journée IA & "Drug Discovery" - Inserm

AI-Driven Prediction of Inhibitors of Metabolizing Enzymes and Transporters for Safer Drug Design

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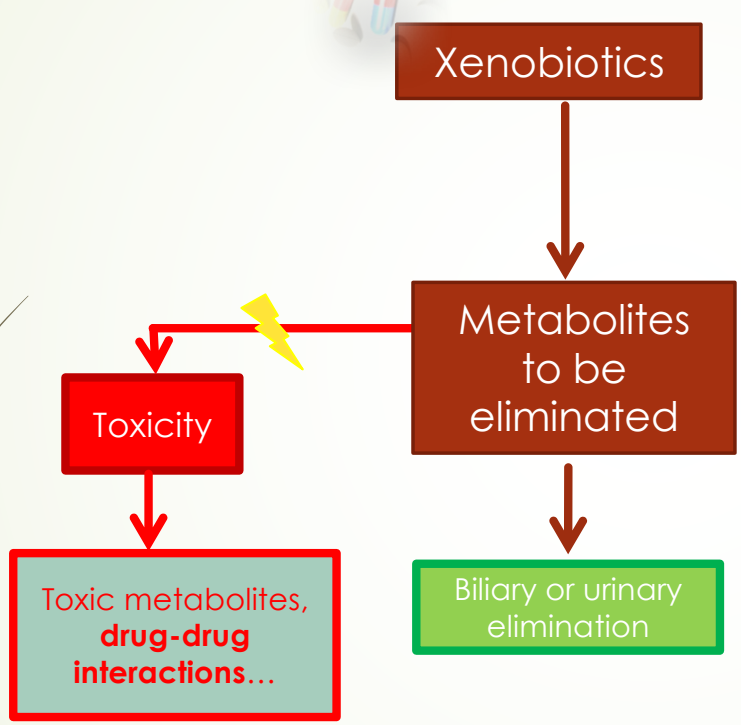
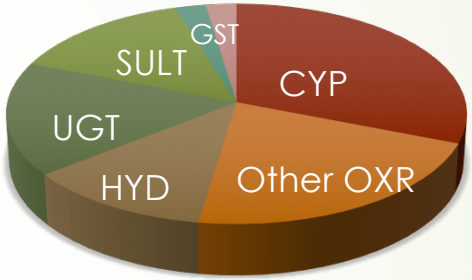
Drug-drug interactions, Drug Metabolizing Enzymes (DME) and Transporters



Phase I DME ***Oxido-reduction***
Cytochrome P450 (CYP), …
Phase II DME ***Conjugation***
Sulfotransferases (SULT),
Uridine Diphosphate
Glucuronosyltransferase (UGT), …



Efflux Transporters

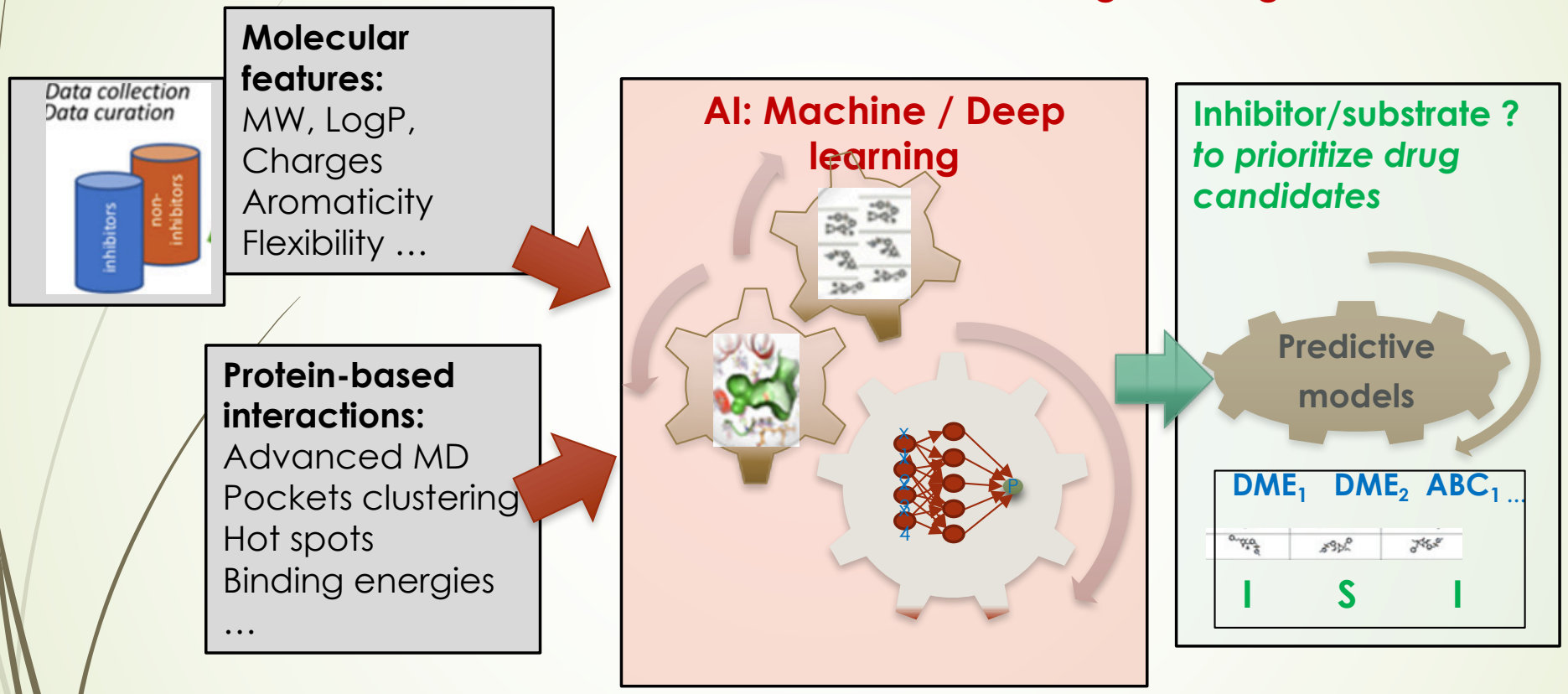
Influx Transporters

Giacomini et al. Nature 2007
Gleeson et al. Nat Rev Drug Discov 2011
Moroy G. et al. Drug Discovery Today 2012
Isvoran et al. Drug Discov Today 2017; 2022
Elbahnsi et al. Pharmaceuticals (Basel). 2024
Dudas & Miteva Trends Pharmacol Sci. 2024

