Metabolomic and Genome-wide Association Studies Reveal Potential Endogenous Biomarkers for OATP1B1

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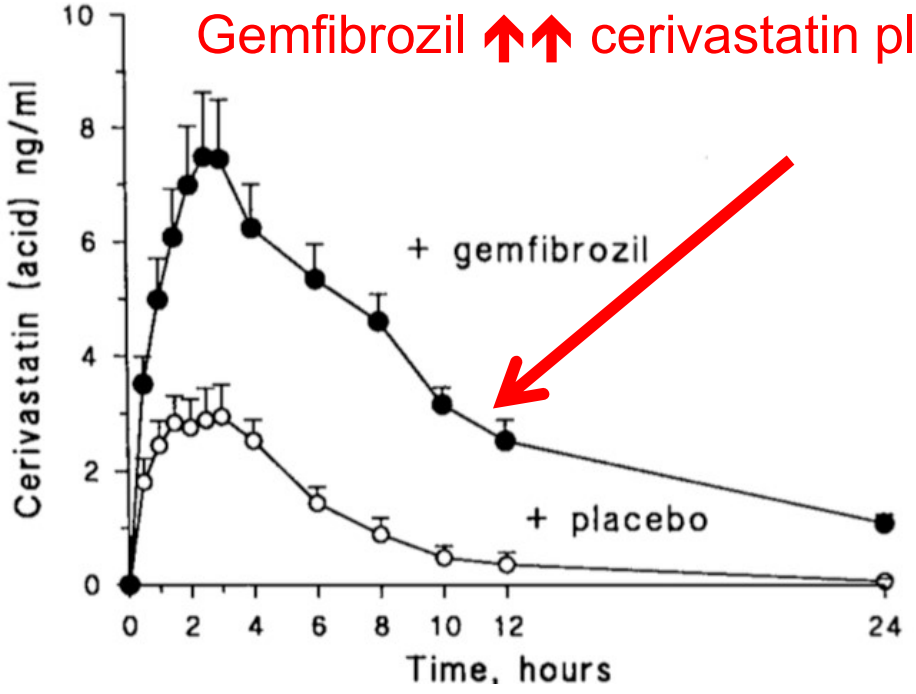
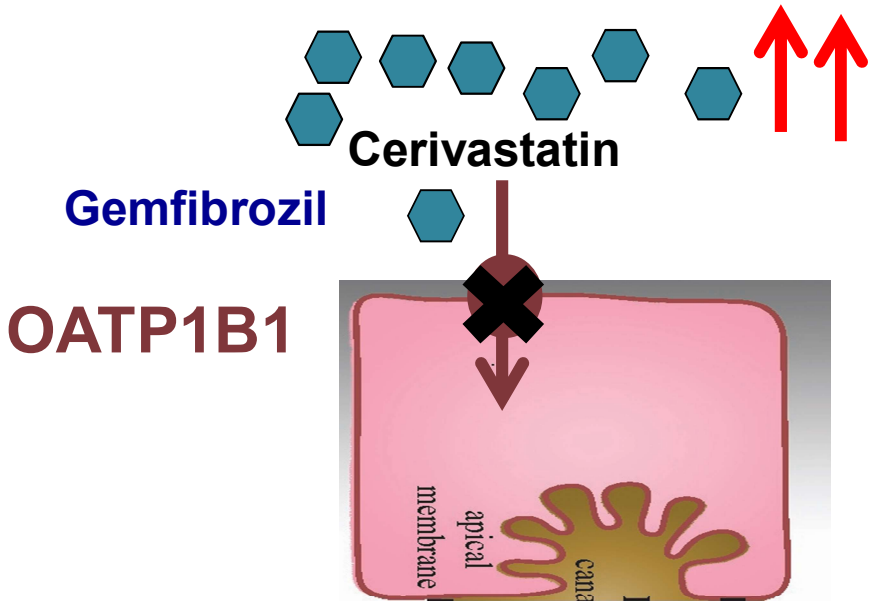
Transporter Mediated Drug-Drug Interactions Can Cause Toxicities

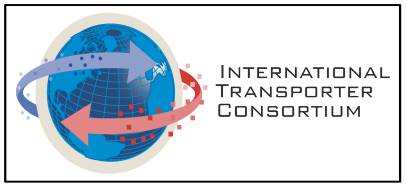
- **Cerivastatin** was withdrawn from market in 2001 because of many cases of rhabdomyolysis
- Half of the cases where patients using **cerivastatin + gemfibrozil**



Backman JT et al. (2002) Clin. Pharmacol. Ther.



