The importance of studying drug transporters in HCV drug development

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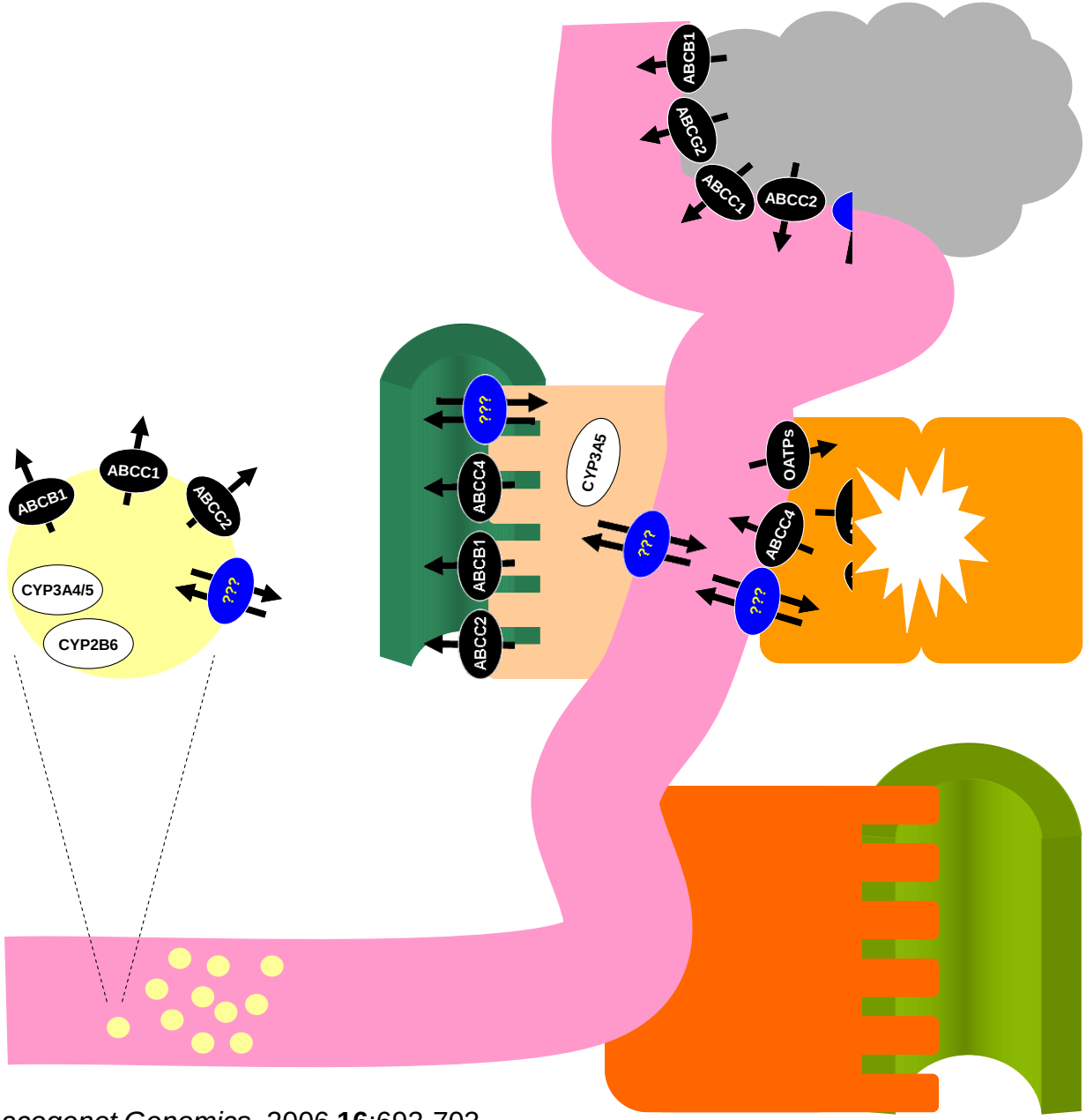
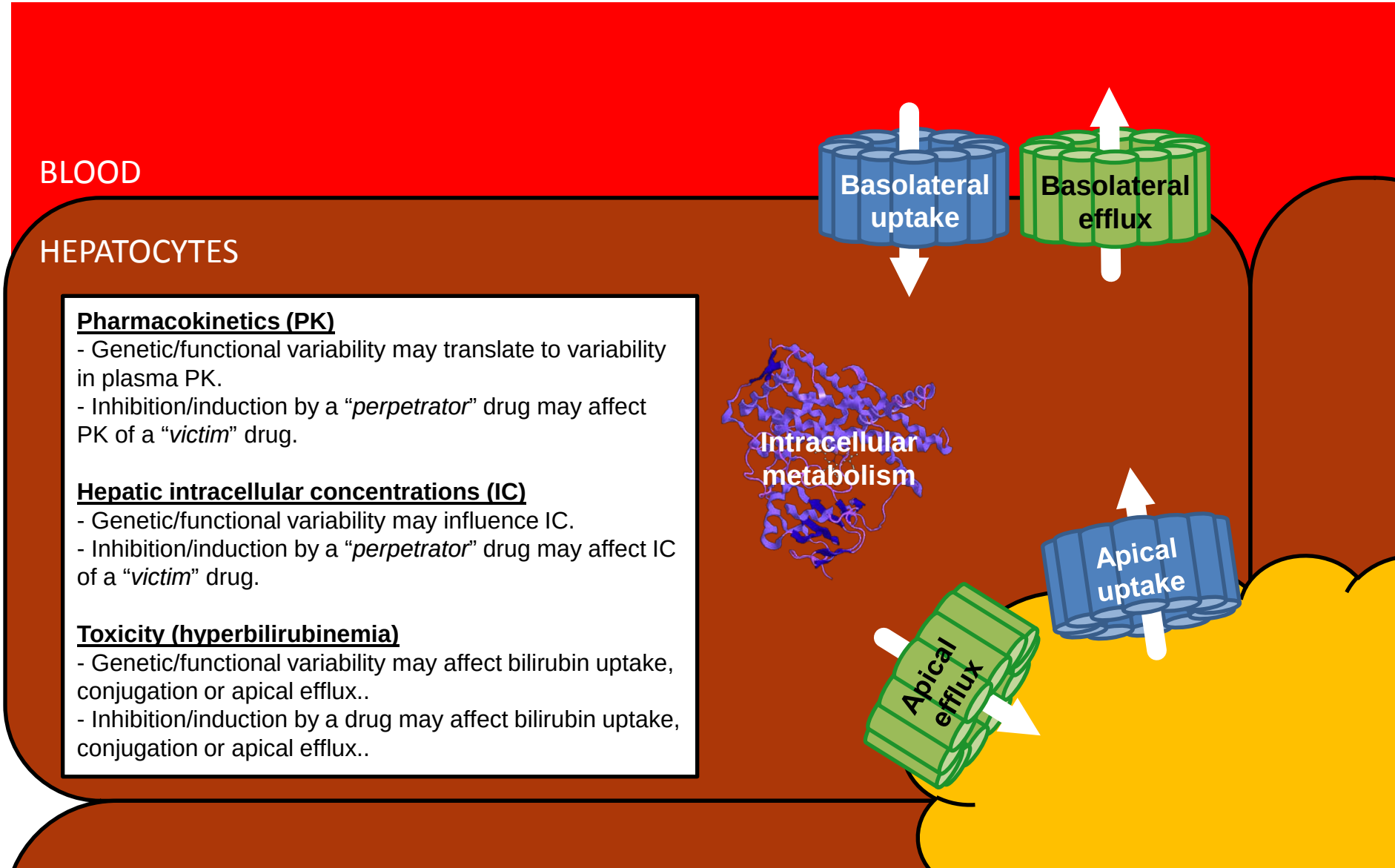
Coordinated drug transport and metabolism



