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

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ASCPT 2018 Oral Abstract Session III – Drug Transporters and Pharmacogenomics
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There is a gap in pediatric drug dosing

- MCM approved in specific pediatric age groups: 22%
- MCM approved in all pediatric patients: 38%
- Not approved in pediatric patients: 40%
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

<table>
<thead>
<tr>
<th>African Americans</th>
<th>Caucasian adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 yrs old</td>
<td>16-30 yrs old</td>
</tr>
<tr>
<td>n = 57</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

- Gene expression analysis
- Quantitative proteomics (LC-MS/MS)
- Review of published pharmacokinetic studies

Figure 2 modified from Hillgren KM et al. Clin. Pharmacol. Ther. 2013
Transcript levels of 4 transporter genes showed age-dependent changes

**OAT3 (SLC22A8)**

$r_s = 0.35$

$p = 0.0081$

**P-gp (ABCB1)**

$r_s = 0.46$

$p = 0.0003$

**BCRP (ABCG2)**

$r_s = -0.43$

$p = 0.0008$

**ThTR2 (SLC19A3)**

$r_s = -0.38$

$p = 0.0031$
Protein levels of 6 renal transporters showed age-dependent changes.

- **OAT1**: $r_s = 0.59$, $p < 0.0001$
- **OAT3**: $r_s = 0.69$, $p < 0.0001$
- **OCT2**: $r_s = 0.41$, $p = 0.0015$
- **P-gp**: $r_s = 0.45$, $p = 0.0004$
- **URAT1**: $r_s = 0.36$, $p = 0.0054$
- **ThTR2**: $r_s = -0.37$, $p = 0.0044$
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!

- ASCPT
- Dr. Kathy Giacomini
- Dr. Shiew-Mei Huang
- Dr. Lei Zhang
- Giacomini Lab
  - Dr. Sook Wah Yee
  - Dr. Huan-Chieh (James) Chien
  - Qi (Roxy) Luo
- NIH NeuroBioBank at the University of Maryland, Baltimore
- UCSF Clinical and Translational Science Institute (UL1TR000004)

- Funding
  - R01GM117163
  - R01DK103729
  - UCSF-Stanford CERSI (U01FD004979)
  - FDA Medical Countermeasures Initiative
  - Oak Ridge Institute for Science and Education (ORISE)
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