Pharmacokinetic Determinants of Statin-Induced Myopathy

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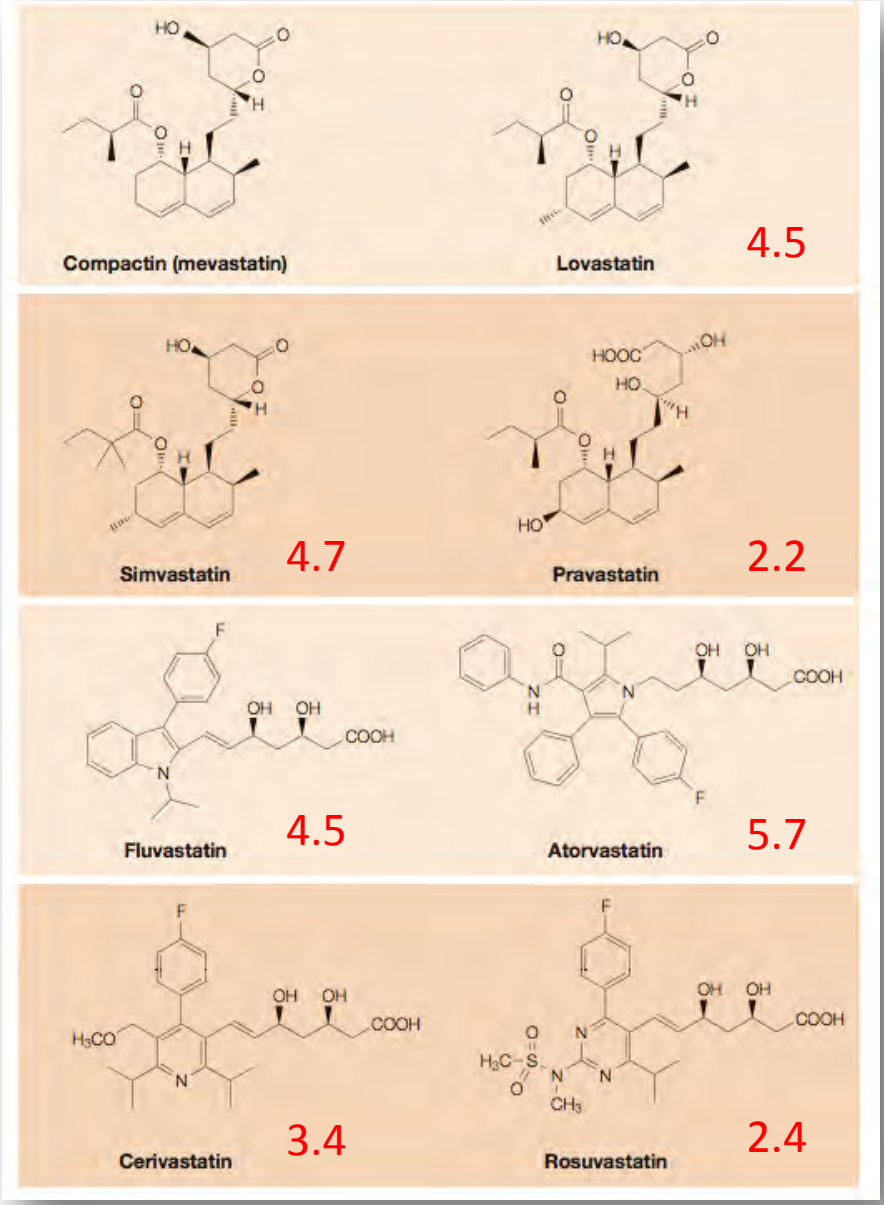
Statins

- HMG-CoA reductase inhibitors
- Inhibit biosynthesis of cholesterol
- Highly effective for the treatment of hypercholesterolemia, a major risk factor for cardiovascular disease
- Lactone and hydroxyacid forms
- Varying in lipophilicity



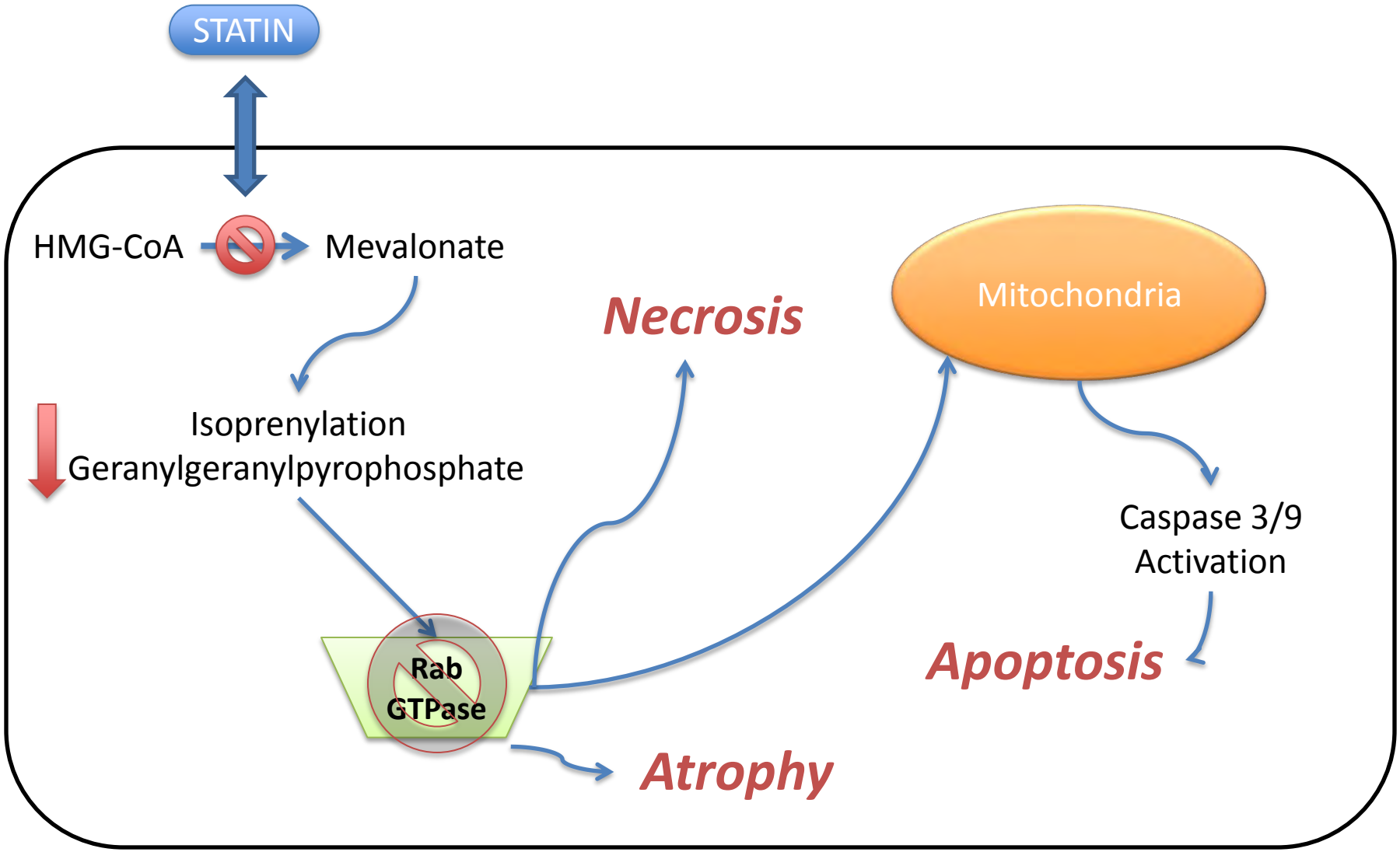
logP in red

Tobert, Nat Rev Drug Discov 2003

Statin-Associated Myopathy

- 30 million Americans on statin therapy
- Well tolerated
- Major complaint – Myalgia
  - Muscle pain/weakness
  - Affects 5-15% of treated patients
  - 3 million Americans experience skeletal muscle side effects
  - Muscle effects range from myalgia to rhabdomyolysis

Proposed Mechanisms of Statin-Associated Myopathy



Risk Factors for Statin-Associated Myopathy

Risk Factors

- Increased age
- Female sex
- Renal or hepatic impairment
- Hypothyroidism
- Small body frame and frailty
- Perioperative periods
- Statin Characteristics
  - Dose
  - Lipophilicity
  - Potential for metabolic drug interactions
- Co-medications
  - Other myotoxic drugs
  - Metabolic inhibitors of CYP or UGT

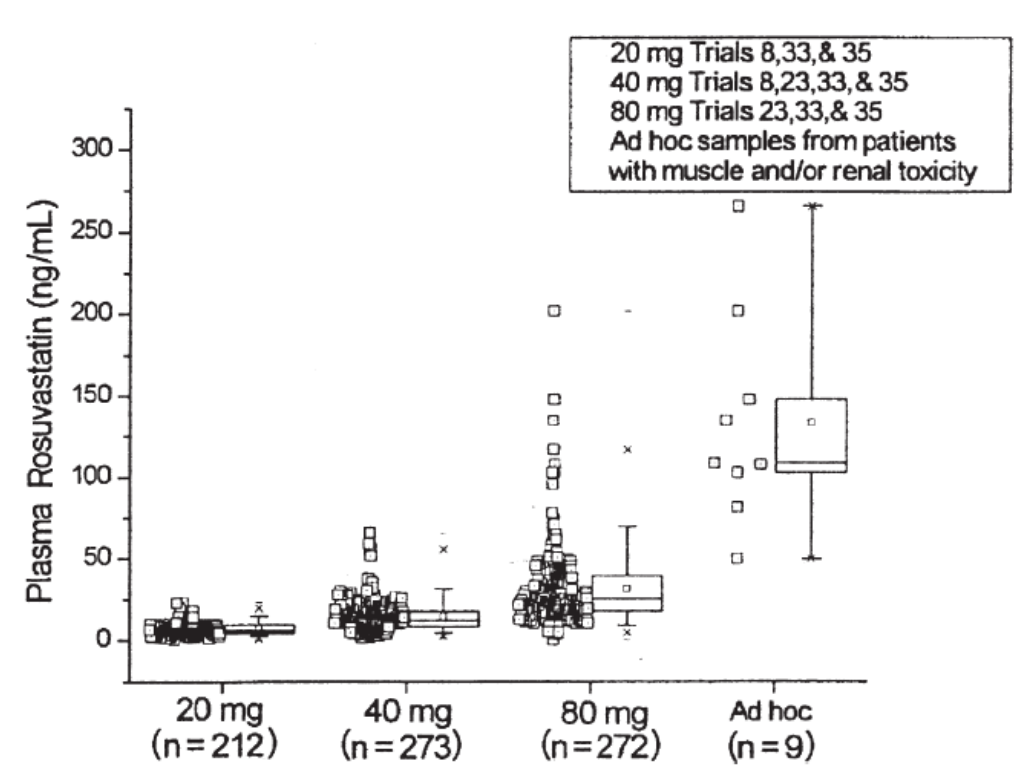
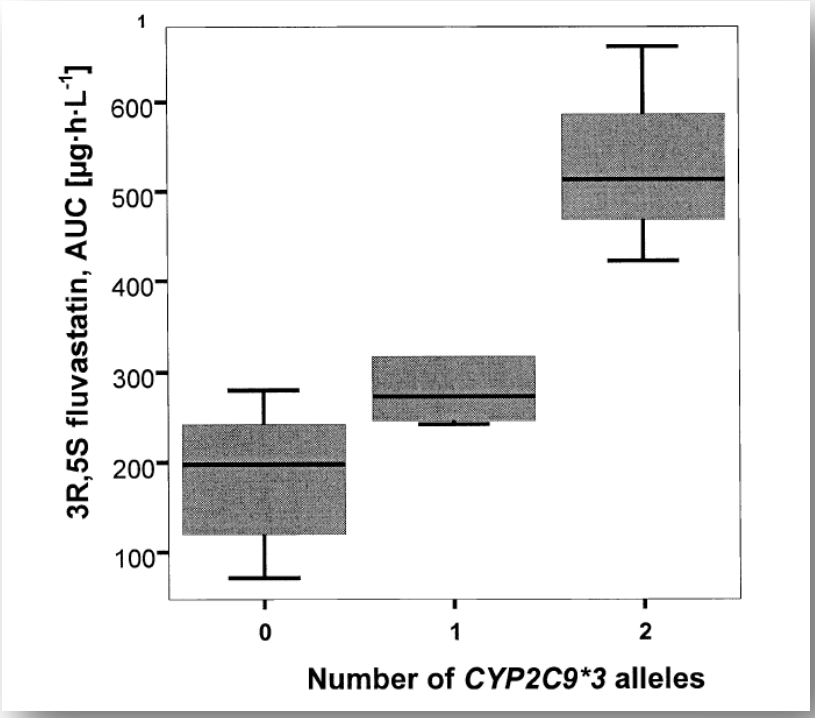


Figure 3. Plasma rosuvastatin concentrations by dose in 6 patients with rhabdomyolysis or renal toxicity. (Adapted from rosuvastatin New Drug Application.[25])

Jacobson, Am J Cardiol 2006

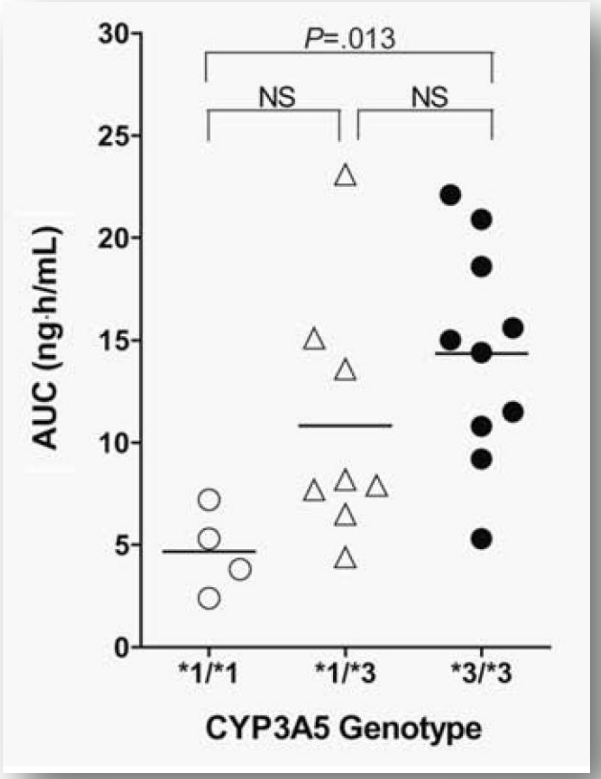
Cytochrome P450 Polymorphisms Associate with Statin Disposition

Fluvastatin



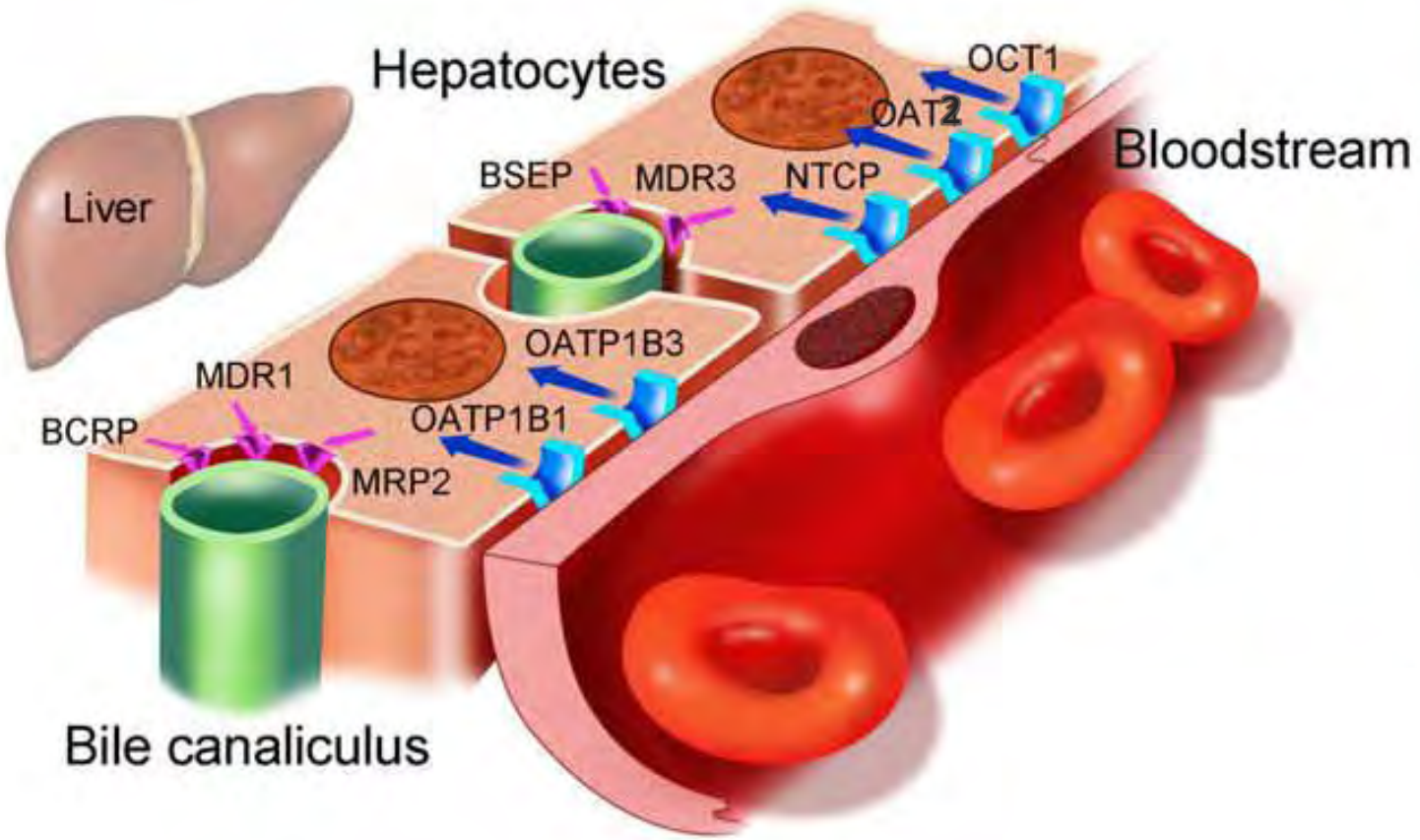
Kirchheiner et al., Clin Pharmacol Ther 2003.

