SCHOOL OF PHARMACY
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Predicting intracellular hepatic concentrations of drugs using proteomic data and PET imaging

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How Can we Measure or Predict Tissue Drug Conc. in Humans?

- 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

Alternative 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)*

AND

verify these conc. for selective probe substrates which interrogate transporters of interest

In vitro CL

CL via transport of interest in cell line expressing the transporter

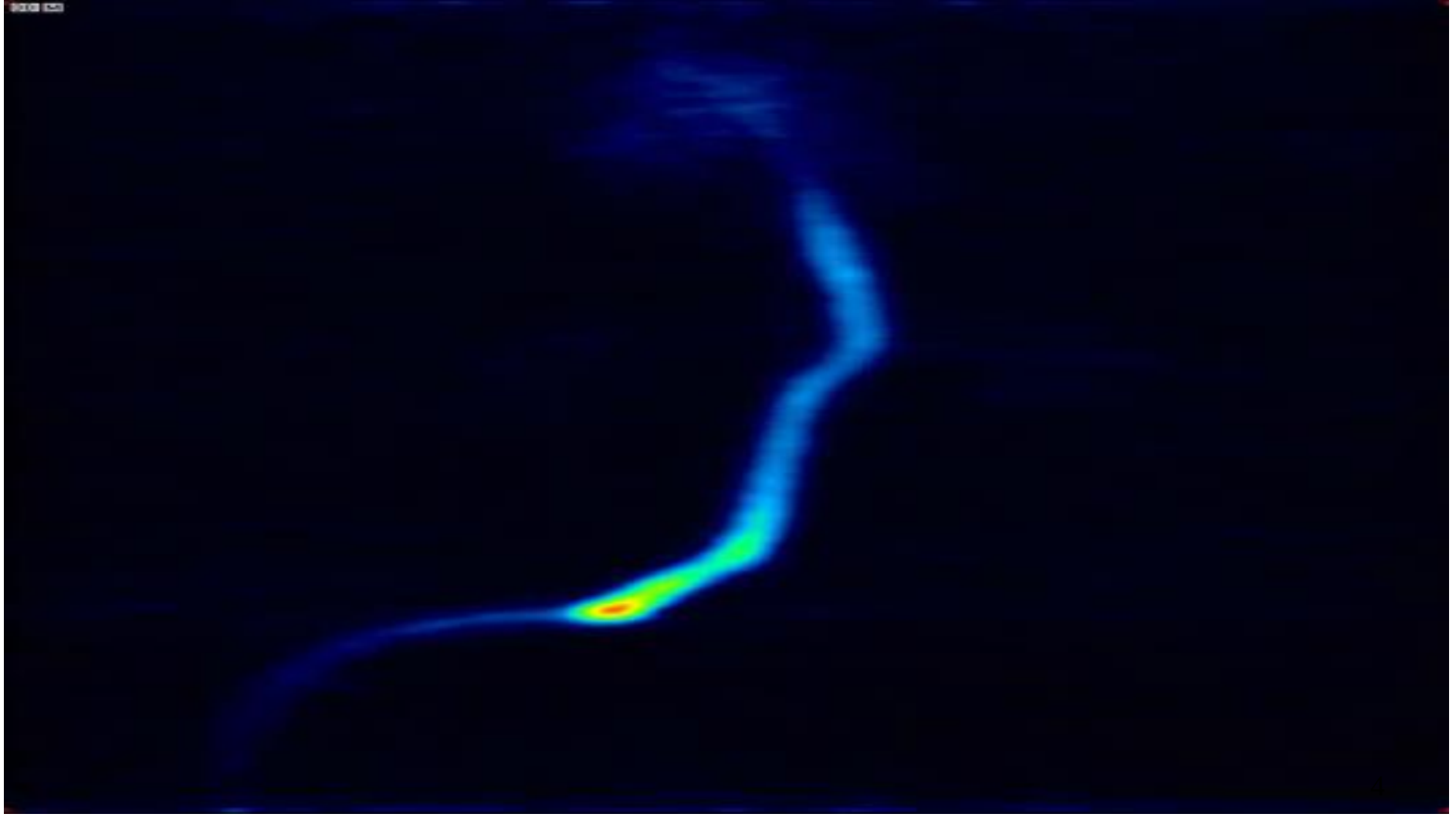
Relative Expression Factor (REF)

