Clinical Significance and Regulatory Framework for the Evaluation of Organic Anion Transporting Polypeptide 1B-Based Drug-Drug Interactions

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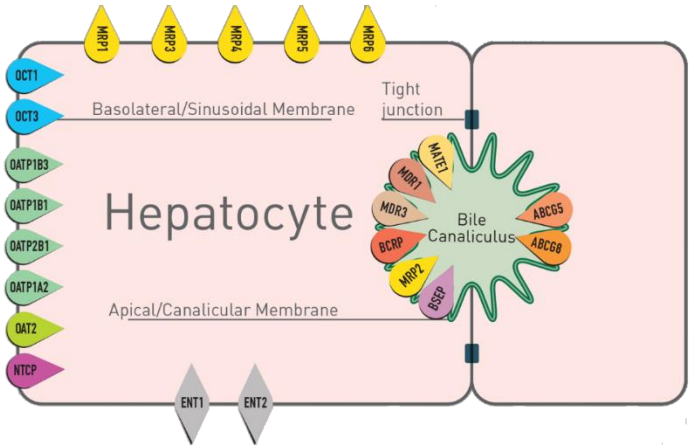
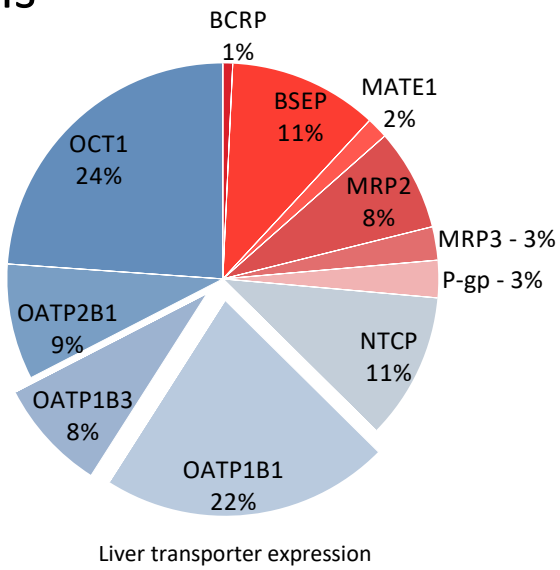
OATP1B1/1B3

- The OATPs belong to the solute-carrier (SLC) family of transporters
  - Assumed to transport compounds based on concentration gradient or ion exchange
- OATP1B1 and 1B3 are uptake transporters exclusively expressed on sinusoidal membrane of hepatocytes
  - OATP1B1 and OATP1B3 share 80% amino acid identity
- Among the liver transporters, OATP1B1 shows the second highest expression (22%) and OATP1B3 expression is approximately one-third of that (8%)

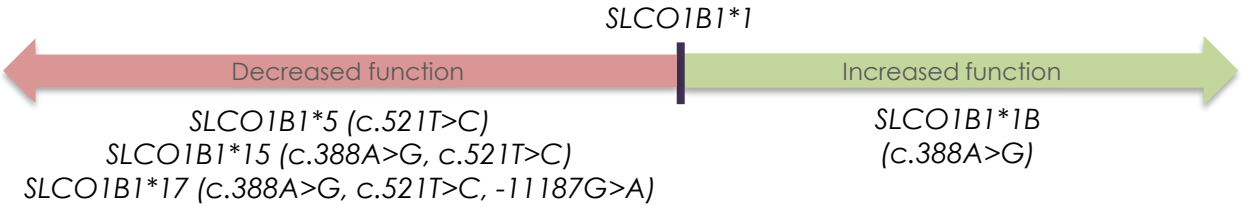




Liver transporter expression

OATP1B1/1B3 Polymorphisms

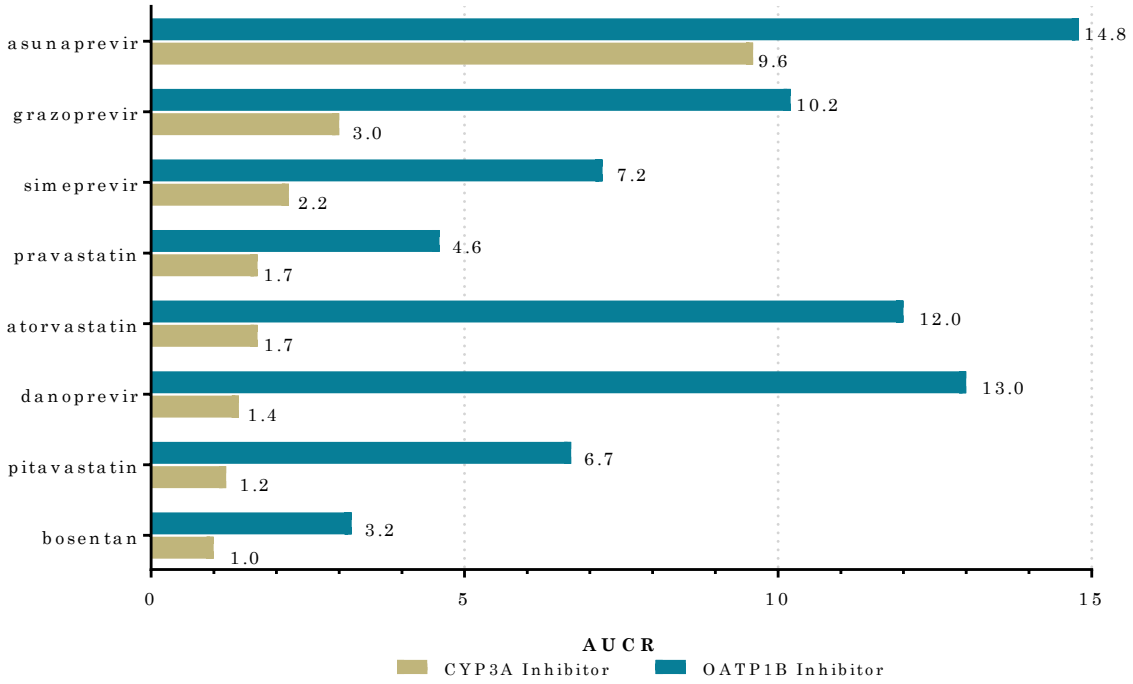
- Genetic variation in both *SLCO1B1* and *SLCO1B3* have been shown to affect function and therefore substrate exposure.
- 21 different *SLCO1B1* variant alleles have been identified to date with varying effects on transport efficiency relative to the wild type (*SLCO1B1*1*)



- Variants of *SLCO1B3* are currently not as well characterized and while many have been identified, clinical effects are mostly unknown.
  - Decreased function *in vitro*: 334T>G, 699G>A, 1564G>T, -5035G>A

