

Mechanistic Basis of Cabotegravir-glucuronide Disposition in Humans

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Mechanistic Basis of Cabotegravir–Glucuronide Disposition in Humans^S

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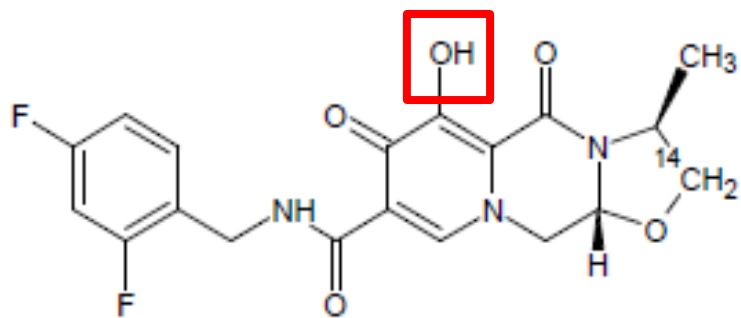
ABSTRACT

Cabotegravir, a novel integrase inhibitor under development for treatment and prevention of HIV, is primarily metabolized by UDP-glucuronosyltransferase (UGT)1A1 and UGT1A9 to a direct

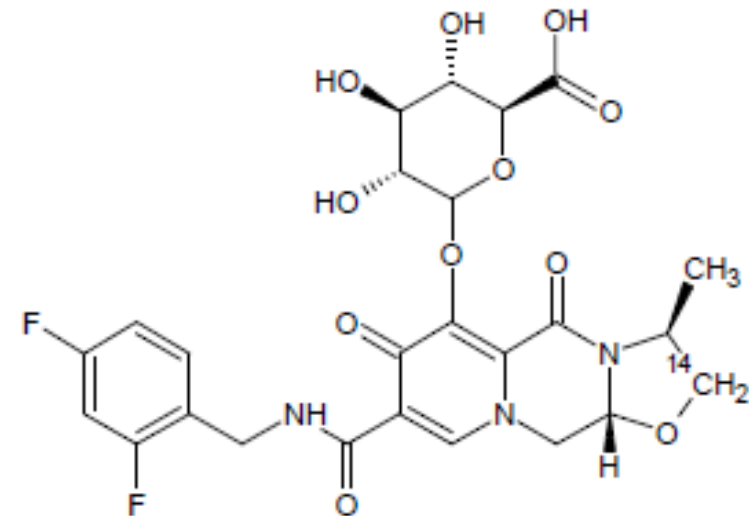
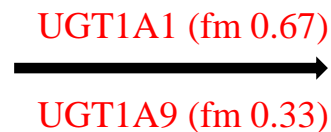
renal clearance, where uptake into the proximal tubule would be mediated by OAT3 (not transported by OAT1), and subsequent secretion into urine by MRP2 (Ft = 0.66) and MRP4 (Ft = 0.34).

Cabotegravir

- HIV-1 Integrase inhibitor
- P-gp and BCRP substrate (ER~3)
- ✓ High passive permeability ($P_{app} \sim 256 \text{ nm/s}$)
- **UGT substrate**

