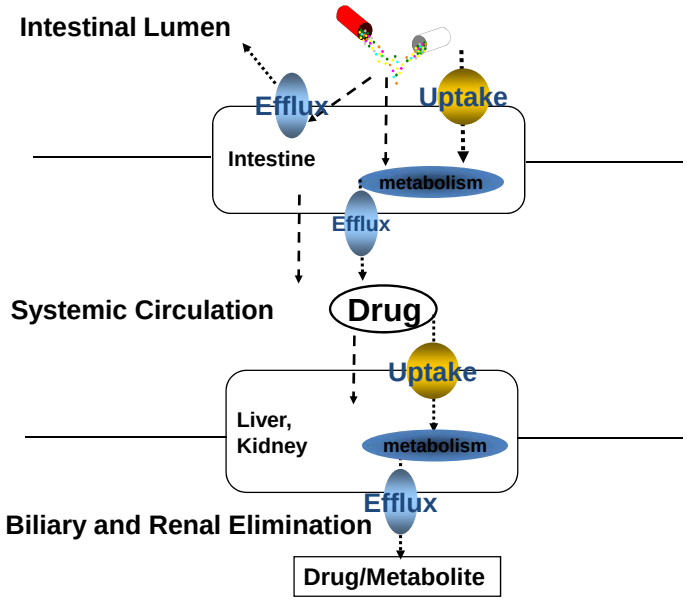
Drug Transporters: In Vitro and Knockout Model Systems, Pharmacogenomics, and Clinical Relevance

Richard B. Kim MD, FRCP(C)

Professor & Chair, Division of Clinical Pharmacology
Director, Centre for Clinical Investigation & Therapeutics
Department of Medicine,
London Health Sciences Centre
Schulich School of Medicine & Dentistry
The University of Western Ontario
richard.kim@Lhsc.on.ca
http://www.uwoclinpharm.ca

Determinants of Drug Disposition



Case Study

- 59 yr old female with type 2 diabetes on metformin presents with a 3 month history of vague abdominal pain and diarrhea.
- Also 3 months ago, started on cimetidine for duodenal ulcer treatment.
- On examination, noted to be agitated, hypotensive (BP 85/40 mmHg). Arterial blood gas showed profound metabolic acidosis (pH 6.5)
- Dx: Metformin induced metabolic acidosis

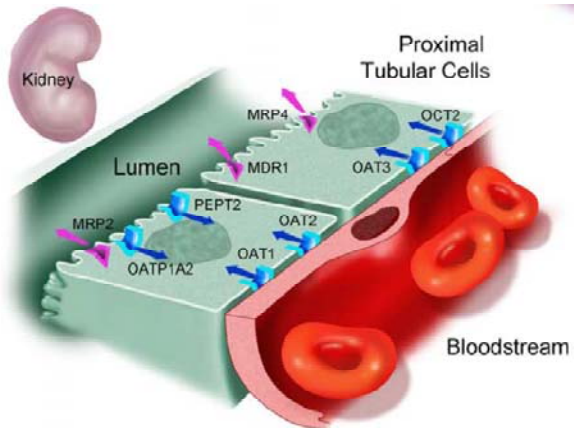
Dawson et al Diabetes Care 26:2471-2472, 2003

Case Study

- Why did she develop this?
- Metformin is not significantly metabolized. It is cleared by glomerular filtration and tubular secretion.
- Cimetidine is known to be capable of inhibiting renal tubular secretion of metformin.

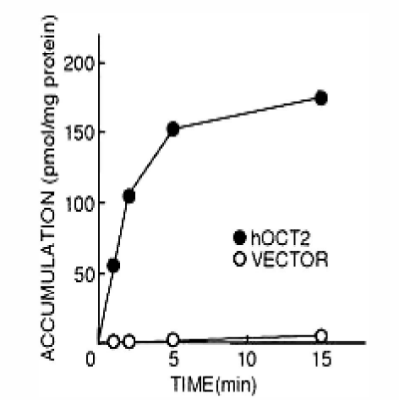
Dawson et al Diabetes Care 26:2471-2472, 2003

Renal Transporters



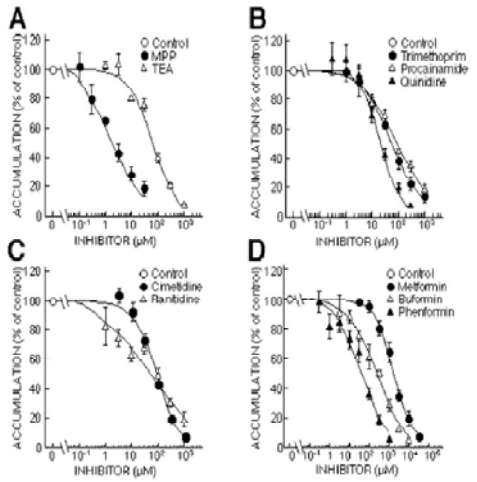
Ho RH and Kim RB Clin Pharmacol Ther, 78:260-77, 2005