Simvastatin



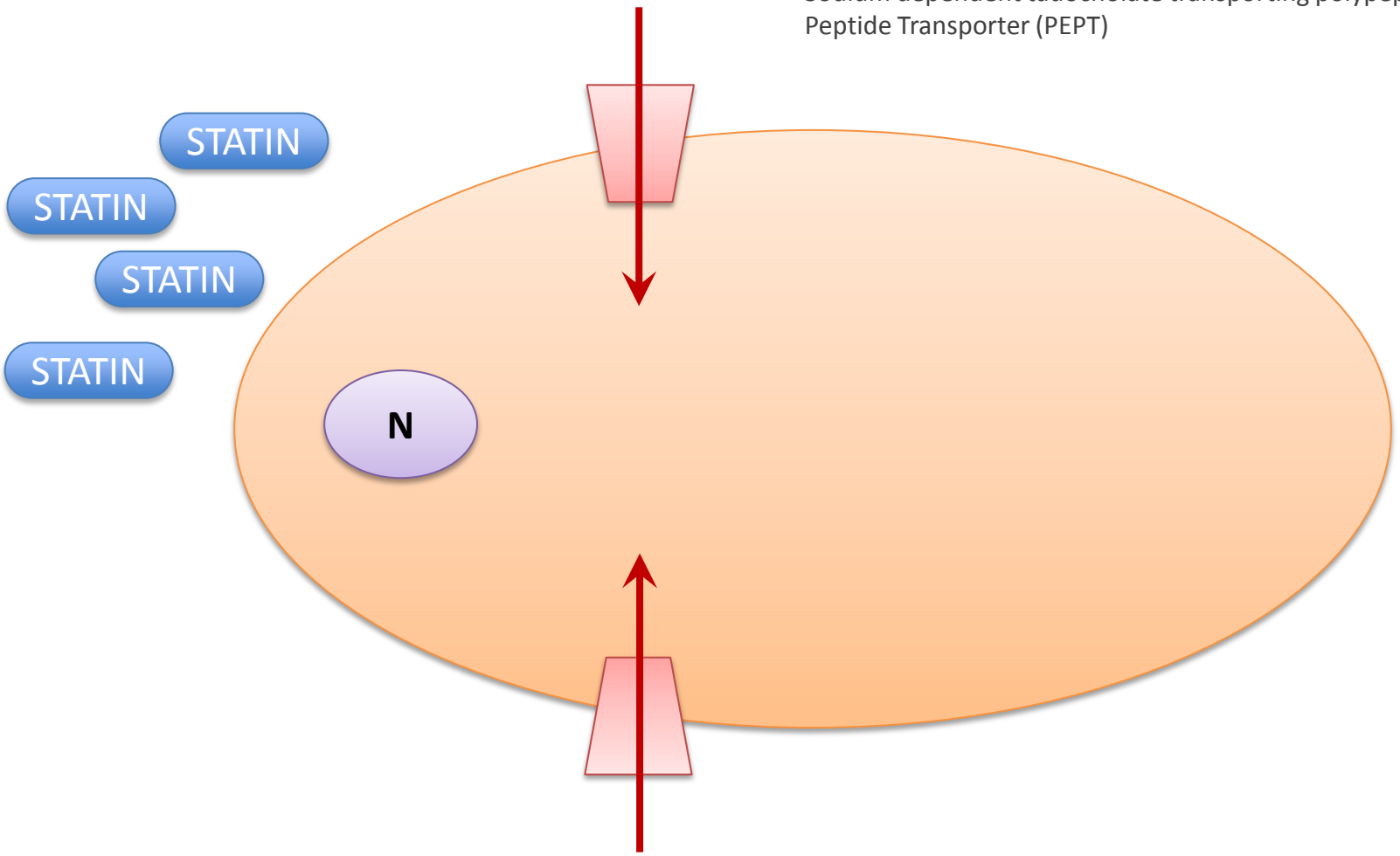
Kim et al., J Clin Pharmacol 2007.

Hepatic Drug Transporters

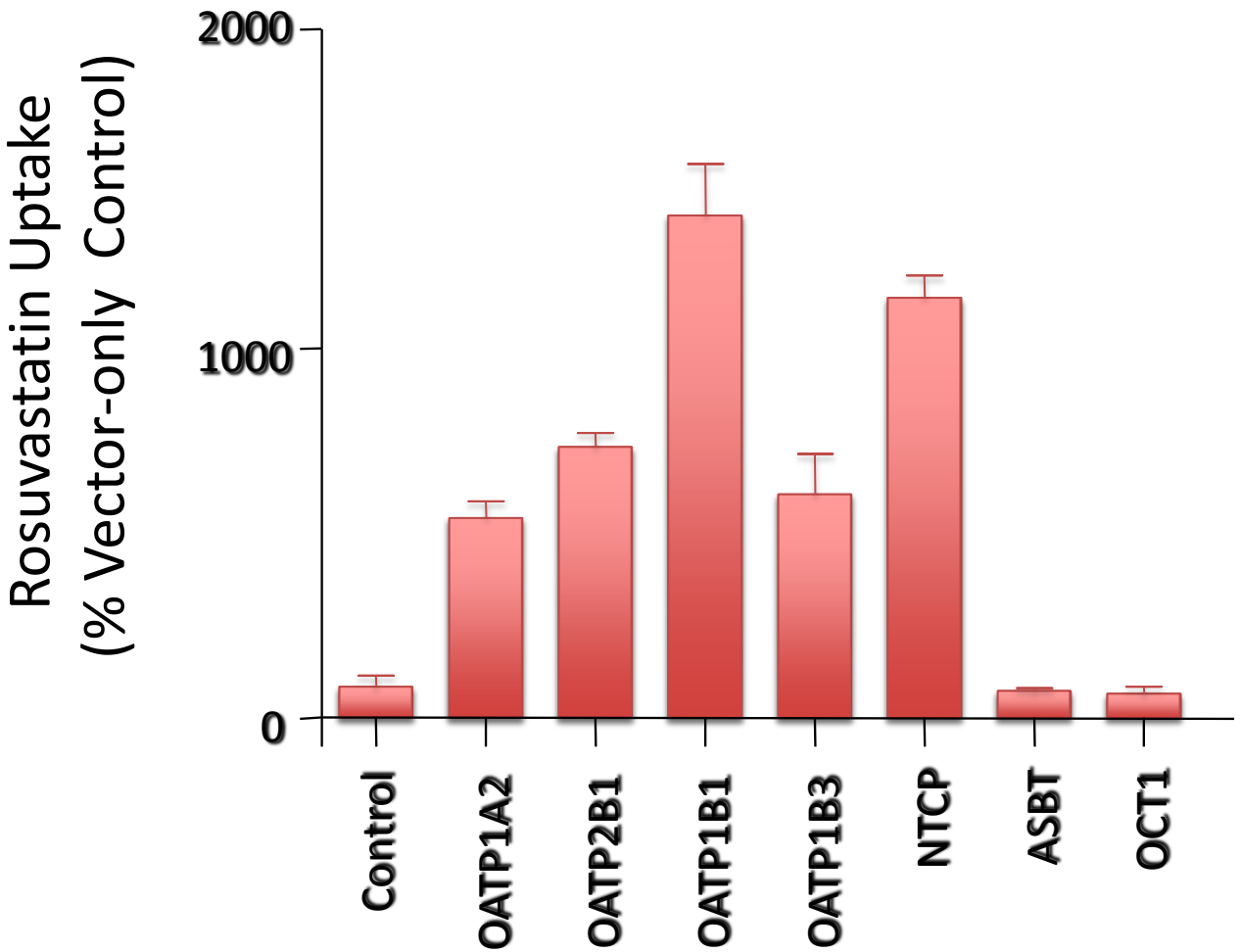


Uptake Transporters

Organic anion transporting polypeptides (OATP)
Organic anion transporter (OAT)
Organic cation transporter (OCT)
Sodium dependent tauocholate transporting polypeptide (NTCP)
Peptide Transporter (PEPT)



Rosuvastatin Uptake Transporters

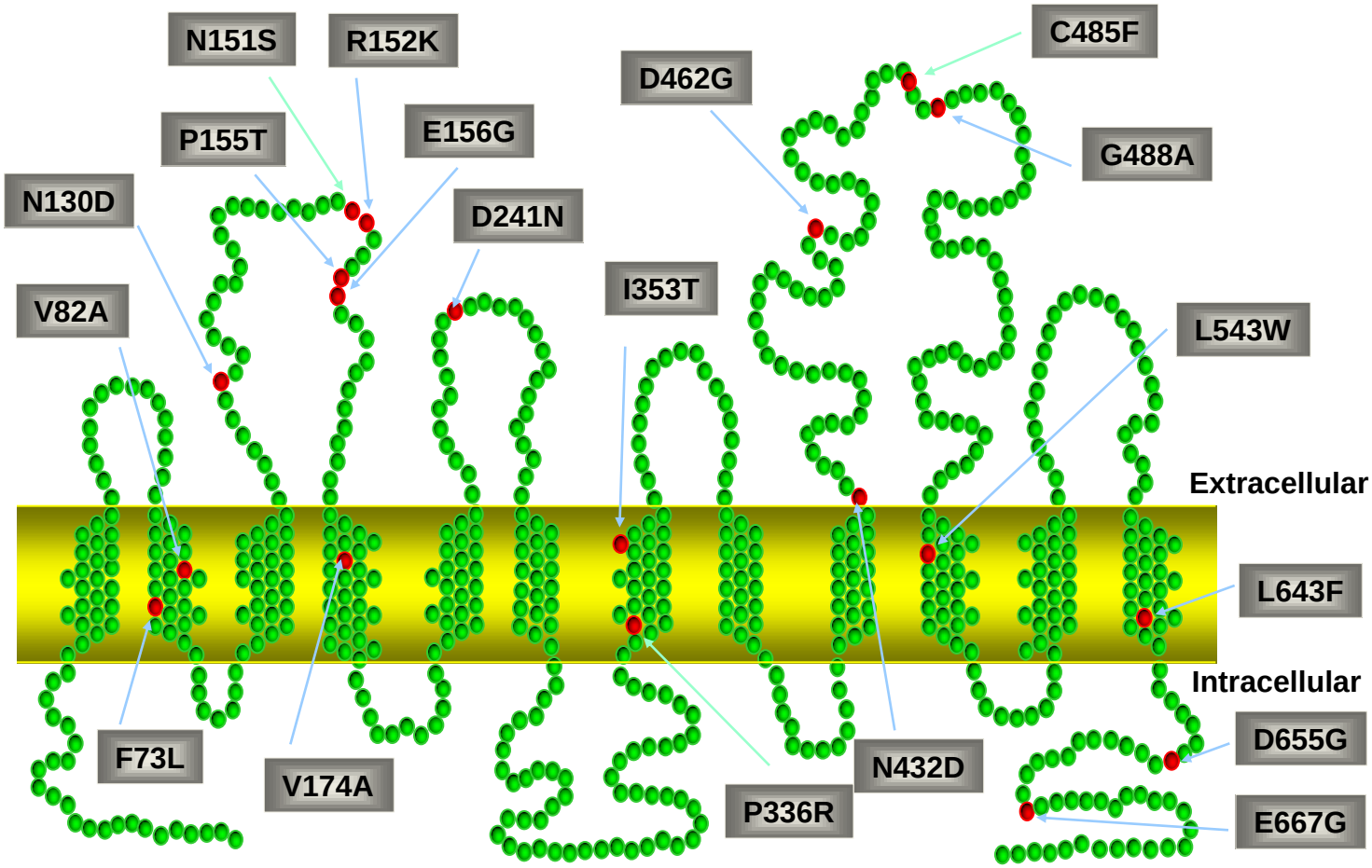


Ho et al., Gastroenterology 2006

Hepatic Statin Uptake Transporters

Transporter	Simvastatin Acid	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
OATP1A2				+	+	+
OATP1B1		+	+	+	+	+
OATP1B3			+	+	+	+
OATP2B1		+	+	+	+	
NTCP				+	+	+

OATP1B1 Variants

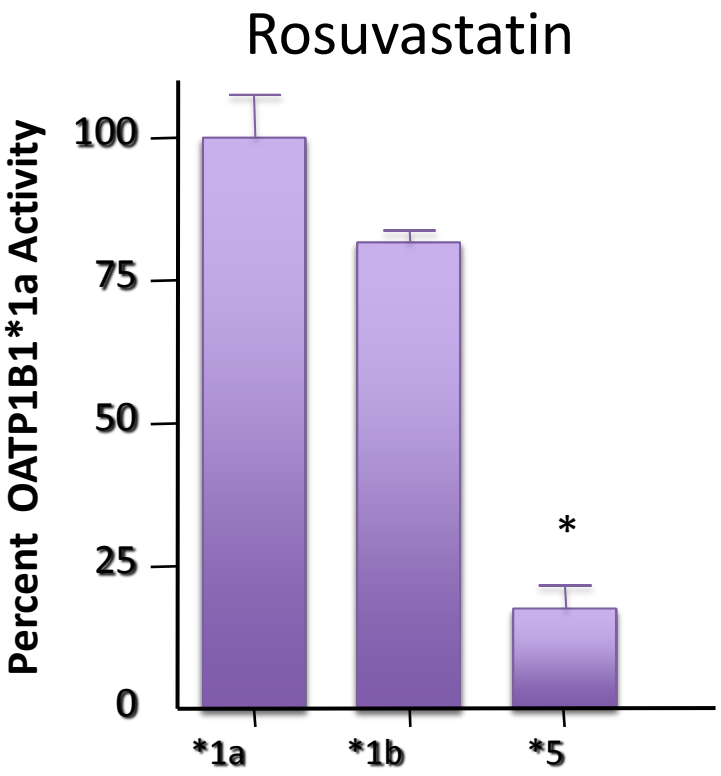


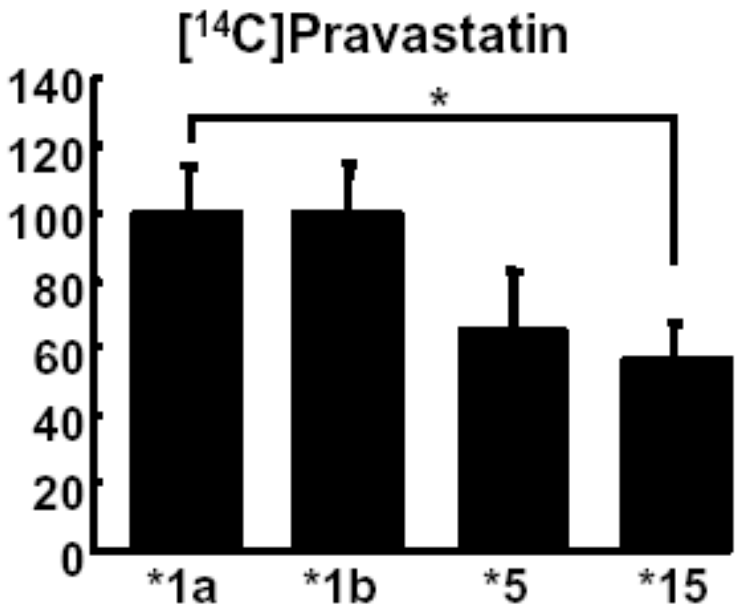
Tirona et al., J Biol Chem 2001

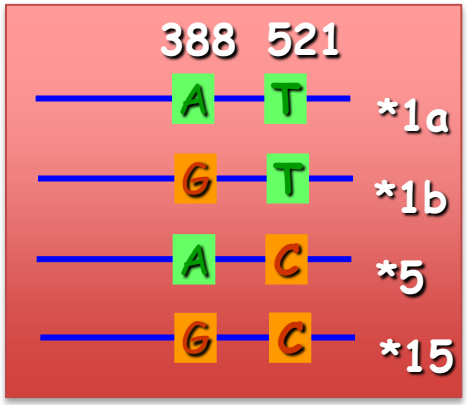
Allelic Frequencies of SLCO1B1 SNPs in Selected Populations

SNP	Frequency					
	African American	Caucasian American	Finnish	German	Japanese	South Asian
c.388G>A (N130D)	0.74	0.30	0.45	0.37	0.62	0.57
c.521T>C (V174A)	0.02	0.14	0.21	0.15	0.14	0.07
Reference	Tirona et al., 2001	Tirona et al., 2001	Niemi et al., 2004	Mwinyi et al., 2004	Nozawa et al., 2002 Nishizato et al., 2003	Jada et al., 2007