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

In vivo CL

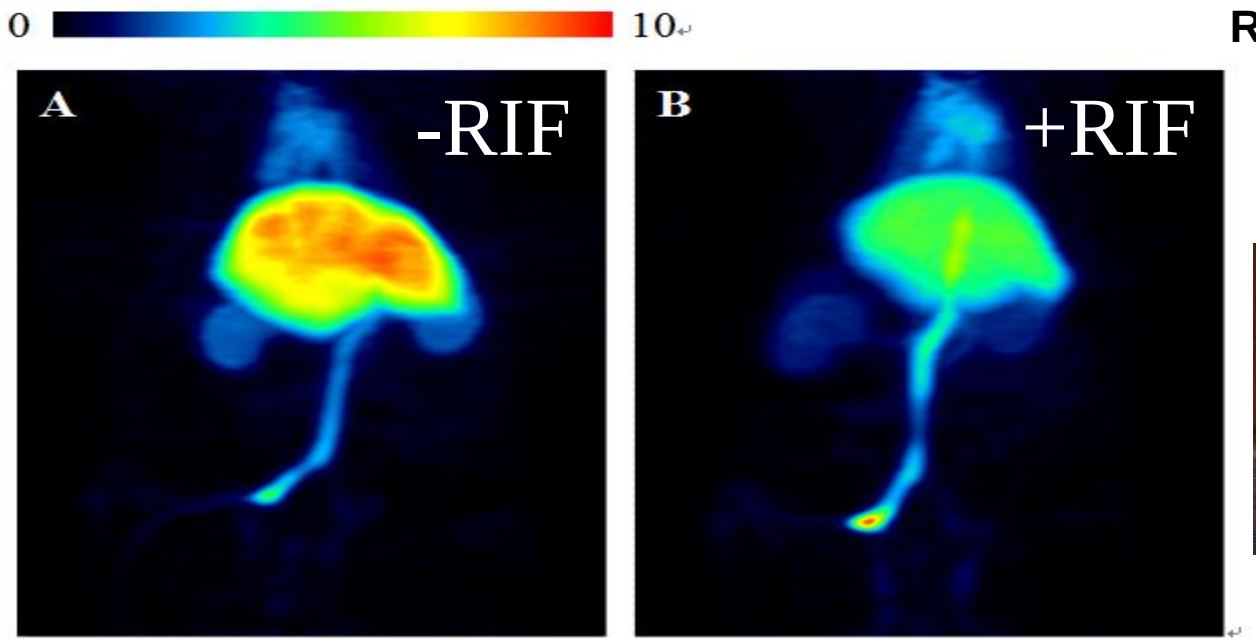
Contribution of individual transporter in tissue uptake/efflux

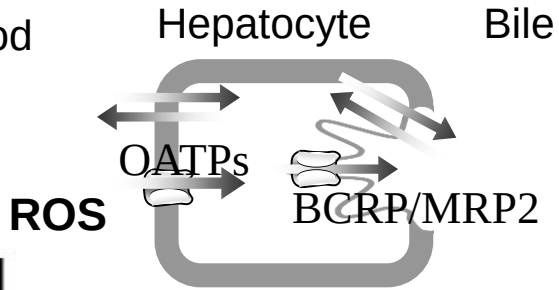
$$REF = \frac{[T]_{ex\ vivo\ in\ organ}}{[T]_{in\ vitro}}$$