OCT2 is the metformin transporter

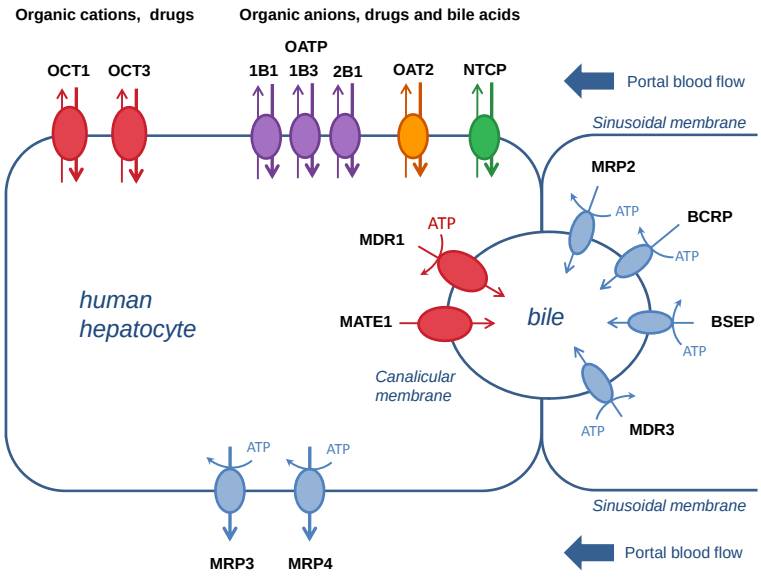


Kimura N et al et al Pharm Res 22:255-259, 2005

OCT2 can be inhibited by cimetidine



Kimura N et al et al Pharm Res 22:255-259, 2005



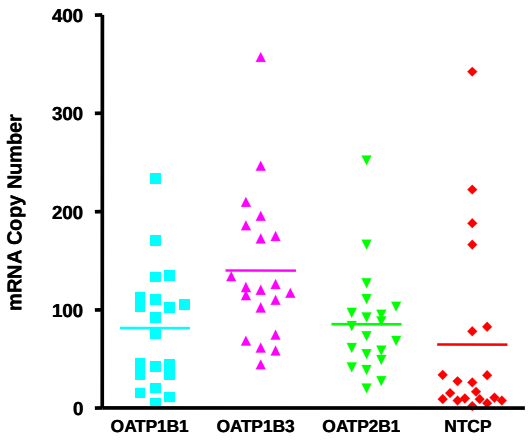
DeGorter MK et al Hepatology, 2009

Hepatic OATP Transporters

OATP1B1 (OATP-C, LST-1, OATP2)	OATP1B3 (OATP8, LST-2)
Endogenous Substrates: Estrone Sulfate, PGE_2, Bilirubin, thyroid hormone (T_3, T_4) Bilirubin-glucuronides Estradiol 17β-d-glucuronide, bile acids	**Endogenous Substrates:** CCK-8, PGE_2 Thyroid hormone (T_3, T_4) Estradiol 17 β -d-glucuronide, Bile acids, Deltophin, DPDPE,
Drug Substrates: Atorvastatin, Cerivastatin, Pravastatin Rosuvastatin, Pitavastatin, Caspofungin, Troglitazone-sulfate, Rifampin, Arsenic, Atrasentan, Valsartan, Olmesartan, Enalapril, MTX, Temocaprilat, **SN-38**	**Drug Substrates:** Pravastatin, Pitavastatin, Rosuvastatin,, Fexofenadine, BQ-123, Oubain, Digoxin, Doxotaxel, Paclitaxel,, Rifampin, MTX, Bilirubin, Repaglinide, Telmisartan, Valsartan, Olmesartan, Enalapril, Temocaprilat, **SN-38**
Toxins: Phalloidin, Microcystin-LR	**Toxins:** Phalloidin, Microcystin-LR

mRNA and Protein Expression

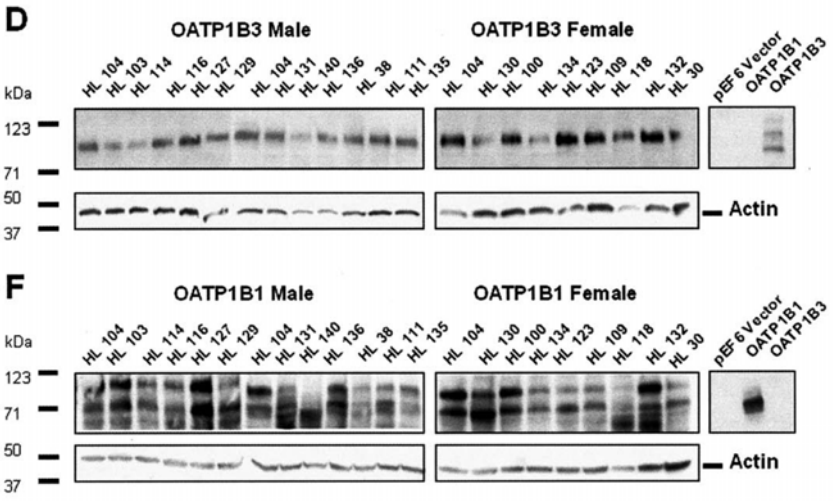
Expression of Hepatic Statin Transporters



Human Liver Samples

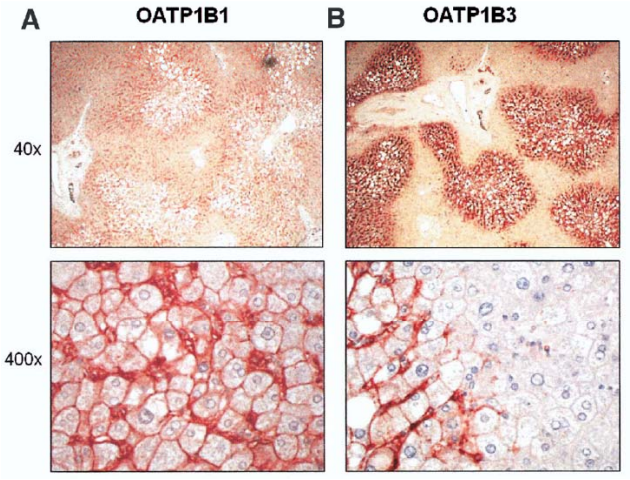
Ho et al., Gastroenterology 2006

Protein Expression of Hepatic OATPs



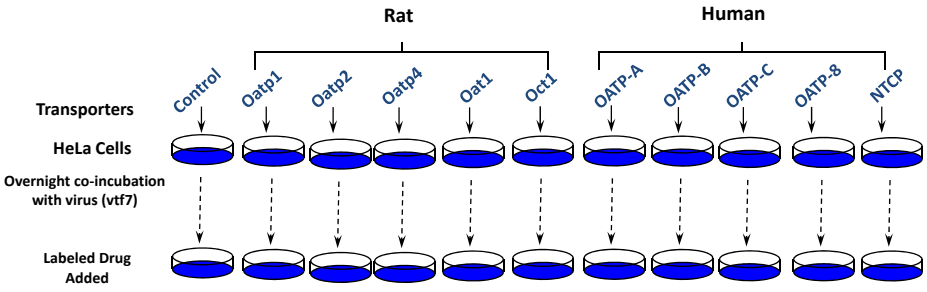
Ho RH et al, Gastroenterology, 130:1793-1806, 2006

Hepatic OATP Expression

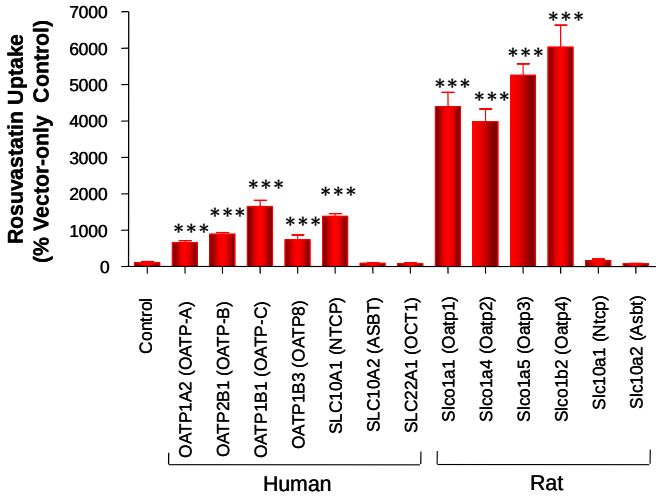


Ho et al., Gastroenterology 2006

Recombinant Transporter Expression Systems

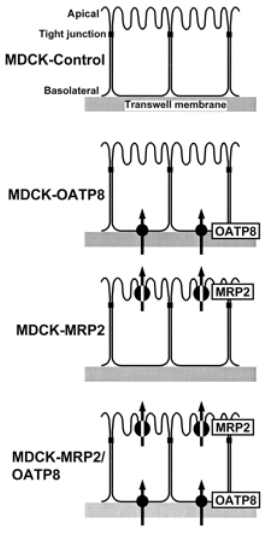


Rosuvastatin Transporters



Ho RH et al, Gastroenterology, 130:1793-1806, 2006

OATP1B3/MRP2 Double Transfected MDCK Cells



Cui Y et al Mol Pharm 60:934, 2002

So what should you do about OATPs??

Richard Kim's OATP Cafe: Menu

Substrates Galore

Appetizer

Hepatocytes (could use rat).
Q. Uptake transport relevant?

Salad

Express OATP1B1, 1B3, 2B1 (consider 1A2).

Consider expressing rat or mouse Oatps.

Entrée

Is uptake 1.5-fold or > than control?
If no, OATPs may not be the relevant transporter(s)

Dessert

Determine Km and Vmax

(use a standardized transporter model system. i.e. do not mix oocytes + Cell lines + vesicles etc)

Beverages

OATP1B1- Consider PGEN

Lots of Inhibition

Appetizer

Consider labeled estradiol 17-B glucuronide as a model substrate

Salad

Express 1B1 and 1B3 (might consider other OATPs).

