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## University of Washington Metabolism & Transport Drug Interaction Database

### January 2012 Newsletter

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The present newsletter summarizes the **December 2011** publications entered so far\* in the Database. The body of articles was classified according to the following categories: *in vivo* (inhibition and induction), *in vitro* metabolism, and *in vitro* transport papers.

One NDA approved in 2011 was added to the database this month: **roflumilast** (NDA #: 022522).

Two **new queries** are now available to retrieve the results of **hepatic** and **renal impairment** studies. They are described on pages 7-8.

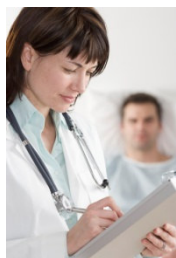
### ***In vivo articles:***

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#### **Highest change in AUC/CL:**

**Bosutinib** is a dual inhibitor of Src and Abl tyrosine kinases, developed for the treatment of chronic myelogenous leukemia. According to preclinical data, CYP3A4 metabolizes bosutinib. In healthy male subjects, the strong CYP3A inhibitor **ketoconazole** (400 mg QD for 4.5 days) increased bosutinib AUC by **8.1-fold**. Nevertheless, the incidence of adverse events was comparable between the 2 treatments (bosutinib alone or with ketoconazole). [[21148045](#)]



#### **Drugs in development and their DDIs:**

**Anacetrapib** is a cholesteryl ester transfer protein (CETP) inhibitor, currently developed for dyslipidemia therapy. In MDR1-transfected LLCPK cells, anacetrapib did not inhibit the P-gp mediated bidirectional transport of **verapamil**. Consistent with this finding, the single-dose pharmacokinetics of **digoxin** were not affected by the coadministration of anacetrapib (100 mg QD for 19 days) in healthy volunteers, indicating that anacetrapib does not inhibit P-gp *in vivo*. [[22031172](#)]



#### **Biologics and their DDIs:**

**Liraglutide** [rDNA origin] is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Liraglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In healthy postmenopausal women,

*\*Because the Database uses the PubMed ID number (PMID) as identifier of publications, the PMID needs to be available for the article to be listed in this document. Some articles may be presented in the month of their availability online (tagged as online early) and in the month of their publication in print.*

liraglutide (0.6-1.8 mg SC QD for 3 weeks) had no effect on the PK parameters of a single dose of **ethinyl estradiol** combined with **levonorgestrel**. [[21228406](#)]

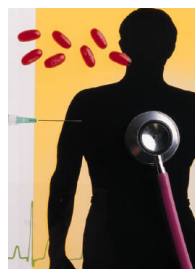
### Herbal/food components and their DDIs:

**St John's wort** (SJW, *Hypericum perforatum*) is one of the most commonly used herbal antidepressants. Depressed patients could be taking SJW as well as hypnotic drugs such as **zolpidem**. Because the metabolism of zolpidem is mainly mediated by CYP3A4, it is likely that the CYP inducer SJW decreases the plasma concentration of zolpidem. Indeed, when a single 20 mg-oral dose of zolpidem was coadministered with SWJ (300 mg TID for 15 days) in healthy subjects, the AUC of zolpidem was reduced by 30%. [[21058968](#)]



### Other in vivo highlights:

**Sibutramine** is an inhibitor of serotonin and norepinephrine reuptake, used in the treatment of obesity. Sibutramine is metabolized by CYP2B6 and to a lesser extent by CYP2C19 and CYP3A into 2 active metabolites, M1 (mono-desmethyl sibutramine) and M2 (di-desmethyl sibutramine). **Clopidogrel** is a mechanism-based inhibitor of CYP2B6 and CYP2C19. In healthy male subjects, all extensive metabolizers for CYP2B6 and CYP2C19, the AUC of sibutramine was increased by 127% when sibutramine was coadministered with clopidogrel (75 mg QD for 7 days). In addition, a significant increase in the AUC of M1 was observed (162% of control phase). [[21209232](#)]