harmacogenet Genomics. 2006 **16**:693-703.

Mechanisms for hepatic residence and clearance of drugs



Pharmacokinetics (PK)
- Genetic/functional variability may translate to variability in plasma PK.
- Inhibition/induction by a "*perpetrator*" drug may affect PK of a "*victim*" drug.

Hepatic intracellular concentrations (IC)
- Genetic/functional variability may influence IC.
- Inhibition/induction by a "*perpetrator*" drug may affect IC of a "*victim*" drug.

Toxicity (hyperbilirubinemia)
- Genetic/functional variability may affect bilirubin uptake, conjugation or apical efflux..
- Inhibition/induction by a drug may affect bilirubin uptake, conjugation or apical efflux..

International Transporter Consortium (ITC)

nature publishing group REVIEW

ITC Recommendations for Transporter Kinetic Parameter Estimation and Translational Modeling of Transport-Mediated PK and DDIs in Humans

MJ Zamek-Gliszczynski[1], CA Lee[2], A Poirier[3], J Bentz[4], X Chu[5], H Ellens[6], T Ishikawa[7], M Jamei[8], JC Kalvass[9], S Nagar[10], KS Pang[11], K Korzekwa[10], PW Swaan[12], ME Taub[13], P Zhao[14] and A Galetin[15]; on behalf of the International Transporter

This white paper provides a critical analysis of r
on proper parameter calculation in various exp
animal findings and application of static and dy
of human transporter-mediated pharmacokine
is to provide appropriate guidance for the use
science.

***IN VITRO* TRANSPORTER KINETICS**

The importance of active uptake and efflux in the inte
kidney, and brain to drug pharmacokinetics has becor
ingly more appreciated.[1,2] Understanding pharmacok
and drug–drug interaction (DDI) implications of t
involvement in absorption, distribution, and excretio
appropriate characterization of uptake and efflux
vitro. Two general types of *in vitro* systems are comm
to study uptake and efflux transport kinetics: (i) expr
tems, including immortalized cell lines (e.g., CHO, H
LLC-PK1, and MDCKII), oocytes, and vesicles, and
cells, such as primary or cultured cells (e.g., hepato
derived cell lines (e.g., Caco-2, HepG2). Expressio
can be directly used to estimate kinetic/inhibition p
for the overexpressed transporter. By contrast, cellul
can be optimized to estimate kinetic parameters
uptake, metabolism, or efflux, as well as the interpl
tiple processes.

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Emerging Transporters of Clinical Importance: An Update from the International Transporter Consortium

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(on behalf of the International Transporter Consortium)

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INTERNATIONAL TRANSPORTER CONSORTIUM

Transporter Studies in Drug Development: Experience to Date and Follow up on Decision Trees from the International Transporter Consortium

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Introduction

The International Transporter Consortium organized a second Workshop in March 2012 to expand on

Transporters in regulatory documents

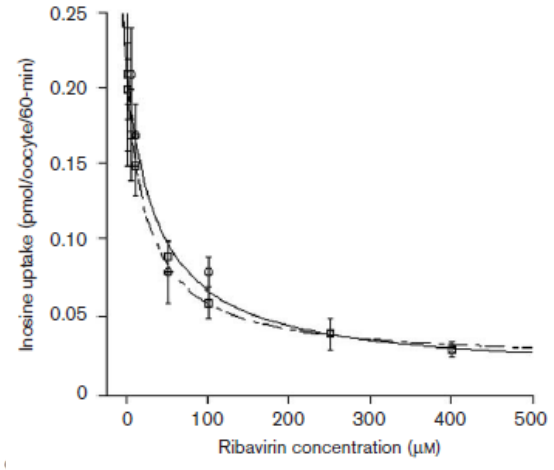
Transporter	Pseudonym(s)	ITC recommendation (Apr 2013)	FDA Guidance (Feb 2012)	EMA Guidelines (June 2012)
ABCB1	P-gp/MDR1	✓	✓	✓
ABCC2	MRP2	✓		
ABCG2	BCRP	✓	✓	✓
ABCB11	BSEP	✓		✓
SLCO1B1	OATP1B1	✓	✓	✓
SLCO1B3	OATP1B3	✓	✓	✓
SLC22A1	OCT1	✓		✓
SLC22A2	OCT2	✓	✓	✓
SLC22A6	OAT1	✓	✓	✓
SLC22A8	OAT3	✓	✓	✓
SLC47A1	MATE1	✓	✓	✓
SLC47A2	MATE2	✓	✓	✓

