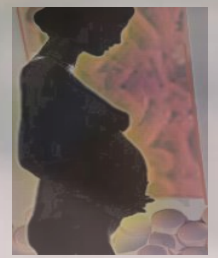

Predicting maternal-fetal exposure to drugs using a mechanistic PBPK model

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Predicting Maternal-Fetal Exposure to Drugs by Phenotyping Studies and a Maternal-Fetal (m-f) PBPK Model

- When pregnant women are given standard drug doses, maternal-fetal exposure to these drugs, and their efficacy and safety, will often differ from that in men or non-pregnant women because the PK of drugs are changed by pregnancy (e.g. CYPs are induced or repressed)

- It is neither feasible nor desirable to determine maternal-fetal exposure to all drugs or natural products/supplements taken by pregnant women

- Therefore, to inform correct maternal dosing regimen and minimize fetal risks, we have developed a systems/mechanistic pharmacology approach to predict maternal-fetal exposure to drugs throughout pregnancy:

  – First, elucidate the extent of changes in drug disposition (e.g. drug metabolism and transport) for model drugs (phenotyping studies)

  – Then use a maternal-fetal **P**hysiologically **B**ased **P**harmaco**k**inetic (m-f PBPK) model to predict the disposition of other drugs that are also metabolized/transported by the same mechanisms

Can Maternal Disposition of CYP-Cleared Drugs be Accurately Predicted by our m-f PBPK Model?