Decreased Statin Transport by OATP1B1 Variants

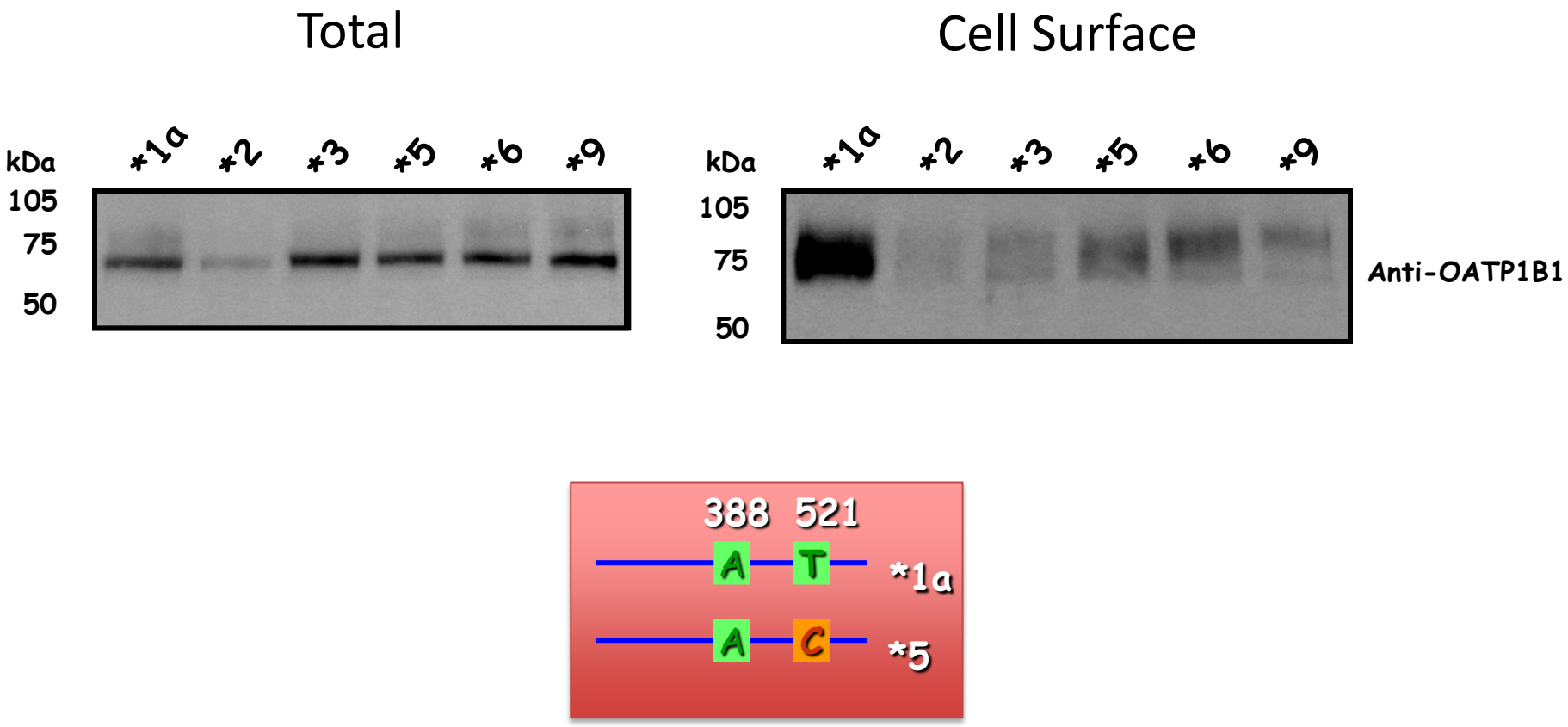






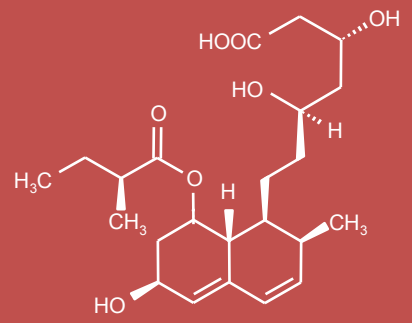
Ho et al., Gastroenterology 2006
Nozawa et al., Drug Metab Disp 2005

Membrane Trafficking Defect in OATP1B1 521C Variant

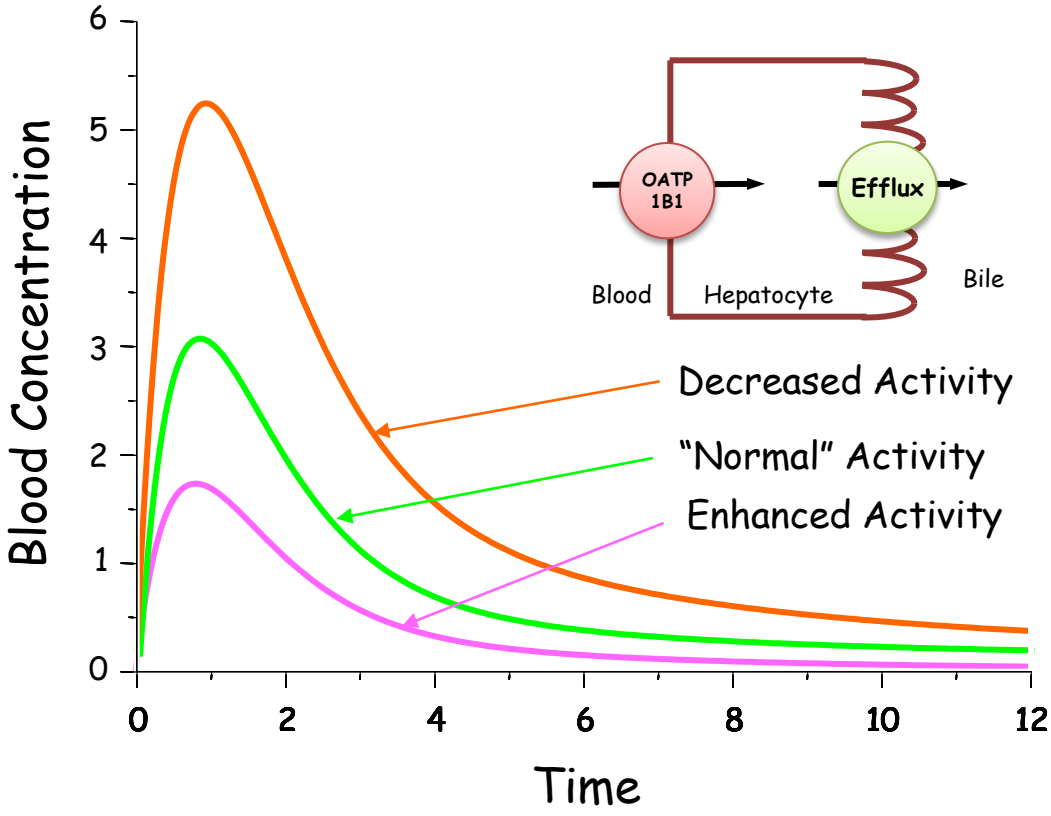


Tirona et al., J Biol Chem 2001

OATP1B1 Variants and Pravastatin Pharmacokinetics

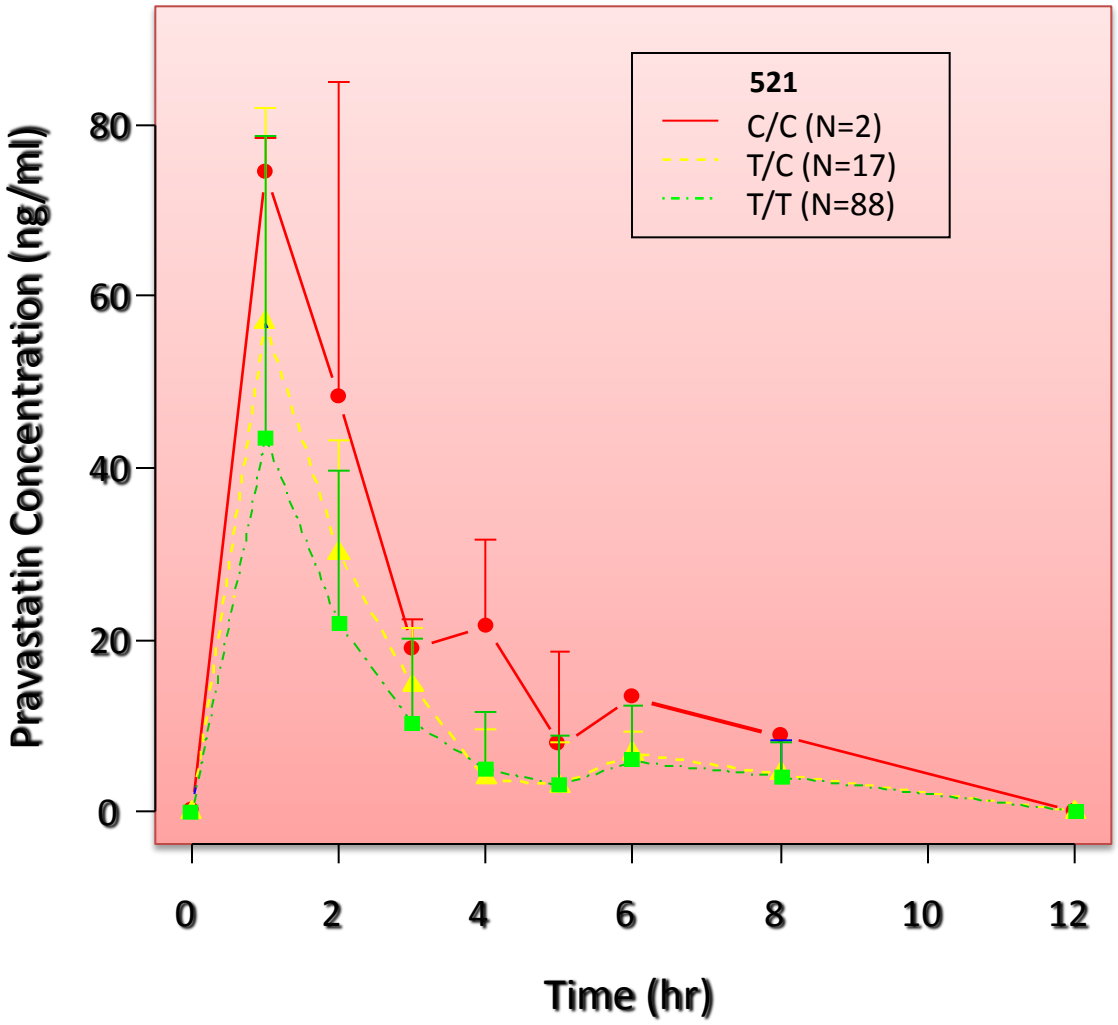


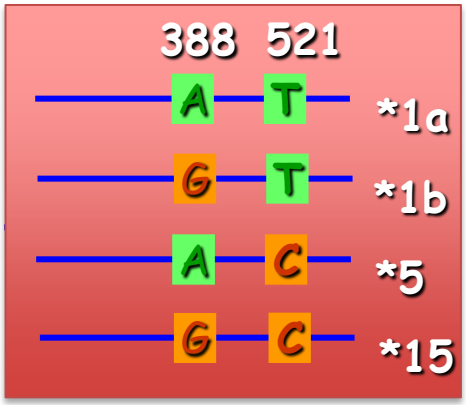
- hydrophillic "statin"
- OATP1B1, OATP2B1 and NTCP substrate
- high liver distribution
- uptake rate-limited
- wide interindividual variability
- not metabolized



(Hsiang et al., JBC 1999; Nakai et al., JPET 2001
Kobayashi et al., JPET 2003; Yamazaki et al., 1996/7;
Neuvonen et al., 1998)

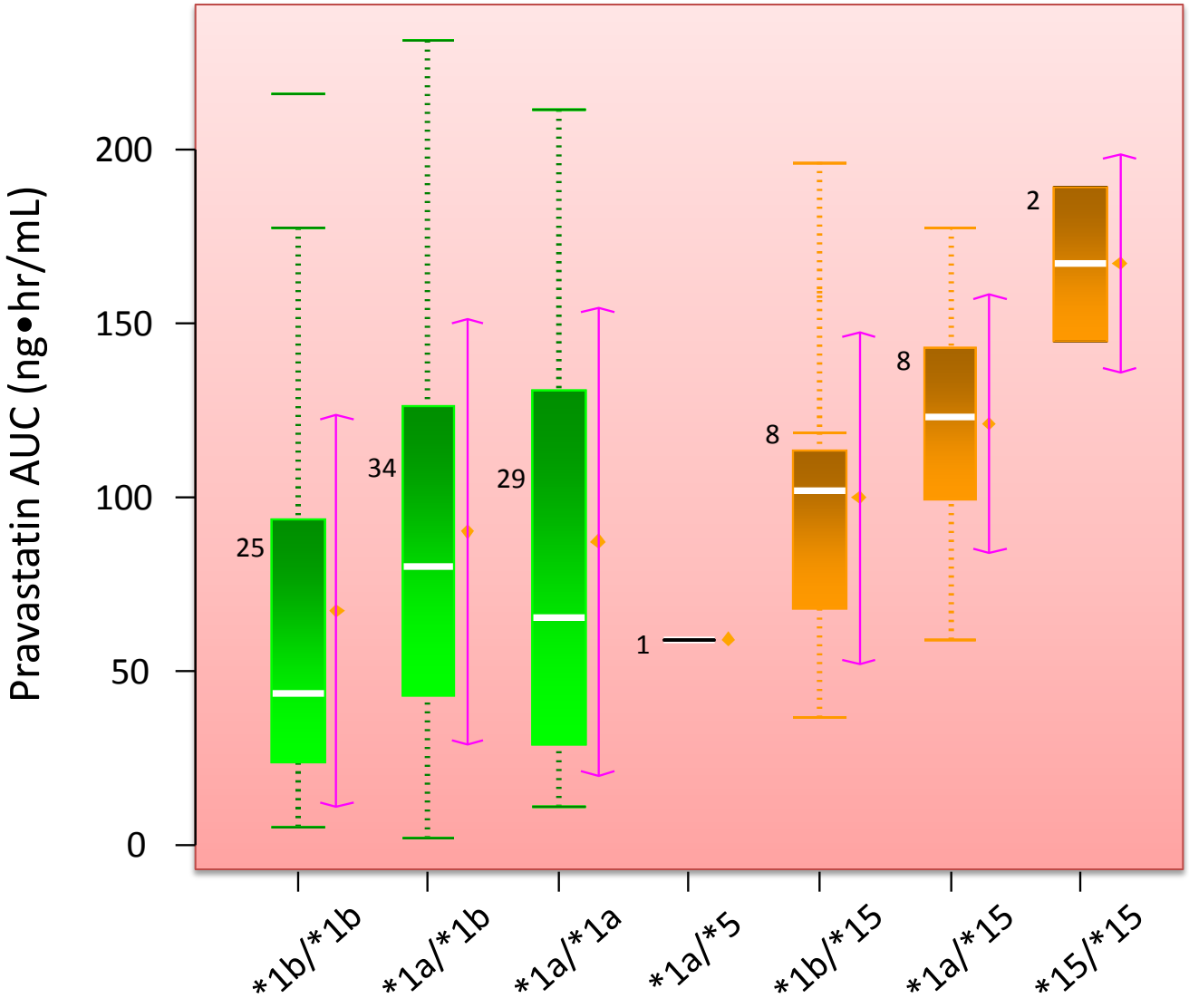
OATP1B1 521 Variants and Pravastatin Pharmacokinetics

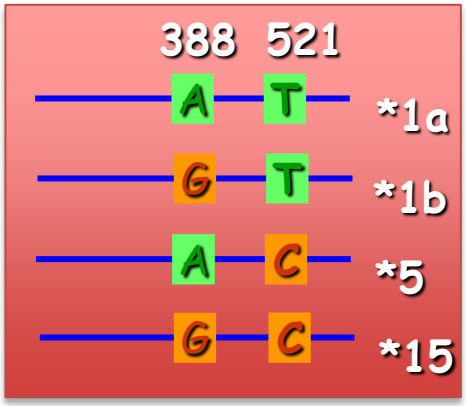




Ho et al., Pharmacogenet Genomics 2007

SLCO1B1 Haplotypes and Pravastatin Pharmacokinetics





Ho et al., Pharmacogenet Genomics 2007

Factors Associated with Pravastatin Exposure

Model covariates	P-value	R^2 (%)
Gender	<0.001	11.1
BSA	<0.001	12.2
Assay sensitivity	0.004	7.8
SLCO1B1 521T>C	0.031	6.5
Race	0.010	6.2
521T>C/Race	0.012	10.0
Gender/BSA/Assay sensitivity/521T>C/Race	<0.001	30.7

