Endogenous Biomarkers for OATP1B: Preclinical to Clinical Translations

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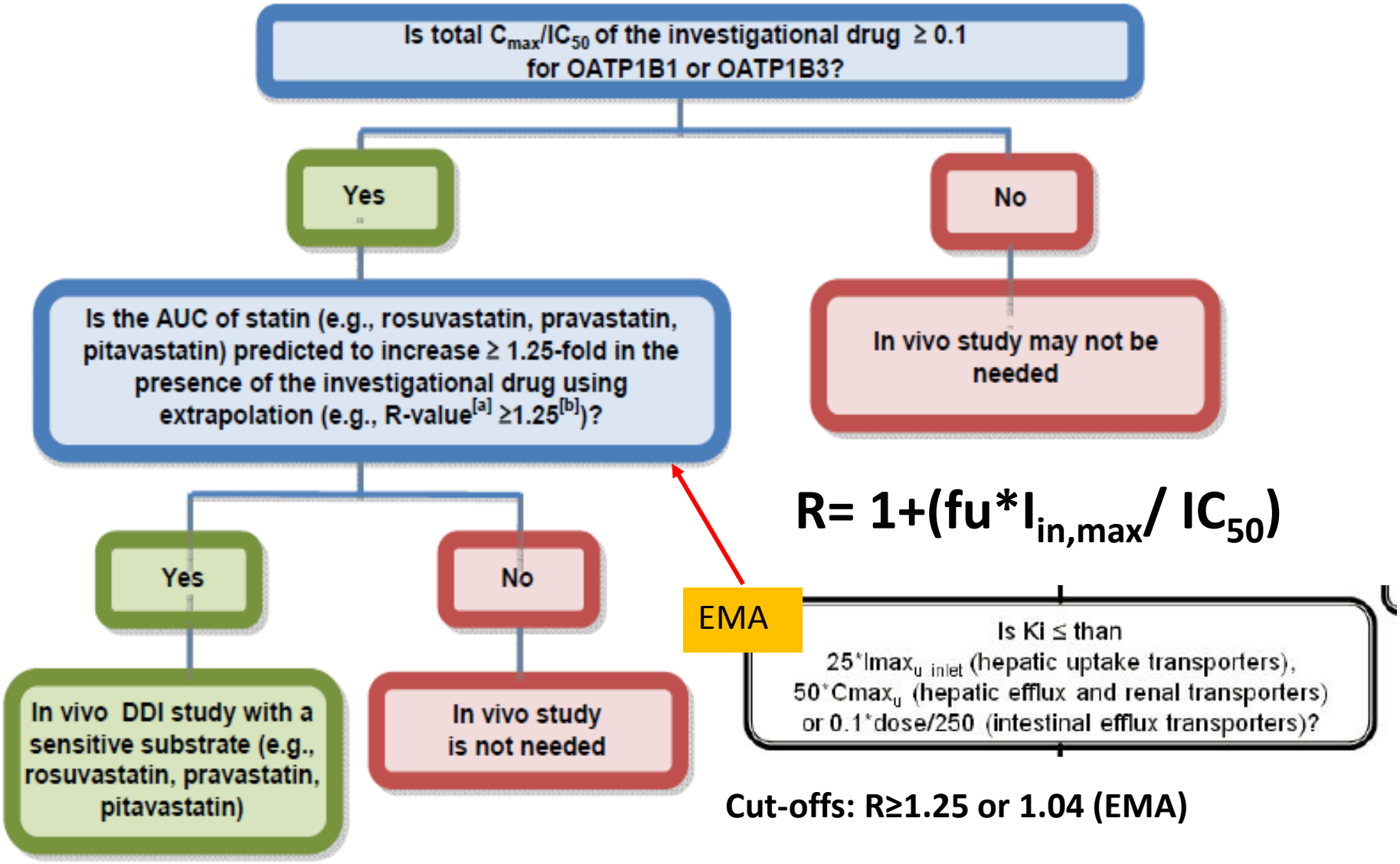
Outlines

- Current strategies to assess clinical DDIs for OATP inhibitor
- Endogenous probes for OATP inhibition
  - Preclinical evaluation
  - Clinical studies
- Summary