In silico approach to predict inhibitors of DME and transporters

LOGINSERM®

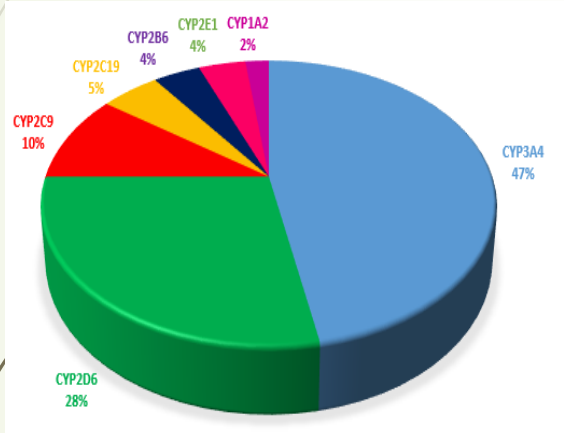
Software DrugME, DrugABC

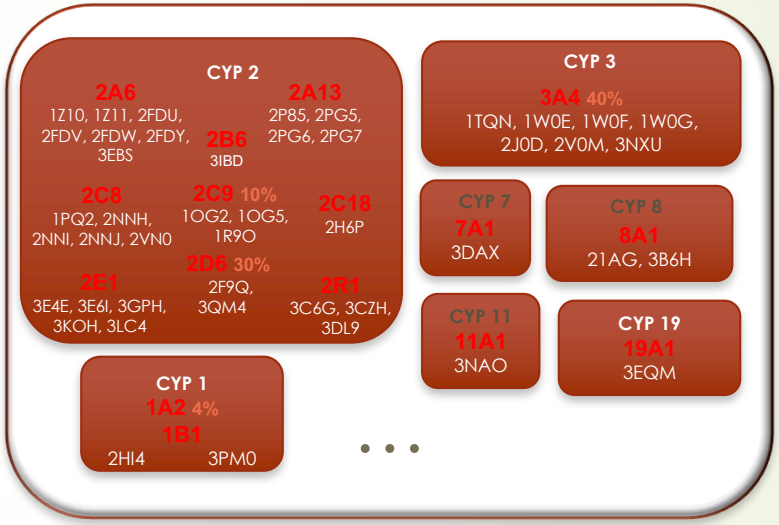


Martiny et al Plos One 2013
Martiny et al. Bioinformatics 2015
Goldwaser et al. PLoS Comput Biol. 2022
Dudas et al. iScience 2022
Elbahsni et al. 2024
Patent PCT/EP2021/070646

CYP 450: major drug metabolizing enzymes

Percentage of drugs metabolized by different CYPs

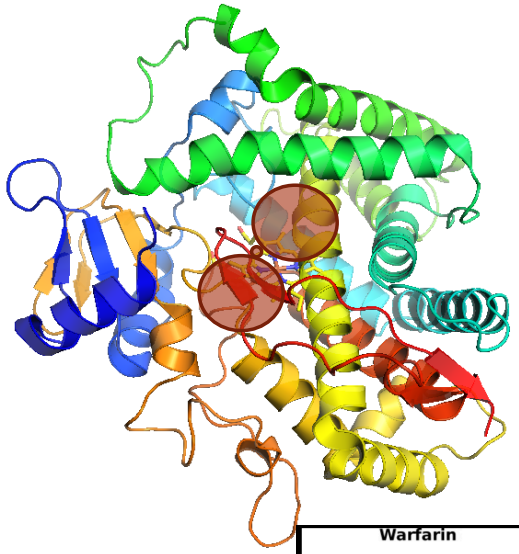




$RH + O_2 + NADPH + H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$

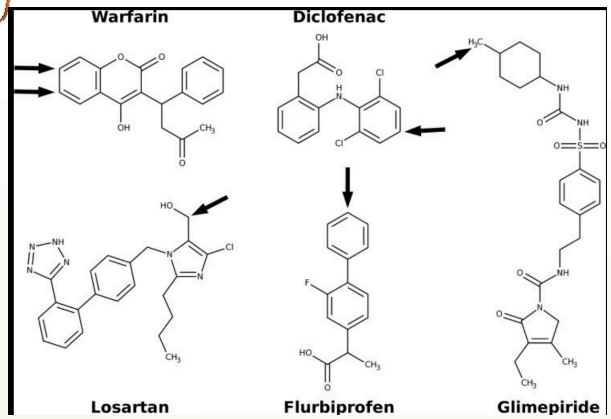
Clarke & Jones, (Eds.). Human cytochromes P450 and their role in metabolism-base drug-drug interactions. New York,, 2002
Zanger al. Naunyn-Schmiedeberg's Arch Pharamcol 2004
Rodriguez-Antonia & Ingelman-Sundberg, Oncogene 2006
Martiny V.Y. & Miteva MA. J. Mol. Biol. 2013
Isvoran et al. Drug Discovery Today 2017

CYP 450: major drug metabolizing enzymes



- CYP 2C9
- Metabolizing ~10 % of drugs
- Highly polymorphic isoform
- >60 alleles

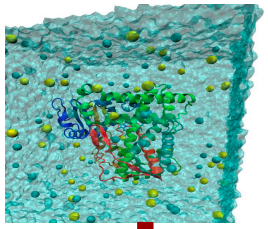
- **Strong flexibility**

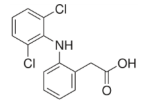


Drugs substrates of CYP2C9

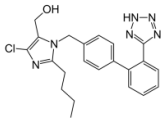
CYP 2C9 flexibility: Generation and selection of ensemble conformations