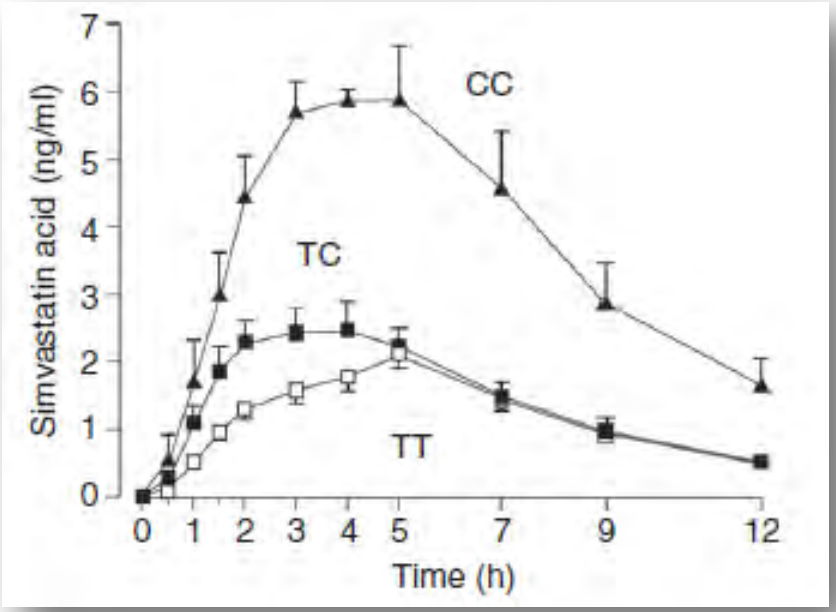
Ho et al., Pharmacogenet Genomics 2008

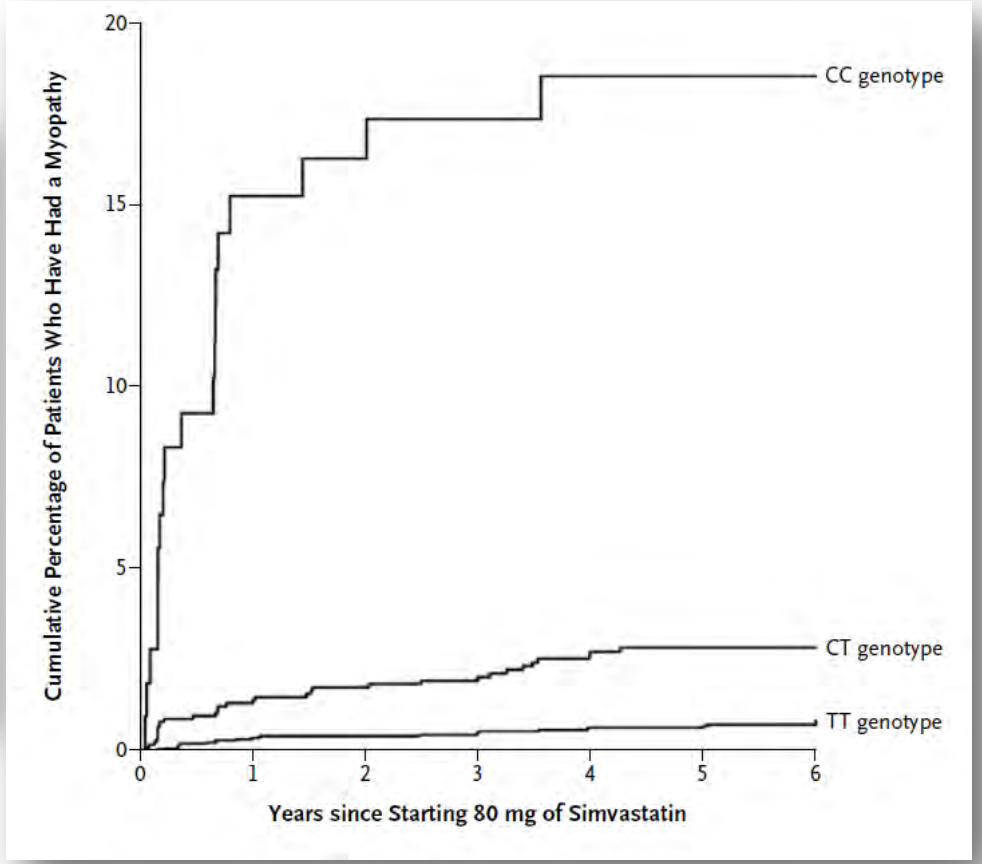
OATP1B1 521T>C Polymorphism Differentially Affects Statin Pharmacokinetics

Statin	Relative Exposure			Reference
	521TT	521TC	521CC	
Pravastatin	1	1.5	2.3	Ho et al., 2007
Simvastatin Acid	1	1.3	3.2	Pasanen et al., 2006
Fluvastatin	1	1.1	1.2	Pasanen et al., 2006
Atorvastatin	1	1.5	2.4	Pasanen et al., 2007
Rosuvastatin	1	1.6	1.6	Pasanen et al., 2007
Pitavastatin	1	1.8		Chung et al. 2005

SLCO1B1 Genetics Associates with Skeletal Muscle Side Effects of Simvastatin

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)



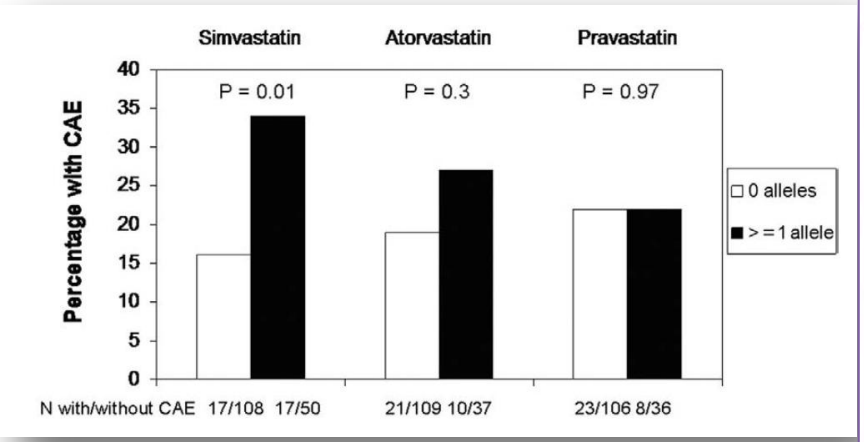


Niemi, Clin Pharmacol Ther 2009

Link et al., NEJM 2008

SLCO1B1 Genetics Associates with Skeletal Muscle Side Effects of Simvastatin

STRENGTH (Statin Response Examined by Genetic Haplotype Markers) Study



Statin Plasma Level (ng/mL)

Metabolite	*SLCO1B1* Genotype		
	*1/*1	*1/*5	*5/*5
Simvastatin acid (20 mg)	28 1.2 [0.5–2.1]	27 1.4 [0.7–2.9]	3 11.2 [7.9–17.2] 0.006*
Simvastatin lactone (20 mg)	28 0.5 [0.3–1.0]	27 0.4 [0.2–0.9]	3 0.4 [0.2–0.6]
Simvastatin acid (80 mg)	28 3.7 [1.3–5.3]	24 3.7 [1.6–9.2]	1 77.5 0.03*
Simvastatin lactone (80 mg)	28 1.1 [0.8–3.5]	24 1.4 [0.7–3.3]	1 3.7
Pravastatin acid (10 mg)	25 0.2 [0.07–0.5]	27 0.2 [0.1–0.5]	1 0.2
Pravastatin lactone (10 mg)	23 0.02 [0.01–0.03]	24 0.01 [0.01–0.02]	1 0.002
Pravastatin acid (40 mg)	26 1.0 [0.4–2.1]	27 1.0 [0.5–3.6]	N/A
Pravastatin lactone (40 mg)	26 0.07 [0.02–0.14]	27 0.05 [0.03–0.10]	N/A

Voora et al., JACC 2009

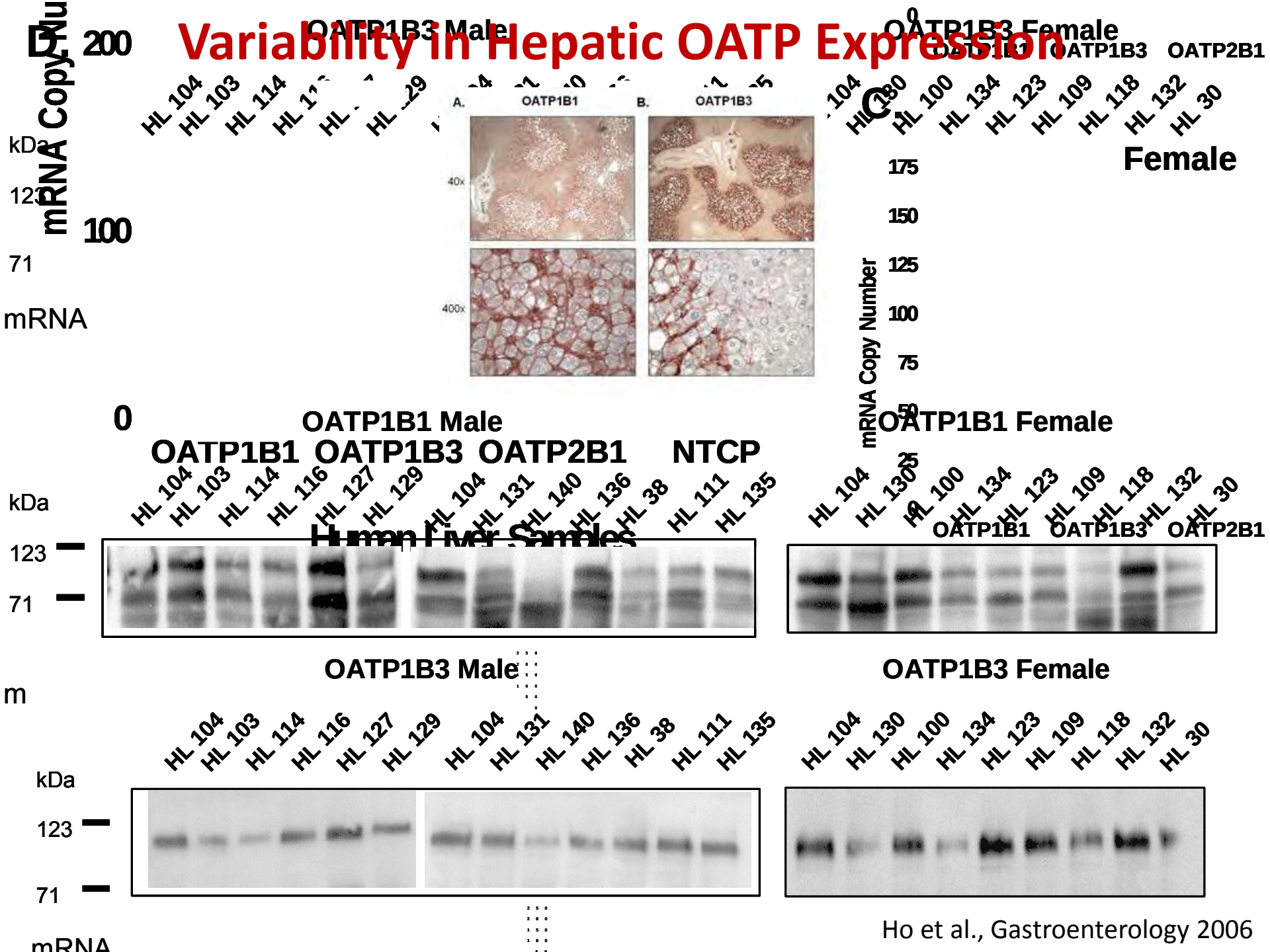
SLCO1B1 Genetics and Dose Recommendations

	SLCO1B1 c.521T>C genotype			
	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

Figure 3 Recommended maximum statin doses for Caucasian adult patients according to *SLCO1B1* genotype. Statin therapy should be started with the starting dose recommended by the manufacturer or half of the recommended maximum dose, whichever is lower. The dose should be titrated up to the minimum effective dose or the suggested maximum dose on the basis of lipid response and tolerability, and the statin should be changed or discontinued as necessary. Other factors known to affect statin pharmacokinetics or myopathy risk should be taken into account when selecting a statin and its dose for an individual patient (interacting drugs, concomitant diseases, age, etc.). *Based on US Food and Drug Administration–approved maximum doses; lower maximum doses may apply in some countries.

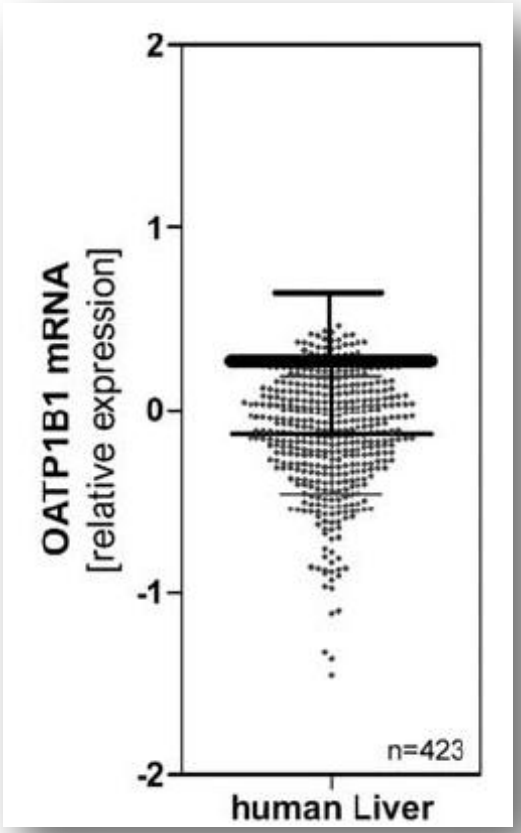
(Niemi, Clin Pharmacol Ther, Nov 2009)

Variability in Hepatic OATP Expression

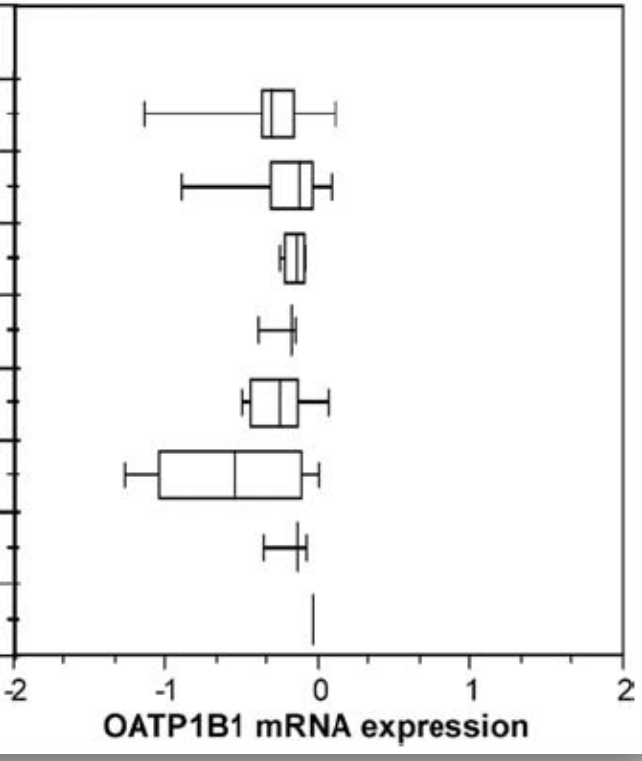


Ho et al., Gastroenterology 2006

Variability in Hepatic OATP Expression

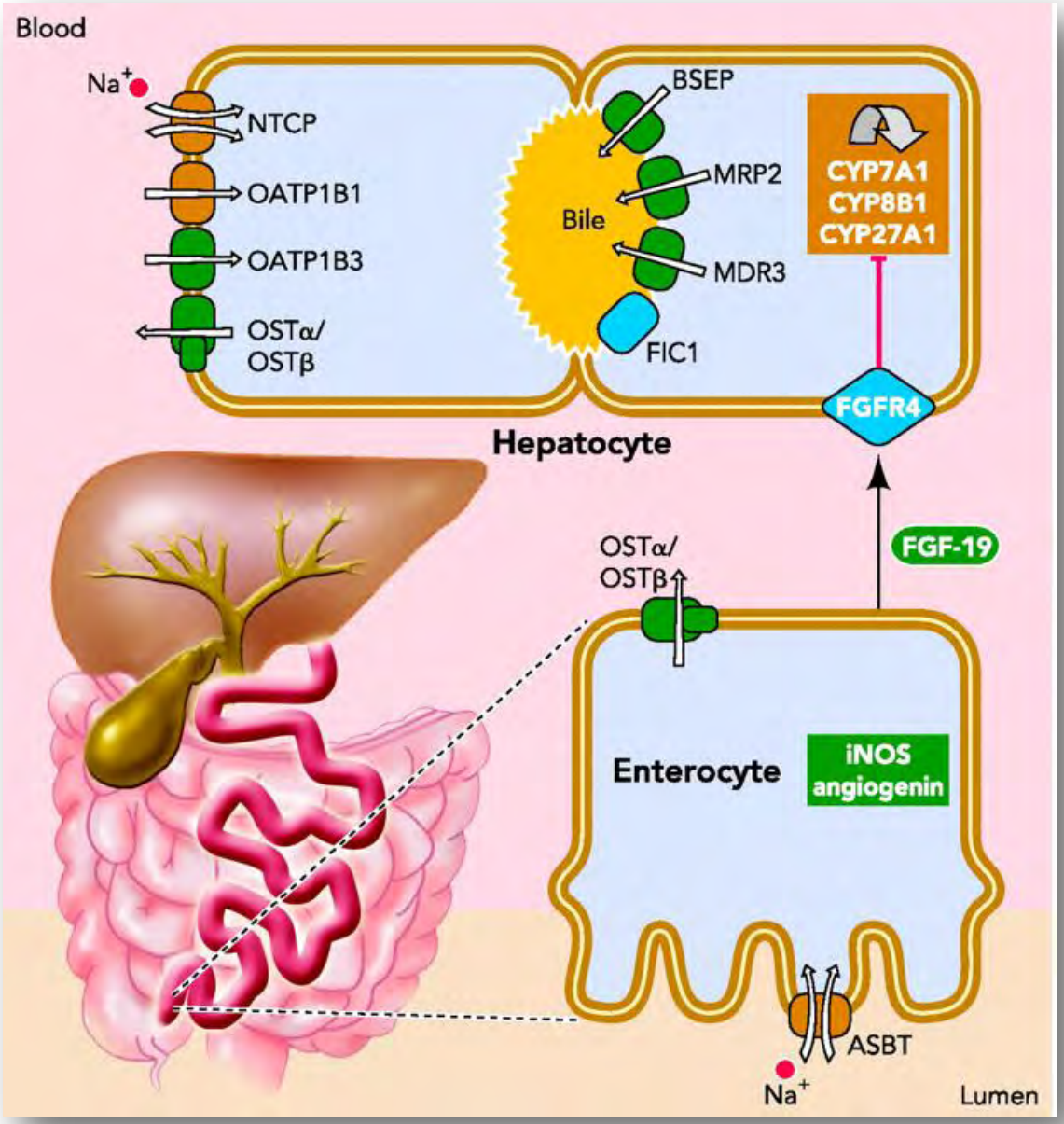


SLCO1B1 388	SLCO1B1 521	haplotype	frequency
A	T	*1a/*1a	33.3% (n=20)
A	T		
A	T	*1a/*1b	26.67% (n=16)
G	T		
G	T	*1b/*1b	6.67 (n=4)
G	T		
A	C	*1a,*5	5.00% (n=3)
A	T		
A	C	*1a/*1b,*5	13.33% (n=8)
G	T		
G	T	*1b, *15	8.33% (n=5)
G	C		
A	C	*5, *15	5.00% (n=3)
A	C		
G	C	*15/*15	1.67%(n=1)
G	C		