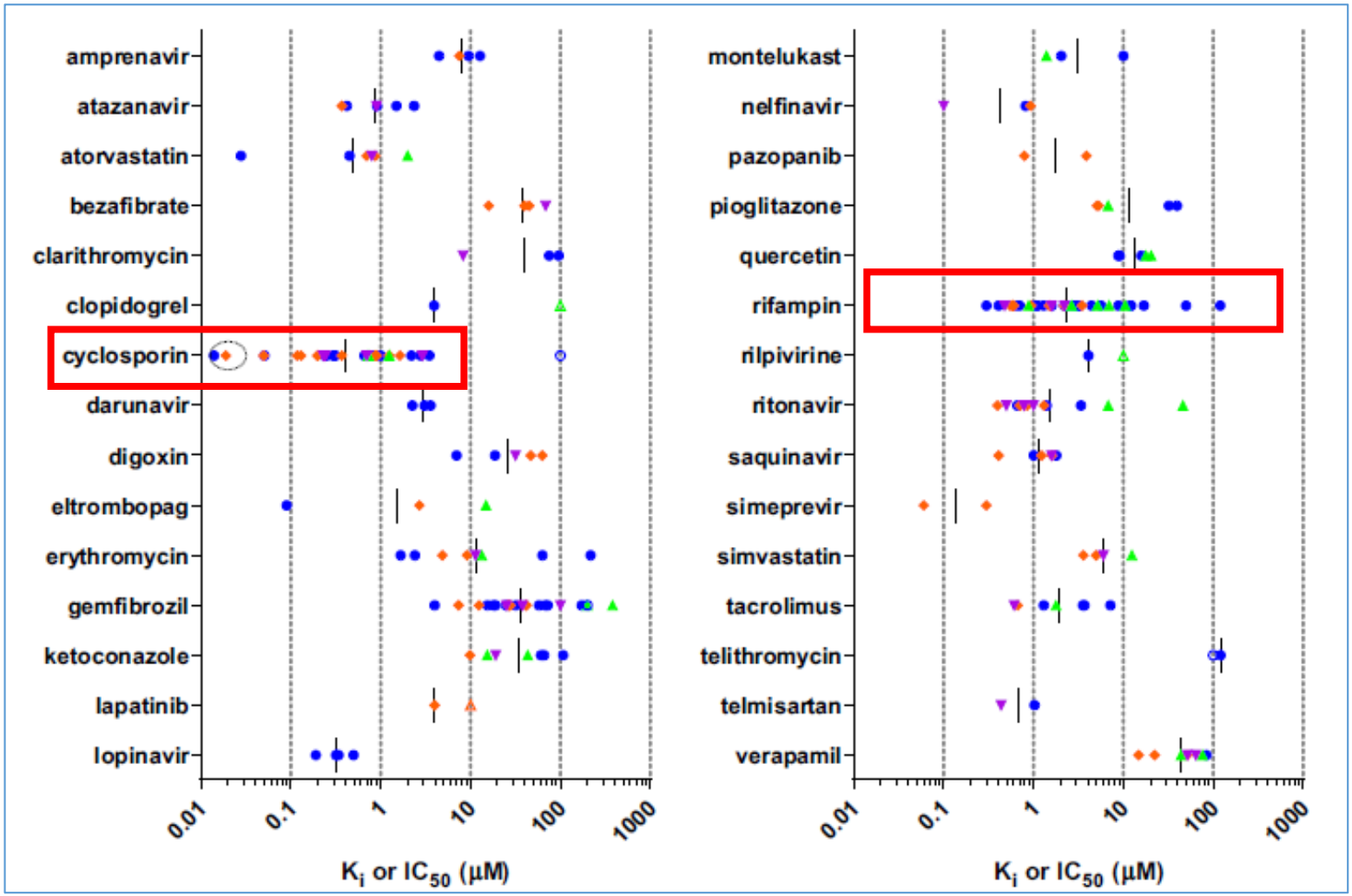
OATP inhibition decision tree



$$R = 1+(fu*I_{in,max}/ IC_{50})$$

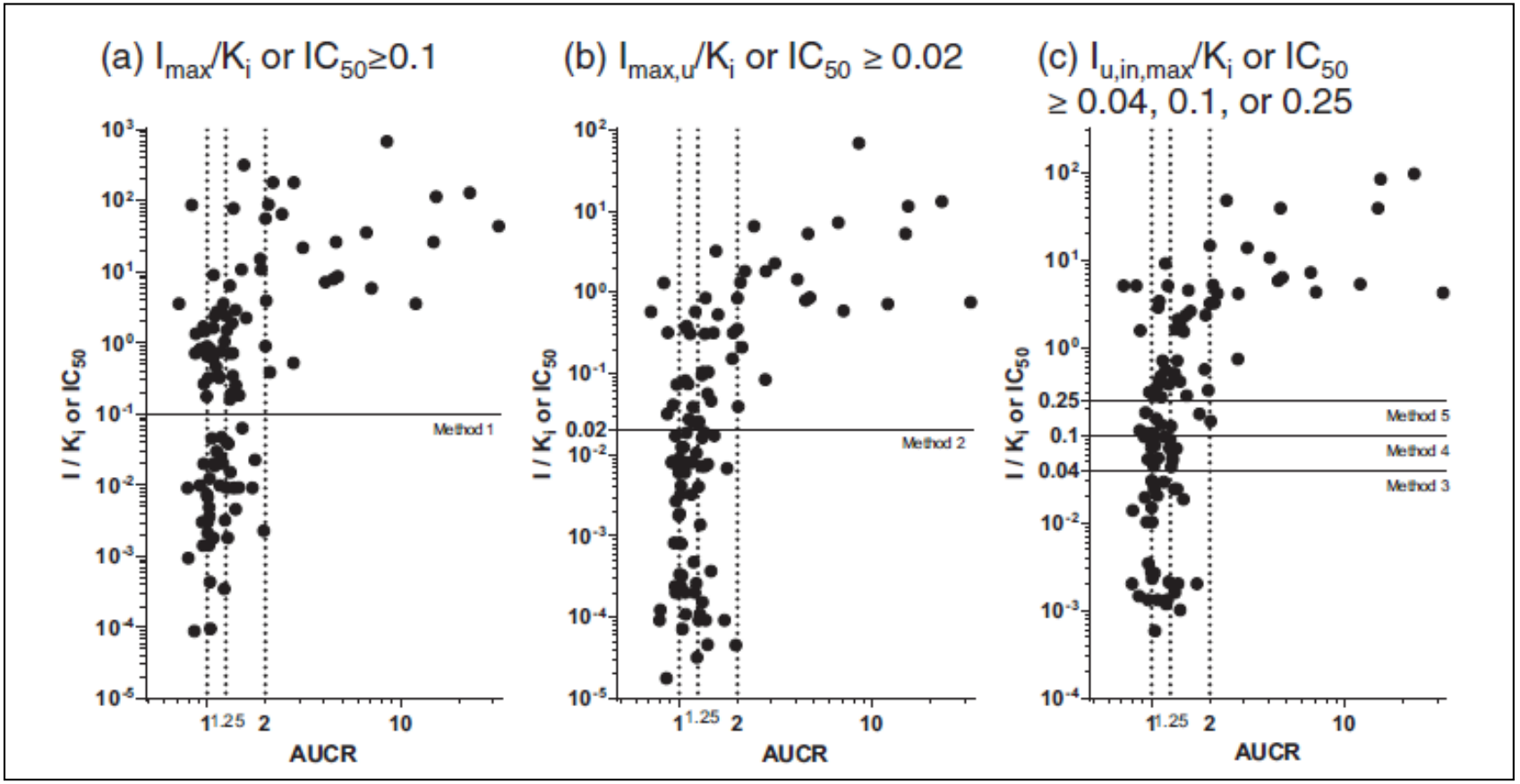
Cut-offs: R≥1.25 or 1.04 (EMA)

Variability in Ki or IC50 of Inhibitors



Vaidyanathan, et al . (2016) *J. Clin. Pharmacol.* **56 Suppl 7**, S59-72

Relationships between observed AUCR and Imax(free)/ Ki or IC50.



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Summary of the challenges in assessing potential OATP inhibition DDIs

- The potential for a high rate of false-positive (and negative) prediction has been a particular concern

  (Prueksaritanont et al., 2013; Tweedie et al., 2013)

- Other challenges
  - Dilemma: the timing for human DDI studies and the selection of does
  - Selection of probe substrates
  - Extrapolating DDIs to different population or ethnic group
  - Complex DDIs

Supplemental material to this article can be found at:
http://jpet.aspetjournals.org/content/suppl/2016/02/23/jpet.116.232066.DC1.html

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J Pharmacol Exp Ther 357:382–393, May 2016

Coproporphyrins I and III as Functional Markers of OATP1B Activity: In Vitro and In Vivo Evaluation in Preclinical Species[S]

Hong Shen, Jun Dai, Tongtong Liu, Yaofeng Cheng, Weiqi Chen, Chris Freeden, Yingru Zhang, W. Griffith Humphreys, Punit Marathe, and Yurong Lai

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J Pharmacol Exp Ther 358:397–404, September 2016

Coproporphyrins in Plasma and Urine Can Be Appropriate Clinical Biomarkers to Recapitulate Drug-Drug Interactions Mediated by Organic Anion Transporting Polypeptide Inhibition[S]

