

<https://toxstar.kitox.re.kr/>

# ToxSTAR for DILI prediction

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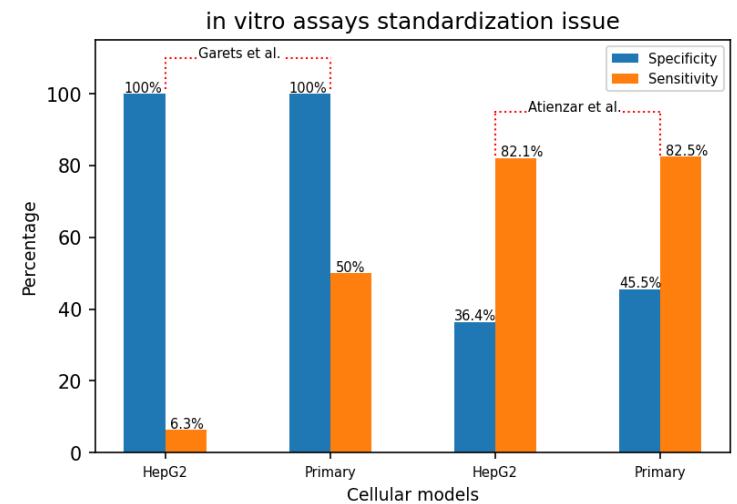
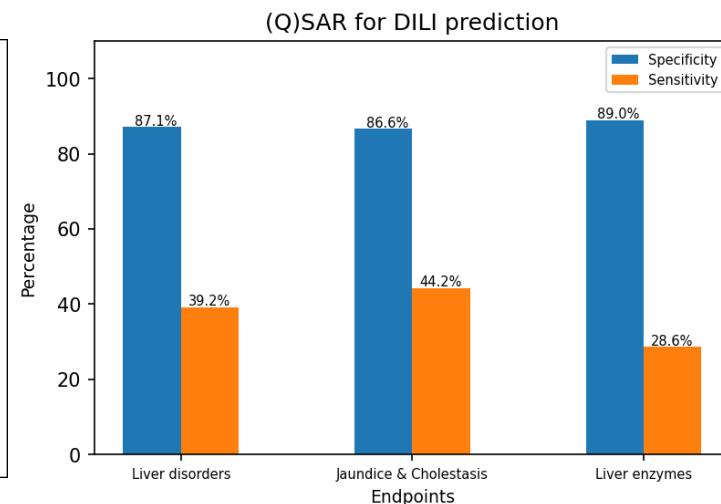
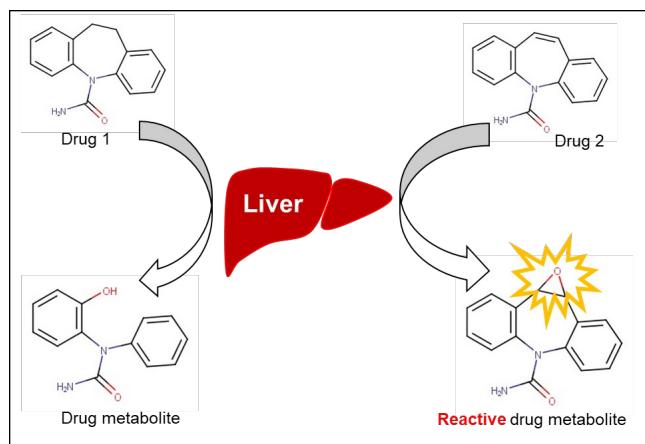
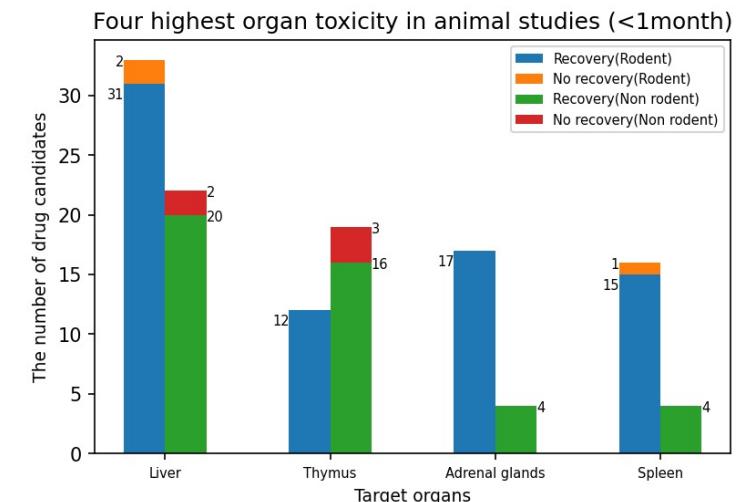
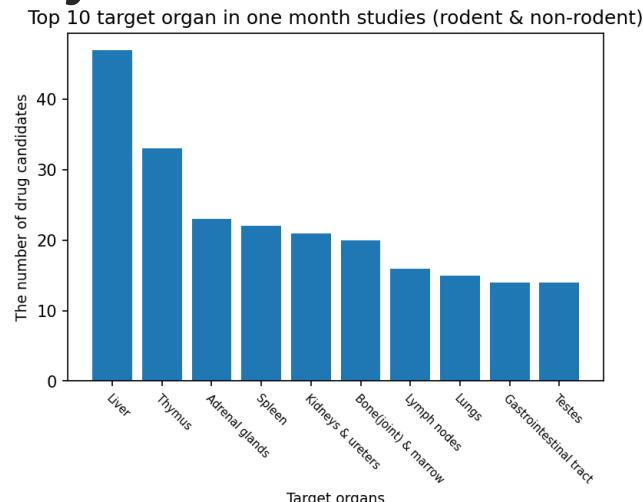
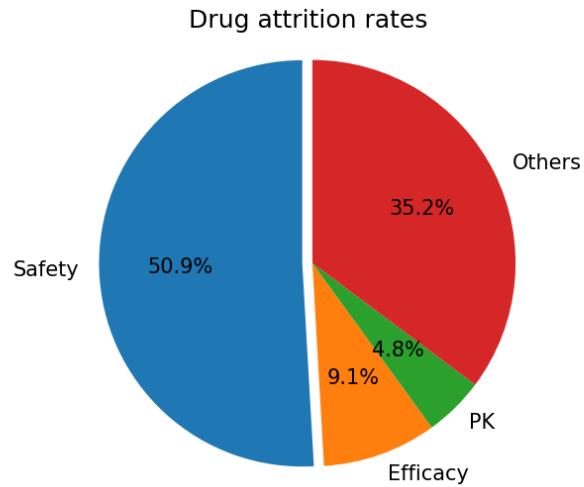
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## DILI prediction