Entrée

Determine IC50.
Include known positive control inhibitors (e.g. RIF).

Dessert

Consider I/IC50 values.

Difficult to know when a clinical interaction study should be carried out.

Beverages

If a clinical study is necessary

Rosuvastatin or pravastatin as substrates

OATP1B3 (mostly) telmisartan

PK + and - your drug could be done

OATP substrates: What to do step-by-step

Step 1:
Hepatocytes (could use rat).
Q. Uptake transport relevant?

Step 2:
Express OATP1B1, 1B3, 2B1 (consider 1A2).
Consider expressing rat or mouse Oatps (why? Species differences).

Step 3:
Is uptake 1.5-fold or > than control?
If no, OATPs may not be the relevant transporter(s)

Step 4:
Determine Km and Vmax
(use a standardized transporter model system. i.e. do not mix oocytes + Cell lines + vesicles etc)

Step 5:
OATP1B1- Consider PGEN in vivo study

OATPs: What to do if you are worried that your compound is an inhibitor

Step 1
Consider labeled estradiol 17-B glucuronide as a model substrate

Step 2
Express 1B1 and 1B3 (might consider other OATPs).

Step 3
Determine IC50.
Include known positive control inhibitors (e.g. RIF).

Step 4
Consider I/IC50 values.
Difficult to know when a clinical interaction study should be carried out.

Step 5
If a clinical study is necessary
- Rosuvastatin or pravastatin as substrates
- OATP1B3 (mostly) telmisartan
- PK of substrate +/- your drug could be done

In vivo relevance

Focus on OATPs

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ACCELERATED COMMUNICATION

Targeted Disruption of Murine Organic Anion-Transporting Polypeptide 1b2 (oatp1b2/*Slco1b2*) Significantly Alters Disposition of Prototypical Drug Substrates Pravastatin and Rifampin

Hani Zaher, Henriette E. Meyer zu Schwabedissen, Rommel G. Tirona, Melissa L. Cox, Leslie A. Obert, Nidhi Agrawal, Joe Palandra, Jeffrey L. Stock, Richard B. Kim, and Joseph A. Ware

Pfizer Global Research and Development, Ann Arbor, Michigan (H.Z., J.P., M.L.C., L.A.O., N.A., J.A.W.) and Groton, Connecticut (J.L.S.); Division of Clinical Pharmacology, Department of Medicine, and Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, Canada (H.E.M.z.S., R.G.T., R.B.K.); Lawson Health Research Institute, London, Ontario, Canada (R.B.K.)

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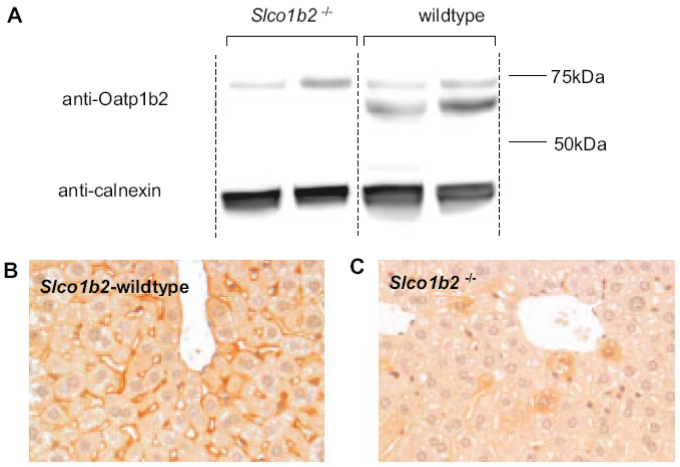
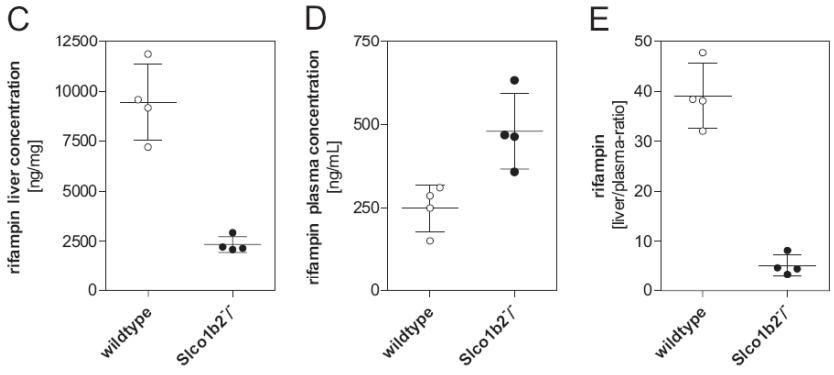
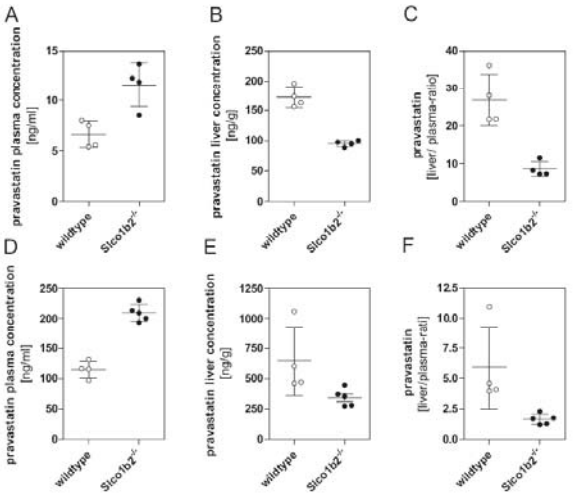
Loss of hepatic Oatp1b2



Rifampin continuous infusion



Pravastatin continuous infusion



Low dose: 8 µg/hr

High dose: 32 µg/hr

Oatp KO mice data

Table 1 Solute carrier knockout mouse models of drug transport

Gene Protein	Localization	Probe drug (dose and route)	Pharmacokinetic or pharmacodynamic effect of gene deletion
Slco1b2 Oatp1b2	Hepatocyte (basolateral membrane)	Rifampin 1 mg/kg IV	1.7-Fold increase in plasma AUC; 2.5-fold decrease in liver AUC
		Rifampin 8 µg/h for 24 h SC infusion	1.9-Fold increase in steady-state plasma concentration; fourfold decrease in steady-state liver concentration
		Pravastatin 8 µg/h for 24 h SC infusion	1.8-Fold increase in steady-state plasma concentration; 1.8-fold decrease in steady-state liver concentration
		Pravastatin 32 µg/h for 24 h SC infusion	1.8-Fold increase in steady-state plasma concentration; 1.9-fold decrease in steady-state liver concentration
		Phalloidin 2.5 mg/kg IP	Oatp1b2$^{-/-}$ mice protected from hepatoxicity: no change in ALT level or histology
		Microcystin-LR 120 µg/kg IP	6 Of 6 Oatp1b2$^{-/-}$ mice survived, compared with 3 of 6 wild-type mice
		Rifampicin 3 mg/kg SC	Fourfold decrease in liver-to-plasma ratio at 0.5 h and 2 h
		Rifamycin SV 3 mg/kg SC	No significant change in liver-to-plasma ratio at 0.5 h and 2 h
		Cerivastatin 3 mg/kg SC	No significant change in liver-to-plasma ratio at 0.5 h and 2 h
		Lovastatin acid 3 mg/kg SC	1.5-Fold decrease in liver-to-plasma ratio at 0.5 h and 2 h
		Pravastatin 3 mg/kg SC	2.5-Fold increase in liver-to-plasma ratio at 2 h
		Simvastatin acid 3 mg/kg SC	No significant change in liver-to-plasma ratio at 0.5 h and 2 h
Slco1a/1b Oatp1a/1b	Liver, kidney, small intestine, brain, testes	Methotrexate 10 mg/kg IV	4.8-Fold increase in plasma AUC
		Methotrexate 10 mg/kg oral	3.8-Fold increase in plasma AUC
		Fexofenadine 1 mg/kg IV	3.3-Fold increase in plasma AUC
		Fexofenadine 1 mg/kg oral	4.6-Fold increase in plasma AUC
		Paclitaxel 10 mg/kg IV	Twofold increase in plasma AUC; twofold decrease in liver AUC

