SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON

UWRAPT

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

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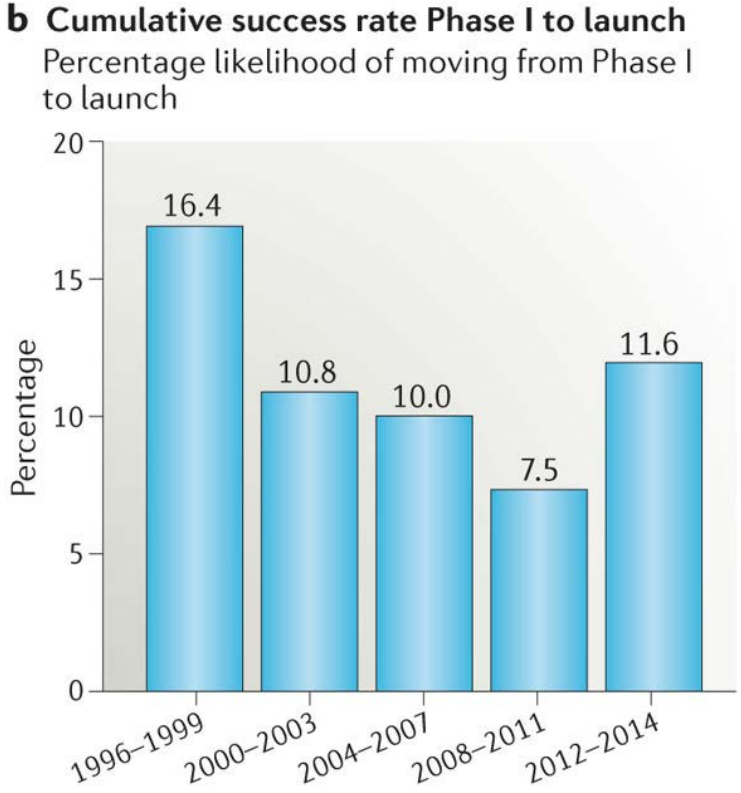
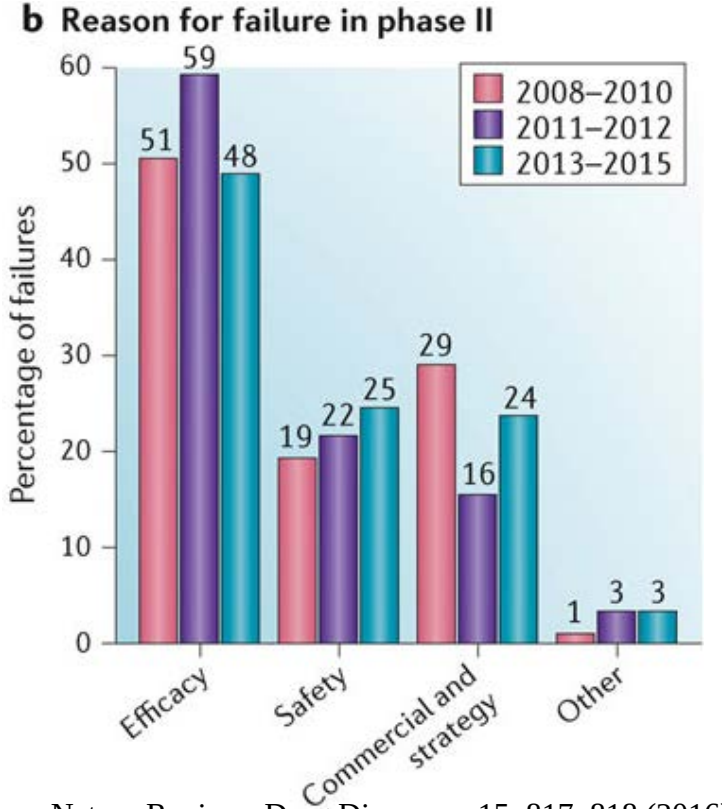
GAPS in ADME: Drug Development Failure Rate and Reasons



Smietana et al., Nature Reviews Drug Discovery 15, 379–380 (2016)

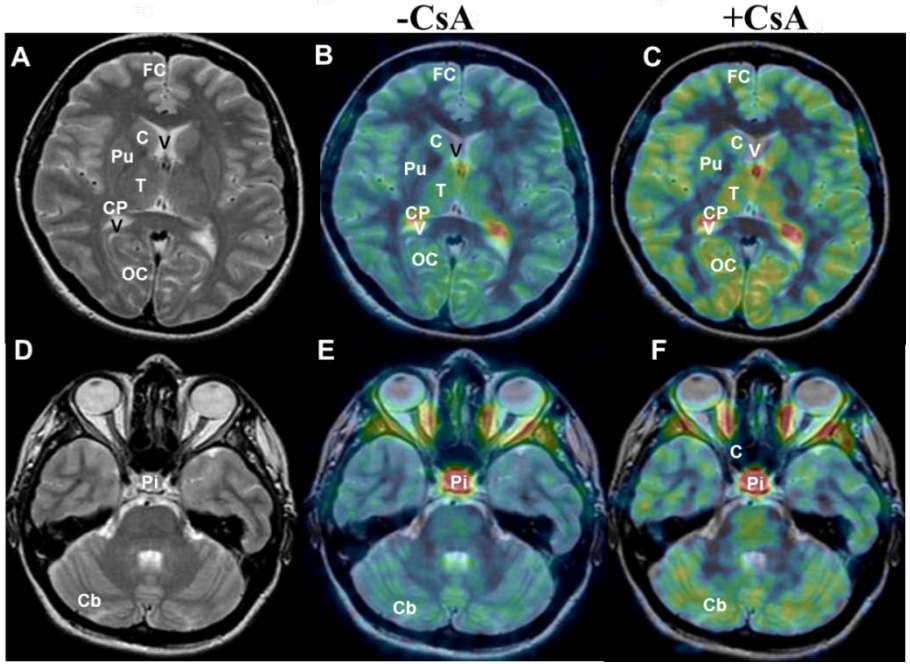


Harrison, Nature Reviews Drug Discovery 15, 817–818 (2016)

One Possible Reason for Lack of Drug Efficacy & Safety

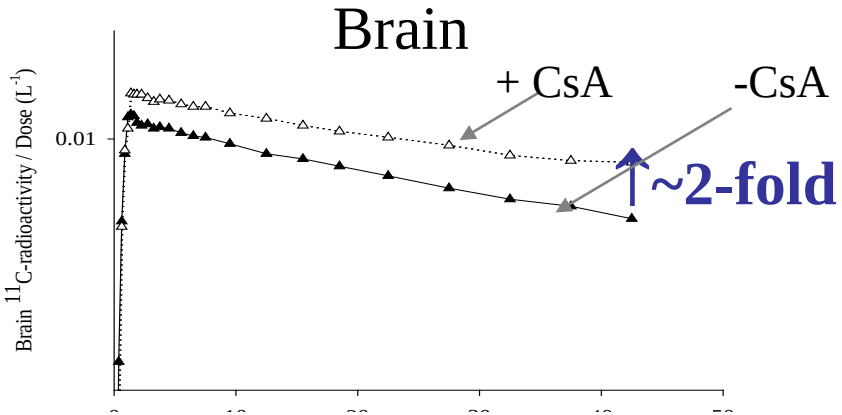
- Unable to routinely measure (or accurately predict) tissue drug conc.-time profile for drugs that are **transported** across tissue:blood barrier
- Transporters at the tissue:blood barrier (e.g. blood:brain barrier, BBB, liver:blood barrier)
  - Unbound tissue conc ≠ unbound plasma conc. i.e. **asymmetry** in tissue:blood conc.
  - Impact differs between non-eliminating (e.g. brain) and eliminating organ (e.g. liver)