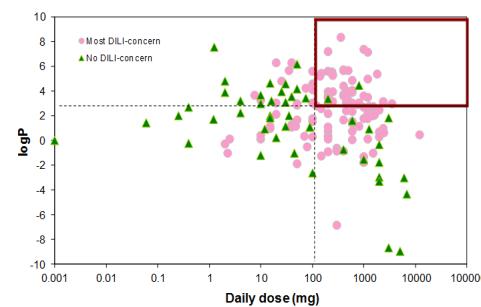
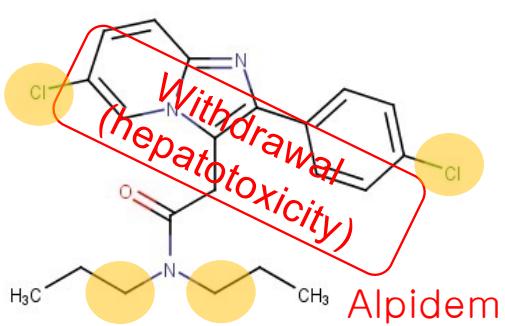
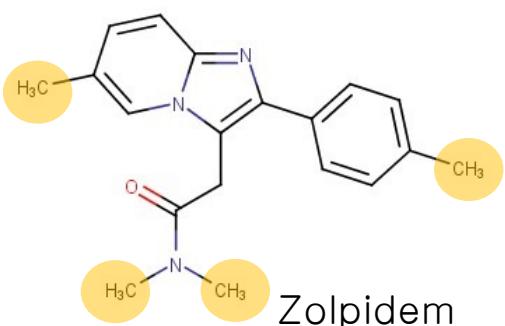
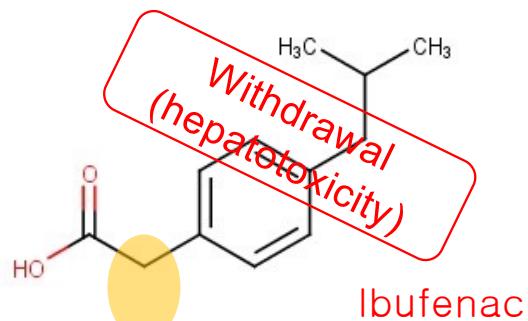
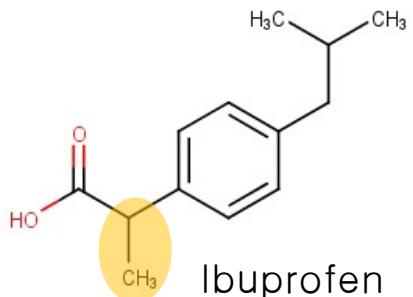
\*DILI: Drug-induced liver injury



