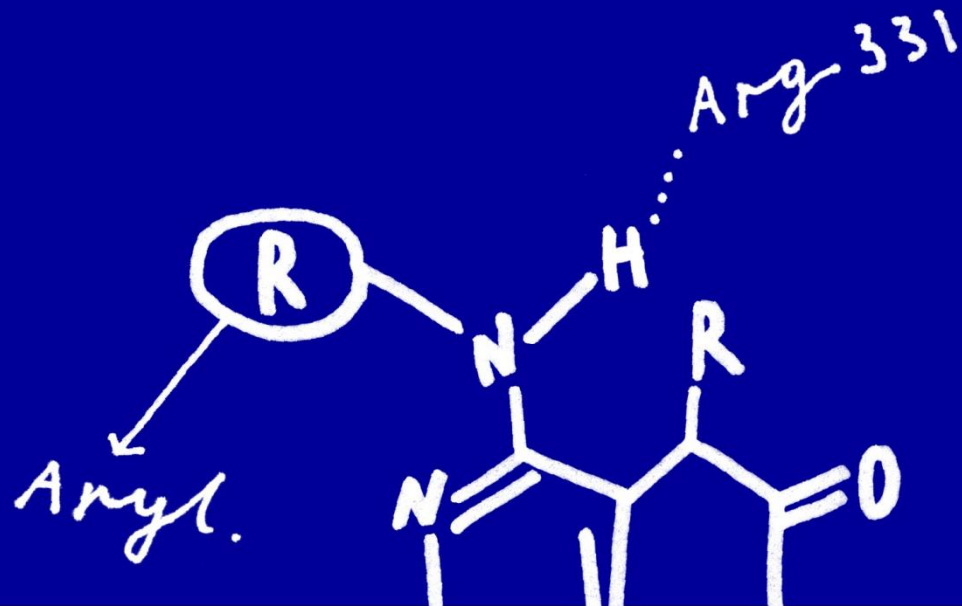


Transporter Drug-Drug Interactions: An evaluation of approaches and methodologies

Dr. Robert Elsby

cyprotex
AN EVOTEC COMPANY



Outline

Drug-Drug Interactions

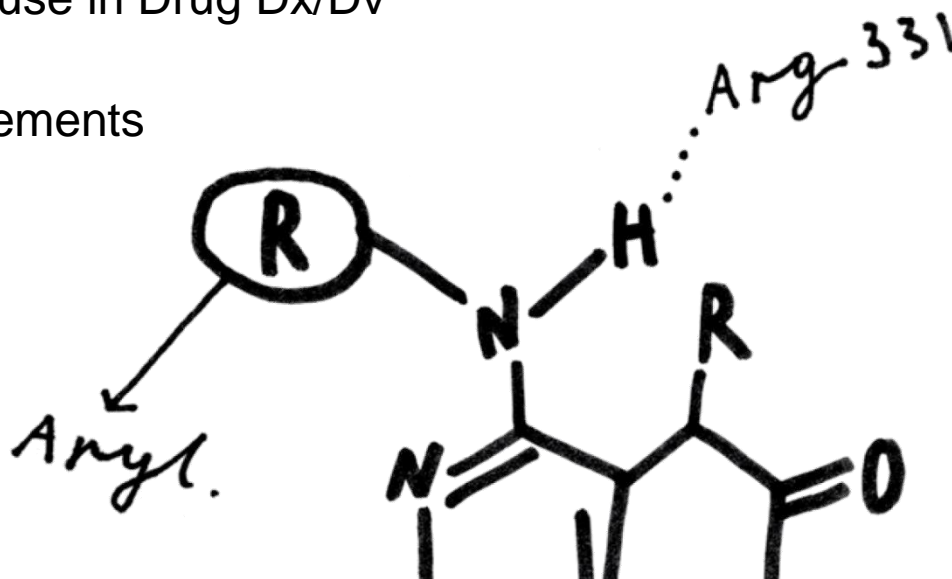
Predicting transporter DDIs in Drug Dx and Dv

Analysis of 4 published mechanistic static models

Suggestions for model use in Drug Dx/Dv

Possible model improvements

Summary



Drug-Drug Interactions

Introduction

- Polypharmacy is increasingly common due to an aging population
 - *1 in 2 patients over 65 years old are prescribed ≥ 5 drugs*
- Furthermore, DDIs continue to account for 5% of UK hospital admissions
- The National Institute of Health and Care Excellence (NICE) recently commented that clinical DDIs are more common than drug-disease interactions for the following 3 major indications:
 - *Type II diabetes*
 - *Heart failure*
 - *Depression*

Hence, the potential for DDI remains a regulatory concern

Why should we be concerned?

