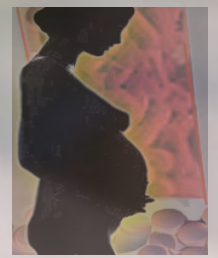

Successful Prediction of Fetal Exposure to Transported and Non-transported Drugs Using In Vitro Studies and PBPK M&S

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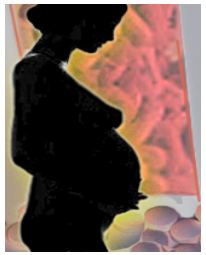


The Pregnant Woman and Her Fetus are Drug Orphans

Medication use in pregnancy is prevalent

- Up to **80%** of pregnant women take drugs during pregnancy
- **90%** of drugs lack **approval** for use in pregnancy
- Some drugs are administered to pregnant women to treat the fetus (e.g. corticosteroids, HIV drugs)

Fetal/neonatal safety and efficacy of drugs is difficult (or often impossible) to determine, but:

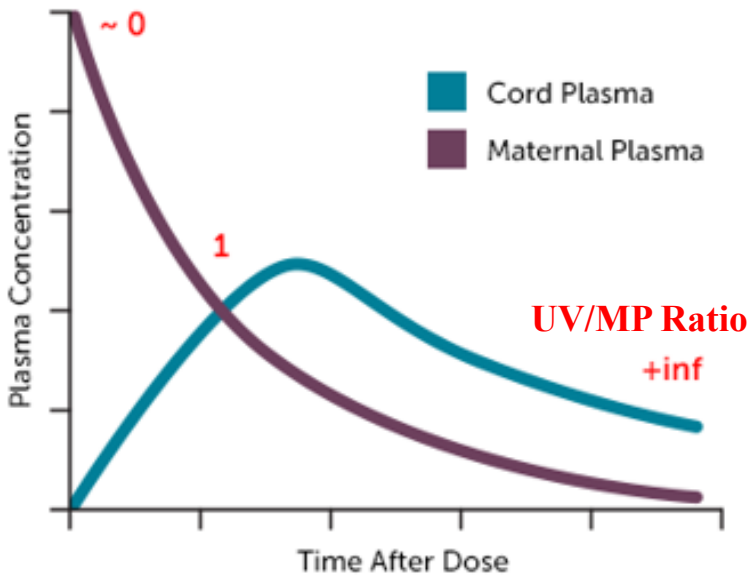
- Fetal/neonatal safety/efficacy is driven by **fetal drug exposure**, which in turn is driven by:
  - Maternal drug exposure
  - Placental transport (often significant) or metabolism (usually negligible)
  - Fetal metabolism (usually negligible)

How can we Assess Fetal Drug Exposure?

Difficult Though Possible

Fetal blood/plasma can be sampled **only once and only at term** (from umbilical vein, UV or artery - UA)

- Umbilical vein plasma/maternal plasma (UV/MP) drug concentration ratio **at term** is often **incorrectly** interpreted as a measure of fetal drug exposure



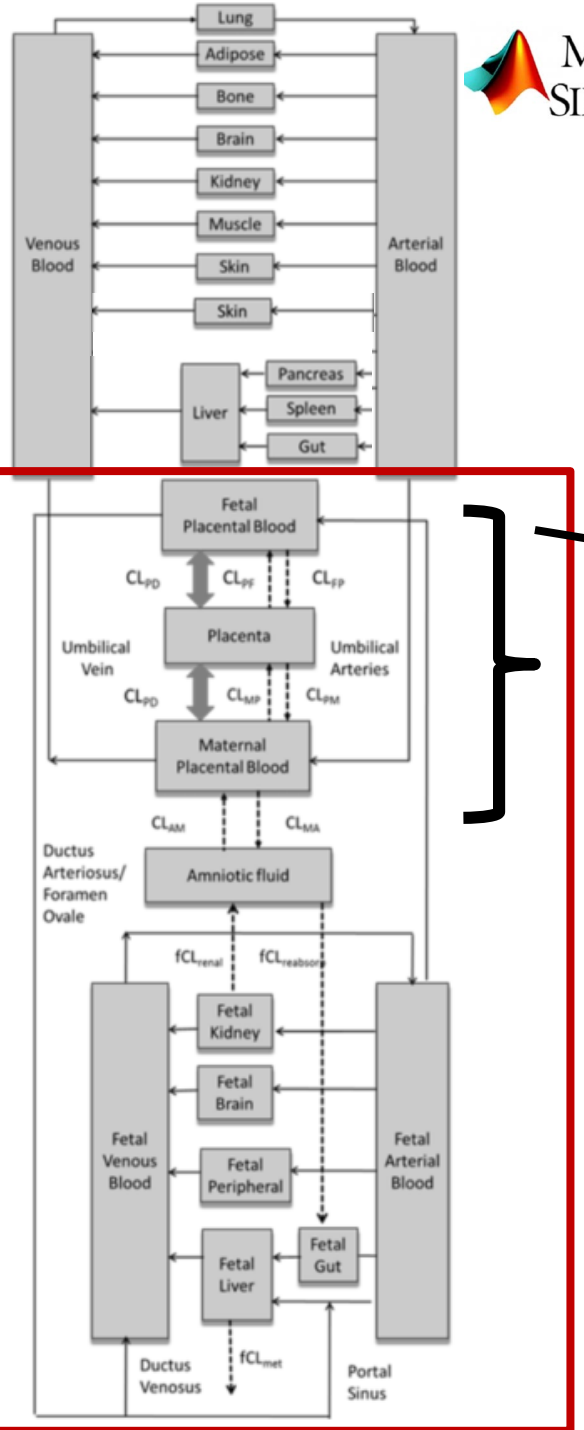
Correct "relative" Fetal Drug Exposure is: $K_{p,uu} = \frac{f_{u,f} \times AUC_f}{f_{u,m} \times AUC_m}$