SLC28 (CNT) and ribavirin

Genetic analysis and functional characterization of polymorphisms in the human concentrative nucleoside transporter, CNT2

Ryan P. Owen[a], Jennifer H. Gray[a], Travis R. Taylor[b], Elaine J. Carlson[b], Conrad C. Huang[b], Michiko Kawamoto[b], Susan J. Johns[b], Doug Stryke[b], Thomas E. Ferrin[b] and Kathleen M. Giacomini[a]

Variant	Mean ± SD K_m (μM)
CNT2-reference	35.5 ± 9.27
CNT2-P22L	40.8 ± 6.47
CNT2-S75R	31.2 ± 15.8
CNT2-S245T	26.7 ± 6.13
CNT2-F355S	49.9 ± 14.6

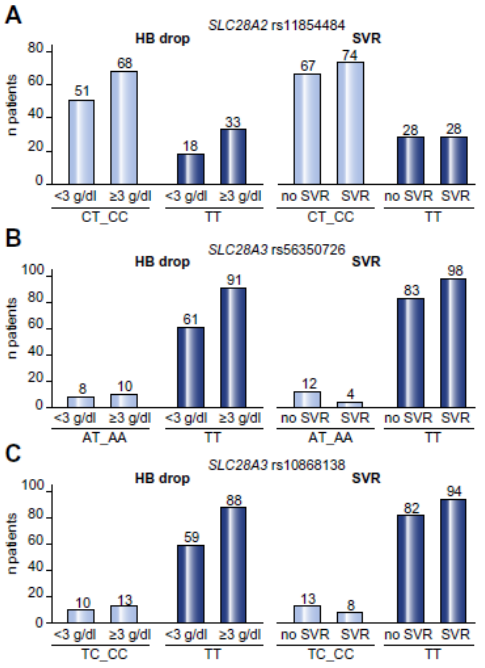


Negative Predictive Value of *IL28B*, *SLC28A2*, and *CYP27B1* SNPs and Low RBV Plasma Exposure for Therapeutic Response to PEG/IFN-RBV Treatment

Antonio D'Avolio, BSc, MSc, SM, Alessia Ciancio, MD, PhD,† Marco Siccardi, BSc, MSc, PhD,‡ Antonina Smedile, MD,† Marco Simiele, BSc, MSc,* Jessica Cusato, BSc, MSc,* Lorena Baietto, BSc, MSc,* Diego Aguilar Marucco, MD,* Giuseppe Cariti, MD,* Andrea Calcagno, MD,* Daniel Gonzalez de Requena, BSc, MSc,* Mauro Sciandra, LT,* Giulia Troshina, BSc, MSc,† Gian Paolo Caviglia, BSc, MSc,† Stefano Bonora, MD,* Mario Rizzetto, MD,† and Giovanni Di Perri, MD, PhD**

Factors	Multivariate OR (95% CI)	*P*
Gender (male)	—	—
Weight (10 kg)	NS	NS
Age (10 yrs)	NS	NS
pegIFN-2a	—	—
RBV dose (mg/kg)	—	—
Dose reduction	—	—
RBV concentrations > 2.5 (μg/mL)	3.94 (1.43–10.91)	0.008
IL28B rs8099917TT	3.06 (1.14–8.1)	0.026
CYP27B1 rs4646536TT	4.5 (1.54–13.1)	0.006
CNT2 rs11854484TT	3.7 (1.3–10.83)	0.014

Impact of genetic *SLC28* transporter and *ITPA* variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection