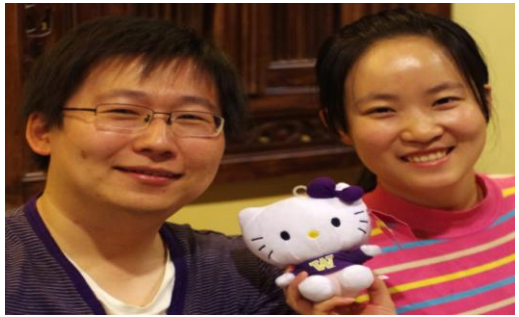


Hepatic Uptake and Biliary Excretion of ^{11}C-Rosuvastatin in the Rat

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

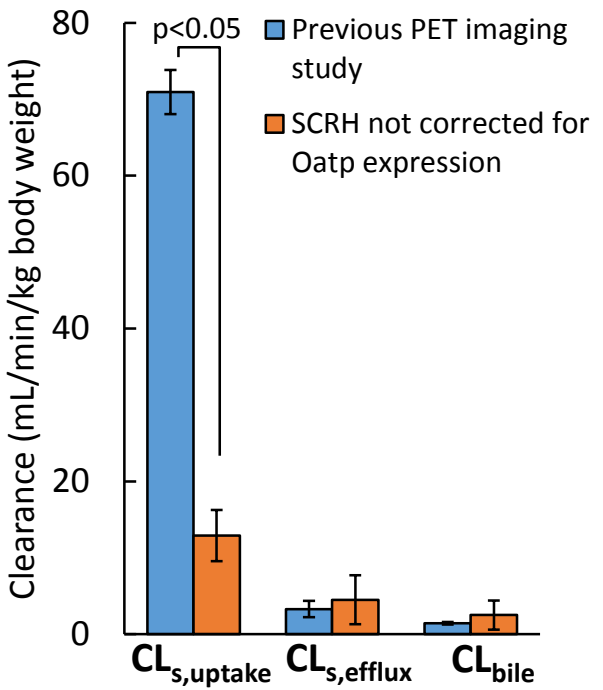


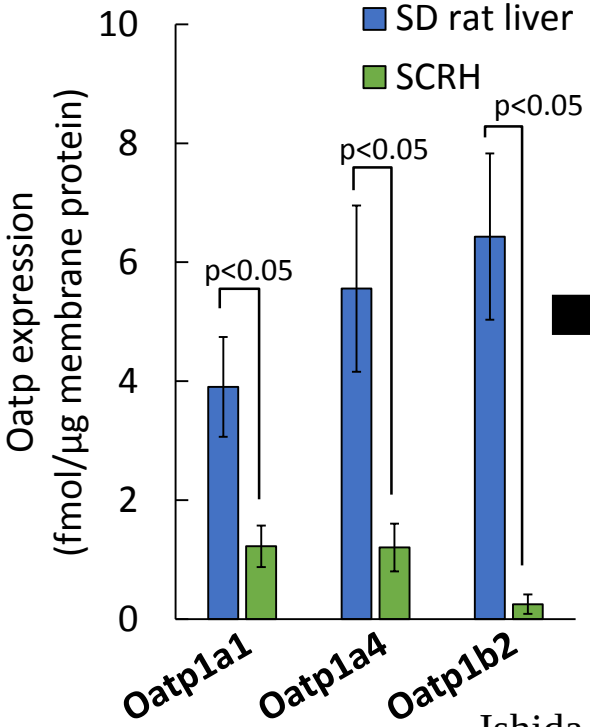


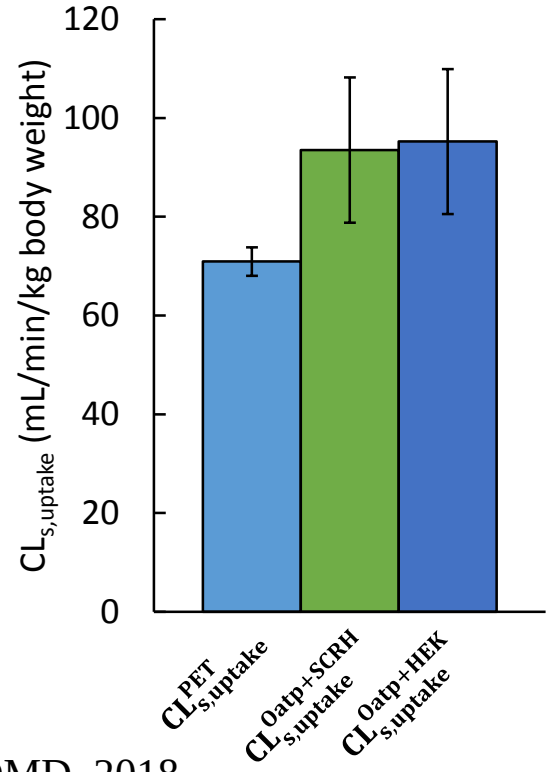