- Kp,uu = 1 for passively diffusing drugs, but <1 for those that are effluxed; need to also predict fetal Cmax
- can be obtained by pooling term data from multiple maternal-fetal dyads; but impossible < term
- therefore, alternative methods are needed to **predict**, rather than measure, Kp,uu

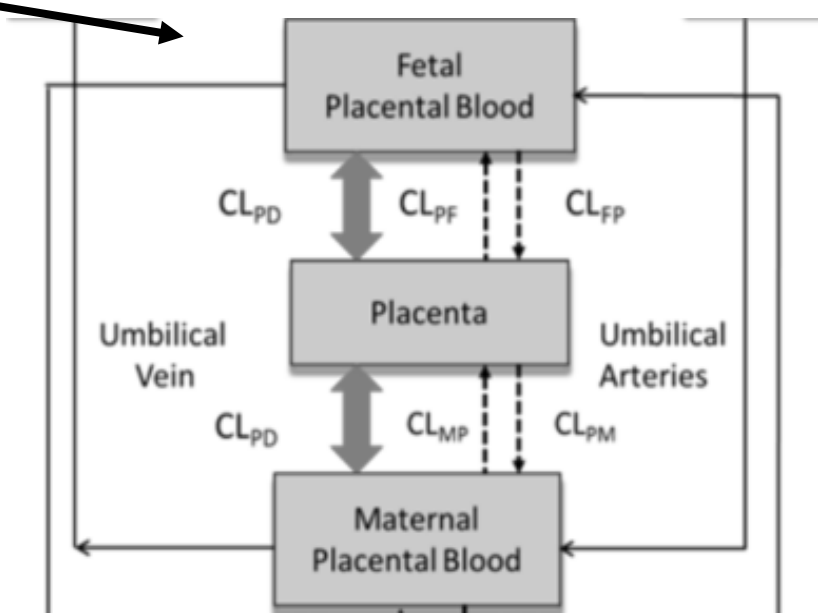
Maternal-Fetal PBPK (m-f PBPK) Model to Estimate $K_{p,uu}$

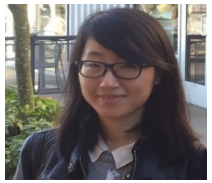
Incorporates changes in all gestational –age dependent physiological parameters including changes in:

- Cardiac output and organ blood flows
- Plasma proteins and plasma protein binding of drugs
- Activity/abundance of drug metabolizing enzymes or transporters including in the **placenta**