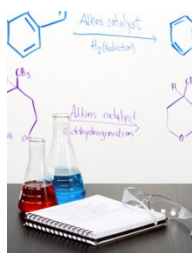


In vivo articles published in December 2011 included:

<a href="#">Journal</a>	<a href="#">Title</a>	<a href="#">Accession #</a>
<b>DDI studies</b>		
Antimicrob Agents Chemother	Interaction between <b>Artemether-Lumefantrine</b> and <b>Nevirapine</b> -Based Antiretroviral Therapy in HIV-1-Infected Patients.	<a href="#">21947399</a>
Biopharm Drug Dispos	<b>Lack of an effect of anacetrapib on the pharmacokinetics of digoxin in healthy subjects.</b>	<a href="#">22031172</a>
Clin Pharmacol Ther	<b>Cannabinoid-opioid</b> interaction in chronic pain.	<a href="#">22048225</a>
Drug Metab Dispos	Complex Drug Interactions of HIV Protease Inhibitors 2: In Vivo Induction and In Vitro to In Vivo Correlation of Induction of Cytochrome P450 1A2, 2B6, and 2C9 by <b>Ritonavir</b> or <b>Nelfinavir</b> .	<a href="#">21930825</a>
Eur J Clin Pharmacol	Effects of <b>Schisandra sphenanthera extract</b> on the blood concentration of <b>tacrolimus</b> in renal transplant recipients.	<a href="#">21656210</a>
Int J Androl	Steady-state pharmacokinetics of oral <b>testosterone undecanoate</b> with concomitant inhibition of 5 $\alpha$ -reductase by <b>finasteride</b> .	<a href="#">20969601</a>
Int J Clin Pharmacol Ther	Pharmacokinetic interaction study with fixed high dose combinations of <b>candesartan</b> cilexetil and <b>hydrochlorothiazide</b> .	<a href="#">22122817</a>
Int J Clin Pharmacol Ther	Pharmacokinetic profiles of <b>hydrochlorothiazide</b> alone and in combination with <b>benazepril</b> or <b>valsartan</b> in healthy Chinese volunteers: evaluation of the potential interaction.	<a href="#">22122818</a>
J Clin Pharm Ther	<b>Drug interaction between St John's wort and zolpidem in healthy subjects.</b>	<a href="#">21058968</a>
J Clin Pharmacol	<b>Effect of ketoconazole on the pharmacokinetics of oral bosutinib in healthy subjects.</b>	<a href="#">21148045</a>

