



Characterizing the ontogeny of ten renal transporters in African Americans using quantitative proteomics, gene expression analysis and clinical data

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Mentors: Kathleen M. Giacomini, PhD, Shiew-Mei Huang, PhD, Lei Zhang, PhD

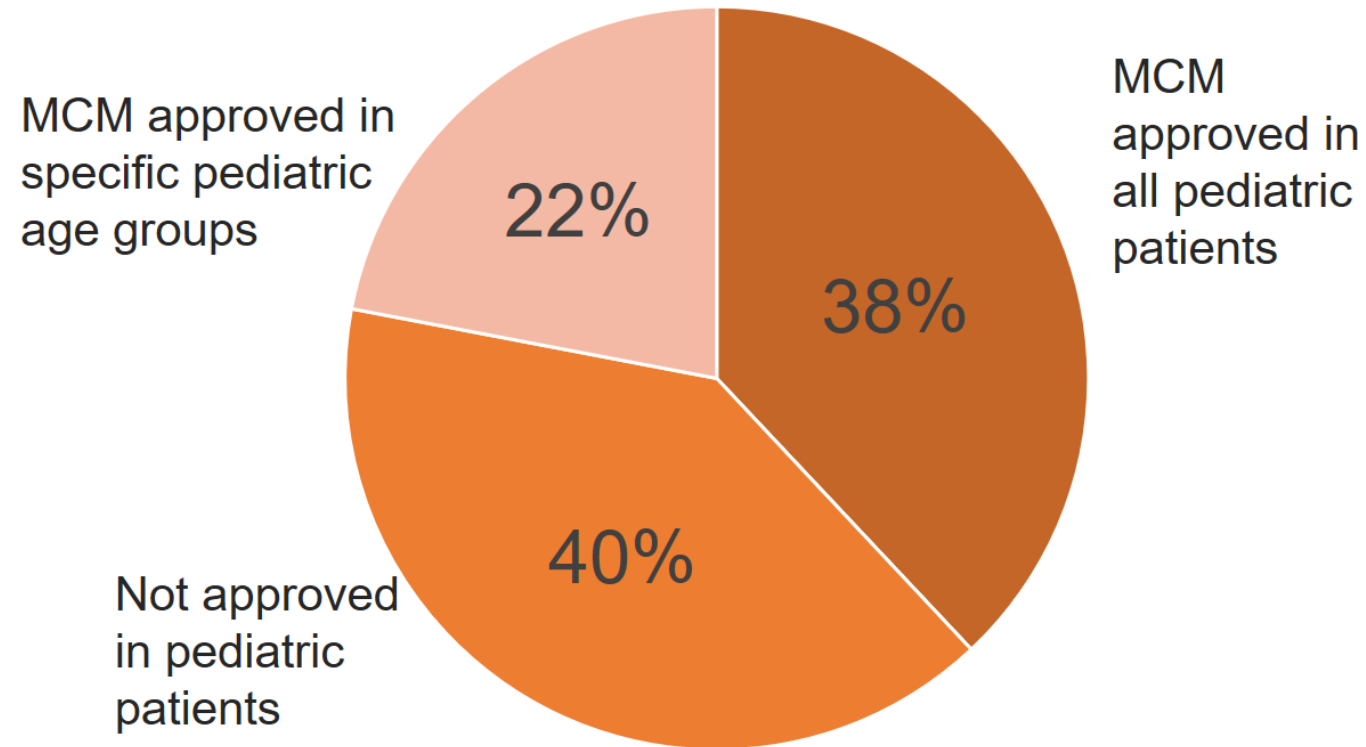
ASCPT 2018 Oral Abstract Session III – Drug Transporters and Pharmacogenomics

Disclaimer

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There is a gap in pediatric drug dosing

