Modeling ABC transporters as potential DILI targets

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Matthew Segall, Peter Hunt, Jon Tyzack

matt.segall@optibrium.com

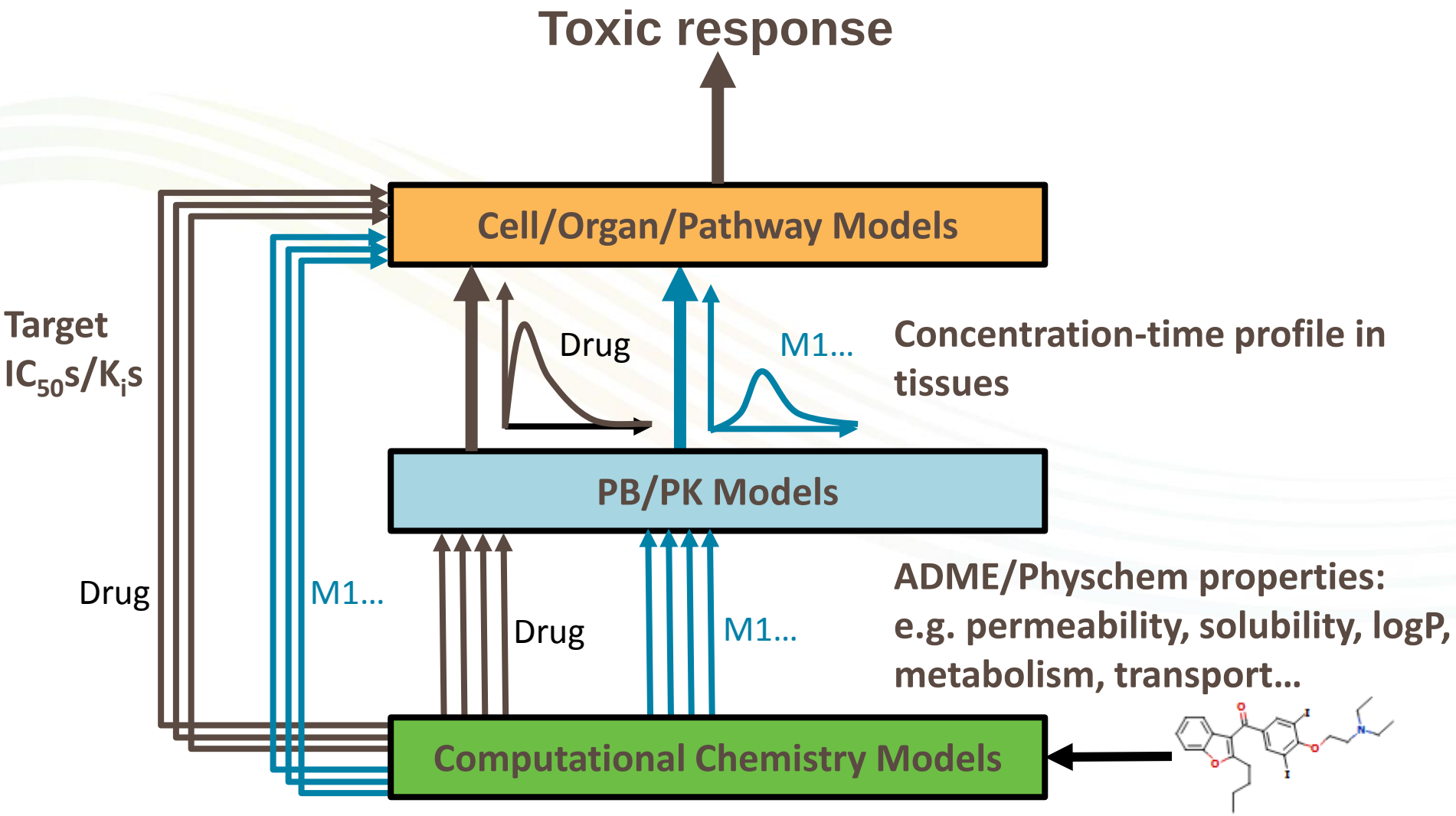
Overview

- Linking *in silico* target interaction models to Adverse Outcome Pathways (AOPs)
  - HeCaToS project
  - Empirical and physiological models
- Example – Modelling BSEP and MRP4 inhibition to predict cholestasis
  - Köck *et al.* Drug Metab. Dispos. (2014) **42** pp. 665-674
  - Welch *et al.* Drug Metab. Dispos. (2015) **43** pp. 725-734
- Future work
- Conclusions

