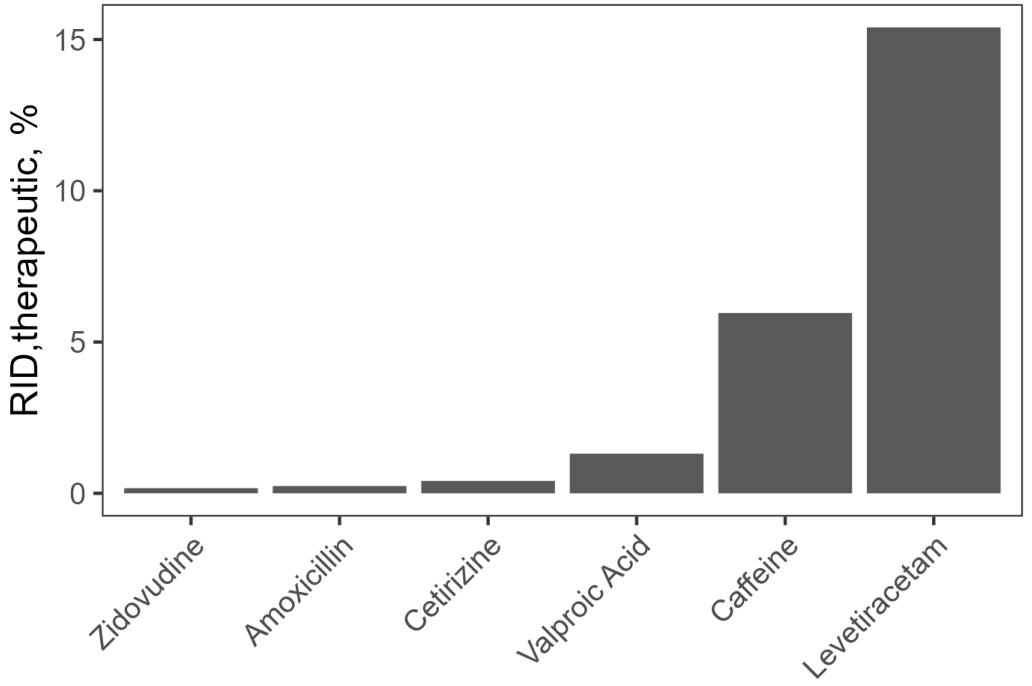
$$\text{Relative therapeutic infant dose } (RID_{therapeutic}, \%) = \frac{Daily\ infant\ dosage}{Daily\ \text{therapeutic infant}\ dosage} * 100\ \%$$

$$\text{Relative infant exposure (RIE, \%)} = \frac{AUC_{plasma,infant}}{AUC_{plasma,mother}} * 100\ \%$$

References: Nauwelaerts et al. (2023)
Abbreviations: Physiologically-based pharmacokinetic modelling (PBPK modelling); Daily infant dosage (DID); relative infant dose (RID); relative infant exposure (RIE), relative therapeutic infant dose ($RID_{therapeutic}$)

Infant Risk Assessment





$$\text{RID}\ (\%) = \frac{Daily\ infant\ dosage}{Daily\ maternal\ dosage} * 100\ \%$$

$$RID_{therapeutic}(\%) = \frac{Daily\ infant\ dosage}{Daily\ \text{therapeutic infant}\ dosage} * 100\ \%$$

The RID, % was low (< 10%) for 8 medicines;

The RID,therapeutic for all medicines was well below (<25%) the common dosing regimens given to infants for therapeutic reasons.

References: Nauwelaerts et al. (2023)
Infant exposure of nevirapine and tenofovir should be interpreted with caution as human milk concentration-time profiles were overpredicted.
Caffeine is administered only to preterm infants.

