The Next Frontier in ADME Science: Predicting and Verifying Tissue Drug Exposure

Jashvant (Jash) Unadkat
Milo Gibaldi Endowed Professor
Dept. of Pharmaceutics
School of Pharmacy
University of Washington
Seattle, WA
jash@uw.edu

https://sop.washington.edu/people/jashvant-unadkat/
GAPS in ADME: Drug Development Failure Rate and Reasons

One Possible Reason for Lack of Drug Efficacy & Safety

- Unable to routinely measure (or accurately predict) tissue drug conc.-time profile for drugs that are transported across tissue:blood barrier

- Transporters at the tissue:blood barrier (e.g. blood:brain barrier, BBB, liver:blood barrier)
  - Unbound tissue conc \(\neq\) unbound plasma conc. i.e. asymmetry in tissue:blood conc.
  - Impact differs between non-eliminating (e.g. brain) and eliminating organ (e.g. liver)
**Asymmetry in Drug Conc. at the Human Brain: Blood Barrier: P-gp Efflux of $^{11}$C-Verapamil**

$^{11}$C-verapamil $\text{AUC}_{\text{brain}} / \text{AUC}_{\text{blood}}$ (20 min) - 0.42 ± 0.04

Eyal et al., *Clin Pharmacol Ther.* 2010
Asymmetry in Hepatic:Blood Conc. of $^{11}$C-Rosuvastatin in the Rat

Coronal 2 min SUV images of $^{11}$C-Rosuvastatin

He et al., Mol Pharm., ’14
Asymmetrical change in rosuvastatin conc. in liver and blood in the presence of rifampin

2.3-fold increase in plasma AUC but no significant increase in liver AUC

He et al., Mol Pharm. 2014
\[^{11}\text{C}]\text{Rosuvastatin biodistribution in a human volunteer}\]
Hepatic Uptake and Biliary Excretion of $[^{11}C]$Rosuvastatin ± CsA

ATP → ADP + Pi

RSV

Liver

GallBladder

Hepatic Uptake and Biliary Excretion of $[^{11}C]$Rosuvastatin ± CsA

1 min  5 min  10 min  30 min

RSV

Liver

GallBladder

RSV + CSA

Liver

GallBladder
How Can we Predict/Measure Tissue Drug Conc. and Tissue:Blood Asymmetry in Humans?

One could actually measure tissue drug conc:

- PET imaging (MRI and other imaging modalities do not have the required sensitivity):
  - Requires sophisticated equipment and radiochemistry
  - Costly (about $20-40K/experiment/subject)

- Therefore we need alternative methods that will allow us to predict tissue conc. of drugs in humans
  - Predict all clearances associated with the tissue:blood barrier
  - Possible using REF but not RAF approach
**Hypothesis:** Predict tissue drug conc. by scaling in vitro CL in transporter expressing cells to in vivo using relative expression factor (REF)

**In vitro CL**
CL via transport of interest in cell line expressing the transporter

**Relative Expression Factor (REF)**
1. Transporter expression/g of tissue
2. Tissue weight

**In vivo CL**
Contribution of individual transporter in tissue uptake/efflux

\[
REF = \frac{[T]_{\text{ex vivo in organ}}}{[T]_{\text{in vitro}}}
\]

- [https://sop.washington.edu/department-of-pharmaceutics/research/research-affiliate-program-on-transporters-uwrapt/](https://sop.washington.edu/department-of-pharmaceutics/research/research-affiliate-program-on-transporters-uwrapt/)
Can the use of these Quantitative Proteomics Data Successfully Predict Transporter-Mediated CL and Tissue Conc. of Drugs?