HeCaToS Project
Hepatic and Cardiac Toxicity Systems

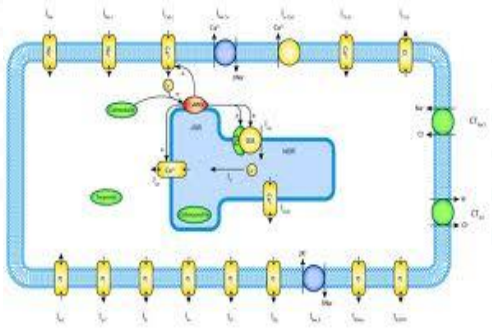
- European Framework 7 project led by University of Maastricht
  - www.hecatos.eu
  - Partners include: Roche, InSphero, Imperial College London, ETH-Zurich, EMBL, Genedata, Luxcel, HULAFE, MicroDiscovery…
- Vertical integration of toxicity prediction systems
  - *In silico*, *in vitro* and clinical data
- Goals
  - HeCaToS aims to develop integrative ***in silico*** tools for predicting human liver and heart toxicity. The objective is to develop an **integrated modeling framework**, by combining advances in computational chemistry and systems toxicology, for modelling toxic perturbations in liver and heart across **multiple scales**

Linking *In Silico* Target Activity Predictions to AOPs



Linking *In Silico* Target Activity Predictions to AOPs

- Empirical
  - Statistical link between target activity and toxicity (often motivated by mechanistic understanding)
  - Identify correlation between IC_{50}, EC_{50}, K_i, etc. and chance of toxicity (hazard)
  - Potentially include exposure information to estimate risk
- Physiological Models
  - Use data on target activities (and exposure) as input to biophysical model of cell/organ
  - Directly simulate changes in organ function
  - Estimate risk of toxicity



Link Between BSEP and MRP4 Inhibition and Cholestasis

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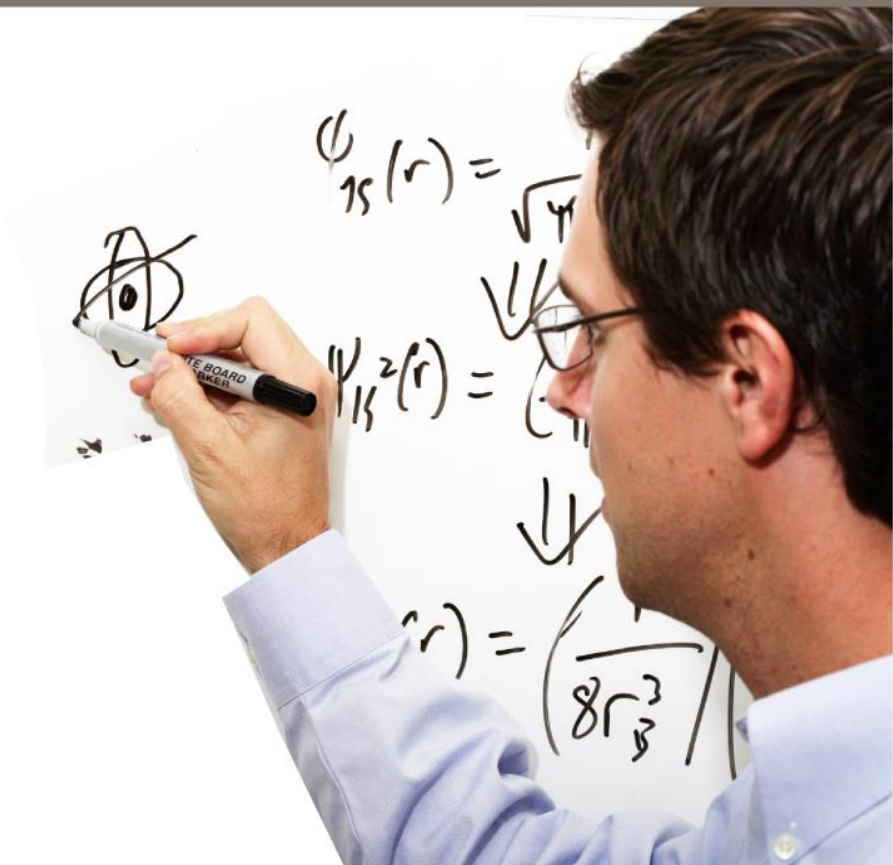


Background

- Inhibition of hepatocyte efflux proteins linked to Cholestasis
  - Bile Salt Export Pump (BSEP)
  - Multidrug Resistance Protein 4 (MRP4)
- Mutations of BSEP gene ABCB11 linked with familial intrahepatic cholestasis type 2
- MRP4 may serve as 'back-up' system for bile acid efflux
- Statistically significant relationship between MRP4 inhibition and probability that a drug was cholestatic, when acompound is not a BSEP inhibitor
- Significant overlap of inhibitors of BSEP and MRP4

Köck *et al.* Drug Metab. Dispos. (2014) **42** pp. 665-674

Welch *et al.* Drug Metab. Dispos. (2015) **43** pp. 725-734

Modelling BSEP and MRP4 Inhibition

- Quantitative Structure-Activity Relationship (QSAR) models built to classify compounds as inhibitors (True) or non-inhibitors (False)
  - BSEP: IC_{50} ≤135 µM
  - MRP4: ≥20% inhibition @ 100 µM
- Data sets*