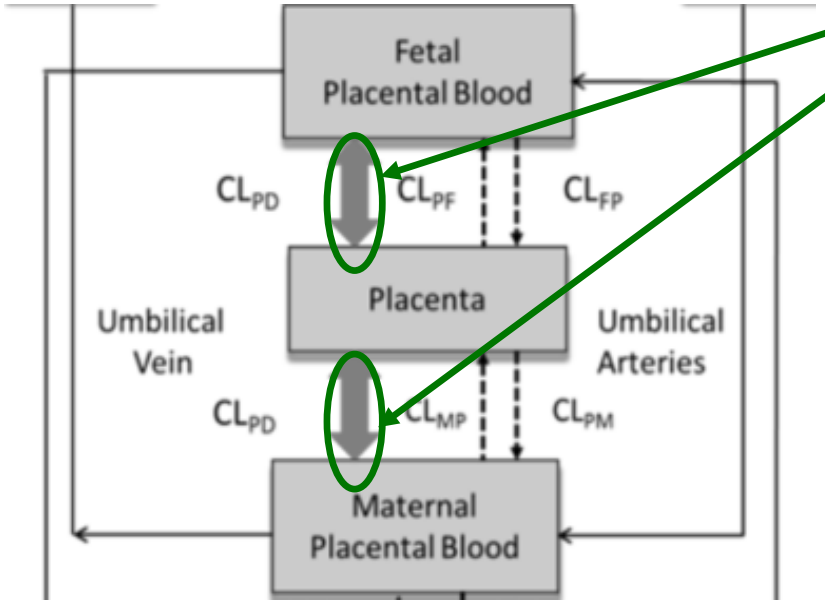
MATLAB SIMULINK

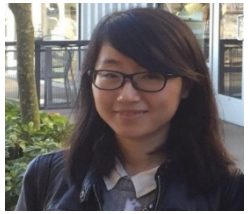




Zhang and Unadkat, 2017 DMD

Successful Prediction of Fetal Exposure to Drugs that Passively Cross the Placenta using our M-F PBPK Model