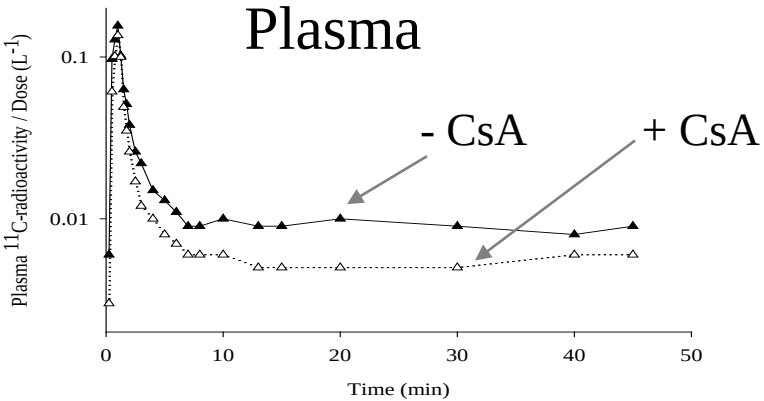
Asymmetry in Drug Conc. at the Human Brain:Blood Barrier: P-gp Efflux of ^{11}C-Verapamil



^{11}C-verapamil AUC_{brain}:AUC_{blood} (20 min) - 0.42±0.04

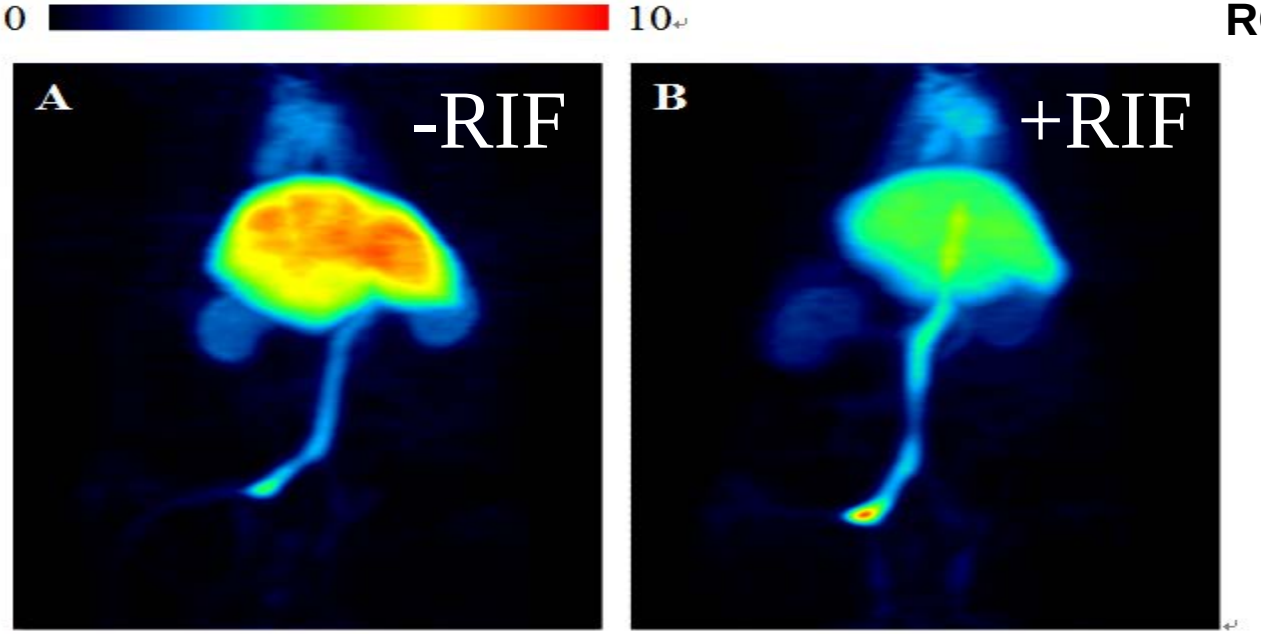
Eyal et al., *Clin Pharmacol Ther.* 2010

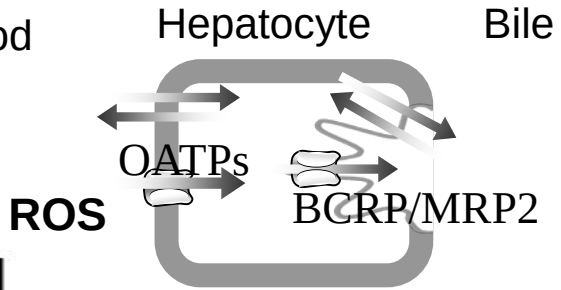




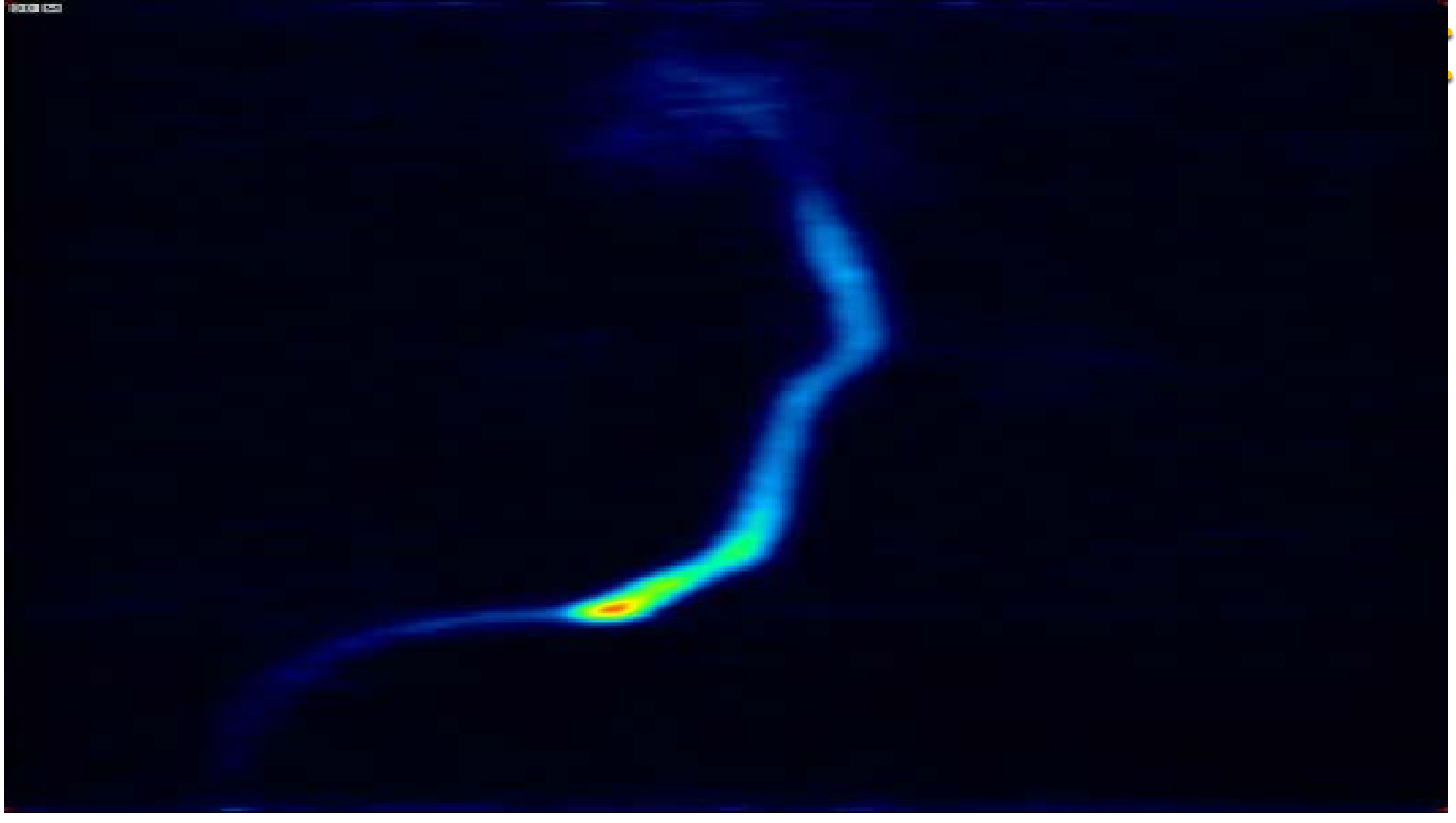
Asymmetry in Hepatic:Blood Conc. of ^{11}C-Rosuvastatin in the Rat