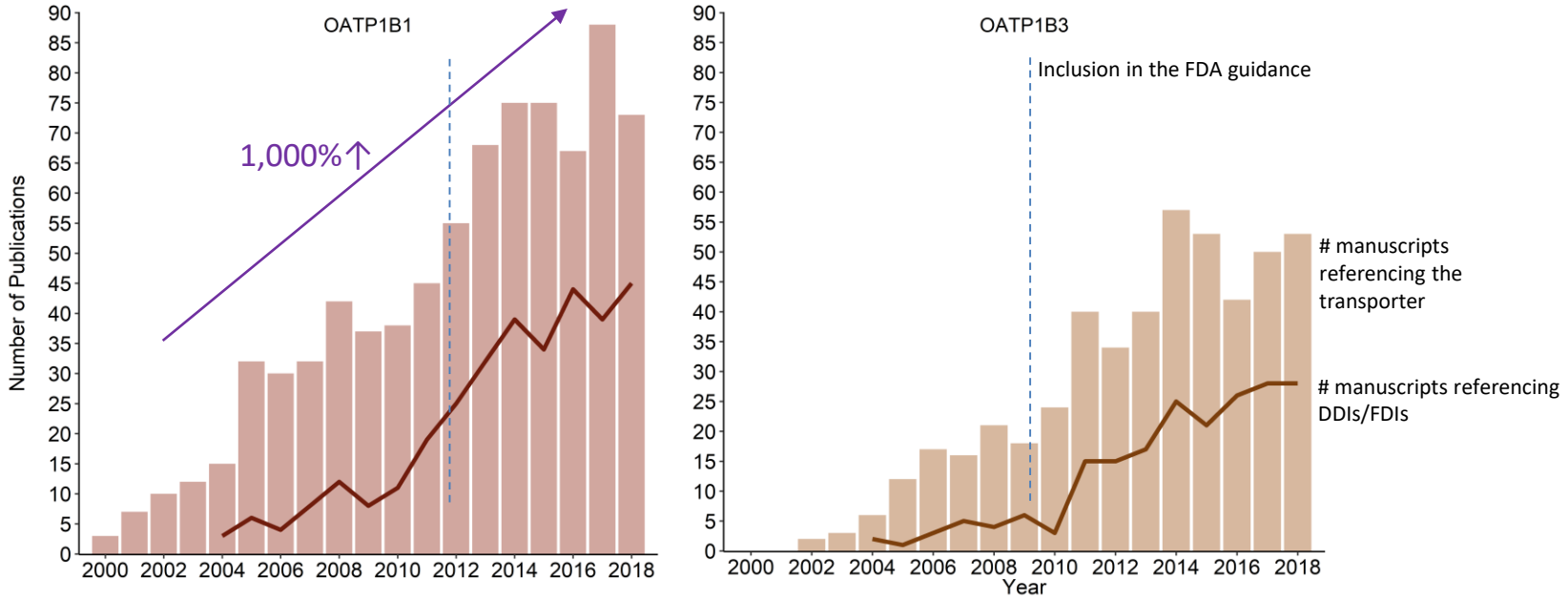
Inhibition Causes Significant Changes in Exposure

- For many compounds, hepatic uptake is a rate-determining step and the effect of inhibition can meet or exceed that observed with CYP inhibition
  - Magnitude of change in exposure is also, on average, much higher than observed with other transporters



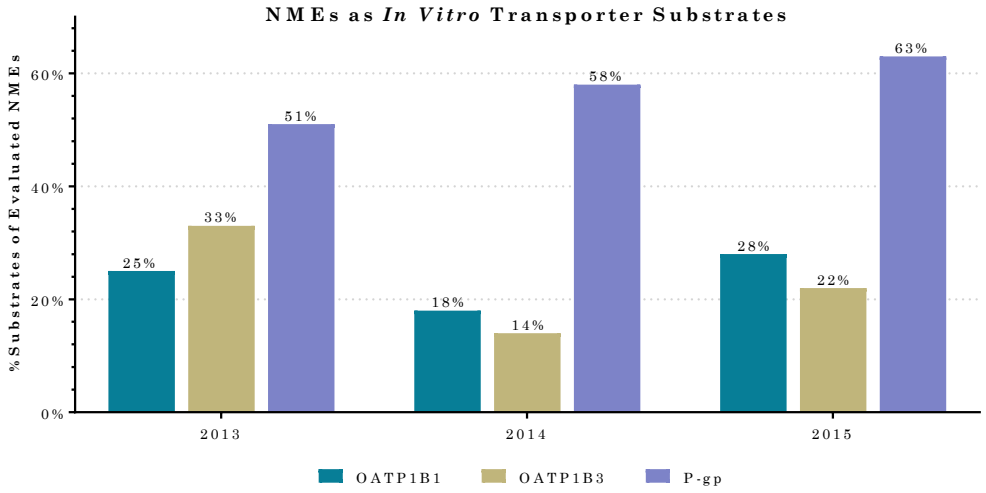
OATP1B1/1B3 Research and Publications

- Since the transporters were identified in the early 2000s, the number of publications on the structure/function has steadily increased
- Recommended for evaluation during drug development in 2012
  - The number of reported drug-drug interactions (DDIs) and food-drug interactions (FDIs) continues to increase



OATPs in recent NDAs

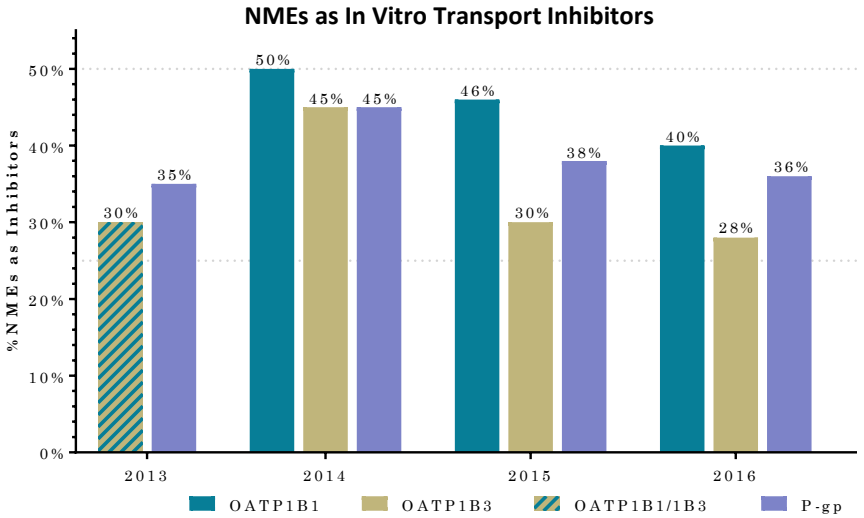
- The 2012 revision to the FDA drug interaction guidance added six transporters, including OATP1B1/1B3, to be considered in the evaluation NMEs
- Based on *in vitro* data, less than 10 new drugs in the last four years are OATP1B1/1B3 substrates
  - P-gp is the most common (>40), followed by BCRP
- Overall, fewer drugs were tested as substrates of OATPs compared to P-gp



Yu et al. 2014, 2015, 2016, 2018; Drugs@FDA

OATPs in recent NDAs

- In the last four years, OATP1B1 is the transporter most commonly inhibited by NMEs (44 drugs) *in vitro*
  - Followed by P-gp (37 drugs) and OATP1B3 (33 drugs)