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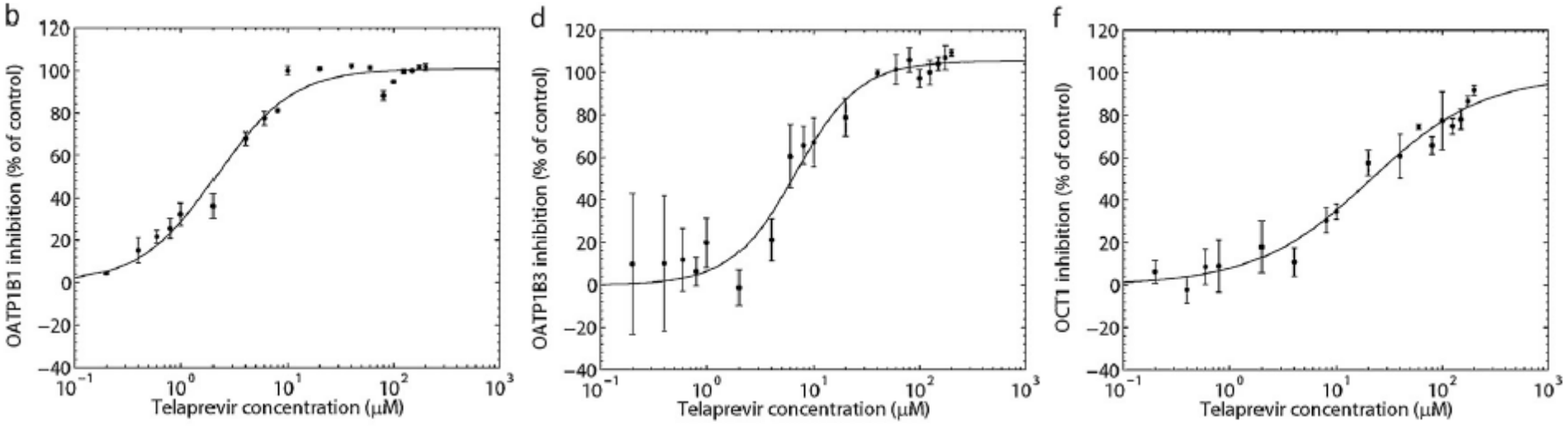
Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

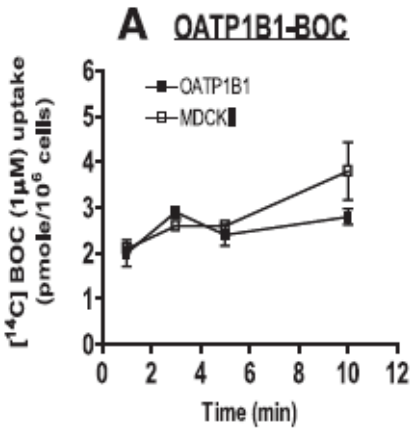
Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters

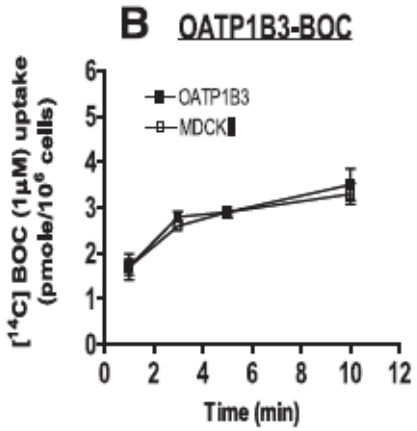


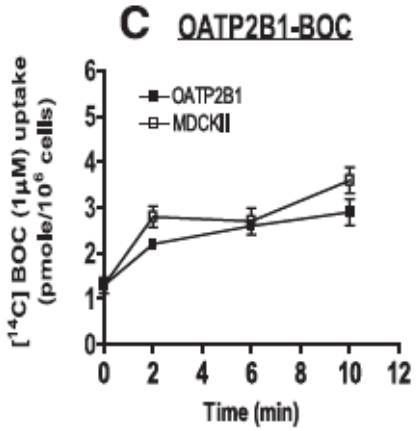
Localization	Transporter	IC_{50}			$\%_{max}$		
		Value (μM)	SD (μM)	*P*	Value (%)	SD (%)	*P*
Kidney	OCT2	6.35	3.45	0.0856	62.29	6.91	<0.001
Kidney	MATE1	22.98	6.72	0.0033	111.76	9.95	<0.001
Liver	OATP1B1	2.15	0.13	<0.001	100.90	2.31	<0.001
Liver	OATP1B3	6.77	0.87	<0.001	105.39	3.88	<0.001
Liver	OCT1	20.67	7.74	0.0175	98.59	10.68	<0.001