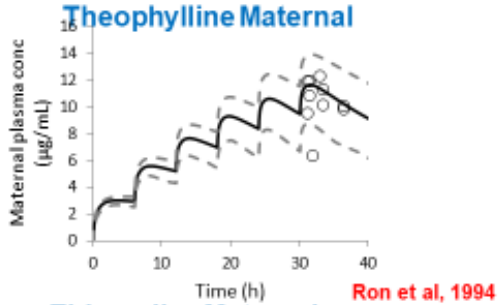




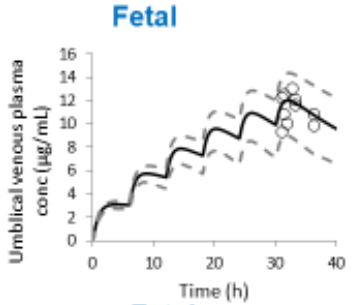
Zhang and Unadkat, 2017 DMD

W UNIVERSITY of WASHINGTON

Model Verification using passive diffusion drugs

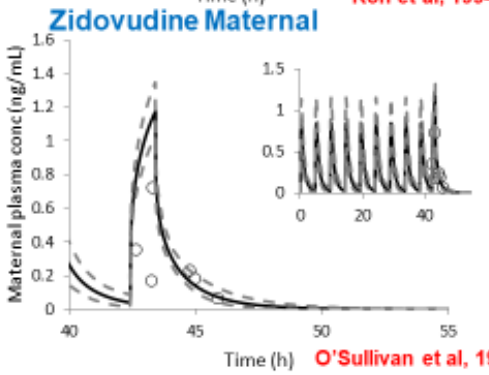


Ron et al, 1994

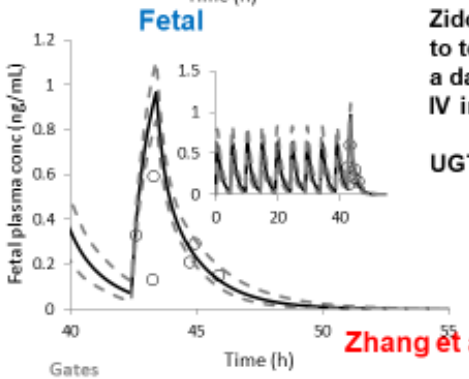


200mg theophylline dosed orally prior to C-section

1A2 substrate



O'Sullivan et al, 1993



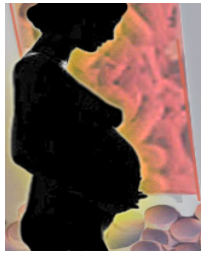
Zhang et al., DMD 2017

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

UGT2B7 substrate

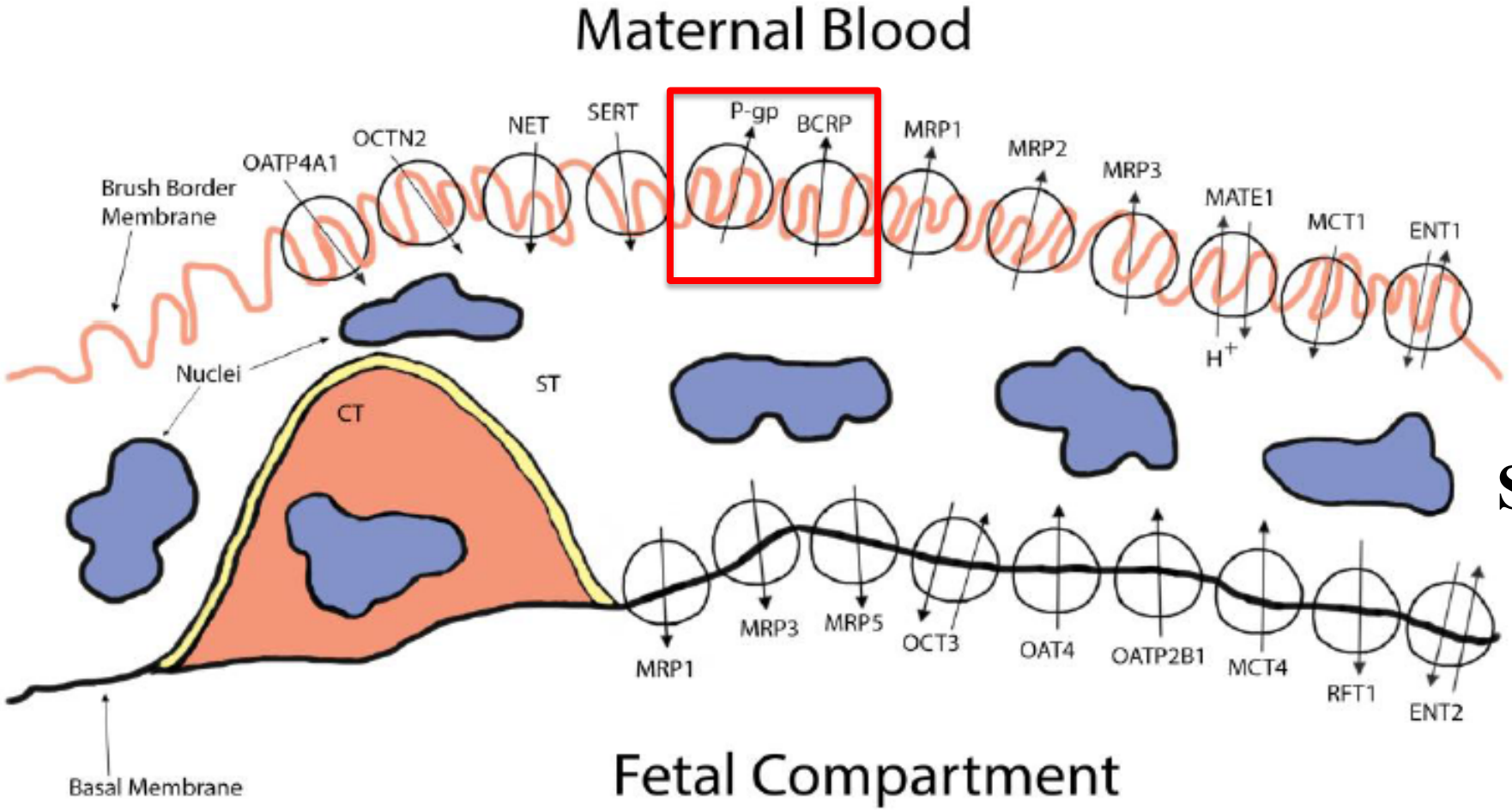
Gates

8

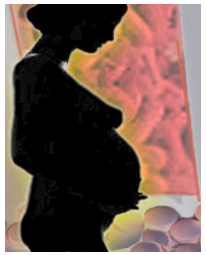


Expansion of our M-F PBPK to Predict Fetal Exposure to Drugs that are Transported Across the Placenta

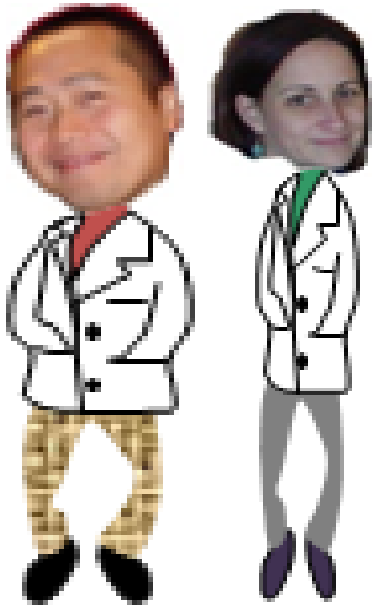
The Human Placenta is Richly Endowed with both Efflux and Influx Drug Transporters, the most important being P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP)