Problem With Current Decision Tree To Determine Need for Transporter-Mediated Clinical DDI Study



Giacomini KM, Huang SM, Tweedie D et al. Nat Rev Drug Discov. 2010 Mar;9(3):215-36.

FDA Draft Guidance: Drug Interaction Studies. (2012)

If the IC_{50} of the NME ≤ 10 times unbound C_{max} then Clinical DDI Study is needed

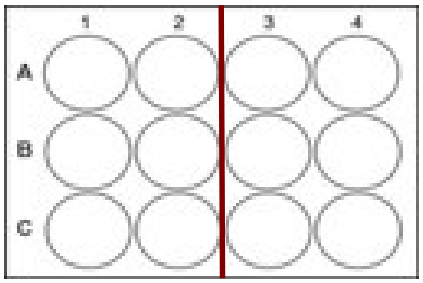
Limitation

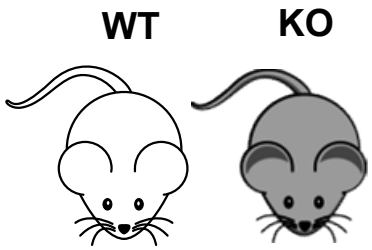
Several False Positive Results of Transporter-Mediated DDI

Fan Y. et al. (2016) J. Clin. Pharmacology, 56(S7) S193.

Motivation: Measuring Biomarkers of Transporters To Determine The Need for Conducting Clinical DDI Study

Several OATP1B1 Biomarkers Were Identified Through Targeted Approaches





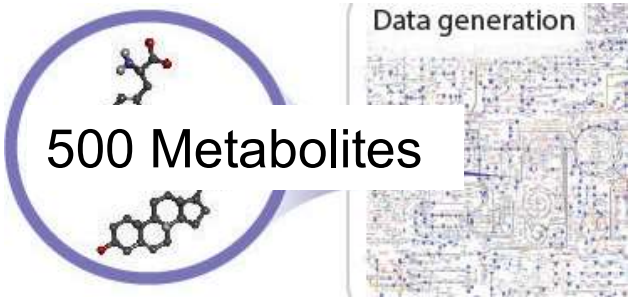
Bile acids, Bilirubin and glucuronide, Coproporphyrins I and III, Glycocholic acid, Taurocholic acid, Thyroxine

Motivation: Are There Other OATP1B1 Biomarkers That May Be A Better OATP1B1 Biomarkers (e.g. selective for OATP1B1)?

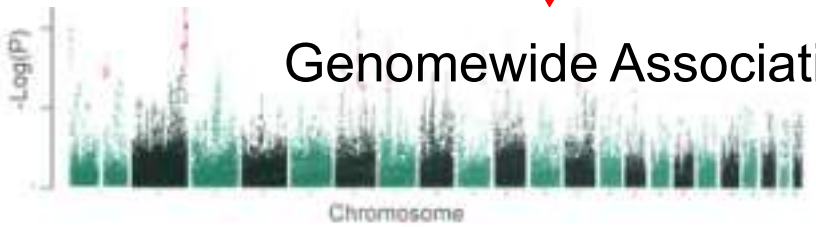
PMID: 19387419, 21245207, 22232210, 25813937, 26907622