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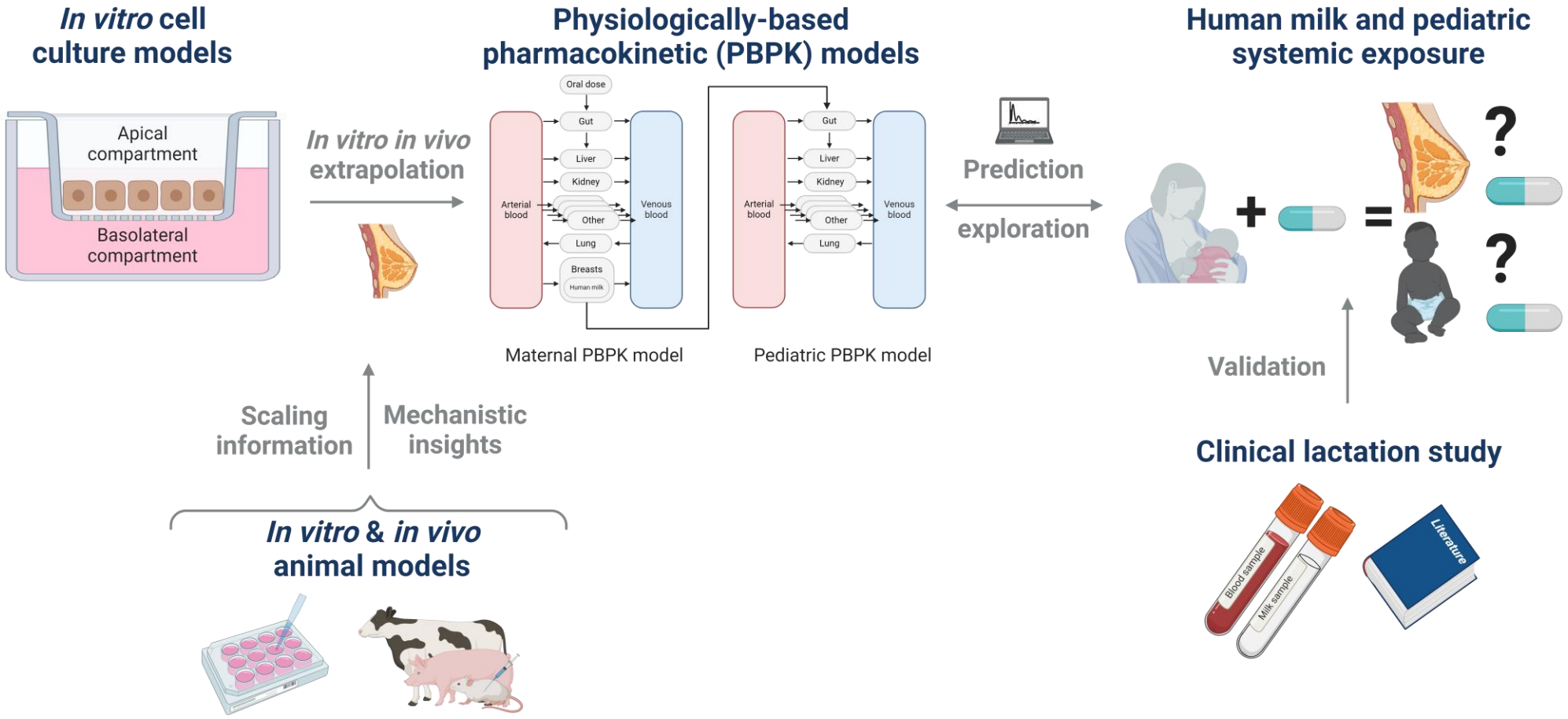
Non-clinical platform for predicting milk and infant exposure to maternal medication