DeGorter M and Kim RB, Clin Pharmacol Ther 2011

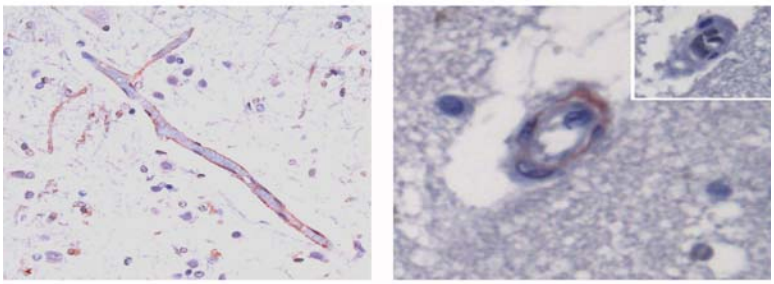
Oat, Oct, and Mate1 KO mice

Slc22a6 Oat1	Kidney (basolateral); Choroid plexus (apical)	Furosemide 0.1–10 mg/kg IV	Fourfold increase in ED_{50}
		Bendroflumethiazide 0.003–1 mg/kg IV	Threefold increase in ED_{50}
Slc22a8 Oat3	Kidney (basolateral); choroid plexus (apical)	Furosemide 0.1–10 mg/kg IV	Threefold increase in ED_{50}
		Bendroflumethiazide 0.003–1 mg/kg IV	Twofold increase in ED_{50}
		Penicillin G 1.87 µg/kg IV	Two- and threefold increase in plasma AUC in male and female mice, respectively
		Ciprofloxacin 5 mg/kg IV	1.25-Fold increase in plasma AUC
		Methotrexate 1.7 mg/kg IV	Reduced clearance in female $Oat3^{-/-}$ mice
		Ro 64-0802 (Oseltamivir) 1 mmol/l intracerebral injection	Threefold increase in brain concentration after 2 h
Slc22a1 Oct1	Kidney, liver, intestine (basolateral)	Metformin 5 mg/kg IV; 150 mg/h/kg IV infusion; 50 mg/kg IP (5 days)	30-Fold reduction in liver concentration after 10 min; protection from metformin-induced lactic acidosis; no effect on fasting plasma glucose levels
		Cisplatin 10 mg/kg IP	No significant change
Slc22a2 Oct2	Kidney (basolateral)	Cisplatin 10 mg/kg IP	No significant change
Slc22a1/2 Oct1/2		Cisplatin 10 mg/kg IP	Twofold decrease in total urinary excretion, no change in plasma AUC
Slc47a1 Mate1a/1b	Kidney (apical)	Metformin 5 mg/kg IV	Twofold increase in plasma AUC after 60 min
		Cisplatin 0.5 mg/kg IV; 15 mg/kg IP	Significant increase in plasma and renal concentration after 1 h; increase in nephrotoxicity after 3 days
		Cephalexin 5 mg/kg IV	1.5-Fold increase in plasma AUC

DeGorter M and Kim RB, Clin Pharmacol Ther 2011

OATPs and CNS Drug Entry?

OATP1A2 is expressed at the level of the BBB



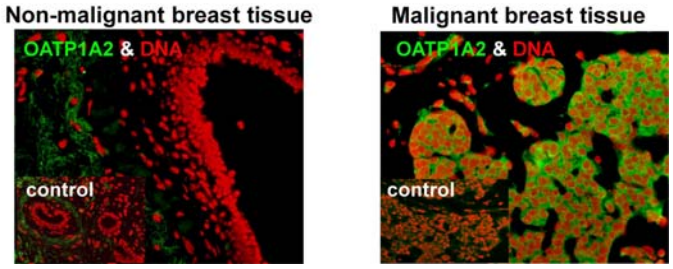
Lee et al, J.Biol.Chem. 2005

OATP1A2

Category	Substrate	Inhibitor
Bile salts	Taurocholate	Ursodeoxycholate, tauroursodeoxycholate, aurochenodeoxycholate, ursodeoxycholate, indocyanine green, glycocholate, cholate, chenodeoxycholate
	Cholate, glycocholate, TCDCA, TUDCA	
Hormones	DHEAS	Tauroursodeoxycholate, taurochenodeoxycholate, E-3-S, dexamethasone
	$E_2$17βG	Bilirubin
	Unconjugated bilirubin	$E_2$17βG
	E-3-S, T_4, T_3, rT_3	
Peptides	Deltorphin II	Naltrindole, naloxone, Leu-enkephalin, E-3-S, DPDPE
	BQ-123, CRC-220, DPDPE	
Organic anions	BSP	Rifampin, rifamycin SV, ouabain, tauroursodeoxycholate, ursodeoxycholate, taurocholate, taurochenodeoxycholate, indocyanine green, glycocholate, cholate, chenodeoxycholate
Organic cations	APD-ajmalinium, *N*-methylquinine, *N*-methylquinidine, rocuronium	
Drugs	Fexofenadine	Grapefruit juice (naringin), orange juice (hesperidin), apple juice, verapamil, saquinavir, ritonavir, quinidine, PSC-833, nelfinavir, lovastatin, ketoconazole, indinavir, erythromycin
	Ouabain	Taurochenodeoxycholate
	Imatinib	Uremic toxins (CMPF)
	Rocuronium	Taurocholate, quinidine, *N*-methylquinidine, K-strophantoside, Azidoprocainamide methiodide
	Chlorambuciltaurocholate, Gd-8 20790, erythromycin, levofloxacin, pitavastatin, pravastatin, rosuvastatin, saquinavir, D-penicillamine, bamet-UD2, bamet-R2, bromosulfophthalein, unprostone, methotrexate	
Toxins	Microcystin	
Eicosanoids	Prostaglandin E_2	

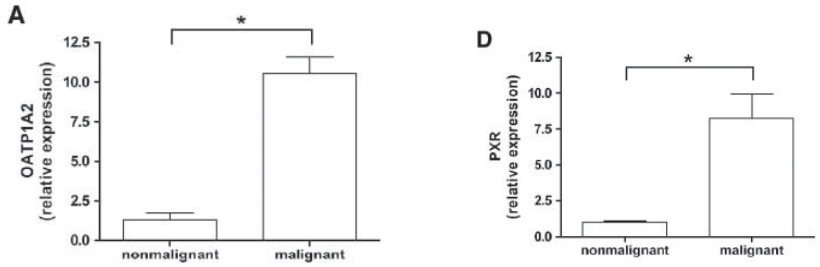
OATPs and Breast Cancer

OATP1A2 is Expressed in Breast Cancer



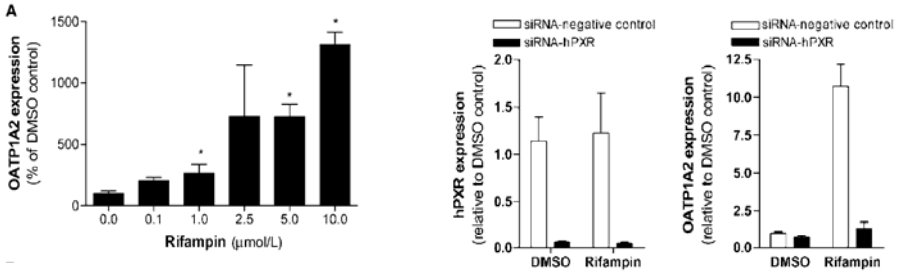
Meyer zu Schwabedissen et al Cancer Res 2008