- MD of CYP 2C9 : 5 x 50 ns



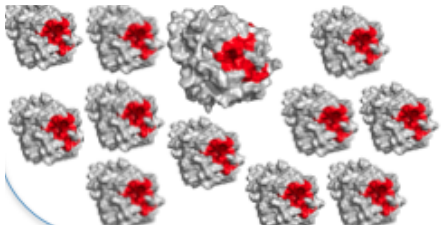


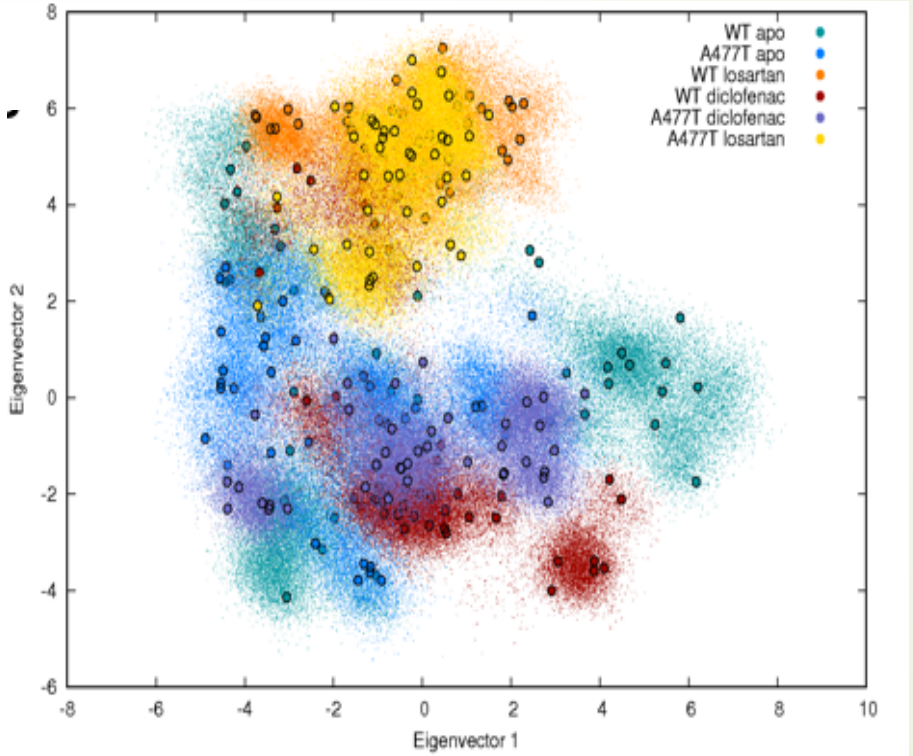
Diclofenac



Losartan

- Most populated clusters: 40 centroids for each CYP 2C9 system





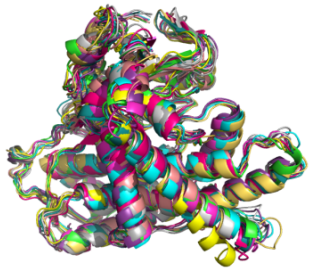
Louet et al. Plos One 2018

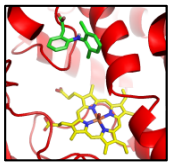
Interaction energies for the integrated ML approach to predict inhibitors of CYP 2C9

Structures

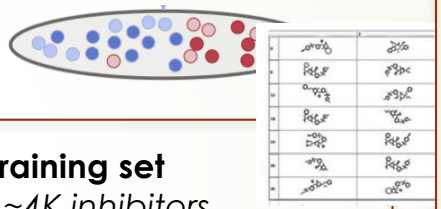
CYP2 C9	Conformation selection MD
WT	**5**
X-ray	**2**

Docking-scoring of 5 substrates on 40 centroids





Chemical library



Training set
~4K inhibitors
~3K non-inhibitors

External test set
~1K inhibitors
~700 non-inhibitors

Louet et al. Plos One 2018

Goldwaser et al Plos Comput Biol 2022

In silico approach to predict inhibitors of DME and transporters

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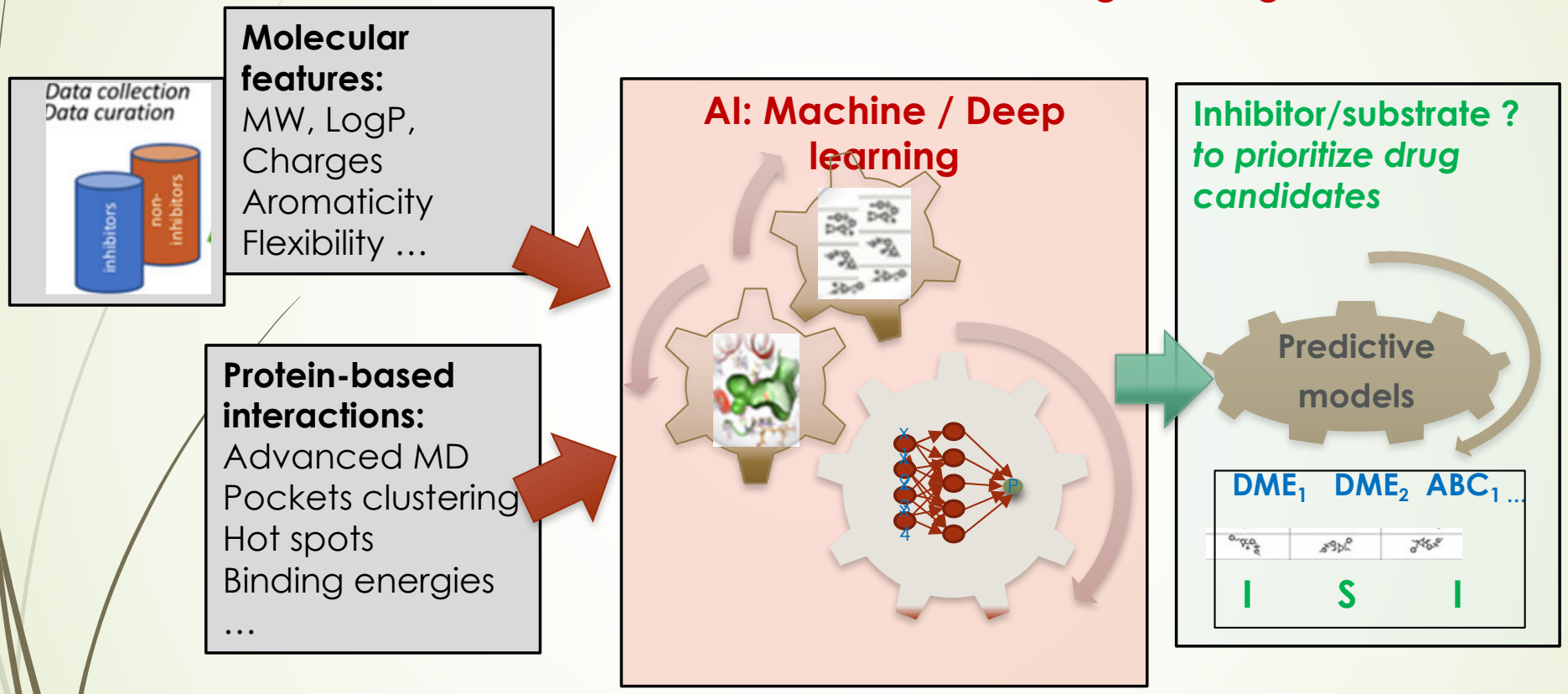
Software DrugME, DrugABC