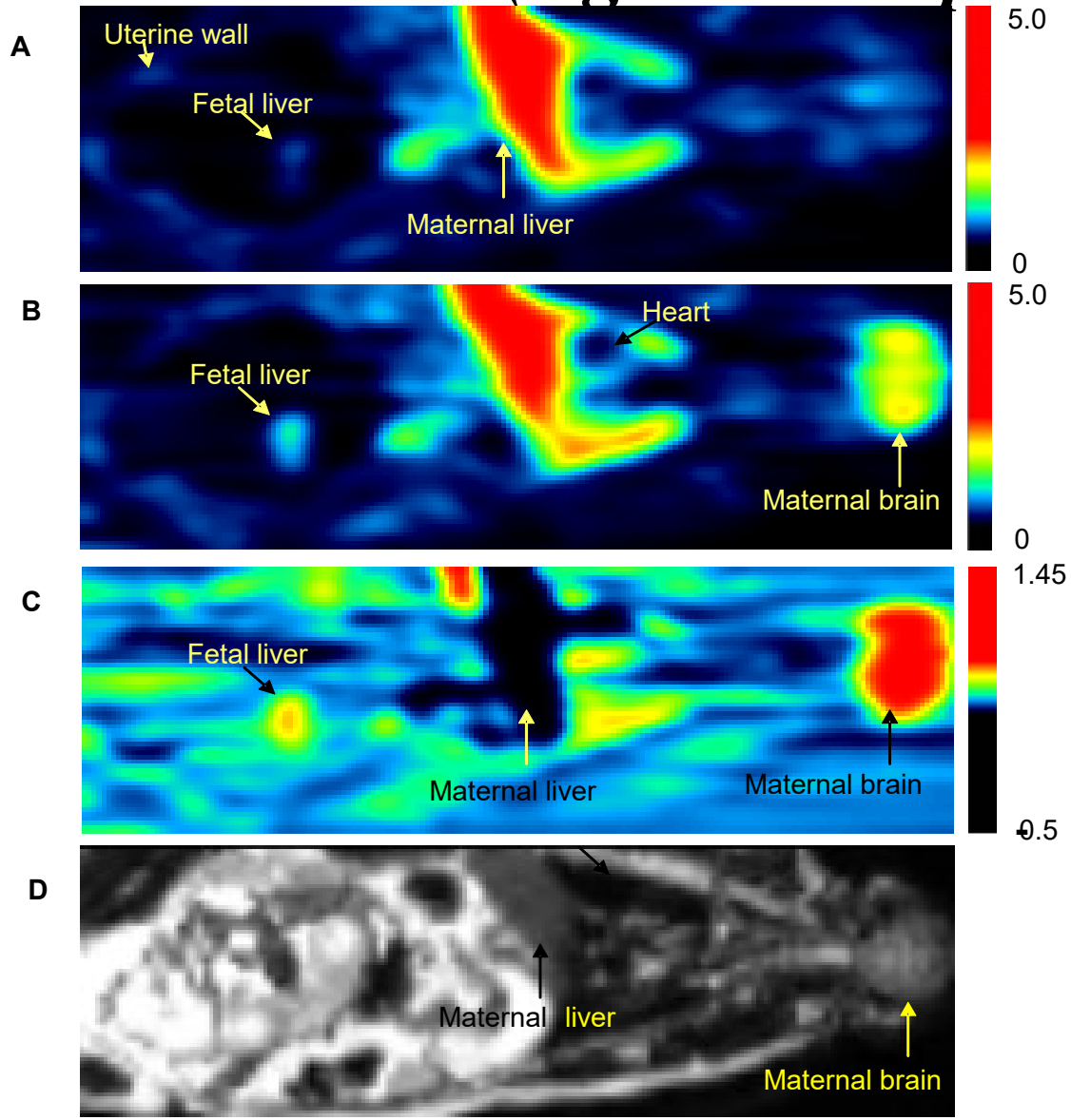
Syncytiotrophoblast



Placental P-glycoprotein (P-gp) Excludes P-gp Substrates from the Fetus (e.g. ^{11}C-verapamil)



