Novartis – PK Sciences

Evaluation of hepatic drug partitioning (Kp_{uu}) and drug-induced cholestasis risk

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Hepatocyte Transporter Network 2019

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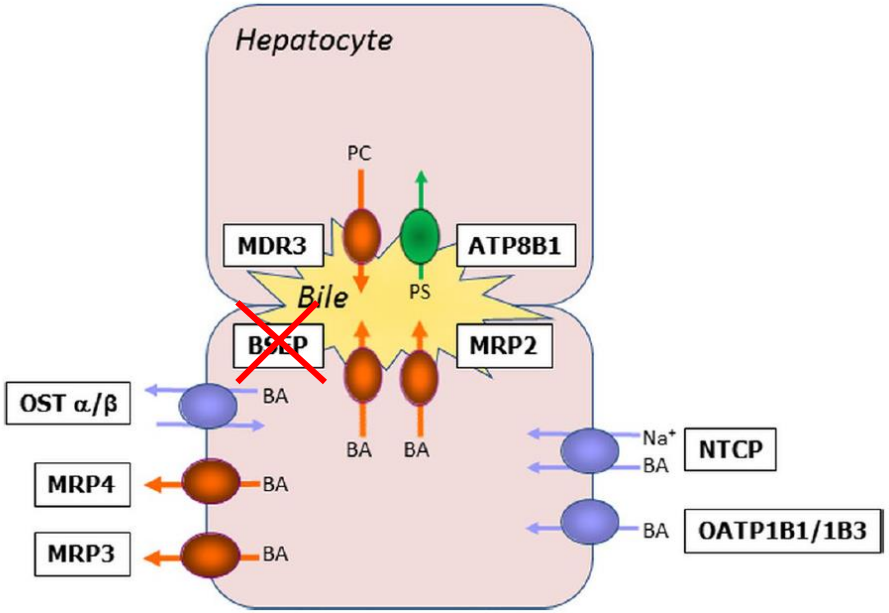
Background

- Drug induced cholestasis (DIC) is a major causative mechanism resulting in Drug-induced liver injury (DILI)
- DIC may be the consequence of reduced bile flow rate due to the inhibition of canalicular BSEP resulting in the accumulation of corrosive bile salts within the hepatocytes
- Early risk assessments for DIC use the *in vitro* BSEP inhibition potential (IC_{50}) and the (predicted) human exposure.



Kenna et al., 2018, Clin Pharmcol Ther;5:916-932

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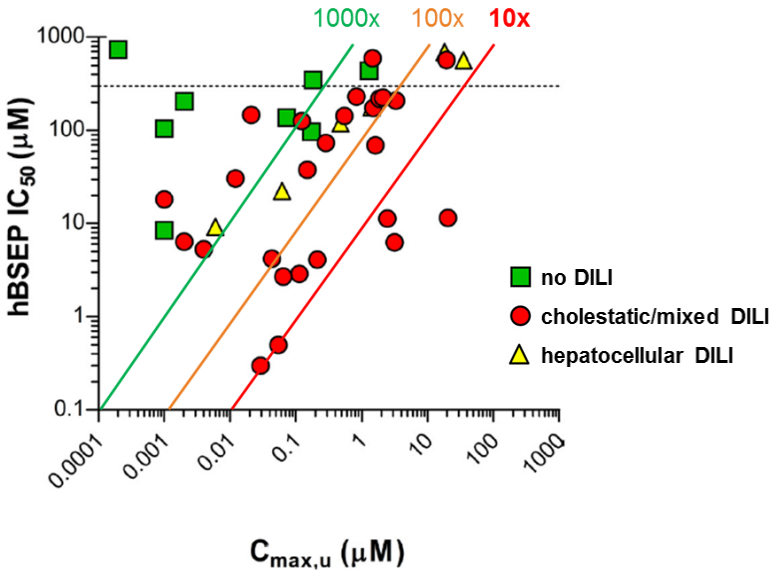
Prediction of drug-induced cholestasis

- DIC/DILI risk poorly correlates with measurements of systemic unbound drug concentrations ($C_{max,u}$)
- Hypothesis: risk assessments may improve when unbound portal vein ($C_{inlet,u}$) or intrahepatic ($C_{hep,u}$) conc. are used

Goals:

1. Conduct risk assessment for DIC using unbound intrahepatic drug concentrations, estimated using *in vitro* Kp_{uu} values
2. Comparison of *in vitro* methods to estimate Kp_{uu}