Unbiased Approach To Discover Endogenous Metabolites of *SLCO1B1*

N > 7,000 Individuals
Blood Sample*



Genomewide Chip



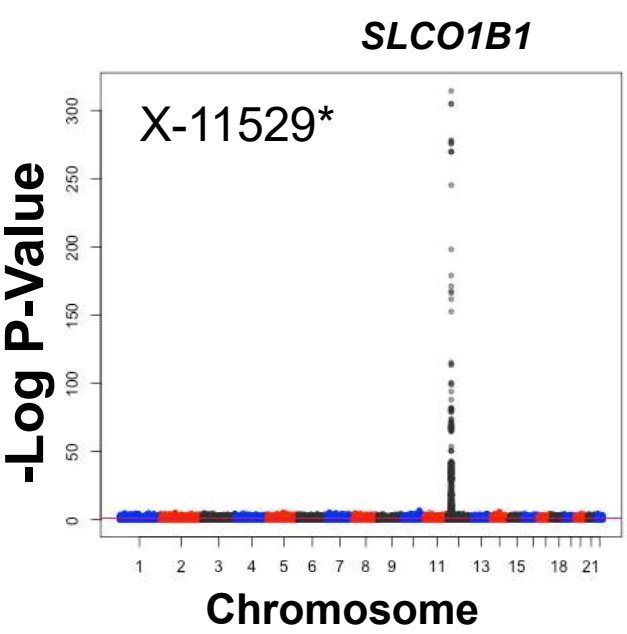
Genomewide Association Studies

Which metabolites associate with *SLCO1B1, 521T>C* (Val174Ala)?

***Shin et al., Nature Genetics, 2014**

Clin Pharmacol Ther. 2016 Nov;100(5):524-536

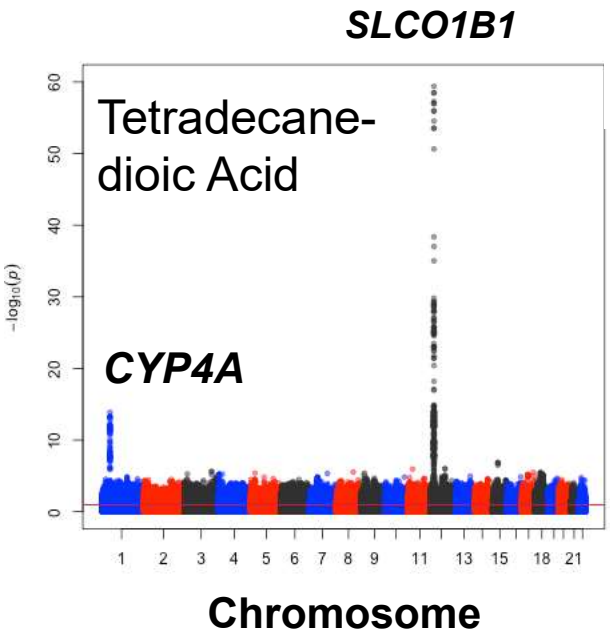
20 Metabolites Associated with SNPs in the *SLCO1B1* Locus with $P<5x10^{-8}$