Eyal et al.,
J Nucl. Med, 2009
Chung et al., Br J Pharmacol, 2010



7

Workflow to Predict Fetal Kp,uu of Transported Drugs

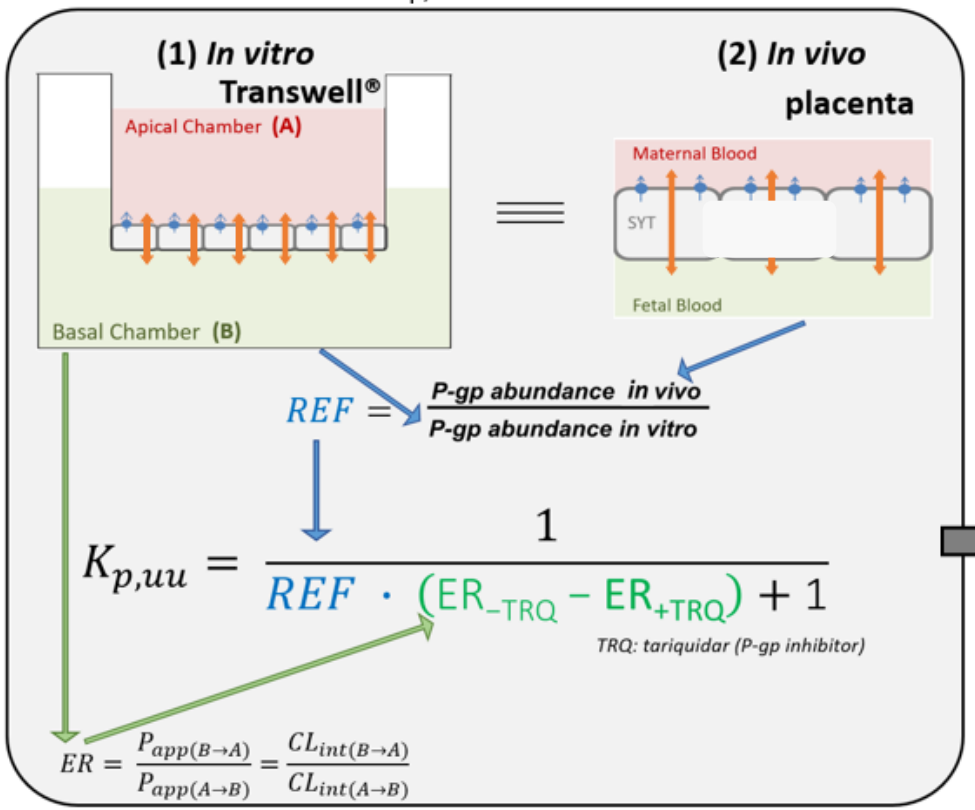
Model Transporter:

P-gp

P-gp Substrates:

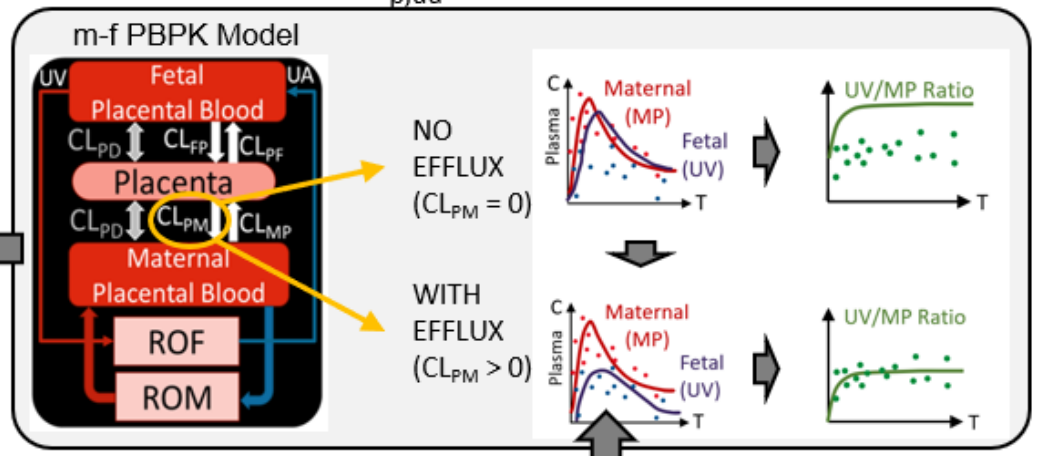
1) *Darunavir (DRV)*
2) *Lopinavir (LPV)*
3) *Dexamethasone (DEX)*
4) *Betamethasone (BET)*

Prediction of $K_{p,uu}$ from *In Vitro* Studies



Predicted $K_{p,uu}$ — VERIFY — Observed $K_{p,uu}$

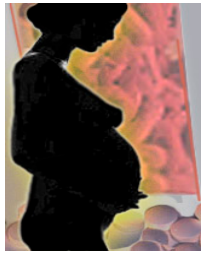
Estimation of $K_{p,uu}$ from Observed *In Vivo* Data