Reference: https://doi.org/10.1016/j.biopha.2020.111038

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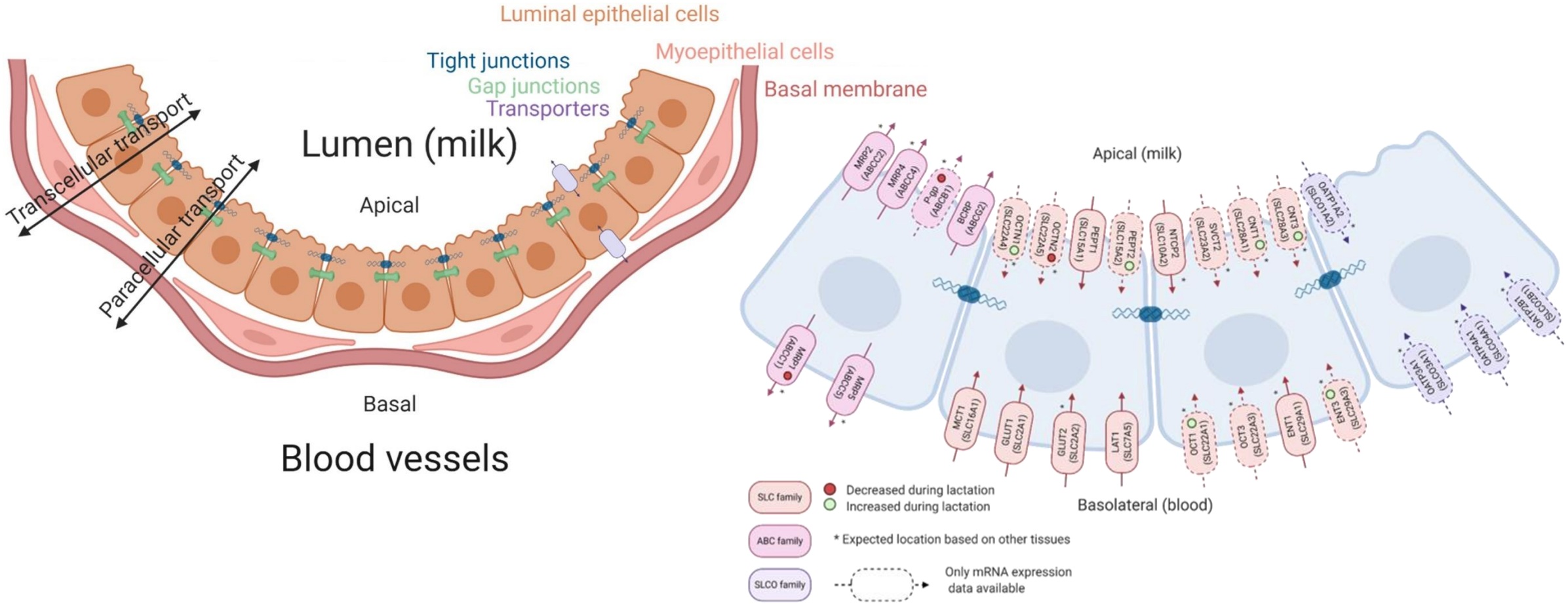
Epithelial cells form a tight barrier between blood and human milk