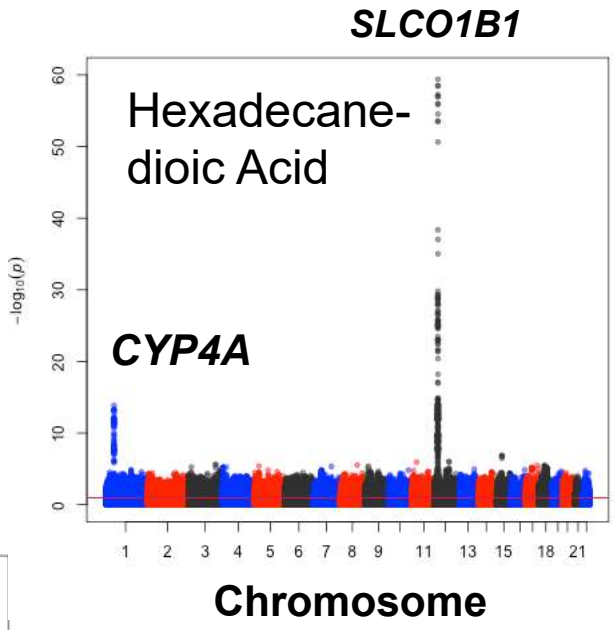
P-value = 5.5×10^{-315}

*glycochenodeoxycholate glucuronide

***SLCO1B1, 521T>C* (Val174Ala) cause increase level of the metabolites**

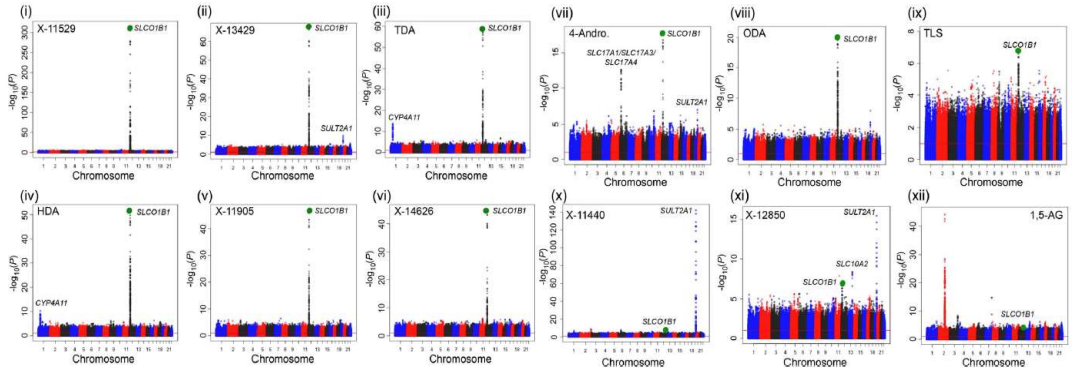


P-value = 3.4×10^{-59}



P-value = 1.6×10^{-61}

Validate Metabolites as Biomarkers of OATP1B1:
Using Pravastatin-CSA Interaction Study



GWAS

Determine whether the metabolites also increase in patients treated with cyclosporine.

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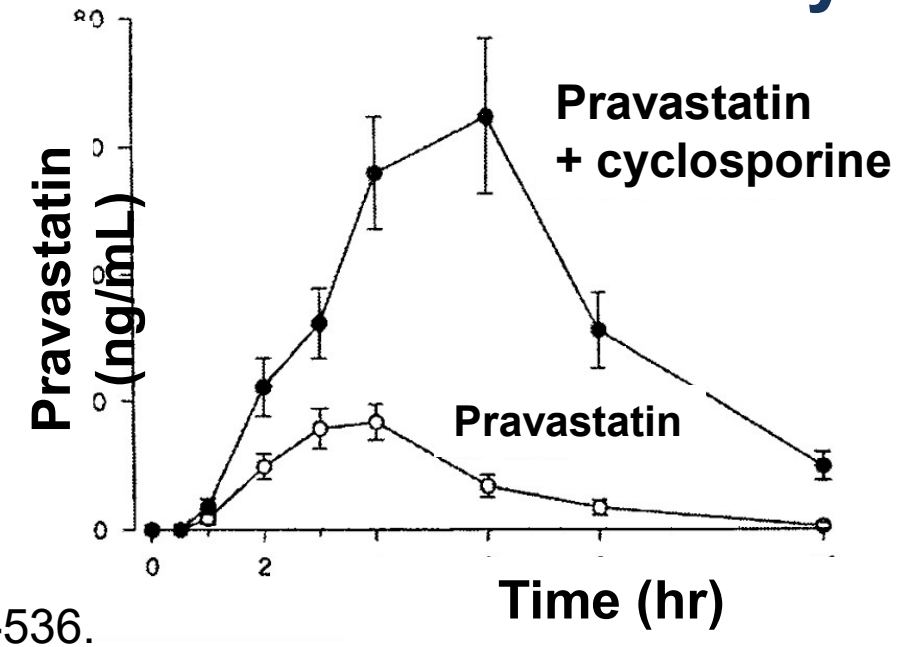
Clinical DDI Study



