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How Can We Predict Fetal Drug Exposure Throughout Pregnancy To Inform Fetal Safety?

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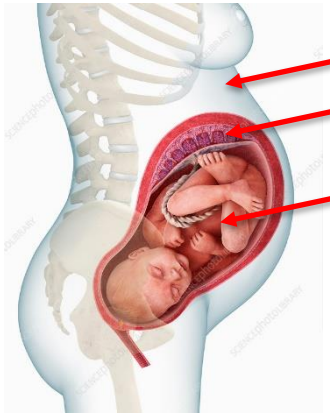
What are the challenges to determining fetal safety?

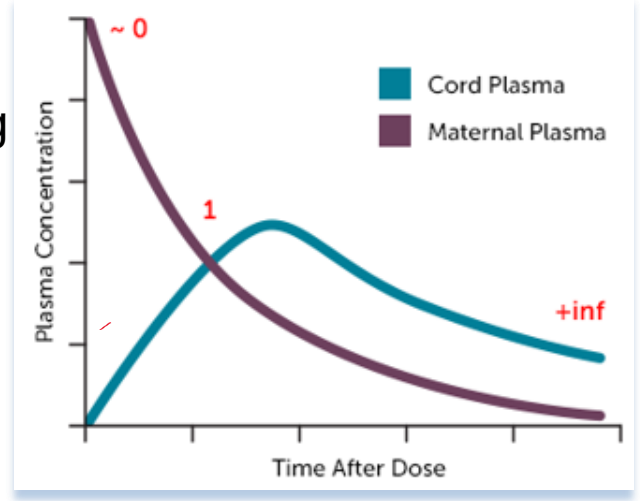
- Difficult (or often impossible) to determine due to logistical and ethical reasons, especially preapproval – RCTs are often not possible, even after approval.
- What are the alternatives?
  - Prospective or retrospective observational studies after approval? Fraught with confounding factors.
  - Animal and *in vitro* studies? Often conducted at doses/concentrations that do not reflect human fetal drug exposure; catch 22 situation!
  - Can human fetal drug exposure be **measured** or **predicted** throughout pregnancy to inform appropriate animal and *in vitro* studies?

Fetal drug exposure and fetal safety

- Fetal safety is driven by **fetal drug exposure**, which in turn is driven by:

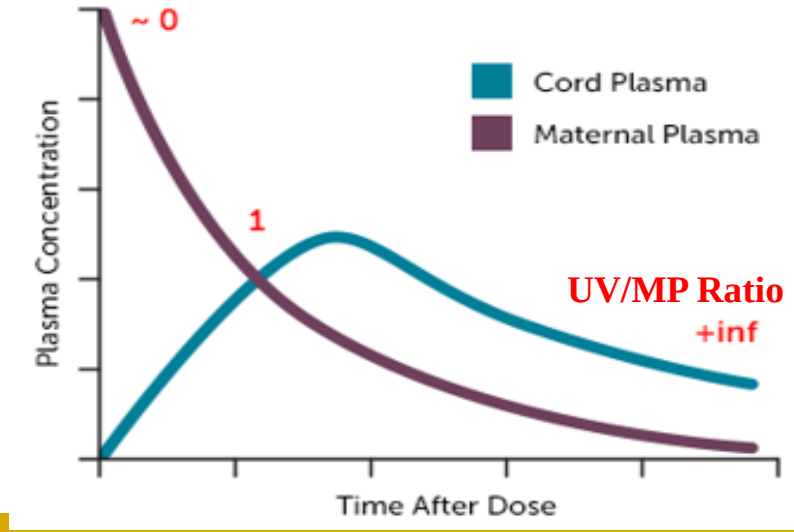


- Which parameters define fetal drug exposure?
  - Fetal plasma/blood AUCss, Cavg,ss and Cmax,ss and their corresponding unbound values during a dosing interval after multiple dose administration – unbound drug is pharmacologically active
  - Kp,uu, the average unbound stead-state fetal plasma conc: unbound maternal plasma conc.
  - Ideally, the above should be at the site of toxicity in the fetus



How can we Determine Fetal Drug Exposure?

- A **single** umbilical vein plasma/maternal plasma (UV/MP) drug concentration ratio **at term** is often **incorrectly** interpreted as a measure of fetal drug exposure – e.g. it could be 0, 1 or almost infinity! (UV rather than UA preferred)
- Solution: collect UV/MP samples at term from multiple maternal-fetal pairs and pool the data to estimate UV and MP AUCu,ss, Cmax,u,ss and Css,u,avg and Kp,uu
- Limitation: possible only at term; fetal exposure at earlier gestational age cannot be determined

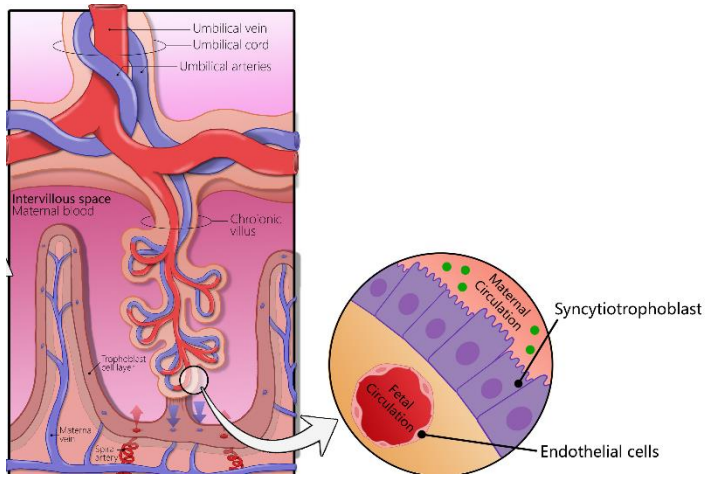


What is Kp,uu?