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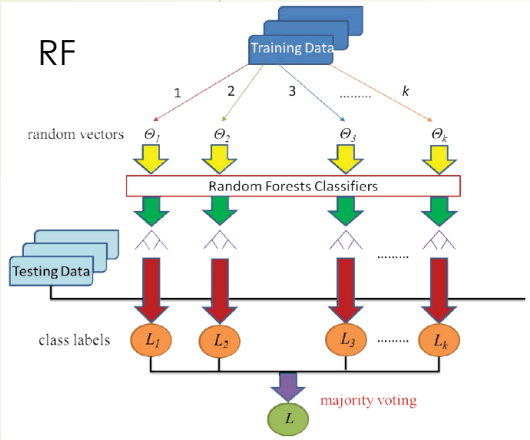
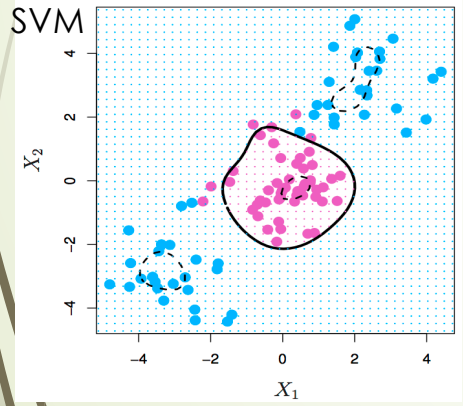
Dudas et al. iScience 2022
Elbahsni et al. 2024
Patent PCT/EP2021/070646

Best RF and SVM models for CYP2C9

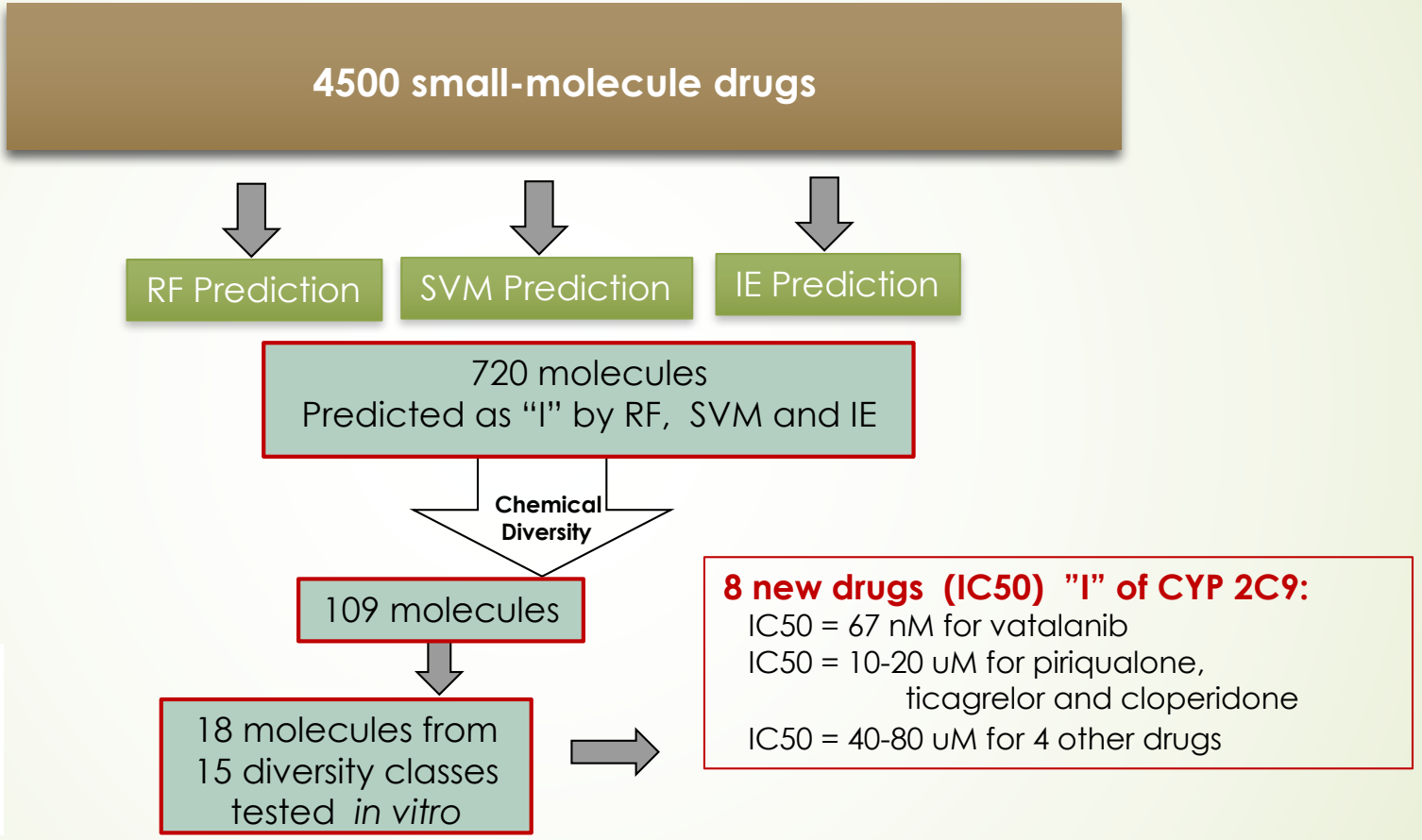




Descriptors selected by importance of 2000 *RF*	**Validation External set**	**Accuracy %**	**Sensitivity %** *Inhibitors*	**Specificity %** *non-inhibitors*
20 Phys-chem + 7 Interaction energies	**SVM**	**83.72**	**88.77**	**75.89**
	RF	**84.45**	**89.57**	**76.52**
36 Phys-chem + 7 Interaction energies	**SVM**	**84.76**	**89.87**	**76.83**
	RF	**85.55**	**89.97**	**78.69**
170 Phys-Chem +7 Interaction energies	**SVM**	**86.22**	**90.87**	**79.00**
	RF	**85.55**	**90.57**	**77.76**