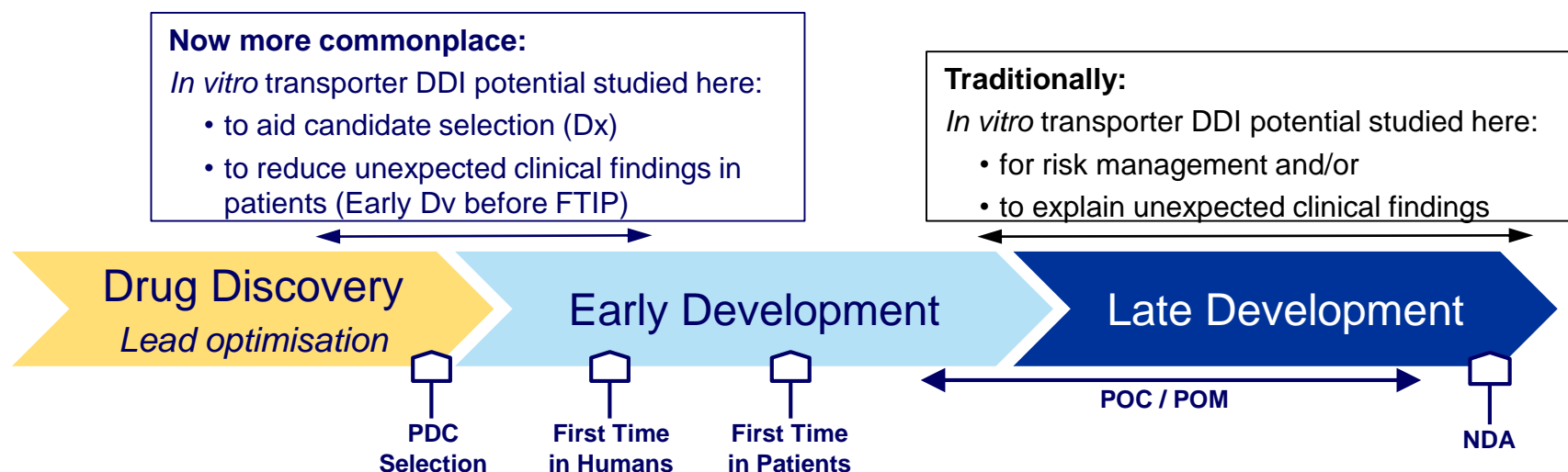
Transporter-mediated DDIs

- Analysis of top 200 marketed drugs in the US revealed that BDDCS Class III compounds are dominated by certain therapeutic classes:
 - *Antimicrobial (bacterial and viral)*
 - *Angiotensin II antagonists*
 - *Statins*
- All these compounds are metabolically stable and have poor permeability
 - *Therefore their disposition is primarily influenced by drug transporters*
- Furthermore, statins are currently the most prescribed drug class in the UK; annual prescriptions in England soared from 0.3 to 52 million between 1998 and 2008
- Additionally, 93% of American adults taking cholesterol-lowering drugs (which rose from 10-28% over last decade) use statins

Due to their prevalence, the potential for DDI with statins is high

Aims in Drug Discovery and Development

Predicting transporter-mediated DDIs



Usually simple hazard identification
 (using basic static equations detailed in regulatory guidance)

Actual risk analysis and mitigation of DDI

Effective and quantitative prediction of DDI using:
 - estimates of likely **unbound** human exposure and dose

Dynamic modelling (PBPK)

- can provide most accurate simulation of single mechanism DDI as perpetrator concentration and inhibitory potency fluctuates with time
- Heavily reliant on empirical data and detailed comprehensive understanding of disposition of victim and perpetrator

“Mechanistic” static modelling

- Requires fewer inputs and assumes perpetrator concentrations maintained at interaction site
- Prediction of an *in vivo* effect may be achieved within 2-fold using such methodology¹

However, we want to move to....

Mechanistic static model approaches

Predicting transporter-mediated DDIs

Mechanistic static approach provides a useful tool in Drug Discovery and Early Development

Requires knowledge of several PK processes and parameters:

Estimation of effective *unbound* perpetrator concentration at interaction site

Inhibition (or induction) potency of perpetrator must be translated to an *in vivo* effect

A detailed comprehensive understanding of parallel intestinal, hepatic and renal disposition pathways of victim drug

Identification of transporters and enzymes responsible for victim drug's disposition

Static models may be refined further by incorporation of Tier 1 ADME parameters e.g. intrinsic clearance

Aim of this talk:

To compare and contrast the performance of 4 recent influential publications describing mechanistic static models used for predicting complex DDIs, that vary in their assumptions and input parameters, as described in the review article of Williamson and Riley (2017)

Comparison of Mechanistic static models

Predicting transporter-mediated DDIs

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2017
<https://doi.org/10.1080/17425255.2017.1404028>

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REVIEW

Hepatic transporter drug-drug interactions: an evaluation of approaches and methodologies

Beth Williamson and Robert J. Riley

Drug Metabolism and Pharmacokinetics, Evotec, Abingdon, UK

Check for updates

Elsby <i>et al.</i> , 2012 Method A	$Fold \Delta = \frac{1}{\frac{f_{e(or m)}}{\left(1 + \frac{[I]}{K_i}\right)} + (1 - f_{e(or m)})}$
Yoshida <i>et al.</i> , 2012 Method B	$CL'_{int} = \frac{CL_{int}}{\left[\frac{\left(1 + \sum_{Co-administered\ drugs} \frac{I_i}{K_{i-uptake,i}}\right)^*}{\left(1 + \sum_{Co-administered\ drugs} \frac{I_i}{K_{i-efflux\ or\ metabolism,i}}\right)} \right]}$
Varma <i>et al.</i> , 2014 Method C	$AUCR = \frac{AUC'_{po}}{AUC_{po}} = \frac{F'_a}{F_a} * \frac{F'_g}{F_g} * \frac{F'_h}{F_h} * \frac{(CL_h + CL_r)}{(CL'_h + CL'_r)}$
Hu. 2013 Method D	$AUCR = \left(1 + \sum_j^n \left(\frac{[I]_j}{OATK_{ij}}\right)\right) * \left(1 + \sum_j^n \left(\frac{[I]_j}{eK_{ij}}\right)\right) * \left(\frac{1}{\frac{CR_{CYP}}{1 + \sum_j^n \left(\frac{[I]_j}{CYPK_{ij}}\right)} + (1 - CR_{CYP})}\right)^* * \left(\frac{1}{F_g + \left(\frac{1 - F_g}{1 + \sum_j^n \left(\frac{[I]_j}{CYPK_{ij}}\right) + \sum_j^n \left(\frac{[I]_j}{eK_{ij}}\right)}\right)}\right) * R = 1 + \sum_j^n \frac{[I]_j * K_{inactj}}{K_{deg} * ([I]_j + K_{ij})}$

Applied victim-specific models requiring relatively few inputs

Applied the extended clearance concept and additional observations

Applied victim-specific models requiring relatively few inputs

Method A – Elsby et al. (2012)

Predicting transporter-mediated DDIs

Model performance (observed versus predicted AUC)

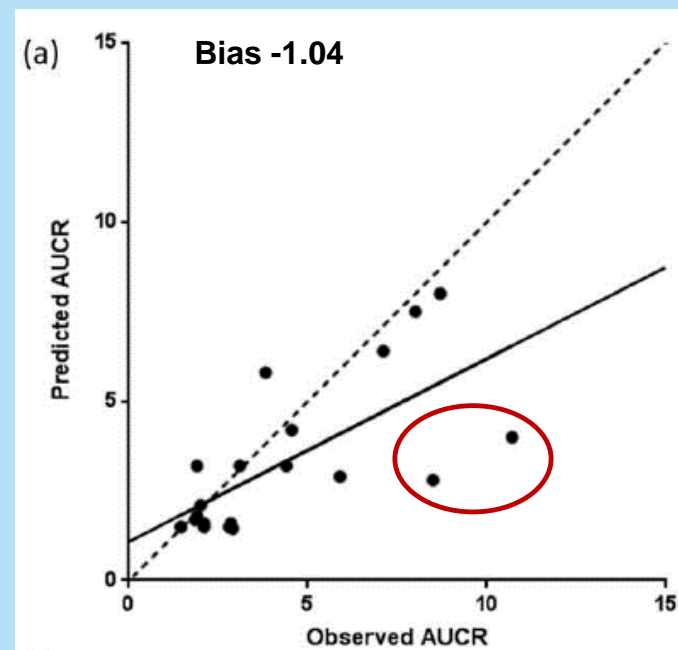
- Predicted AUCR for statin DDIs via pathways:
 - OATP-mediated inhibition
 - Intestinal BCRP-mediated inhibition
 - Intestinal/hepatic CYP3A4-mediated inhibition (reversible)
- Based on adapted Rowland-Matin equation¹ putting $[I]/K_i$ into context with fraction eliminated / metabolised (f_e / f_m)
- Victim-specific models successfully applied by defining enzymes/transporters responsible for victim's disposition (*from human ADME, clinical PGx and clinical DDI evidence*)
- Used unbound maximum hepatic inlet concentration ($I_{\max in, u}$) for OATP
- 20 DDIs were analysed for 6 statins
- **90% of DDIs predicted within 2-fold of observed AUCR**