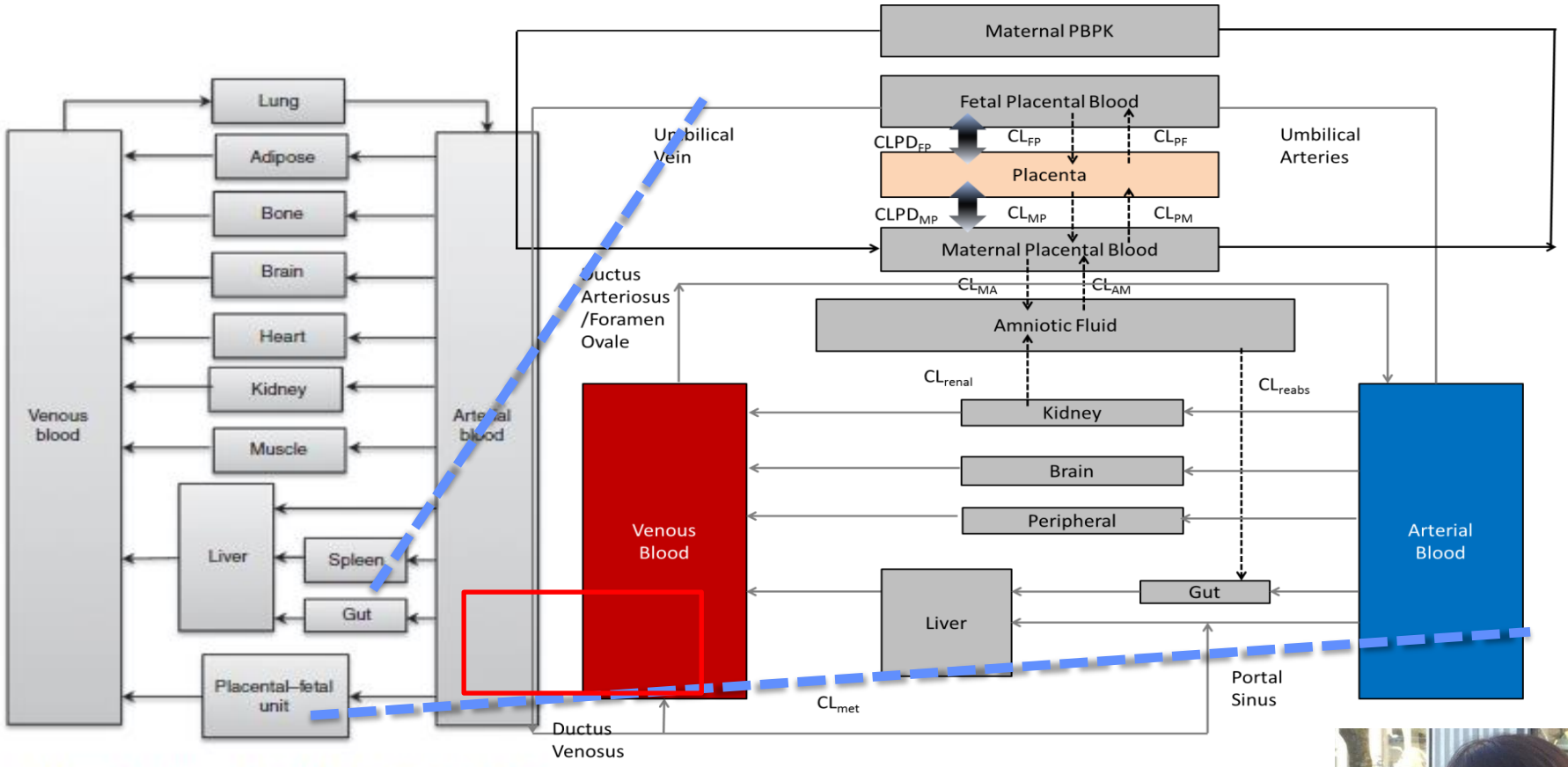


Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic model (PBPK) model. The PBPK model is an extension of the Simcyp 13-compartment full-PBPK model, and includes a lumped compartment to represent placental–fetal organs including the fetus, placenta, and the amniotic fluid. Reproduced from Lu *et al.* 2012.[19]

Zhang et al. DMD 2017

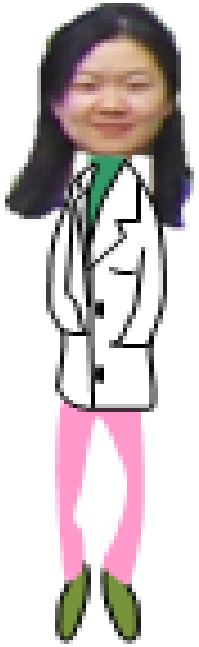
Ke et al 2012

- Populate the model by pregnancy-specific physiological mechanistic data e.g. changes in CYP and transporter activity
- Then, predict the changes in m-f exposure to drugs not studied in pregnancy

3

Validation of our m-f PBPK model

CYP3A **Midazolam (Dextromethorphan)** **Nifedipine, Indinavir**	**CYP1A2** **Caffeine** **Theophylline**
CYP2D6 **Metoprolol** **Dextromethorphan/Dextrorphan, Paroxetine, Clonidine**	**Multiple CYPs** **Methadone, Glyburide**