Goldwaser et al Plos Comput Biol 2022

Experimental validation of drugs predicted as inhibitors of CYP 2C9

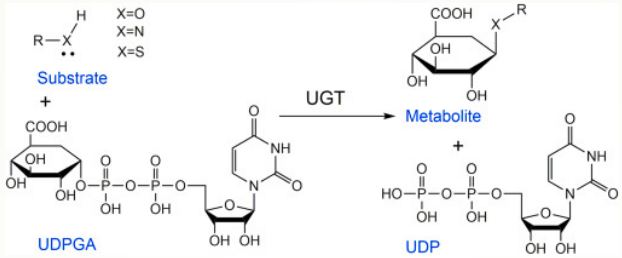


ToxME
Collab. Pr. MA. Loriot

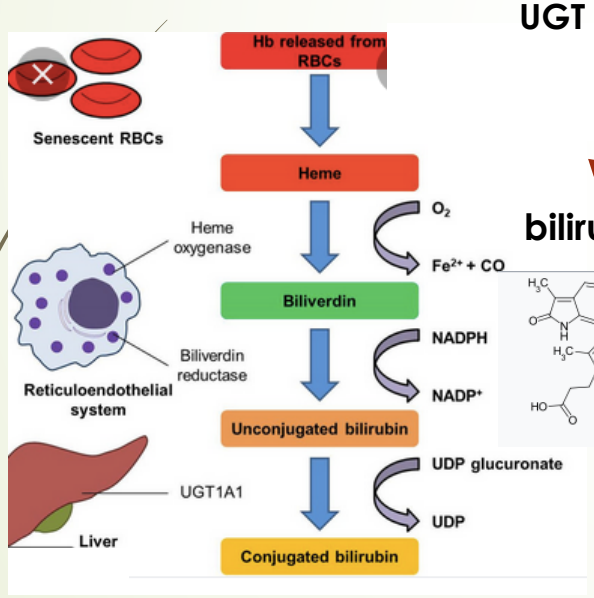
Goldwaser et al Plos Comput Biol 2022

Uridine 5'-diphosphate - glucuronosyltransferase (UGT)

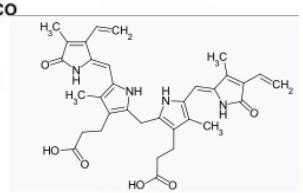
35 % of phase II drug metabolism



UGT 1A1 : 15% of all UGT drug metabolism



bilirubin

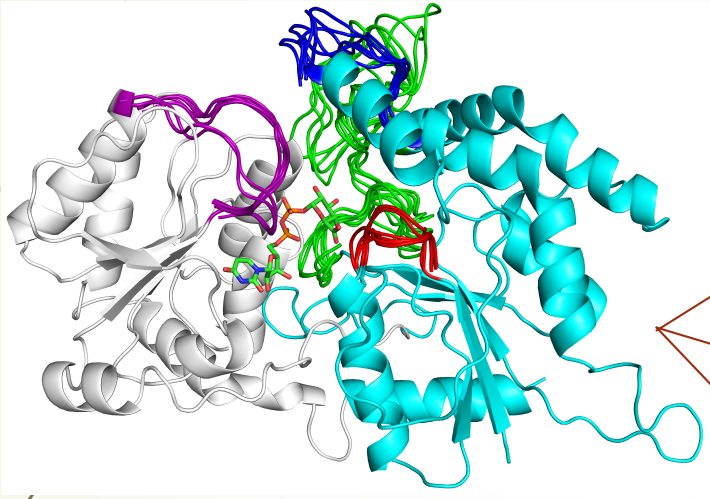


drugs

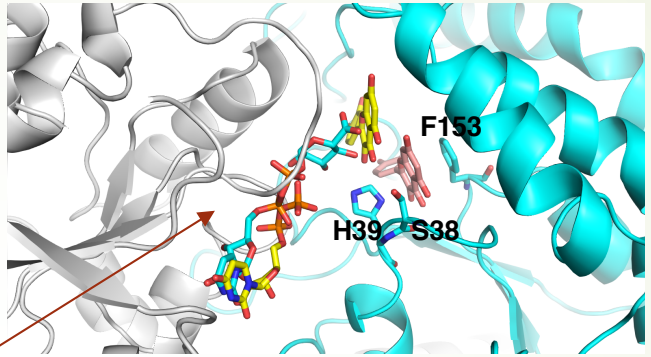
irinotecan (SN38), raloxifene , estrogens, lamotrigine, protease inhibitors

Testa et al. Drug Discov. Today 2012
Oda et al. Drug Metab. Pharmacokinet. 2015

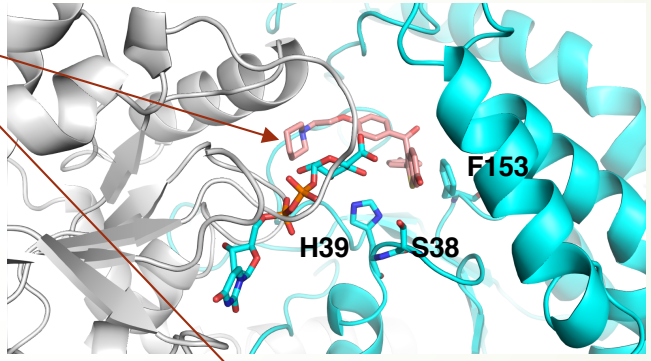
UGT 1A1 structure, dynamics and ligand interactions