OATP1A2 and PXR go together



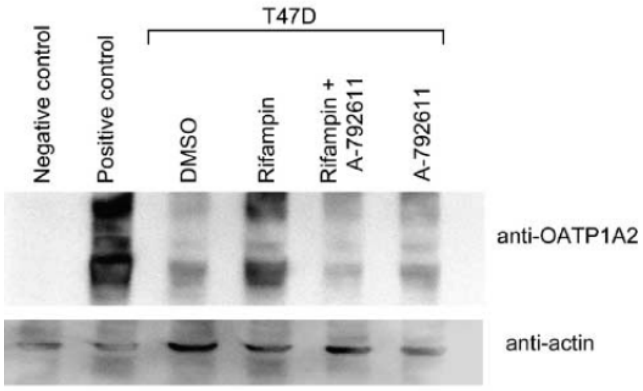
Meyer zu Schwabedissen et al Cancer Res 2008

Modulation of PXR alters OATP1A2 Expression



Meyer zu Schwabedissen et al Cancer Res 2008

PXR antagonist A792611 reduces PXR effect on OATP1A2 expression



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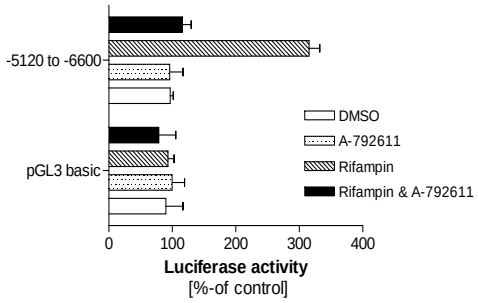
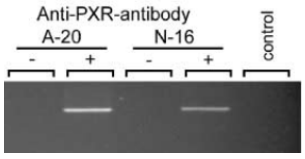
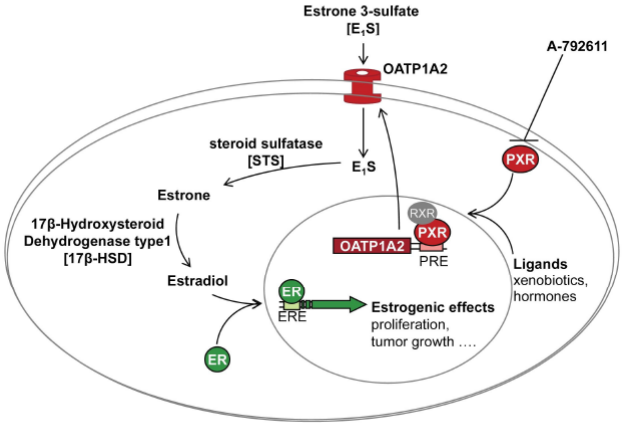
OATP1A2 is regulated by PXR





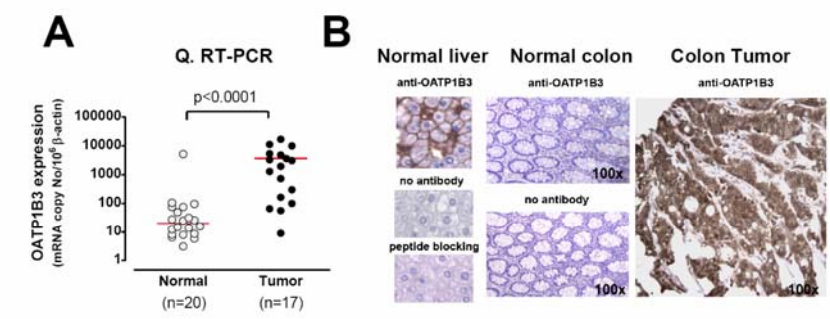
PXR, OATP and Breast Cancer Proliferation



Meyer zu Schwabedissen et al Cancer Res 2008

OATPs and Colon Cancer

Expression of OATP1B3 in Colon Cancer

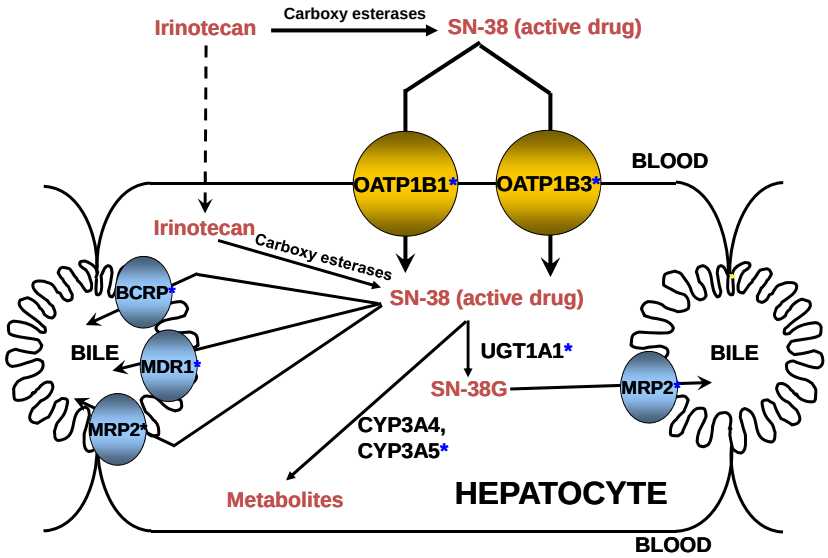


Lee et al, Cancer Res., 2008

OATPs and Irinotecan (CPT-11) Chemotherapy

- Topoisomerase I inhibitor used to treat colorectal cancer.
- Active drug, SN-38 undergoes hepatic transport and metabolism.
- Emerging evidence suggest hepatic OATP1B1 and 1B3 transporters affect SN-38 uptake and disposition.

Irinotecan Disposition Pathway



OATPs and Statin Therapy

30 million Americans take them everyday…..

Case Study

- 52 yr old female, renal failure secondary to polycystic kidney disease, underwent renal transplant in 1996.
- Presents in May 1999 complaining of myalgia and muscle weakness.
- From Dec 1996 to Nov 1998, had been on simvastatin (10 mg/day) without any side effects.
- April 1999, switched to cerivastatin 0.1 mg/day. Also on cyclosporine, mycophenolate, prednisone, and ranitidine.

Rodriguez *et al* Ann Int Med 132:598, 2000

Case Study

- On admission, CK 12,615 U/L.
- Cerivastatin discontinued.
- CK level normalizes in 10 days.

Rodriguez *et al* Ann Int Med 132:598, 2000

In vivo human relevance

Functional Polymorphisms in OATP1B1 (OATP-C)

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 276, No. 38, Issue of September 21, pp. 35669–35675, 2001

Printed in U.S.A.