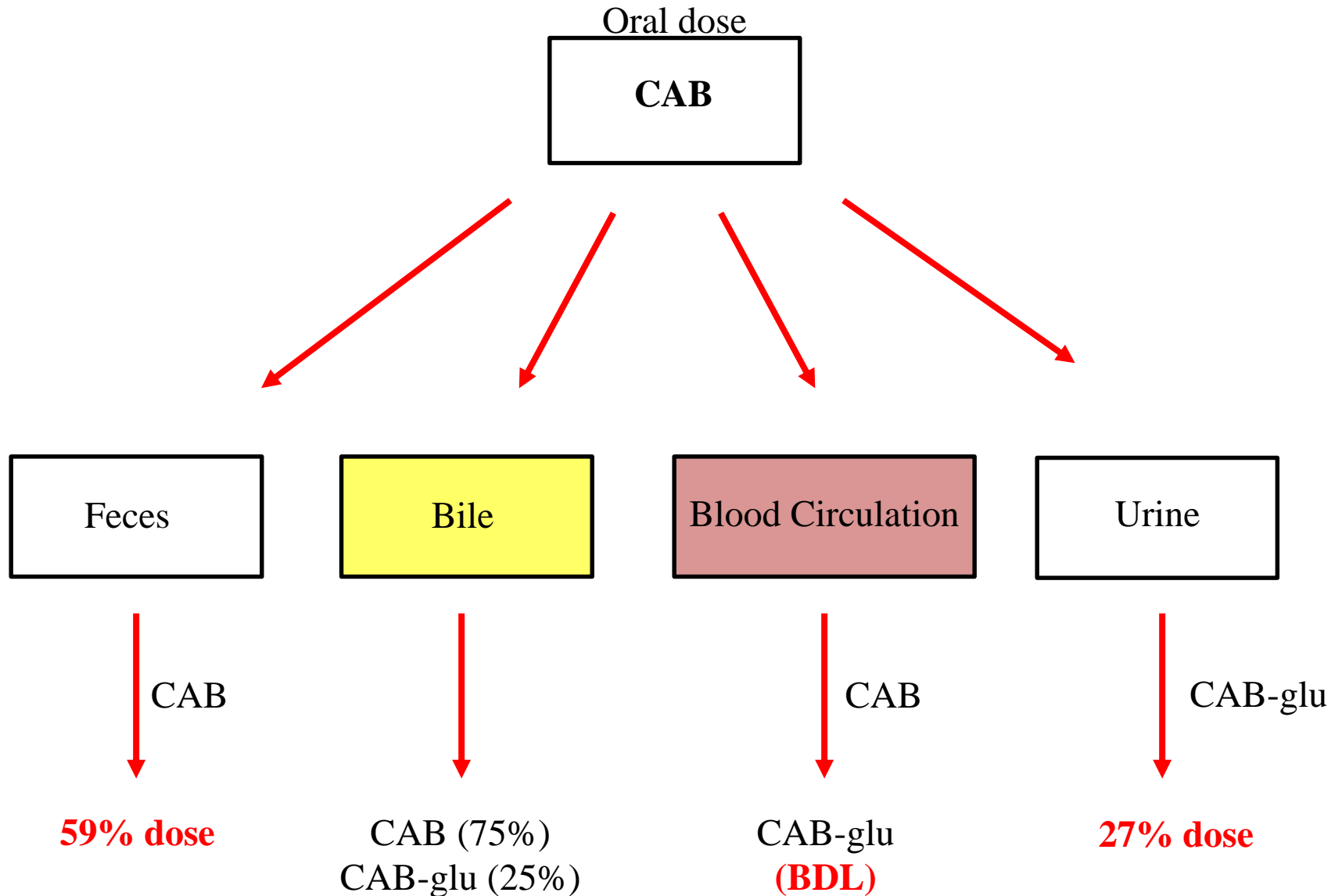


**Cabotegravir
(CAB)**

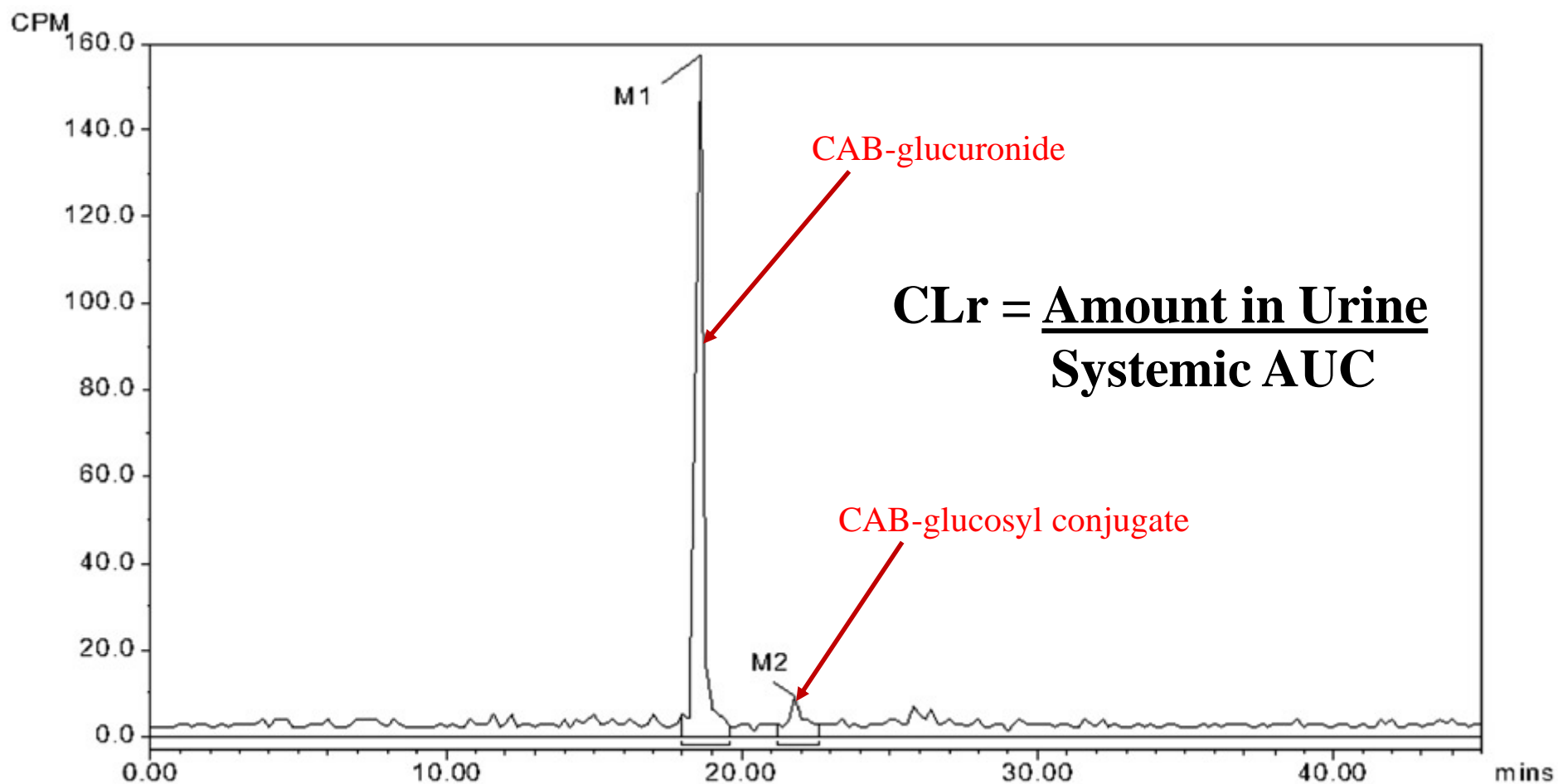


**Cabotegravir-glucuronide
(CAB-glu)**

Clinical Mass Balance and Pharmacokinetics



Human Urine Radiochromatogram



Parent not observed in the urine

CAB-glu Microsomal Formation Rate

Scaled to total tissue weight using REF

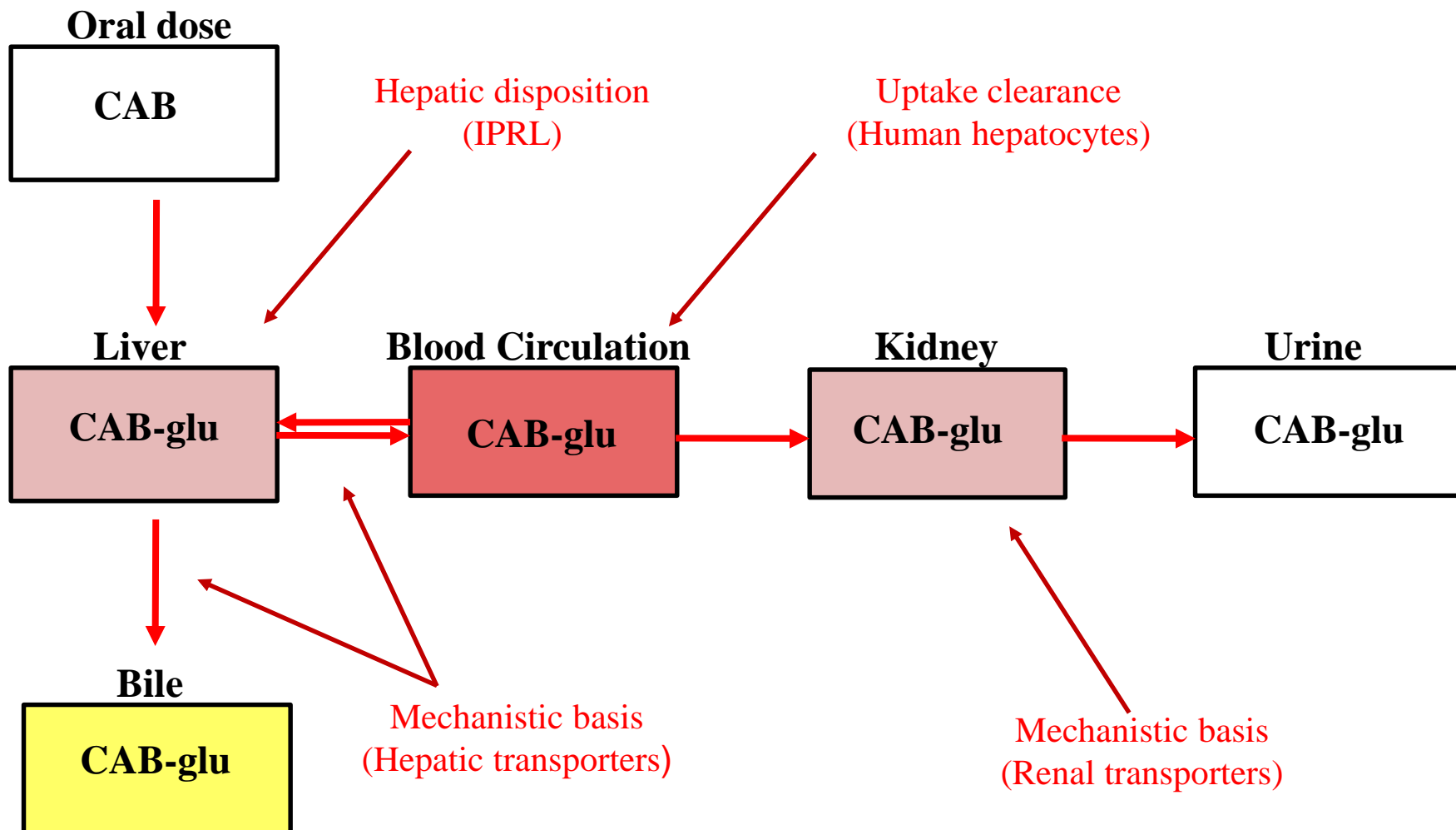
Tissue	Liver	Kidney	Intestine
(L/min)	12.7	0.39	0.25
% Contribution	95	3	2