Assumptions

- If $[I_{\text{gut}}]/K_i > 10$, assumed 100% inhibition of intestinal transporter or enzyme to give maximum theoretical fold AUC change for pathway

$$[I_{\text{gut}}] = \text{dose (mol)} / 250\text{mL}$$

Linear regression analysis



Absence of CYP3A4 TDI in model

Method B – Yoshida et al. (2012)

Predicting transporter-mediated DDIs

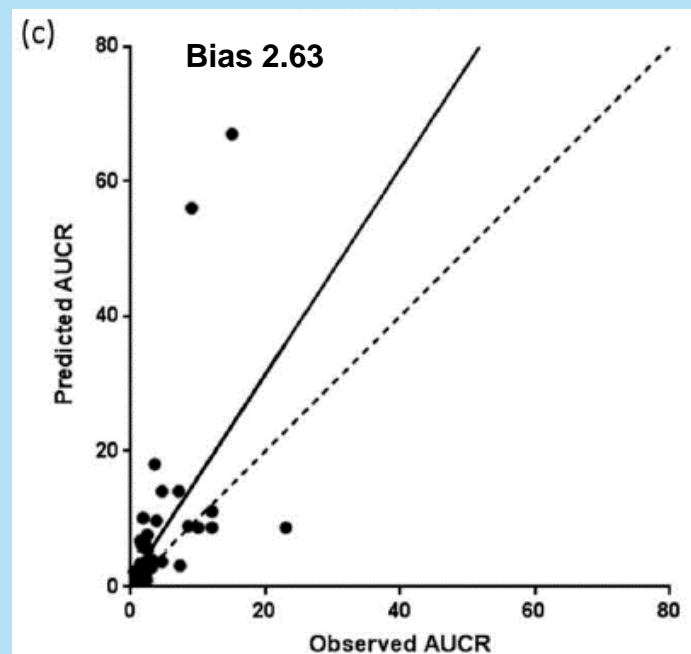
Model performance (observed versus predicted AUC)

- Predicted AUCR for range of DDIs via pathways:
 - OATP-mediated inhibition
 - Intestinal transporter/enzyme-mediated inhibition
 - Hepatic CYP3A4-mediated inhibition
- Based on extended clearance concept
- Used unbound maximum hepatic inlet concentration ($I_{\max in, u}$) for OATP
- 12 victims and 20 perpetrators were analysed for 58 DDI combinations
- **76% of DDIs predicted within 2-fold of observed AUCR**
- False negative frequency = 9%

Assumptions

- Assumed $F_a F_g = 1$ when intestinal transporter or enzymes were inhibited as judged by DIN (drug interaction number = dose/K_i)
 - CYP3A4 >2.8 L, P-gp >10.8 L, BCRP >10.8 L
- To avoid false negatives in final analysis, CYP TDIs were removed

Linear regression analysis



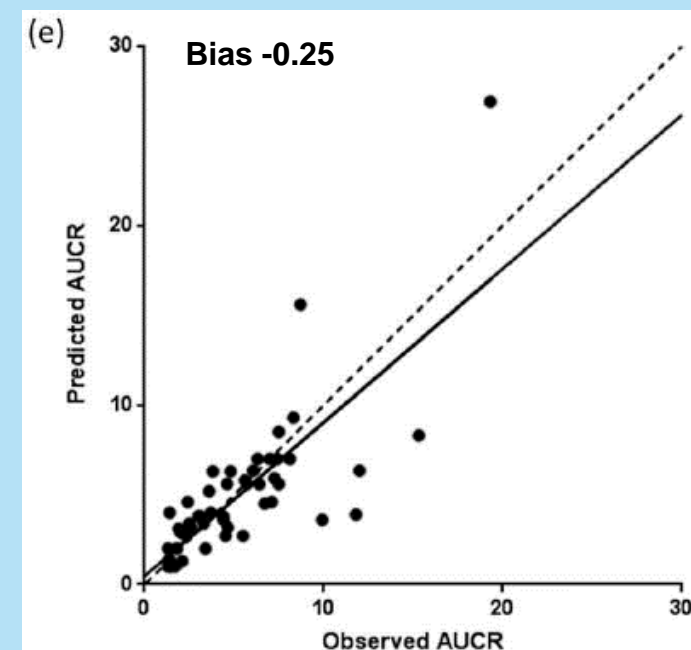
Method C – Varma et al. (2014)

Predicting transporter-mediated DDIs

Model performance (observed versus predicted AUC)

- Predicted AUCR for range of DDIs via pathways:
 - OATP-mediated inhibition
 - Intestinal transporter/enzyme-mediated inhibition
 - Hepatic CYP3A4-mediated inhibition (reversible, TDI)
- Applied an extended clearance concept model
- Used unbound maximum hepatic inlet concentration ($I_{\max, \text{in}, u}$) for OATP
- 10 victims and 6 perpetrators were analysed for 62 DDI combinations
- Looked at subset of 53 DDIs (minus CYP induction involvement)
- Interplay between enzyme-transporter interactions in clearance of victim required (victim-specific models for f_e / f_m)
- **94% of DDIs predicted within 2-fold of observed AUCR**