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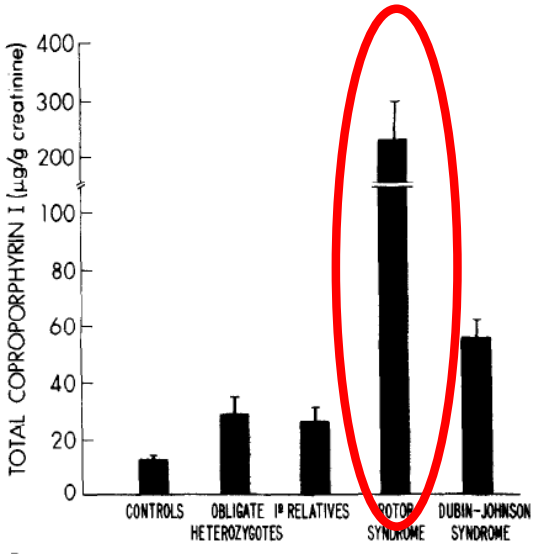
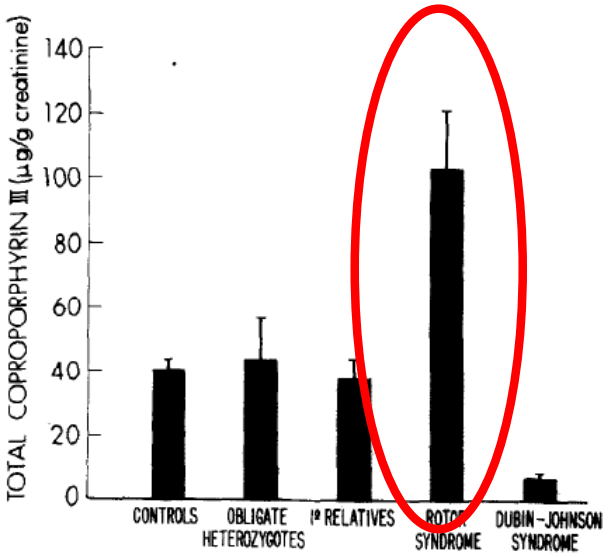
Learning from "Rotor Syndrome"

Rotor Syndrome: complete deficiency of OATP1B1 &1B3

Coproporphyrin I



Coproporphyrin III



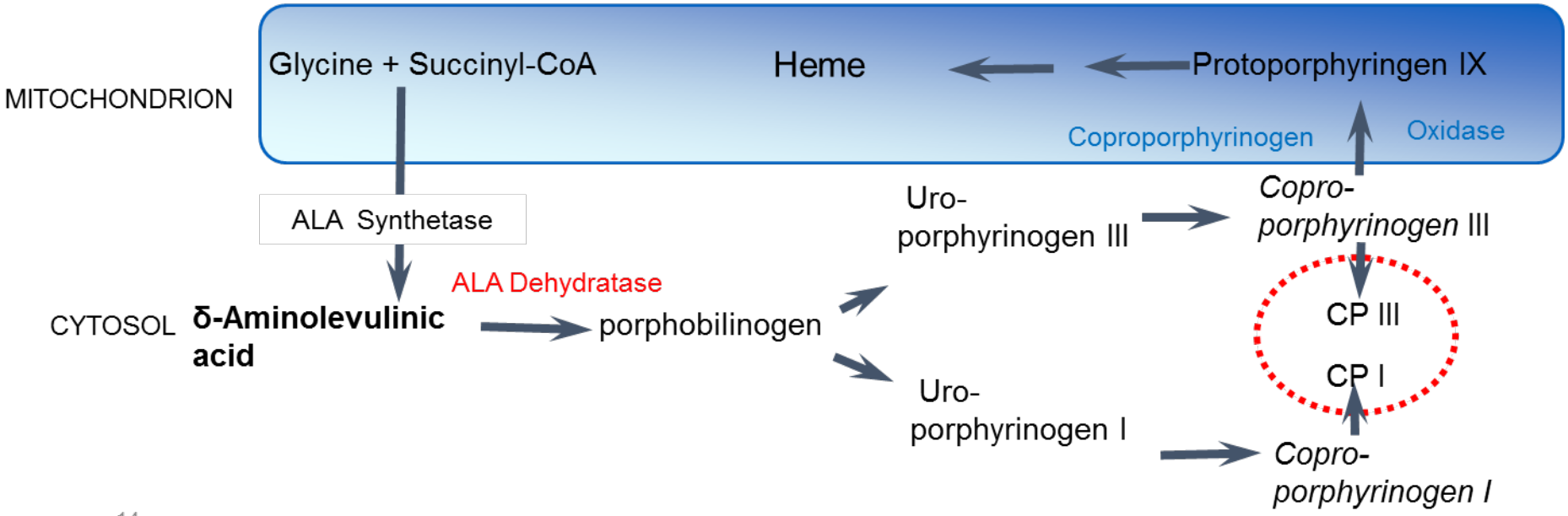
Genotype	Urinary Ratio of CP I (%)	Urinary Ratio of CP III (%)
Reference Subjects	**~30**	**~70**
Rotor Syndrome	**~70**	**~30**

Wolkoff et al., *Am J Med* 1976, 60: 173

Van de Steeg et al., *JCI* 2012, 122:519

Coproporphyrin I and III (CP I and III)

- CP I and CP III are byproducts of heme synthesis.
- They are not further metabolized by the liver and excreted in bile and urine. CP I predominates (70%) over CP III in bile whereas the reverse is found in urine.

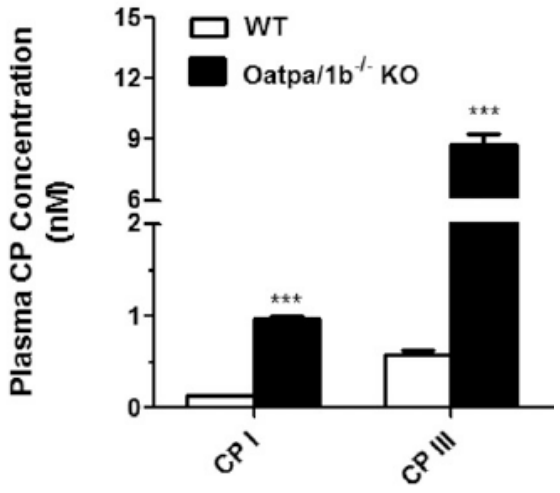


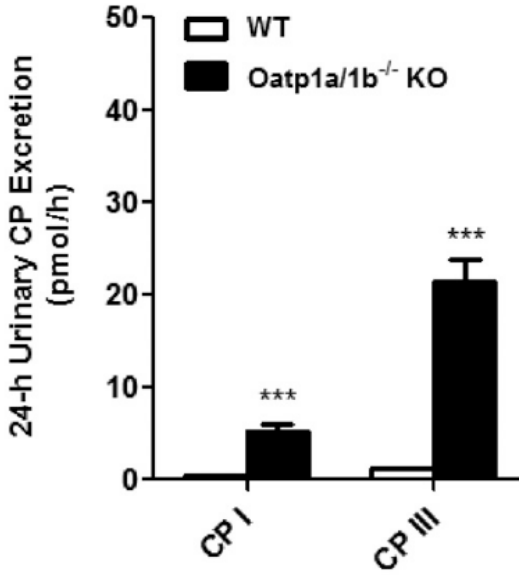
Substrate specificity of CPs

- CP-I and CP-III are substrates of OATP1B1 and 1B3
- Both CP-I and III are not substrates for OAT1/2/3/4, OCT2, MATE1 and MATE2k
- CPs are metabolically stable in human, monkey and mouse hepatocytes