Scaling factors: Liver microsomal protein, 39.7 mg per g liver; kidney microsomal protein, 12.8 mg per g kidney; intestinal microsomal protein, 0.6 mg protein per g intestine.

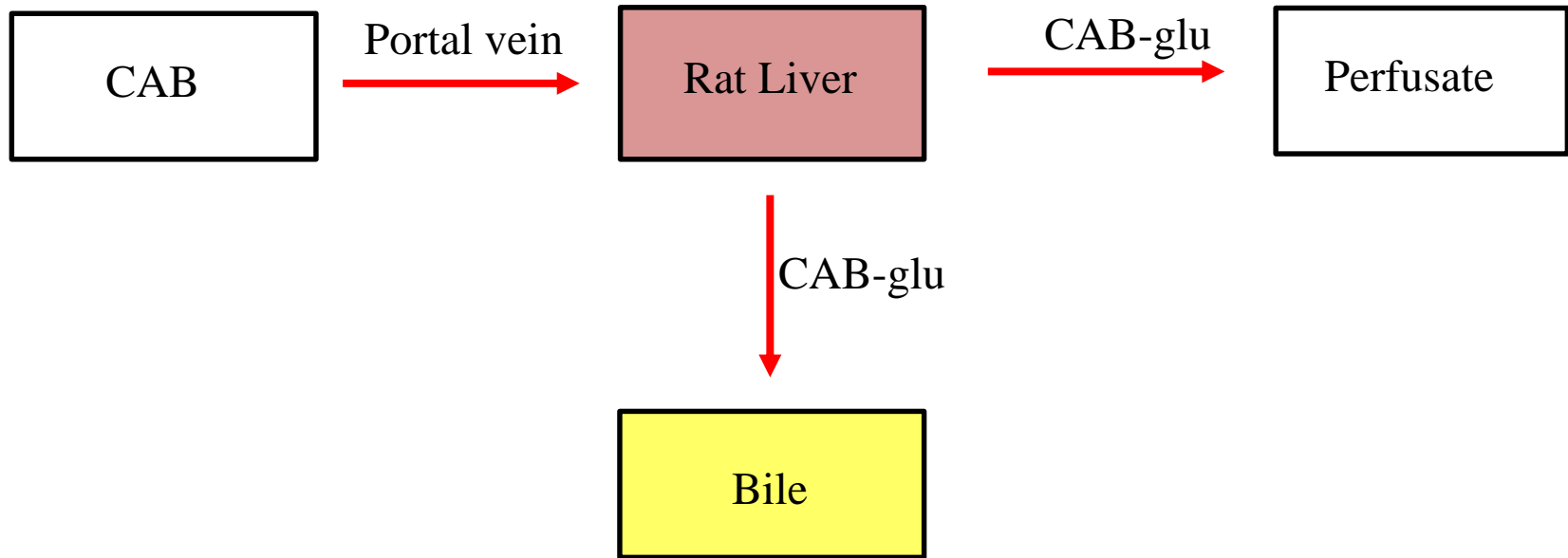
Weight of tissue: Liver, 1800g; kidney, 352g; gut, 5000g

CAB-glu formation is predominantly hepatic

Hypothesis



Single-Pass In-Situ Rat Liver Perfusion

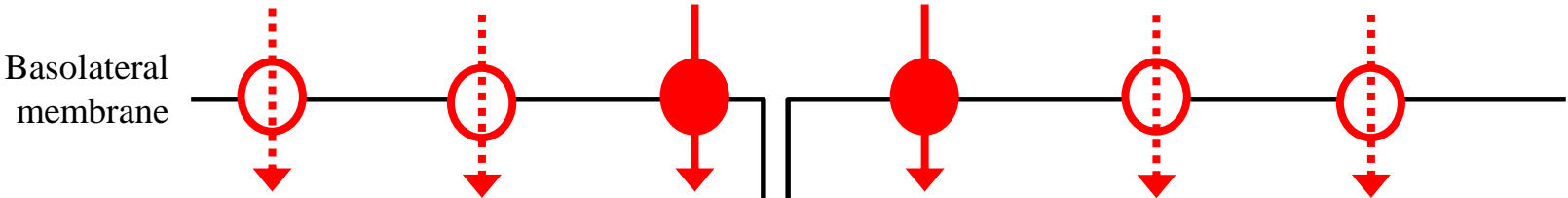


Canalicular clearance = SS Biliary Exc. Rate/Liver Conc. = **0.16 ± 0.05 mL/min/kg**