He et al., Mol Pharm., ‘14

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



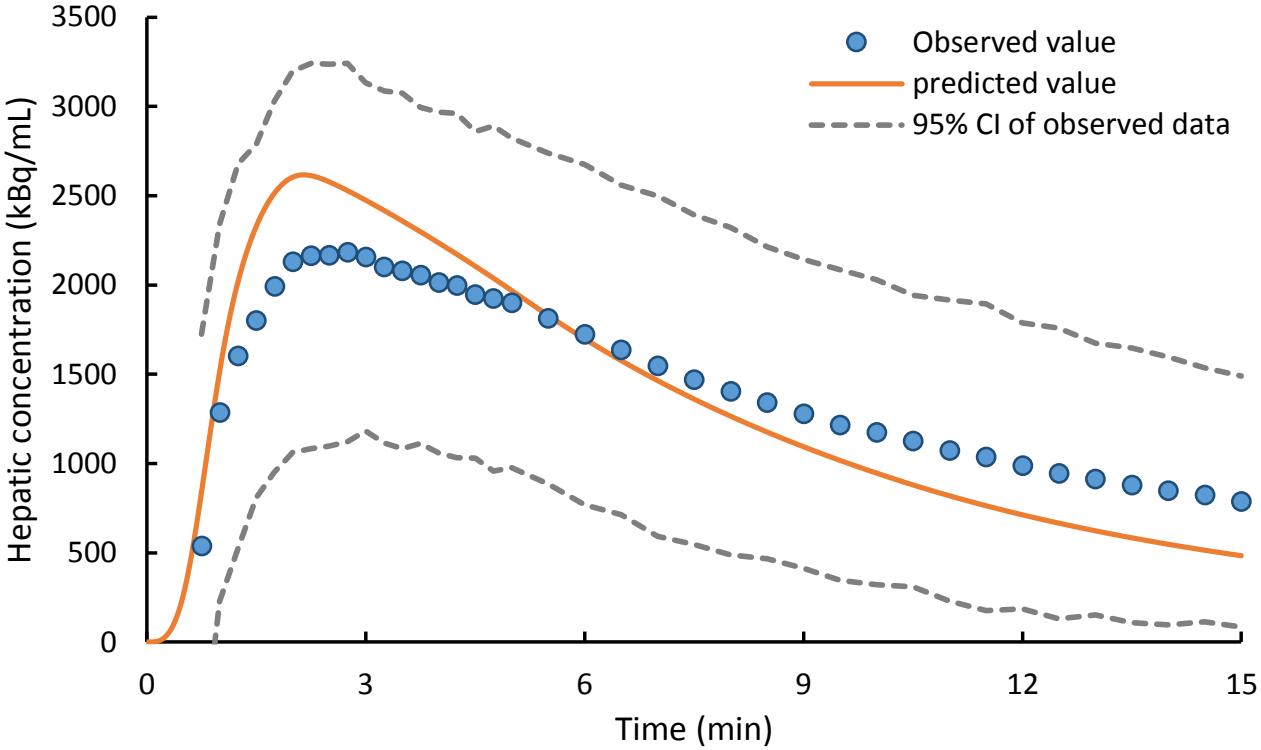


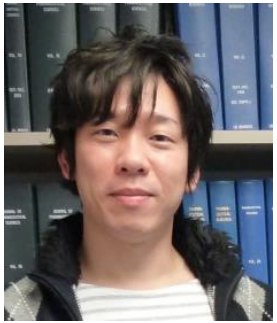


$CL_{s,uptake}$; sinusoidal uptake
$CL_{s,efflux}$; sinusoidal efflux
CL_{bile}; canalicular efflux