(Shen et al., *JPET* 2016)

Deletion of Oatp1a/1b genes increased plasma conc. and urinary excretion of CPs in mice





CP Plasma Levels at 3 h:

7.4- and 15.2-fold for CP-I and III, respectively

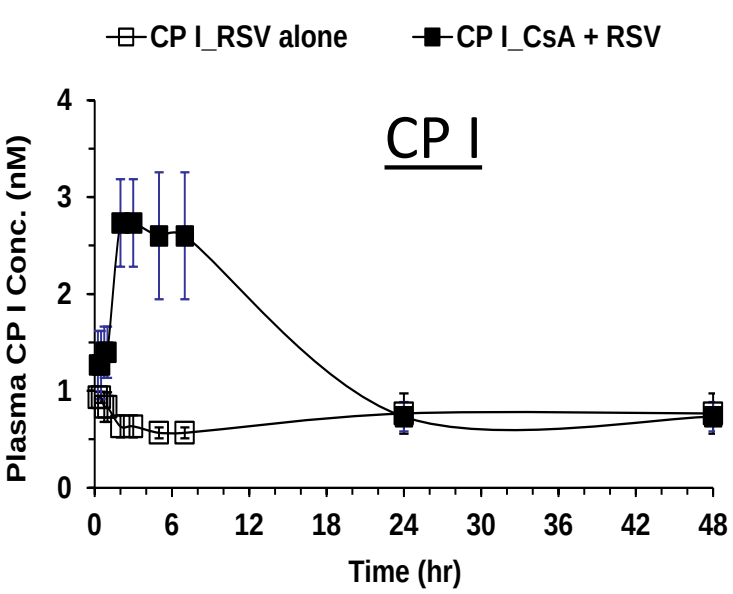
CP Urinary Excretion over 24 h:

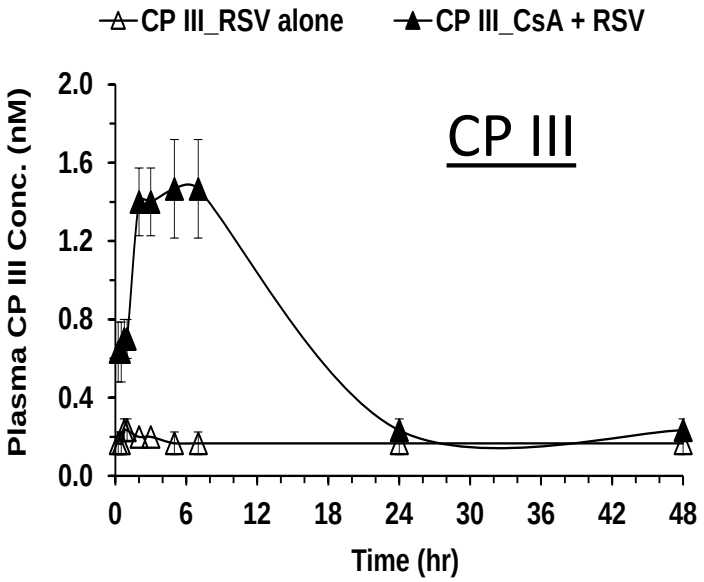
12.4- and 18.4-fold for CP-I and III, respectively

- Oatp1a/1b cluster genes deleted: *Slco1a1*, *1a4*, *1a5*, *1a*6 and *1b2*.