# Drug-induced liver injury



# Challenges in DILI prediction


**Rule of two**

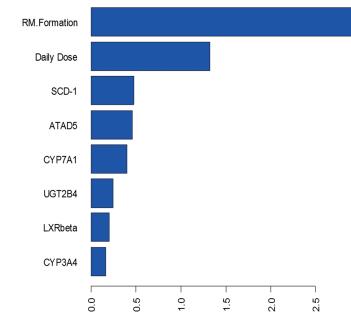
1. Daily dose  $\geq 100$  mg/day
2.  $\log P \geq 3$

Khadka et al., ALTEX (2019) 37, 187-196

Chen et al., Hepatology (2013) 58, 388-396

Parameters	Univariate Logistic Regression
Daily dose	0.501 (0.094)***
$C_{max}$	0.378 (0.067)***
$\log P$	0.876 (0.323)**
RM formation	2.940 (0.384)***

Chen et al., Hepatology (2016) 64, 931-940





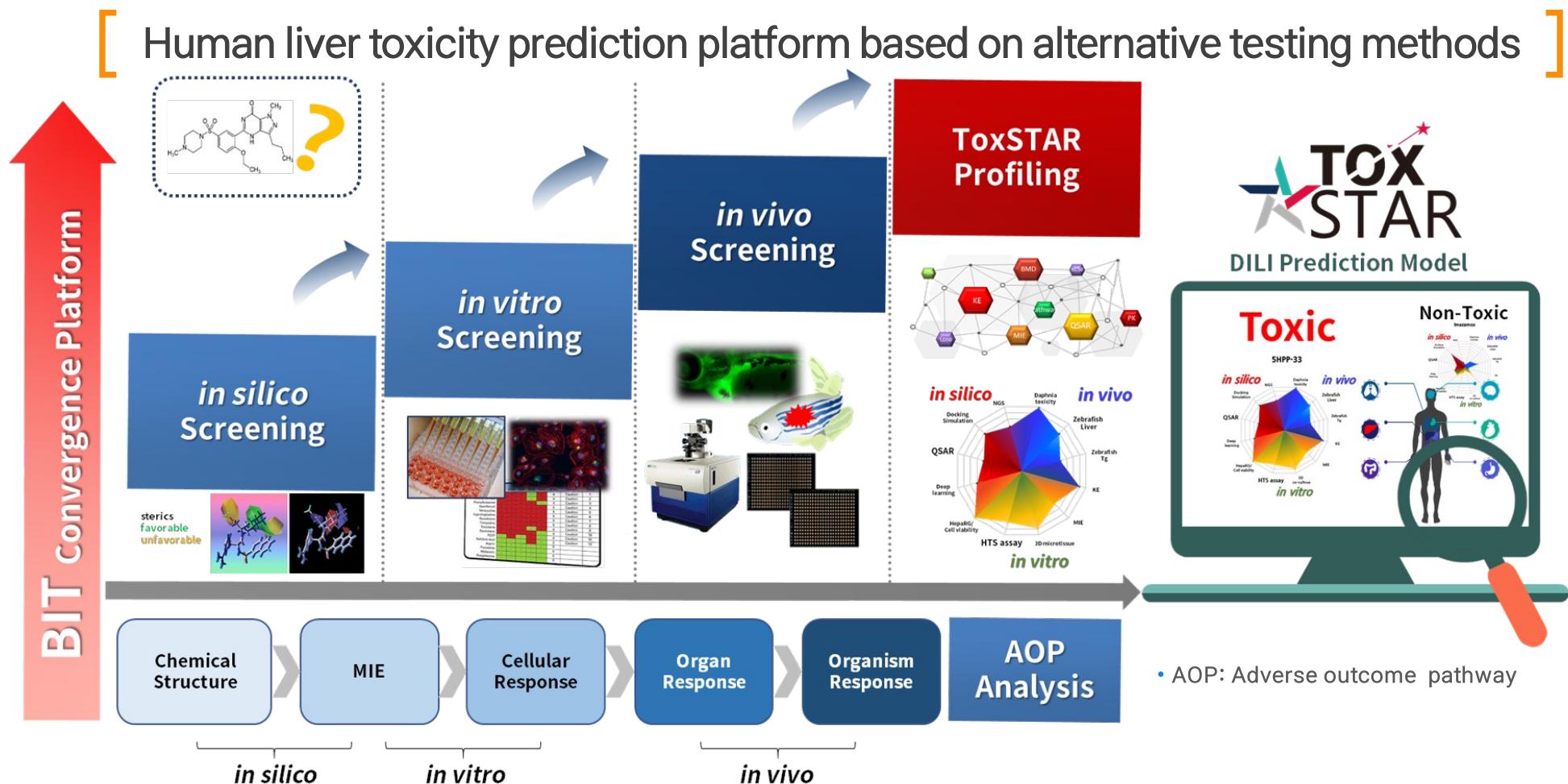
DILI prediction

# Available DILI prediction SW



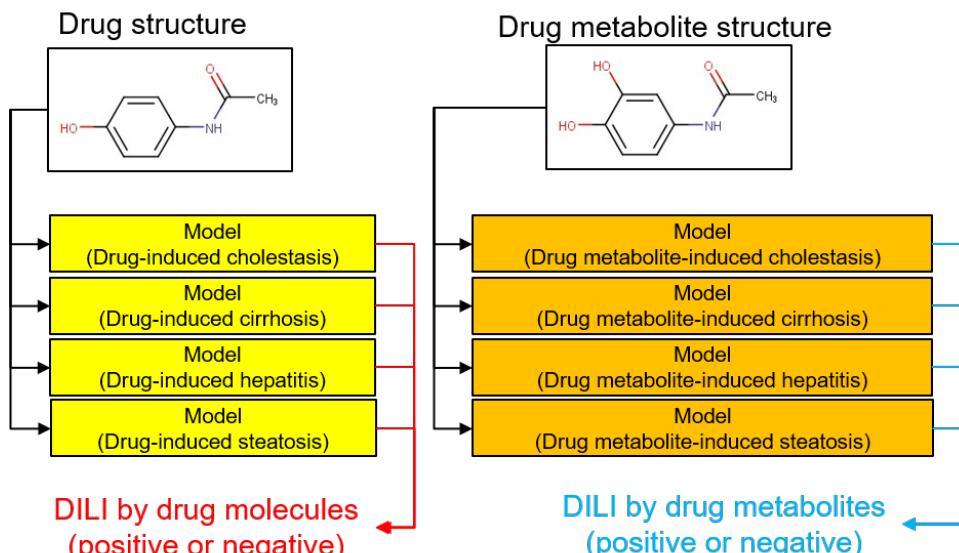
Name	Endpoint	Model type	License type
ADMET predictor	Elevation of DILI biomarkers (ALP, AST, LDH)	Binary classification	Commercial software (GUI program)
Derek Nexus	Severity of DILI	Rule-based classification with certainty of prediction	Commercial software (GUI program)
VEGA	Hepatotoxicity	Rule-based classification (Positive / Unknown / Negative)	Freely available (GUI program)
	Liver NOAEL and LOAEL	Regression	
	Hepatic steatosis MIEs (PXR / PPAR $\alpha$ / PPAR $\gamma$ / NRF2)	Binary classification	
ProTox –II	Hepatotoxicity	Binary classification	Freely available (Web program)
ToxSTAR	Cholestasis, Cirrhosis, Hepatitis, and Steatosis	Binary classification	Freely available (Web program)