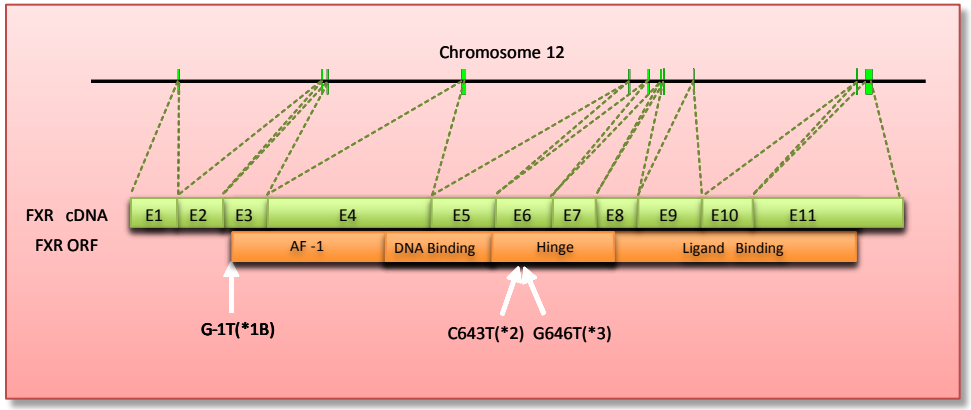
Meyer zu Schwabedissen et al., Hepatology 2010

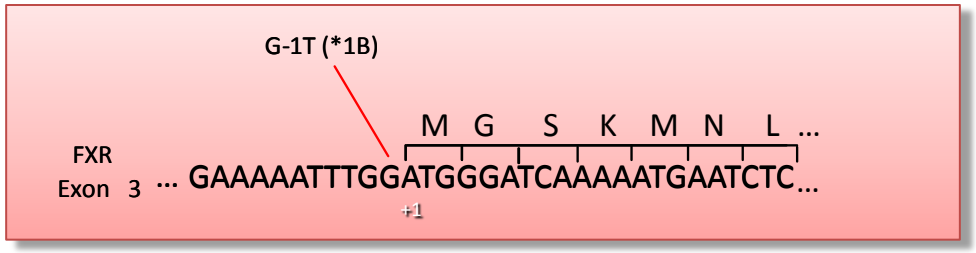
Regulation of Transporters by the Bile-Acid Sensor, Farnesoid X Receptor

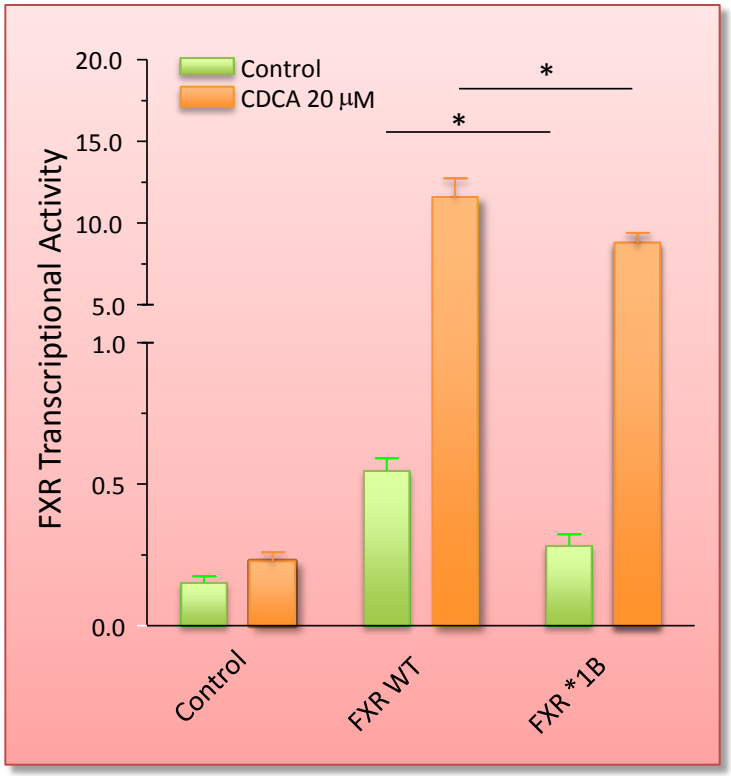


Eloranta et al., Physiology 2008

A Common Polymorphism in the Farnesoid X Receptor With Decreased In Vitro Activity



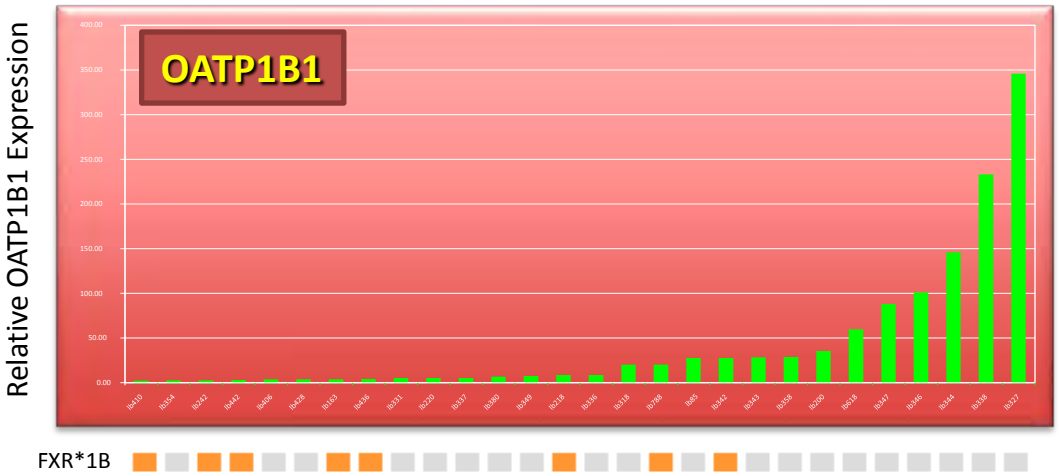


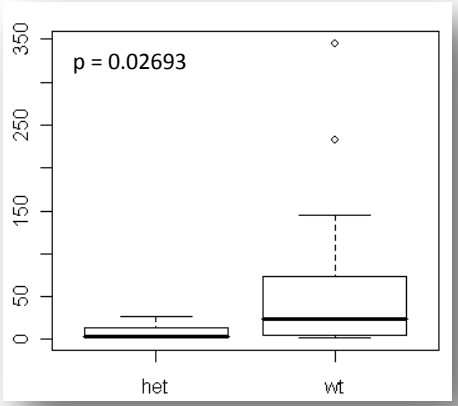


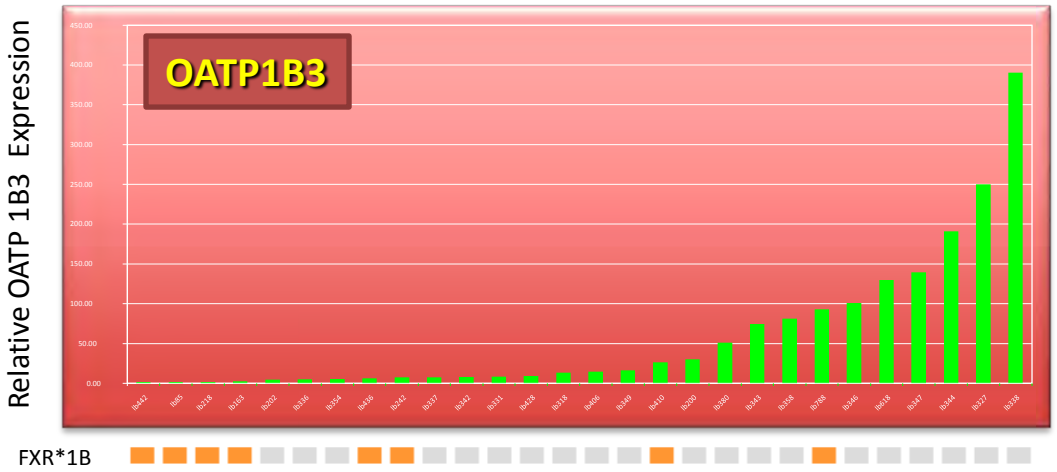
SNP	Exon	Amino acid change	Allele frequencies (%)			
			European	African	Chinese	Hispanic
G-1T(*1B)	3	non coding	2.5	3.2	12.1	5.8
C643T (*2)	6	H215Y	0.7	0	0	0
G646T (*3)	6	A216S	0	0	0.5	0
C783T	7	N261N	0	0	0.5	0
C1341T	11	H447H	0	0	0	0.5

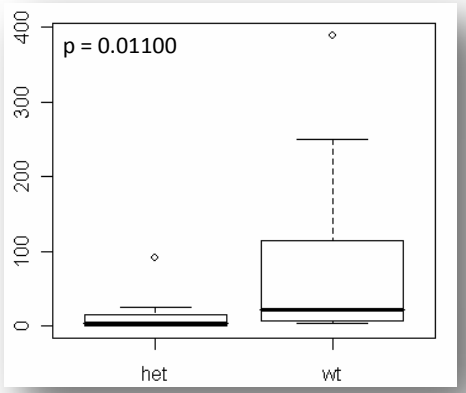
Marzolini et al., Mol Endocrinol 2007

FXR*1b Polymorphism is Associated with Decreased Hepatic OATP mRNA Expression





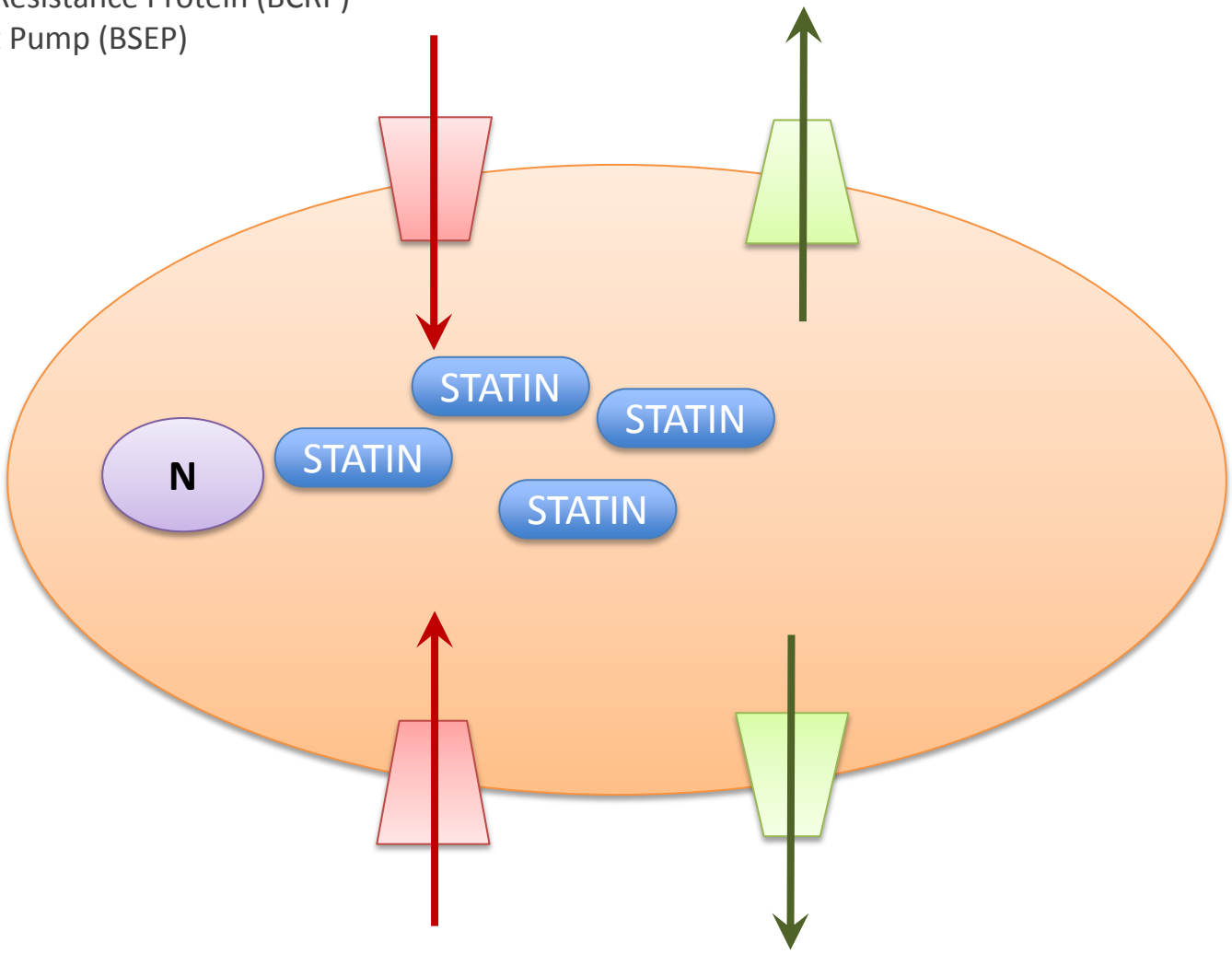




Marzolini et al., Mol Endocrinol 2007

Efflux Transporters

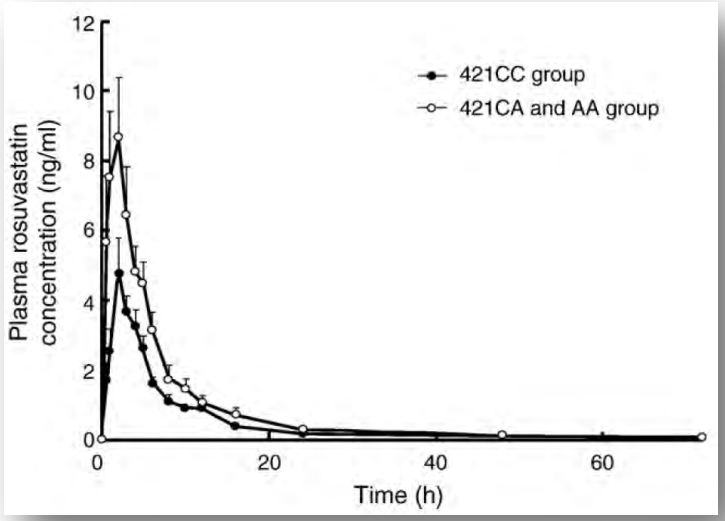
P-glycoprotein (P-gp)
Multidrug Resistance Associated Proetin (MRP)
Breast Cancer Resistance Protein (BCRP)
Bile Salt Export Pump (BSEP)



Hepatic Statin Efflux Transporters

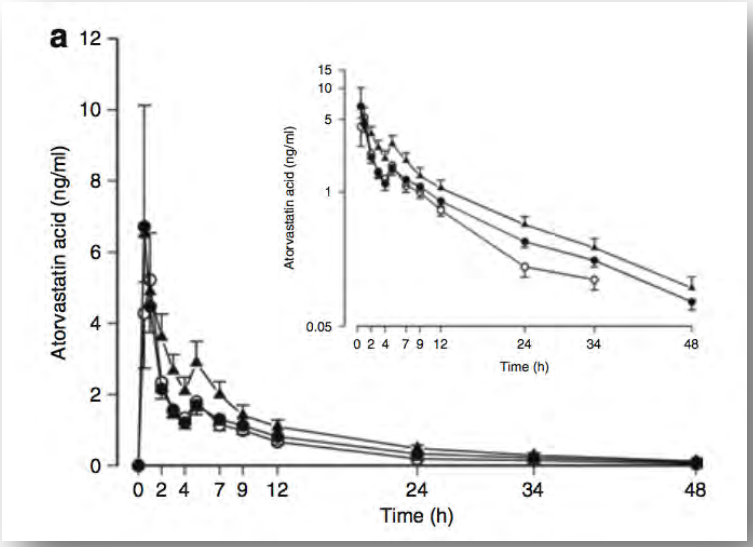
Transporter	Simvastatin Acid	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Pitavastatin
P-gp	+			+	+	+
MRP2		+		+	+	+
BCRP		+		+	+	+
BSEP		+				