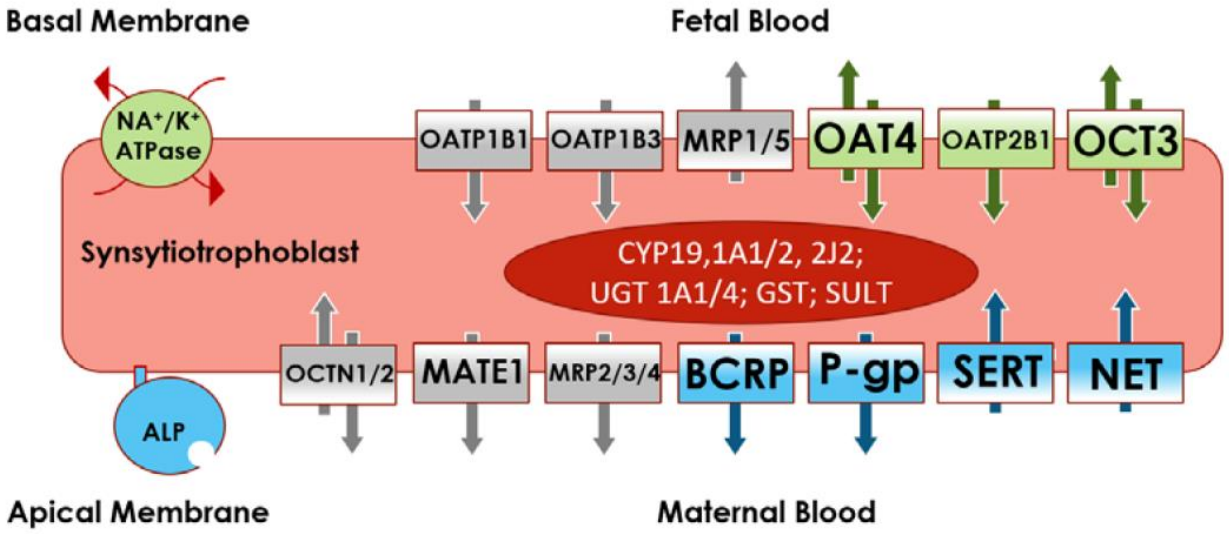
- Kp,uu is unbound fetal drug exposure "relative" to unbound maternal drug exposure at steady-state (e.g. in the plasma):

$$K_{p,uu} = \frac{f_{u,f} \times fetal\ Css,avg}{f_{u,m} \times maternal\ Css,avg} \text{ or } K_{p,uu} = \frac{f_{u,f} \times AUC_f}{f_{u,m} \times AUC_m}$$

  - Kp,uu = 1 for passively diffusing drugs i.e. fetal Css,u,avg = maternal Css,u,avg; not so for Cmax,u,ss
  - Kp,uu <1 for drugs that are effluxed

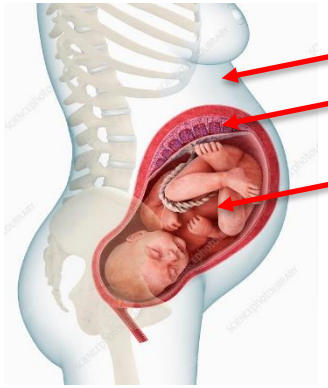


Shared by Dr. Fattahi



Can Human Fetal Drug Exposure be Predicted Through In Vitro Studies and Modeling?