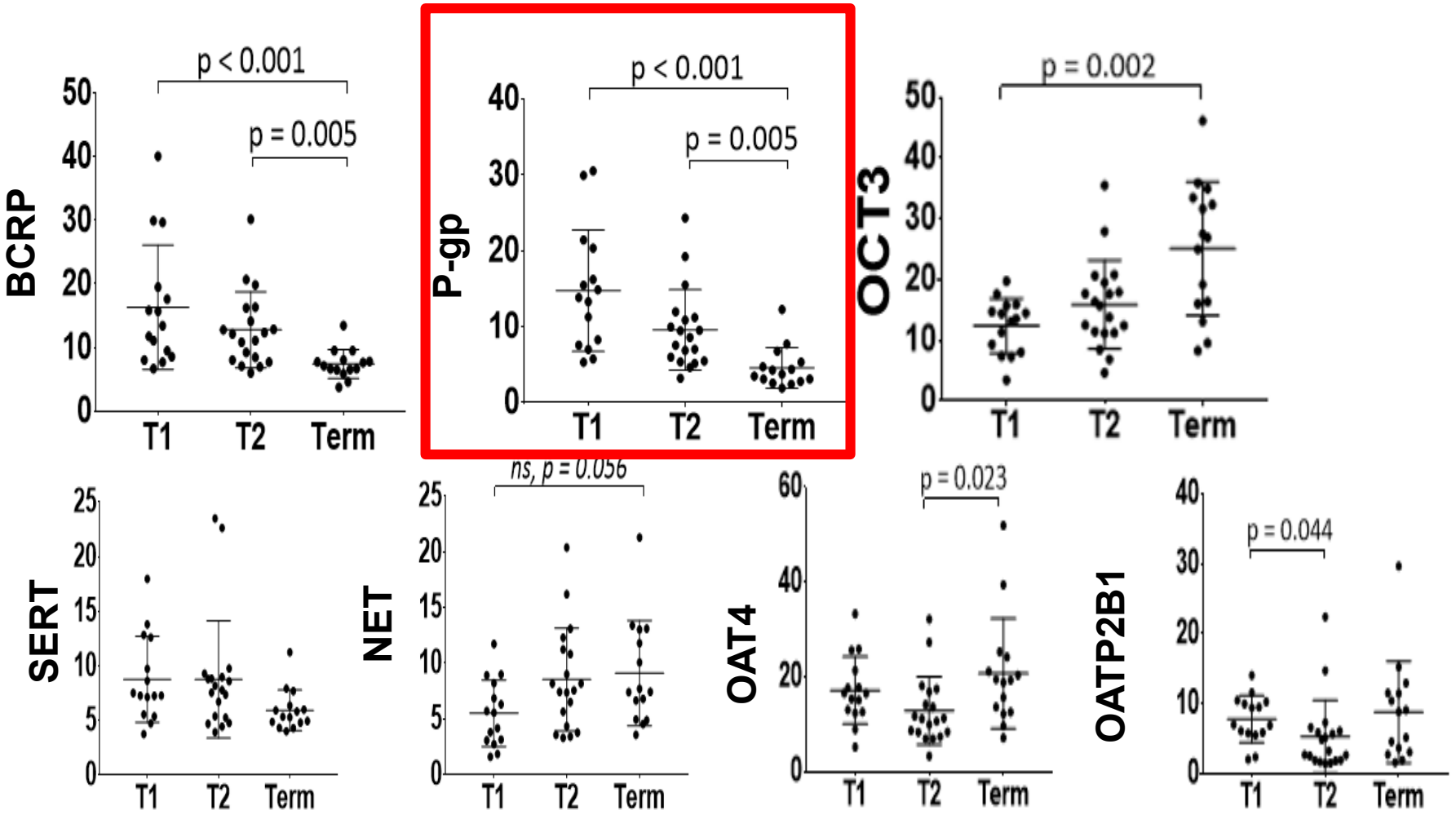
Observed *In Vivo* Data

Dots: Paired observed umbilical vein (UV) and maternal plasma (MP) drug concentrations at term. Each pair obtained from a single maternal-fetal dyad

Anoshchenko *et al.*, DMD 2021



The Abundance of Placental Transporters (pmole/g placenta) Changes with Gestational Age