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

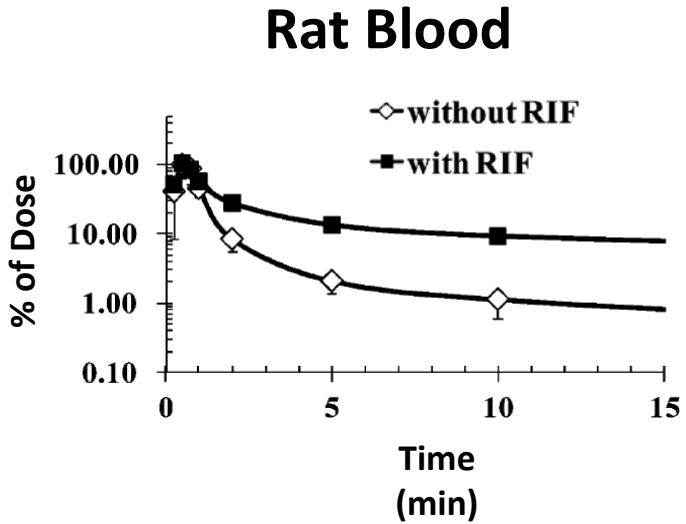


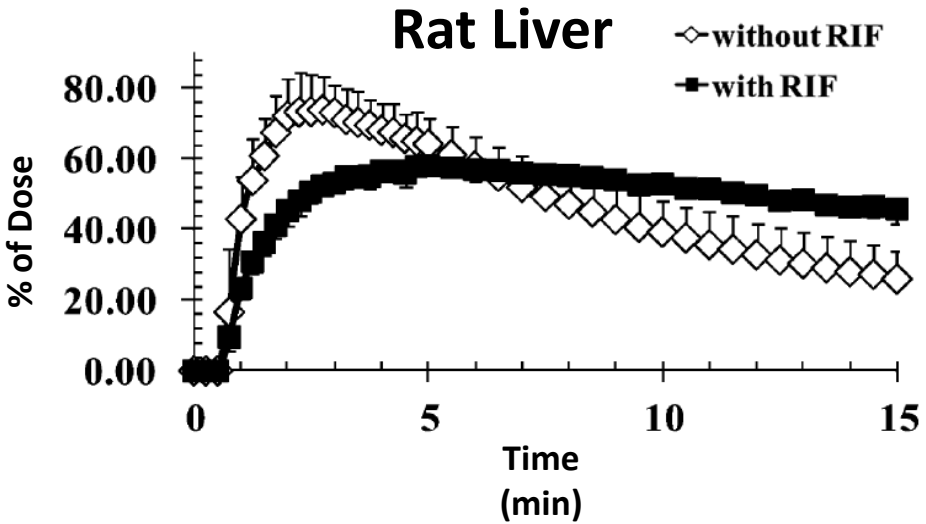


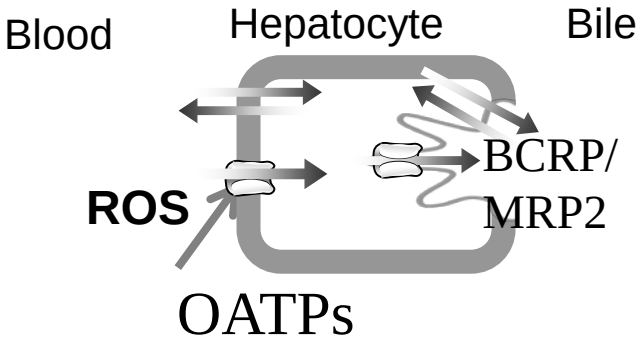
He et al., Mol Pharm., ‘14



Asymmetrical change in rosuvastatin conc. in liver and blood in the presence of rifampin