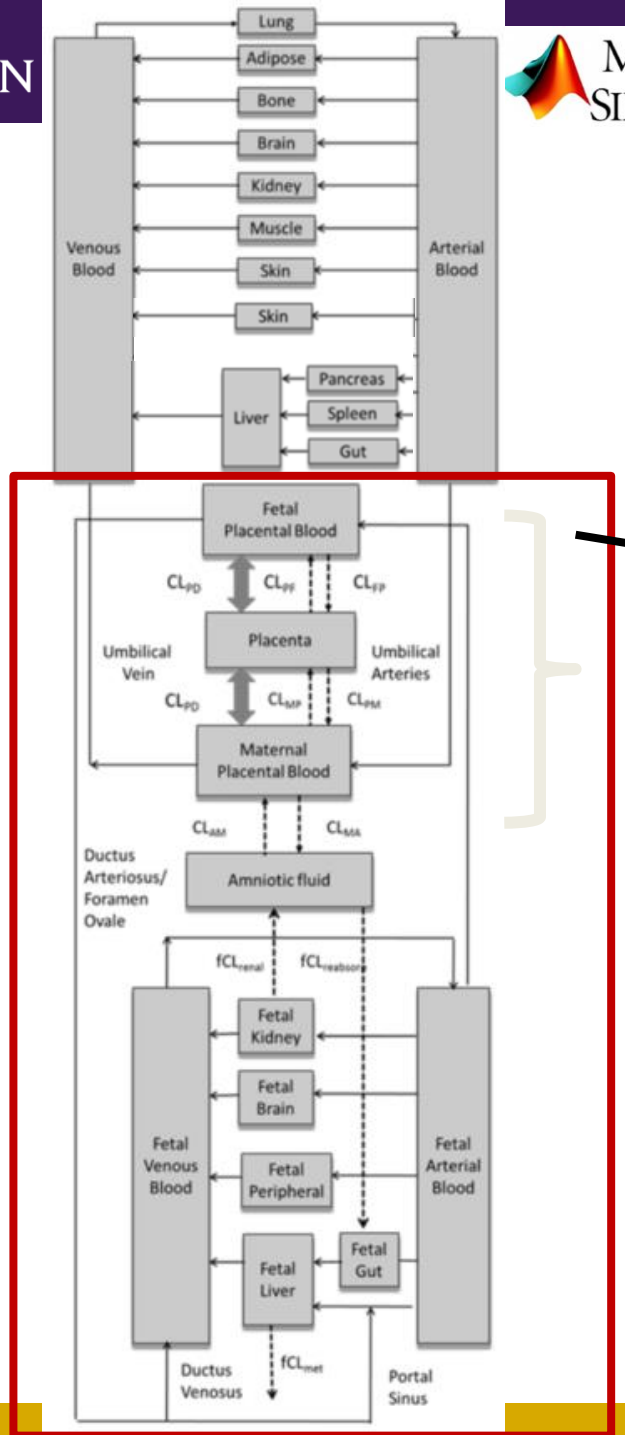
- Yes! Through maternal-fetal PBPK Modeling and Simulations (M&S)
- Fetal drugs exposure is driven by

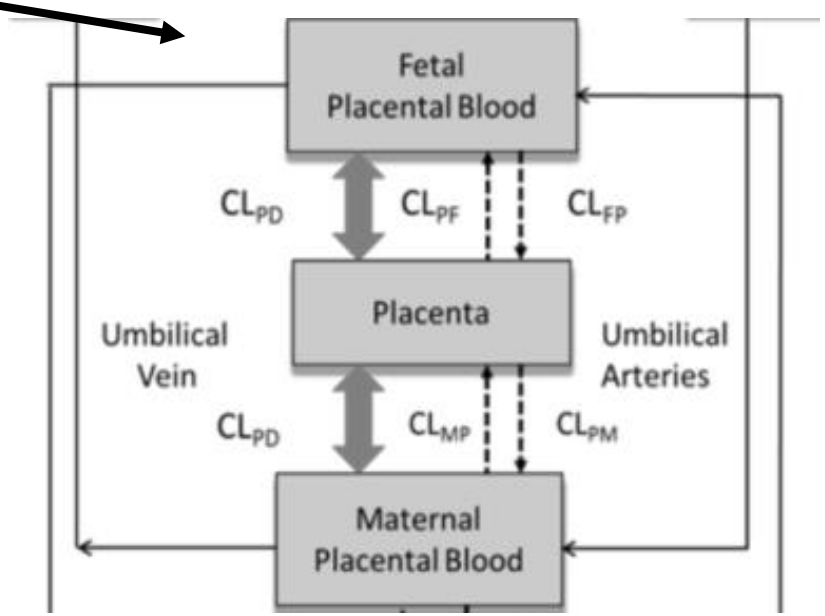


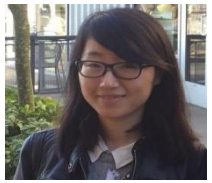
- Conduct *in vitro* studies to predict all the above *in vivo*
- Populate the m-f PBPK model with these in vitro data and data on gestational age-dependent physiological changes throughout pregnancy:
  - Cardiac output, tissue blood flows, changes in hepatic and renal activity/expression of enzymes and transporters etc.
- Verify maternal and fetal exposure at term for model drugs through observations in clinical studies