Shen et al., *JPET* 2016, 357: 382

CsA increased plasma CPs and urinary excretion of CP-I in monkeys

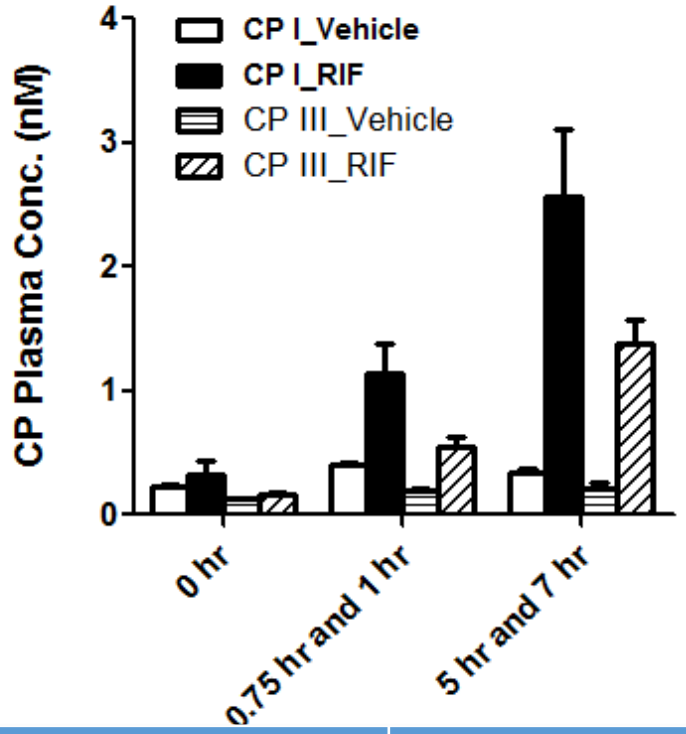




Fold Change	CP I	CP III
C_{max}	3.3	6.9
$AUC_{(0\text{-}24\ h)}$	2.6	5.2

Shen et al., *JPET* 2016, 357: 382

RIF significantly increased plasma conc. and urinary excretion of CPs in monkeys

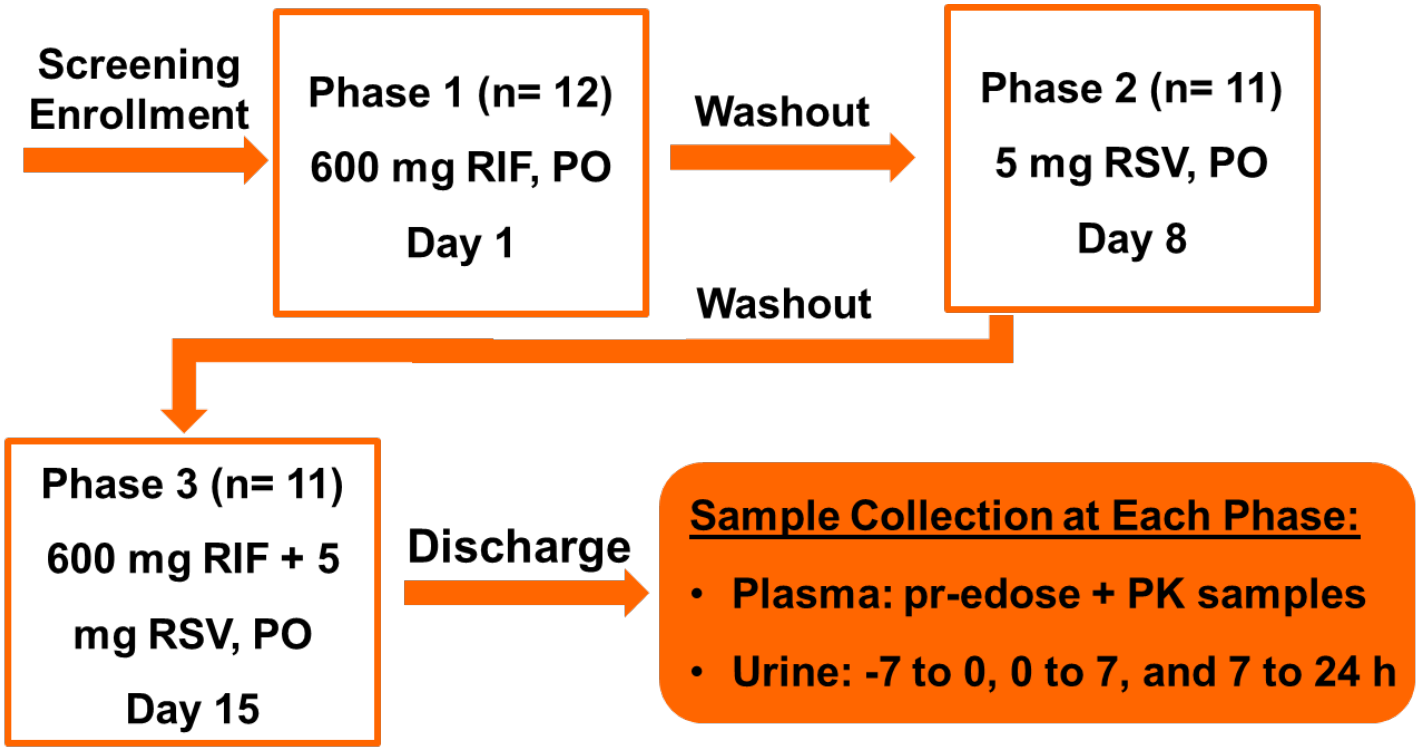


Shen et al., *JPET* 2016, 357: 382

Fold Change	CP I	CP III
$C_{5\sim7\ hr}$	7.5	6.3
$AUC_{(0\text{-}24\ h)}$	3.7	4.9
$X_{e\ (0\text{-}24\ h)}$	6.3	2.8

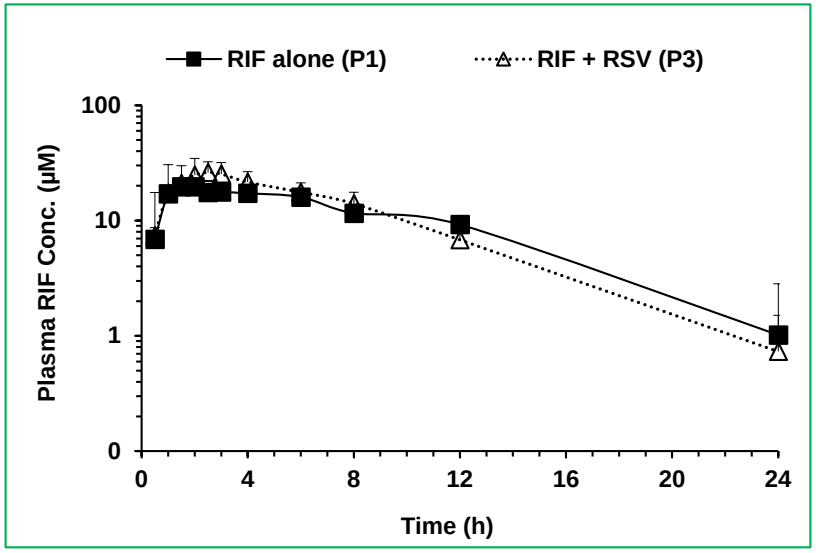
Clinical study on CPs as probes for OATP inhibition

Open label, three-treatment, three-period, single dose crossover study in twelve healthy male adult subjects without carrying OATP1B1*5, *15, *17 polymorphisms.



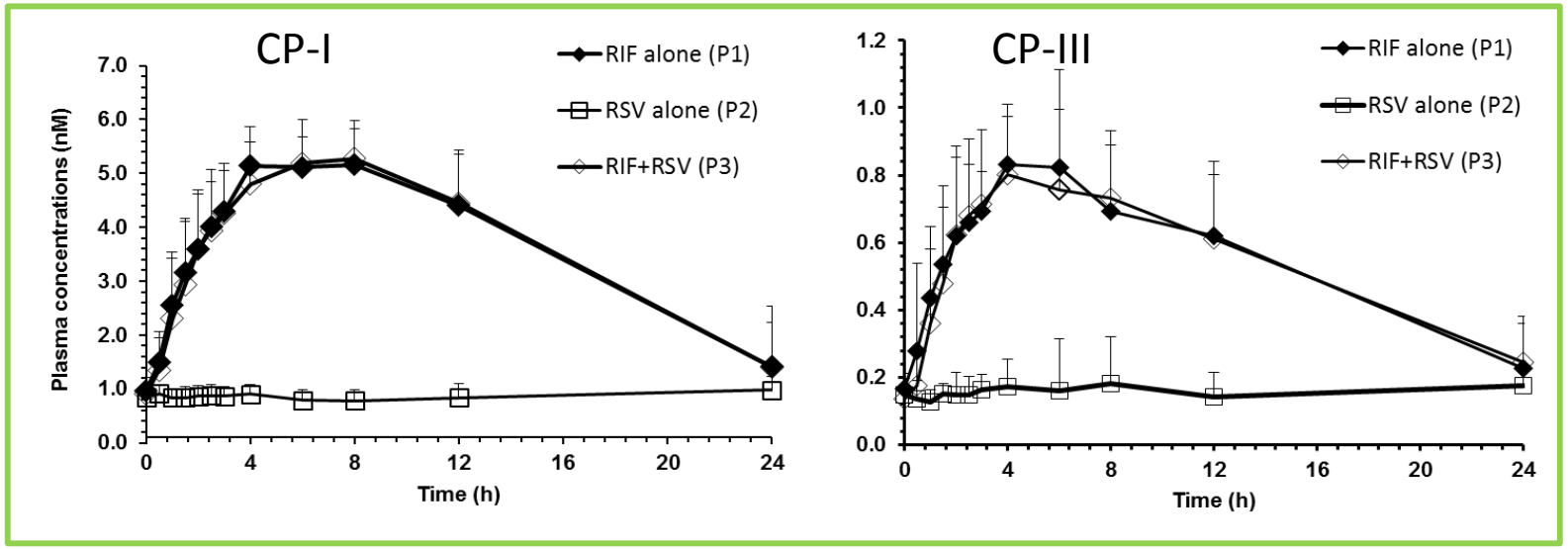
RIF Pharmacokinetics

- C_{max} and $C_{24\ h}$ of ~30 and 1 µM, respectively.
- IC50 values of OATP1B1/1B3-mediated CP transport were
- Systemic exposure of RIF was comparable to literature reports
- Similar exposure when dosed alone or in combination with RSV