Dawson et al., 2012, Drug Metab Dispos;40:130-138

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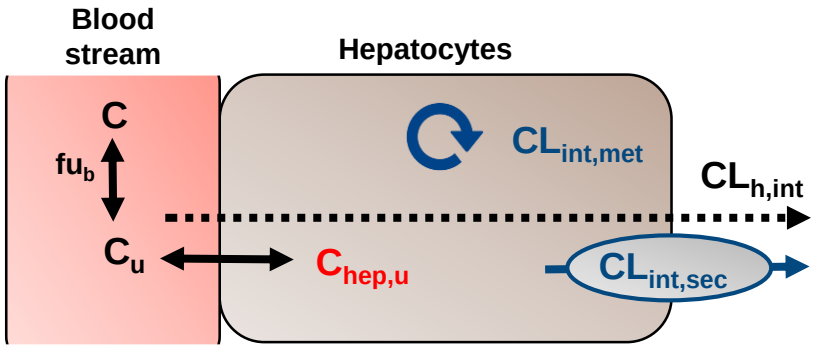
Hepatic drug disposition

Traditional approach to estimate $C_{hep,u}$: *Free-drug hypothesis*



$$C_u = C_{hep,u}$$

$$CL_{h,int} = CL_{int,met} + CL_{int,sec} = CL_{int}$$

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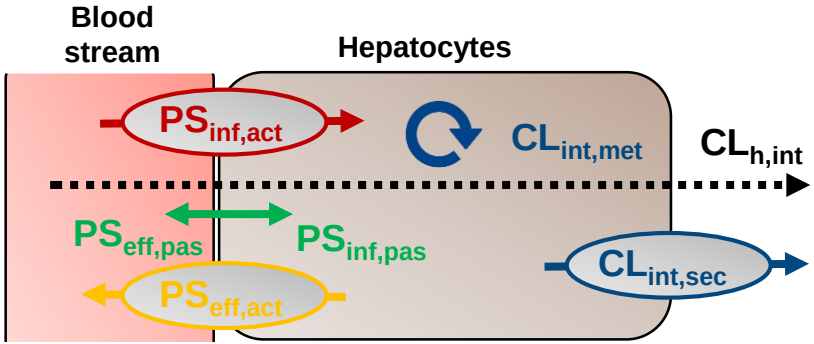
Hepatic drug disposition

Recent approach to estimate $C_{hep,u}$: *Extended Clearance Model (ECM)*



$$CL_{h,int} = \frac{PS_{inf,act} + PS_{inf,pas}}{PS_{eff,act} + PS_{eff,pas} + CL_{int}} \times CL_{int}$$

→ hepatic clearance processes can be measured *in vitro*

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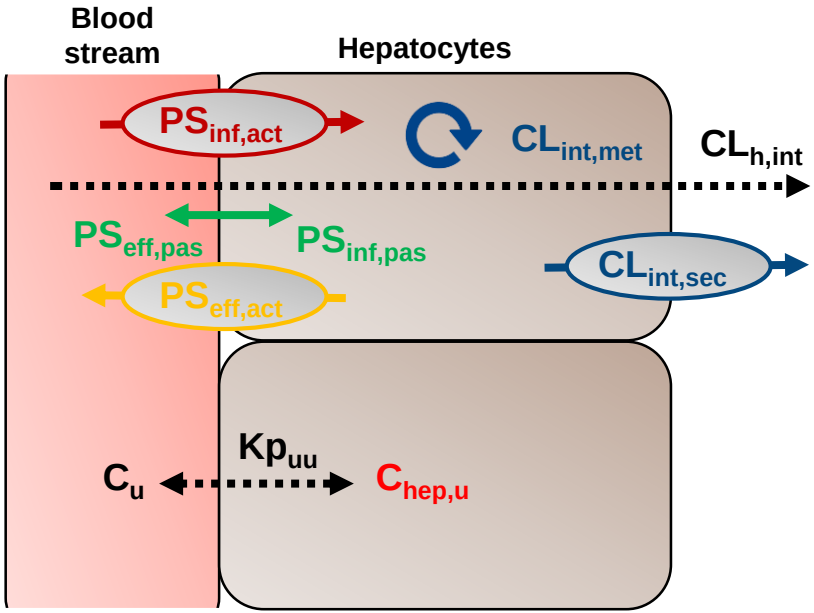
Hepatic drug disposition