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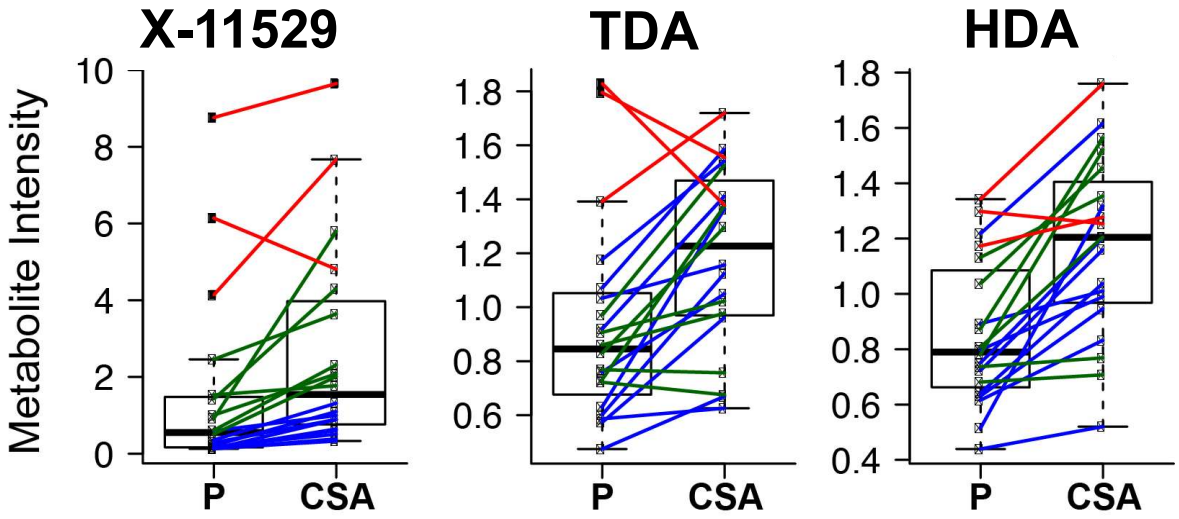
12 Potential Metabolites as Biomarkers of OATP1B1

OATP1B1 Inhibitor, Cyclosporine, increased level of the metabolites



Metabolite Intensities	
Placebo	0.6
CSA	1.5
P-value	0.0017

Metabolite Intensities	
Placebo	0.9
CSA	1.2
P-value	0.0013

Metabolite Intensities	
Placebo	0.8
CSA	1.2
P-value	$1x10^{-5}$

Clin Pharmacol Ther. 2016 Nov;100(5):524-536.

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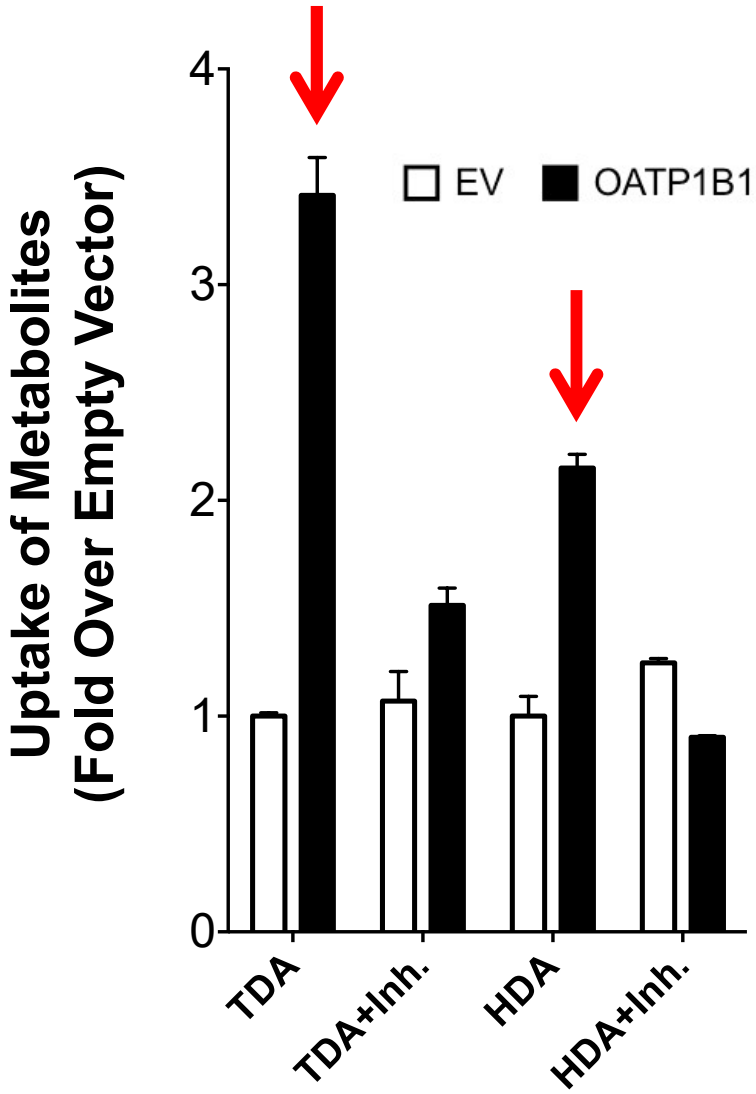
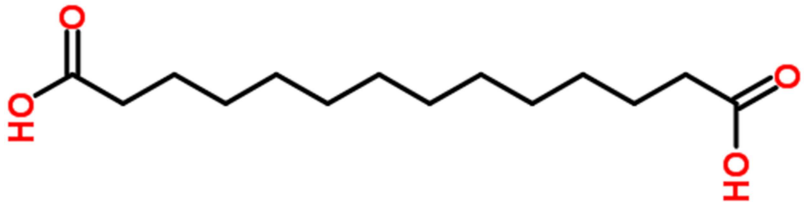
Validate TDA and HDA as Substrates of OATP1B1