Linear regression analysis



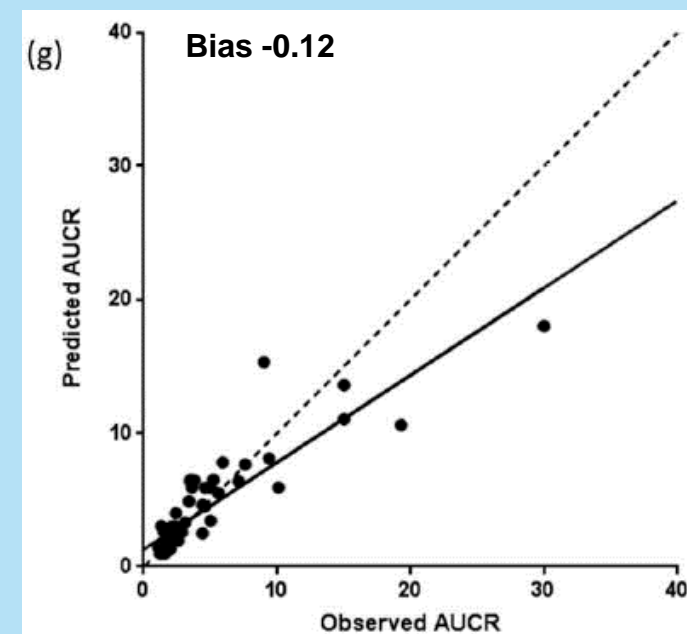
Method D – Hu (2013)

Predicting transporter-mediated DDIs

Model performance (observed versus predicted AUC)

- Predicted AUCR for range of DDIs via pathways:
 - OATP-mediated inhibition
 - Intestinal transporter/enzyme-mediated inhibition
 - Hepatic CYP3A4-mediated inhibition (reversible, TDI)
- Victim-specific models validated by defining enzymes/transporters responsible for victim's disposition (fraction metabolised by enzymes only; CR_{CYP})
- Used unbound maximum hepatic inlet concentration ($I_{\max in, u}$) for OATP
- 13 victims and 22 perpetrators were analysed for 62 DDI combinations
- **98% of DDIs predicted within 2-fold of observed AUCR**
- Relied on substantial amount of historical victim data to apply a disposition-pathway dependent prediction (DPDP)

Linear regression analysis



Comparison of Mechanistic static models

Predicting transporter-mediated DDIs

Are all input parameter values/assumptions
consistent across the different models?

Perpetrator Absorption – k_a , F_a , F_g

Input parameters

- The value used for k_a will impact the predictive accuracy of [I]:
 - enterocyte concentration (I_g)
 - unbound hepatic inlet concentration ($I_{\max in, u}$)
- This could significantly impact the DDI estimate if a high value is used for a perpetrator with a low absorption rate

Rate of absorption (k_a)

Methods A&B
 $k_a = 0.1 \text{ min}^{-1}$
 (adopting FDA conservative approach if unknown for a drug)

Methods C&D
 $k_a = 0.03 \text{ min}^{-1}$
(previous studies have demonstrated for CYP TDI and induction in liver that this is sufficiently conservative and reduces likelihood of false positives)

Method C also used perpetrator-specific k_a value if known

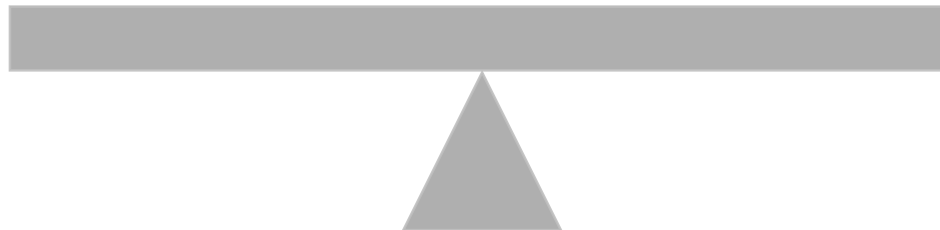
Extent of absorption ($F_a F_g$)

Default $F_a=1.0$ and a victim specific correction for $F_a F_g$ was applied by all Methods with different assumptions

Method A & B - when intestinal enzymes/transporters were inhibited as predicted by either $[I_2]/K_i > 10$ or DIN, respectively, then assumed maximum value $F_a F_g=1$

Method C & D – used victim specific F_g values

- The value used for $F_a F_g$ will also impact the predictive accuracy of [I]:
 - enterocyte concentration (I_g)
 - unbound hepatic inlet concentration ($I_{\max in, u}$)
- This could significantly impact the DDI estimate