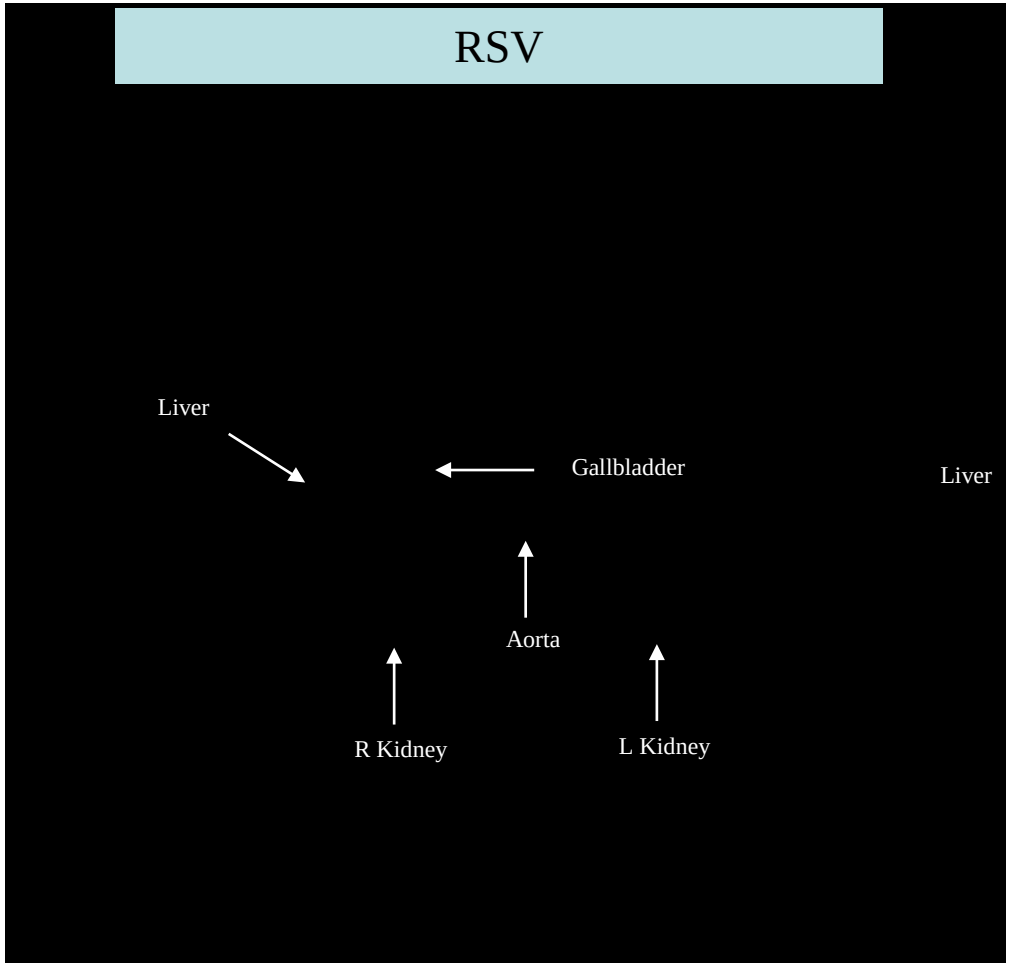


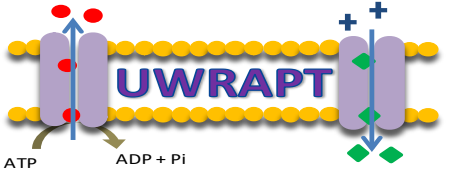




2.3-fold increase in plasma AUC but no significant increase in liver AUC

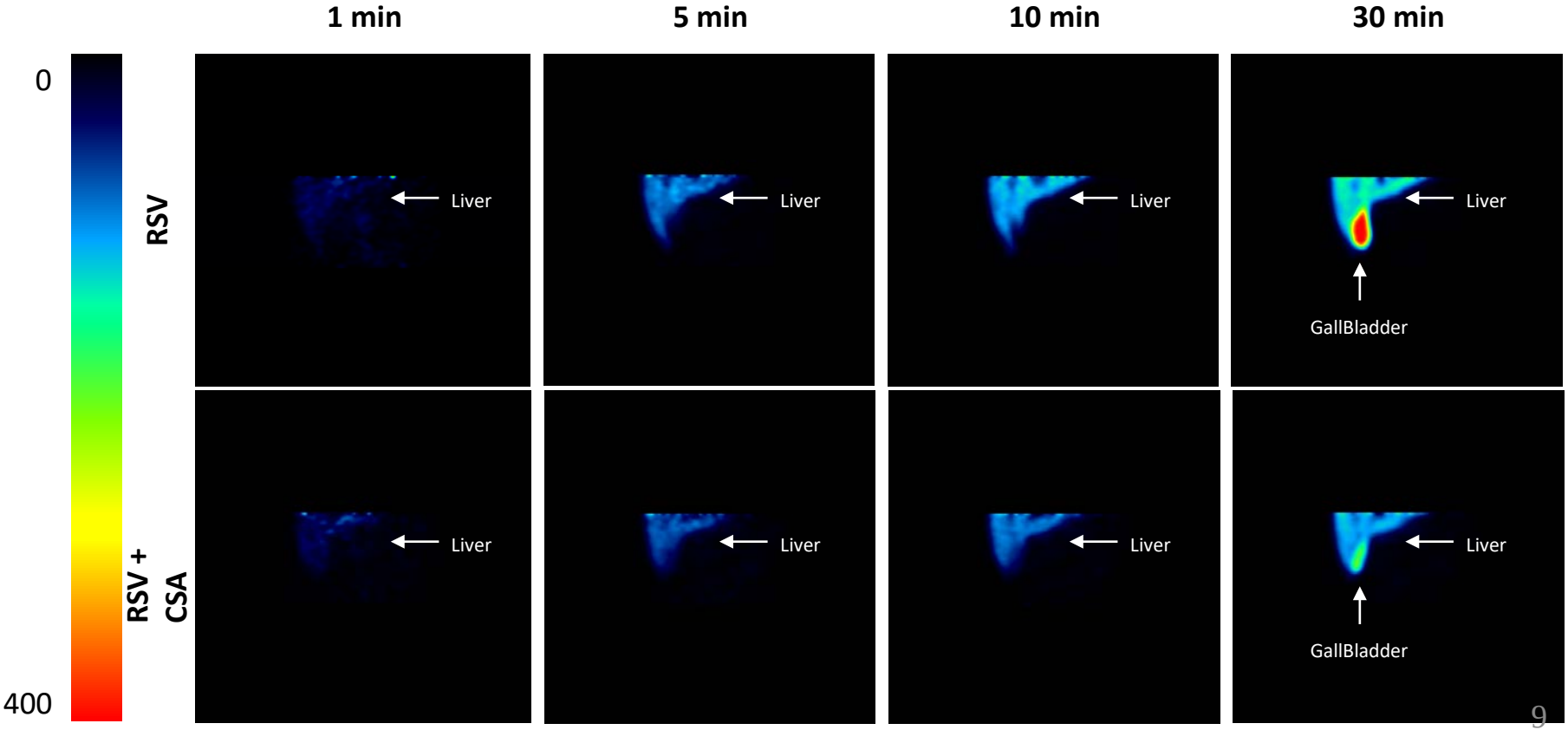
He et al., Mol Pharm. 2014





[^{11}C]Rosuvastatin biodistribution in a human volunteer

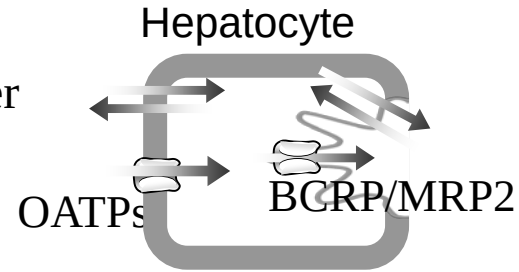
Hepatic Uptake and Biliary Excretion of [^{11}C]Rosuvastatin ± CsA



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



REF Method to Predict Tissue Drug Conc.

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

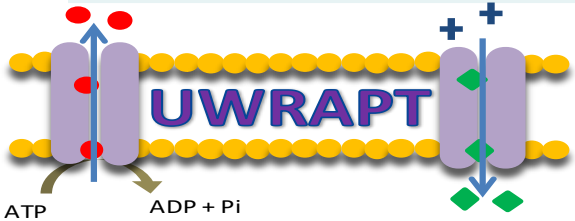
CL via transport of interest in cell line expressing the transporter

Relative Expression Factor (REF)

1. Transporter expression/g of tissue
2. Tissue weight

In vivo CL

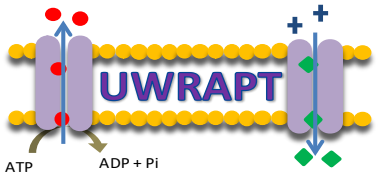
Contribution of individual transporter in tissue uptake/efflux



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

- https://sop.washington.edu/department-of-pharmaceutics/research/research-affiliate-program-on-transporters-uwrapt/

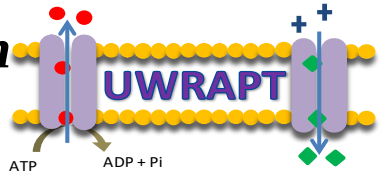
Can the use of these Quantitative Proteomics Data Successfully Predict Transporter-Mediated CL and Tissue Conc. of Drugs?



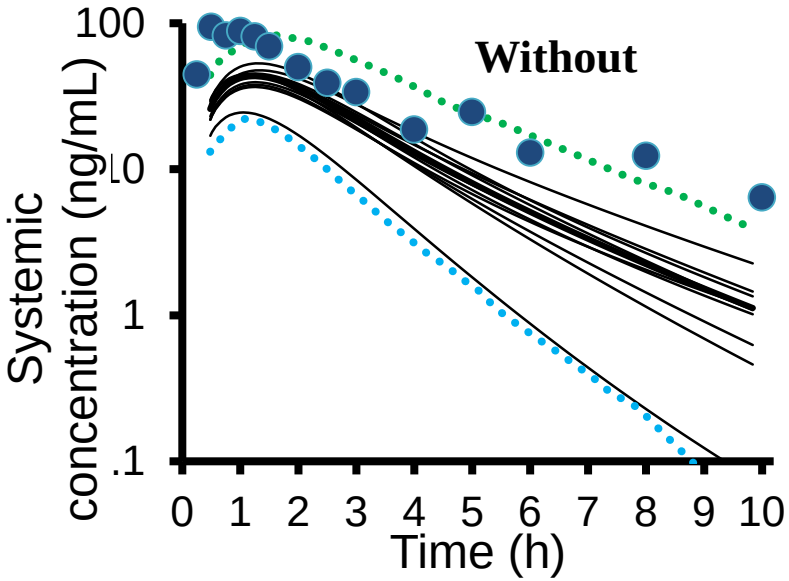
Criteria of success: within 2-fold of observed value

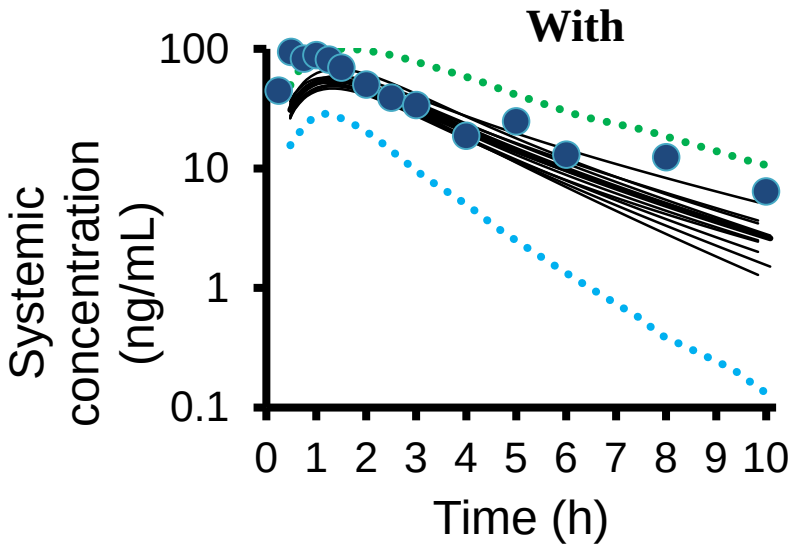
- Changes due to hepatic impairment (e.g. chirrohsis)
- Renal secretory CL of drugs
- Hepatic CL and tissue conc. of drugs – rat and human