Ishida et al., DMD, 2018

Rat Hepatic Rosuvastatin Conc. well Predicted by REF approach



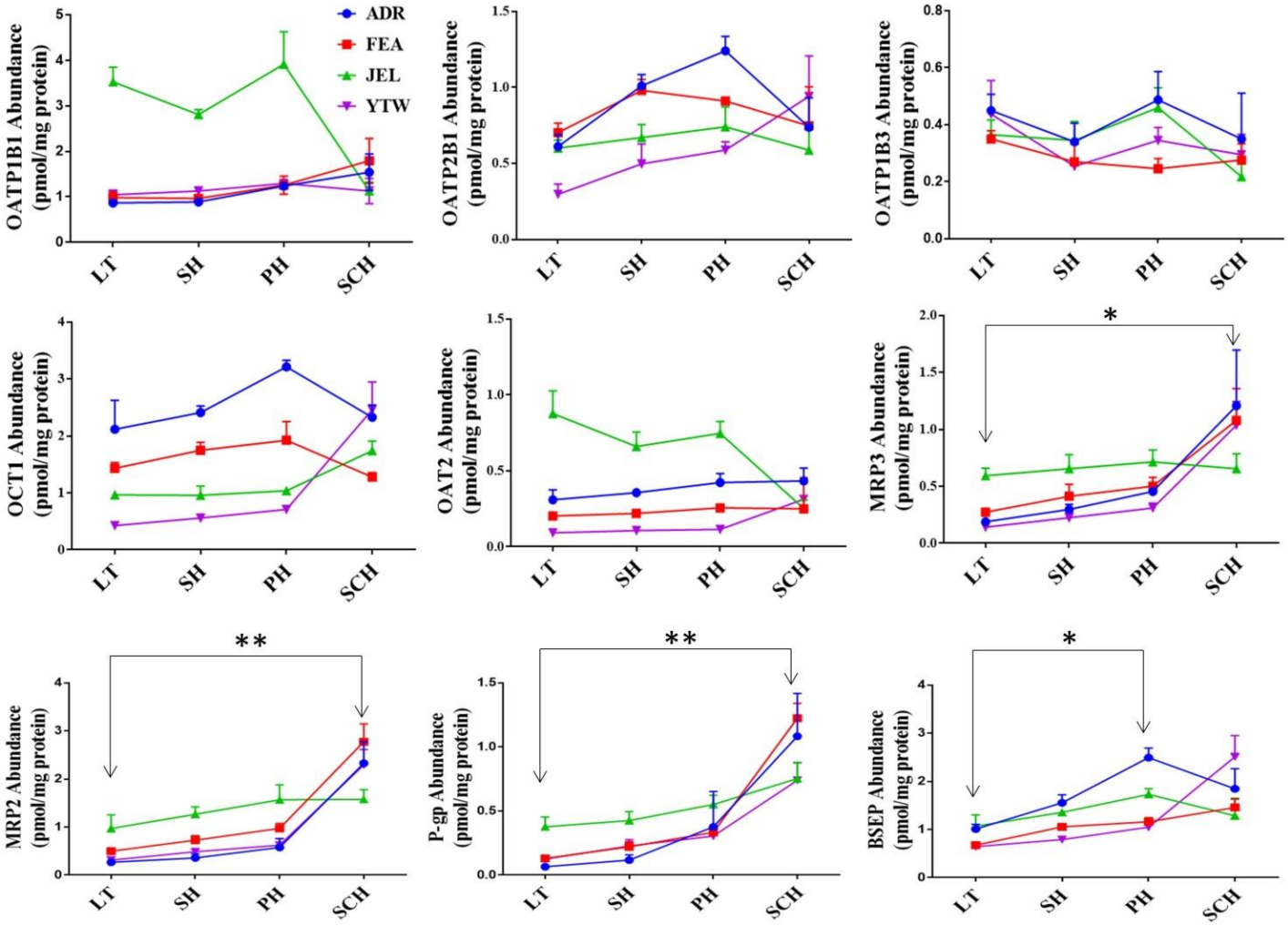


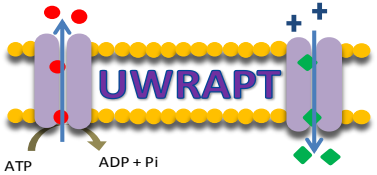
Kazuya Ishida

Ishida et al., DMD 2018

Can Rosuvastatin Hepatobiliary CL and Hepatic Conc. be Predicted in Humans by Quantitative Proteomics using REF?

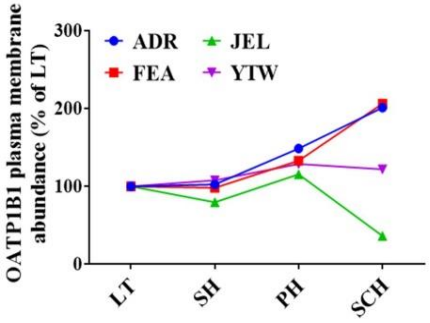
Vineet Kumar

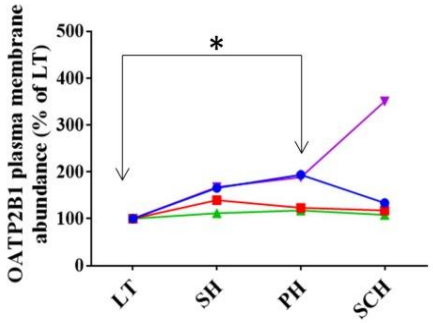


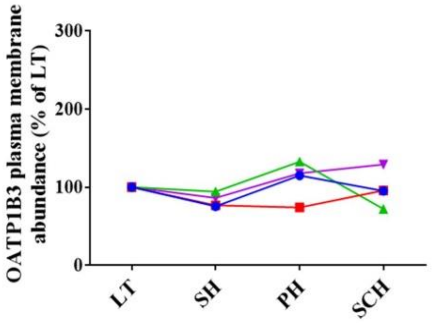


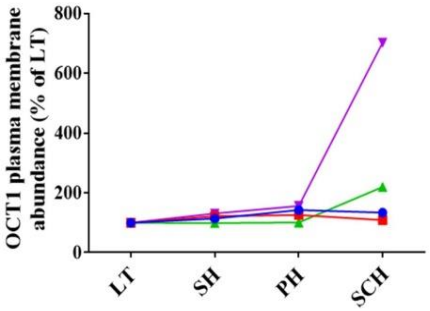
Total transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes and liver tissue