MATLAB SIMULINK

Maternal-Fetal PBPK (m-f PBPK) Model to Estimate Fetal Drug Exposure

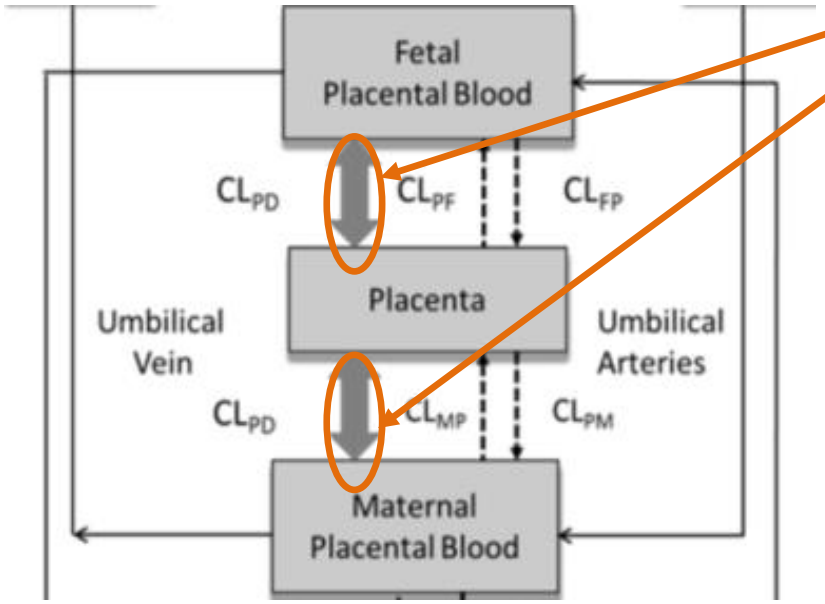


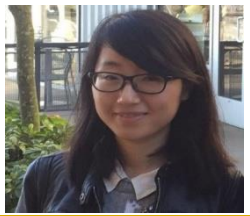




Zhang and Unadkat, 2017 DMD

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





Zhang and Unadkat, 2017 DMD

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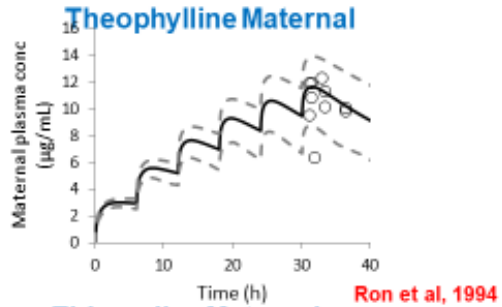
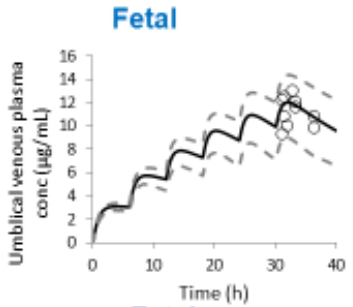
Model Verification using passive diffusion drugs

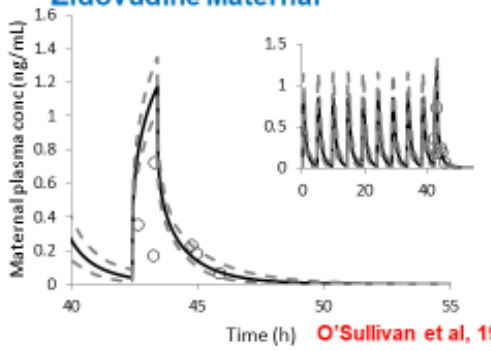


Ron et al, 1994

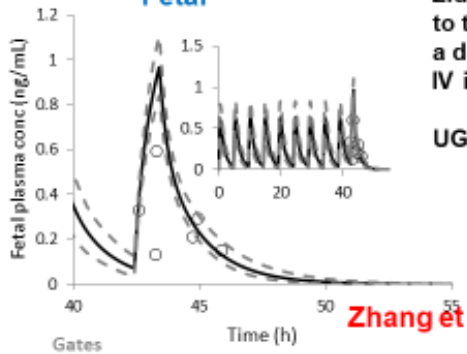


200mg theophylline dosed orally prior to C-section

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

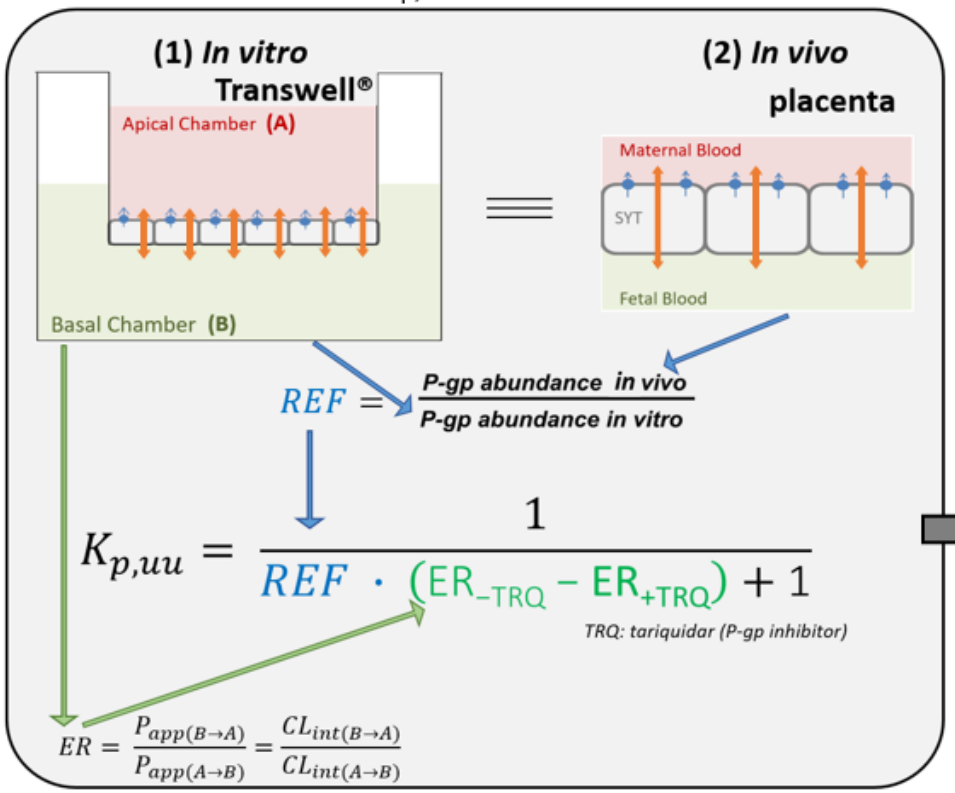
UGT2B7 substrate

Gates

8

Can we predict fetal exposure to drugs that are extensively effluxed by placental P-gp or BCRP+P-gp through in vitro studies?