TDA and HDA Are Dicarboxylate Fatty Acids



TDA and HDA are not substrates and inhibitors of OATP1B3, OATP2B1 and OATP1A2

TDA: Tetradecanedioic Acid

HDA: Hexadecanedioic Acid

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Summary and Future Studies

1. Unbiased approach with GWAS reveal novel metabolites which are substrates of OATP1B1.

1. These metabolites were also increased after administration of OATP1B1 inhibitor in human subjects.

2. In vitro studies confirmed that TDA and HDA metabolites are novel substrates of OATP1B1.

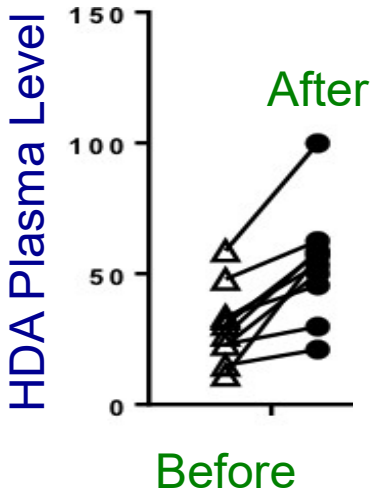
3. **<u>Future studies:</u>**
   - Determine whether TDA and HDA also increased upon administration of other OATP1B1, OAT1 and OAT3 inhibitors.
   - Determine the sensitivity, selectivity, other factors that could modulate these biomarkers.