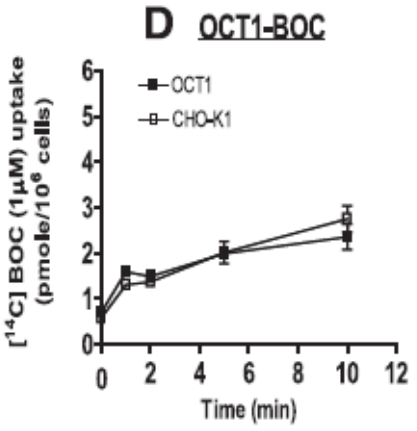
In Vitro Assessment of Drug-Drug Interaction Potential of Boceprevir Associated with Drug Metabolizing Enzymes and Transporters[S]

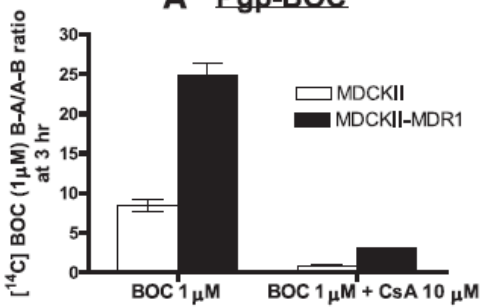
Xiaoyan Chu, Xiaoxin Cai, Donghui Cui, Cuyue Tang, Anima Ghosal, Grace Chan, Mitchell D Green, Yuhsin Kuo, Yuexia Liang, Cheri M Maciolek, Jairam Palamanda, Raymond Evers, and Thomayant Prueksaritanont