Medical Countermeasure (MCM) in National Stockpile with Pediatric Indication



Overcoming the pharmacokinetic challenge in pediatric drug development

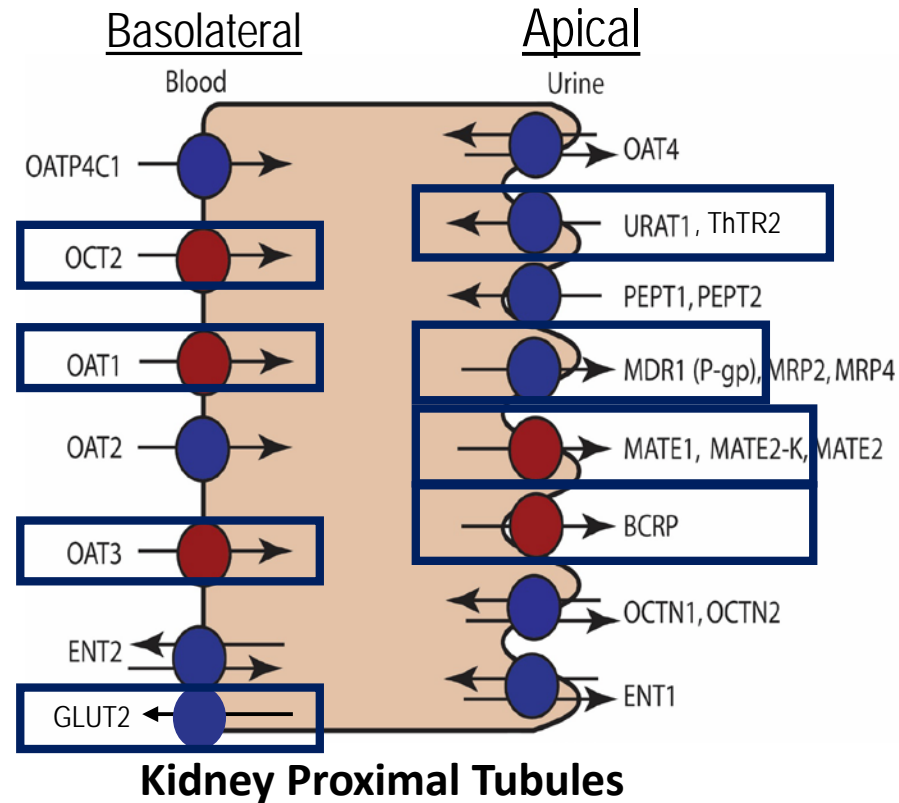
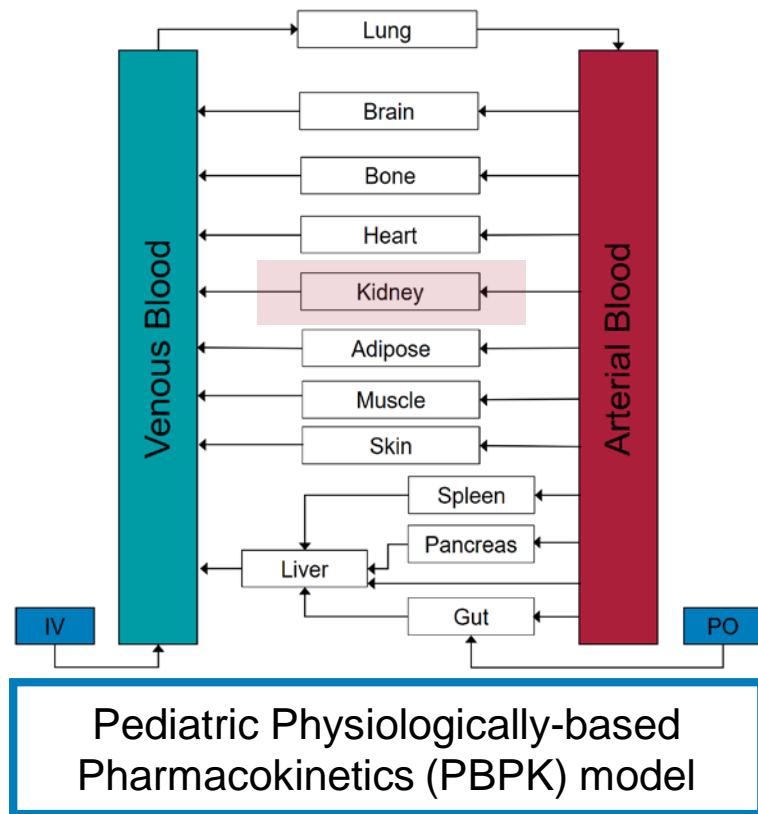
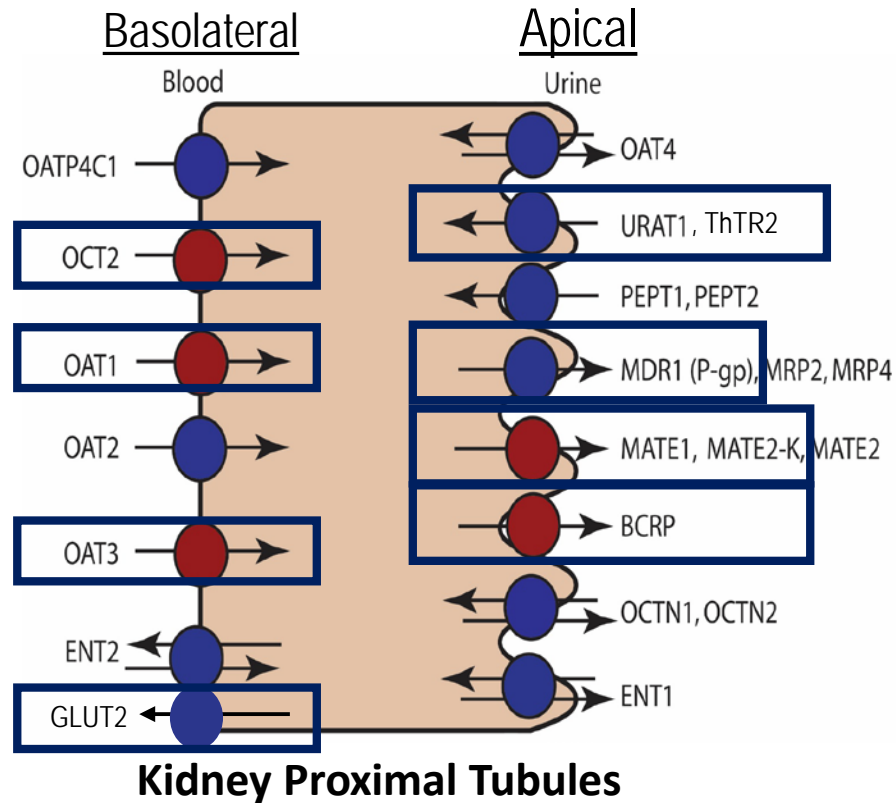
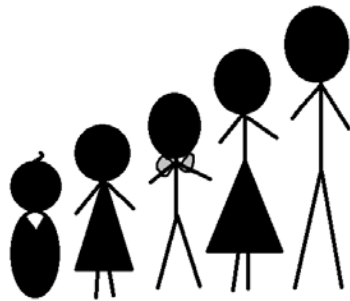