	MRP4 (T/F)	BSEP (T/F)
Training set	57 (34/23)	171 (43/128)
Test set	29 (17/12)	85 (22/63)

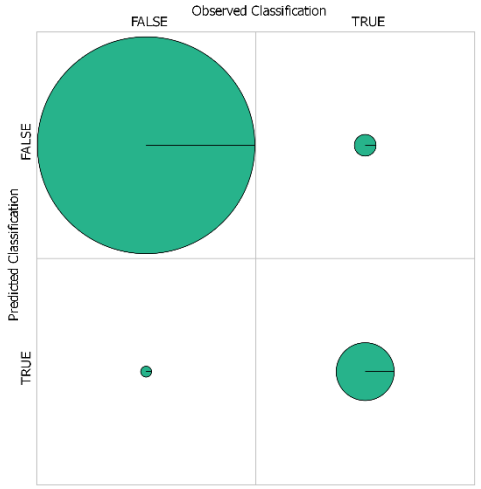
- 330 descriptors used as input, including whole molecule properties (logP, V_x, TPSA…) and 2D SMARTS
- Modelling methods
  - Random forests, Gaussian processes
  - Built with StarDrop Auto-Modeller™

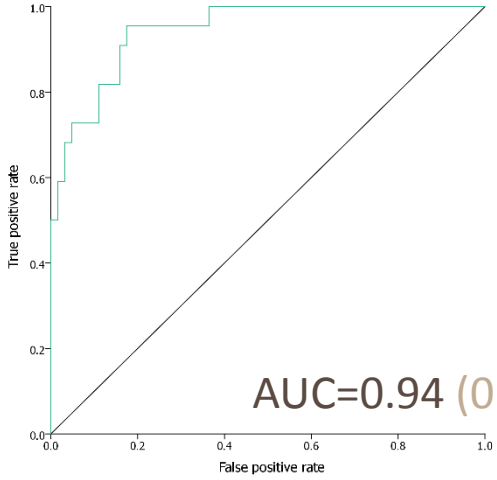
*Welch *et al.* Drug Metab. Dispos. (2015) **43** pp. 725-734

BSEP Model

Gaussian process classifier – Independent test set

- Accuracy 89% (83%*)
  - True sensitivity 73%
  - True specificity 84%
  - False sensitivity 95%
  - False specificity 91%
- κ statistic = 0.71
- Matthews correlation coefficient = 0.71 (0.58*)

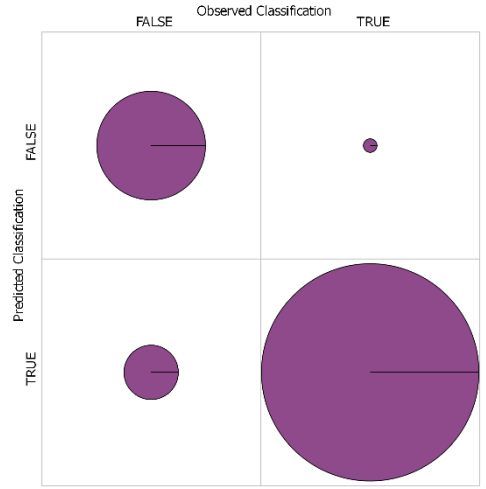


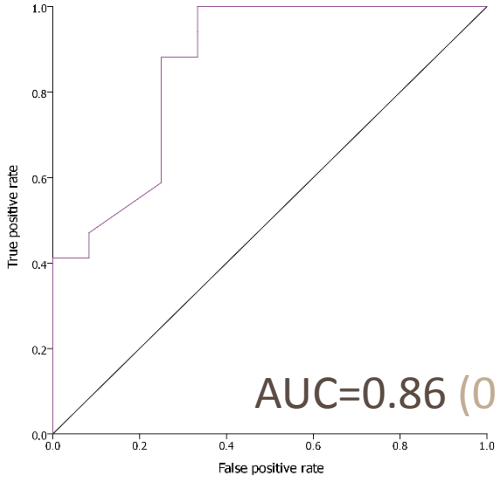


*Welch *et al.* Drug Metab. Dispos. (2015) **43** pp. 725-734

MRP4 Model
Random forest classifier – Independent test set

- Accuracy 83% (66%*)
  - True sensitivity 94%
  - True specificity 80%
  - False sensitivity 67%
  - False specificity 89%
- κ statistic = 0.63
- Matthews correlation coefficient = 0.65 (0.42*)