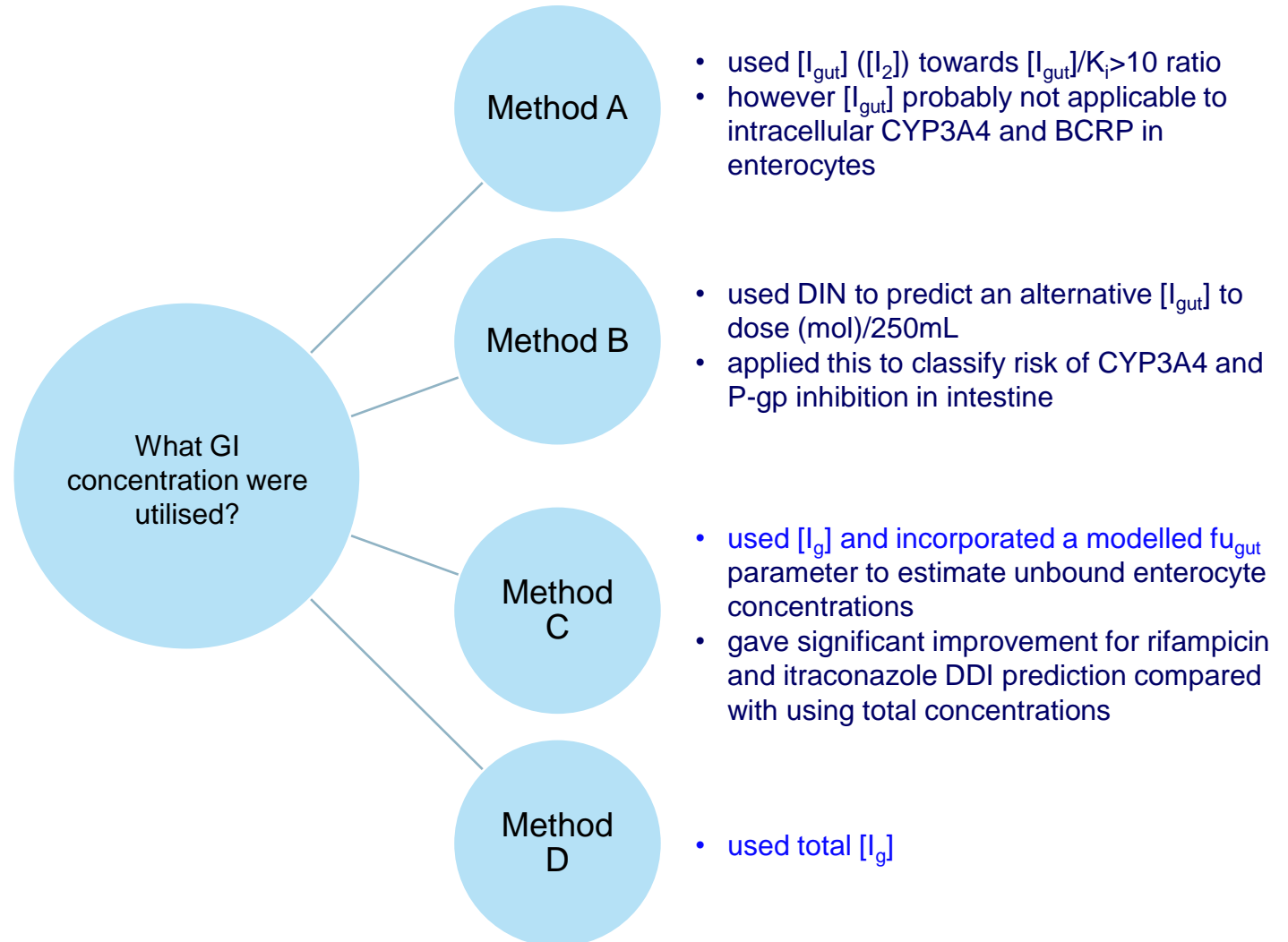


Perpetrator Absorption – Intestinal concentrations

Input parameters

- For orally administered drugs inhibition of CYPs and efflux transporters in the intestine is of particular clinical concern due to their high expression levels
- Need to consider high first pass metabolism and the potential for GI fluid to both limit perpetrator concentrations in the intestinal lumen ($[I_{gut}]$) and enterocyte
- Concentrations in the enterocyte $[I_g]$ offer:
 - a more dynamic approach by incorporating fraction and rate of absorption and intestinal blood flow
 - overcomes limitations of $[I_{gut}]$ for poorly soluble compounds

$$[I_g] = k_a \times F_a F_g \times \text{dose (mol)} / Q_{ent}$$



Perpetrator Inhibitory Potency (K_i)

Input parameters

- Numerous *in vitro* assay formats exist to quantify the inhibition potential of a compound, including the choice of probe substrate and the absence or presence of an inhibitor preincubation step
- Whilst it is preferred to use the K_i for the same substrate *in vitro* and *in vivo*, the occurrence of false negative/positive predictions did not vary significantly if the lowest reported K_i was adopted
- Williamson & Riley (2017) noted trends in the inhibition potencies of the perpetrators used in the four methods following comparison of the data:
 - Method D appeared to report the weakest inhibitory potency values and quantified the AUCR for the main disposition pathway of the victim only
 - In contrast, Method C used more potent inhibition values (up to 20-fold lower than Method D) and predicted the AUCR with the most comprehensive dataset
- Despite these differences in K_i values, both methods displayed similar predictive accuracy. Possible reasons for similar model performance may include:
 - The model parameters included may be correlated and therefore inclusion of all in one method over another may be counterintuitive
 - Some of the parameters cited may not be informative for the model e.g. if clinical exposure [I] is significantly $> K_i$, then variability in K_i values used may only have a modest impact on final prediction
- While the 4 methods described employ variable inhibition values, it is recommended that each laboratory generates their own parameter estimates for using in subsequent DDI predictions