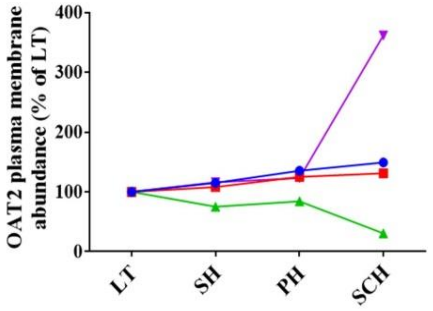
Kumar et al., DMD, 2019

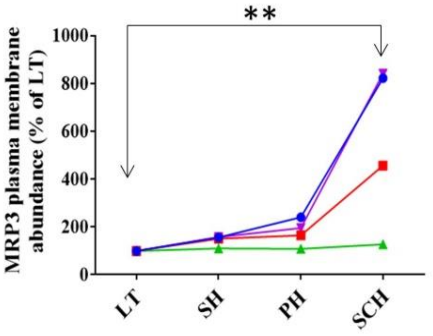


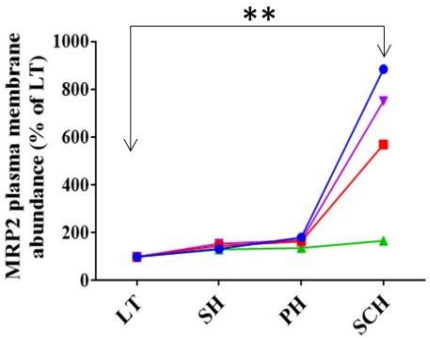


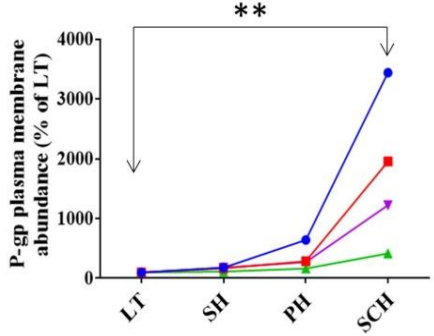


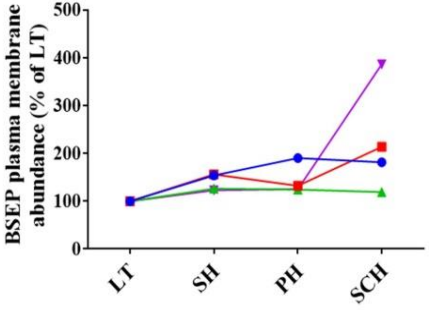


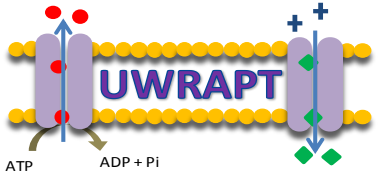








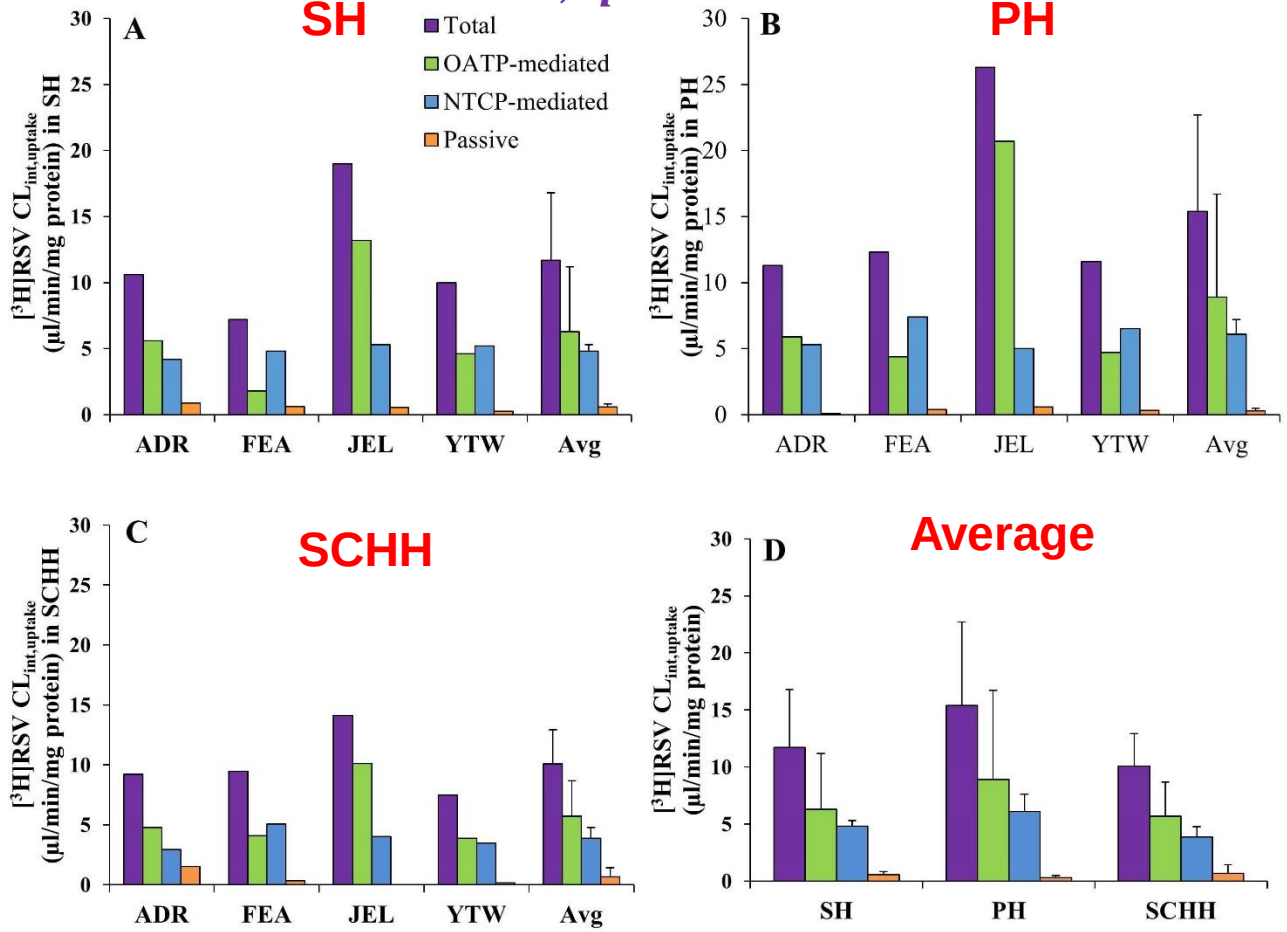




Plasma membrane transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes cf liver tissue