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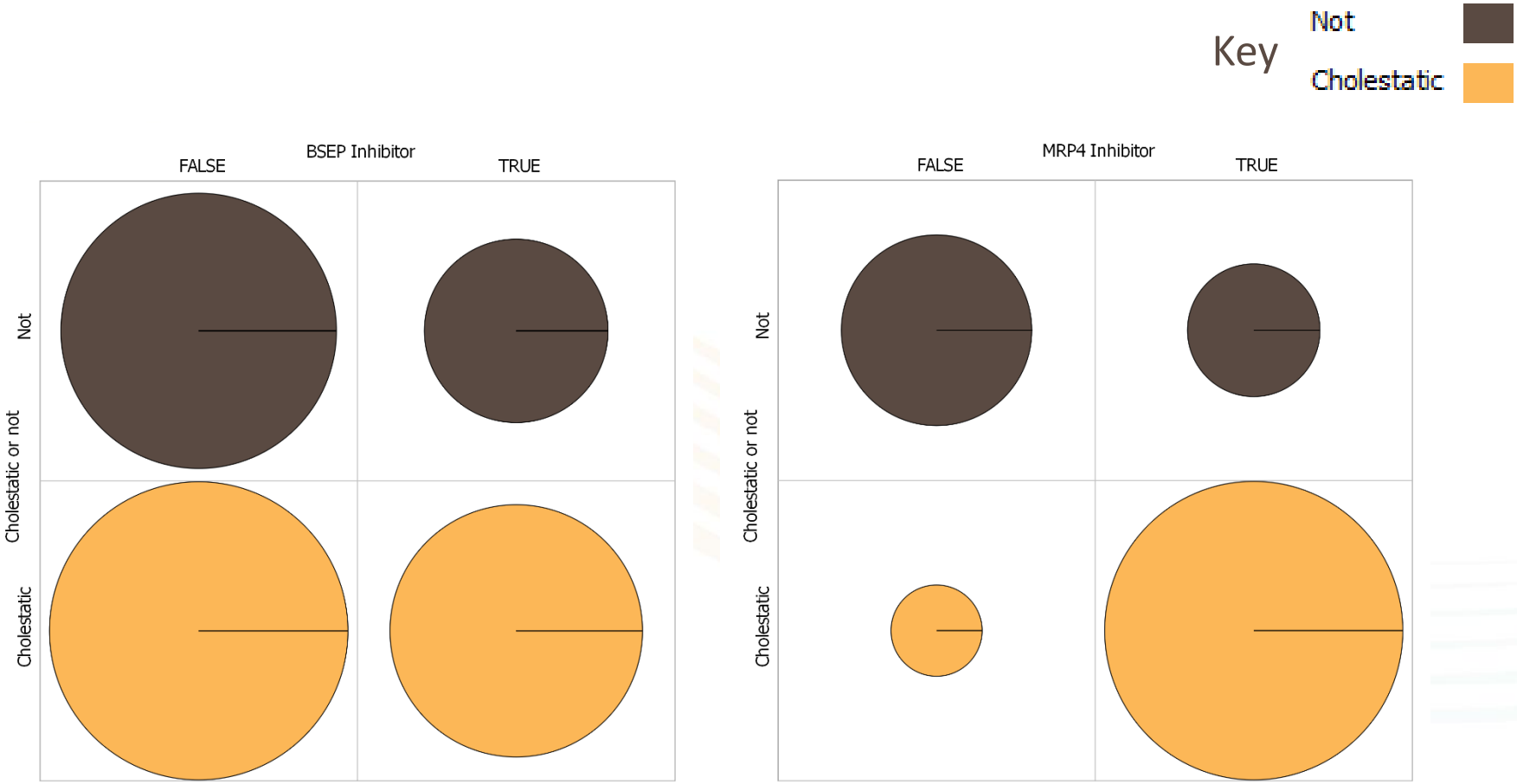
BSEP and MRP4 Inhibition vs Cholestasis