Recent approach to estimate $C_{hep,u}$: *Extended Clearance Model (ECM)*



$$CL_{h,int} = \frac{PS_{inf,act} + PS_{inf,pas}}{PS_{eff,act} + PS_{eff,pas} + CL_{int}} \times CL_{int}$$

→ hepatic clearance processes can be measured *in vitro*

$$C_{hep,u} = Kp_{uu} \times C_u$$

$$Kp_{uu} = \frac{PS_{inf,act} + PS_{inf,pas}}{PS_{eff,act} + PS_{eff,pas} + CL_{int}}$$

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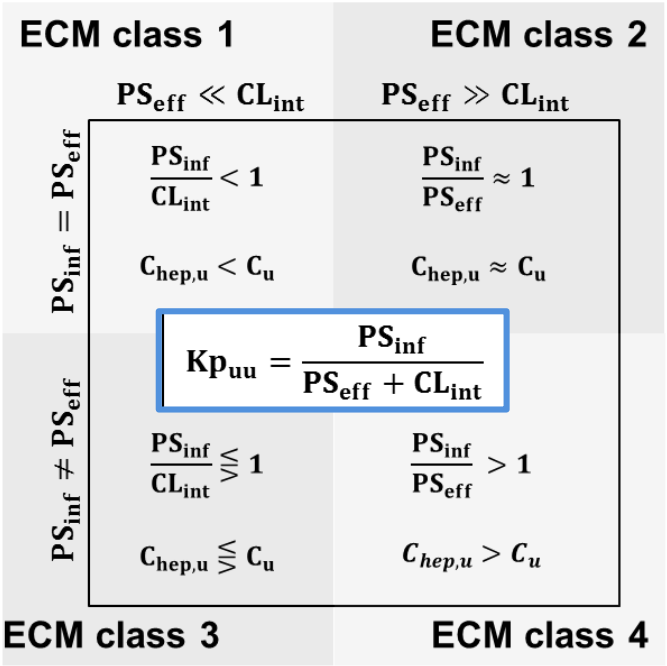
Kp_{uu} *in vitro* - Extended Clearance Model

Hepatic clearance determines Kp_{uu}

Interplay of uptake and clearance determines Kp_{uu}



Kp_{uu} ~1

Hepatic uptake determines Kp_{uu}

Riede et al, 2017, Drug Metab Dispos;45:523-531.

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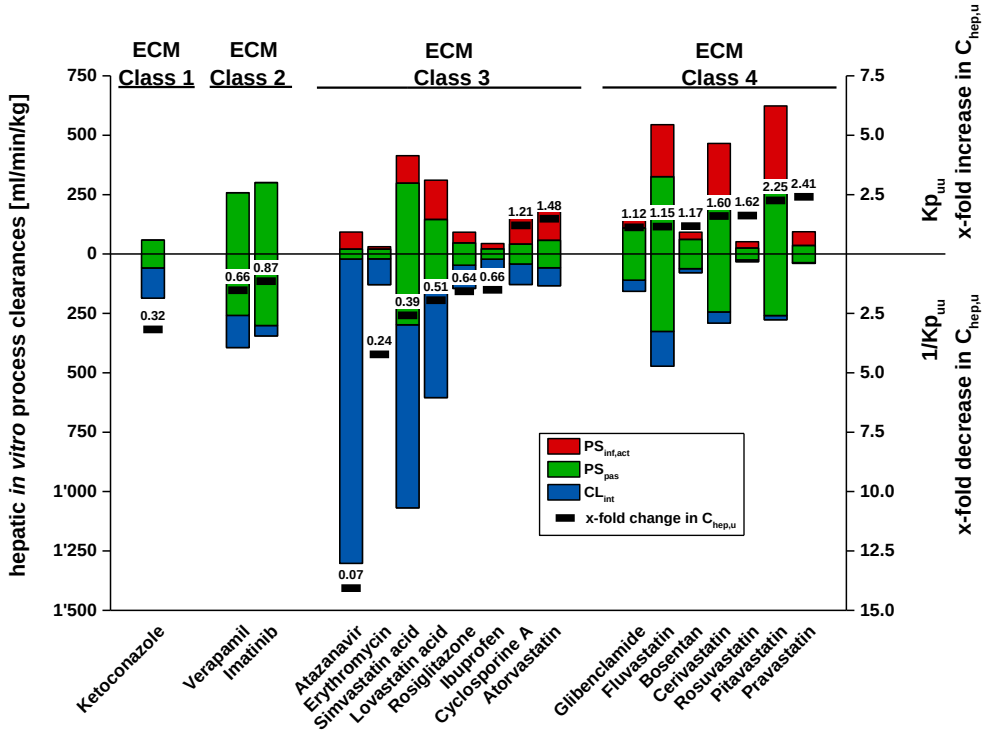
Kp_{uu} *in vitro* - Extended Clearance Model