Polymorphisms in *OATP-C*

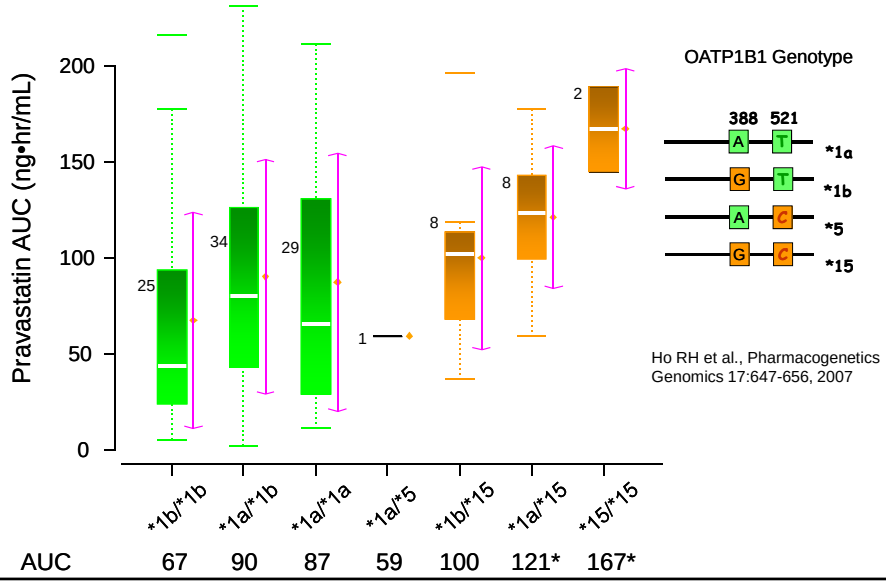
IDENTIFICATION OF MULTIPLE ALLELIC VARIANTS ASSOCIATED WITH ALTERED TRANSPORT ACTIVITY AMONG EUROPEAN- AND AFRICAN-AMERICANS*

Received for publication, April 27, 2001, and in revised form, June 28, 2001
Published, JBC Papers in Press, July 26, 2001, DOI 10.1074/jbc.M103792200

Rommel G. Tirona, Brenda F. Leake, Gracia Merino, and Richard B. Kim‡

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6602

Impact of OATP1B1 Haplotypes to Pravastatin Pharmacokinetics



Ho RH et al., Pharmacogenetics Genomics 17:647-656, 2007

Genetics and Statin-Induced Muscle Injury

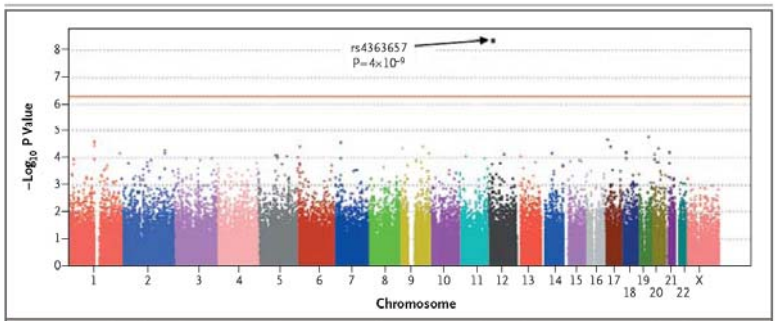


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

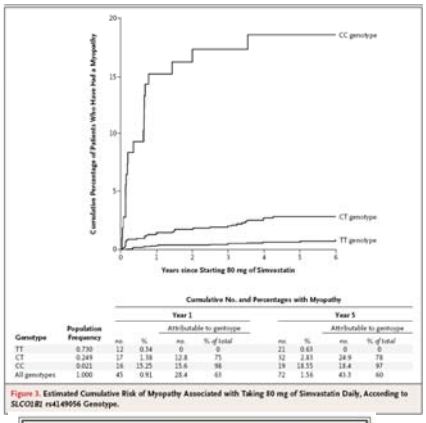
P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

The NEW ENGLAND JOURNAL of MEDICINE

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

Aug, 2008

The genetic defect turned out to be one my group had first identified in 2001



Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1		Year 1 Attributable to genotype		Year 5		Year 5 Attributable to genotype	
		no.	%	no.	% of total	no.	%	no.	% of total
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	52	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Figure 3. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype.

The NEW ENGLAND JOURNAL of MEDICINE

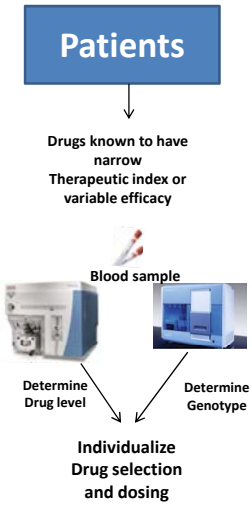
Aug, 2008

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

What about clinical relevance?

Our Group's Approach



FRIDAY, SEPTEMBER 12, 2008 ■ THE LONDON FREE PRESS LOCAL | A3

lfp LOCAL

HEALTH CARE: A person's genetic makeup is used to help determine treatment options

New clinic glimpse of future

BY JOHN MINER

London has taken a pioneering step into the world of personalized medicine, opening a hospital clinic that will decipher an individual's genetic code to determine their dose of a blood-thinning drug.

More such clinics using a person's genetic makeup to decide specific treatments will be opened in the city in the coming months, including possibly one for cancer.

"This will be one of many. This is the future of therapeutics for London health sciences and for Canada," said Dr. David Hollomby, chief of medicine and senior medical director at London Health Sciences Centre.

The clinic at University Hospital will serve patients referred by their family doctors, who have irregular heart beats and would be candidates for the blood thinner warfarin.

Though, it can be highly effective in preventing potentially fatal blood clots, warfarin reacts differently in individuals. A dose that would help one individual can be fatal for another.

Traditionally, doctors have worked on a trial and error basis, prescribing a particular dose and then monitoring the patient to see if it works.

"The ability of personalized medicine to understand before we start therapy how a patient is likely to react is an enormous step forward, both in terms of making sure we treat the patient appropriately or that we improve patient safety and we avoid complications," Hollomby said.

Earlier this year, Lawson Health Research Institute scientists Richard Kim and Ute Schwarz published their discovery that two genes were primarily responsible for the different individual reaction.

Patients referred to the clinic will have blood taken and their DNA tested. That information will be used to prescribe their individual warfarin dose.

Kim said patients will still have to be monitored, but using the genetic information will give doctors a head start in finding the right dose.

"It is in fact ready for prime time," said Kim, who was recruited with his renowned research team from Vanderbilt University School of Medicine in Nashville two years ago.

Often patients wonder how research will actually improve their health care. This can serve as an example, Kim said.

James Koropatnick, director of the cancer research program at the Lawson Health Research Institute, said he is excited about the prospects for using genetic information for cancer treatments.

The development of personalized medicine will benefit both individual patients and the health-care system, said Neil Johnson, vice-president of medical services for LHSC.

Adverse drug reactions are responsible for about 6,800 visits by patients to the city's emergency departments each year and the admission of 1,600 to 1,700 people to hospital.