Based on Experimental Data (88 compounds)*



κ statistic = 0.10

κ statistic = 0.36

*Köck et al. Drug Metab. Dispos. (2014) **42** pp. 665-674

BSEP and MRP4 Inhibition vs Cholestasis

Based on Experimental Data (88 compounds)*

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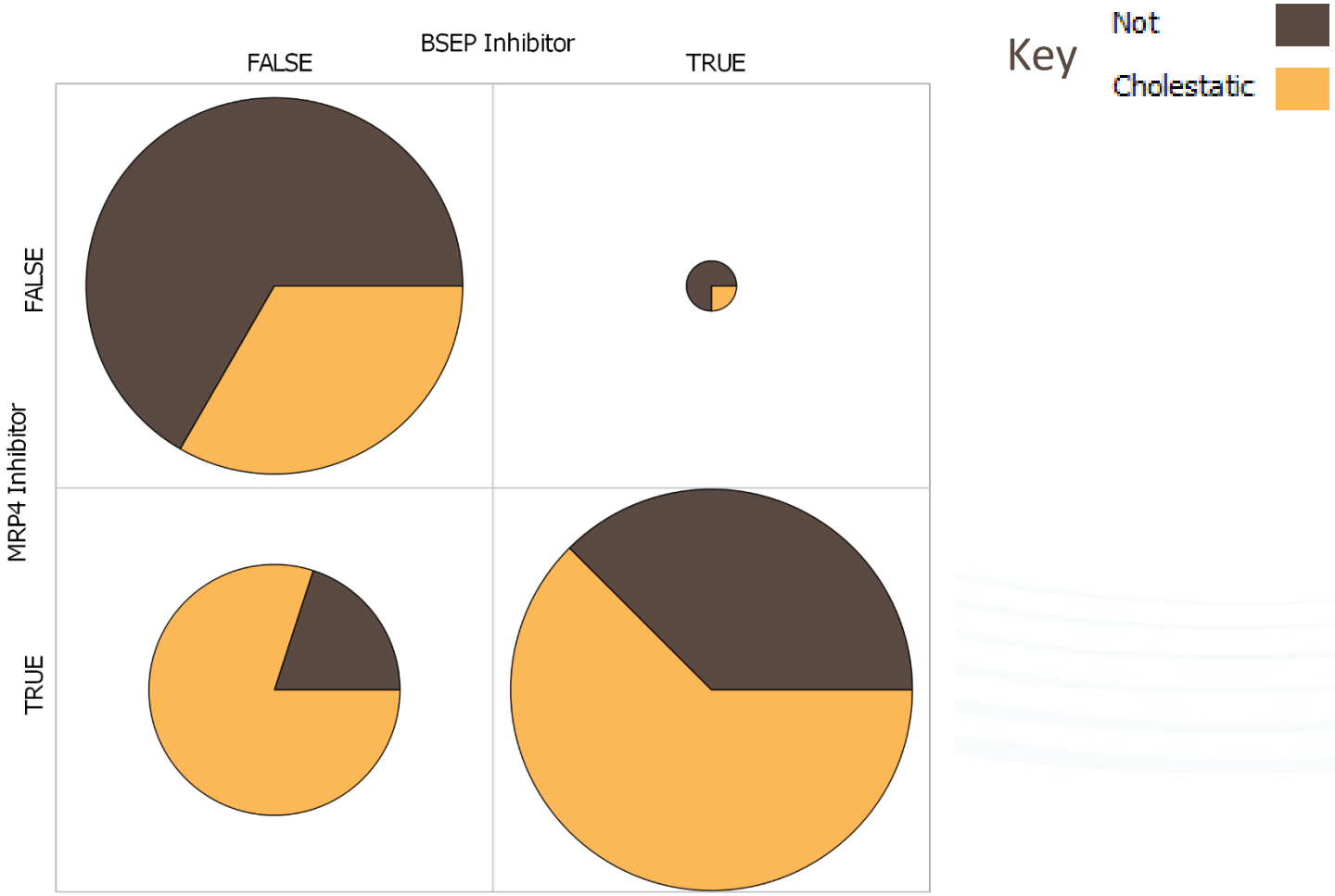

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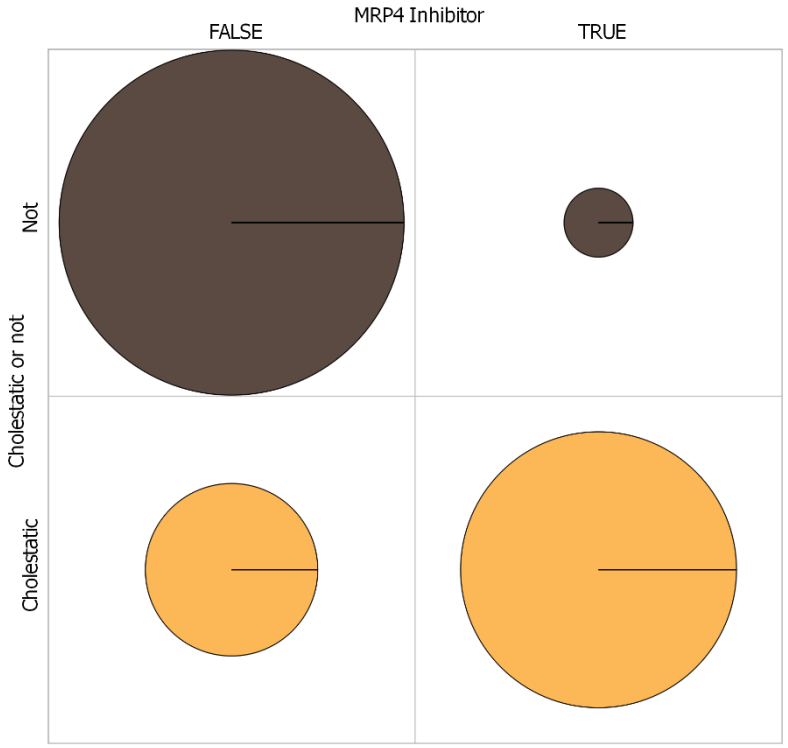
BSEP and MRP4 Inhibition vs Cholestasis