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



P-gp Substrates:

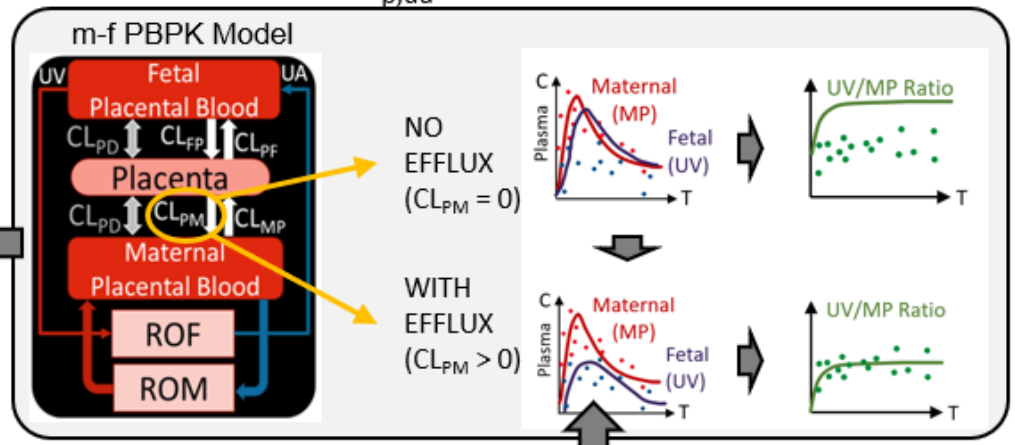
1) *Darunavir*
2) *Lopinavir*
3) *Nelfinavir*
4) *Dexamethasone*
5) *Betamethasone*

Dual P-gp/BCRP Substrates:

1) *Glyburide*
2) *Imatinib*

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

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



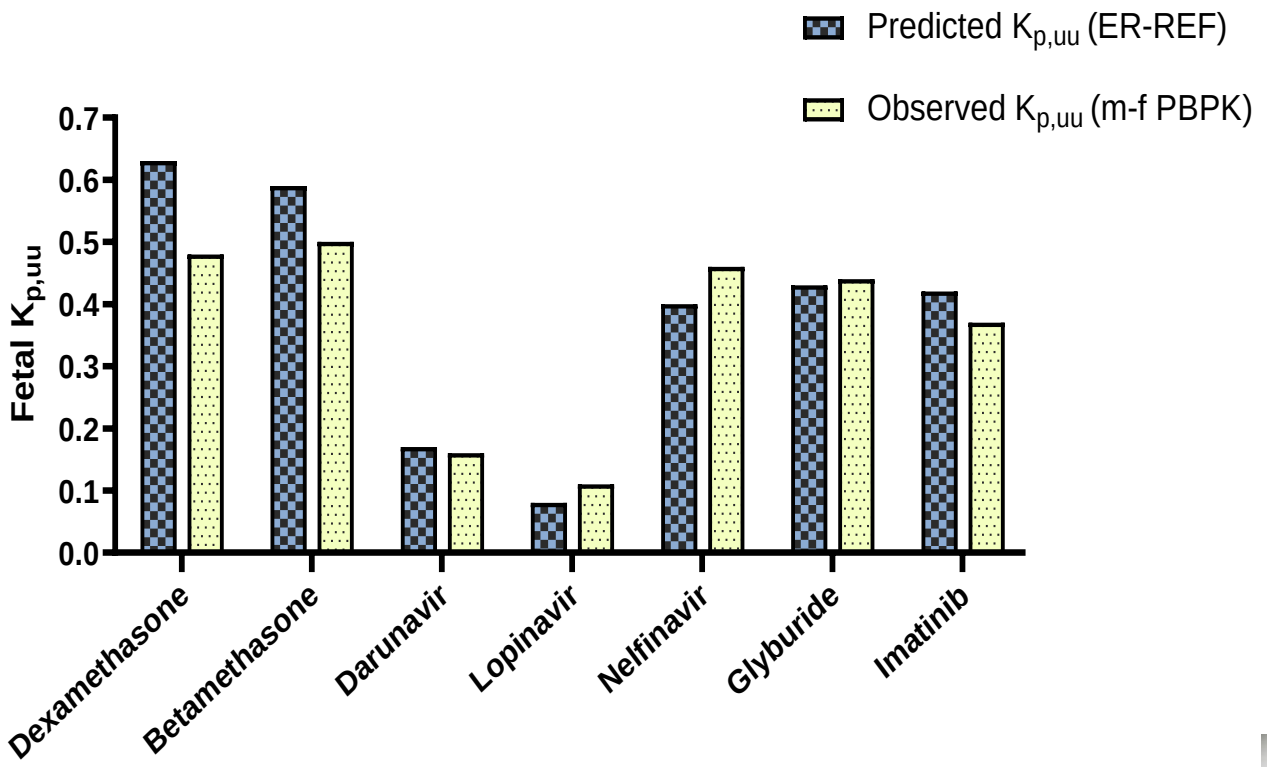
Observed *In Vivo* Data

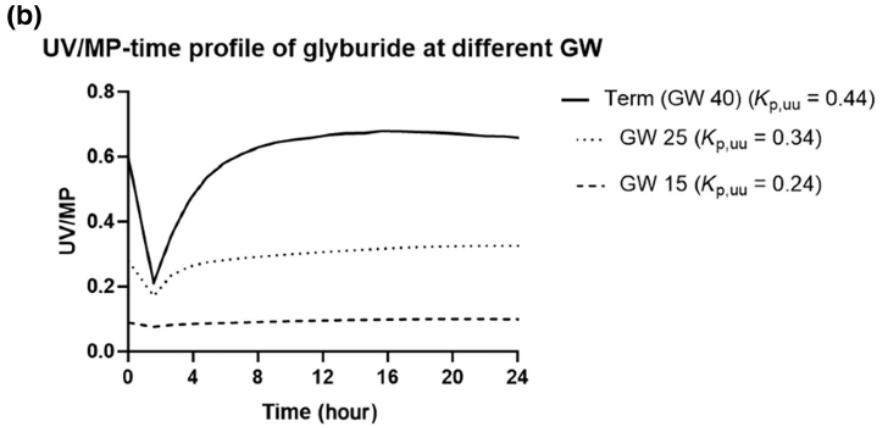
Dots: Paired observed umbilical vein (UV) and maternal plasma (MP) drug concentrations at term. Each pair obtained from a single maternal-fetal dyad

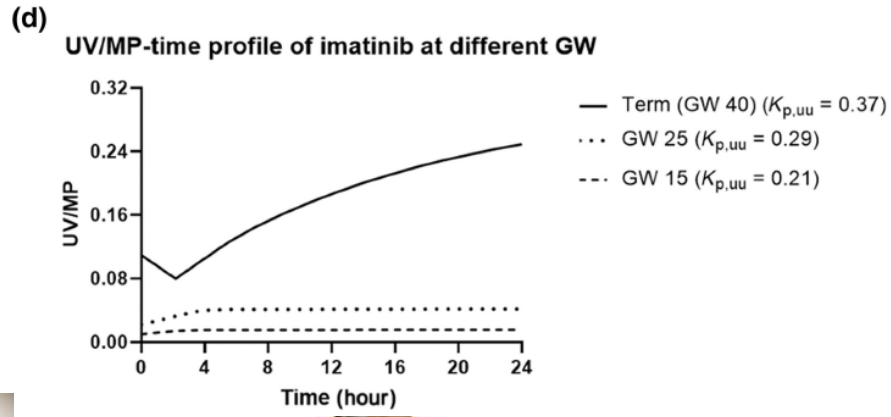
Anoshchenko *et al.*, DMD 2021

Balhara et al., CPT, 2024

Successful Prediction of Fetal Exposure at term to Drugs ($K_{p,uu,}$) Effluxed by Placental P-gp or BCRP+P-gp using the REF approach



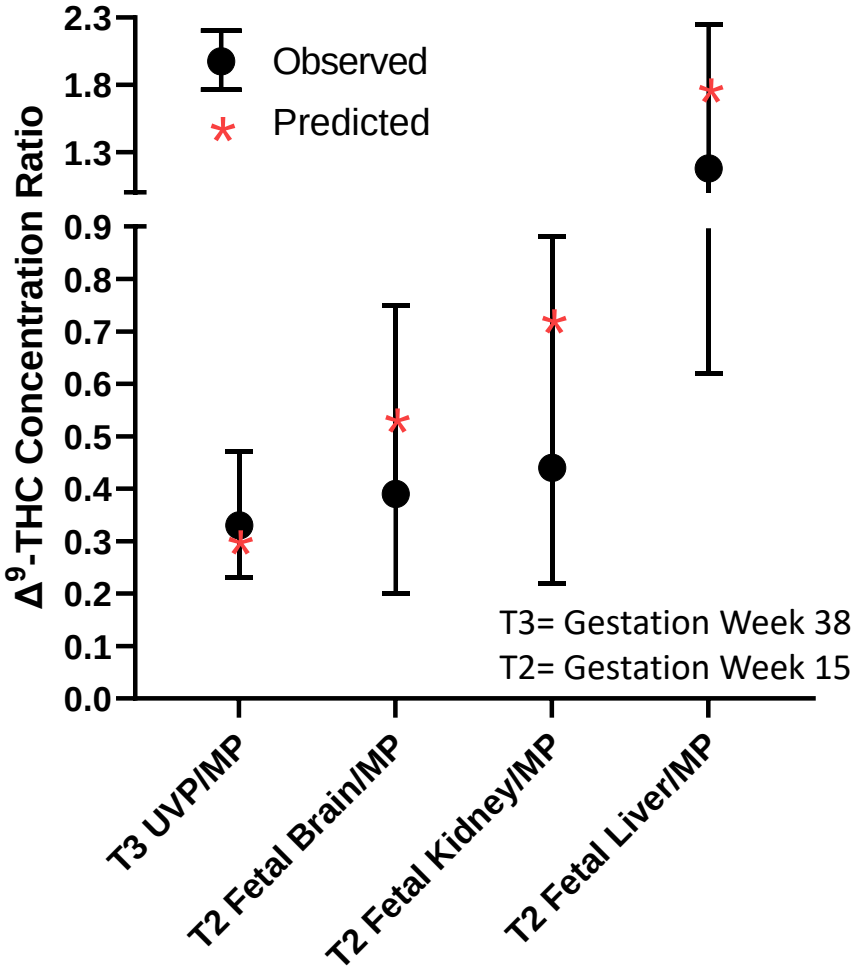




Anoshchenko *et al.*, DMD 2021

Balhara et al., – CPT, 2024

Can we predict fetal tissue concentrations through m-f PBPK modeling? A THC study



m-f-PBPK Model Predicted fTissue/MP at GW15 and UVP/MP at GW38 (T3) Fell within the Acceptance Criteria