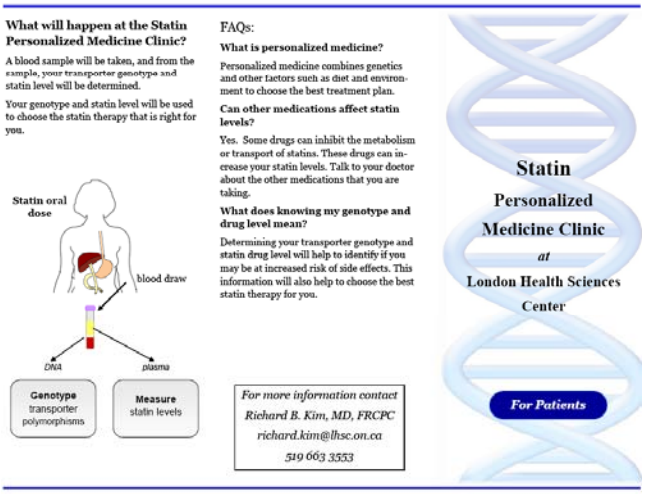
"It is a real issue, it is a real problem for health care in general. That's why we feel so strongly that personalized medicine for the benefit of our patients and the benefit of the health system is the way we will be going in the future," Johnson said.

John Miner is a Free Press health reporter.

SUE REEVE

Scientist Richard Kim speaks at yesterday's launch of the oral anti-coagulation clinic at University Hospital.

We have a Personalized Statin Clinic



What will happen at the Statin Personalized Medicine Clinic?

A blood sample will be taken, and from the sample, your transporter genotype and statin level will be determined.

Your genotype and statin level will be used to choose the statin therapy that is right for you.

Statin oral dose

blood draw

DNA

plasma

Genotype transporter polymorphisms

Measure statin levels

FAQs:

What is personalized medicine?

Personalized medicine combines genetics and other factors such as diet and environment to choose the best treatment plan.

Can other medications affect statin levels?

Yes. Some drugs can inhibit the metabolism or transport of statins. These drugs can increase your statin levels. Talk to your doctor about the other medications that you are taking.

What does knowing my genotype and drug level mean?

Determining your transporter genotype and statin drug level will help to identify if you may be at increased risk of side effects. This information will also help to choose the best statin therapy for you.

For more information contact
Richard B. Kim, MD, FRCPC
richard.kim@lhsc.on.ca
519 663 3553

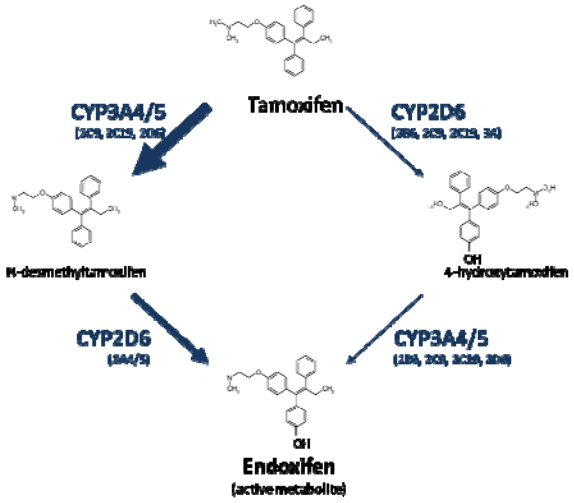
Statin
Personalized
Medicine Clinic
at
London Health Sciences Center

For Patients

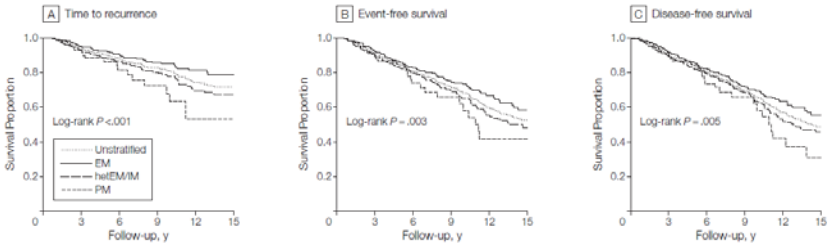
TAMOXIFEN PERSONALIZED MEDICINE CLINIC AT LHSC

When Considering Tamoxifen Therapy:
Request CYP2D6 Genotyping
or
Patients on Tamoxifen Therapy:
Request CYP2D6 Genotyping and Drug Level Analysis
(Must be on Tamoxifen for >1month)

Tamoxifen



CYP2D6 has a major impact to tamoxifen therapy



Schroth et al JAMA 302:1429-1436, 2009

Drug level and genetic testing at our clinic

Collect blood → Obtain Plasma → Extract DNA

Drug Level Analysis ↓

Genotyping ↓

TSQ Vantage

CYP2D6 and Clinical Relevance

Breast Cancer Therapy

Case

- 60 year old female, dx (R) breast cancer Aug 2008.
- ER/PR positive
- Chemo: FEC-D
- Tried aromatase inhibitor but discontinued due to side effects (arthralgia)
- Tamoxifen started April 2010
- Referred to Personalized Tamoxifen Clinic at UH

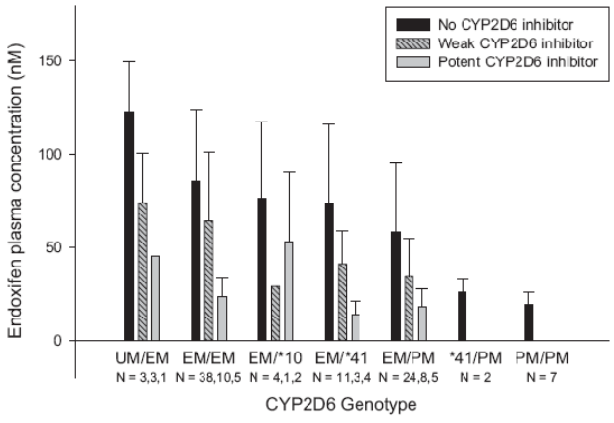
Current medications

- insulin 30/70 46 units BID
- furosemide 40 mg once a day
- enalapril 5 mg once a day
- bupropion 150 mg once a day
- Celebrex 200 mg once a day
- potassium supplement 600 mg once a day
- metformin 500 mg BID
- aspirin 81 mg once a day
- Lipitor 10 mg once a day
- calcium and vitamin D
- Ativan 1 mg QHS
- Mirapex 0.25 mg in the evening for restless leg syndrome

Genotype and drug levels

- Date of Blood Sample: August 4, 2010
  - CYP2D6 genotype: *1/*1
  - Tamoxifen level: 247 ng/ml (667 nM)
  - Endoxifen level: 3.85 ng/ml (10.3 nM)
- How do you interpret the genotype?
- Should you stay on tamoxifen?

CYP2D6 genotype and Endoxifen levels



CYP2D6 inhibitors:

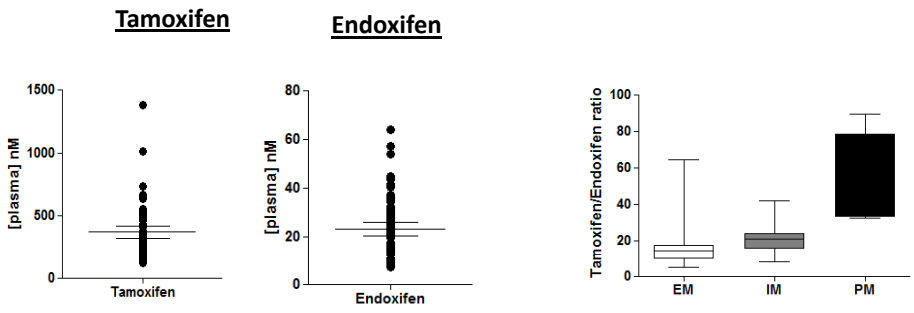
Minimal:
SSRI
venlafaxine
(Effexor)

Weak:
SSRI
sertraline
(Zoloft)
citalopram
(Celexa)

Strong:
SSRI
paroxetine
(Paxil)
fluoxetine
(Prozac)
buproprion
(Wellbutrin, Zyban)

Borges et al. 2006. Clin. Pharm. Ther. 80: 61

What have we learned from our clinic?

