Pirogov Russian National Research Medical University

XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery

IBMC Institute of Biomedical Chemistry

TIP: WEB APPLICATION FOR PREDICTING DRUG–TRANSPORTER INTERACTIONS

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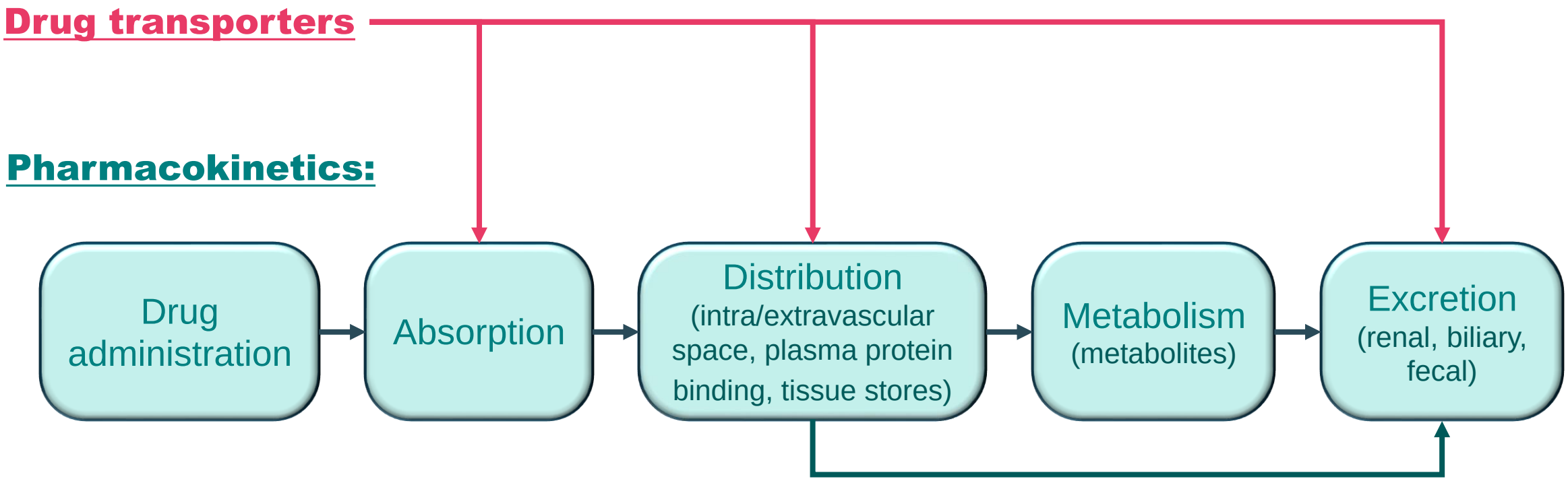
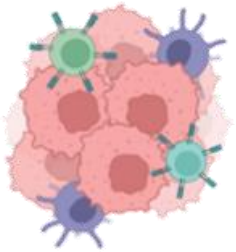
The activity of drug transporters affects pharmacokinetic parameters of drugs



Clinical Consequences of Transporter Dysfunction

organ dysfunction

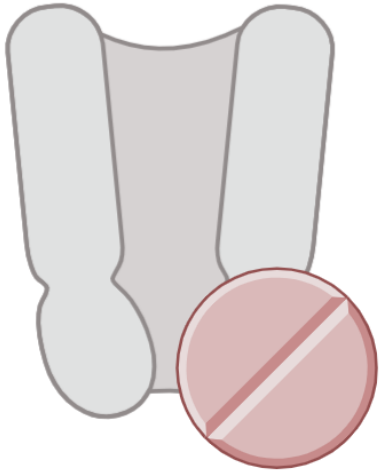


immune-related diseases and tumours

neurodegenerative disorders

metabolic syndromes

Up to 30% of adverse events



QSAR-Driven Solutions for Drug–Transporter Interactions

SwissADME

SwissDrugDesign

Deep-PK

PreADMET

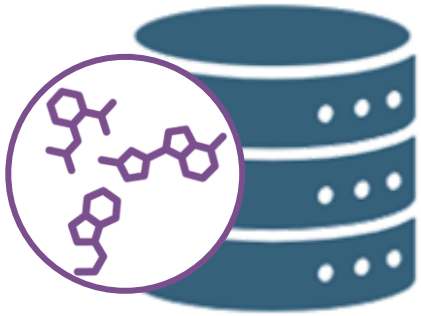
pkCSM

PASS

Research objectives

In this study we aim to creation of classificational structure-activity relationship (SAR) models for the enabling rapid screening of small molecules for potential inhibition across a broad panel of human transportersand deploying in a freely accessible web application.