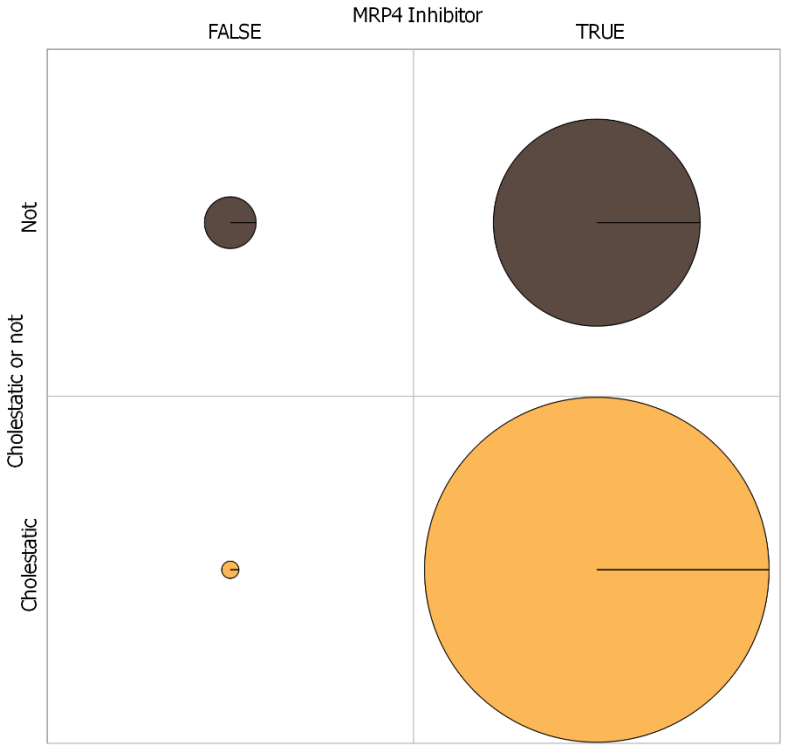
Based on Experimental Data (88 compounds)*

BSEP Inhibitor = FALSE



κ statistic = 0.44

BSEP Inhibitor = TRUE



κ statistic = 0.17

Conclusion: MRP4 Inhibition **may** help to reduce false negatives from measurements of BSEP inhibition. But **neither** are sufficiently predictive of Cholestasis.

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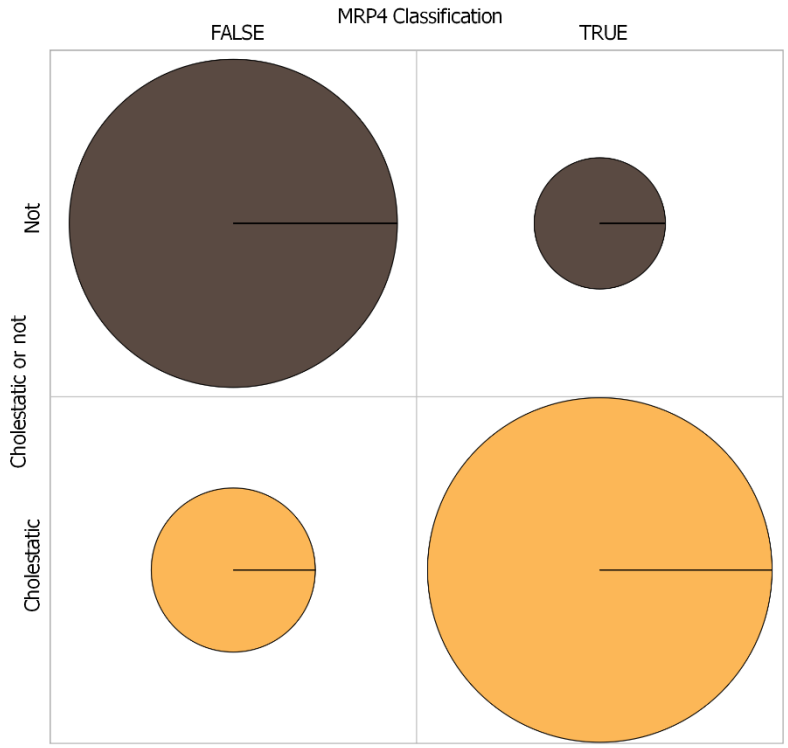
BSEP and MRP4 Inhibition vs Cholestasis