$$Kp_{uu} = \frac{PS_{inf,act} + PS_{pas}}{PS_{pas} + CL_{int}}$$

Riede et al, 2017, Drug Metab Dispos;45:523-531.

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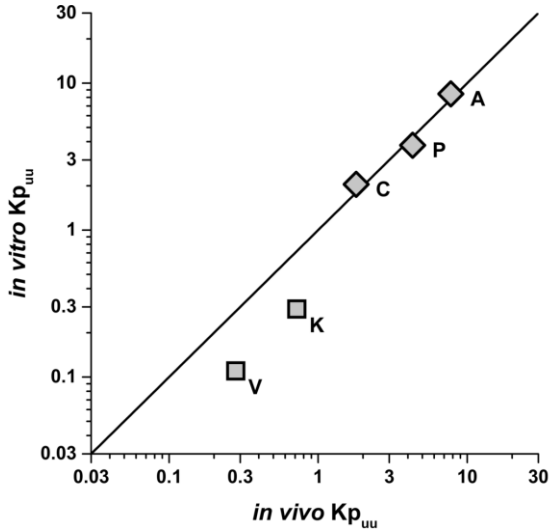
Kp_{uu} *in vitro-in vivo* correlation in rat

- Kp_{uu} *in vitro* was determined based on the ECM method
- Kp_{uu} *in vivo* was obtained from Kp liver and fu_{hep} data
- **Good IVIVC of Kp_{uu} for drugs with predominant uptake (A, P) or metabolism (V, K)**



A: atorvastatin
C: cyclosporine A
K: ketoconazole
P: pravastatin
V: verapamil

Riede et al, 2017, Drug Metab Dispos;45:523-531.

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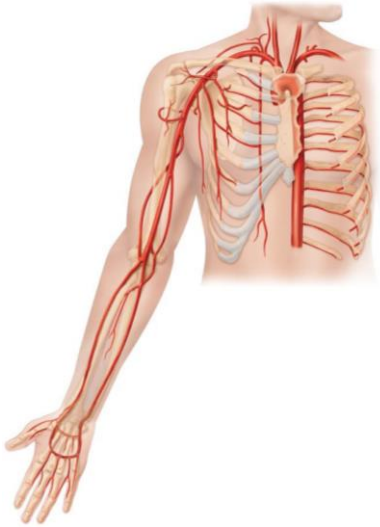
Reference conc. for DIC risk assessments

unbound systemic

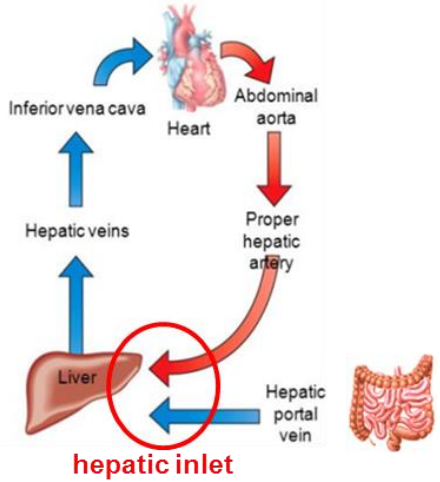
free-drug hypothesis



$$C_{sys,u}$$

unbound hepatic inlet

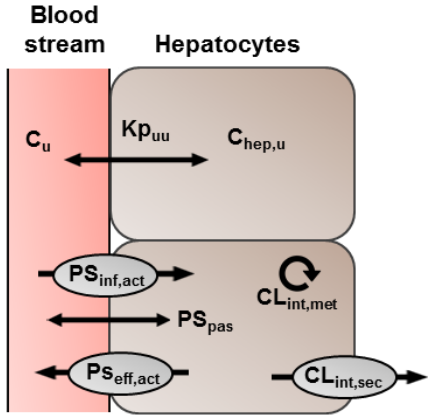
free-drug hypothesis



$$C_{inlet,u} = C_{sys,u} + \frac{fu_b \cdot k_a \cdot F_a \cdot F_g \cdot D}{Q_h}$$