Materials and methods



ChEMBL v.35

35,296 compounds with IC_{50} or Ki

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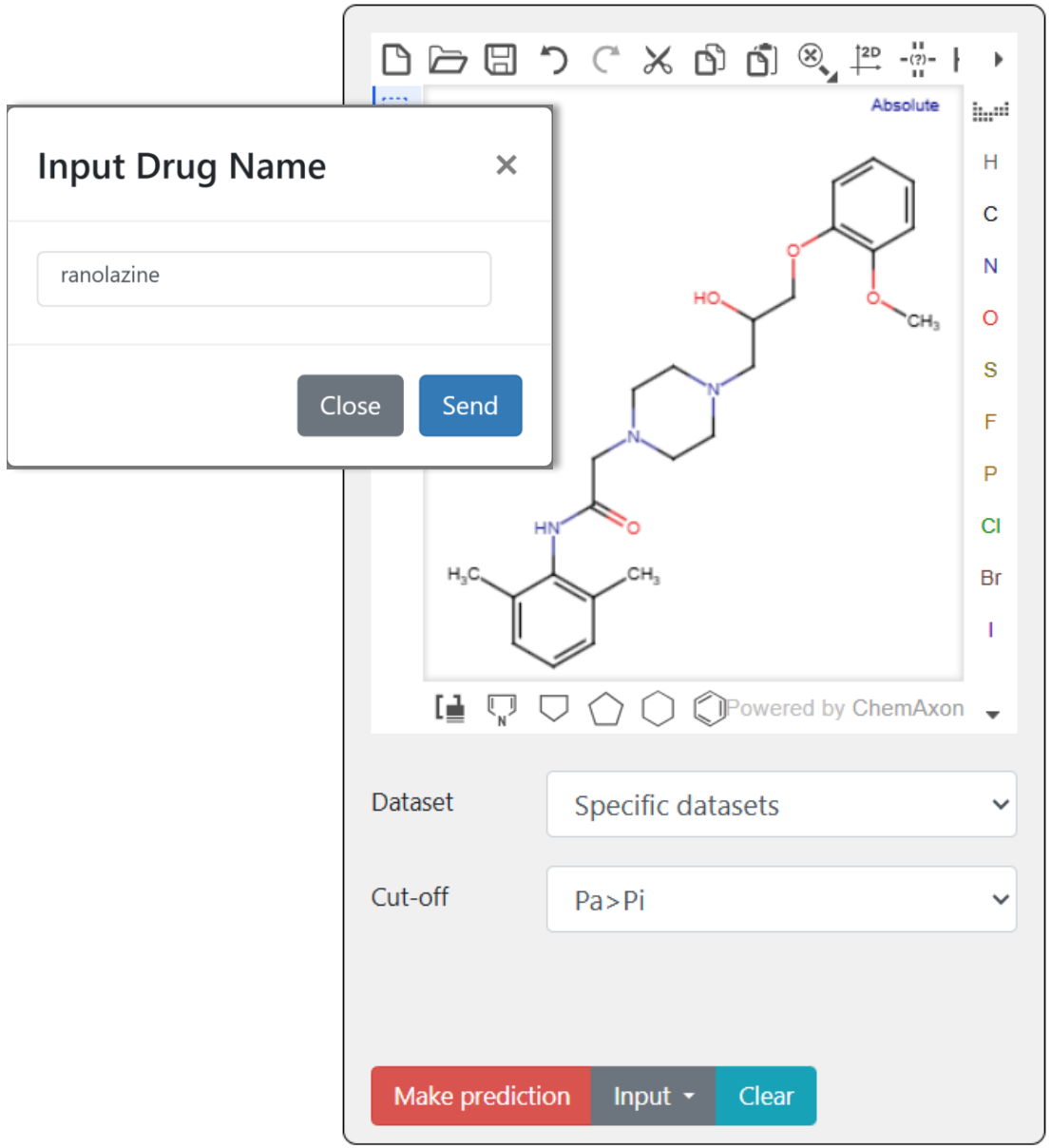
177 human transporters

20 SAR bases: 19 for specific transporters & Comprehensive SAR model covering 99 transporters.

Quality Control & Validation

5-fold CV LOO: average IAP of 0.95

Prediction results for Ranolazine in TIP web application



A

Pa	Pi	Action	Transporter	Gene
0.660	0.055	Inhibitor	Multidrug and toxin extrusion protein 2	SLC47A2
0.585	0.136	Inhibitor	Multidrug and toxin extrusion protein 1	SLC47A1
0.522	0.096	Inhibitor	Multidrug resistance-associated protein 4	ABCC4
0.502	0.103	Inhibitor	Solute carrier family 22 member 2	SLC22A2
0.388	0.080	Inhibitor	Bile salt export pump	ABCB11
0.330	0.120	Inhibitor	Solute carrier family 22 member 1	SLC22A1
0.316	0.177	Inhibitor	Solute carrier organic anion transporter family member 2B1	SLCO2B1
0.304	0.058	Inhibitor	Solute carrier family 22 member 3	SLC22A3
0.271	0.155	Inhibitor	Sarcoplasmic/endoplasmic reticulum calcium ATPase 3	ATPase
0.254	0.149	Inhibitor	Solute carrier family 12 member 2/member 5	SLC12A2/ SLC12A5
0.240	0.139	Inhibitor	Canalicular multispecific organic anion transporter 1	ABCC2
0.233	0.040	Inhibitor	P-glycoprotein 1	ABCB1
0.233	0.096	Inhibitor	Solute carrier organic anion transporter family member 1B1	SLCO1B1
0.224	0.211	Inhibitor	Synaptic vesicular amine transporter	SLC18
0.218	0.097	Inhibitor	Solute carrier organic anion transporter family member 1B3	SLCO1B3
0.075	0.063	Inhibitor	GABA transporter 3	SLC6A11

B

Pa	Pi	Action	Transporter	Gene
0.372	0.057	Inhibitor	P-glycoprotein 1	ABCB1
0.237	0.227	Inhibitor	Equilibrative nucleoside transporter 1	SLC29A1

Conclusions

1. We developed computational models to predict inhibition for a wide range of membrane transporters, thereby substantially expanding the capabilities of existing publicly available methods.
2. Using the PASS algorithm, we built both a comprehensive model covering 99 transporters and dedicated models for key ABC and SLC transporters; each demonstrated high predictive performance.
3. Building on these models, we created the TIP web application (https://www.way2drug.com/tip/), which enables researchers to assess a compound's potential to inhibit clinically relevant transporters. TIP covers significantly more transporters than other freely available web applications such as pkCSM, Deep-PK, preADME, and ADMETlab 2.0.

This study was supported by the Russian Science Foundation under project No. 25-25-00148, https://rscf.ru/project/25-25-00148/.

Thank you for your attention

https://www.way2drug.com/tip/