Alice Ke

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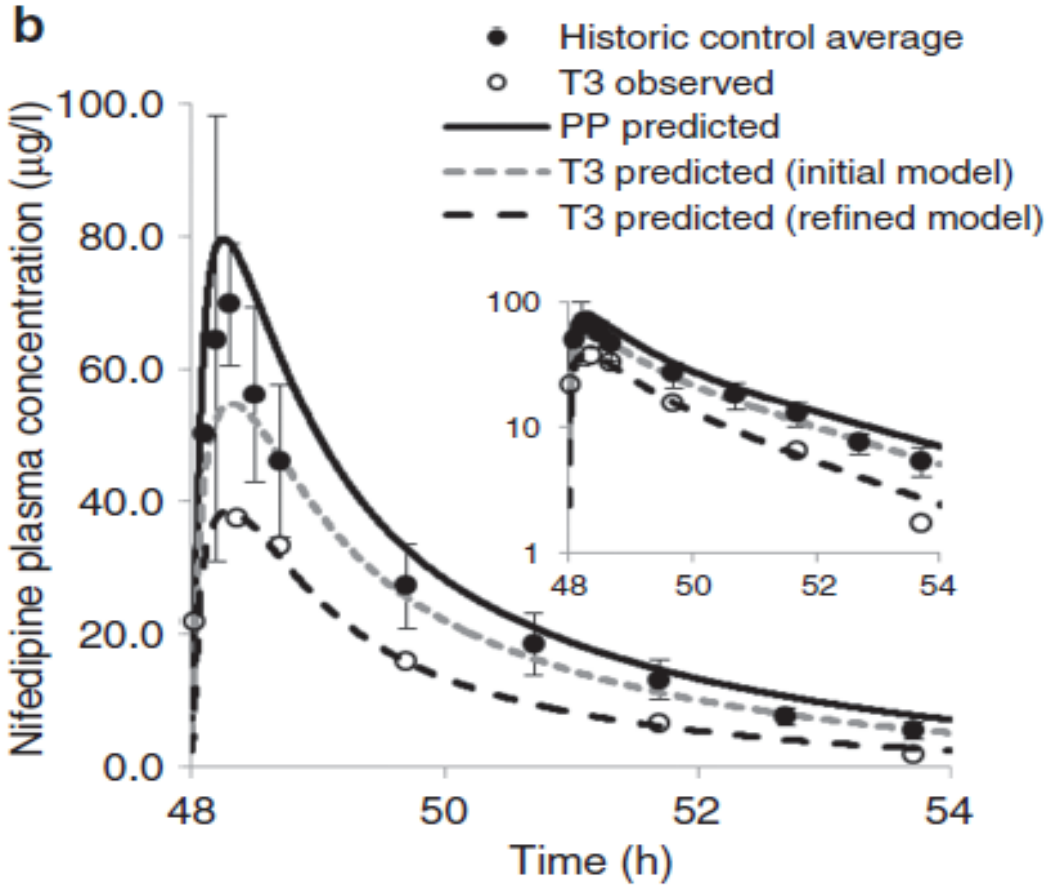
Successful Prediction of the Disposition of Several CYP3A-cleared Drugs during T3 Based on Midazolam Phenotyping Data