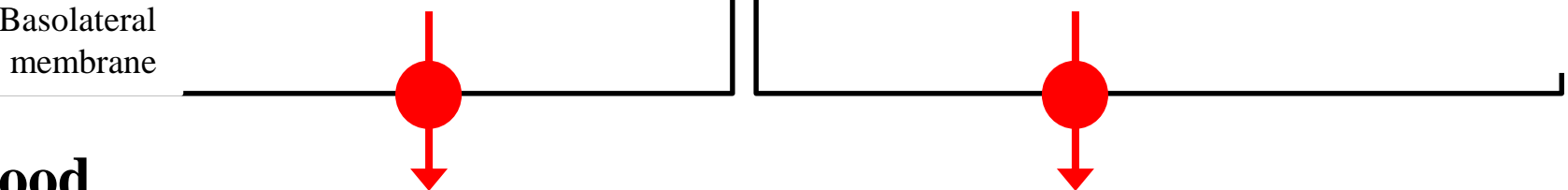
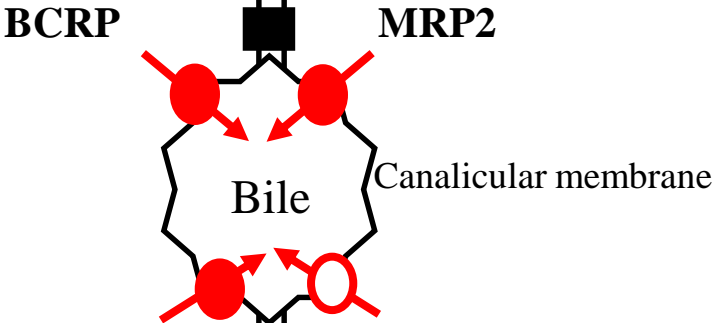
Basolateral clearance = SS Perfusate Exc. Rate/Liver Conc. = **0.21 ± 0.06 mL/min/kg**

Hepatic Transport of Glucuronide

Blood

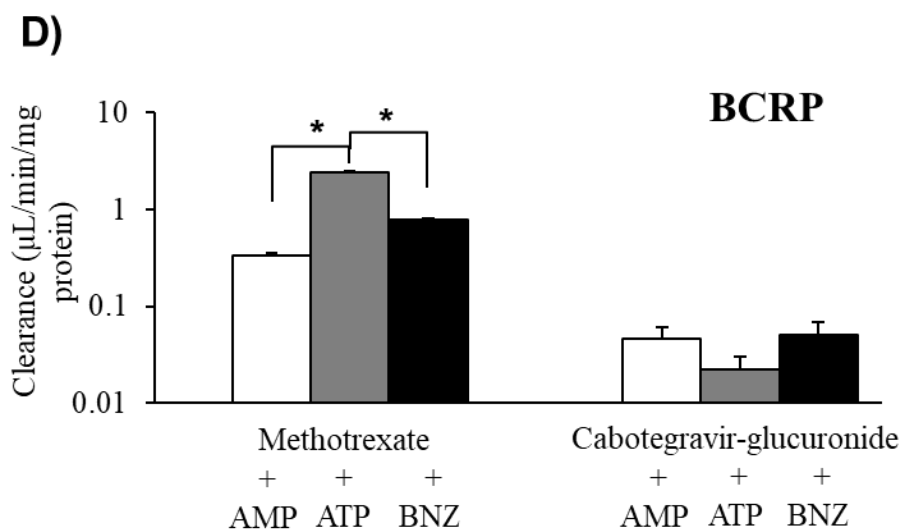
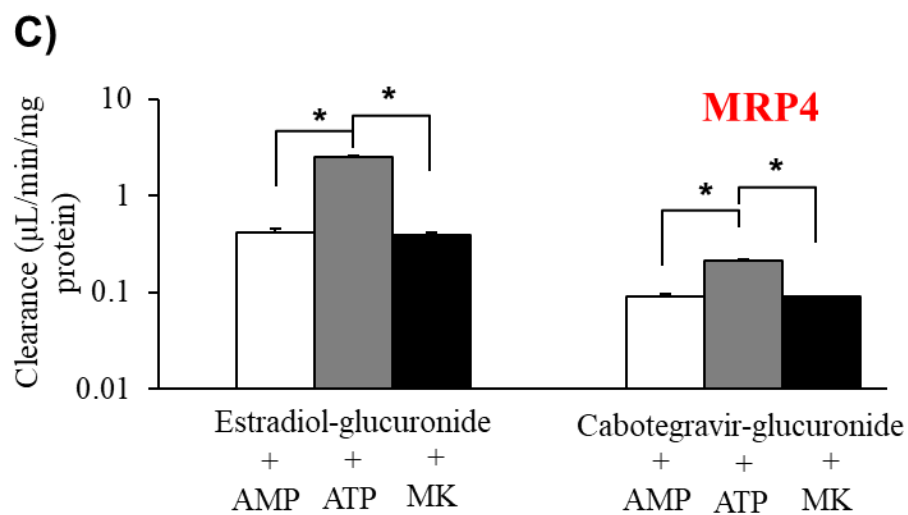
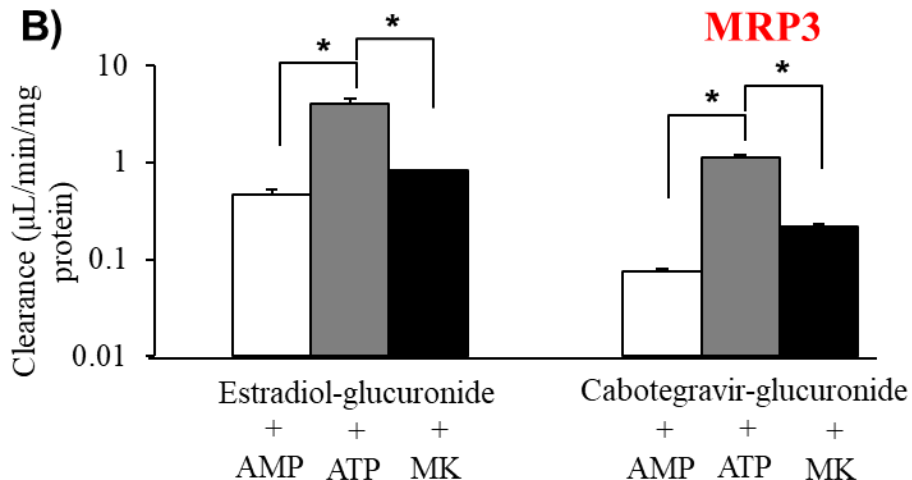
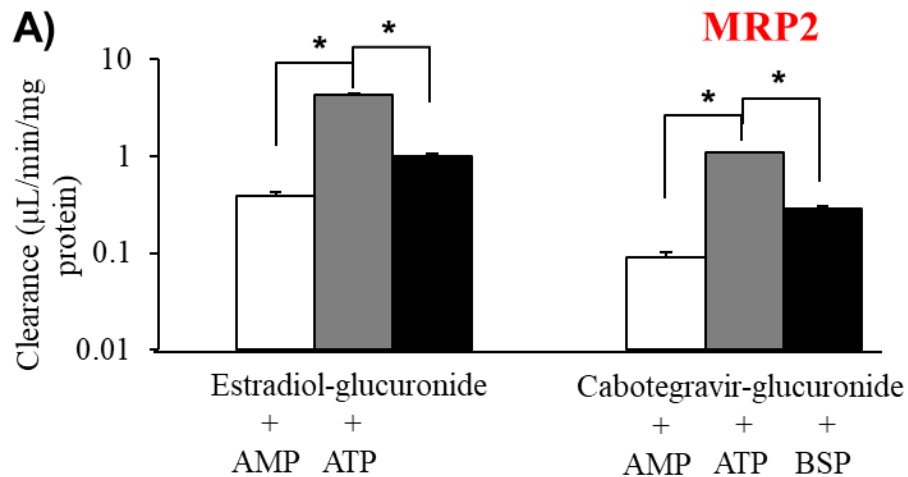


