Computational Modeling of OATP1B1 Inhibitors

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Introduction

- **O**rganic **A**nion **T**ransporting **P**olypeptide **1B1** (OATP1B1)
- Highly expressed uptake transporter in human hepatocytes
- Interacts predominantly with negatively charged species
- Inhibited by cyclosporine A and rifampicin
- Important in drug-drug interactions (DDIs) because inhibition by one drug may lead to **systemic toxicity** due to elevated levels in the blood or **subtherapeutic** levels of another in the liver
- Considered one of the seven most important transporters in drug disposition by the International Transporter Consortium

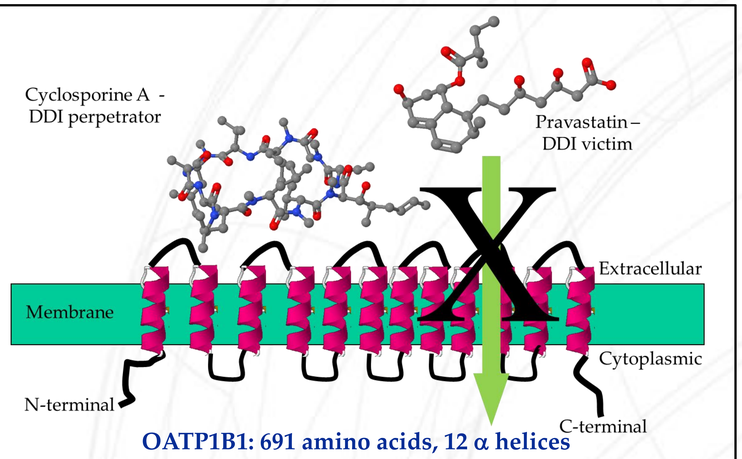

Figure 1 – Cyclosporine A inhibits OATP1B1 transport of pravastatin. When orally administered pravastatin is taken with cyclosporine A, the area under the curve of pravastatin increases almost 900%, potentially leading to toxicity.

An artificial neural network ensemble (ANNE) classification model was created from OATP1B1 inhibition data for 336 compounds. The model was used to predict OATP1B1 inhibition of a subset of about 2,300 compounds from the World Drug Index (WDI).

Data Sets

	Karlgren et al. [1,2]	Wu et al. [3]
Substrate	Estradiol-17β-glucuronide	Estrone-3-sulfate
Substrate conc.	0.52 μM	50 nM
K_m	12.8 μM	68 nM
No. of cmpds.	225*	136**
Test conc.	20 μM	100 μM

* Drugs and druglike molecules ** natural products

OATP1B1 Inhibition Criteria

IC_{50} values were estimated from %inhibition using:

$$IC_{50} = [I]\left(\frac{100 - \%inhibition}{\%inhibition}\right)$$

where $[I]$ is the concentration of test compound

Data Sets (continued)

IC_{50} values were converted to K_i values using Cheng-Prusoff equation:

$$K_i = \frac{IC_{50}}{\left(\frac{S}{K_m} + 1\right)}$$

where S is the substrate concentration.

If K_i < 20 μM, the compound was classed as an OATP1B1 inhibitor

- >50% inhibition for Karlgren data set
- >74% inhibition for Wu data set

OATP1B1 Inhibition Classification Model

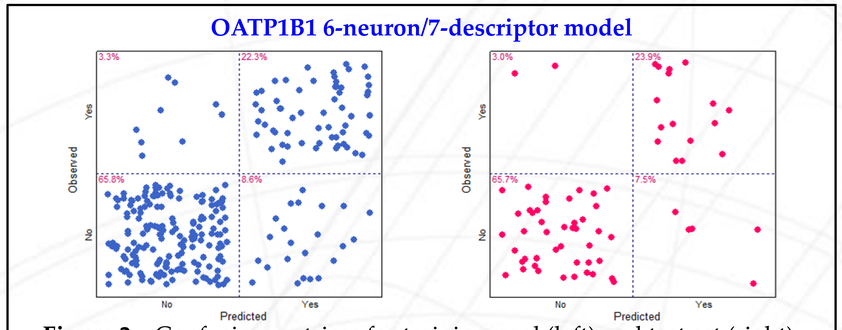

Figure 2 – Confusion matrices for training pool (left) and test set (right).