unbound intrahepatic

Extended Clearance Model



$$C_{hep,u} = C_{sys,u} \times Kp_{uu}$$

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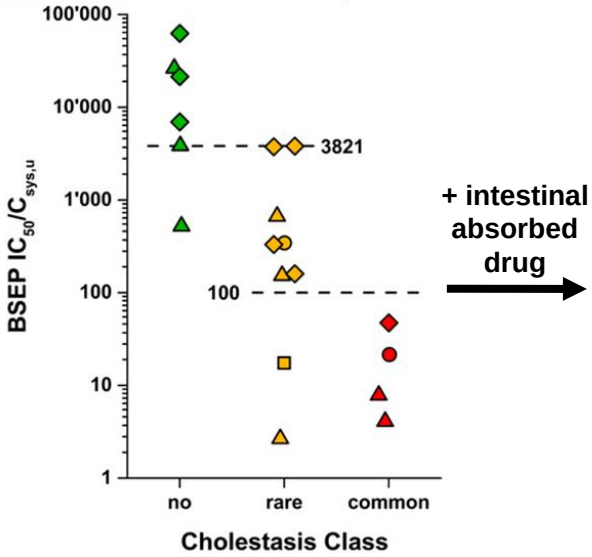
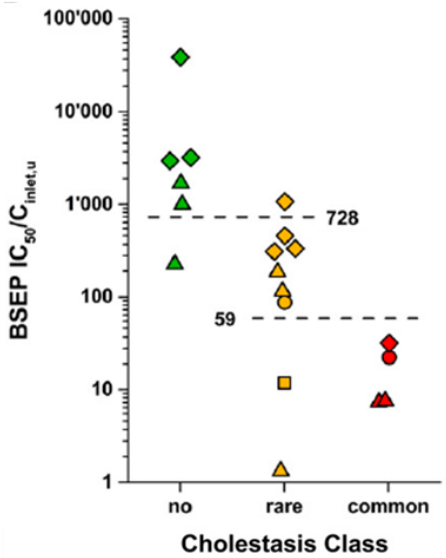
Improved DIC risk assessment using unbound liver concentrations

unbound systemic drug concentration



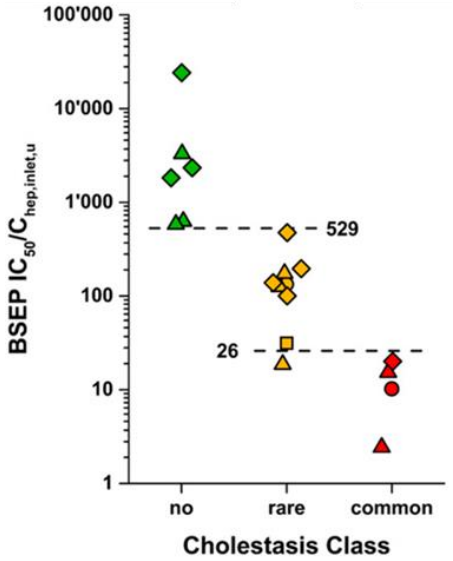
+ intestinal absorbed drug

unbound hepatic inlet drug concentration



x Kp_{uu}

unbound intrahepatic drug concentration



Riede et al, 2017, Drug Metab Dispos;45:523-531.

Alternative *in vitro* Kp_{uu} liver methods

- Extended Clearance Model
  Riede et al., 2017

$$Kp_{uu} = \frac{PS_{inf,act} + PS_{inf,pas}}{PS_{eff} + CL_{met} + CL_{sec}}$$

- Temperature method
  Shitara et al., 2013
- Homogenization method
  Mateus et al., 2013
- $logD_{7.4}$ method
  Yabe et al., 2011