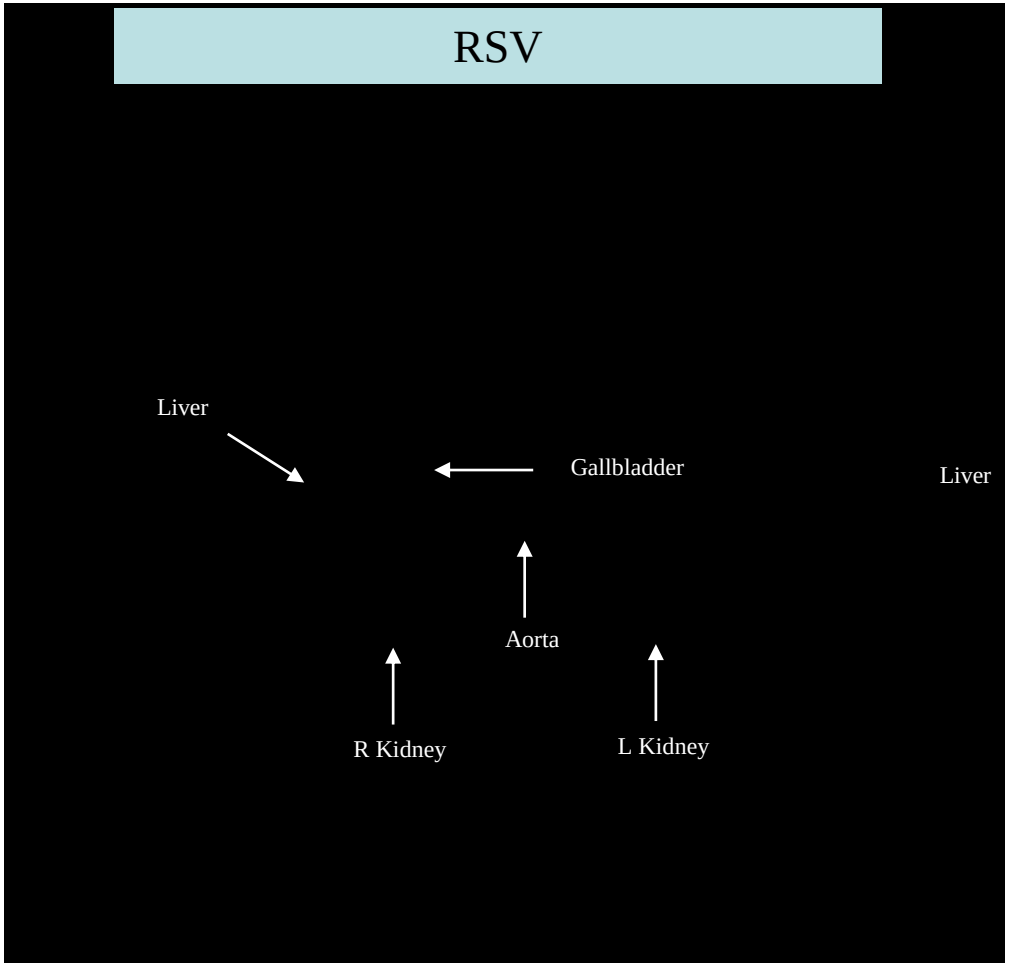
Kumar et al., DMD, 2019

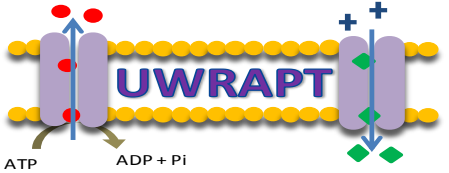
RSV sinusoidal $CL_{int,uptake}^{hep}$ in SH, PH and SCHH was similar



[³H]Rosuvastatin: 30 nM, Rosuvastatin (cold): 70 nM
Bromsulphthalein (BSP): 200 µM

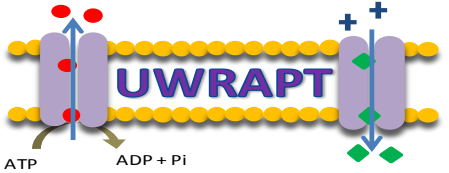
Statistical test: Wilcoxon matched-pair signed rank
No significant difference in total uptake