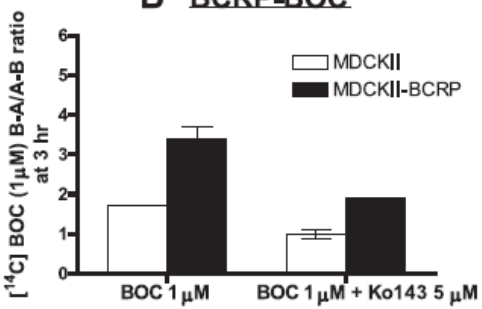


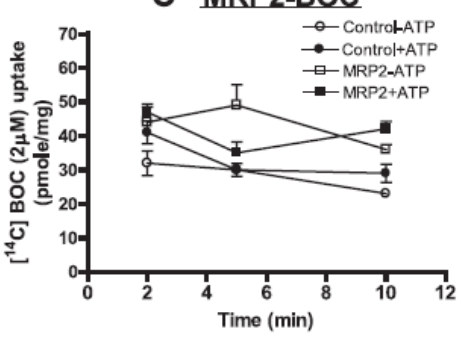


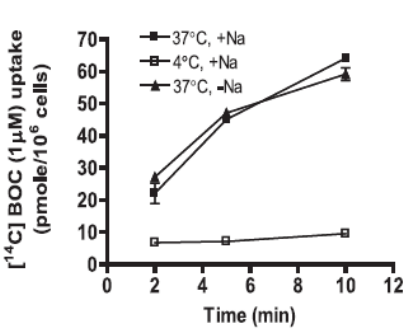




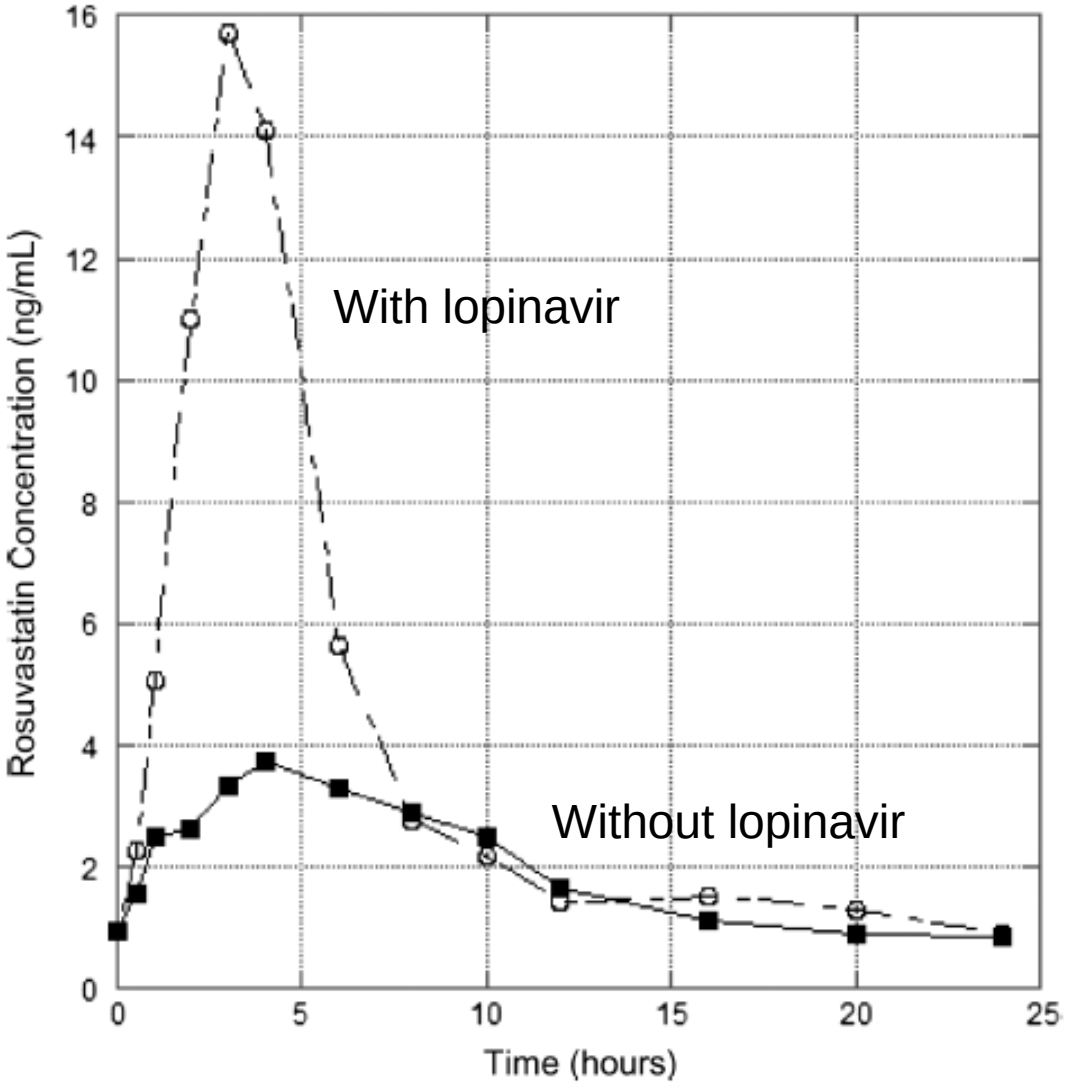








In Vitro Assessment of Drug-Drug Interaction Potential of Boceprevir Associated with Drug Metabolizing Enzymes



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HCV, liver disease and transporters

Pharmacological Reports
2012, 64, 927–939
ISSN 1734-1140

Drug Metab. Pharmacokinet. 25 (2): 190–199 (2010).

Regular Article

Hepatitis C Virus-related Cirrhosis is a Major Determinant of the Expression Levels of Hepatic Drug Transporters