ABCG2 (BCRP) 421C>A Polymorphisms Differentially Affect Statin Pharmacokinetics



Zhang et al., Clinica Chimica Acta 2006

ABCG2	Caucasian	African	Asian
c.421C>A Q141K	0.15	0.05	0.30



Keskitalo et al. Clin Pharmacol Ther 2009

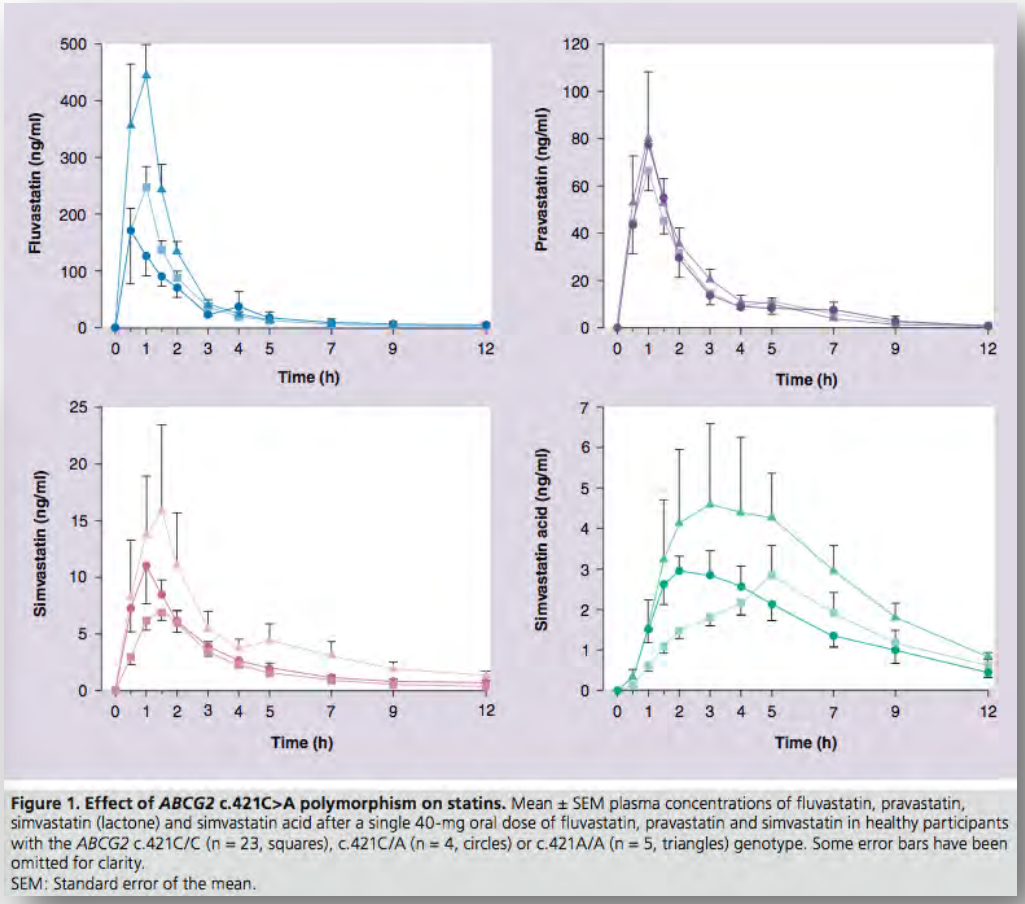


Figure 1. Effect of *ABCG2* c.421C>A polymorphism on statins. Mean ± SEM plasma concentrations of fluvastatin, pravastatin, simvastatin (lactone) and simvastatin acid after a single 40-mg oral dose of fluvastatin, pravastatin and simvastatin in healthy participants with the *ABCG2* c.421C/C (n = 23, squares), c.421C/A (n = 4, circles) or c.421A/A (n = 5, triangles) genotype. Some error bars have been omitted for clarity.
SEM: Standard error of the mean.

Keskitalo et al., Pharmacogenomics 2009

ABCB1 (P-gp) Polymorphisms Differentially Affect Statin Pharmacokinetics

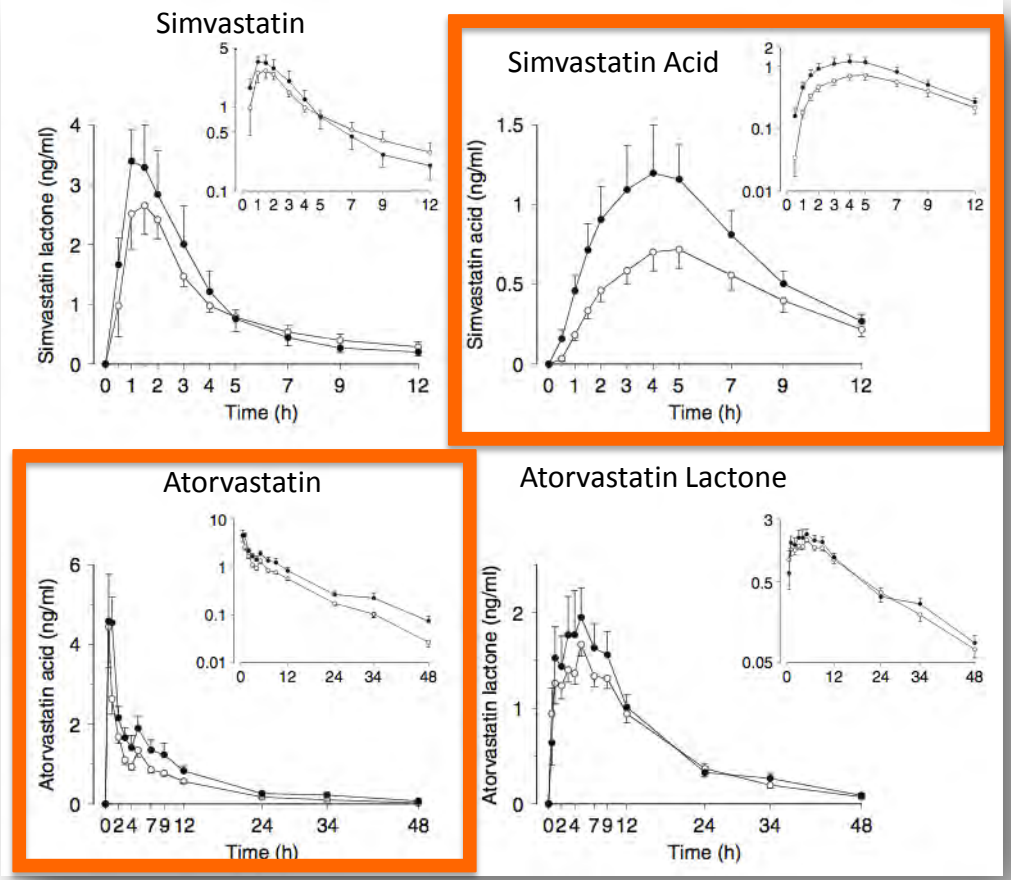


Figure 1 Mean (±s.e.m.) plasma concentrations of simvastatin (lactone), simvastatin acid, atorvastatin (acid), and atorvastatin lactone after a single 20 mg oral dose of simvastatin or atorvastatin in 24 healthy white subjects with different *ABCB1* genotypes. Open circles indicate subjects with the c.1236C/C-c.2677G/G-c.3435C/C genotype ($n = 12$) and solid circles indicate those with the c.1236T/T-c.2677T/T-c.3435T/T genotype ($n = 12$). The insets depict the same data on a semilogarithmic scale.

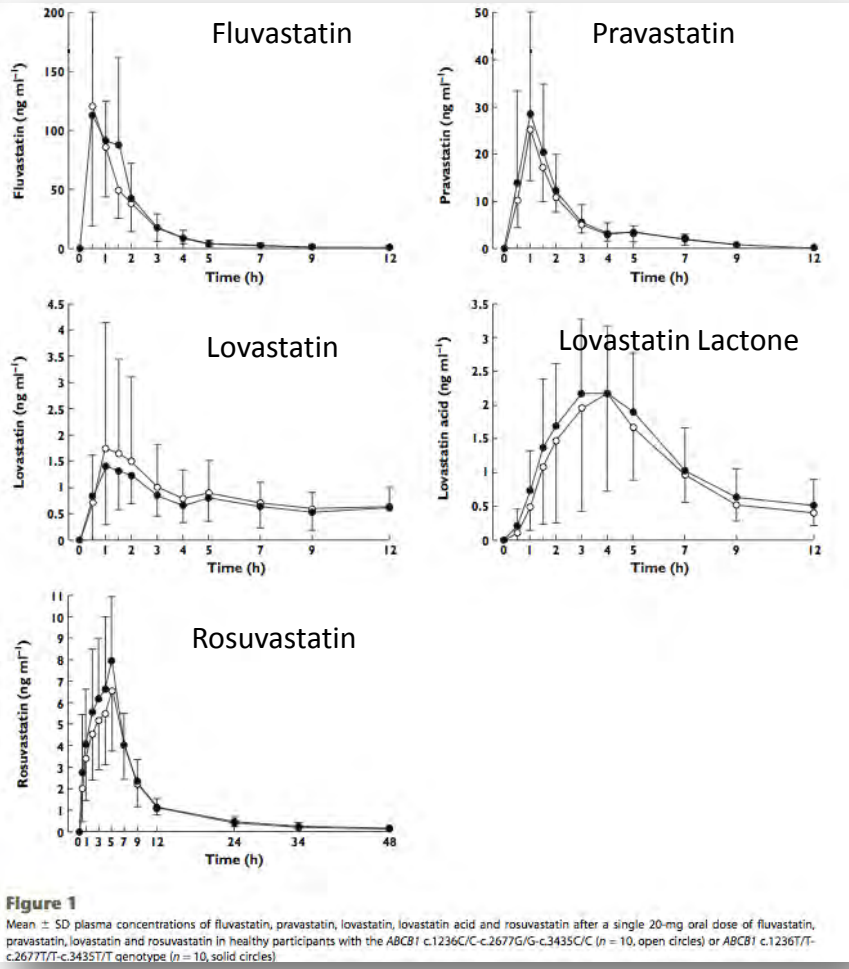
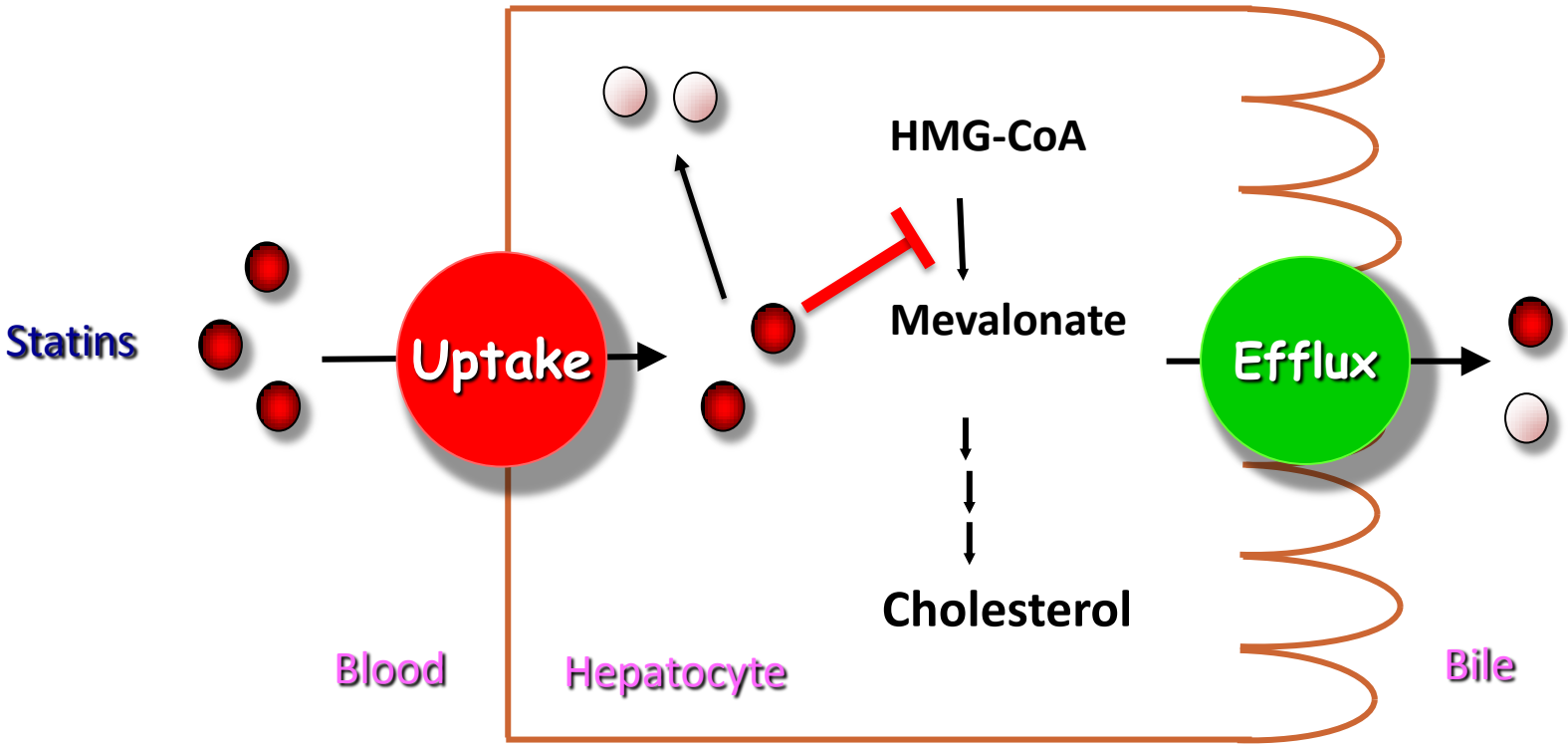


Figure 1
Mean ± SD plasma concentrations of fluvastatin, pravastatin, lovastatin, lovastatin acid and rosuvastatin after a single 20-mg oral dose of fluvastatin, pravastatin, lovastatin and rosuvastatin in healthy participants with the *ABCB1* c.1236C/C-c.2677G/G-c.3435C/C ($n = 10$, open circles) or *ABCB1* c.1236T/T-c.2677T/T-c.3435T/T genotype ($n = 10$, solid circles)

2677TT – 893Ser
2677GG – 893Ala

Keskitalo et al., CPT 2008
Keskitalo et al., Br J Clin Pharm 2009

Statin Transporter Polymorphisms and Pharmacodynamics

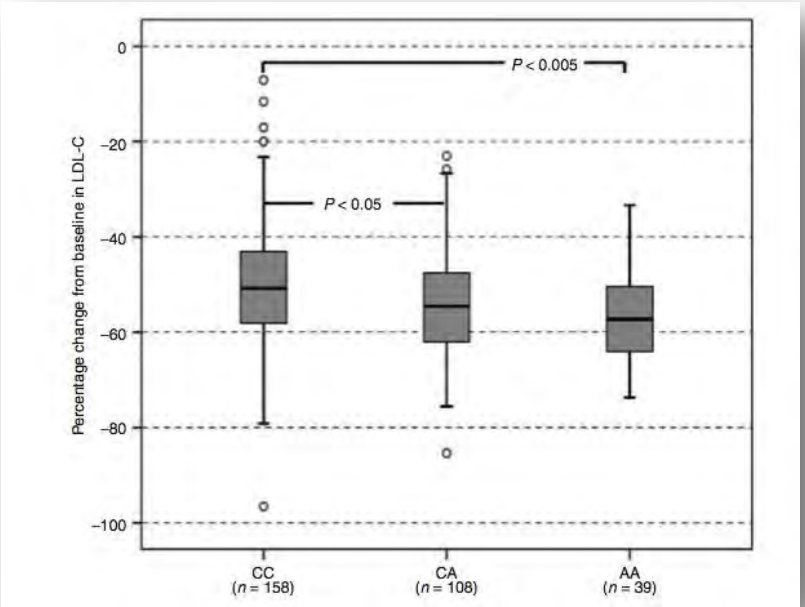


OATP1B1 521T>C Transporter Polymorphisms and Pharmacodynamics

Statin (daily dose in mg)	Number of Subjects	Effect of SNP on Lipid Response	Reference
Several Statins (dose not controlled)	66	Reduced effect on LDL-C lowering	Tachibana-Iimori et al., Drug Metab Pharmacokinet 2004
Several Statins (dose not controlled)	2735	Enhanced effect on HDL-C for AVA and FVA	Thompson et al., Pharmacogenomics J 2005
Pravastatin (40 mg)	16	No effect on lipids	Igel et al., CPT 2006
Pravastatin (mean 9.4 mg)	33	Reduced effect on Tchol and LDL-C lowering at 56 days	Takane et al., J Human Gen 2006
Pravastatin (20 mg)	45	Reduced effect on Tchol	Zhang et al., Br J Clin Pharmacol 2007
Simvastatin (40 mg)	16660	Reduced effect on LDL-C lowering	Link et al., NEJM 2008