- When evaluated *in vivo*, only 10% significantly increased OATP1B1/1B3 substrate exposure

DRUG INTERACTION SOLUTIONS

Yu et al. 2014, 2015, 2016, 2018; Drugs@FDA

Regulatory Guidance on Transporter Assessment

- *In Vitro*
  - As Substrate: ≥ 25% of CL_{total} is hepatic/biliary; site of action in the liver
    - Uptake Ratio ≥ 2, decreases with known inhibitor by ≥ 50%
  - As Inhibitor: all new compounds must be evaluated
    - R-value ≥ ~~1.25~~ 1.1
- *In Vivo*
  - Positive *in vitro* result(s)
    - Change in AUC ≥ 1.25-fold
- Recommended index drugs
  - Substrates: pitavastatin, pravastatin, rosuvastatin
  - Inhibitors: cyclosporine, single dose rifampin

OATP1B1/1B3 Marker Compounds

- Recommended marker substrates and inhibitors are similar between agencies, but limited
  - Inhibitors: cyclosporine, single dose rifampin

> *"Results from most transporter inhibition studies are not easily extrapolated to other drugs, because most inhibitors are not specific for a single transporter"*

  - Substrates: pitavastatin, pravastatin, rosuvastatin

> *"Several drugs are substrates of more than one transporter. For example, rosuvastatin is a substrate for BCRP and OATP."*

Despite the increase in research on OATP1B1/1B3 since these transporters were included in the 2012 guidance, little has been updated regarding their evaluation

It has been well established in recent years that OATP1B1/1B3 are clinically relevant transporters for drug-drug interactions and should be considered during development, yet the current regulatory guidance offers a limited choice of selective substrates.

By analyzing clinical and preclinical literature data, it is hypothesized that more sensitive and selective substrates and inhibitors of OATP1B1/1B3 can be identified, which can, in turn, be used to evaluate and improve the translatability of *in vitro* data to *in vivo* prediction.

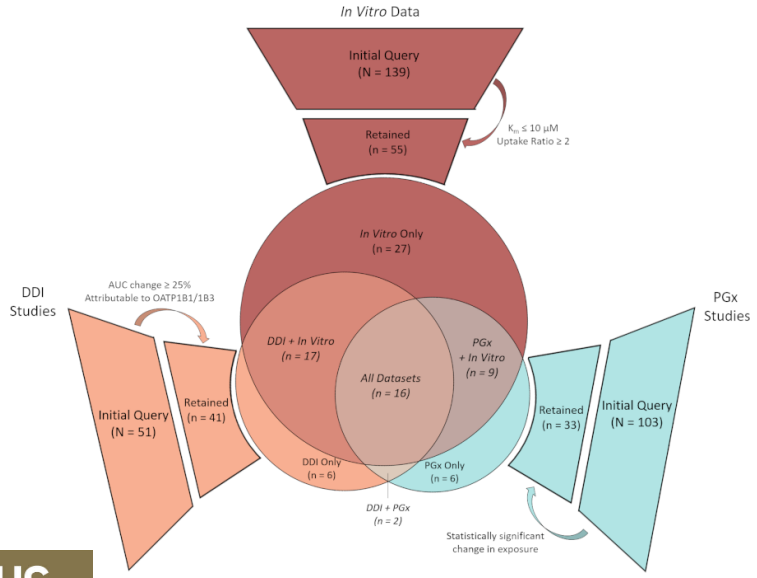
- *Aims of the evaluation:*
  - Identify potential *in vivo* substrates of OATP1B1/1B3 and evaluate the identified compounds for clinical relevance using a novel indexing system
  - Evaluate the sources of variability in the *in vitro* evaluation of OATP1B/1B3 inhibitors and the effect on clinical interaction predictions
  - Identify potential inhibitors of OATP1B1/1B3 and evaluate the identified compounds for clinical relevance

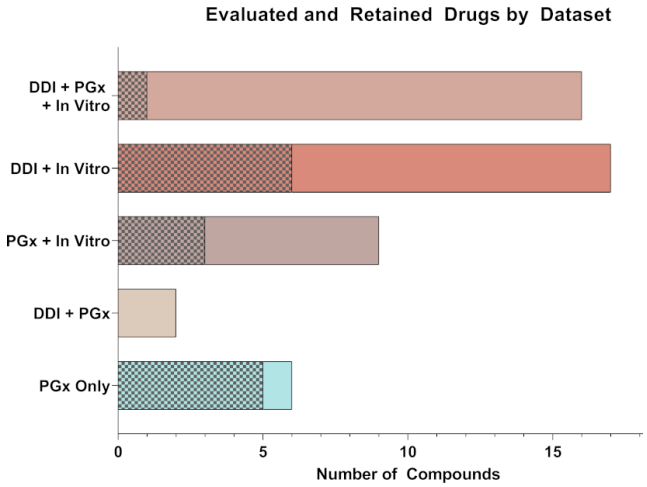
SUBSTRATE IDENTIFICATION

McFeely SJ et al. Identification and Evaluation of Clinical Substrates of Organic Anion Transporting Polypeptides 1B1 and 1B3. Clin Transl Sci. 2019 Jul 1;12(4):379–87.

Substrate Identification

- Queries of the *in vitro*, clinical DDI, and pharmacogenetic modules of the UW DIDB were completed to identify potential clinical substrates of OATP1B1/1B3
  - 53% of identified *in vitro* substrates did not have corresponding clinical data and were unable to be evaluated further.
  - 26% of substrates (22/83) had *in vitro* and either clinical DDI or PGx data
  - 19% of substrates (16/83) had data from all three sources