	mRNA levels (amol/μg total RNA)				
	HCV (−), LC (−)	HCV (+), LC (−)	HCV (−), LC (+)	HCV (+), LC (+)	Ratio [(+), (+)/(−), (−)]
OCT1	16.63 ± 8.91	13.64 ± 9.23	10.70 ± 4.60	8.87 ± 5.56***	0.53
OCTN2	0.70 ± 0.32	0.83 ± 0.47	0.55 ± 0.24	0.75 ± 0.39	1.07
OAT2	11.86 ± 7.36	13.37 ± 8.62	10.06 ± 4.03	10.27 ± 5.66	0.87
OAT7	0.62 ± 0.33	0.56 ± 0.30	0.47 ± 0.19	0.47 ± 0.20	0.76
OATP1B1	10.55 ± 6.71	8.04 ± 4.78	6.72 ± 2.95	5.91 ± 2.89***	0.56
OATP1B3	3.83 ± 2.27	2.91 ± 1.95	2.80 ± 1.54	1.98 ± 1.15**	0.52
OATP2B1	31.20 ± 13.72	32.50 ± 20.18	24.13 ± 10.17	24.36 ± 10.91	0.78
MATE1	3.14 ± 2.04	2.13 ± 1.27	2.04 ± 0.93	1.34 ± 0.68***	0.43
PEPT1	1.01 ± 0.55	1.24 ± 0.66	0.81 ± 0.39	0.94 ± 0.32	0.93
MDR1	1.15 ± 0.52	1.56 ± 0.87	1.07 ± 0.35	1.40 ± 0.43*	1.22
MRP1	0.25 ± 0.14	0.40 ± 0.26	0.27 ± 0.17	0.51 ± 0.53*	2.04
MRP2	2.96 ± 1.77	2.44 ± 1.66	1.45 ± 0.68	1.45 ± 0.54***	0.49
MRP3	2.58 ± 1.31	2.64 ± 1.34	1.68 ± 0.55	2.18 ± 1.09	0.85
MRP4	0.09 ± 0.05	0.16 ± 0.14	0.11 ± 0.05	0.18 ± 0.13***	2.06
MRP5	0.07 ± 0.04	0.10 ± 0.06	0.06 ± 0.02	0.11 ± 0.08	1.49
MRP6	3.41 ± 2.16	3.13 ± 1.76	2.50 ± 1.28	2.33 ± 1.15	0.68
BCRP	0.57 ± 0.33	0.45 ± 0.25	0.33 ± 0.17	0.31 ± 0.22***	0.53

GSTA1 SULT1A1 SULT2A1 UGT1A1 UGT1A4 UGT1A6 ABCB1 ABCC2 ABCC3 ABCC4 ABCG2

Investigational (Phase 2+) HCV DAAs

Protease Inhibitors	
BI 201335 (Faldaprevir)	CYP3A substrate Moderate inhibitor of CYP3A
TMC435 (Simeprivir)	CYP3A substrate Weak inhibitor of CYP3A and P-gp
ABT-450	CYP3A substrate Boosted by ritonavir
BMS-650032 (Asunaprevir)	Weak inhibitor of CYP2D6 and P-gp Weak inducer of CYP3A4
RG7227 (danoprevir)	CYP3A substrate boosted by ritonavir

Back and Else, The importance of drug-drug interactions in the DAA era (In Press)

Investigational (Phase 2+) HCV DAAs

Non-nucleoside polymerase inhibitors	
BI 207127	No data
Filibuvir (PF-868554)	CYP3A substrate Weak inducer and inhibitor
GS-9190 (Tegobuvir)	Metabolism (limited) by CYP1A2 No CYP inhibition and induction
ART-333	Metabolised by CYP2C8, 3A4, 2D6

Back and Else, The importance of drug-drug interactions in the DAA era (In Press)

Investigational (Phase 2+) HCV DAAs

NS5A Inhibitors	
BMS-790052 (daclatasvir)	CYP3A substrate; P-gp substrate P-gp inhibitor
Nucleoside polymerase inhibitors	
GS-7977 (sofosbuvir)	Not a CYP3A substrate Renally excreted

Back and Else, The importance of drug-drug interactions in the DAA era (In Press)

Summary and conclusions

- Transporters play a key role for inter-patient variability in pharmacokinetics, distribution, drug interactions and safety
- Robust interpretation of transporter data relies on knowledge of tissue and cellular transporter localisation which may be influenced by disease
- Over 400 transporters are coded within the human genome and relatively few have been studied for xenobiotic transport
- There is a paucity of published literature on the interaction of HCV drugs with transporters

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