Criteria of success: within 2-fold of observed value

• Changes due to hepatic impairment (e.g. cirrhosis)

• Renal secretory CL of drugs

• Hepatic CL and tissue conc. of drugs – rat and human
Improved PBPK Prediction of Repaglinide Pharmacokinetics in Liver Cirrhosis Patients When the Effect of Cirrhosis on OATP1B1 Abundance is Incorporated

Virtual population (10 trials and n=12 for each trial)

Wang et al., DMD, 2016
Metformin renal clearance is reasonably well-predicted using OCT2 expressing cells

Observed metformin renal secretory clearance in humans: 432 (range 215-643) mL/min

Kumar et al., DMD 2018
Renal Secretory CL by OATs: RAF vs. REF

- 31 drugs secreted by renal OATs
- RAF used tenofovir (OAT1), acyclovir and ganciclovir (OAT2), and benzylpenicillin/oseltamivir acid (OAT3) as probe substrates
- REF used quantitative proteomics data on renal OATs in human kidney cortex and transfected cells which were also used to determine *in vitro* uptake CL of the drugs.

Collaboration with Manthena Varma (Pfizer)
Hypothesis: Predict Transporter-Mediated In-Vivo Hepatobiliary CL and Hepatic Concentrations of Drugs in Rats/Humans using REF

1. transporter-mediated drug CL
2. transporter abundance using quantitative proteomics
3. Obtain REF

Predict *in-vivo* hepatobiliary CL using REF and traditional approach

Verify predictions using PET imaging
REF (using HEK293 cells or PHH) better predicts Hepatic Uptake CL of metformin (as measured by PET imaging) vs. PHH

Hepatic Uptake and Biliary Excretion of $^{11}$C-Rosuvastatin in the Rat

Coronal 2 min SUV images of $^{11}$C-Rosuvastatin

He et al., Mol Pharm., ‘14
Successful prediction of the hepatobiliary clearance of rosvastatin using cell lines, sandwich-cultured rat hepatocytes and quantitative proteomics

**Graphical Representation:**

- **Y-axis:** Clearance (mL/min/kg body weight)
- **X-axis:** Oatp expression (fmol/µg membrane protein)

**Legend:**
- Blue bar: Previous PET imaging study
- Orange bar: SCRH not corrected for Oatp expression
- Grey bars: SD rat liver
- Green bars: SCRH

**Statistical Significance:**
- p<0.05

**Equations:**

- \(\text{CL}_{s,\text{uptake}}\): sinusoidal uptake
- \(\text{CL}_{s,\text{efflux}}\): sinusoidal efflux
- \(\text{CL}_{bile}\): canalicular efflux

**Textual Representation:**

Ishida et al., DMD, 2018
Rat Hepatic Rosuvastatin Conc. well Predicted

- ATP
- ADP + Pi

Ishida et al., DMD 2018
Can Rosuvastatin Hepatobiliary CL and Hepatic Conc. be Predicted in Humans?
Total transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes and liver tissue

Kumar et al., DMD 2019
Plasma membrane transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes cf liver tissue

Kumar et al., DMD 2019
Summary

• Predicting transporter-mediated CL & tissue concentrations and therefore efficacy and toxicity of a drug is the next frontier in ADME research

• The hepatic ECL model clarifies when transporters will or will not affect the systemic and tissue PK of a drug

• Tissue conc. measurement is possible using PET. However, this method cannot be routinely applied

• IVIVE using transfected cells and quantitative transporter proteomics is a promising technique to predict tissue drug conc

• These predictions should be validated using PET imaging probes that interrogate multiple drug transporters
Major Contributors

Gabriela Patilea-Vrana

YuYang

Jiake He

Li Wang

Sarah Billington

Vineet Kumar

Kazuya Ishida

Bhagwat Prasad

Anand Deo
Other Collaborators

Dept. of Radiology: Jeanne Link, David Mankoff, Todd Richards, Janet Eary, Satoshi Minoshima, Ken Maravilla, Mark Muzi, Steve Shoner, Shirely Rene, David Lewis, Jean Lee and the PET suite team

Dept. of Medicine: Ann Collier and her team; Scott Lee and his team

Dept. of Anesthesiology: Karen Domino, Matthew Pennington

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ATP  ADP + Pi