Propose To Measure Biomarkers in Phase I Clinical Study

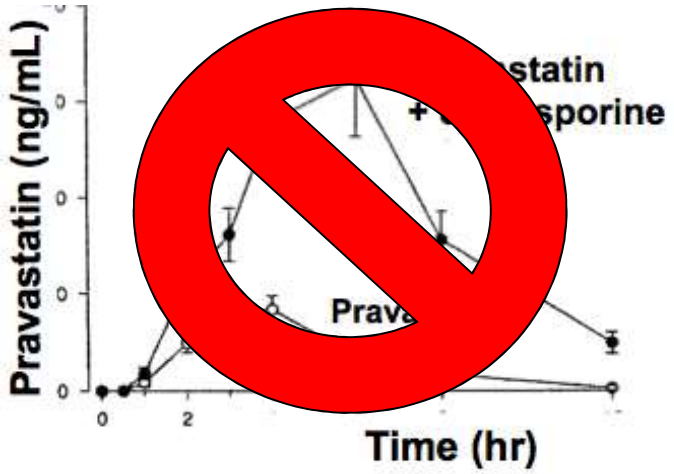
Phase I Study of NME

Measure Biomarker Before And After NME Administration

If Biomarker(s) Increases: Consider Clinical DDI Study



If No Increase: No Clinical DDI Study



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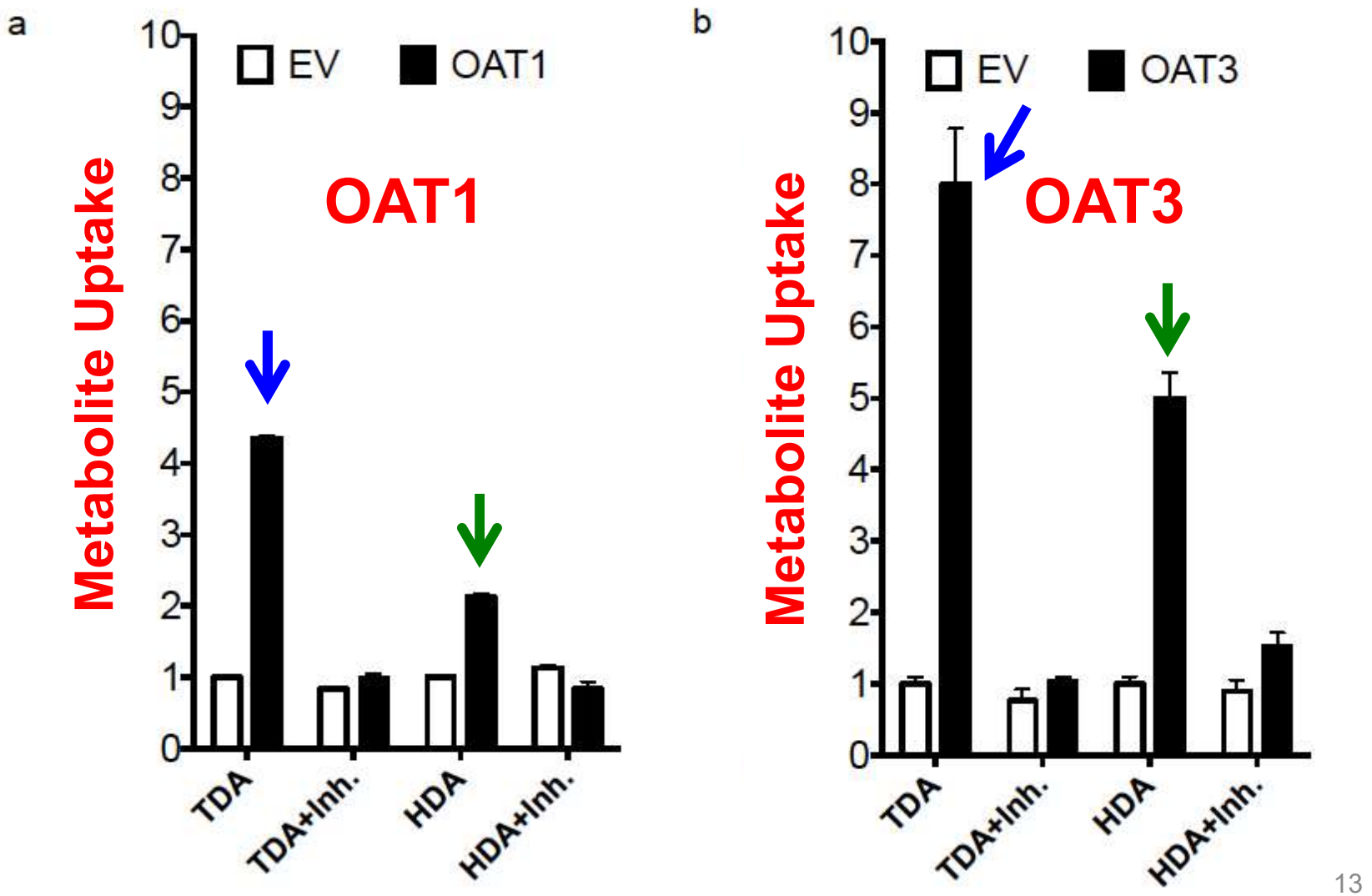
Dietmar Weitz, Sanofi, Frankfurt

Jason Kinchen
Jeff Buckthal

TDA and HDA Are Also Substrates of Other Organic Anion Transporters



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