Improved PBPK Prediction of Repaglinide Pharmacokinetics in Liver Cirrhosis Patients When the Effect of Cirrhosis on OATP1B1 Abundance is Incorporated



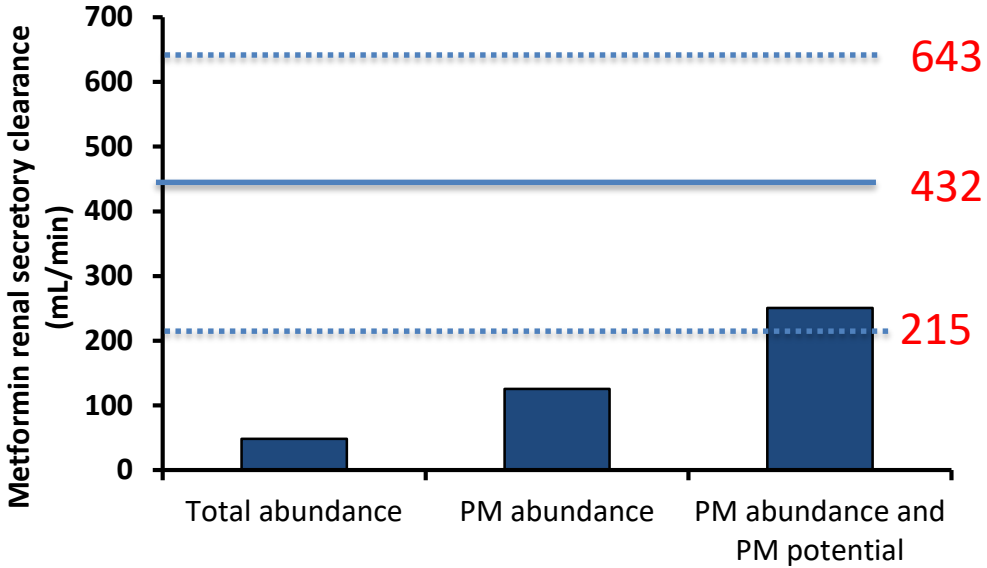
Virtual population (10 trials and n=12 for each trial)

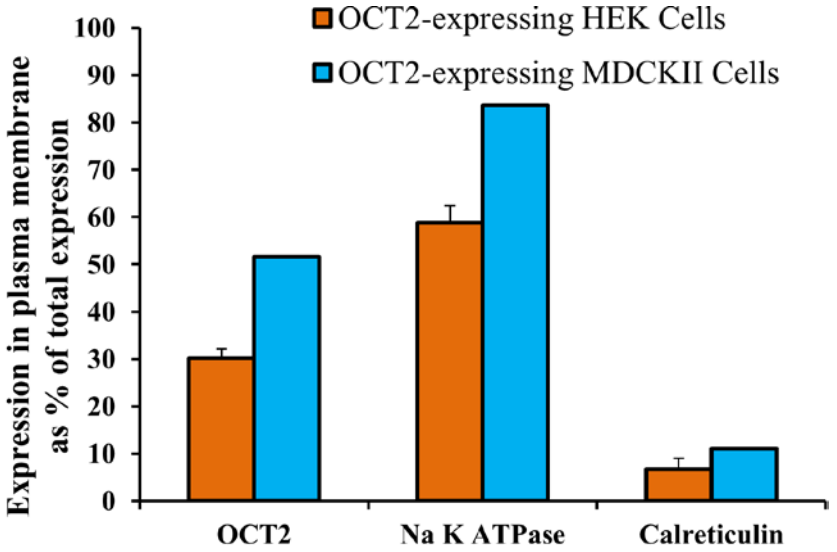




Wang et al., DMD, 2016

Metformin renal clearance is reasonably well-predicted using OCT2 expressing cells



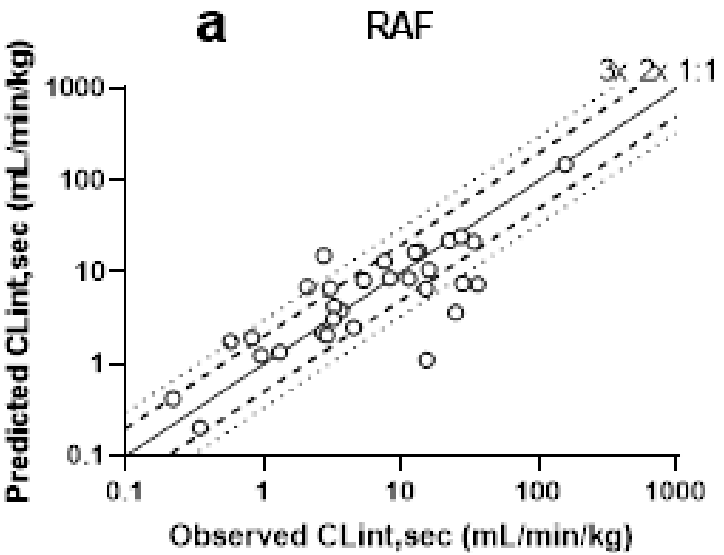


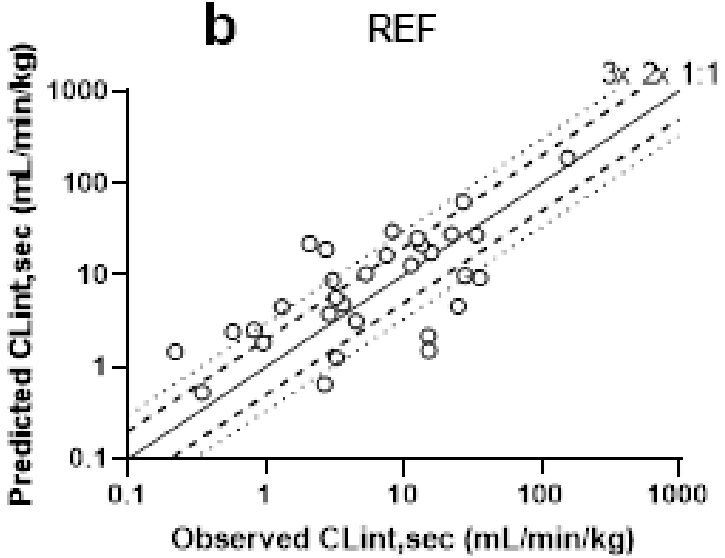
Observed metformin renal secretory clearance in humans: 432 (range 215-643) mL/min

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)

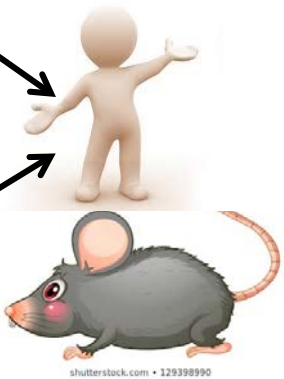
Hypothesis: Predict Transporter-Mediated In-Vivo Hepatobiliary CL and Hepatic Concentrations of Drugs in Rats/Humans using REF

Transporter-expressing cells

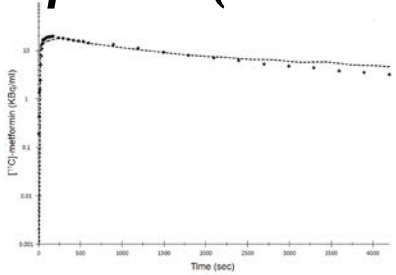
1. transporter-mediated drug CL
2. transporter abundance using quantitative proteomics
3. Obtain REF

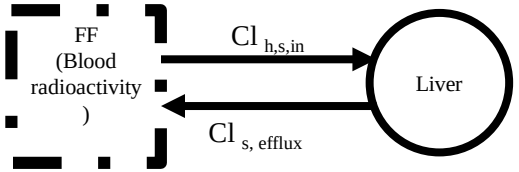
Predict *in-vivo* hepatobiliary CL using REF and traditional approach