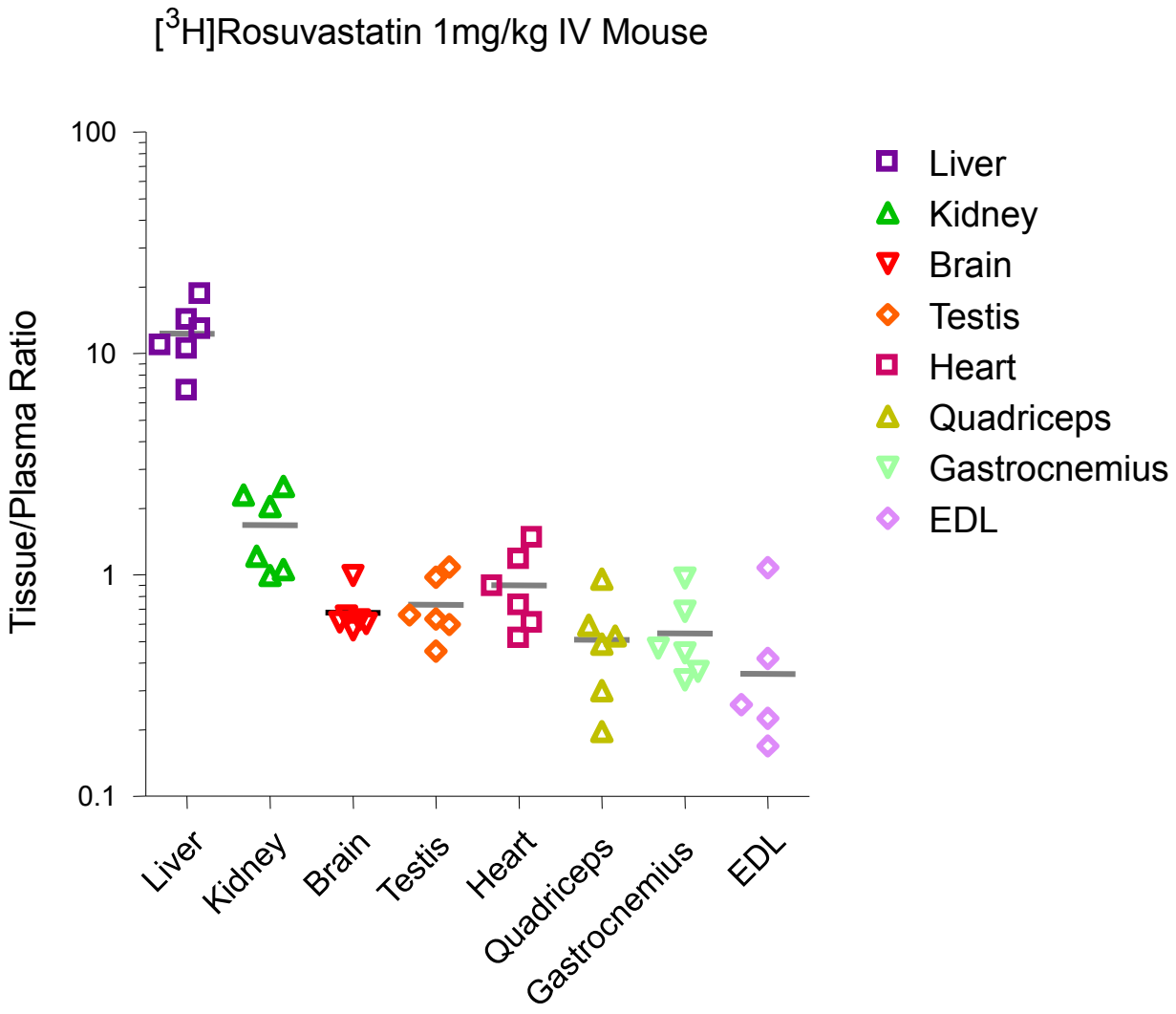
Breast Cancer Resistance Protein (ABCG2) Polymorphisms and Pharmacodynamics

Transporter (SNP)	Statin (dose in mg)	Number of Subjects	Effect of SNPs on Lipid Response	Reference
421C>A	Rosuvastatin (10 mg)	305	Enhanced effect on LDL-C	Tomlinson et al., CPT 2010
421C>A	Rosuvastatin	300	Enhanced effect on LDL-C	Bailey et al., Circ Cardiovasc Genet 2010

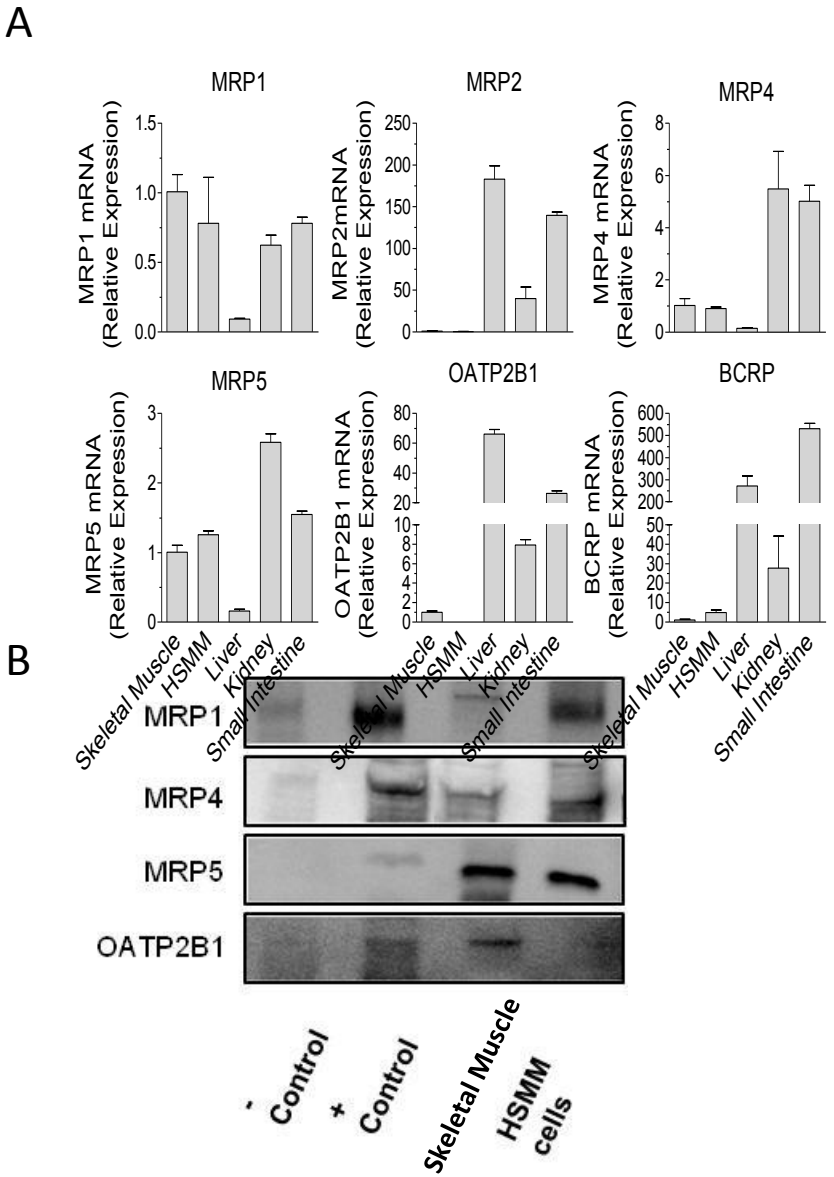


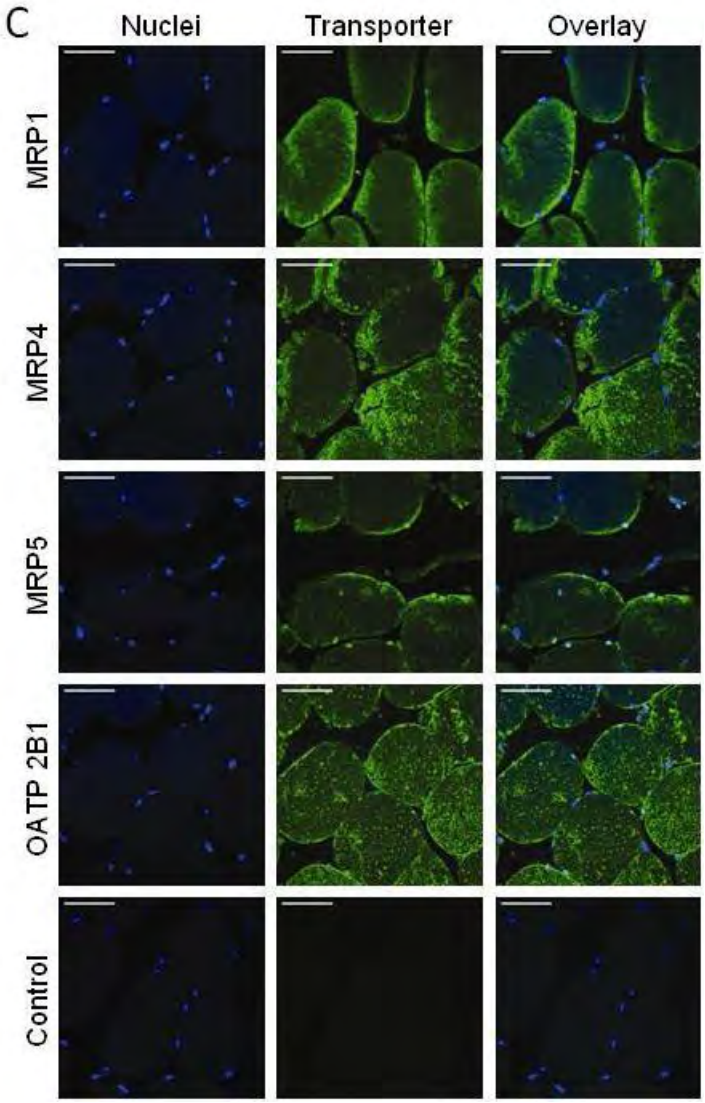
What about skeletal muscle distribution of statins?

Tissue Distribution of Rosuvastatin in the Mouse



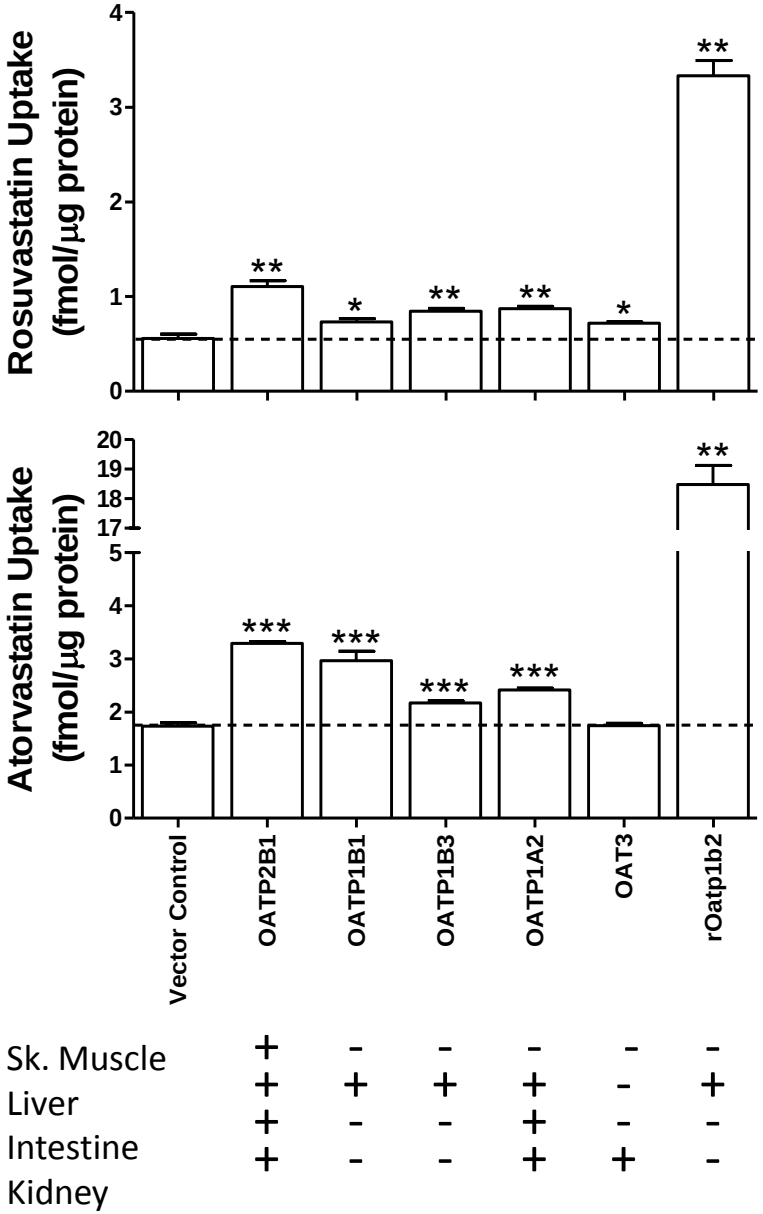
Drug Transporter Expression in Human Skeletal Muscle

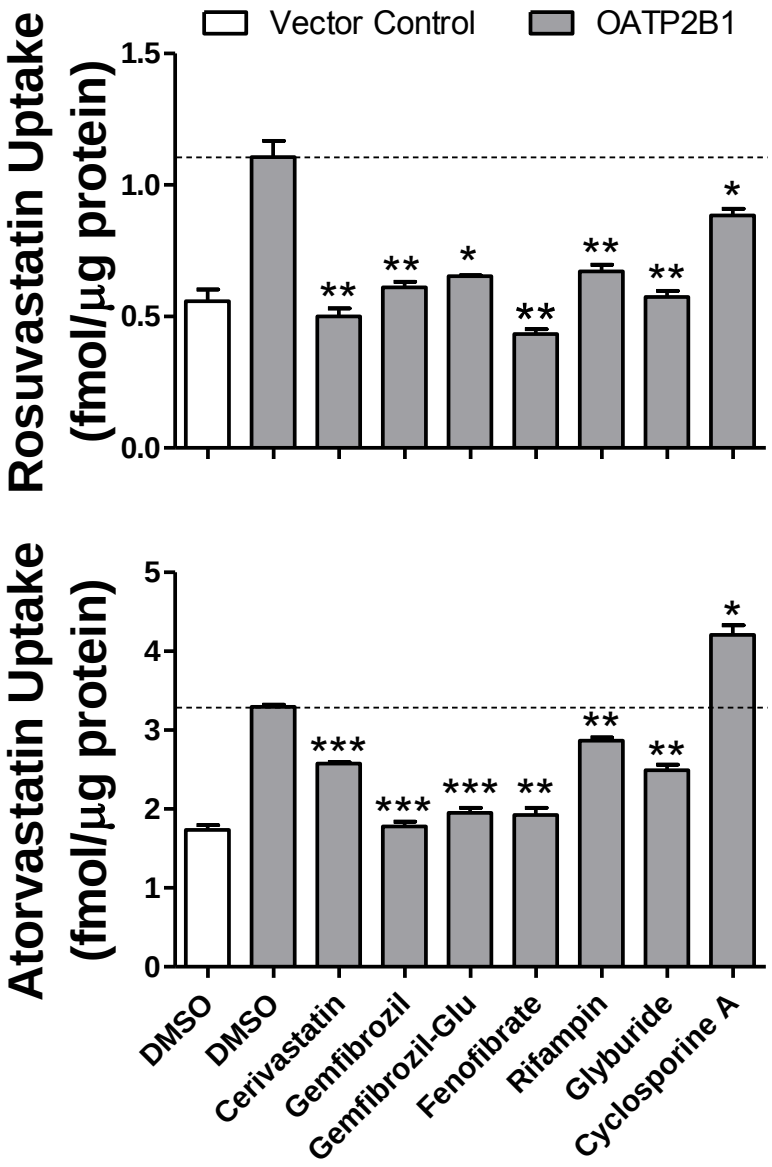




Knauer et al., Circ Res 2010

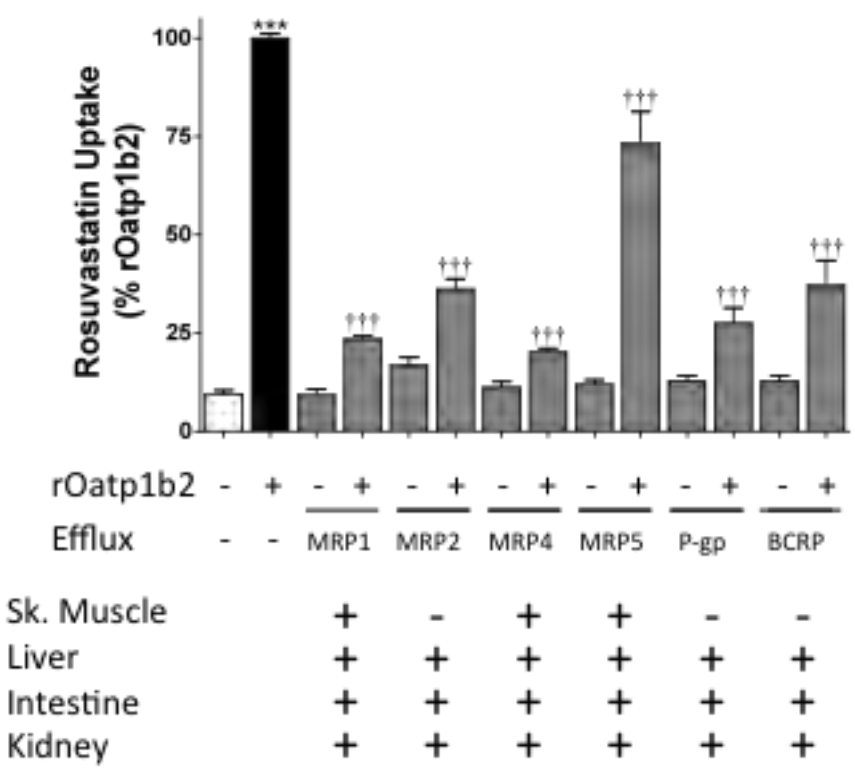
OATP2B1 in Skeletal Muscle Transports Statins