J Clin Pharmacol	Effects of <b>clopidogrel</b> on the pharmacokinetics of <b>sibutramine</b> and its active metabolites.	<a href="#">21209232</a>
J Clin Pharmacol	Pharmacokinetics of Oral <b>Dexamethasone</b> and <b>Midazolam</b> When Administered With Single-Dose Intravenous 150 mg <b>Fosaprepitant</b> in Healthy Adult Subjects.	<a href="#">21209230</a>
J Clin Pharmacol	Safety and pharmacokinetics of <b>sorafenib</b> combined with <b>capecitabine</b> in patients with advanced solid tumors: results of a phase 1 trial.	<a href="#">21209247</a>
J Clin Pharmacol	Treatment With <b>Liraglutide</b> --a Once-Daily GLP-1 Analog--Does Not Reduce the Bioavailability of <b>Ethinyl Estradiol/Levonorgestrel</b> Taken as an Oral Combination Contraceptive Drug.	<a href="#">21228406</a>
Ther Drug Monit	<b>Oseltamivir</b> , an influenza neuraminidase inhibitor drug, does not affect the steady-state pharmacokinetic characteristics of <b>cyclosporine</b> , <b>mycophenolate</b> , or <b>tacrolimus</b> in adult renal transplant patients.	<a href="#">22105586</a>
Am J Cardiovasc Drugs	Comparing Antihypertensive Effect and Plasma <b>Ciclosporin</b> Concentration between <b>Amlodipine</b> and <b>Valsartan</b> Regimens in Hypertensive Renal Transplant Patients Receiving Ciclosporin Therapy.	<a href="#">22149319</a>
Clin Pharmacokinet	Effect of Cytochrome P450 <b>3A4 Inducers</b> on the Pharmacokinetic, Pharmacodynamic and Safety Profiles of <b>Bortezomib</b> in Patients with Multiple Myeloma or Non-Hodgkin's Lymphoma.	<a href="#">22087865</a>
<b>Single drug PK</b>		
Clin Ther	Effects of the CYP Oxidoreductase Ala503Val Polymorphism on CYP3A Activity In Vivo: A Randomized, Open-Label, Crossover Study in Healthy Chinese Men.	<a href="#">22177374</a>
Clin Ther	Pharmacokinetics and tolerability of nasal versus intravenous <b>midazolam</b> in healthy dutch volunteers: a single-dose, randomized-sequence, open-label, 2-period crossover pilot study.	<a href="#">22078155</a>
<b>Case reports</b>		
Br J Clin Pharmacol	Effect of <b>grapefruit juice</b> on the pharmacokinetics of <b>docetaxel</b> in cancer patients: a case report.	<a href="#">21692829</a>
Int J Clin Pharmacol Ther	<b>Simvastatin</b> -induced myopathy with concomitant use of <b>cyclosporine</b> : case report.	<a href="#">22122820</a>
Invest New Drugs	Pharmacokinetic interaction involving <b>sorafenib</b> and the calcium-channel blocker <b>felodipine</b> in a patient with hepatocellular carcinoma.	<a href="#">20706860</a>

## *In vitro articles:*



### Drugs in development and their DDIs:

**1- C-1305**, an analogue of C-1311, is an imidazoacridinone anti-tumor agent. Incubation studies showed that C-1305 was transformed to an N-oxide derivative with HLMs, HepG2 hepatoma cells and with human recombinant FMO1, FMO3 but not with CYPs. In addition, C-1305 was found to inhibit CYP1A2 and CYP3A4, with IC50 values of 0.94  $\mu\text{M}$  and 3.12  $\mu\text{M}$ , respectively.

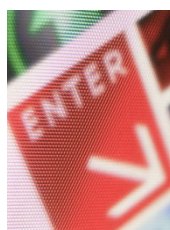
[\[21859392\]](#)

**2- Pracinostat** is a hydroxamic acid histone deacetylase (HDAC) inhibitor, currently in Phase 2 of development for the treatment of solid tumors. Enzyme phenotyping studies showed that pracinostat is primarily metabolized by



	interactions.	
Pharmacogenomics	Functional analysis of UGT1A4(P24T) and UGT1A4(L48V) variant enzymes.	<a href="#">22047493</a>
Toxicol In Vitro	Inhibitory effects of <b>limonin</b> on six human cytochrome P450 enzymes and P-glycoprotein in vitro.	<a href="#">22001672</a>
Xenobiotica	Determination of cytochrome P450 enzymes involved in the metabolism of <b>(-)-terpinen-4-ol</b> by human liver microsomes.	<a href="#">22054099</a>
Xenobiotica	Flavin monooxygenases, FMO1 and FMO3, not cytochrome P450 isoenzymes, contribute to metabolism of anti-tumour triazoloacridinone, <b>C-1305</b> , in liver microsomes and HepG2 cells.	<a href="#">21859392</a>
Biochem Pharmacol	Characterizing the effect of UDP-glucuronosyltransferase (UGT) 2B7 and UGT1A9 genetic polymorphisms on enantioselective glucuronidation of <b>flurbiprofen</b> .	<a href="#">21856293</a>
Biochemistry	The Structural Basis for Homotropic and Heterotropic Cooperativity of <b>Midazolam</b> Metabolism by Human Cytochrome P450 3A4.	<a href="#">21992114</a>