Hepatocyte

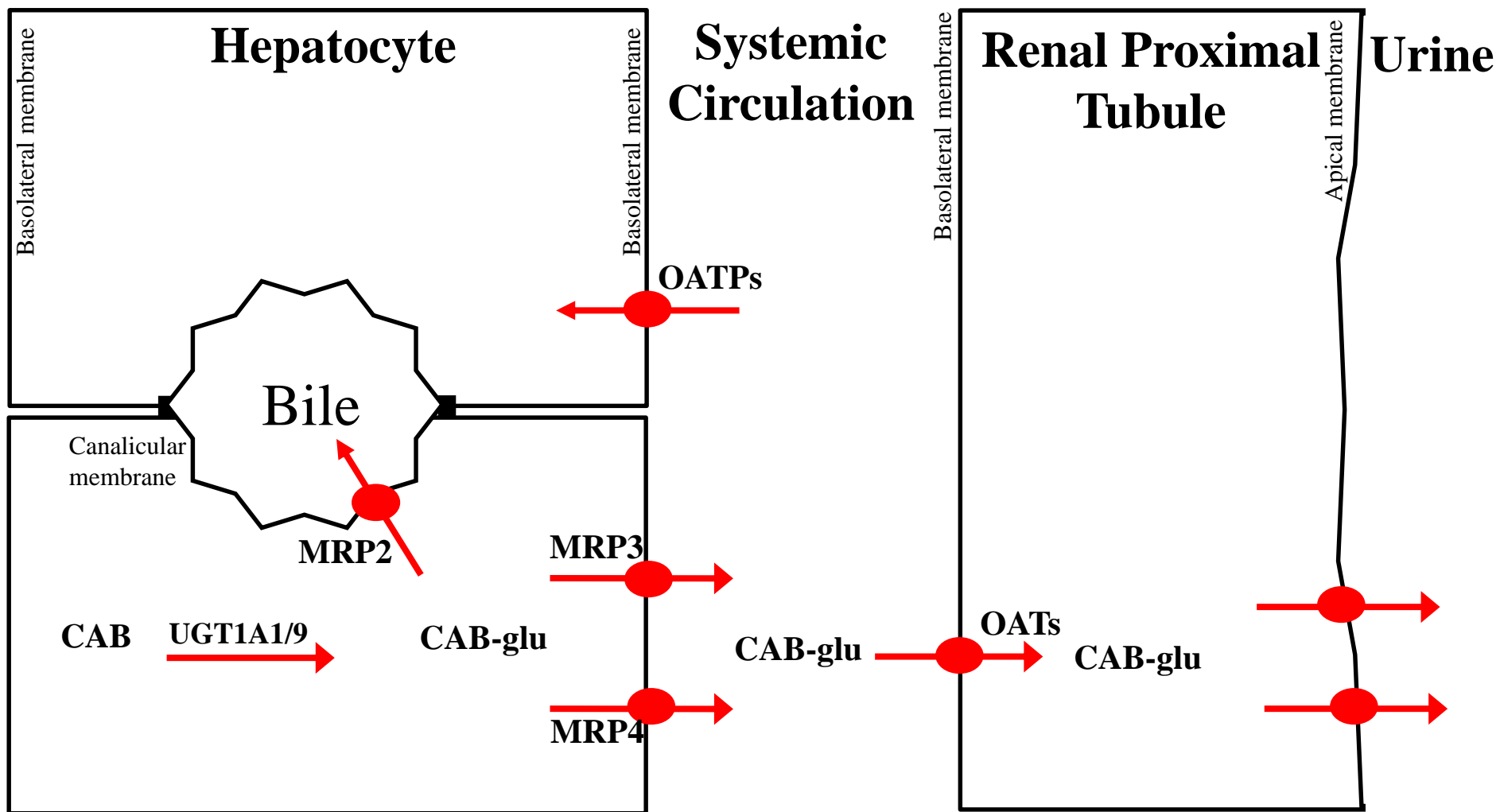


Blood

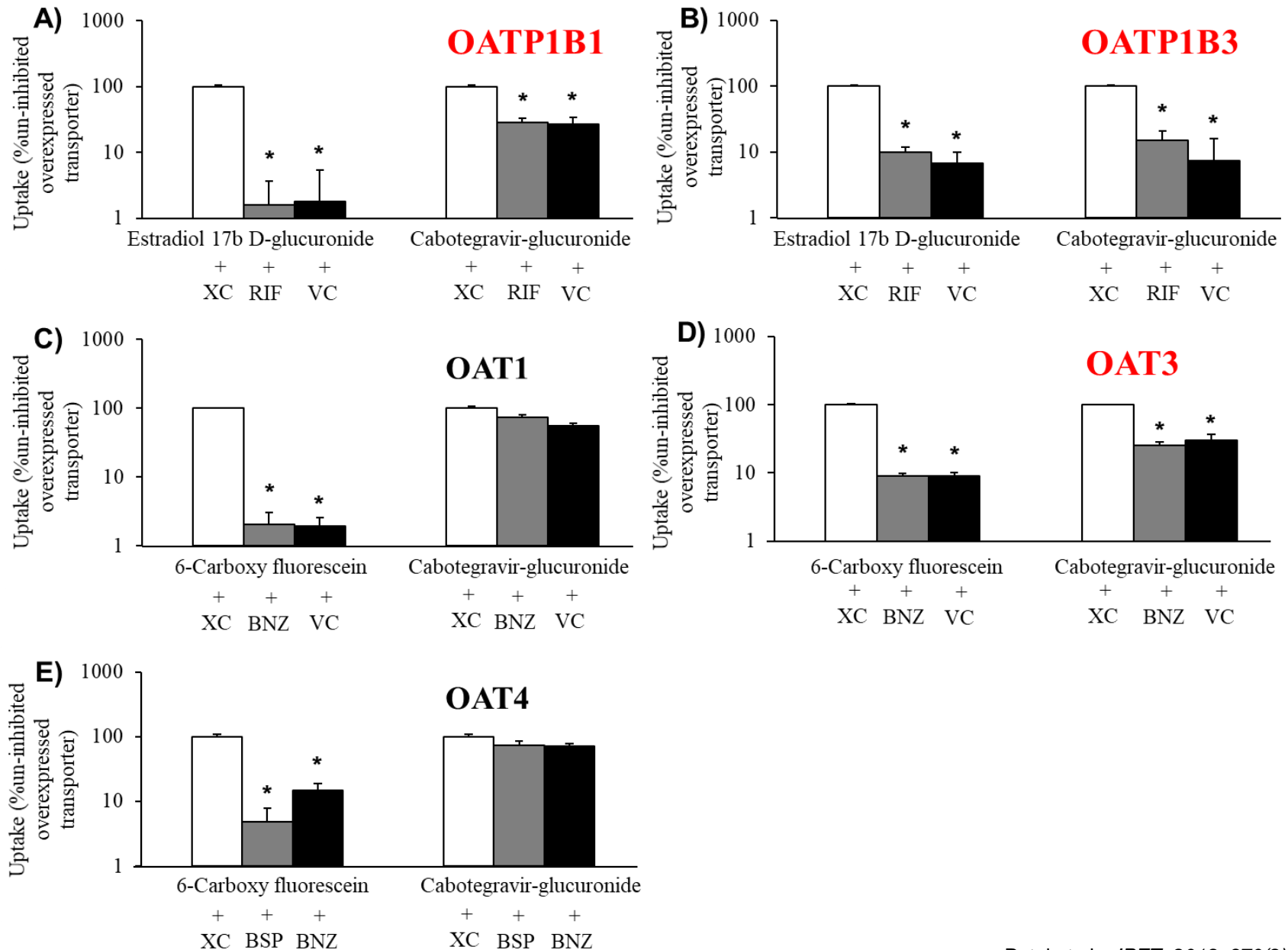
Substrate Studies For Hepatic Efflux Transporters



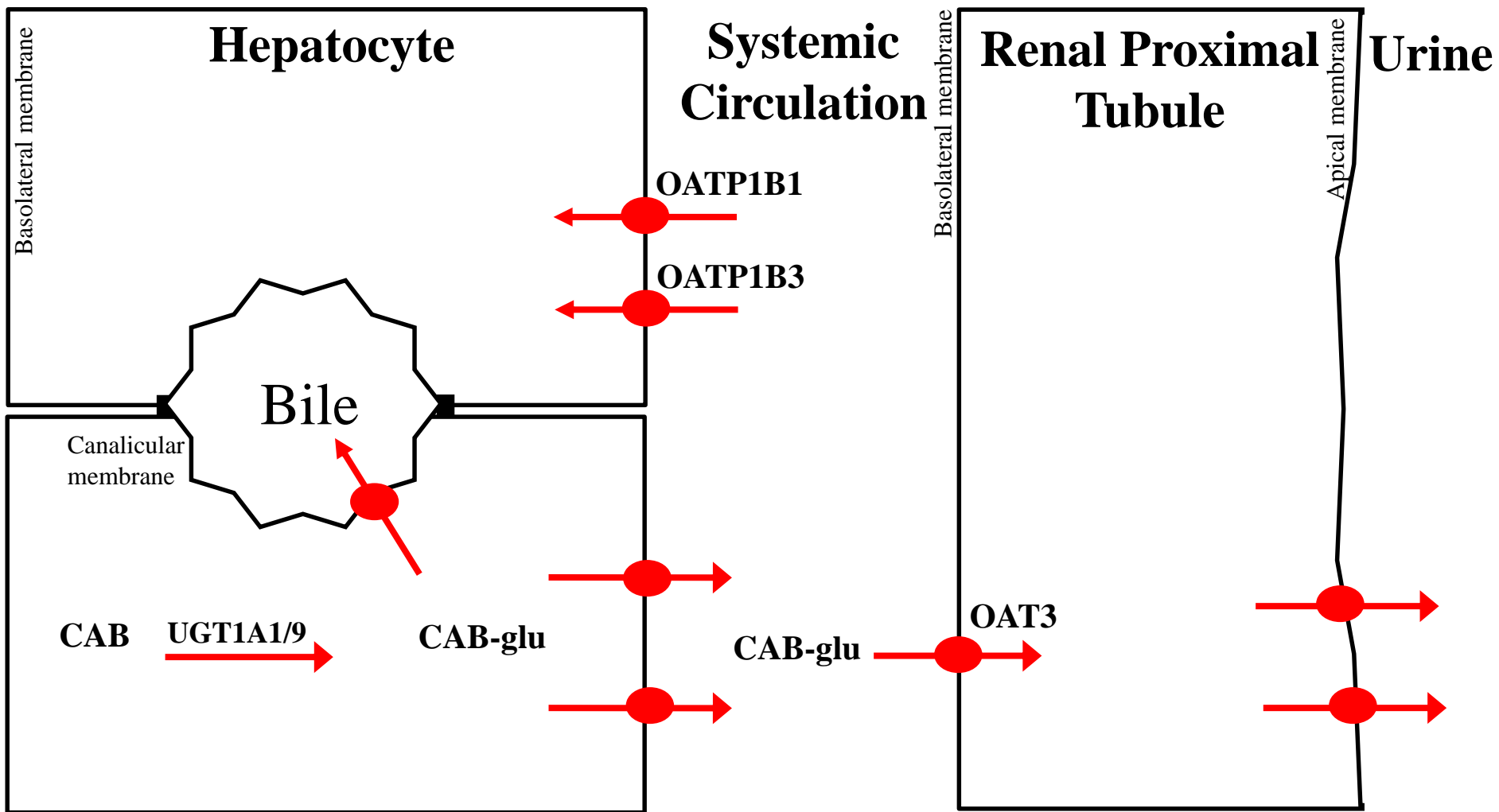
Hepatic Disposition of Cabotegravir-glucuronide



Substrate Studies For Uptake Transporters



Hepatic Uptake of Cabotegravir-glucuronide



Hepatic Uptake Clearance

Intrinsic uptake clearance = 0.17 ± 0.02 $\mu\text{L}/\text{min}/\text{million cells}$