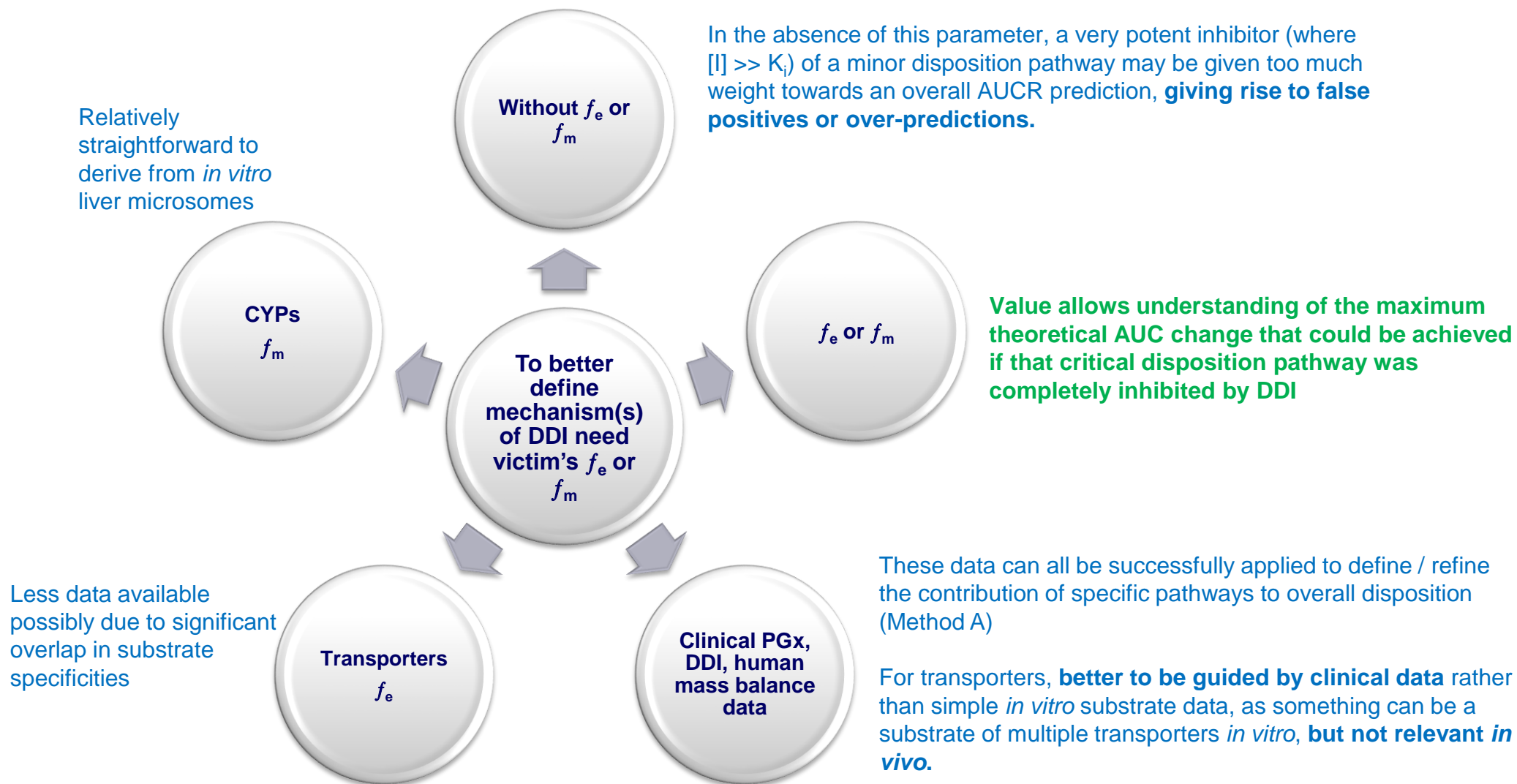
Perpetrator hepatic $K_{p,u,u}$

Input parameters

- Understanding the unbound partition coefficient ($K_{p,u,u}$) *in vivo* is required to define the distribution of the unbound compound in tissue and plasma
- For uptake transporter substrates, the unbound concentration in the liver will not equal the unbound concentration in the plasma and **their liver concentrations will significantly exceed their unbound hepatic inlet concentration** (unless reasonable hepatic efflux exists in parallel)
- However, inhibition of the uptake transporter can decrease $K_{p,u,u}$ by 75-90% (Varma *et al.*, 2014) thereby impacting on the intracellular concentrations of perpetrator available to inhibit hepatic enzymes (if it was an uptake substrate), which could potentially impact DDI predictions
- Neither Methods A, B or D utilised the $K_{p,u,u}$ parameter in their models
- In contrast, **Method C did incorporate a predicted $K_{p,u,u}$**

Contribution of disposition pathways (fraction metabolised/eliminated)

Input parameters



How do the four methods compare with regard to incorporation of f_e or f_m ?

Input parameters

Method A	Method B	Method C	Method D
<p>Included f_e for multiple transporters and f_m for CYPs</p> <p>Derived from published clinical PGx, clinical DDI and human radiolabelled mass balance data</p>	<p>Did not incorporate f_e or f_m parameters, rather included clearance data towards quantifying magnitude of DDI</p> <p>Reported a false positive rate of 25% likely resulting from over-prediction of the maximum theoretical AUC change possible for each major disposition pathway</p>	<p>Included f_m for all CYP substrates but as f_e data was limited for transporters, only one main transporter was included in analysis</p> <p>Additional inclusion of clearance data towards quantifying magnitude of DDI</p> <p>However, for uptake substrates IVIVE was limited and a correction factor was applied to estimate the <i>in vivo</i> clearance of 70% of compounds</p>	<p>Refined f_m for CYPs to reflect ratio of hepatic enzyme contribution to observed DDI (CR_{CYP})</p> <p>$CR_{CYP} = f_{m,CYP}$ if one enzyme involved in DDI</p> <p>$CR_{CYP} = 0$ if inhibition did not contribute to DDI</p> <p>When efflux transporter inhibition and CYP inhibition effects were additive, CR_{CYP} was reduced and contribution of efflux was integrated (CR_E)</p> <p>However, f_e for uptake transporters was not present</p>

AUCR variation in clinical DDIs and proposed mechanisms underpinning DDIs

Input parameters

- **Comparison of different method performance complicated by the following:**
 - Numerous sources of clinical DDI data resulting in marked differences in reported AUCR values between models
 - AUCR values varied even with same doses of perpetrator and victim
 - Plus there is a wide choice of victim and perpetrator doses to choose from for each DDI combination
 - e.g. Atorvastatin and Cyclosporine was evaluated in all models, but using clinical data derived from 5 different doses
- Furthermore, when comparing predictive accuracies are the proposed mechanisms underlying each DDI the same for each victim/perpetrator combination across the different methods (*i.e. are we comparing like for like*)?

Not always!

Atorvastatin & Cyclosporine					Fluvastatin & Fluconazole			
Method	OATP1B1	P-gp	CYP3A4	BCRP	MRP2	Method	OATP1B1	CYP2C9
A	✓		✓	✓		A		✓
B	✓	✓	✓			B	✓	✓
C	✓		✓	✓	✓	C	NA	NA
D	✓	✓	✓			D	✓	✓

Mechanistic static models summary of analysis

Predicting transporter-mediated DDIs

Table 1. (a) Summary of assumptions and input parameters for each model detailed above. (b) Inhibition potency (k_i , μM) for the transporter and CYP included in the AUCR calculation for atorvastatin/CsA and fluvastatin/fluconazole. Methods compared include A, Elsby et al., 2012; B, Yoshida et al., 2012; C, Varma et al., 2014; D, Hu, 2013 [18,31–33].

Parameter	Method A	Method B	Method C	Method D
(a)				
Clearance: CL_H , CL_R , $CL_{R,sec}$, CL_{bile}	–	++	++++	–
Transporter clearance	–	–	+	–
F_a	1	1	1/known perpetrator value	1
k_a (min^{-1})	0.1	0.1	0.1/known perpetrator value	0.03
F_g	Victim specific	Victim specific	Victim specific	Victim specific
Intestinal concentrations	$[I]_{gut}$	DIN	$[I]_{g,u}$	$[I]_g$
$K_{pu,u}$	–	–	+	–
Inhibition	k_i only	k_i only	k_i , K_i/K_{inact} (3A4 $k_{deg} = 0.029 \text{ h}^{-1}$, 2C8 $k_{deg} = 0.019 \text{ h}^{-1}$)	k_i , K_i/K_{inact} (3A4 $k_{deg} = 0.029 \text{ h}^{-1}$, 2C8 $k_{deg} = 0.019 \text{ h}^{-1}$)
Fraction metabolized/eliminated	+	–	+	+
Liver inlet concentrations: $[I] = fu_b \cdot (C_{max} + k_a \cdot F_a \cdot D / Q_H)$	+	+	+	+

+: single parameter included in the model; ++: two parameters included in the model; ++++: all four parameters included in the model; –: no parameter included; CL_H : hepatic clearance; CL_{bile} : biliary clearance; CL_R : renal clearance; $CL_{R,sec}$: renally secreted clearance; $[I]_g$: concentration in the enterocyte; $[I]_{gut}$: concentration in the intestine; DIN: drug interaction number; k_i : inhibition constant; K_{inact} : maximum inactivation; K_i : concentration at 50% K_{inact} ; k_a : absorption rate constant; F_a : fraction of drug absorbed; F_g : fraction of drug escaping the intestine; NA: not applicable.