## *In vitro transport articles:*



### **In vitro transport highlight:**

**YM155**, a novel survivin suppressant, is being tested as an anticancer drug in phase II clinical trials in combination with other agents. Previous studies have shown that influx transporters play important roles in the uptake of YM155 into hepatocytes and possibly into cancer cells, but efflux transporters (e.g. P-gp) have yet to be investigated. A bidirectional transporter assay using Caco-2 and LLC-MDR1 cells showed low permeability and no vectorial transport of YM155.

However, vectorial transport across LLC-OCT1/MDR1 cells was observed, using a newly established cell line which expresses basal OCT1 and apical MDR1. Furthermore, the vectorial transport was inhibited by the P-gp inhibitor **cyclosporine A**. The authors suggested that the discrepancy between the LLC-OCT1/MDR1 and both the Caco-2 and LLC-MDR1 results is due to an insufficient expression of basal uptake transporter in Caco-2 and single-transfected LLC-MDR1. In conclusion, these findings suggest that YM155 is a substrate of MDR1 in vitro.

[\[21918035\]](#)

In vitro transport articles published in December 2011 included:

<a href="#">Journal</a>	<a href="#">Title</a>	<a href="#">Accession #</a>
Biopharm Drug Dispos	Stereoselective inhibitory effect of <b>flurbiprofen</b> , <b>ibuprofen</b> and <b>naproxen</b> on human organic anion transporters hOAT1 and hOAT3.	<a href="#">22072415</a>
Drug Metab Dispos	Development of a highly sensitive method using liquid chromatography-multiple reaction monitoring to quantify membrane p-glycoprotein in biological matrices and relationship to transport function.	<a href="#">21949244</a>
Drug Metab Dispos	Intestinal Ciprofloxacin Efflux: The Role of Breast Cancer Resistance Protein (ABCG2).	<a href="#">21930826</a>
Drug Metab Dispos	Utility of P-Glycoprotein and Organic Cation Transporter 1 Double-Transfected LLC-PK1 Cells for Studying the Interaction of <b>YM155</b> Monobromide, Novel Small-Molecule Survivin Suppressant, with P-Glycoprotein.	<a href="#">21918035</a>
Pharmacogenet	Functional defect caused by the 4544G>A SNP in ABCC2: potential impact for drug	<a href="#">22027652</a>

Genomics	cellular disposition.	
Pharmacogenomics J	Genotype-dependent effects of inhibitors of the organic cation transporter, OCT1: predictions of metformin interactions.	<a href="#">20567254</a>
Eur J Pharmacol	Breast cancer resistance protein BCRP (ABCG2)-mediated transepithelial <b>nitrofurantoin</b> secretion and its regulation in human intestinal epithelial (Caco-2) layers.	<a href="#">22004608</a>

## NEW NDA: Roflumilast

Roflumilast is a **selective inhibitor of Phosphodiesterase 4 (PDE4)**, indicated as a treatment to reduce the risk of **COPD** exacerbations, in patients with severe COPD.

Roflumilast is **extensively metabolized** via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The **N-oxide metabolite (pharmacologically active)** is the only major metabolite observed in human plasma. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of the total dose administered in plasma.

In vitro studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is primarily mediated by **CYP3A4** and to a minor extent by **CYP1A2**.

Consistent with these findings, coadministration of **fluvoxamine** (a potent CYP1A2 and moderate CYP3A inhibitor, 50 mg daily for 14 days) with a single oral dose of 500 µg roflumilast increased roflumilast and roflumilast N-oxide AUC by 156% and 52%, respectively.