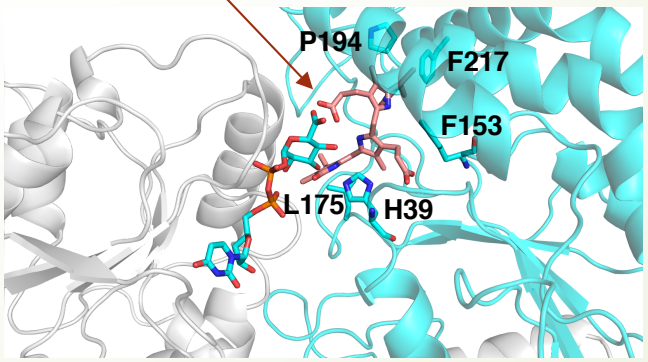
3 replicas x 100 ns MD, clustering



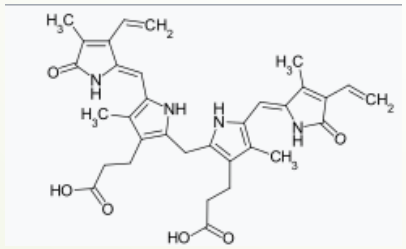
quercetin



raloxifene



bilirubin
(~ NMR conformation)



Dudas et al. iScience 2022

Best RF and SVM models for UGT 1A1

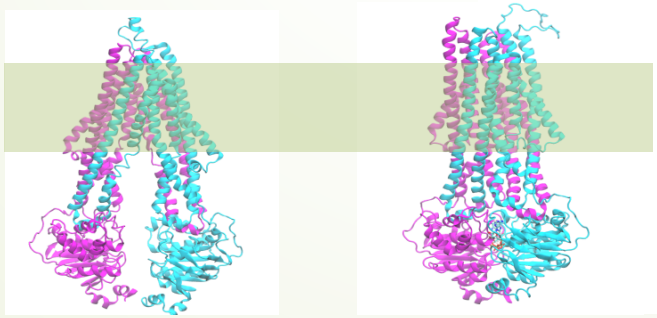
Molecular features	ML	Balanced Accuracy % on the external set	Sensitivity % *inhibitors*	Specificity % *non-inhibitors*
56 Phys-chem +6 Interaction energies	SVM RF	90.7 93.7	88.9 92.6	92.5 93.6

Dudas B, Bagdad Y, Picard M, Perahia D, Miteva MA. iScience 2022

ATP-binding cassette transporters

- Energy of ATP hydrolysis to translocate substrates across membrane
- Exports endogenous substrates, toxins, drugs
- 2 transmembrane domains (**TMD**)
- 2 nucleotide-binding domains (**NBD**)

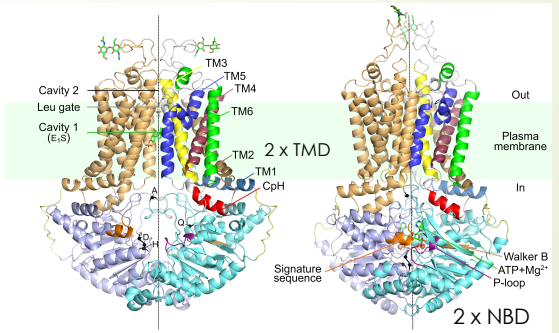
P-gp (ABCB1)
P-**g**lyco**p**rotein



Inward *occluded*

Outward

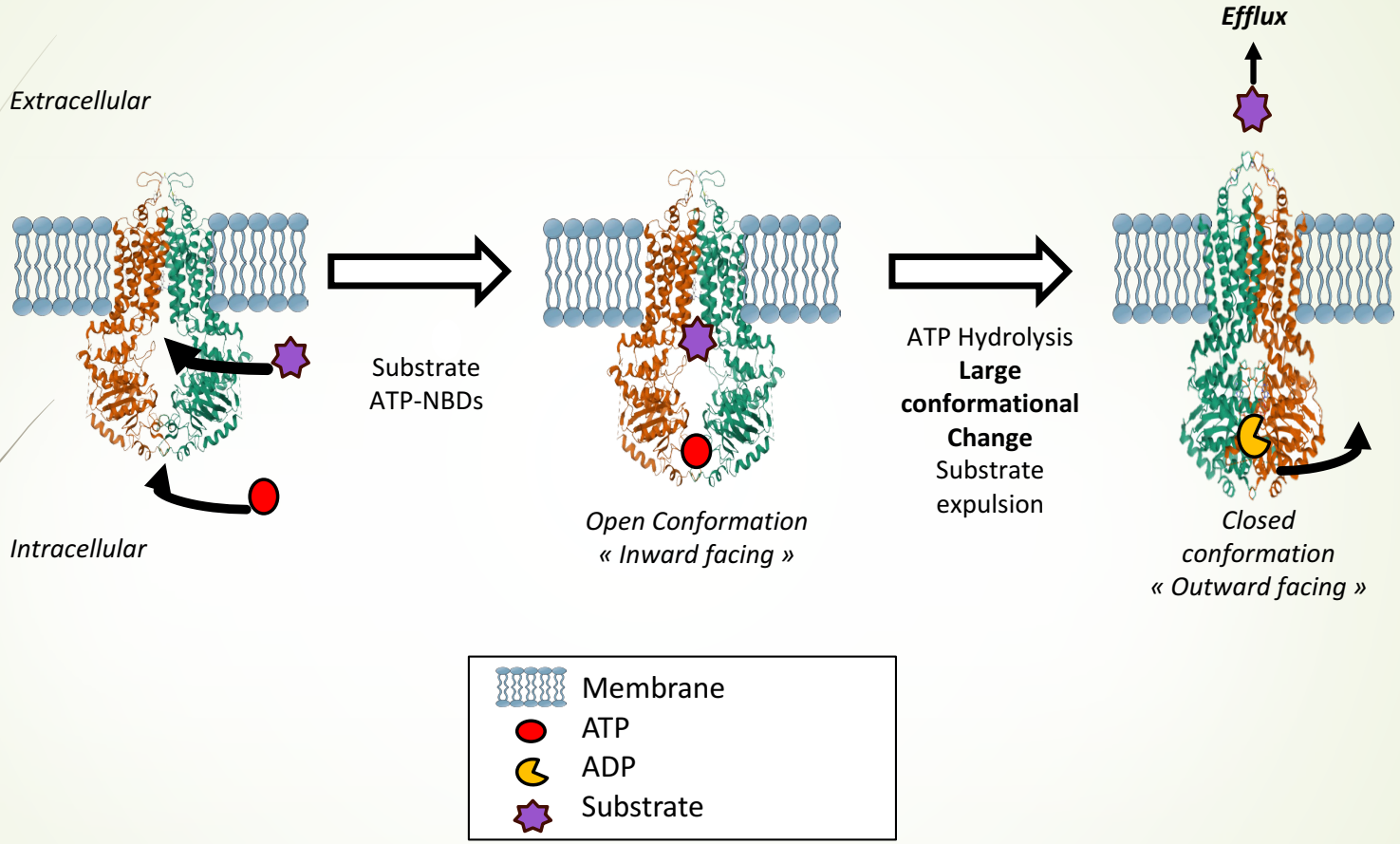
BCRP (ABCG2)
Breast **C**ancer **R**esistance **P**rotein