Kumar et al., Nature Communications – in revision

Observed data are presented as Geometric Mean **and Acceptance Criteria**

Summary

- PBPK M&S/REF can predict maternal-fetal exposure and fetal tissue drug concentrations including those that are actively transported by placental transporters
- Now that our predictions have been verified, such predictions, possible for all stages of pregnancy, can be done ***without conducting in vivo studies***
- These predictions can be used to inform appropriate preclinical animal toxicity studies and optimize dosing regimens for the pregnant person and her fetus
- Nevertheless, much research remains to be done on how pregnancy can affect fetal drug exposure, PD, safety and therefore optimize drug therapy for these orphan populations
- ***Four Transporter Elucidation Centers Funded by NIH (Univ. of WA, JHU, Rutgers Univ., UCSF, 2023-2028)***
  Goals: To increase understanding of the **understudied** human solute carrier (SLC) and ATP-binding cassette (ABC) families of transporter proteins in the **placenta, lactating mammary gland, developing gut, and blood brain barrier** to transport **nutrients, dietary supplement constituents, and drugs**

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Unadkat lab contributors

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- **Sara Eyal**
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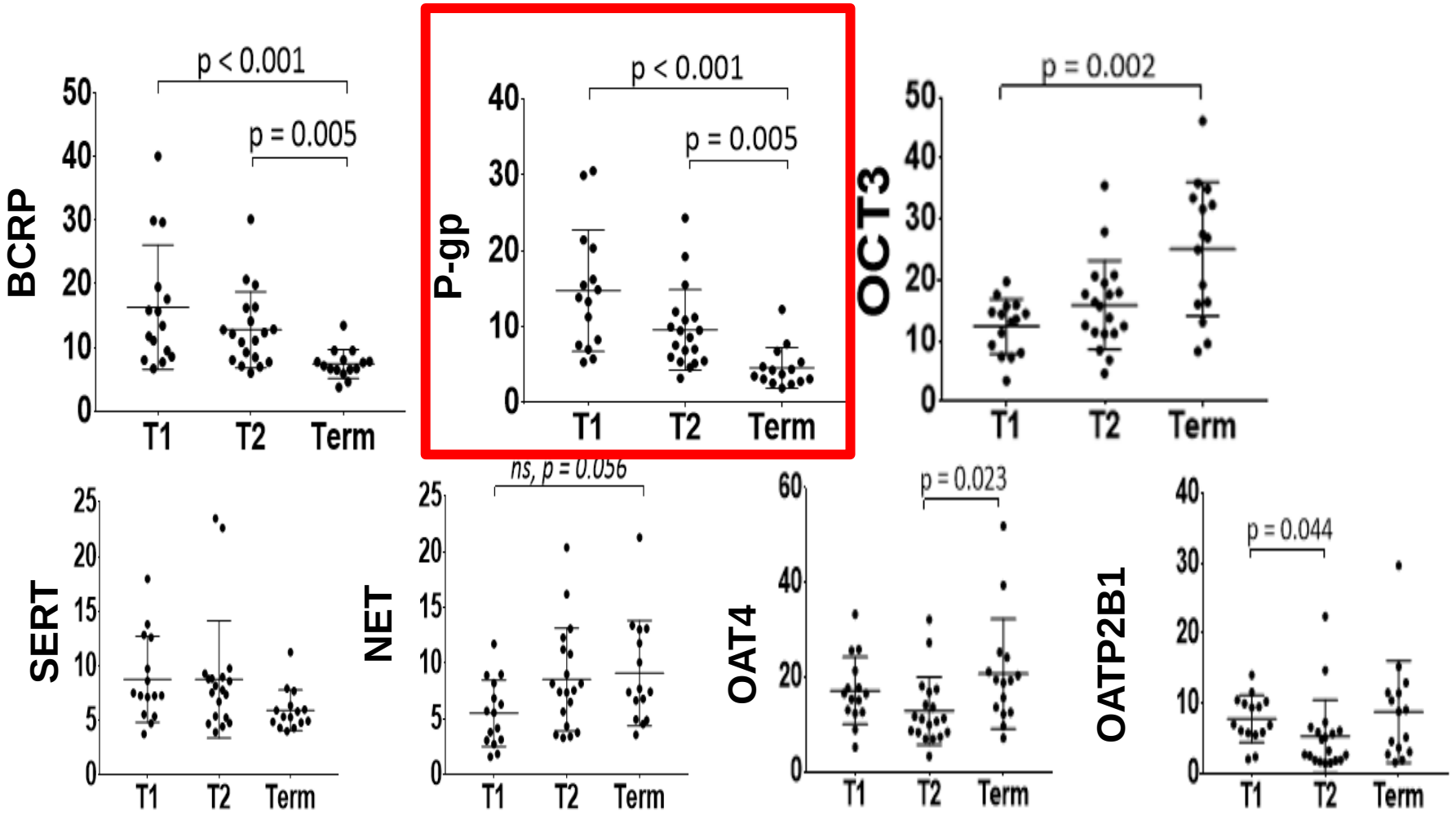
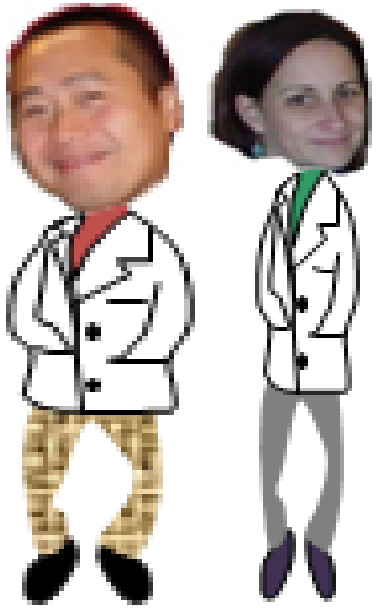
Backup slides