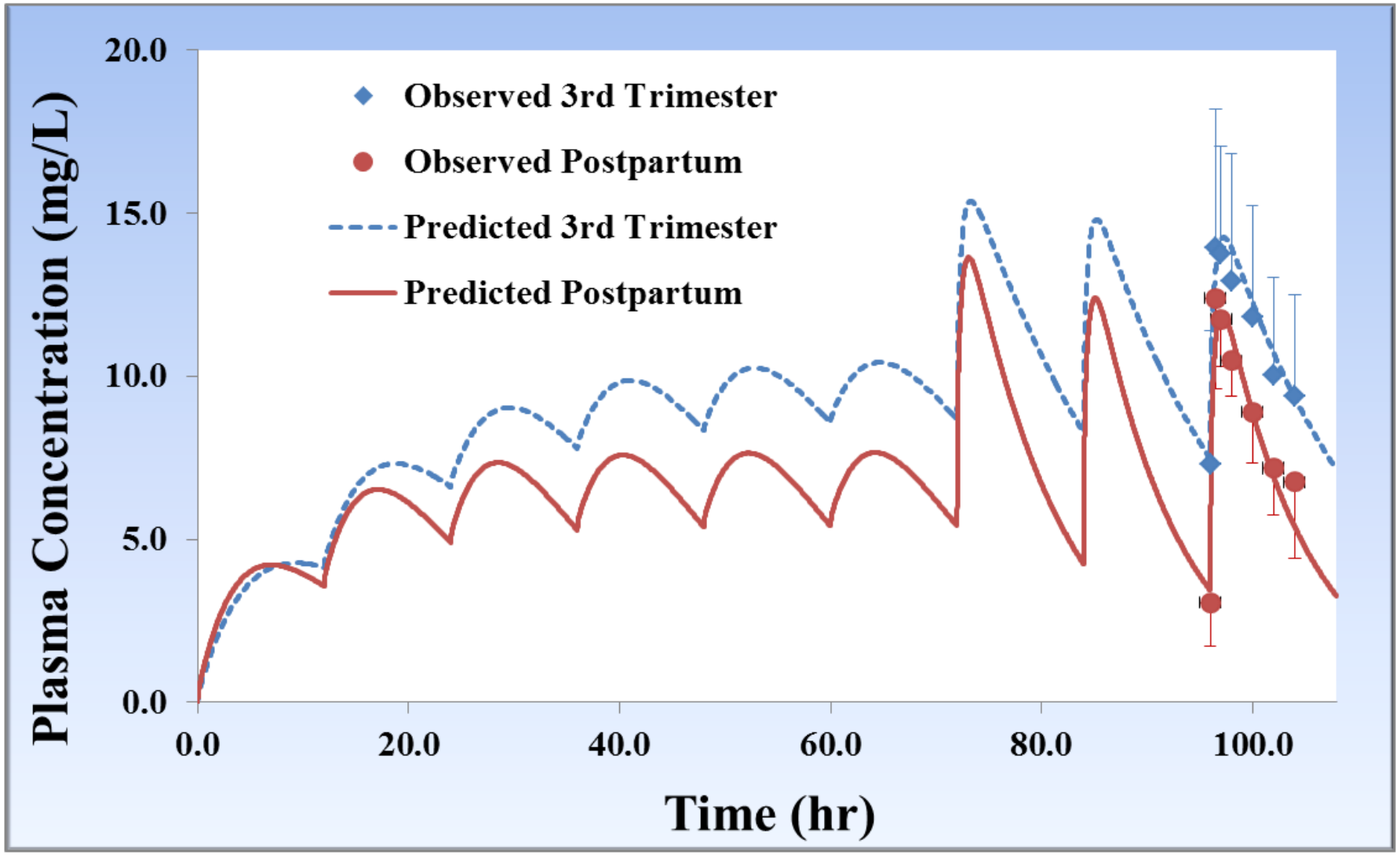


- Based on midazolam data, our m-PBPK model successfully predicted the 3rd trimester (T3) disposition of two predominantly CYP3A-cleared drugs (i.e. nifedipine and indinavir)
- This induction is hepatic rather than intestinal