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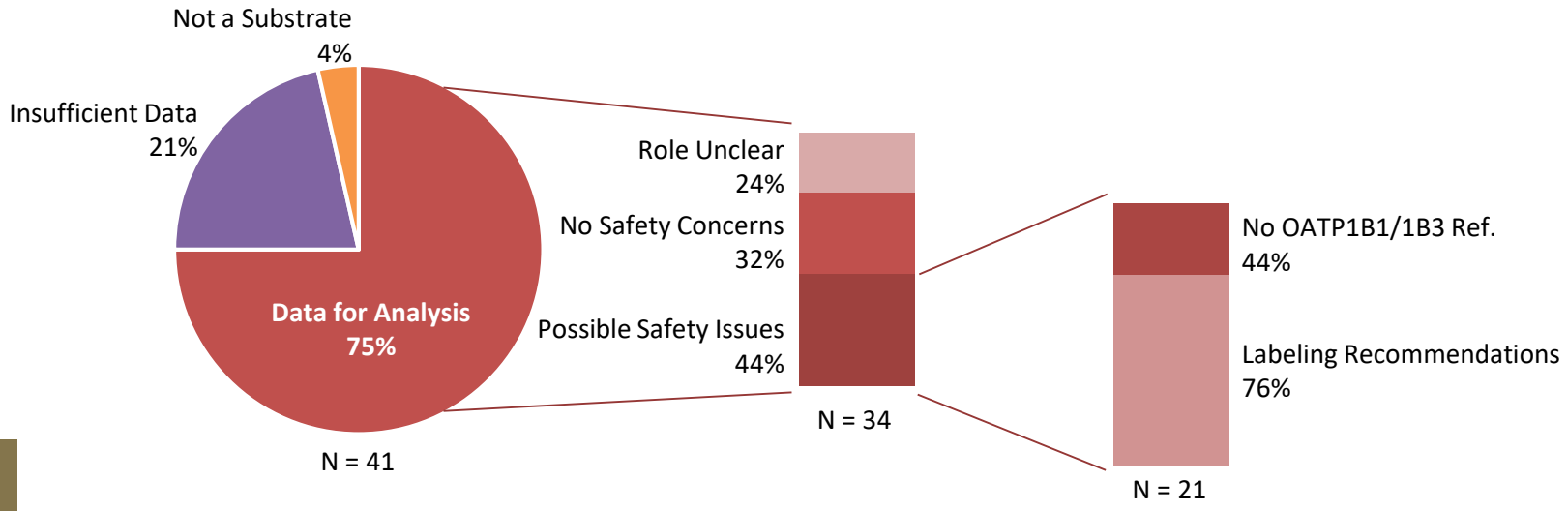
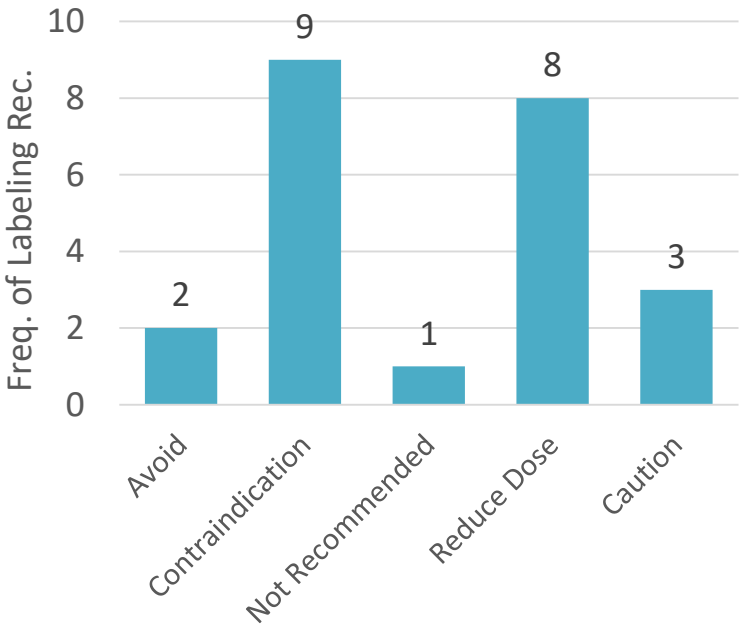
Clinical Substrates of OATP1B1/1B3

- Of the 41 drugs identified as potential substrates, 34 (83%) had sufficient data to support a clinically significant role of OATP1B1/1B3
  - 21 show possible significant safety issues associated with OATP1B1/1B3 inhibition
  - 6 did not have sufficient data to determine the clinical impact of inhibition
  - 1 not a substrate of OATP1B1/1B3
- 16/21 identified substrates (76%) have labeling recommendations regarding OATP1B1/1B3 inhibition.



Labeling Recommendations for Identified Substrates

- 16 of the 22 identified substrates (72%) have statements in the labeling regarding OATP1B1/1B3 inhibition.
  - 23 specific statements
  - Includes language towards “OATP inhibitors” (5) and specific inhibitors (11)
- 5 drugs (24%) do not currently have recommendations regarding OATPs



Identified substrates with no OATP1B1/1B3 labeling recommendations

Drug	AUC Ratio	Possible Reason for Lack of Recommendation
caspofungin	1.6 (RIF)	caution recommended with CsA
danoprevir	15.6 (CsA)	not approved in US/Europe
docetaxel	1.6 (CsA)	reduce dose with strong CYP3A inhibitor (2.4-fold, keto)
lovastatin	5.0 (CsA)	avoid GEM or CsA (CYP3A)
SN-38	2.1 (PGx)	active metabolite of irinotecan

DRUG INTERACTION SOLUTIONS

Probe Index

An index was developed to quantitatively and objectively evaluate substrates for utility as an OATP1B1/1B3 probe substrate.

Primary Evaluation Categories

Additional Criteria

TOTAL SCORE	15	(top of each category + all positive criteria)
Sensitivity to OATP1B1/1B3 inhibition[a]	0	No PGX data or clinical studies with a specific inhibitor for OATP1B1/1B3 -or- AUC Ratio < 1.25
	1	1.25 ≤ AUCR < 2
	2	2 ≤ AUCR < 3.5
	3	3.5 ≤ AUCR < 5
	4	5 ≤ AUCR < 7.5
	5	7.5 ≤ AUCR < 10
	6	AUCR ≥ 10
Specificity[b]	0	Sensitive substrate for at least 2 metabolic enzymes or transporters (AUCR ≥ 5 for each pathway)[c,d]
	1	Moderate sensitive substrate for at least 2 metabolic enzymes or transporters (2 ≤ AUCR < 5 for each pathway)[c,d]
	2	Sensitive substrate of one metabolic enzyme or transporter (AUCR ≥ 5)
	3	Weak substrate for at least 2 metabolic enzymes or transporters (AUCR < 2 for each pathway)[c,d]
	4	Moderate sensitive substrate of one metabolic enzyme or transporter (2 ≤ AUCR < 5)
	5	Weak substrate of one metabolic enzyme or transporter (AUCR < 2)
	6	Only OATP1B1/1B3 contributes to the disposition of the compound
Safety Profile	-2	Unfavorable safety profile for a single dose (narrow therapeutic range or expected significant side effects) or clinical safety has not been fully evaluated at this time
	1	Can be administered as a single, low dose with a low risk of adverse events in a healthy population or is well tolerated over a wide dose range, no concerns administering to a healthy population
Additional Criteria:		
Positives	1	PGx studies completed showing an impact of *SLCO1B1* or *1B3* variants
	0.5	Microdosing validated
	0.5	Published and validated PBPK model
Negatives	-2	Only available as a combination therapy
	-0.5	Non-linear pharmacokinetics
	-0.5	Half-life longer than 24 h
	-0.5	Very low bioavailability (F < 5%)