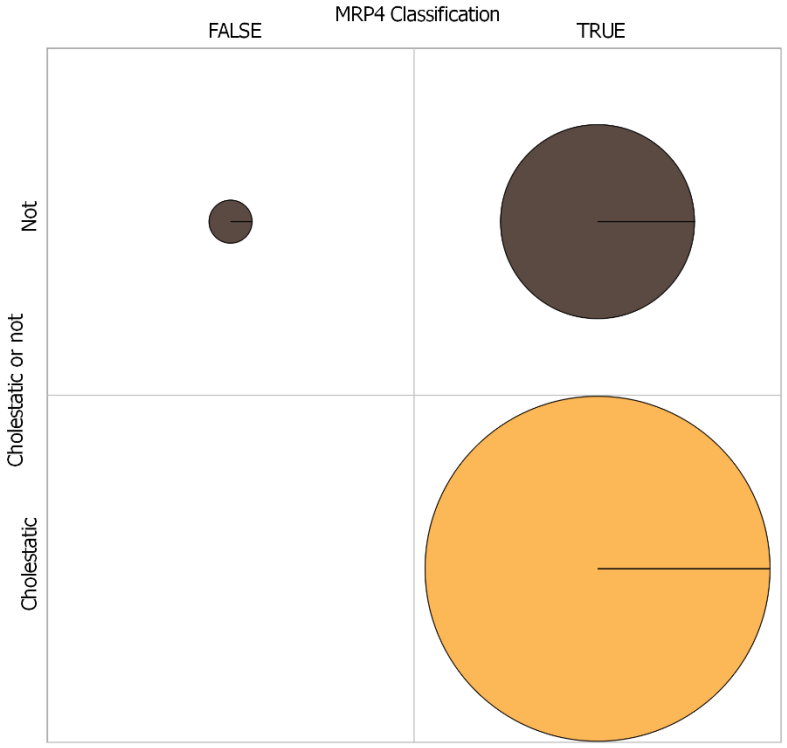
Based on Predictions (88 compounds)*

BSEP Inhibitor = FALSE



κ statistic = 0.39

BSEP Inhibitor = TRUE



κ statistic = 0.21

Conclusion: Relationship between predictive models and cholestasis is similar to experimental inhibition data, but experimental data does **not** support prediction.

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Where Next?

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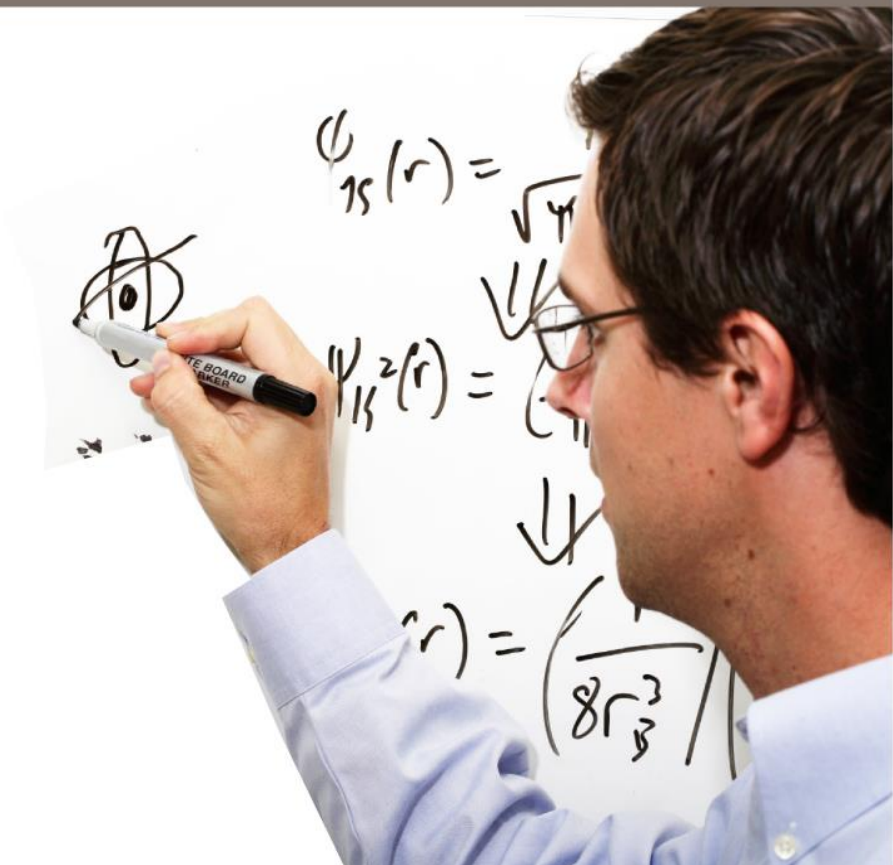
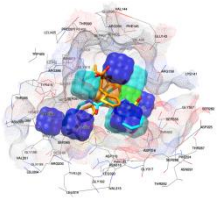
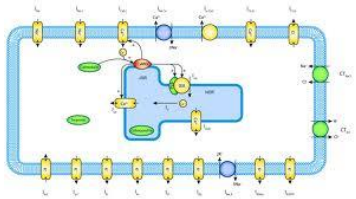