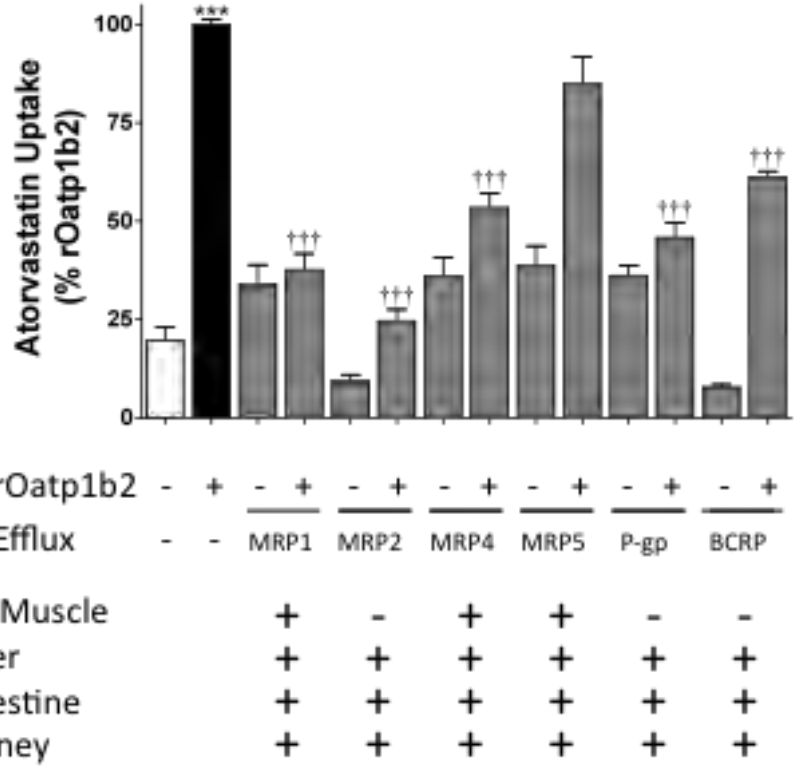




Knauer et al., Circ Res 2010

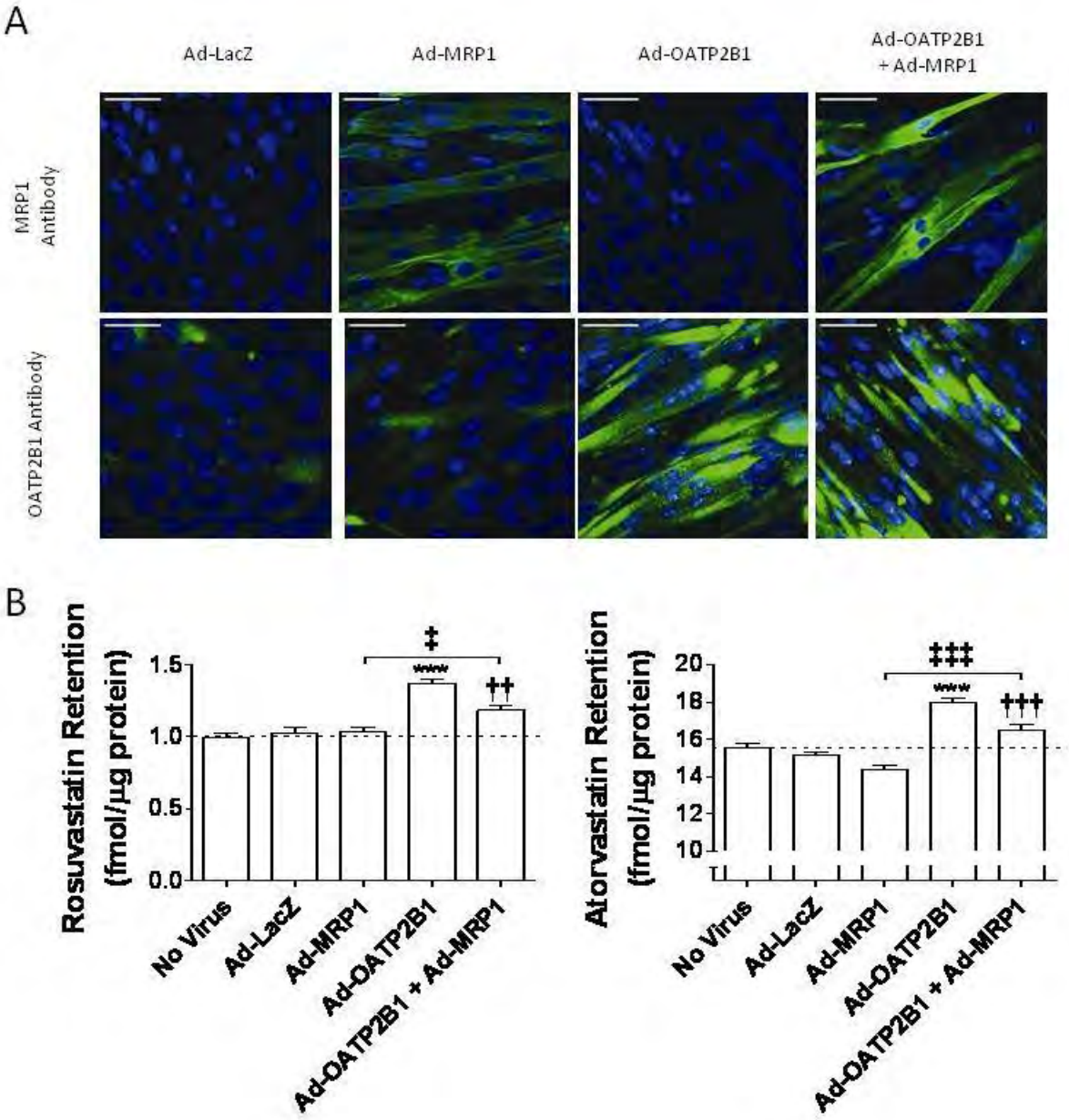
Novel Statin Efflux Transporters in Skeletal Muscle





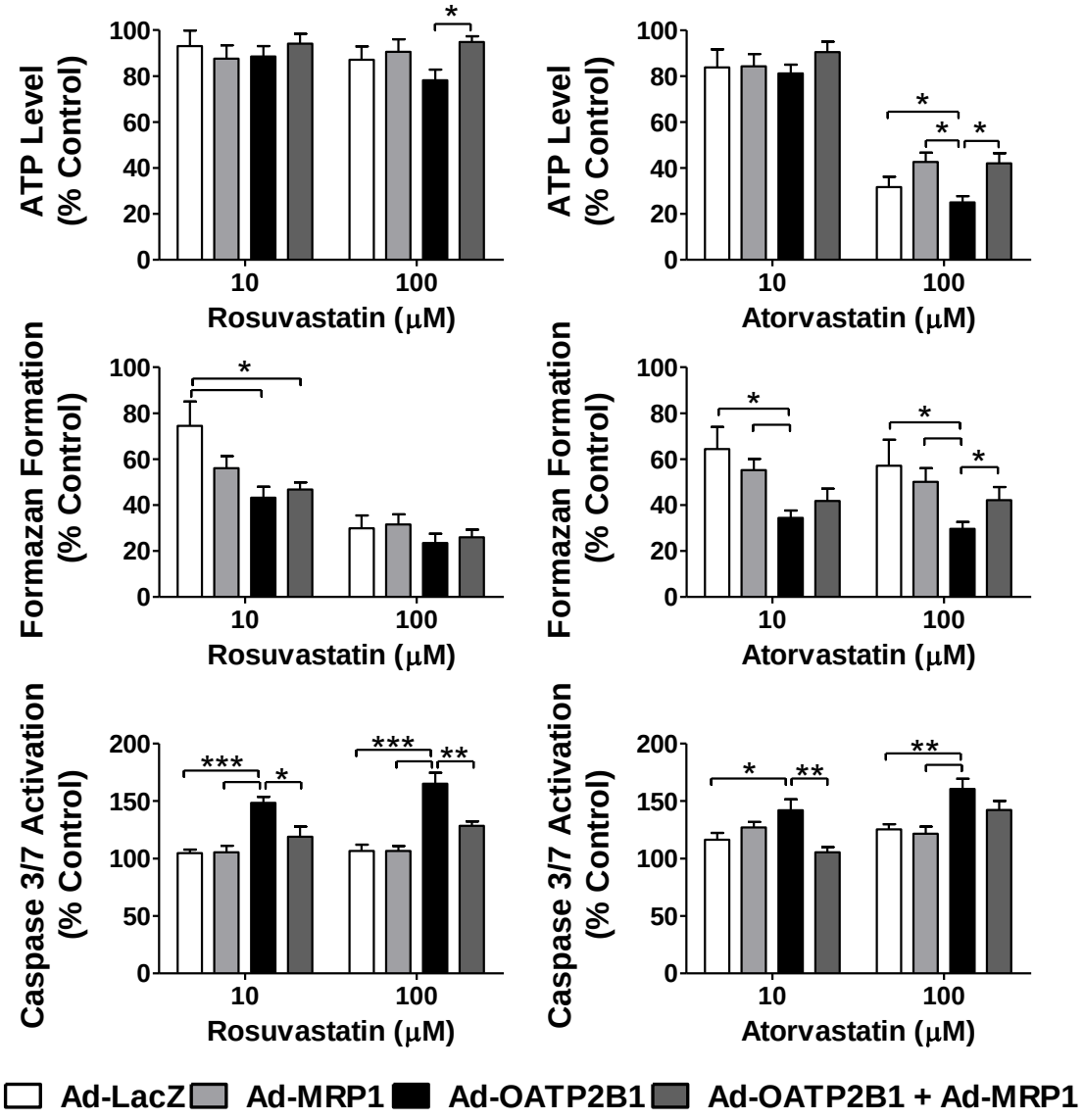
Knauer et al., Circ Res 2010

OATP2B1 and MRP1 Modulate Statin Accumulation in



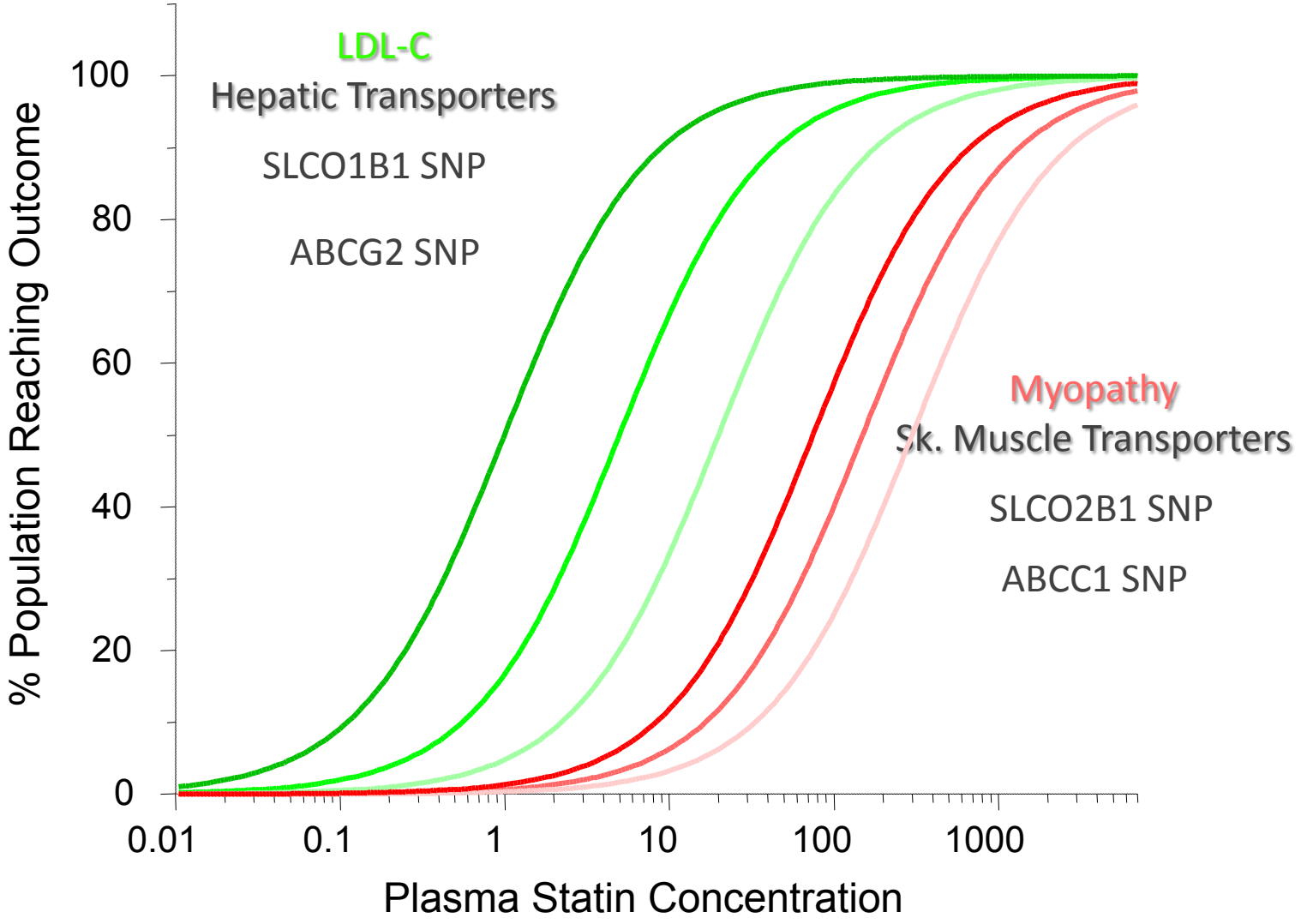
Knauer et al., Circ Res 2010

OATP2B1 and MRP1 Modulate Statin Toxicity in Cultured Skeletal Myotubes



Knauer et al., Circ Res 2010

Liver - Skeletal Muscle Transporter Axis And Statin Therapeutic Window



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John Schuetz

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Ethnic Difference in Rosuvastatin Pharmacokinetics

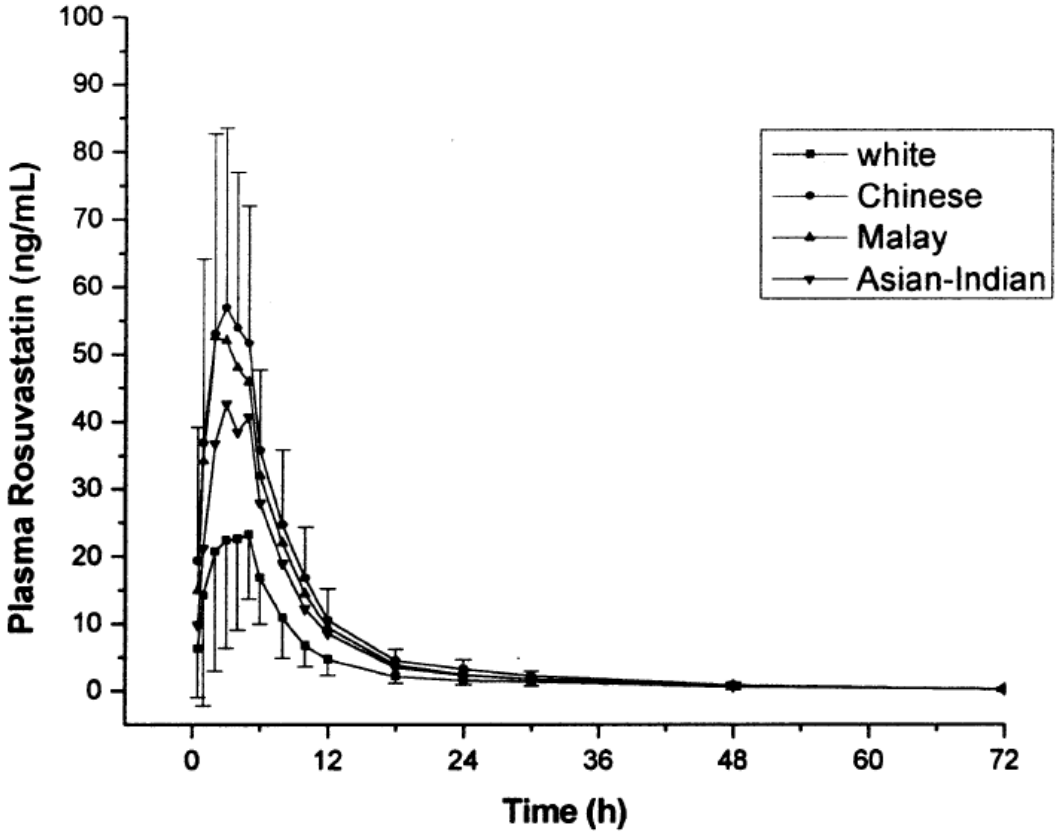

Fig 1. Plasma concentration–time profiles across white and Asian ethnic groups (arithmetic mean ± SD).

P-glycoprotein (ABCB1) Polymorphisms and Pharmacodynamics

SNPs	Statin (daily dose in mg)	Number of Subjects	Effect of SNPs on Lipid Response	Reference
2677G and 3435C	Atorvastatin (10 mg)	344	Reduced effect on LDL-C in women	Kajinami et al., Am J Cardiol 2004
2677G>T	Atorvastatin (10 mg)	1902	Reduced effect on LDL-C	Thompson et al., Pharmacogenomics J 2005
2677G>T/A	Simvastatin (20 mg)	116	Increased LDL-C response	Fiegenbaum et al., CPT 2005
4 allele haplotype	Fluvastatin (40 mg)	76	Increased LDL-C response	Bercovich et al., Atherosclerosis 2006
2677G>T/A	Pravastatin (40 mg)	~ 700	Reduced effect on LDL-C	Mega et al., ATVB 2009