Coadministration of **ketoconazole** (200 mg BID for 13 days), a potent CYP3A inhibitor, with a single dose of roflumilast resulted in 99% increase in roflumilast AUC, while the moderate inhibitor **erythromycin** (500 mg TID for 13 days) increased the AUC of roflumilast by 70%. **Enoxacin** (400 mg BID for 12 days), a strong CYP1A2 inhibitor, increased roflumilast AUC by 56%.

On the other hand, coadministration of the strong CYP3A4 inducer **rifampicin** (600 mg QD for 11 days) with a single dose of roflumilast resulted in reduction of roflumilast AUC by 79%. **Cigarette smoking** (CYP1A2 inducer) did not affect roflumilast exposure.

No significant drug interactions were observed when roflumilast was administered with drugs likely to be coadministered such as salbutamol, formoterol, budesonide, and montelukast. However, coadministration of a single dose of roflumilast with repeated doses of a fixed combination **oral contraceptive** containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 51% increase of roflumilast AUC.

Based on in vitro results, therapeutic plasma concentrations of roflumilast do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5. In hepatocytes, roflumilast caused a weak induction of CYP2B6 activity at the highest concentration studied (0.1 µM), which is about 10 times the C<sub>max</sub> in plasma. Roflumilast had no effect on the activities of the other enzymes tested (CYP1A2, CYP2A6, CYP2C19, CYP2C9, CYP3A). Therefore, roflumilast is not expected to alter the pharmacokinetics of coadministered drugs to a clinically significant extent.

Roflumilast is neither a **P-gp** substrate nor a P-gp inhibitor in vitro. In vivo, no significant drug interaction was observed when roflumilast was administered with digoxin.

The AUC of roflumilast (250 µg) was increased by 51% in Child-Pugh A subjects and by 92% in Child-Pugh B subjects, as compared to healthy subjects. Therefore, roflumilast is not recommended for use in patients with moderate or severe **liver impairment**.

In subjects with severe renal impairment administered a single dose of 500 µg roflumilast, roflumilast AUC was decreased by 21%. No dosage adjustment is necessary for patients with **renal impairment**.

## New Features:

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Two **new queries** are now available to retrieve the results of **hepatic** and **renal impairment** studies.

### 1- A new **Pharmacokinetics** query (#3): **“PK of Object with HI/RI”**

This query retrieves the PK parameters of a given drug in HI or RI situations:

View PK Parameters of Object:  [load list](#)

HI Studies  
HI Studies  
RI Studies  
RI or HI Studies

HI / RI = Hepatic Impairment / Renal Impairment

### 2- An **AUC/CL Changes** query (#6): **“% AUC or CL or renal CL with HI/RI”**

This query retrieves objects’ AUC, oral or renal CL changes versus controls available in HI or RI studies, organized by severity of the disease (mild, moderate, severe impairment, as well as ESRD- End Stage Renal Disease):

% AUC or CL or renal CL with HI / RI

Find Objects with:  HI Studies

Providing:  Percent Change in AUC

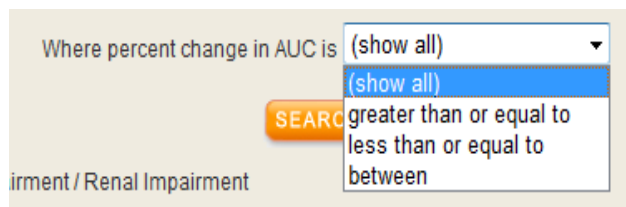
With Associated Pathologies:  Mild Hepatic Impairment

Where percent change in AUC is  show all

[SEARCH](#)

HI / RI = Hepatic Impairment / Renal Impairment

A filtering option allows users to identify drugs that exhibit any given degree of change in PK in the impaired population. The filter works exactly the same way than for the other AUC/CL queries (enter positive values for AUC changes and negative values for CL changes).



As for all existing queries, download to a Table View, or Excel & Word documents is available. The Table View can be re-ordered using any column header.



If you have any **questions** or **comments** on the DIDB newsletter, please contact us at:

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