Parameter	RIF	
	RIF alone	RIF + RSV
Cmax (µM)	26.7 ± 10.7	30.6 ± 7.8
Tmax (h)	2.5 ± 1.7	2.2 ± 0.9
$AUC_{(0\text{-}24\ h)}$ (µM*h)	206.8 ± 70.9	219.5 ± 57.9
AUC_{tot} (µM*h)	215.4 ± 79.4	224.5 ± 61.9
T1/2 (h)	4.2 ± 1.4	3.5 ± 1.2

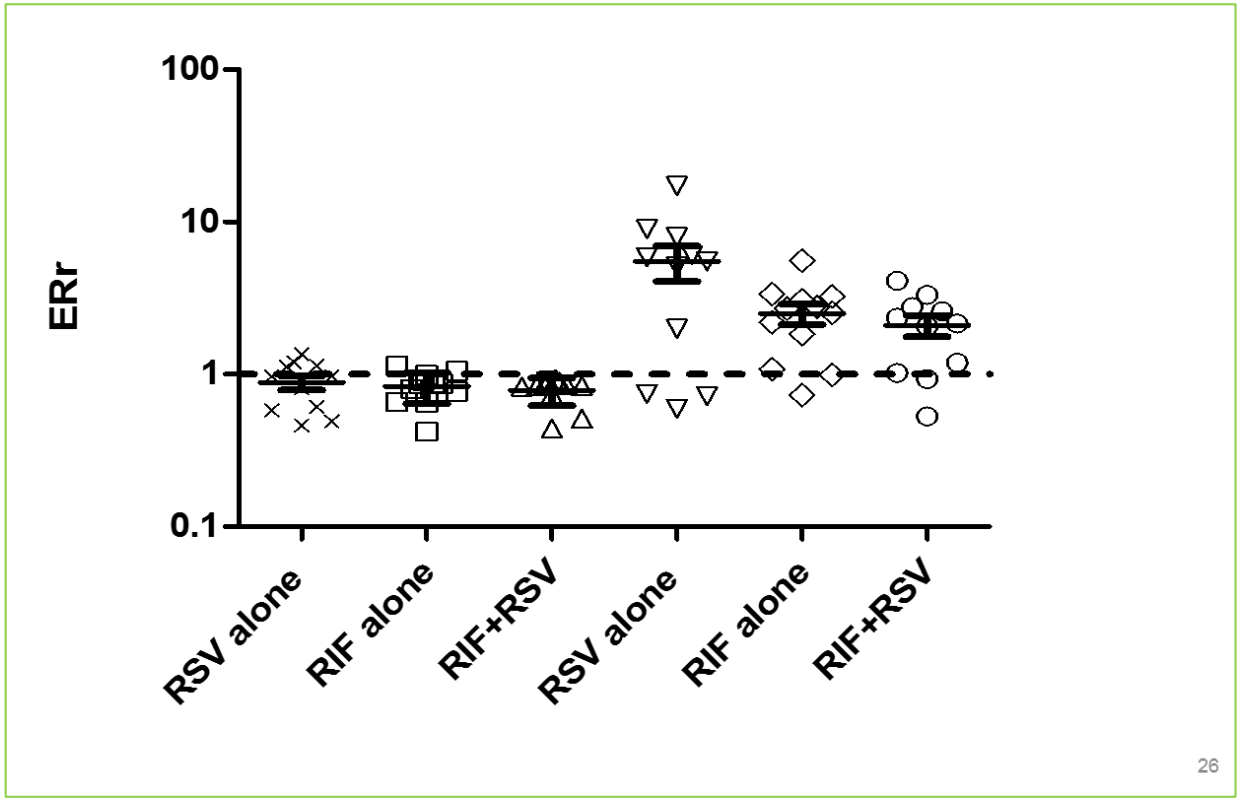
RIF significantly increased plasma conc. of CP-I and CP-III, and urinary excretion of CP-I



Fold Change	CP-I (RIF, RIF+RSV)	CP-III (RIF, RIF+RSV)	RSV
C_{max}	5.7, 5.9	5.4, 6.5	13.2
$AUC_{(0\text{-}24\ h)}$	4.01, 3.8	3.4, 3.3	5.0
$X_{e\ (0\text{-}24\ h)}$	3.6, 3.4	2.1, 1.34*	1.6, 1.4