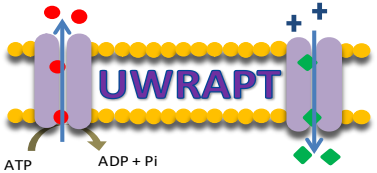
Verify predictions using PET imaging



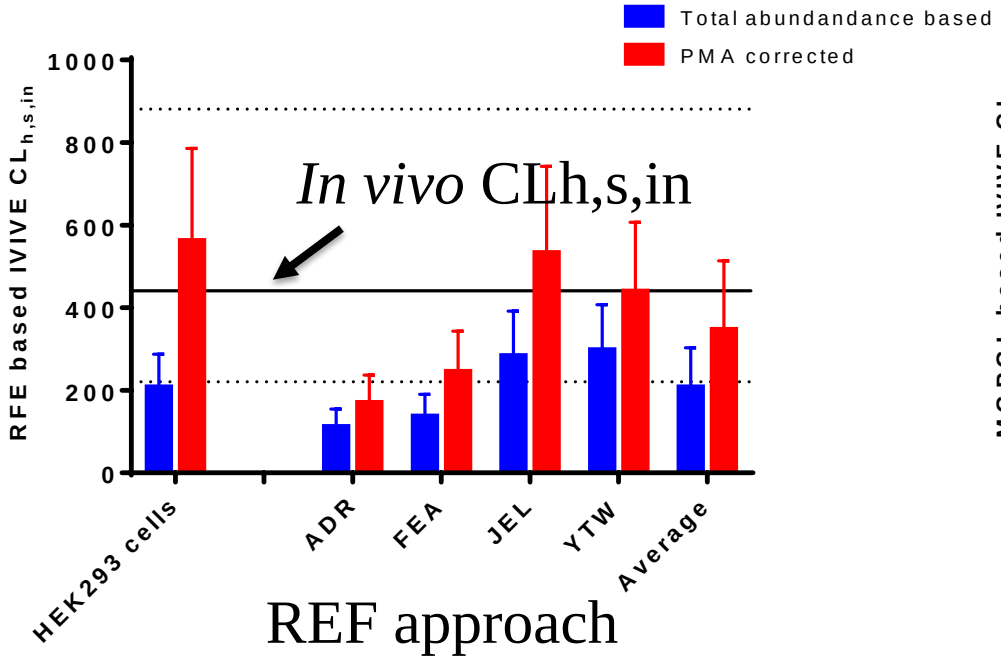
REF (using HEK293 cells or PHH) better predicts Hepatic Uptake CL of metformin (as measured by PET imaging) vs. PHH



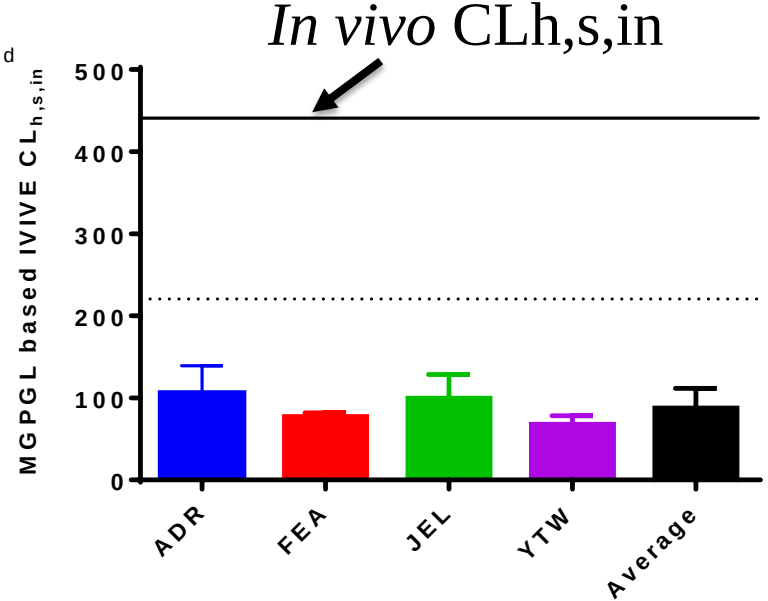




Gormsen, et al., J Nucl Med **57**(12): 1920-1926.