Figure 2 modified from Hillgren KM et al. *Clin. Pharmacol. Ther.* 2013

Overcoming the pharmacokinetic challenge in pediatric drug development

Goal:

To characterize the developmental changes in the expression levels of renal membrane transporters in African Americans



Methods

Frozen postmortem renal cortical tissues

African Americans	Caucasian adults
0-30 yrs old n = 57	16-30 yrs old n = 5

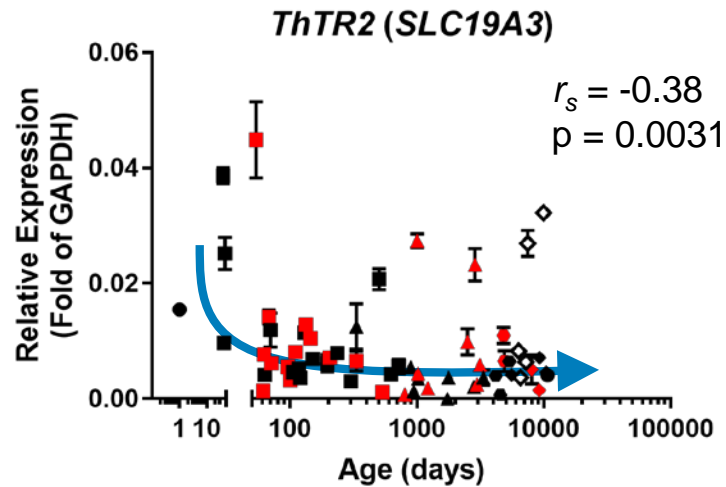
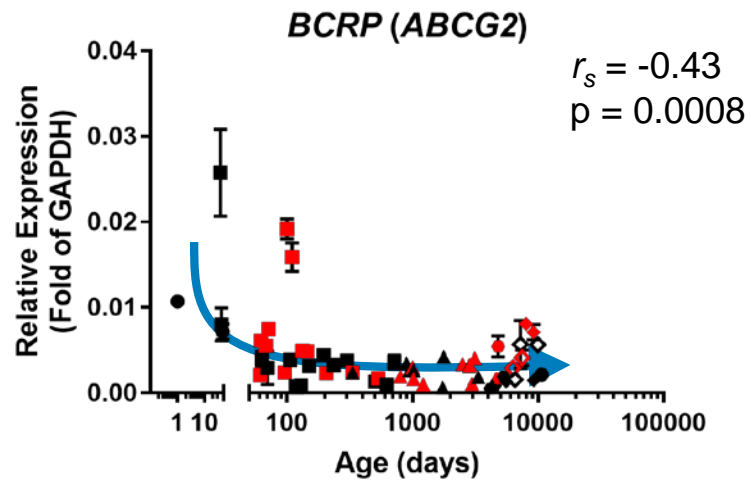
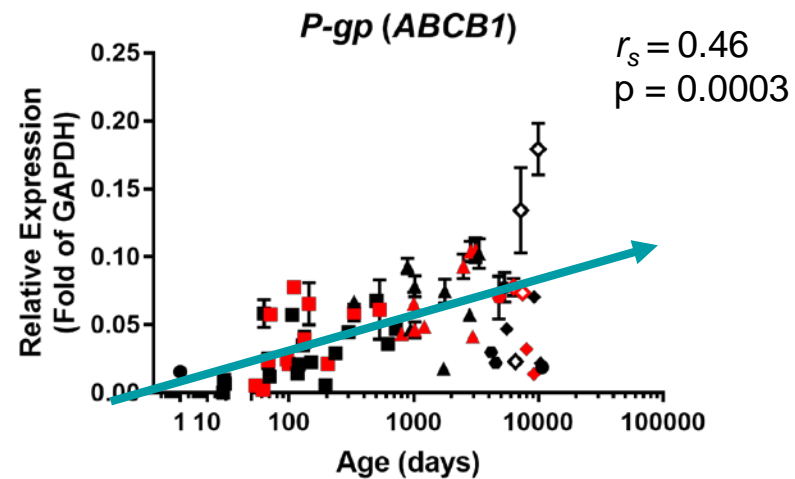
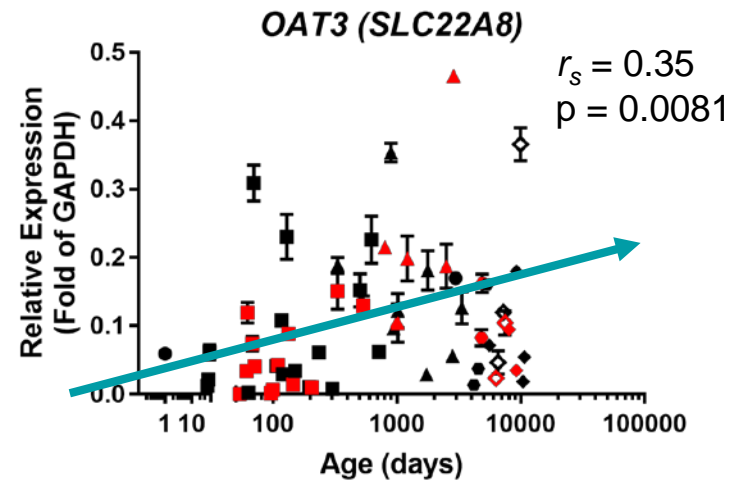
Gene expression analysis

Quantitative proteomics
(LC-MS/MS)