DRUG INTERACTION SOLUTIONS

Probe Index

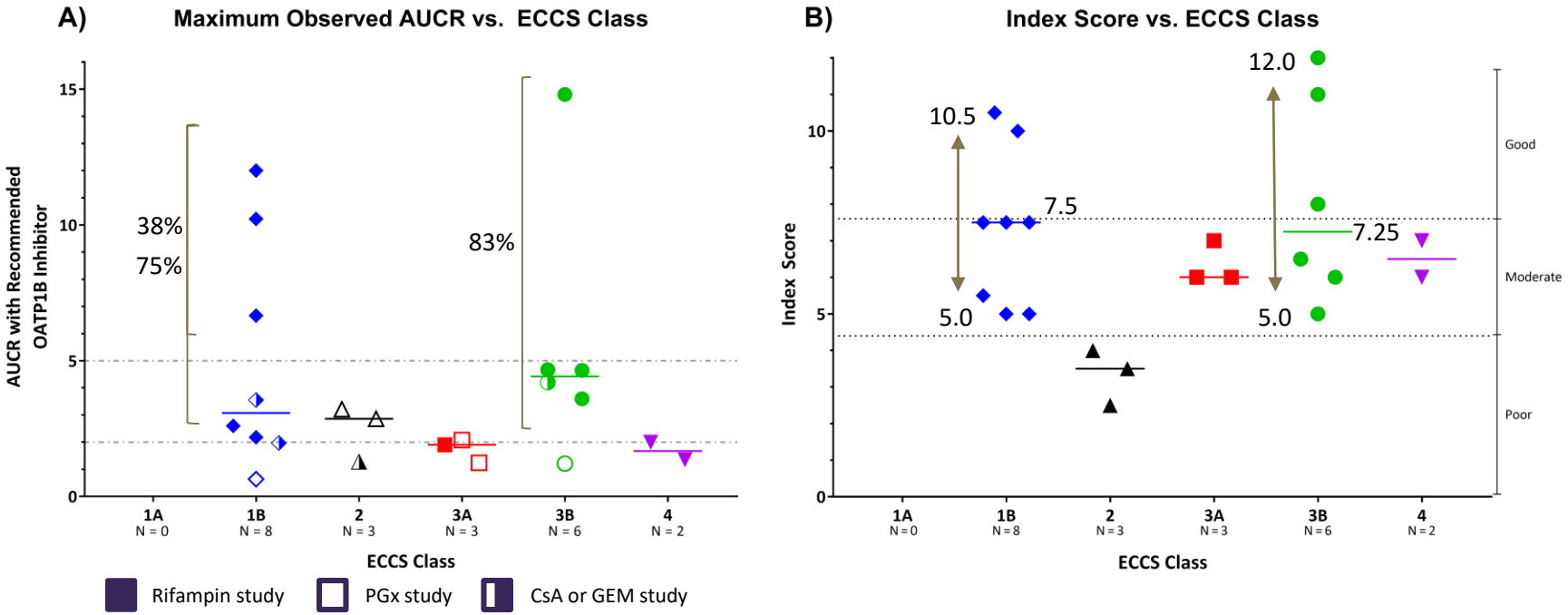
- Six drugs are proposed as potential clinical marker substrates
  - High sensitivity towards OATP1B1/1B3 inhibition
  - Low or manageable contribution of other metabolism/transport
  - Favorable clinical safety profile

Drug	Rank	Index Score	ECCS Classification	Therapeutic Area	Highest Reported AUC Ratio	Highest Observed PGX Effect	Other Metabolism / Transport
pravastatin*	1	12.0	3B	statin	4.64	3.81	BCRP/OATP2B1/ P-gp
rosuvastatin*	2	11.0	3B	statin	4.67	2.18	CYP2C9 BCRP/OATP2B1/ P-gp
pitavastatin*	3	10.5	1B	statin	6.67	3.85	BCRP/OATP2B1/ P-gp
atorvastatin*	4	10.0	1B	statin	12.0	2.51	CYP3A BCRP/P-gp
eluxadoline	5	8.0	3B	GI agent	4.20 (CsA)	2.01	N/A
letermovir	5	8.0	--	antiviral	2.10 (CsA)	1.40	N/A

*FDA/ITC Recommended Substrate

Comparison to ECCS

- The ECCS evaluates drugs based on a combination of permeability, ionization state, molecular weight, and the separation of metabolic and transport rate- determining steps
  - The 1B and 3B classes should be the most promising OATP1B1/1B3 markers