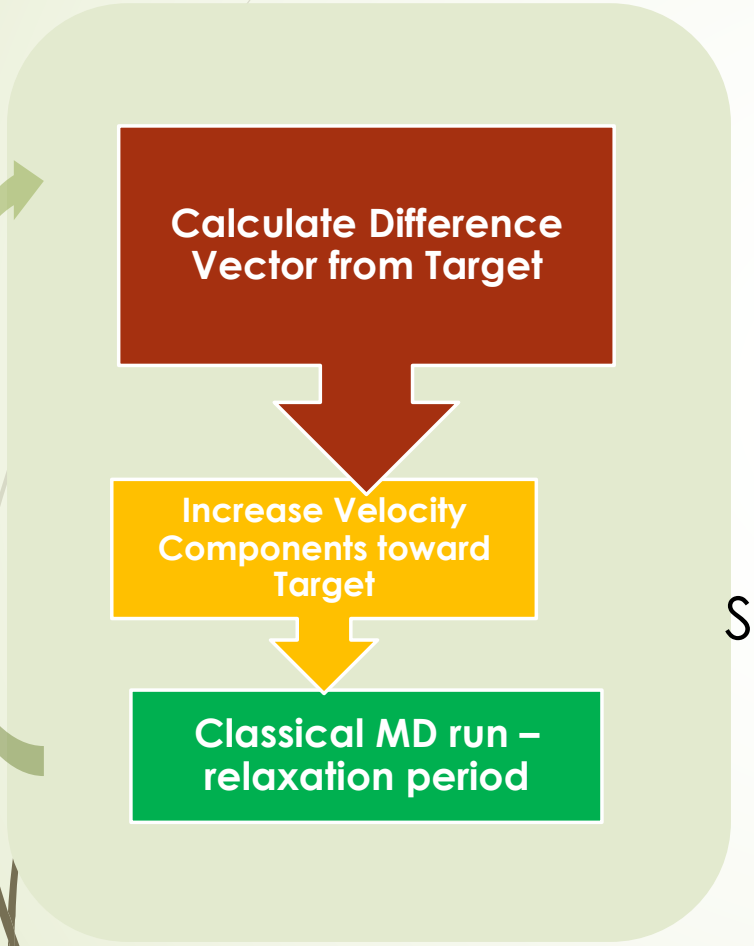
Inward

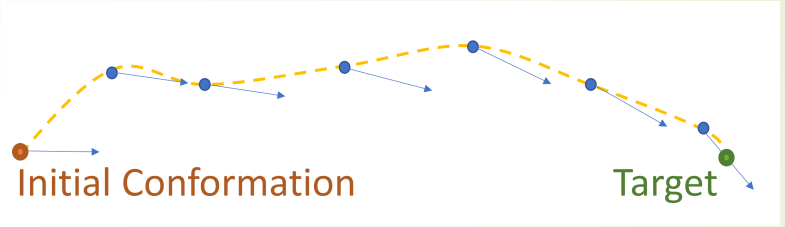
Outward

BCRP and P-gp transport cycle



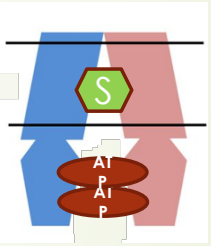
Kinetically excited targeted MD (ketMD)



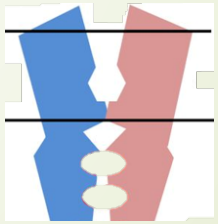


- 40 excitation cycles, each with 5 ps relaxation period

Substrate- & ATP-bound IFS

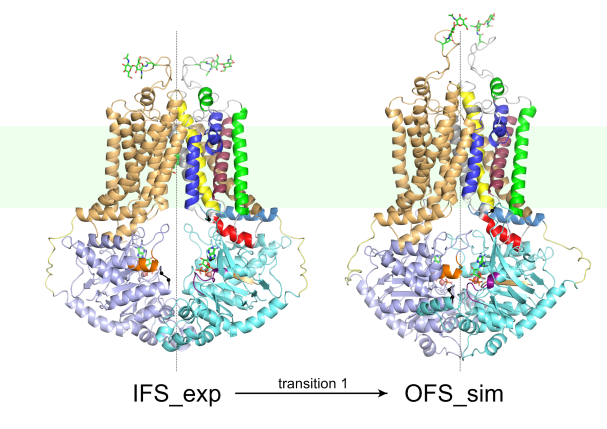


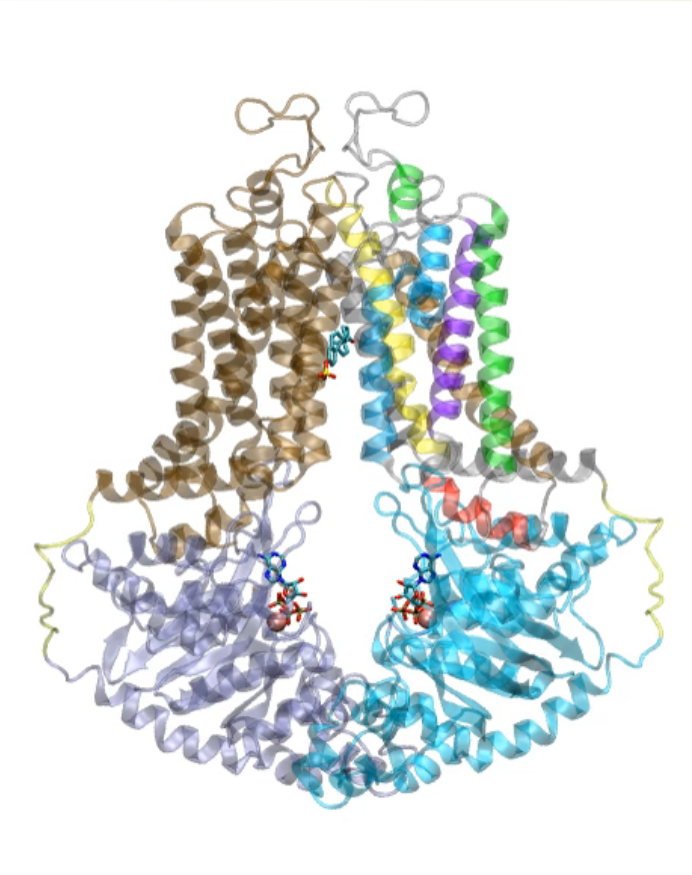
Nucleotide-free OFS



Dudas B, Decleves X, Cisternino S, Perahia D, Miteva MA. *Comput Struct Biotechnol J. 2022*