Anoshchenko L et al., DMD 2020

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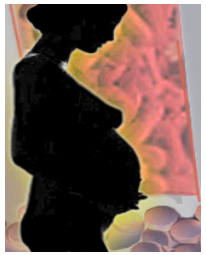
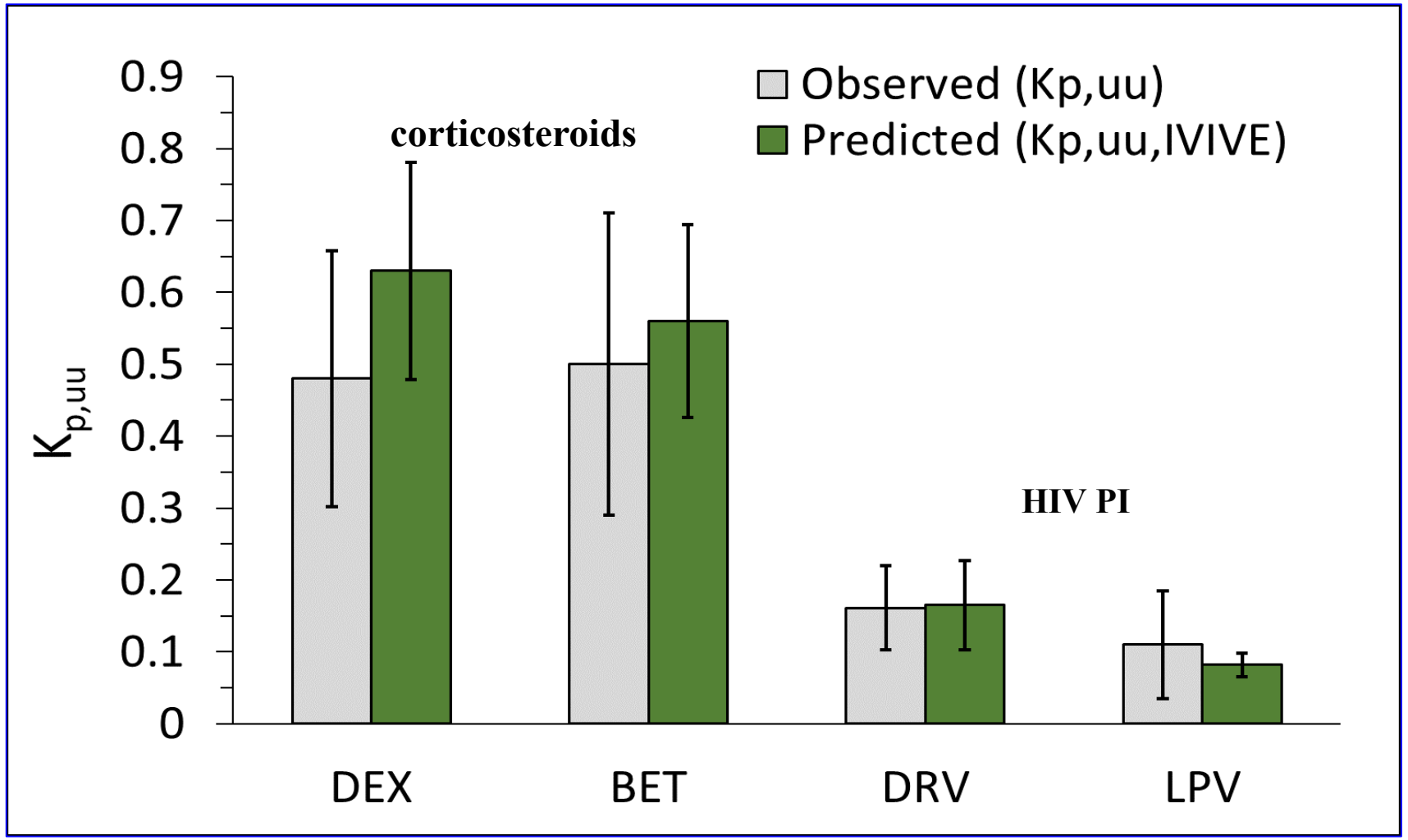


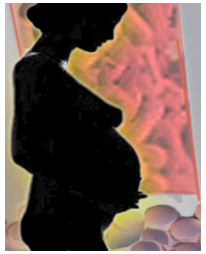
Successful Prediction of Fetal $K_{p,uu}$ Using the ER-REF Approach and our M-F PBPK Model



P-gp Substrates:

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

Anoshchenko *et al.*, DMD 2021



Significance of Findings

- **This success provides confidence in using the ER-REF approach and PBPK M&S to estimate fetal drug exposure ($K_{p,uu}$, fetal AUC or C_{max}):**
  - **to other placental P-gp substrate drugs or drugs of other/multiple placental transporters (e.g., BCRP and P-gp)**
  - **at earlier gestational ages**
- **Our ER-REF approach and PBPK M&S can now be used to predict fetal exposure to any drug irrespective of whether it passively diffuses across the placenta or is also transported**
- **Prediction of fetal $K_{p,uu}$ is necessary to inform fetal efficacy and toxicity and optimize drug dosing regimen for pregnant women**

Acknowledgement

Unadkat lab contributors

- Faye Zhang
- Marjorie Imperial
- Alice (Ban) Ke
- Gabriela Patilea-Vrana
- Olena Anoshchenko
- Flavia Storelli
- Sara Eyal
- Francisco Chung

Collaborators

- UWPKDAP faculty
- PACTG team
- Ping Zhao (Gates Foundation) and Shrikant Nalini (FDA)
- Masoud Jamei, Gaohua Lu and Janak Wedagedera (SimCYP®Ltd,UK)
- Bhagwat Prasad, Qingcheng Mao, Joanne Wang

Collaborators

Jeanne Link, David Mankoff and the PET suite team, Dept. of Radiology

Data Generously Supplied By:

- William J. Jusko, SUNY, Buffalo
- Timothy Tracy, University of Kentucky
- Uwe Fuhr, University of Cologne, Cologne, Germany
- Mia Wadelius, Uppsala University, Uppsala, Sweden

Supported by NIH P01 DA032507, P50HD44404, Bill and Melinda Gates Foundation

Univ. of WA Health Sciences