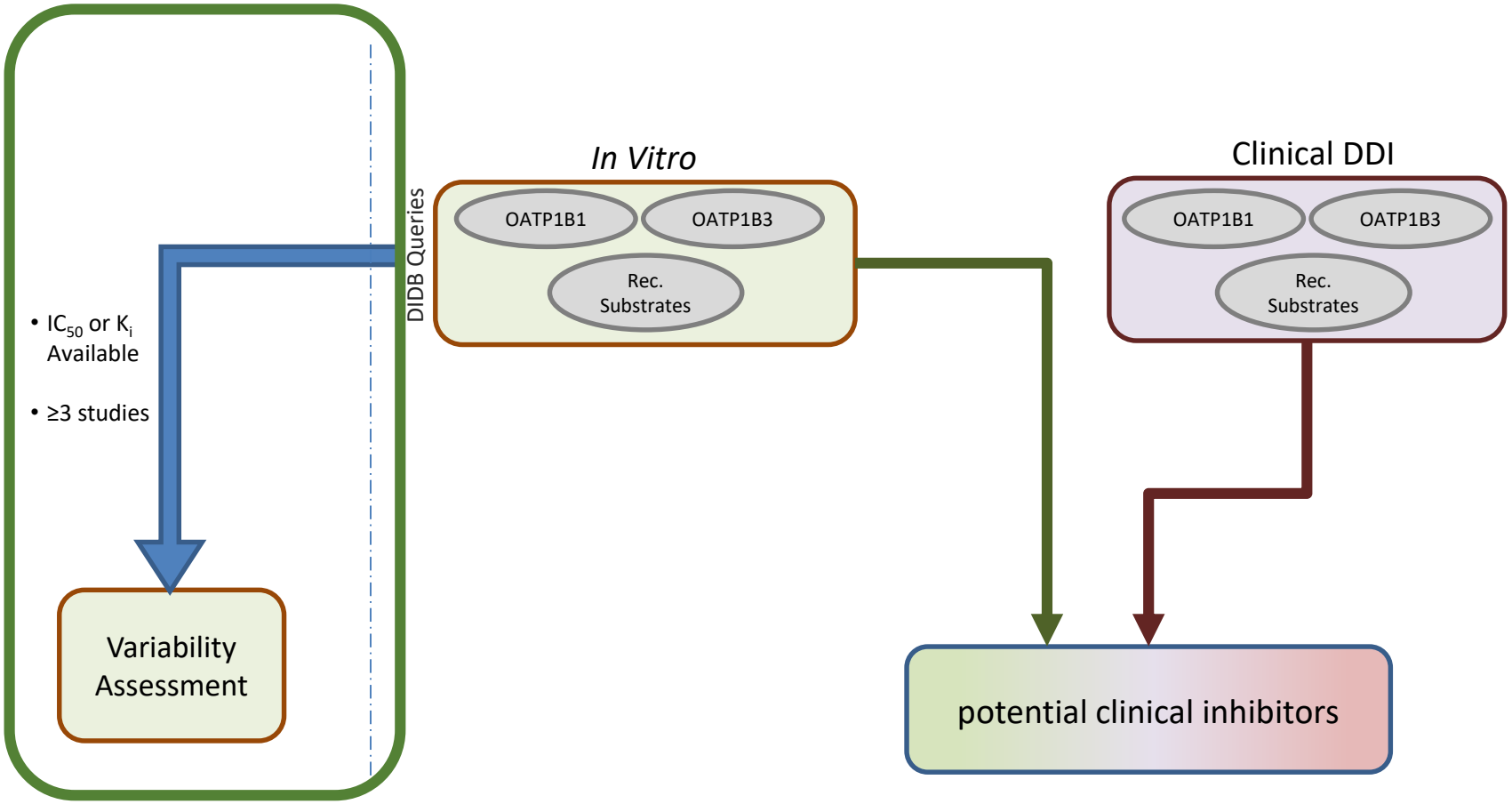
Substrate Summary

- 34 drugs were identified as clinical substrates of OATP1B1/1B3
  - Of these, 6 were identified using a novel ranking system as potential marker compounds
- A thorough understanding of the clinical disposition of these drugs allows for use of a fit-for-purpose marker
  - Isolate the contribution of OATP1B1/1B3 using a selective compound
    - Ex: pravastatin, pitavastatin, eluxadoline
  - Determine a "worst-case scenario" effect if the NME is an inhibitor of multiple pathways
    - CYP3A/P-gp/OATP1B: atorvastatin
- The current regulatory approach to *in vitro* substrate data has limitations
  - Uptake ratios are highly variable and currently do not have established acceptance or reporting criteria

INHIBITOR IDENTIFICATION AND VARIABILITY

McFeely SJ, et al. Variability in *In Vitro* OATP1B1/1B3 Inhibition Data: Impact of Incubation Conditions on Variability and Subsequent Drug Interaction Predictions. Clin Transl Sci. 2019 [Epub ahead of print].

Compound Identification



University of Washington Drug Interaction Database (DIDB®, www.druginteractioninfo.org)

In Vitro Variability

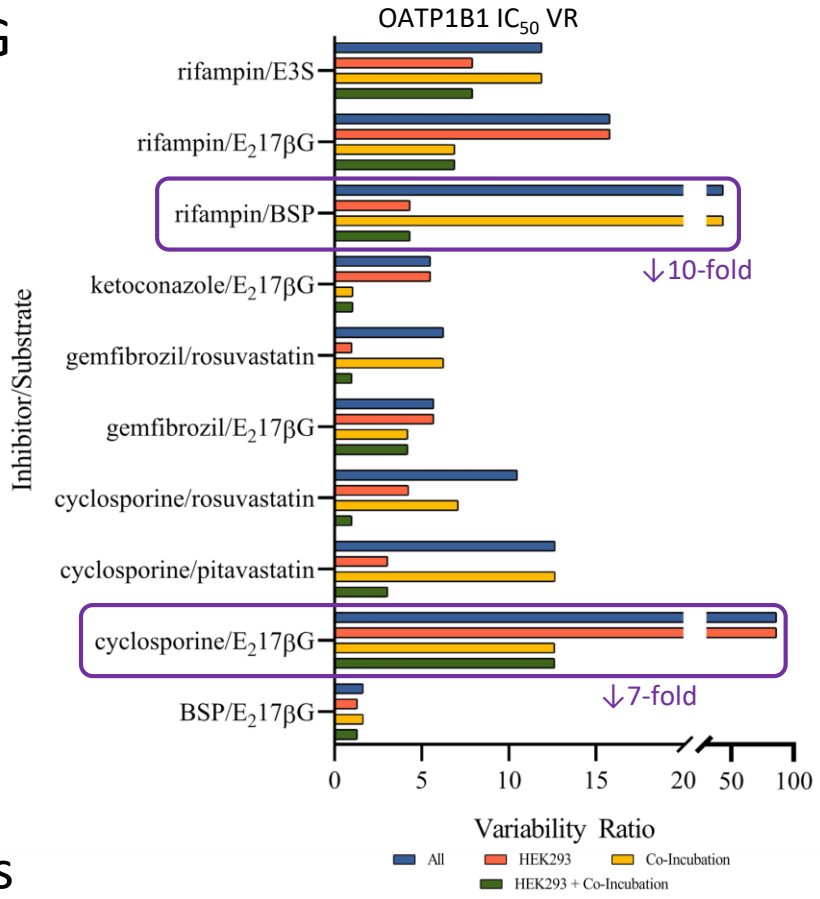
- 128 studies evaluated from 44 publications
  - Required to have ≥ 3 studies for retention
  - OATP1B1
    - IC_{50} values: 21 substrate/inhibitor pairs
    - K_i values: 7 substrate/inhibitor pairs
  - OATP1B3
    - IC_{50} values: 2 substrate/inhibitor pairs
- Inhibitors: rifampin (27%), cyclosporine (25%), gemfibrozil (18%)
- Substrates: estradiol-17-β-gluc (62%), atorvastatin (15%)
- Cell type: HEK293 (79%)

Variability ratios (highest IC_{50} or K_i relative to the lowest) were calculated for each pair

R-values were calculated from each inhibitor constant

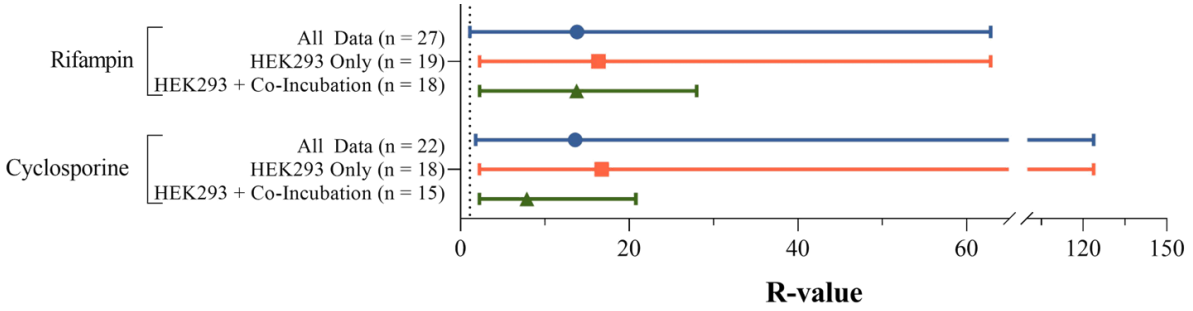
IC_{50} and K_i Variability

- The VR for the entire dataset = 12.4
  - $VR_{IC50,OATP1B1}$ = cyclosporine/E_2-17β-G (86.4, n = 11)
  - $VR_{Ki,OATP1B1}$ = gemfibrozil/ E_2-17β-G (7.2, n = 3)
  - $VR_{IC50,OATP1B3}$ = rifampin/ E_2-17β-G (58.2, n = 7)
- Accounting for cell type and co-incubation reduced dataset variability (VR = 5.23)
- Substrate also contributed to variability
  - Highest VR for non-clinical substrates
    - cyclosporine/E_2-17β-G (86.4, n = 11)
    - cyclosporine/pitavastatin (12.7, n = 4)
  - Reduced by controlling for cell type and co-incubation