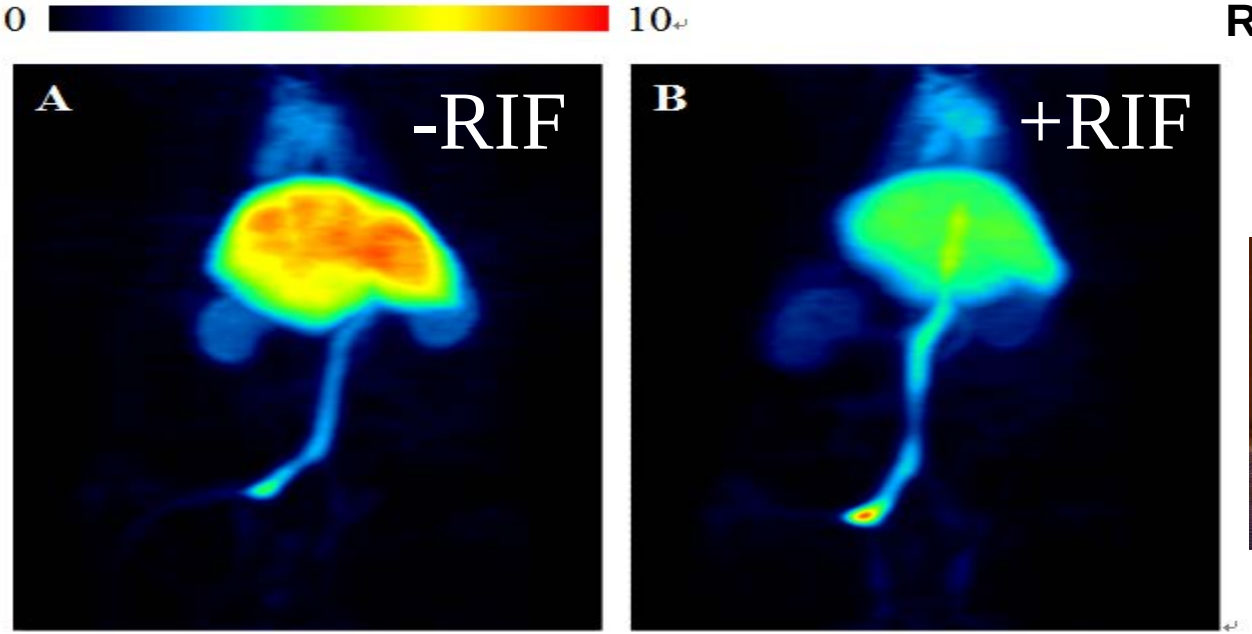
REF approach

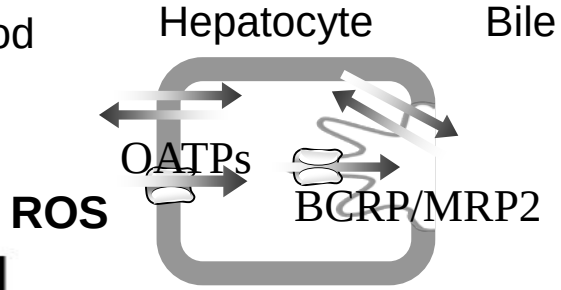


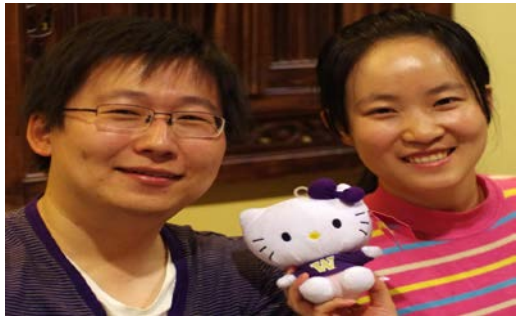
Human Hepatocytes

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

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

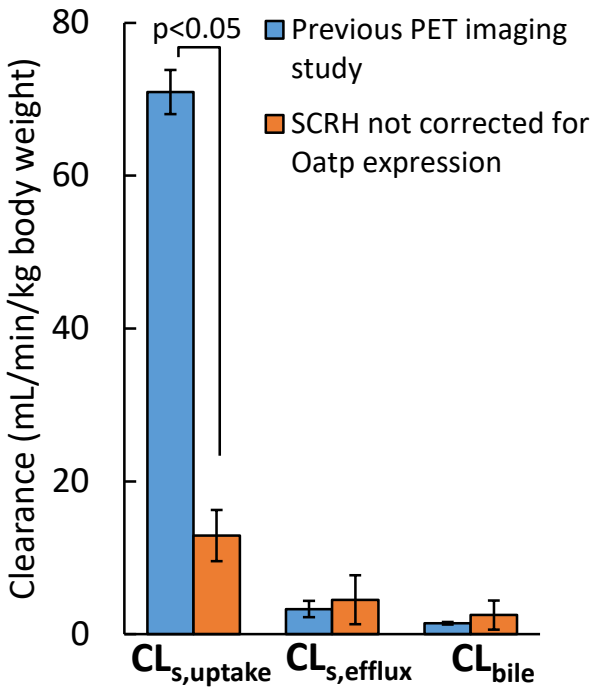




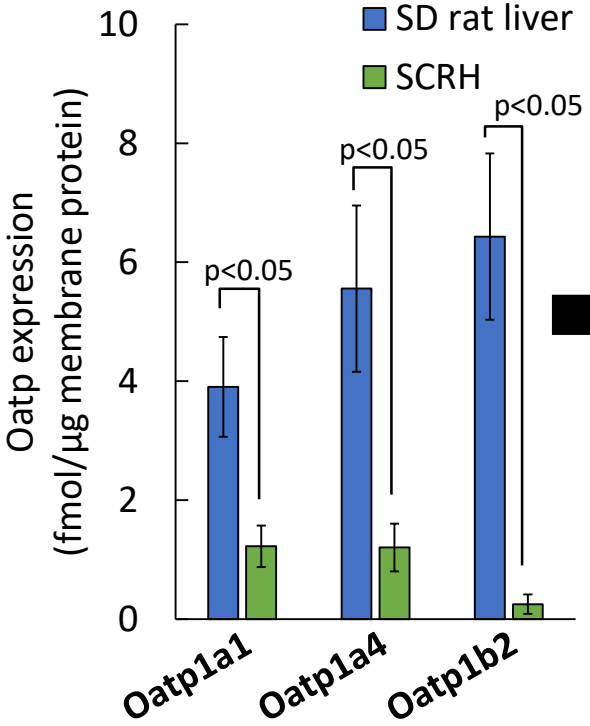


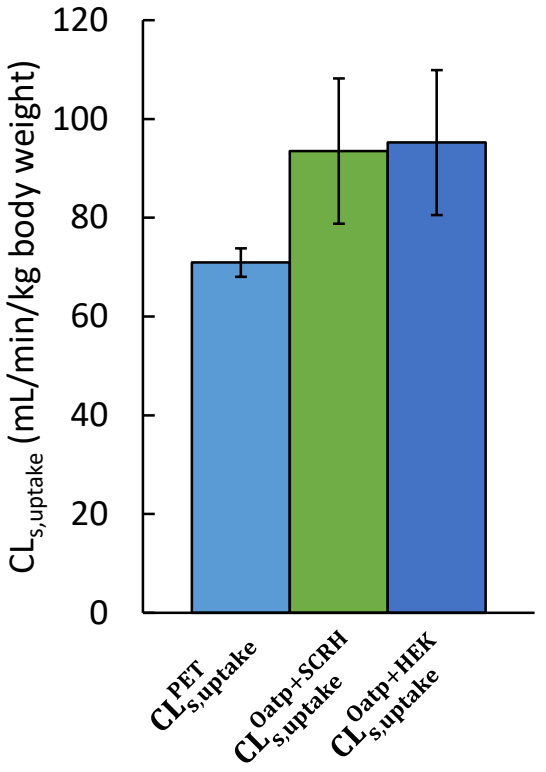
He et al., Mol Pharm., ‘14

Successful prediction of the hepatobiliary clearance of rosuvastatin using cell lines, sandwich-cultured rat hepatocytes and quantitative proteomics



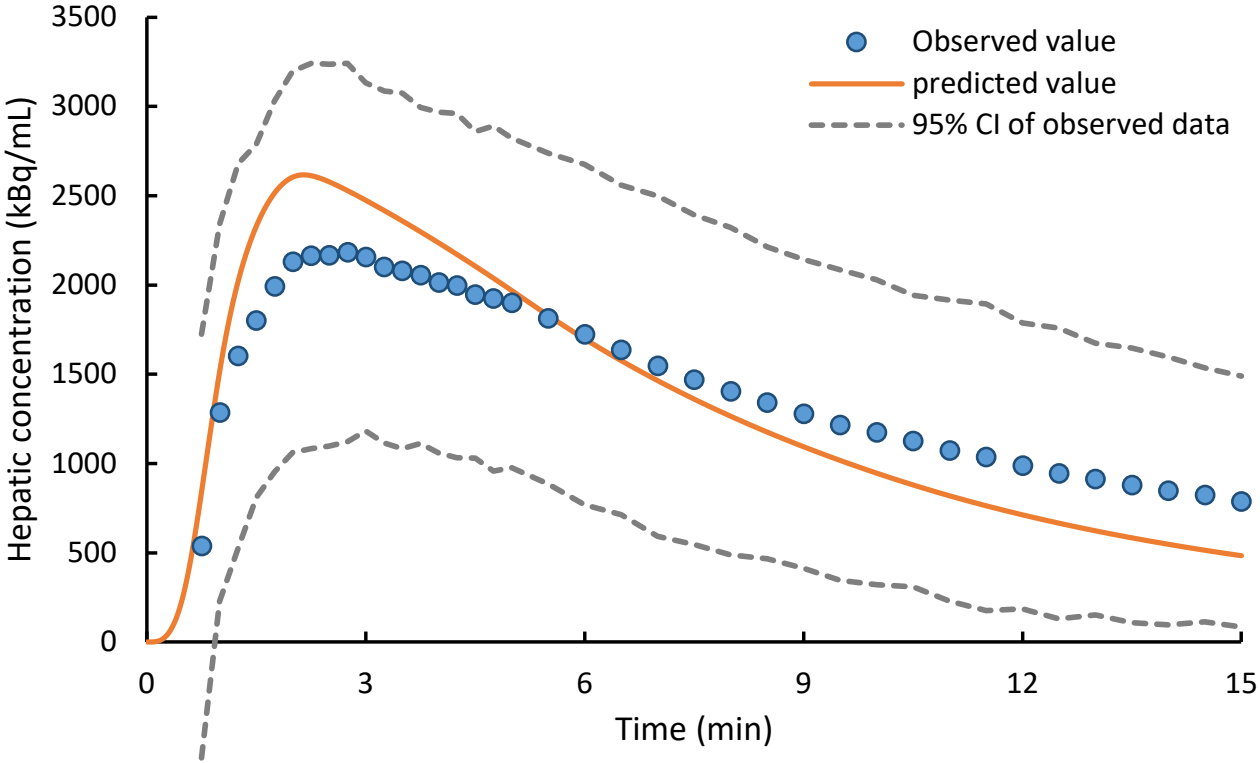
$CL_{s,uptake}$; sinusoidal uptake
$CL_{s,efflux}$; sinusoidal efflux
CL_{bile}; canalicular efflux