Reference: https://doi.org/10.1016/j.biopha.2020.111038

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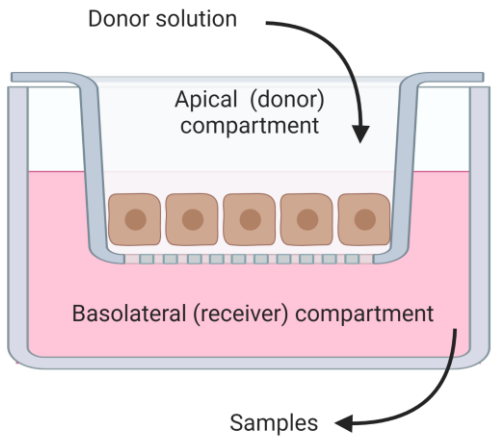
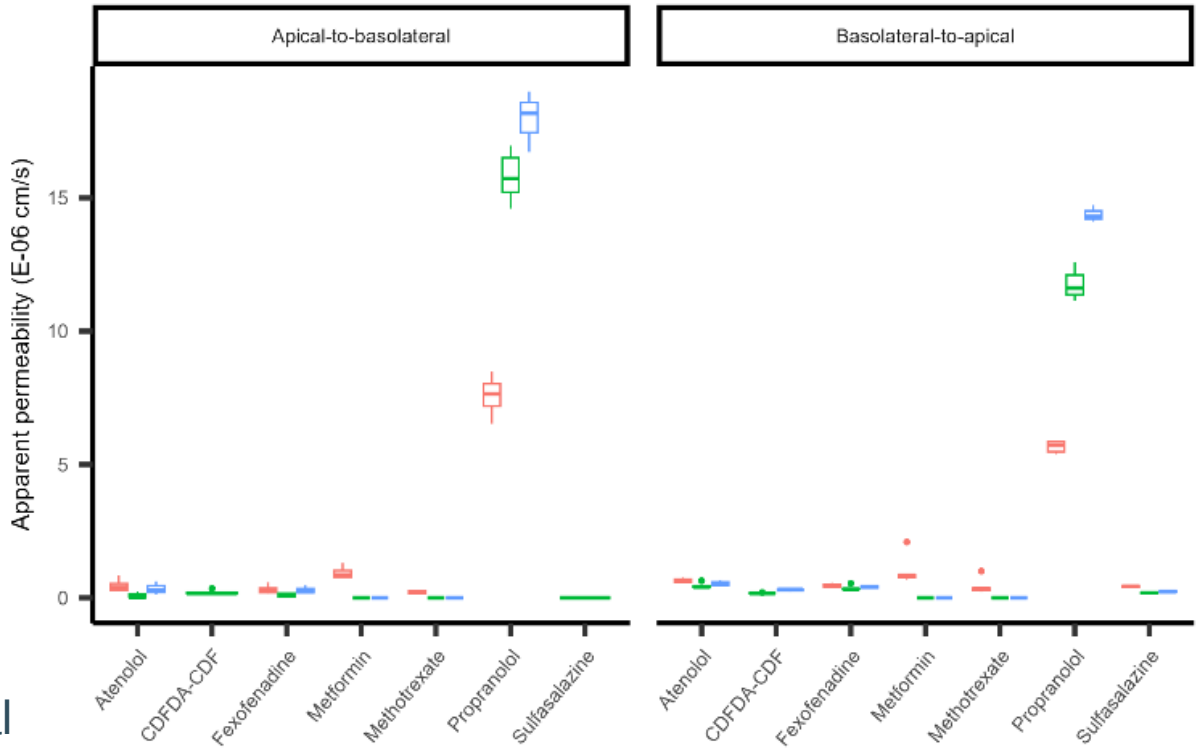
Bidirectional permeability coefficients were obtained in human mammary epithelial cells (hMECs)



$$P_{app} = \left(\frac{dQ}{dt}\right)\left(\frac{1}{AC_0}\right)$$