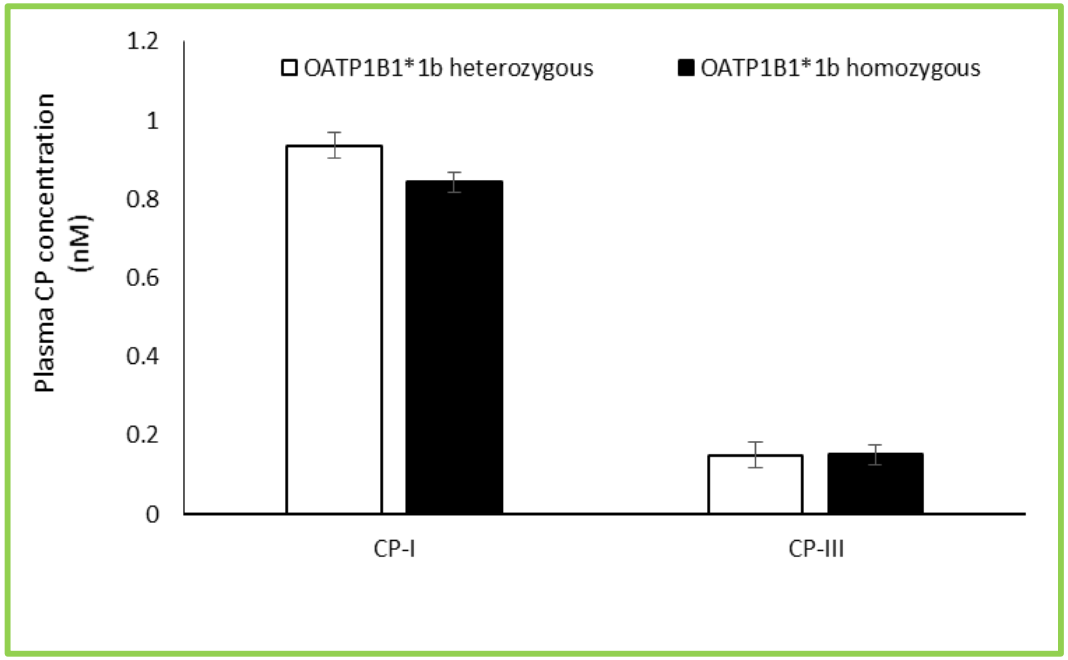
*NS

Urinary excretion of CPS



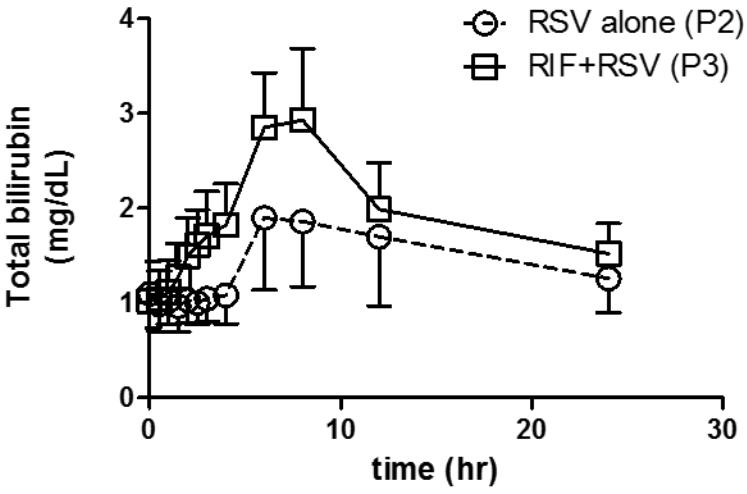
CP-I appears to be passively filtered, but CP-III is actively secreted with a large inter-individual variability

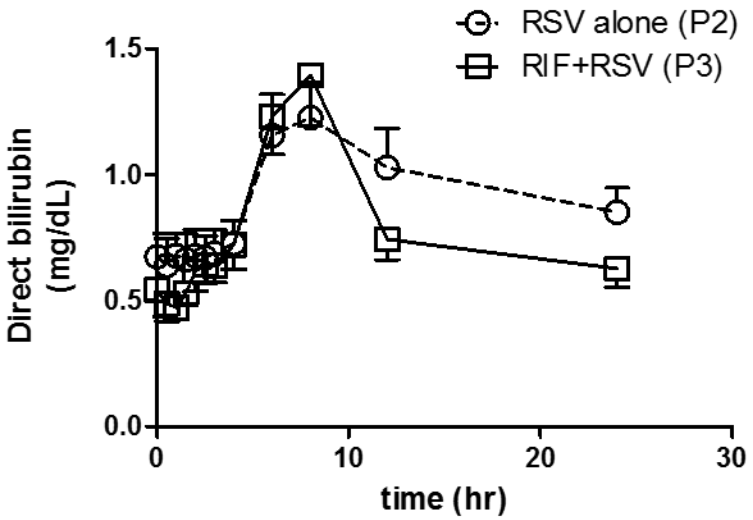
Plasma conc. of CPs in OATP1B1*1b heterozygous (9) and homozygous (3)

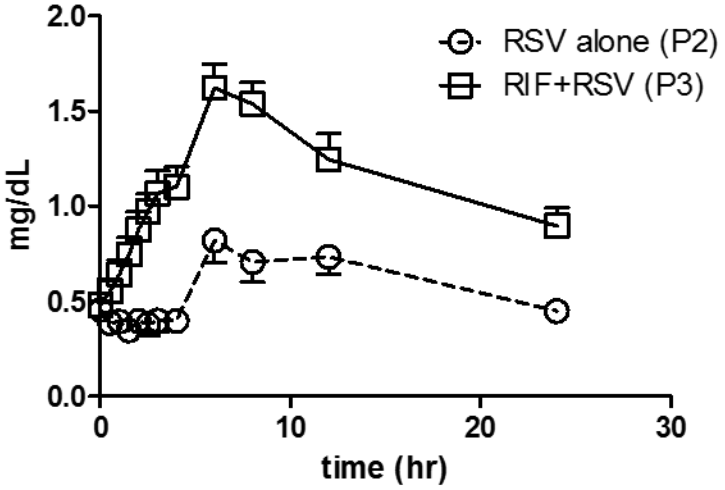


20% reduction of CP-I in plasma was detected in *1b homozygous, but there is no statistically significant difference (likely small N?)

RIF increased (marginally) the levels of total- and indirect-, but not direct-bilirubin in plasma