- Human hepatocyte studies suggest that CYP3A enzymes are equally induced throughout pregnancy

Ke et al. CPT: Pharmacometrics & Systems Pharmacology, 2012

5

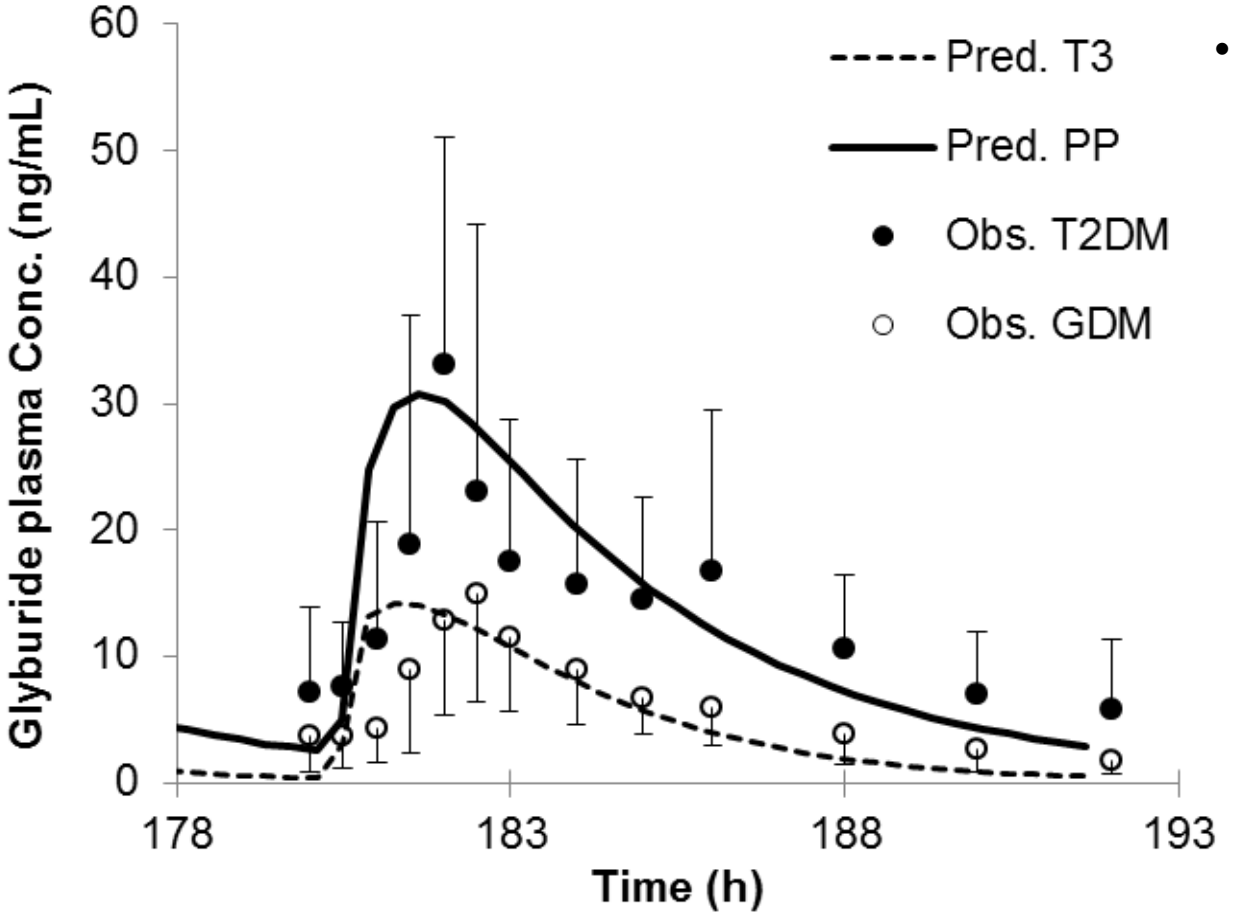
Successful Prediction of the Steady-State PK of a CYP1A2-metabolized drug, Theophylline, during T3, Based On Caffeine Phenotyping Data