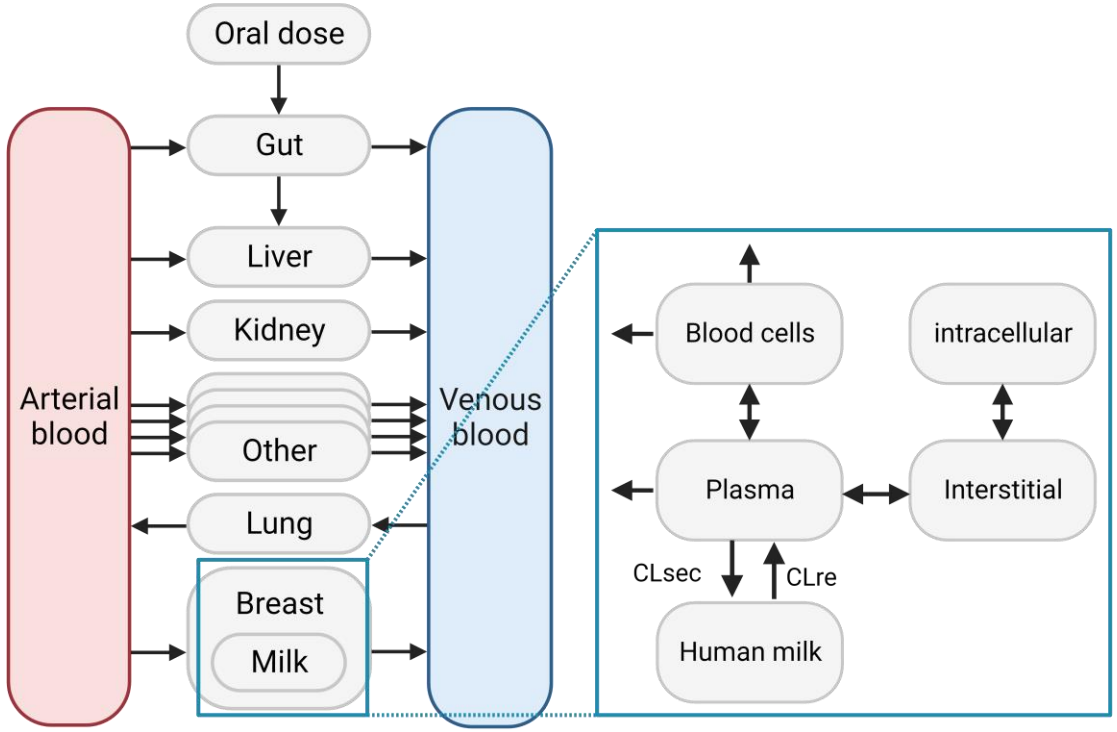
- hMECs *in vitro* model covered a 50-fold range of permeability values, differentiating between passive transcellular (propranolol) and paracellular (atenolol) mediated transport.
- There is a correlation between the basolateral-to-apical apparent permeability (i.e. representing secretion towards human milk) in hMECs and the *in vivo* M/P ratio.