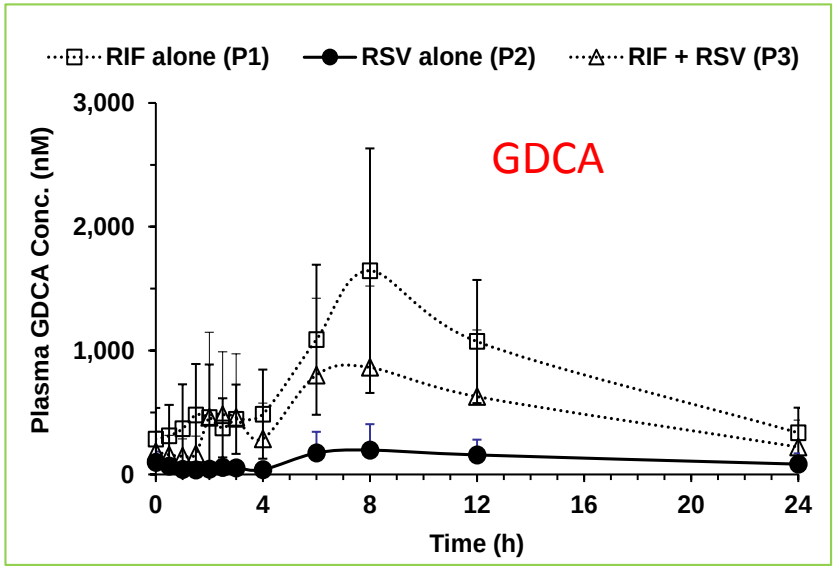


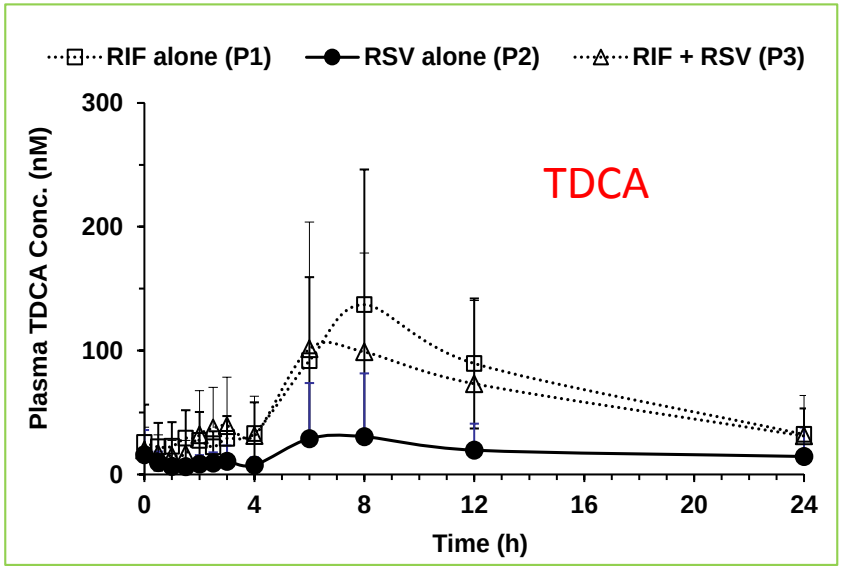


	$AUC_{0\sim24hr}$ (mg/dL*hr) (mean ± SEM)		
	RSV alone (P2)	RIF+RSV (P3)	ratio
Total bilirubin	35.7 ± 3.60	47.10±2.64	1.32*
Direct bilirubin	22.7 ± 2.88	19.4 ± 2.21	0.85
Indirect bilirubin	14.3 ± 1.27	27.7 ± 2.39	1.94*

*P<0.05

Plasma conc. of bile acids—with statistical significance





Fold changes	GDCA (RIF, RIF+RSV)	TDCA (RIF, RIF+RSV)
C_{max}	7.6, 4.3	**4.4, 3.4**
$AUC_{(0\text{-}24\ h)}$	6.5, 4.0	**3.6, 3.1**

Endogenous probes for DDI assessment

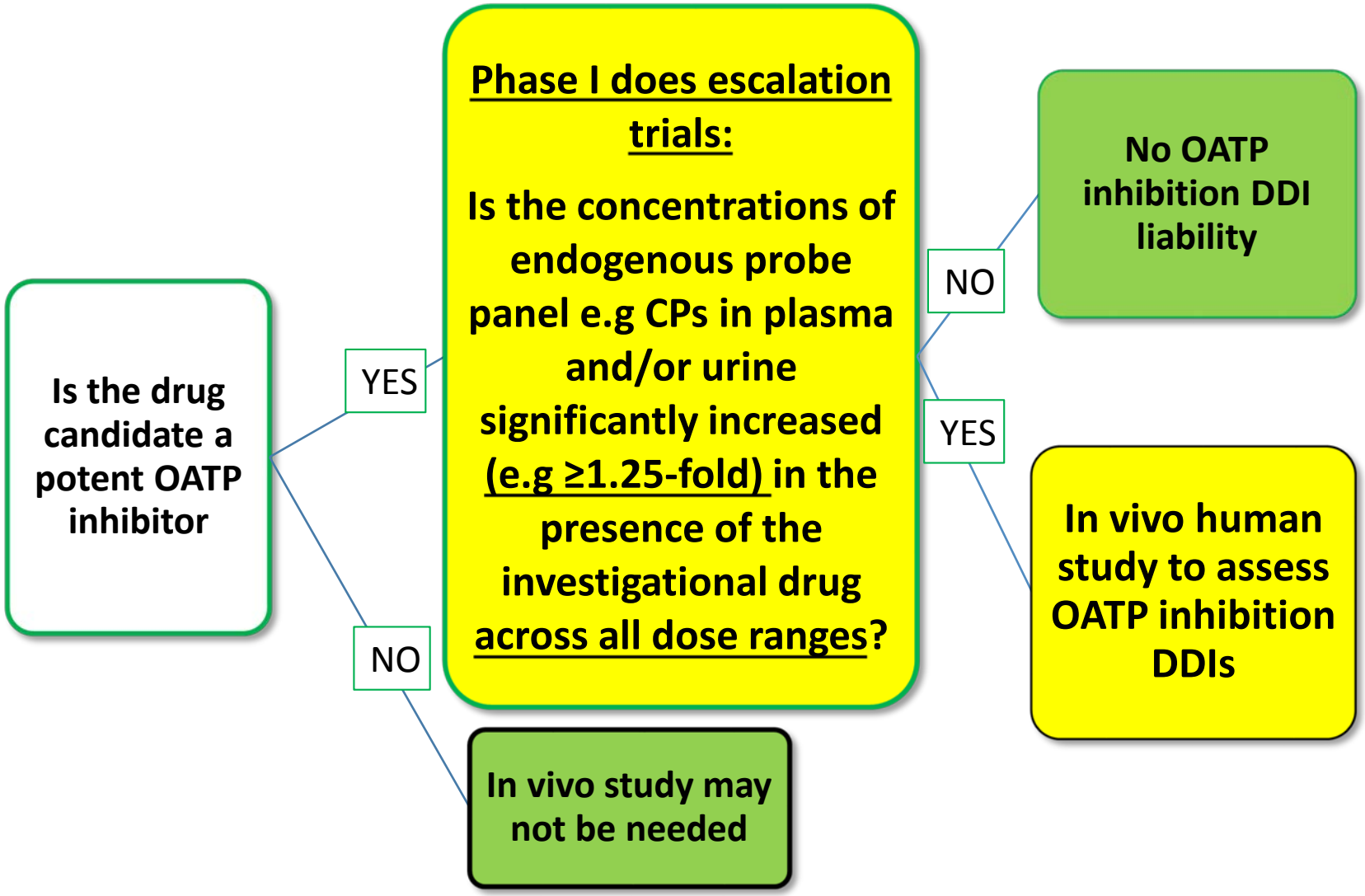
- **Specific**
  - A specific endogenous substrate of the transporter
  - Not a biomarker of a disease or a dietary constituent—
    - rejecting bile acids and bilirubin as probes
  - Reflect instant response, v.s. delayed (compensatory) effects
- **Predictive and Translational**
  - Correlate with the extent of transporter inhibition, e.g fold increases of statins?
  - Reflect site of inhibition, e.g Imax/IC50
- **Accessible**
  - Non-invasive sampling from either blood or urine
  - Can be monitored during early drug development phase, e.g Phase I does finding trials
- **Reproducible**
  - Rapid, accurate and reproducible detection, e.g LC/MS
- **Cost effective**
  - Manageable lists

Modified from Dr. Giacomini AAPS transporter workshop 2015

Summary

- Plasma CP-I and CP-III are relatively consistent, with minimum fluctuation over the three study periods.
- CPs are determined by LC/MS which is is amendable to high throughput, GLP setting
- OATP inhibitor, RIF, significantly increased plasma conc. of CP-I and CP-III.
- CPs in plasma or CP-I in urine could serve as endogenous probes for OATP inhibition, and be monitored during phase I dose finding trials
- Changes of CPs with less potent OATP inhibitors, and the impacts of genetic polymorphisms, gender/age, disease state, and organ impairments etc need to be further investigated

Integration of endogenous probes into OATP DDI decision trees



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Thank you