Ke AB et al., Drug Metab Dispos: 2013.

Gardner et al., Eur J Clin Pharmacol 1987 (n=10)

Successful Prediction of the Disposition of Drugs Cleared by Multiple CYP Enzymes during T3 e.g. Glyburide - CYP3A4 (~50%), CYP2C9 (~30%) and CYP2C19 (~20%)



- **Hepatic OATP1B1 or 2B1 activity was assumed to remain constant throughout pregnancy.**

Ke AB et al., Brit J Clin Pharmaco: 2013

Can our m-f PBPK Successfully Predict Fetal Exposure to Drugs that Passively and Actively Cross the Placenta?

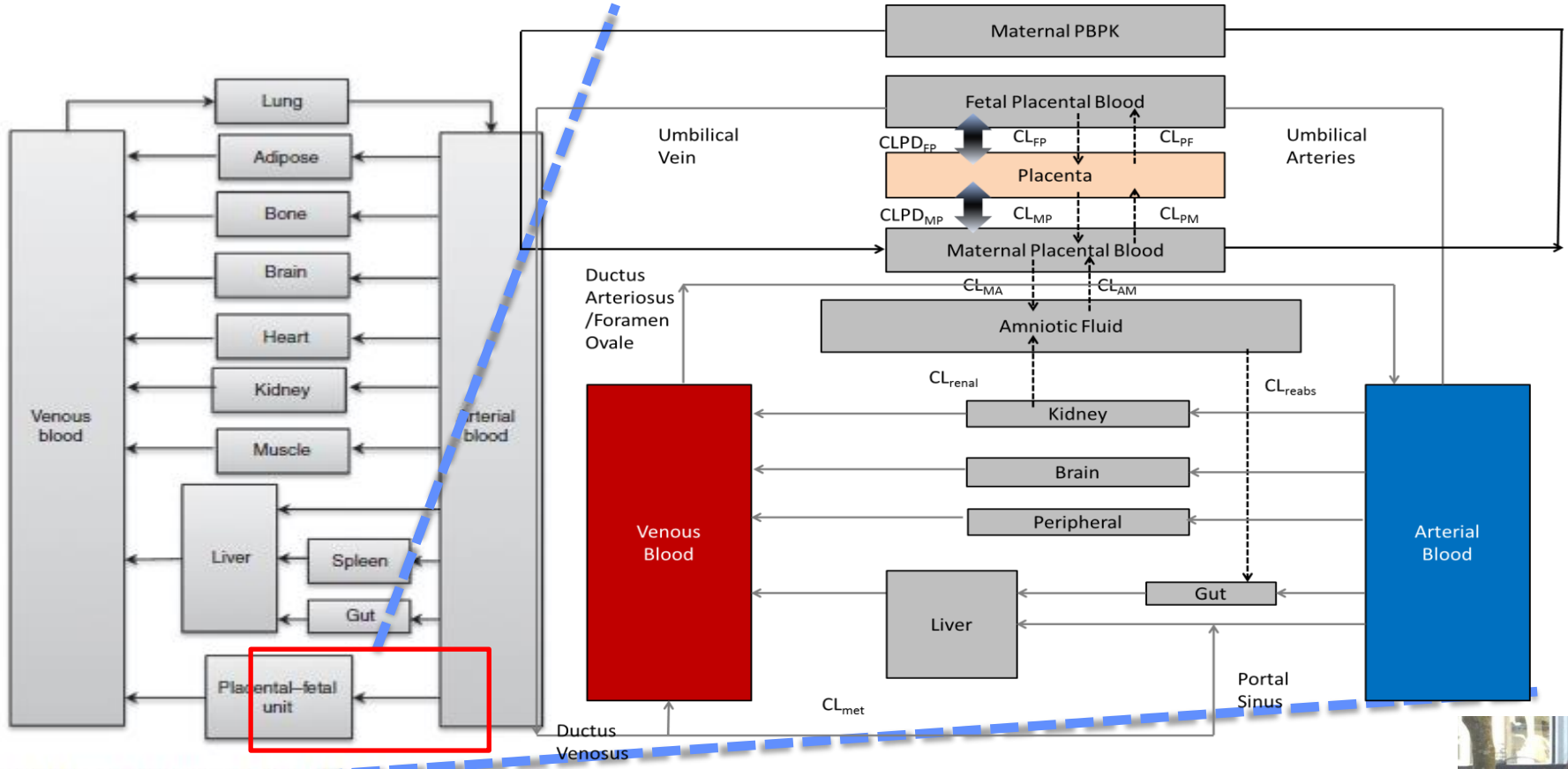
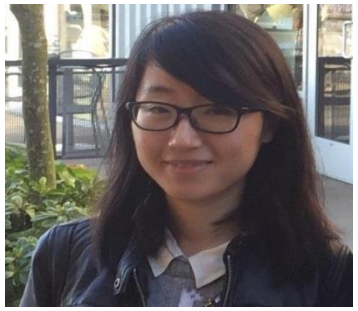


Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic model (PBPK) model. The PBPK model is an extension of the Simcyp 13-compartment full-PBPK model, and includes a lumped compartment to represent placental–fetal organs including the fetus, placenta, and the amniotic fluid. Reproduced from Lu *et al.* 2012.[12]

Ke et al 2012

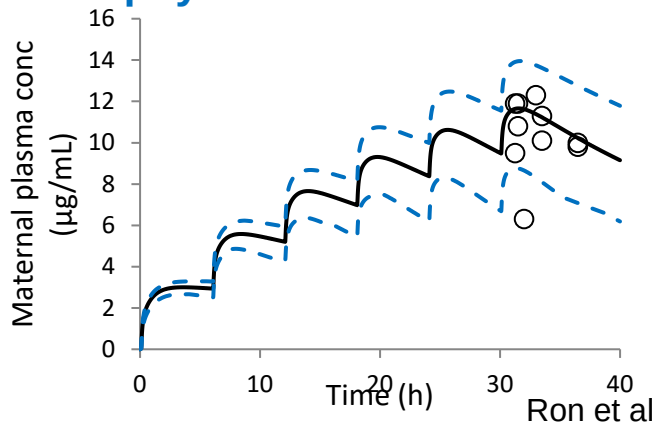
Contains fetal organs that are important for fetal drug disposition
Zhang et al. DMD 2017



8

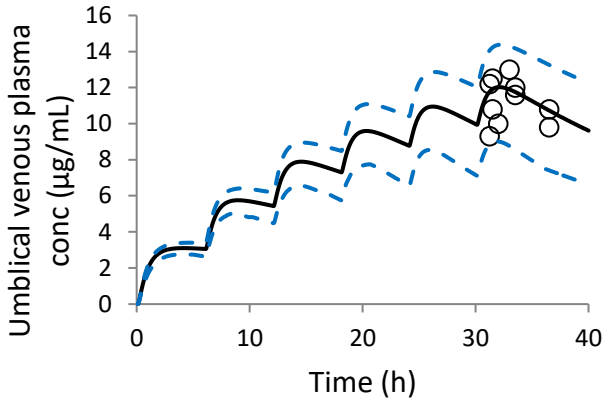
Successful Prediction of Fetal Exposure to Drugs that Passively Cross the Placenta: Theophylline and Zidovudine (AZT)