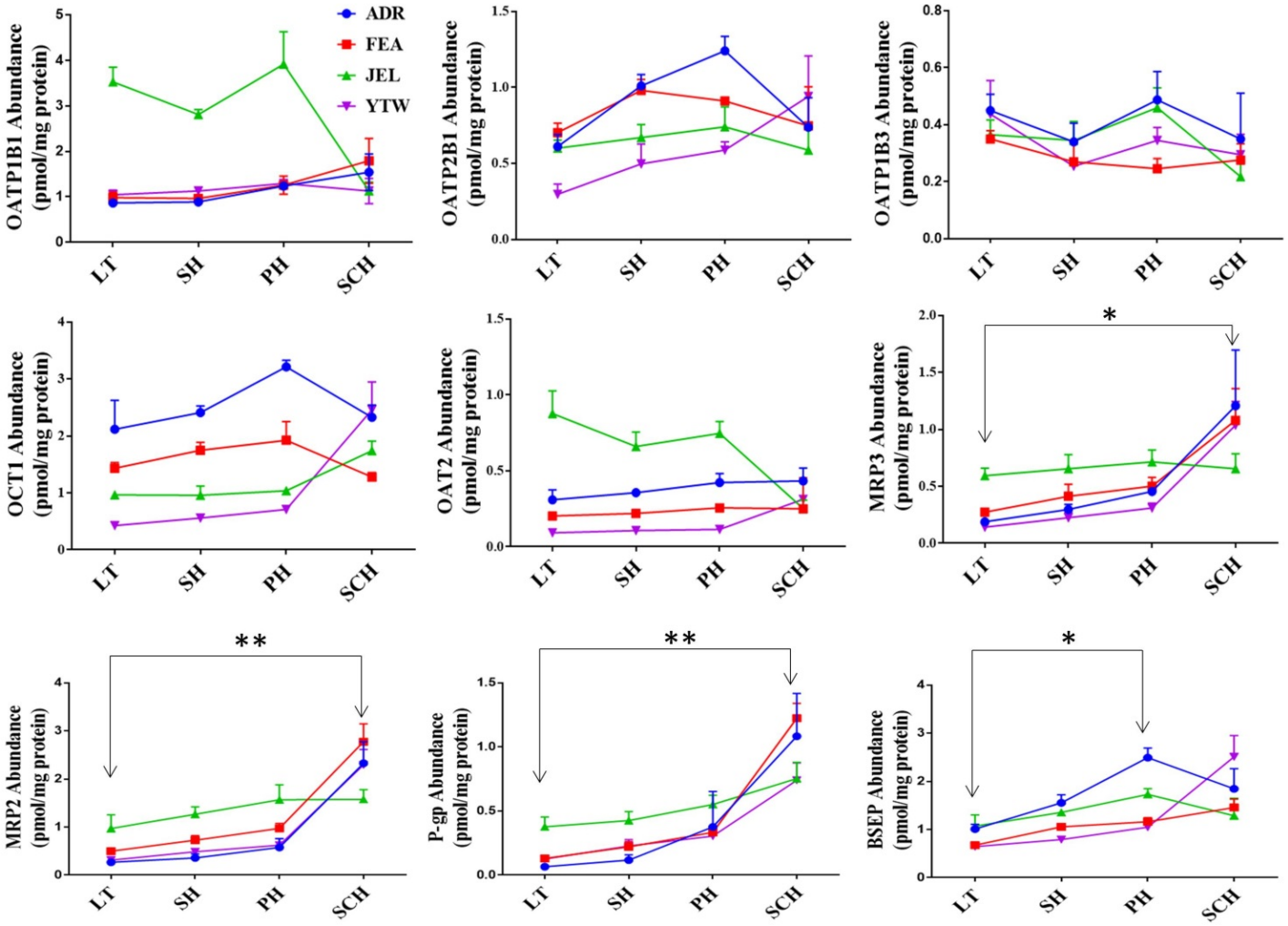
Ishida et al., DMD, 2018

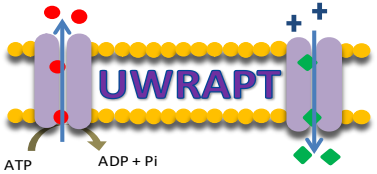
Rat Hepatic Rosuvastatin Conc. well Predicted



Ishida et al., DMD 2018

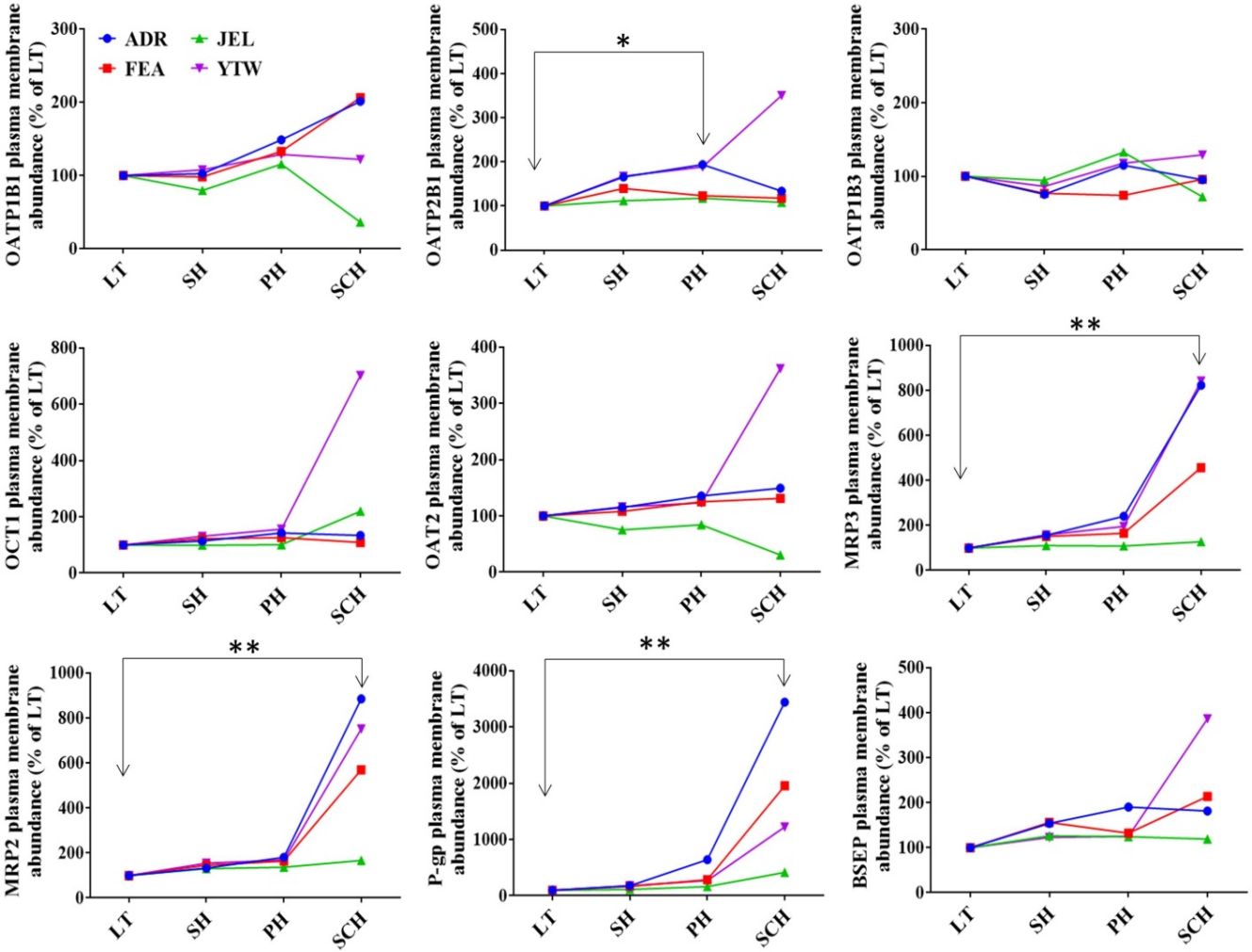
Can Rosuvastatin Hepatobiliary CL and Hepatic Conc. be Predicted in Humans?

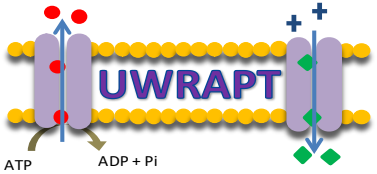




Total transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes and liver tissue

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

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Dept. of Anesthesiology: Karen Domino, Matthew Pennington

Dept. of Pharmaceutics: Bhagwat Prasad, Edward Kelly, Carol Collins, Joanne Wang

Kidney Research Institute: Jonathan Himmelfarb

Univ. of Greifswald: Stefan Oswald and team

Children's Mercy Hospitals: Steven Leeder and team

Aarhus University Hospital, Aarhus, Denmark, Dr. Gormsen

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UWRAPT
ATP
ADP + Pi