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

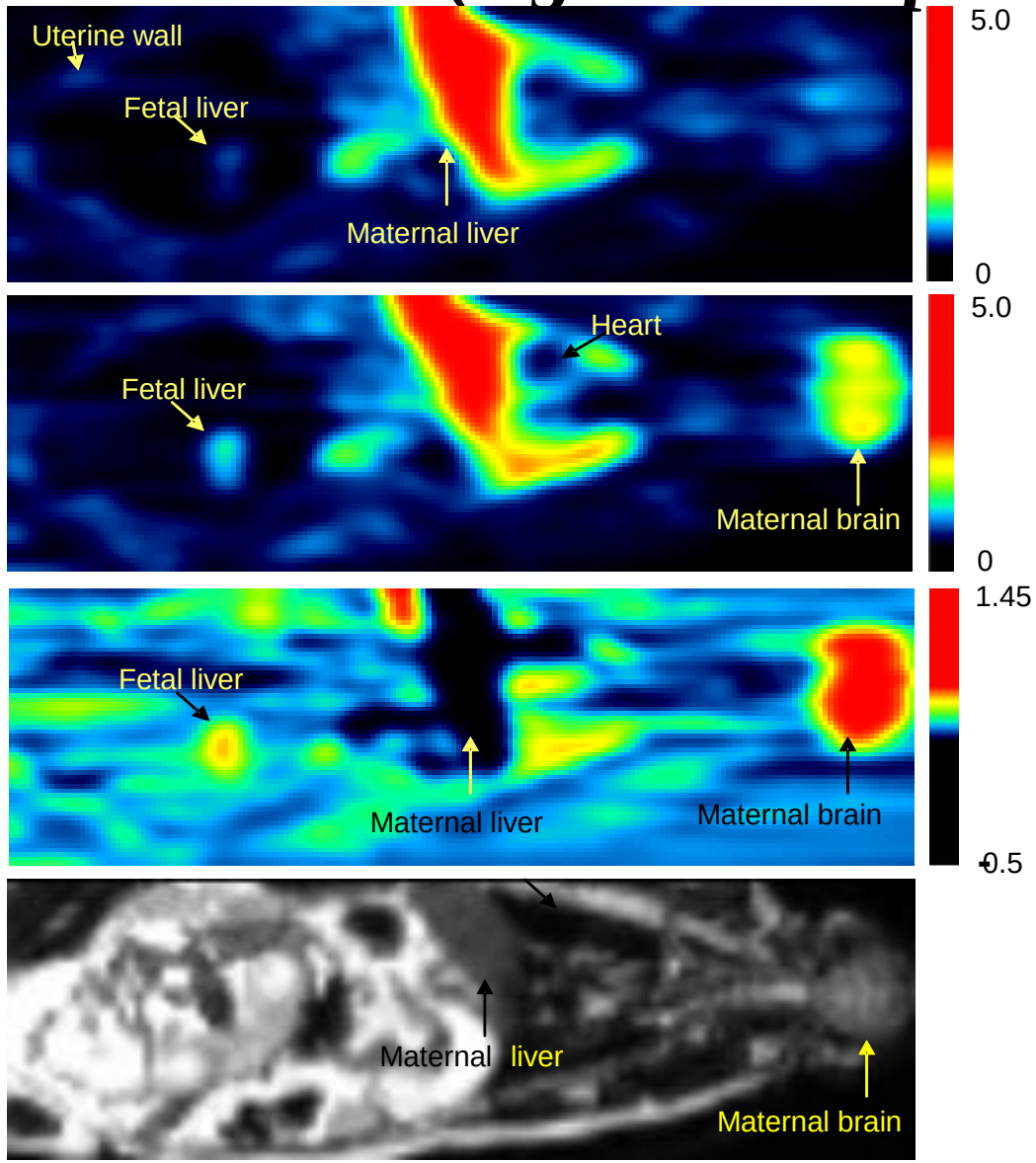


Anoshchenko L et al., DMD 2020

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



PET – before CsA

PET – during CsA

PET – pixel-by-pixel subtraction of A from B

MRI