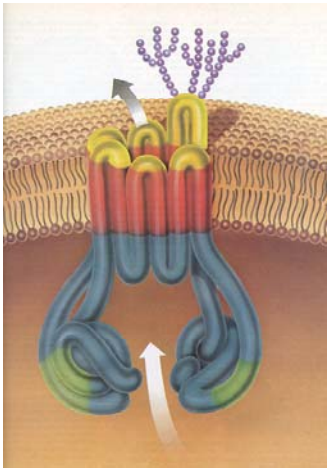


How is endoxifen eliminated from the body??

Drug Transporters

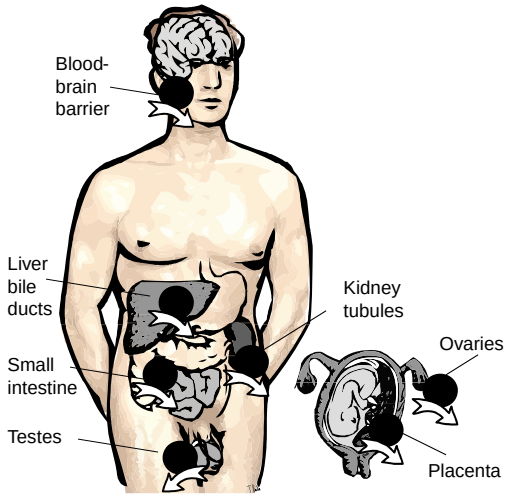
P-Glycoprotein

- ATP-dependent efflux pump encoded by *MDR1* gene in humans.
- Can actively extrude various anticancer agents from intracellular to extracellular compartment, thus preventing cell death.
- Expression in some cancer cells result in the phenomenon of multidrug resistance (MDR).



Kartner N and Ling V, *Sci Am* 1989;260(3):44-51

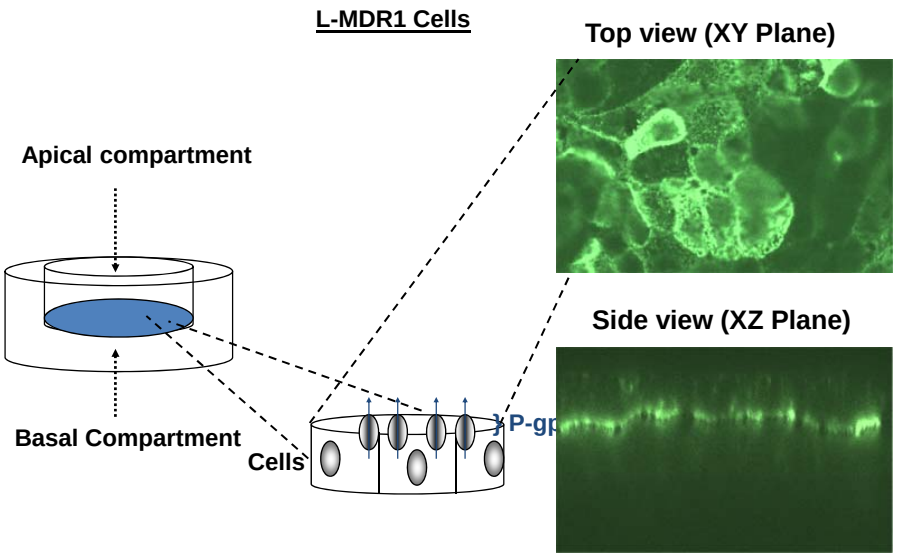
P-glycoprotein (MDR1) Expression



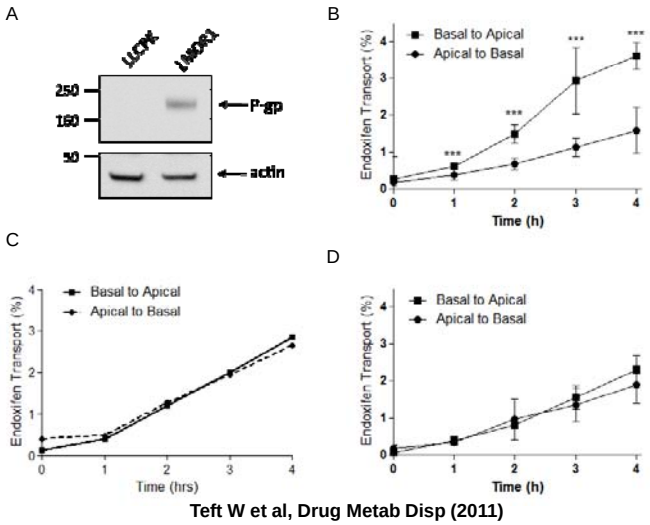
P-glycoprotein and Drug Interactions

- Substrates
  - Digoxin
  - Fexofenadine (Allegra)
  - Cyclosporine
  - Tacrolimus
  - Quinidine
  - Verapamil (but not nifedipine or felodipine)
  - Taxol
  - HIV protease inhibitors
  - Erythromycin
- Inhibitors
  - Quinidine
  - Verapamil
  - Ketoconazole
  - Itraconazole
  - Cyclosporine
  - HIV protease inhibitors
  - Erythrmycin
  - Clarithromycin
- **Inducers**
  - **Rifampin**
  - **St John's wort**

P-gp: Identifying Drug Substrates

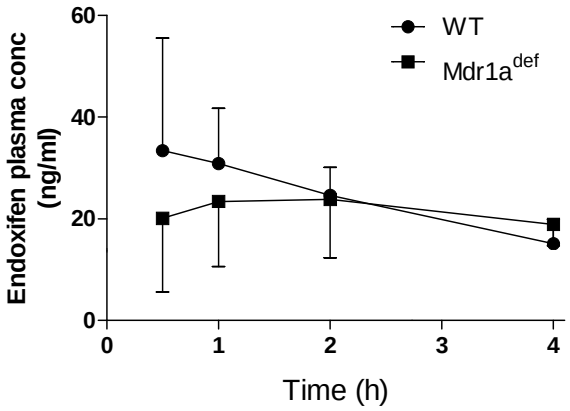


Exdoxifen is a P-gp substrate



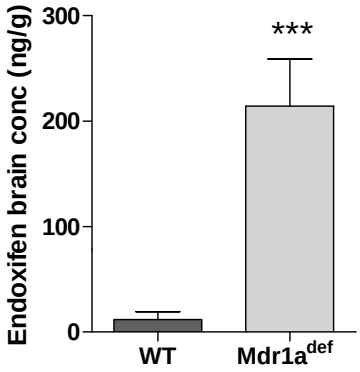
Teft W et al, Drug Metab Disp (2011)

Endoxifen Plasma Level in P-gp wildtype and deficient mice



Teft W et al, Drug Metab Disp (2011)

Brain endoxifen levels are far higher in P-gp deficient mice



Teft W et al, Drug Metab Disp (2011)

Conclusion

- Certain transporters have very broad substrate specificity.
- Drug uptake transporters should be considered earlier in the drug development process
- Many drug transporters exhibit tissue specific expression.
- Genetic variation in transporters exist.
- Drug transporters may be important to drug disposition and disease.
- Drug transporters could be targeted to enhance drug delivery
- Drug transporters are relevant to optimal drug therapy