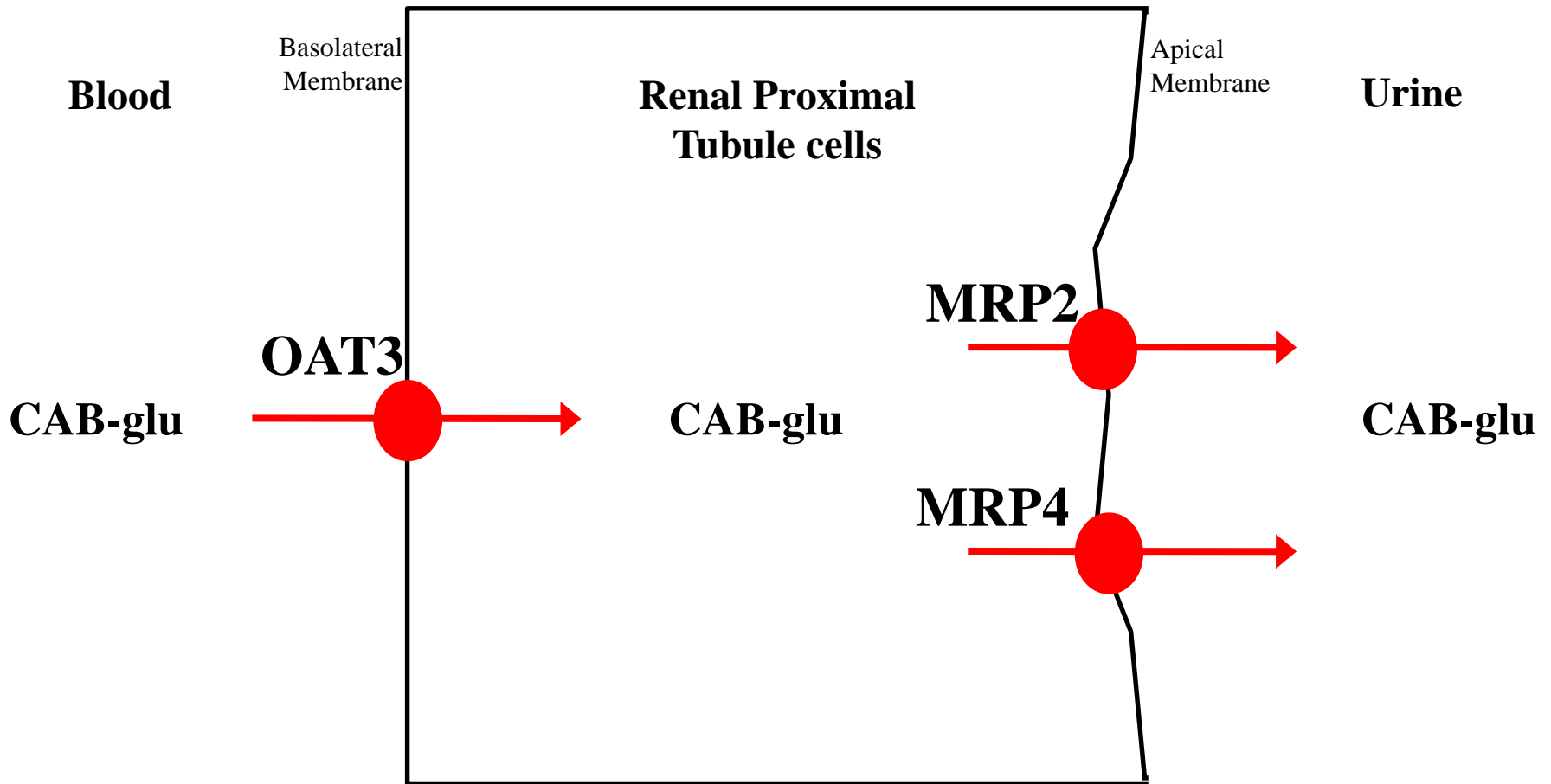
Predicted *in vivo* hepatic uptake clearance = 0.51 ± 0.04 $\text{mL}/\text{min}/\text{kg}$

Extraction ratio: Uptake CL_H/Q_H = 0.025

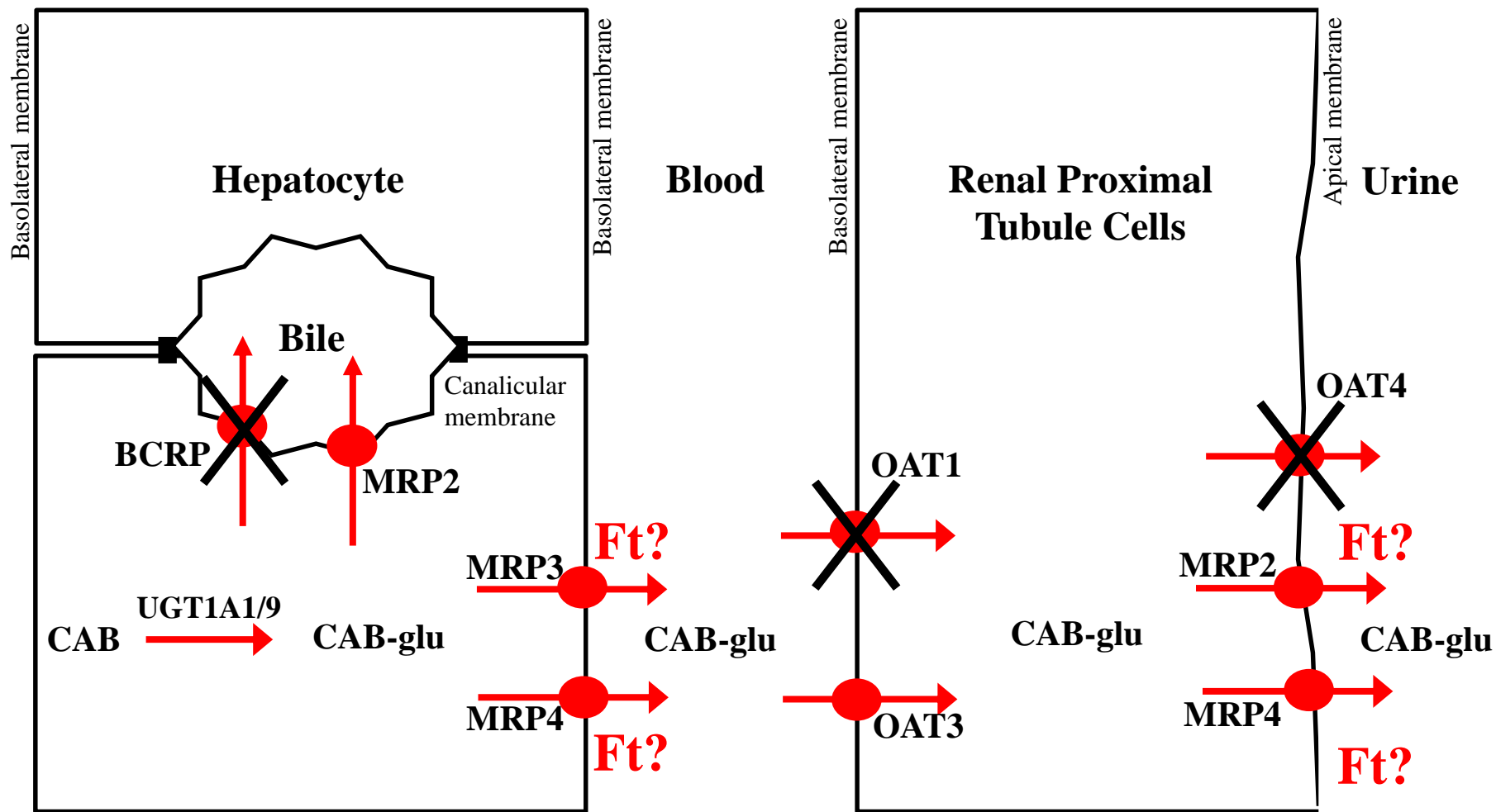
Note: Extraction ratio is **<0.3** for low extracted compounds