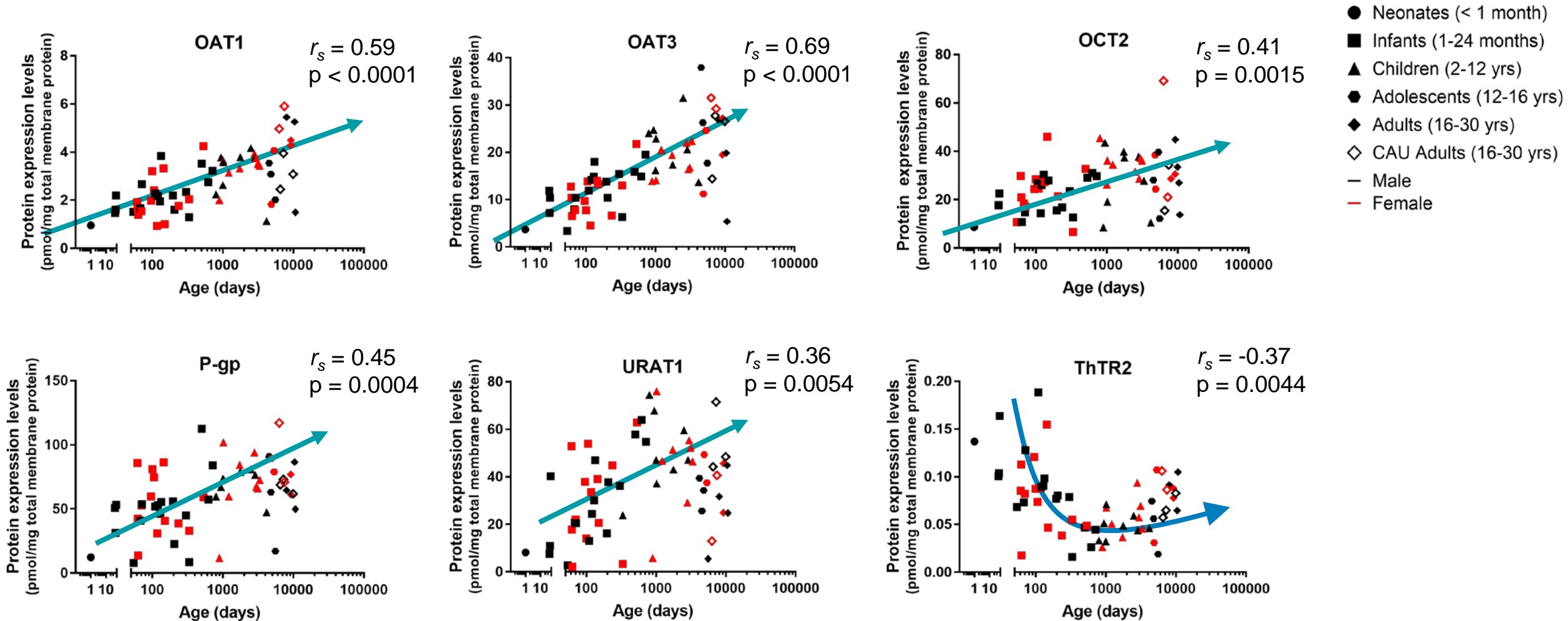
Review of published pharmacokinetic studies