Integration of QSAR with Biophysical Models

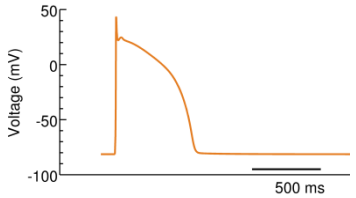
ChEMBL



QSAR Model

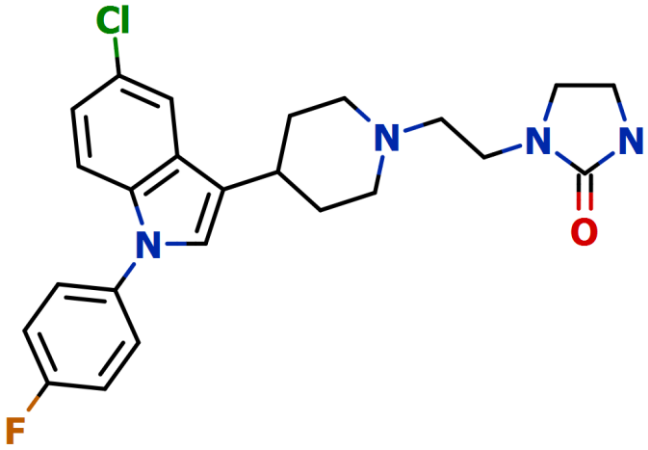


Biophysical Model



Function

Risk



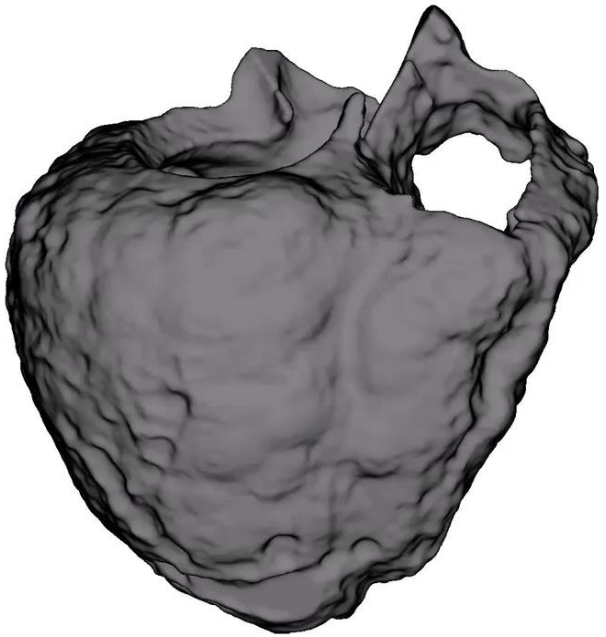
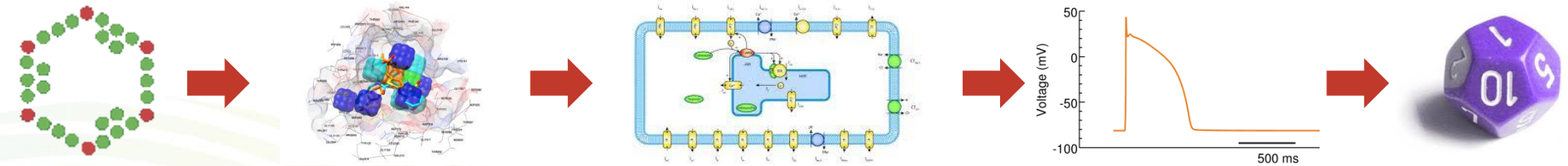


Figure and video courtesy of Dr Steven Niederer, King's College London

Integration of QSAR with Biophysical Models
Requirements



ChEMBL QSAR Model Biophysical Model Function Risk

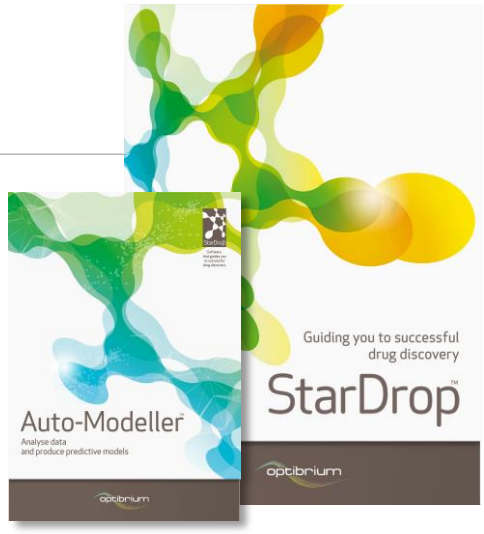
- Data of sufficient quality and diversity
- Accurate numerical models of target activities
- Well validated biophysical model
- Good estimate of exposure at cell/organ

Figure and video courtesy of Dr Steven Niederer, King's College London

Integration of QSAR with Biophysical Models
Challenges

- Availability of data for toxicity-related targets
  - Many tox-related targets are not ‘standard’ screening targets in pharma
- Domains of applicability of QSAR models
  - Given limitations of data above
- Are biophysical models stable within typical range of QSAR model uncertainties (~0.8-1.0 log units)?
- Can we estimate concentrations at target cell/organ
  - Free versus bound concentrations
  - What about intracellular concentrations?

Conclusions



- QSAR models of sufficient quality can be generated for targets related to AOPs
  - Care must be taken with domain of applicability
- Need to consider if association between target(s) and adverse outcome is strong enough to be predictive
- Linking target interactions to AOPs via biophysical models may provide a good approach
  - Significant challenges remain to be addressed…
- Acknowledgement
  - This research has received funding from the European Union Seventh Framework Programme(FP7/2007-2013) under the grant agreement no602156