Hepatic uptake clearance is not the major mechanism

Renal Disposition of Cabotegravir-glucuronide



Mechanisms in Cabotegravir-glucuronide Disposition



Relative Expression Factor (REF)

- Ratio of expression level between *in vitro* recombinant system and pooled tissue samples

Transporter	Log2 Hepatic REF	Log2 Renal REF
OAT1	ND	3.6 ± 0.3
OAT3	ND	0.30 ± 0.3
OAT4	ND	1.7 ± 0.1
MRP2	8.4 ± 0.3	8.0 ± 0.2
MRP3	7.4 ± 0.4	ND
MRP4	7.0 ± 0.1	6.6 ± 0.1

Note: ND represents not detected in that tissue. Geometric mean ± S.E.M., n = 6.

Fraction Contribution (Ft)

Hepatic Basolateral Excretion (Transport from Hepatocyte to Sinusoidal Blood)

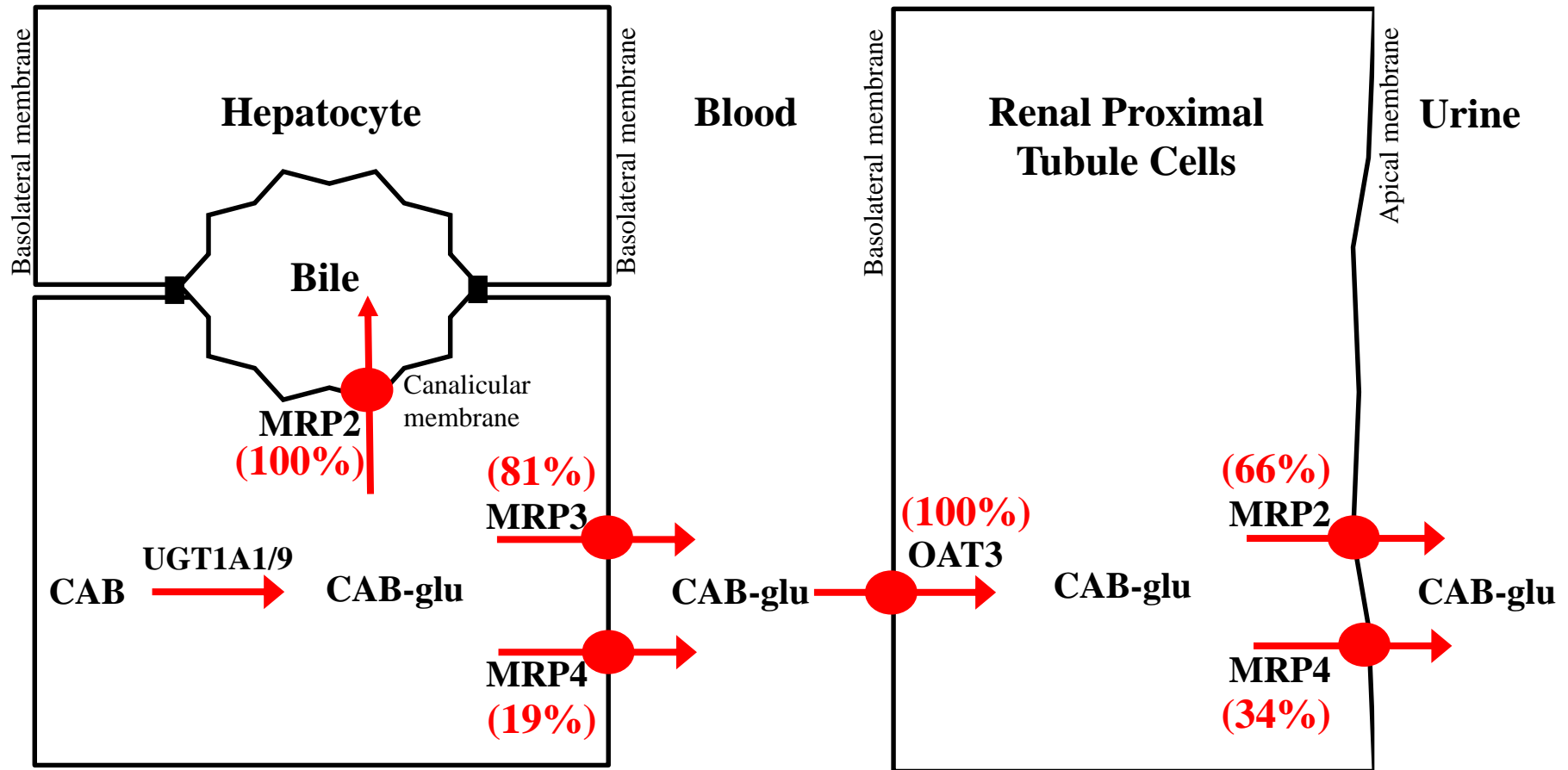
Transporters Involved	MRP3	MRP4
CLint (uL/min/mg protein)	1.13	0.21
	Apply Hepatic REF to above CLint	
REF normalized CLint (uL/min/mg protein)	6.81	1.64
Ft	0.81	0.19

Fraction Contribution (Ft)

Apical Urinary Excretion (Transport from Proximal Tubule to Urine)

Transporters Involved	MRP2	MRP4
CLint (uL/min/mg protein)	1.1	0.21
	Apply Renal REF to above CLint	
REF normalized CLint (uL/min/mg protein)	4.4	2.23
Ft	0.66	0.34

Summary on Transporter Mechanisms in Cabotegravir-glucuronide Disposition



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Thank you

Hepatic Disposition of Cabotegravir-glucuronide