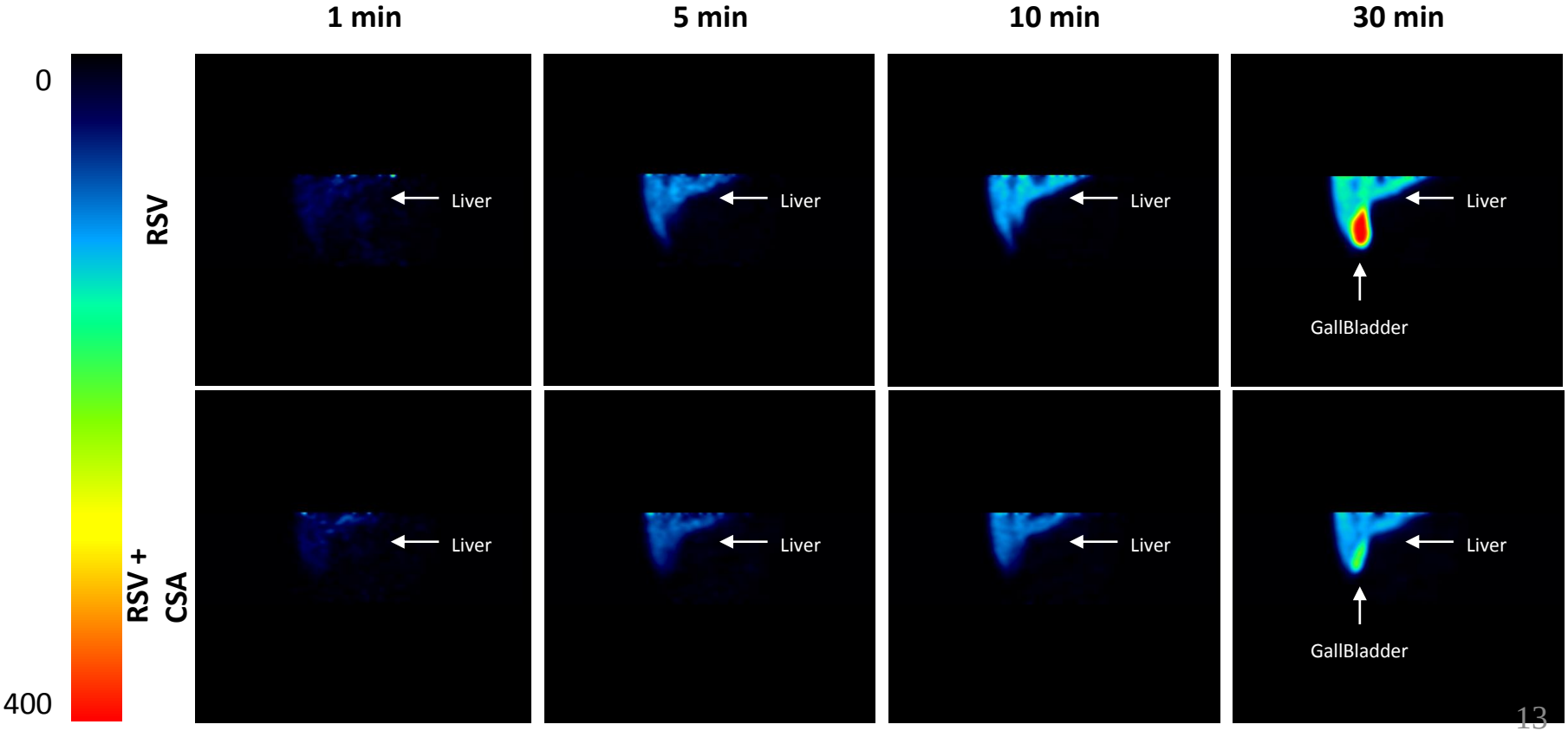




[^{11}C]Rosuvastatin biodistribution in a human volunteer

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





Summary

- Predicting tissue concentration 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 REF is a promising technique to predict tissue drug conc.
- These predictions should be verified using PET imaging probes that individually interrogate drug transporters of interest

Major Contributors

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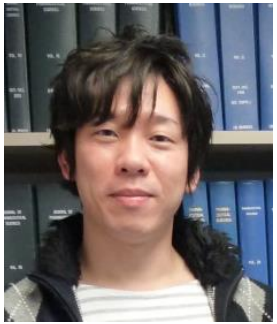

Kazuya Ishida

Bhagwat Prasad Anand Deo

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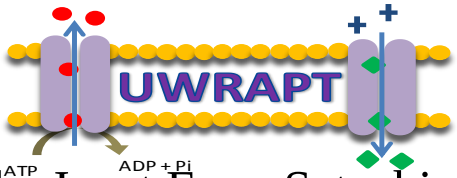

Other Collaborators

Dept. of Radiology: Jeanne Link, David Mankoff, Todd Richards, Janet Eary, Satoshi Minoshima, Ken Maravilla, Mark Muzi, Steve Shoner, 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

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

Roche, Basel: Mohammed Ullah

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UWRAPT
ATP
ADP + Pi