Theophylline Maternal



Ron et al, 1994

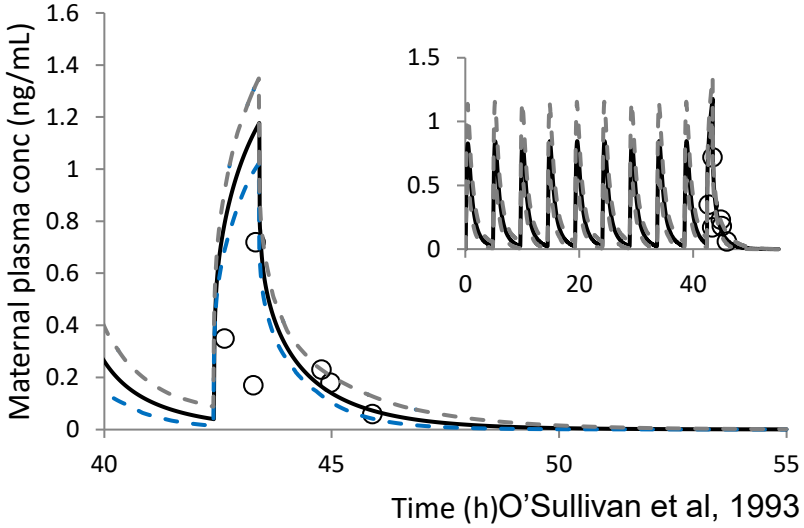
Fetal



200mg theophylline dosed orally prior to C-section

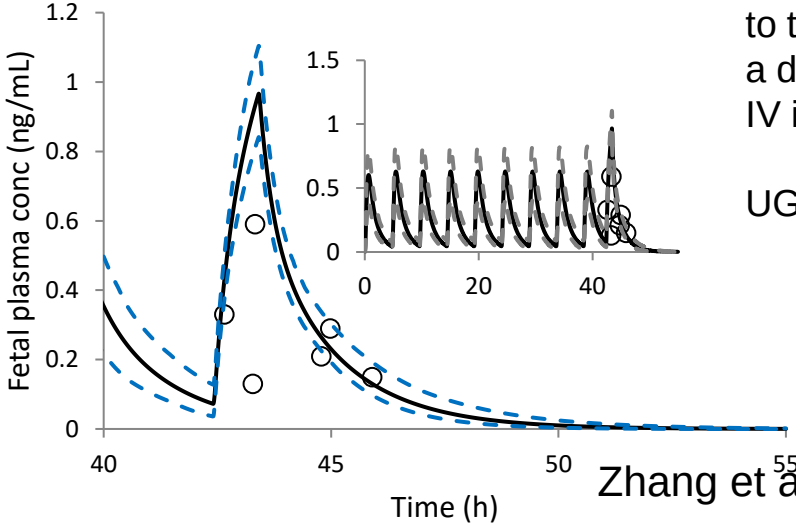
CYP 1A2 substrate

Zidovudine Maternal



O'Sullivan et al, 1993

Fetal



Zidovudine was dosed to term women 5 times a day followed by a 1-h IV infusion

UGT2B7 substrate

Zhang et al., DMD 2017

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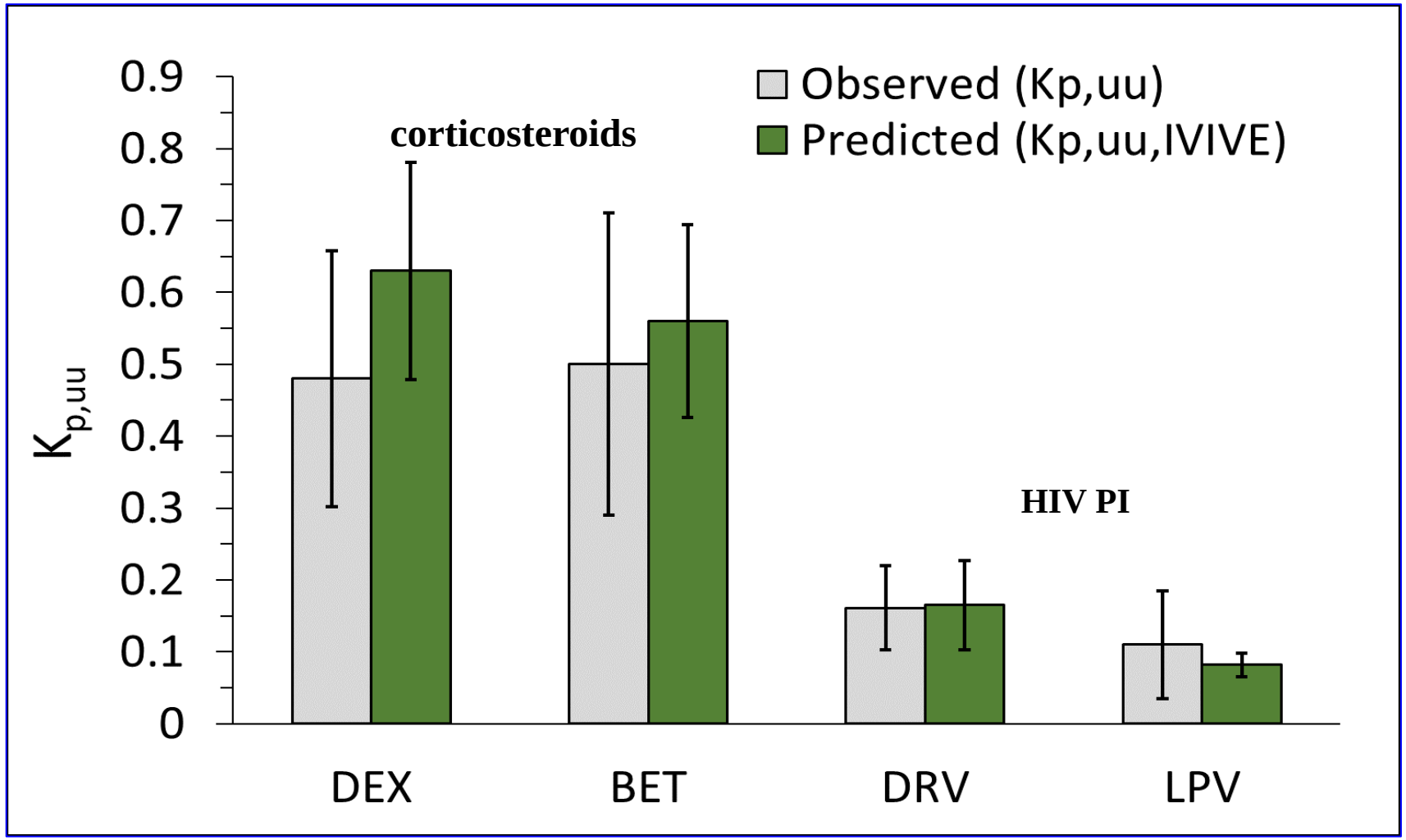
Successful Prediction of Fetal Exposure to Drugs ($K_{p,uu}$, fetal –to-maternal unbound steady-state plasma conc. ratio) Effluxed by Placental P-gp



P-gp Substrates:

- **Dexamethasone (DEX)**
- **Betamethasone (BET)**
- **Darunavir (DRV)**
- **Lopinavir (LPV)**

Anoshchenko *et al.*, DMD 2021

Significance of Our Findings

- This success provides confidence in using our m-f PBPK model to predict maternal-fetal exposure throughout pregnancy:

  - To drugs predominately metabolized by the common CYP enzymes

    AND

  - Drugs that passively cross the placenta or are transported by placental P-gp or other/multiple placental transporters (e.g., BCRP and P-gp)

- Such predictions can help guide design of drug dosing regimens for pregnant women that are safe and efficacious for the maternal-fetal dyad

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