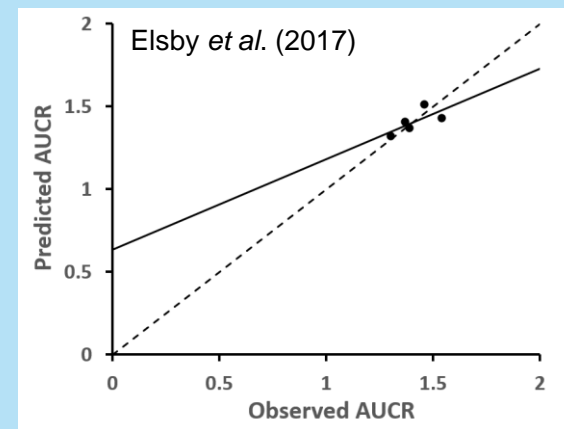
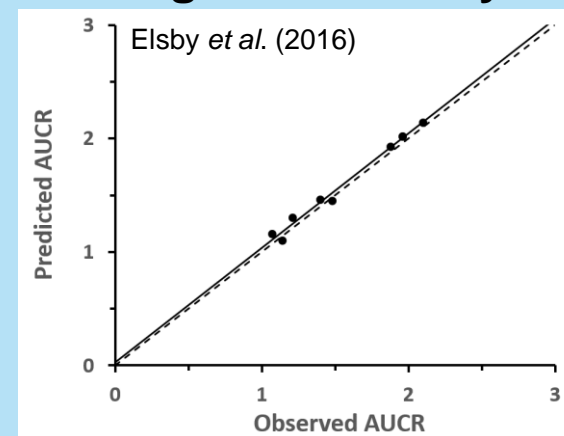
Additional Learning for Method A since Williamson and Riley analysis

Predicting transporter-mediated DDIs – 2 key victims

Model performance (observed versus predicted AUC)

- Predicted AUCR for 9 rosuvastatin DDIs (2016)
 - Applied maximum theoretical enterocyte concentration (I_g) with f_e for BCRP in place of $[I_{gut}]/K_i > 10$ (2012). Plus OATP1B1 prediction.
 - **100% of DDIs predicted within 1.25-fold of observed AUCR**
- Predicted AUCR for 5 metformin DDIs (2017)
 - Using a renal MATE1 apparent oral $f_e = 0.39$ and $C_{max,u}$ as $[I]$ to comply with the fact that any inhibitor that is a substrate of OCT2 cannot concentrate inside the cell due to the passive facilitative nature of OCT2.
 - **100% of DDIs predicted within 1.25-fold of observed AUCR**

Linear regression analysis



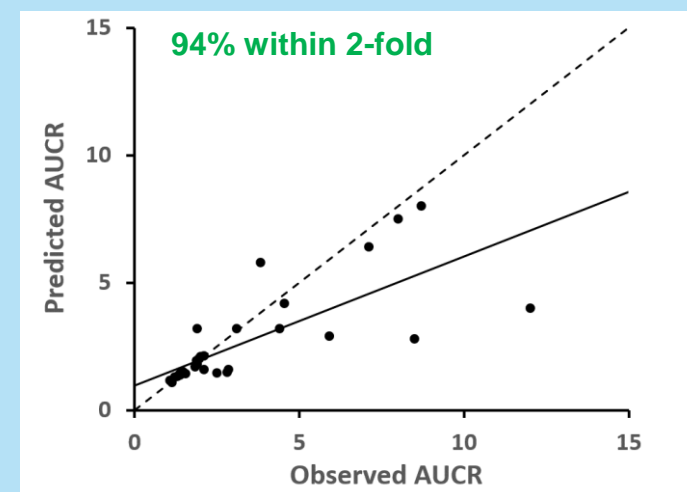
Additional Learning Summary

Predicting transporter-mediated DDIs

Model performance (observed versus predicted AUC)

- Combined all of:
 - original statin DDIs (2012)
 - additional rosuvastatin DDIs (2016)
 - metformin DDIs (2017)
- **31 DDIs – 29 out of 31 predicted within 2-fold (94%)**
- 2 not predicted due to possible absence of 3A4 TDI component?
- Use of enterocyte concentration ($[I_g]$) (rather than assuming complete intestinal inhibition if $[I_{gut}]/IC_{50} > 10$) would likely benefit wider predictions from 2012

Linear regression analysis

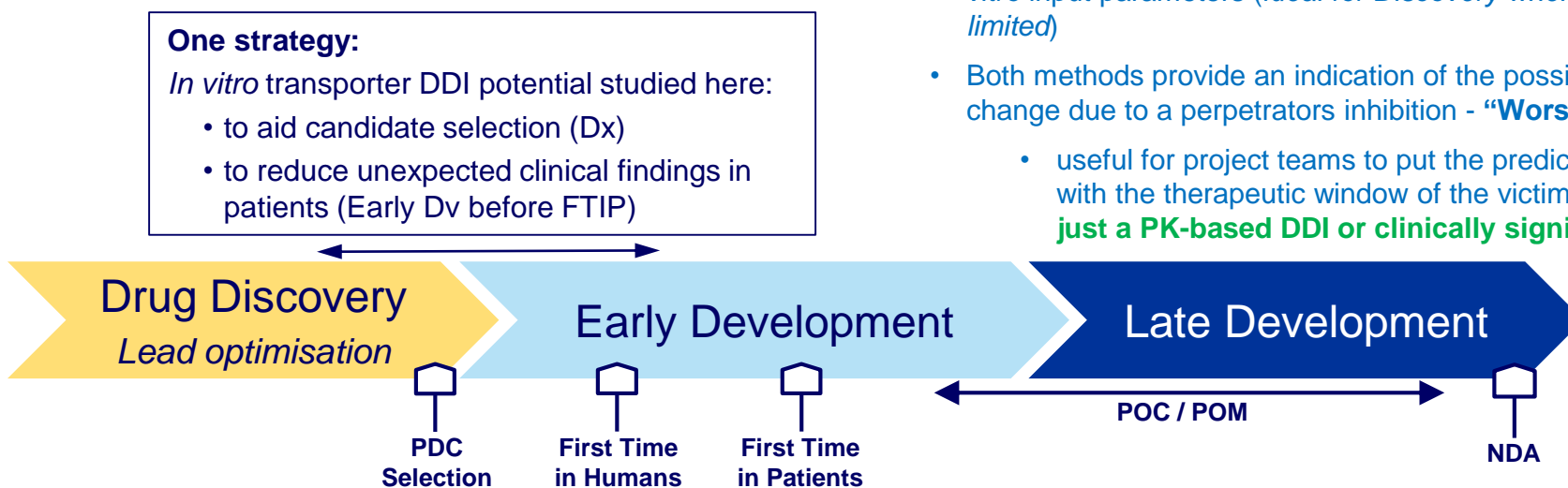


Which model do we use for Drug Discovery?