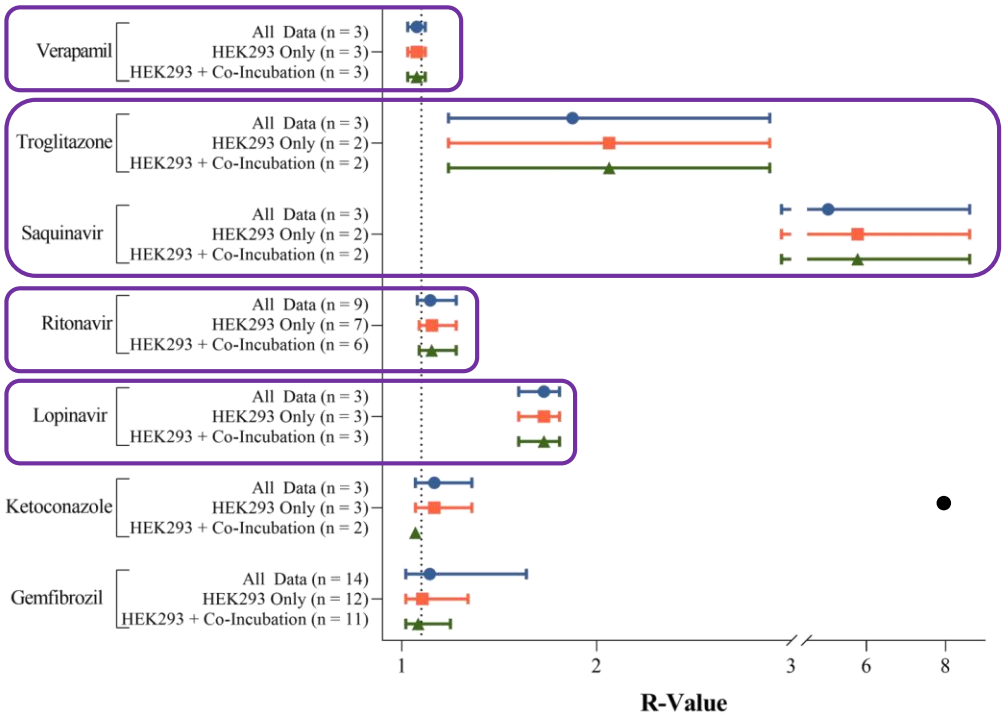


R-Value Variability

- Despite changes in VR when accounting for incubation conditions, resulting R-values did not show a significant shift relative to the FDA cut-off value of 1.1
- The recommended index inhibitors rifampin and cyclosporine had all R-values ≥ 1.1
  - Maximum fold-change was reduced when accounting for incubation conditions
    - Rifampin: 12.8 → 5.7
    - Cyclosporine: 51.1 → 8.6
- In contrast, only 5/14 (36%) of the R-values calculated for gemfibrozil met the FDA cut-off
  - Likely due to not accounting for inhibitory metabolites



R-Value Variability

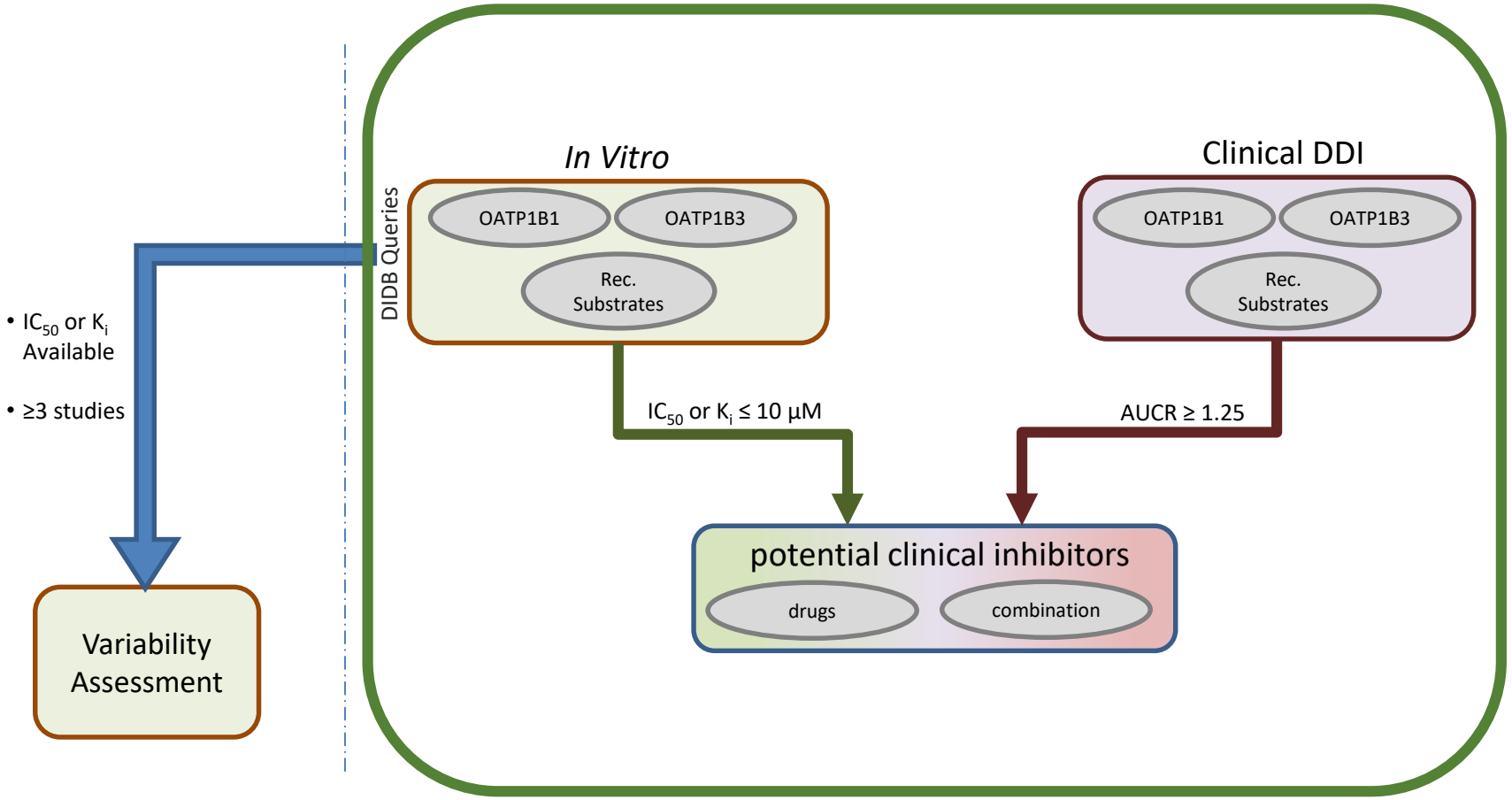


- Remaining drugs had mixed effects of incubation conditions on R-value
  - 4 showed all values ≥ 1.1 regardless of conditions
  - 2 resulted in R-values above and below the cutoff for all datasets
  - Ketoconazole did not have any R-values ≥ 1.1 for the most uniform dataset
- Very few drugs had clinical data available
  - Trend towards less variability in significance for strong inhibitors