Transcript levels of 4 transporter genes showed age-dependent changes



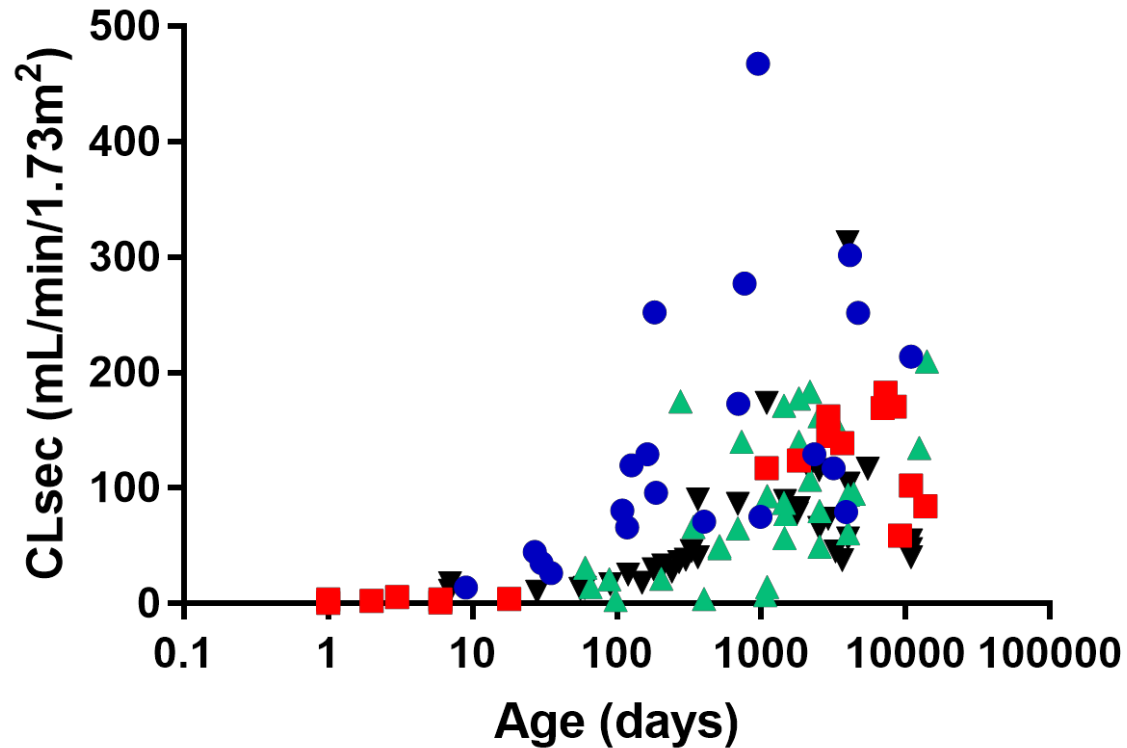
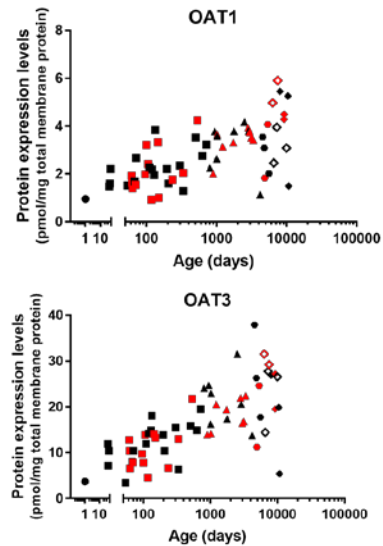
- Neonates (< 1 month)
- Infants (1-24 months)
- ▲ Children (2-12 yrs)
- Adolescents (12-16 yrs)
- ◆ Adults (16-30 yrs)
- ◇ CAU Adults (16-30 yrs)
- Male
- Female

Protein levels of 6 renal transporters showed age-dependent changes



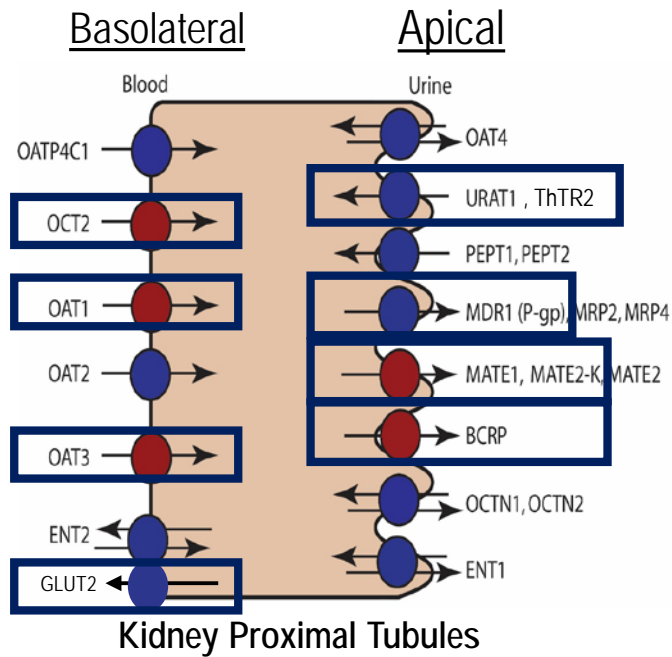
Net secretory clearances of 4 drugs increased with age, paralleling protein expression levels

Developmental changes in OAT1/3 net secretory clearance estimated from published PK data of 4 drugs



- Famotidine
- ▲ Tazobactam
- Furosemide
- ▼ Oseltamivir Carboxylate

Integrating transporter absolute abundance and ontogeny data into PBPK modeling could improve prediction of pediatric dosing



Renal membrane transporters studied using samples from African Americans showed postnatal maturation in their expression levels.