Predicting transporter-mediated DDIs

- Application and utility of Methods A-D towards quantitative prediction of DDI may be dependent on the timing and interpretation of drug transporter studies

- Need to have confidence in translation of *in vitro* inhibition data to enable decision making (e.g. *OATP1B1*, *BCRP* inhibition – *statin* risk assessment)
- **Method A and Method D** may be pragmatic choices - require very few *in vitro* input parameters (*ideal for Discovery when measured data may be limited*)
- Both methods provide an indication of the possible maximum theoretical AUC change due to a perpetrator's inhibition - **“Worst-case scenario”**
 - useful for project teams to put the predicted AUC change into context with the therapeutic window of the victim co-med, i.e. **whether it is just a PK-based DDI or clinically significant DDI**



Method A - ideal for understanding DDI risk versus statin co-meds (most prescribed drugs in UK)
 - 94% predictive accuracy (caveat – currently no CYP TDI component)

Method D - ideal for hepatic transporter DDIs more broadly (complete with CYP TDI)
 - 98% predictive accuracy

Which model do we use for later Drug Development?

Predicting transporter-mediated DDIs



- Method A (e.g. for metformin DDIs) and Method D could still be applied later in Development
 - understanding DDI risk from *in vitro* transporter inhibition studies (e.g. OAT1, OAT3, OCT2, MATE1 & MATE2-K) that do not necessarily impact candidate selection, but rather inform clinical protocol design and ultimately drug labelling before going into patients
- Additionally as a project progresses further into Development and more detailed, mechanistic ADME understanding of the molecule emerges to inform drug labelling, then Method C may become more value adding
- Whichever strategy is adopted, it is critical that the *in vitro* drug transporter studies conducted (and their translation) are aligned with the proposed clinical plan encompassing patient population, co-medication and likely therapeutic area

Improving Models

Predicting transporter-mediated DDIs

Method	Possible considerations for improving model performance
A	<p>Inclusion of CYP time dependent inhibition parameters</p> <p>Use of perpetrator specific F_a, k_a values</p>
B	<p>Inclusion of fraction metabolised/excreted for victim substrate disposition pathways</p> <p>Use of $[I_g]$ for intestinal interactions</p> <p>Use of perpetrator specific F_a, k_a values</p> <p>Inclusion of CYP time dependent inhibition parameters</p>
C	<p>Inclusion of fraction excreted values for multiple transporters (where applicable to critical disposition)</p> <p>Improved IVIVE for <i>in vivo</i> uptake transporter clearance</p>
D	<p>Inclusion of fraction excreted values for transporters based on derivation used by Method A (PGx etc)</p> <p>Use of perpetrator specific F_a, k_a values</p> <p>Inclusion of extended clearance concept may benefit predictions for some perpetrators</p>

Summary

- Due to polypharmacy, DDIs continue to account for 5% of UK hospital admissions and as such remain a major regulatory concern (particularly for common co-meds such as statins)
- Within Drug Discovery and Development we are moving away from relatively simple hazard identification of DDI potential (using basic static equations detailed in regulatory guidance) **to actual risk analysis and mitigation using quantitative prediction of DDI**
- The mechanistic static model approach highlighted by Methods A, B, C and D can provide a useful tool in Drug Discovery and Early Development towards this goal:
 - *Use of unbound exposure preceded recent FDA guidance but is consistent*
 - *Multiple CYP/transporter interactions now achievable – goes beyond current guidance*
 - *Use of an extended clearance concept alone may not offer a clear advantage*
- However, key to the successful accurate routine application of such models is:
 - their crucial requirement to understand and correctly quantify (f_e/f_m) the **clinically-relevant critical disposition pathways of victim drugs** that underpin the mechanisms behind DDI
 - a **consensus agreement reached for each victim-specific disposition mechanism** such they can be adopted by all mechanistic and PBPK models

Acknowledgments

Beth Williamson (formerly Evotec, DMPK Team Leader)

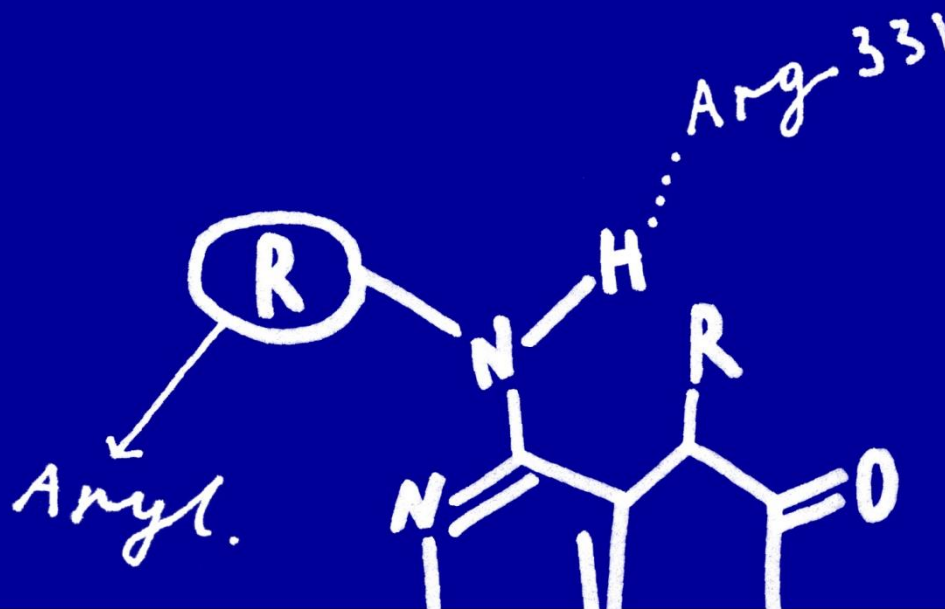
Rob Riley (Evotec, EVP Global ADME-Tox & DMPK)



Your contact:

Dr. Robert Elsby
Principal Scientist – Head of Drug Transporter Sciences
Cyprotex Discovery Ltd, Cheshire, UK

R.Elsby@cyprotex.com





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QUESTIONS
AND ANSWERS