$$Kp_{uu} = Kp \times fu_{hep}$$

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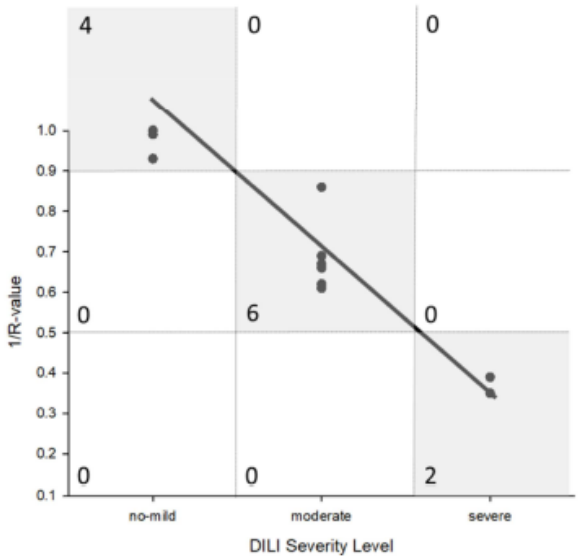
Outlook – Beyond BSEP inhibition

- Besides BSEP inhibition of other bile acid transporters and enzymes are discussed to contribute to DIC
- New model established incorporating inhibition of BSEP, MRP2, OATP1B1,OATP1B3, NTCP, UGT1A1, CYP3A4 TDI
- 1/R values are calculated based on the ECM and drug plasma concentrations

$$\frac{CL_{int,all,i}}{CL_{int,all}} = \frac{\left(\frac{1}{1+\sum\frac{[I]}{K_{i,upt}}}+1\right)\cdot\left[\left(\frac{1}{1+\sum\frac{[I]}{K_{i,sec}}}\right)+\left(\frac{1}{1+\sum\frac{[I]}{K_{i,met}}}\right)\cdot\left(\frac{1}{1+\sum\frac{k_{inact}\cdot[I]}{k_{deg}\cdot(K_{I,met}+[I])}}\right)\right]}{2+\left(\frac{1}{1+\sum\frac{[I]}{K_{i,sec}}}\right)+\left(\frac{1}{1+\sum\frac{[I]}{K_{i,met}}}\right)\cdot\left(\frac{1}{1+\sum\frac{k_{inact}\cdot[I]}{k_{deg}\cdot(K_{I,met}+[I])}}\right)} = \frac{1}{R}$$

Analysis for 13 NVS compounds



Camenisch 2019, Int J Pharm Chem;5:15-19.

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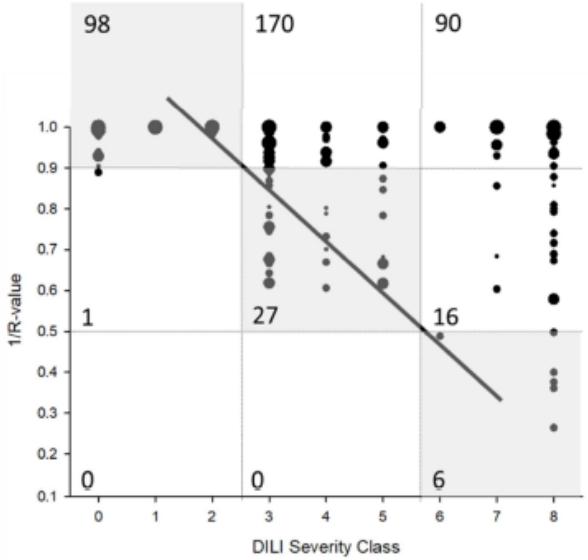
Outlook – Beyond BSEP inhibition

- Analysis of 408 marketed drugs reveals that inhibition of multiple pathways increases the DILI severity
- *In vitro* DDI data were only partially available
- To identify and validate risk factors for DIC/DILI and to support *in silico* models and machine learning, large in vitro datasets are required
- Sharing knowledge and databases via industry/academic consortia would enhance this development

Analysis for 408 marketed drugs



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Conclusions

- The extended clearance model (ECM) allows the determination of hepatic Kp_{uu} from *in vitro* clearance data
- The frequency of DIC events was well estimated using BSEP IC_{50} data and unbound intrahepatic concentrations estimated from unbound hepatic inlet concentrations and Kp_{uu}
- Several *in vitro* methods are available to estimate Kp_{uu}
  - The estimation of fu_{hep} is strongly influenced by the *in vitro* measurement method and the physicochemical properties of test compounds
  - The "temperature method" provides comparable Kp_{uu} estimates as the "ECM method" for compounds w/o predominant CL_{int}
- More complex models, including additional targets in addition to BSEP will need to be identified to further improve the DIC and DILI risk predictions

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- Gian Camenisch
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Thank you for your attention

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