Independent experiments are shown in red (n=6), green (n=6) and blue (n=3).

Reference: **https://doi.org/10.3390/ijms252111454**

Abbreviations: Permeability coefficient (Papp, cm/s); steady-state flux (dQ/dt); Surface area of the filter (A); Initial donor concentration (C_0)

In vitro permeability coefficients can inform lactation PBPK models



$$\frac{dN_{milk}}{dt} = C_{plasma} * fu_{plasma} * CL_{sec}$$

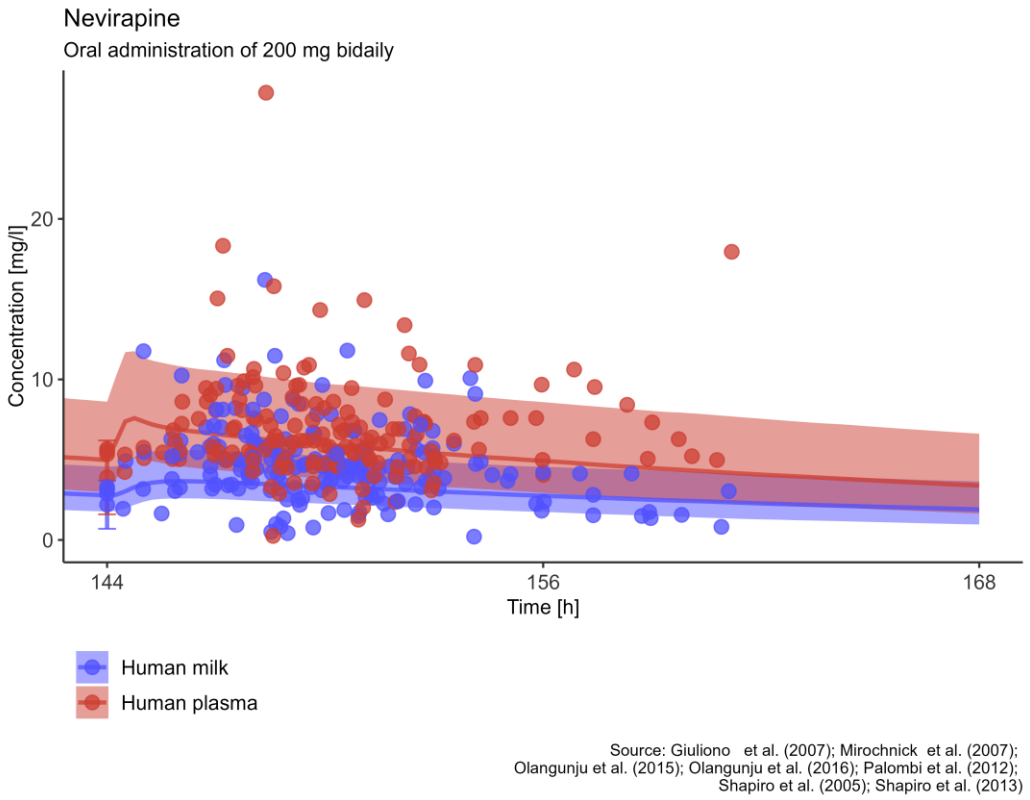
$$CL_{sec} = \text{SA} * P_{app,BA}$$

$$\frac{dN_{plasma}}{dt} = C_{milk} * fu_{milk,total} * CL_{re}$$

$$CL_{re} = \text{SA} * P_{app,AB}$$

Abbreviations: Permeability coefficient (Papp, cm/s); apical-to-basolateral (AB), basolateral-to-apical (BA) , surface area (SA); change in amount of medicine in human milk over time (dNmilk/dt); change in amount of medicine in human plasma over time (dNplasma/dt)

Integration of *in vitro* permeability coefficients improved human milk predictions of nevirapine



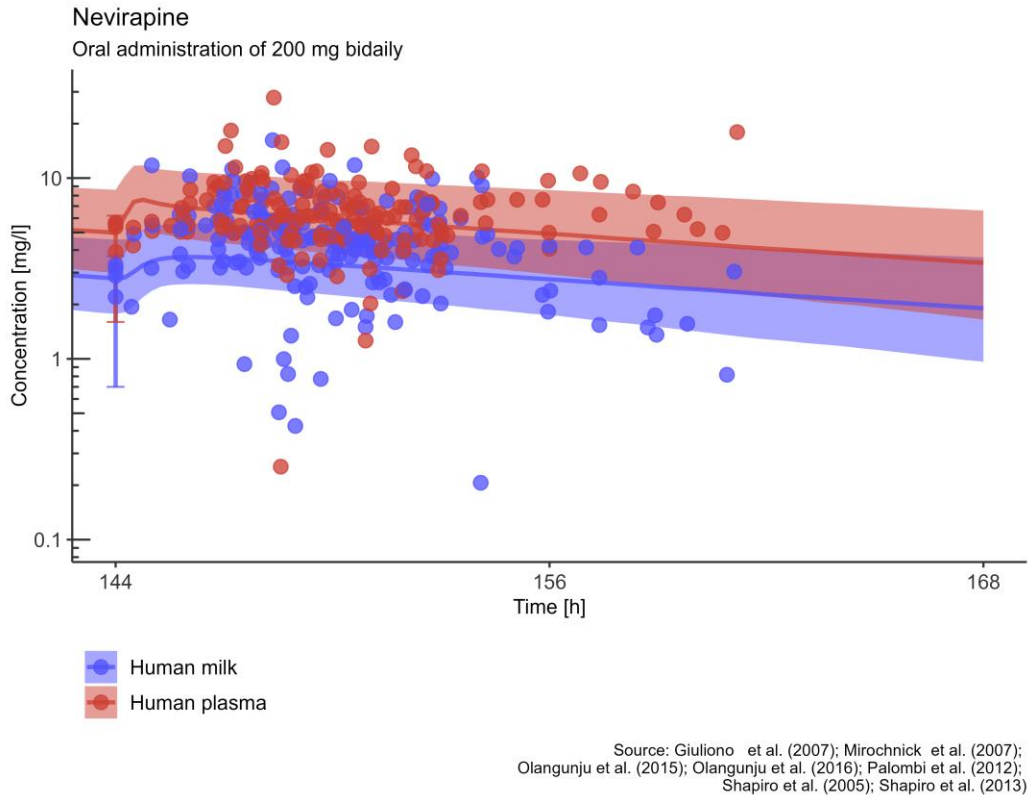


Figure on the right panel shown the data with the y-axis on a log scale.

Conclusions and future perspectives

- Lactation PBPK models carry the promise for “early” *in silico* prediction of medicine milk concentration time profiles
- Ongoing efforts will implement *in vitro* permeability coefficients across the blood – milk barrier
- PBPK-based simulations are expected to support decisions about medication use during lactation

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Justine Badee (Novartis Institutes for BioMedical Research)

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Publication

Thank you!

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