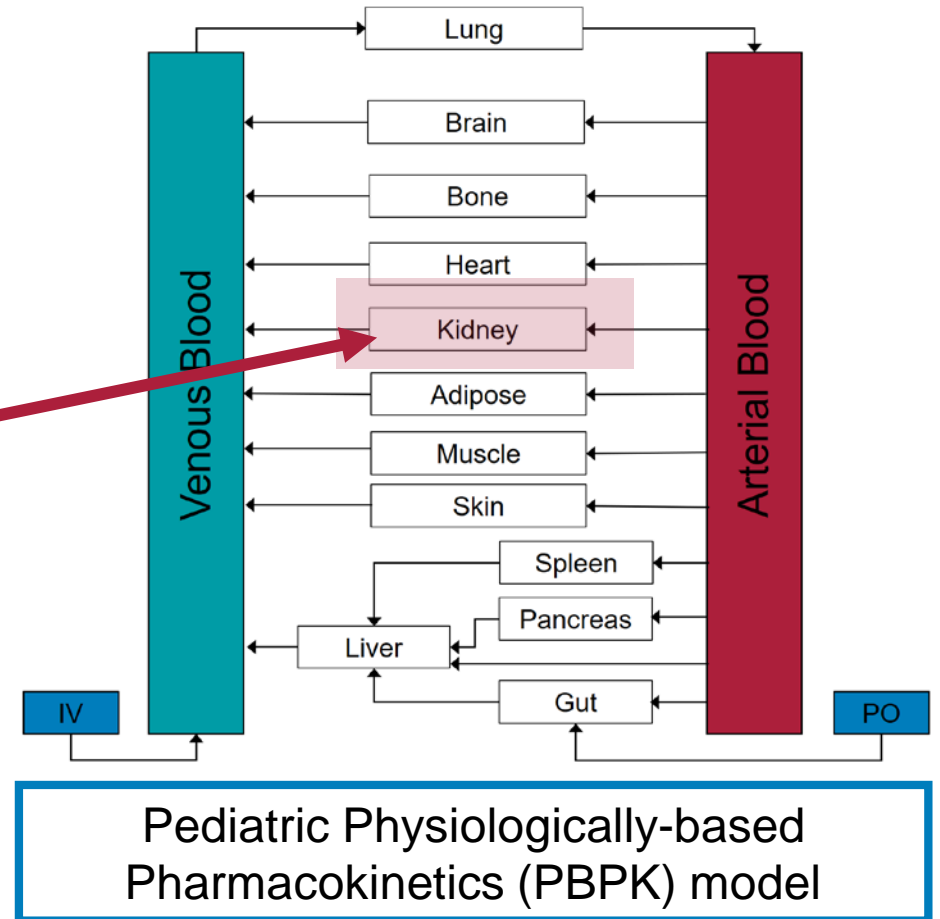
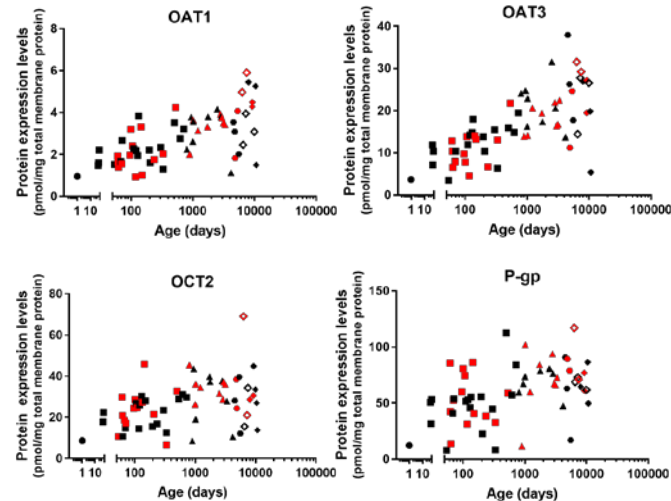


Figure 1 modified from Hillgren KM et al. *Clin. Pharmacol. Ther.* 2013

Thank you!



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