	Noninhibitors	Inhibitors	Total	Correct	Concord.	Sens.	Spec.
Training	200	69	269	237	88.1%	87.0%	88.5%
Test	49	18	67	60	89.6%	88.9%	89.8%

Descriptor	Description
MlogP	Moriguchi estimation of logP
QAvgPos	Population average of the net formal positive charge across ionized species
FAnion	Fraction anionic at pH = 7.4
EEM_NFon	Minimum scaled sigma Fukui index on N and O
NPA_AQc	Sum of absolute value of natural population analysis (NPA) charges on carbon
NPA_Q3	Third component of the autocorrelation vector of NPA charges
Pi_Q2	Autocorrelation vector of p partial charges

World Drug Index (WDI) Predictions

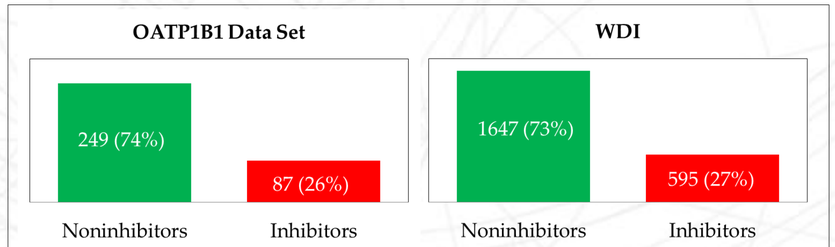

Figure 3 – Number of noninhibitors and inhibitors in the OATP1B1 data set (left) and predictions for the WDI subset (right).

World Drug Index (WDI) Predictions

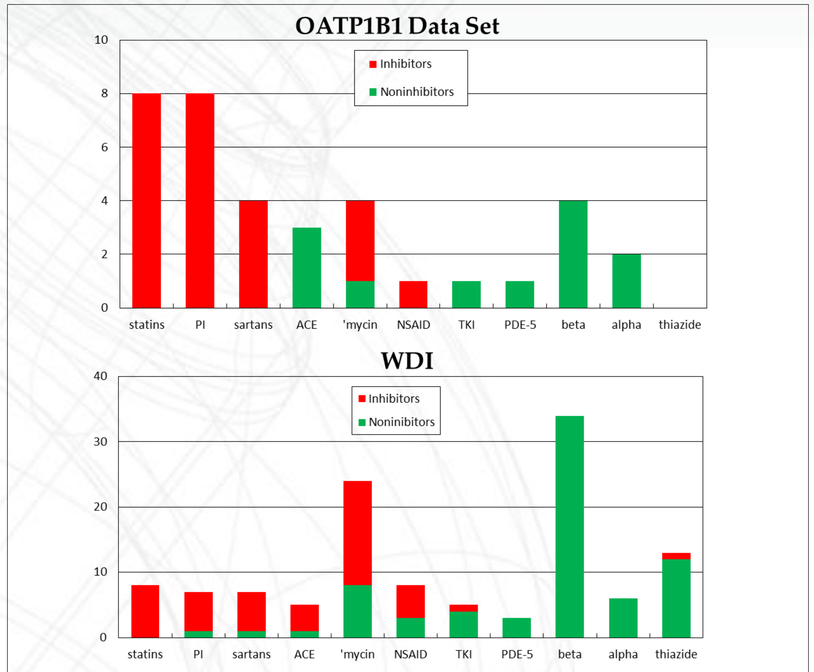

Figure 4 – Distribution of noninhibitors and inhibitors for experimental values from the OATP1B1 data set (top) and predictions for the WDI subset (bottom). Abbreviations: statins (HMG-CoA reductase inhibitors), PI (protease inhibitors), sartans (angiotensin II receptor antagonists), ACE (angiotensin-converting-enzyme inhibitors), 'mycin (antibiotics), NSAID (nonsteroidal anti-inflammatory drugs), TKI (tyrosine kinase inhibitors), PDE-5 (phosphodiesterase-5 inhibitors), beta (β-blockers), alpha (α1-adrenergic receptor antagonists), and thiazide (diuretics).

Conclusions

A six-neuron/seven-descriptor artificial neural network ensemble model was constructed from literature data on OATP1B1 inhibition. The model's accuracy is close to 90% for the training and test sets. It was used to predict OATP1B1 inhibition for a ~2,300 molecule subset of the World Drug Index, a quarter of which were predicted to inhibit OATP1B1.

References

[1]M. Karlgren, G. Ahlin, C.A.S. Bergstrom, R. Svensson, J. Palm, and P. Artursson. *Pharm. Res.* **2011**, *29*, 411-426.

[2]M. Karlgren, A. Vildhede, J. R. Wisniewski, E. Kimoto, Y. Lai, U. Haglund, and P. Artursson. *J. Med. Chem.* **2012**, *55*, 4740-4763.

[3]L. Wu, C. Guo, Q. Qu, J. Yu, W. Chen, G. Wang, L. Fan, Q. Li, W. Zhang, and H. Zhou. *Xenobiotica*, **2012**, *42(4)*, 339-348.

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