Substrate translocation of BCRP





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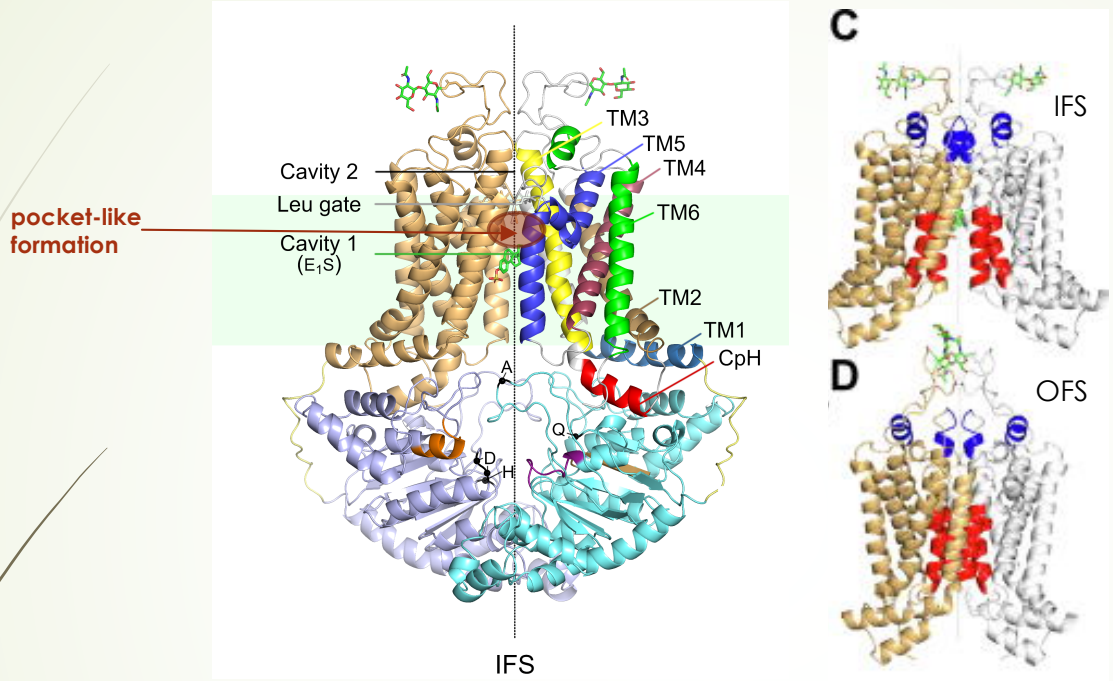
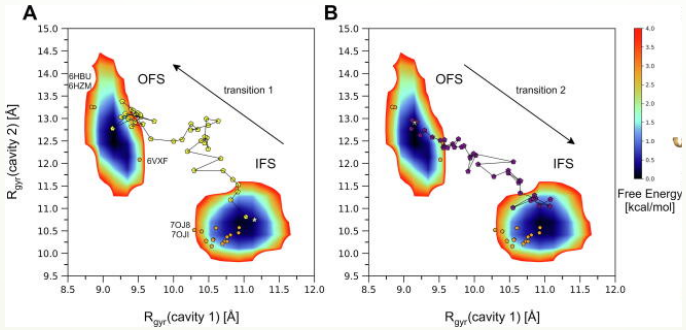
Substrate translocation of BCRP





Dudas B, Decleves X, Cisternino S, Perahia D, Miteva MA.
Comput Struct Biotechnol J. 2022

Performance of our AI models predicting inhibitors of BCRP

Predicted		External dataset
Non-inhibitors	Inhibitors	Experimental
97	6	103 non-inhibitors
3	132	135 inhibitors

Accuracy = 96,2 %
Sensitivity = 97.8 %
Specificity = 94.2 %

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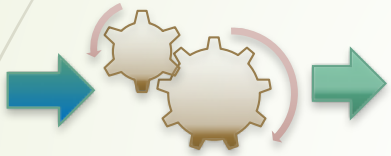
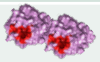
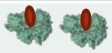
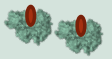
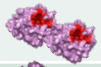
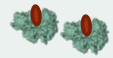
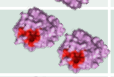
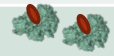
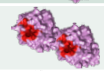
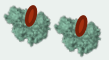
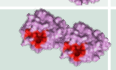
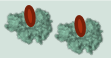
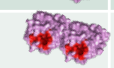
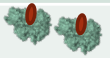
DRUGME / DRUGABC SOFTWARE

INPUT

Small molecule in 3D MOL2



OUTPUT

Compounds		Models For each DME				RISK	Models For each ABC			
		ML1 ML2	IE3	Inter. Energy	Best Poses		ML1 DL2	IE3	Inter. energy	Best poses
		I I		-5 **-6**		Medium	I	I	**-7** -2	
		I I	I	**-12** -4		High	I	I	-8 **-11**	
		I		+3 **-1**		Low		I	-2 **-7**	
				+5 **-2**		0			+7 **-1**	
			I	**-8** -4		Low			+4 **-4**	
		I	I	**-9** -3		High	S	S	**-11** -6	
		S I		**-6** +1		Medium	I	I	**-9** -5	

DME: CYP 2D6, 2C9, 3A4
UGT 1A1
SULT 1A1, 1A3
ABC: BCRP, P-gp

Conclusions and Perspectives

- *ketMD: original approach to study efflux mechanisms of ABC transporters for further prediction of inhibitors and substrates*
- *Integration of SB and ML/DL methodologies to predict inhibitors and substrates of DME and ABC transporters*
- *Multiscale models*
- *Helpful to predict DDI for safer drugs in drug discovery and clinics*

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