Conclusions

- Two aspects of study design – cell type and preincubation – significantly contribute to *in vitro* variability
  - FDA recommends a 30-min preincubation as of the 2017 guidance
  - Over 80% of experiments performed in the last 5 years were completed in HEK293 cells
  - Substrate was also found to have an effect
- *In vitro* variability does not appear to have an effect on clinical predictions for the inhibitors evaluated
  - Weaker inhibitors may show predictions above and below the cut-off value
- Despite the broad range of values found in this work, the overall variability is lower than what has been observed for P-gp
  - P-gp showed over 700-fold variability for a single inhibitor/substrate pair

Clinical Inhibitor Identification

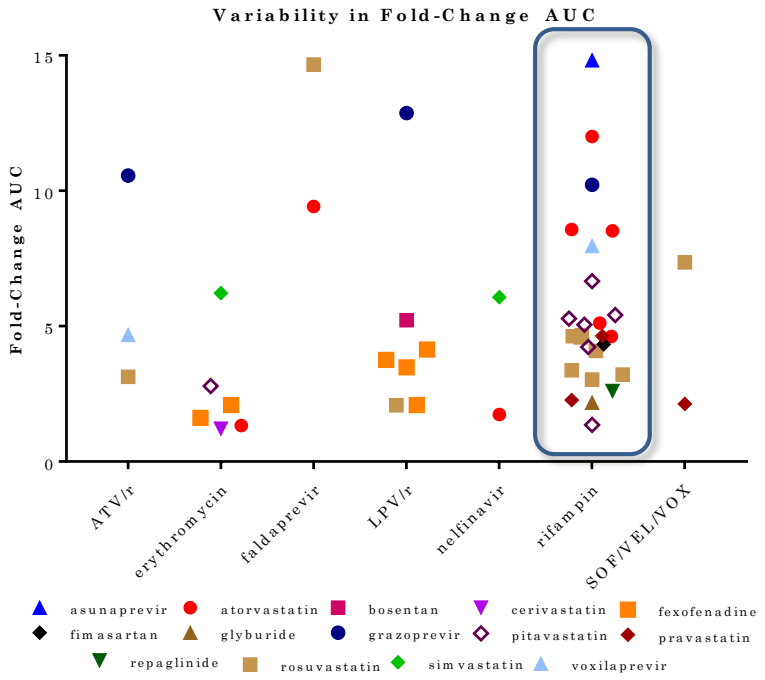


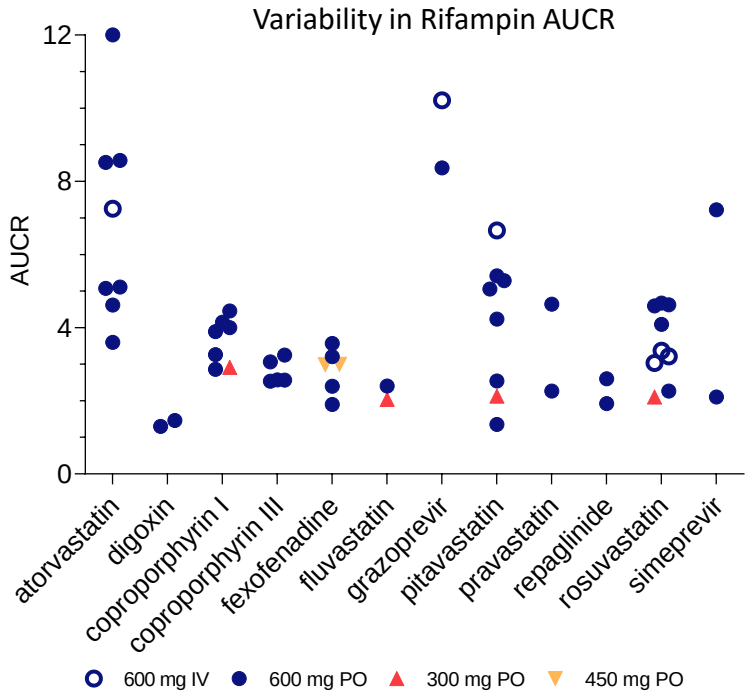
Rifampin as a Marker Inhibitor

- Despite the long-standing use of rifampin, many aspects of its disposition and use as an index inhibitor have not been fully evaluated
  - Reproducibility and variability
  - Time-dependent inhibition
    - FDA now recommends a 30 min pre-incubation with inhibitor for *in vitro* evaluation
  - Induction / inhibition balance
- Areas for future research [regulatory perspective]
  - Impact of lower doses
  - Route / timing of administration
  - Use of PBPK modeling
- Clinical Use
  - Populations / regions where data is most relevant
  - What is known about the impact of RIF on co-meds

Rifampin as a Marker Inhibitor

- *In vivo*, there is high variability observed in the AUCR for a given inhibitor-substrate pair
  - pitavastatin – rifampin, 5-fold variation
  - atorvastatin – rifampin, 2.6-fold





Rifampin as a Marker Inhibitor

- Currently, 89% of studies use a 600 mg dose of rifampin with 76% using a single, oral dose (68% overall)
  - Limited data for other doses
  - Alternate doses are almost exclusively multiple dose studies
- Static predictions for doses ranging from 300 mg - 900 mg show little difference for the sensitive substrate pravastatin (2.53 – 2.67)
  - Likely due to plasma concentrations >> lowest reported $K_{i,OATP1B1}$
- Lower doses of rifampin could likely be used in inhibition studies, reducing risk to patients while still providing maximal inhibition

Inhibitor Summary

- Over 60% of *in vitro* OATP1B1/1B3 inhibitors met the regulatory criteria for further clinical evaluation
  - Clinical data is limited – less than 40% of these compounds have study data available
- Using clinical data for identified sensitive substrates, 13 drugs and 16 combination treatments were identified as inhibitors of OATP1B1/1B3
  - Majority of interactions are weak (47%, AUCR < 2)
  - 14% of identified interactions have an AUCR ≥ 5
- No novel clinical index inhibitors were identified in this analysis, but these findings further support the utility of cyclosporine and rifampin as worst-case-scenario and targeted inhibitors, respectively
  - Despite the frequent use, many aspects of rifampin study design have not been fully evaluated
  - There is a limited understanding of the underlying causes of variability in AUCR for specific interactions

Conclusions

- Thorough analysis of the clinical data identified 12 marker compounds for OATP1B1/1B3
  - Includes drugs from multiple therapeutic areas
  - 9/12 have labeling recommendations regarding OATP1B inhibition
- 13 clinical inhibitors have been identified from studies with known marker compounds
  - Most interactions result in AUCR < 2
  - A high number of potent *in vitro* inhibitors, yet clinical data are limited
  - Data supports the regulatory use of rifampin and cyclosporine
- Translating *in vitro* transport data to *in vivo* effects is inherently difficult
  - Uptake ratios are not currently well defined
  - High variability in IC_{50}/K_i values could contribute to poor predictions of clinical effect
  - Contribution of other metabolic and transport pathways confound clinical interpretation

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