# ToxSTAR concept

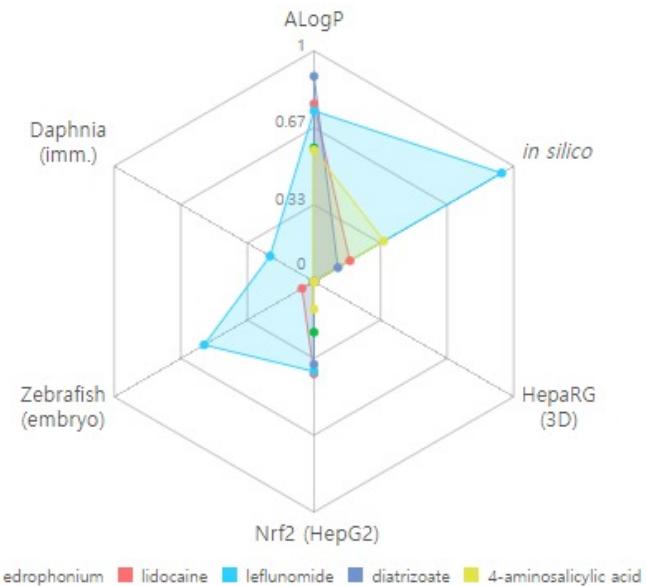


# ToxSTAR webpage

## In-house *in silico* model



## STAR plot



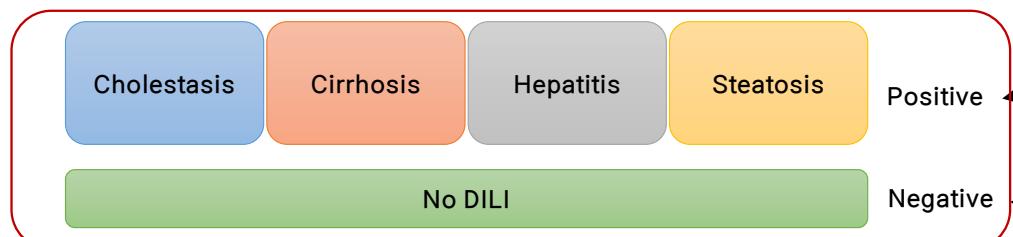
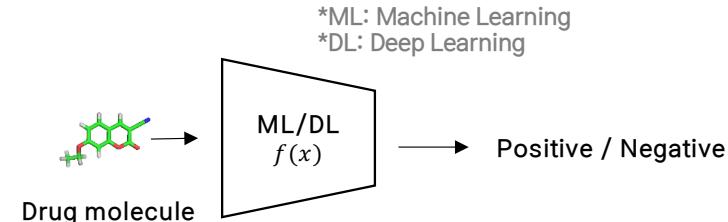
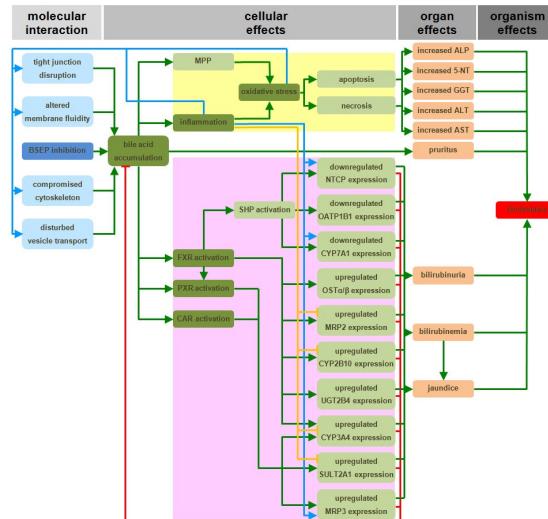
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## ToxSTAR (Q)SAR part

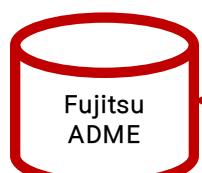


# Liver disease specific prediction model



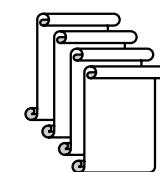
Drugs: 4 models  
Drug metabolites: 4 models

Drug metabolites



Mechanism of DILI  
Drug metabolites

?



FDA post-market reports

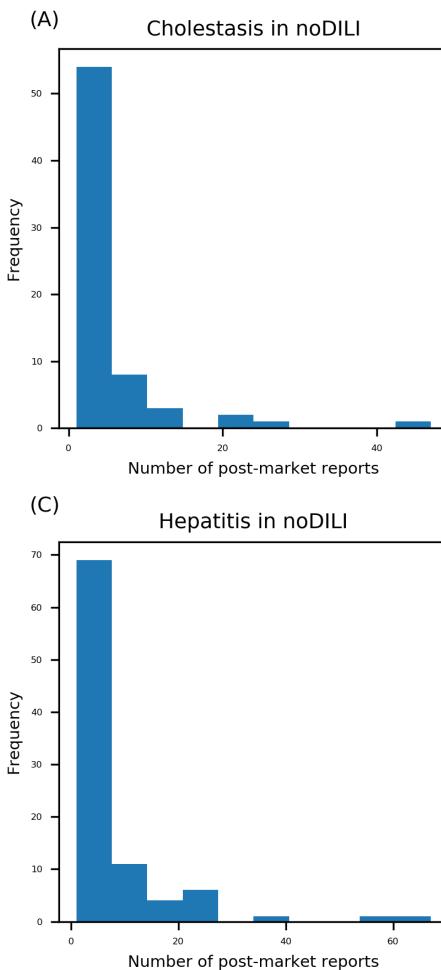
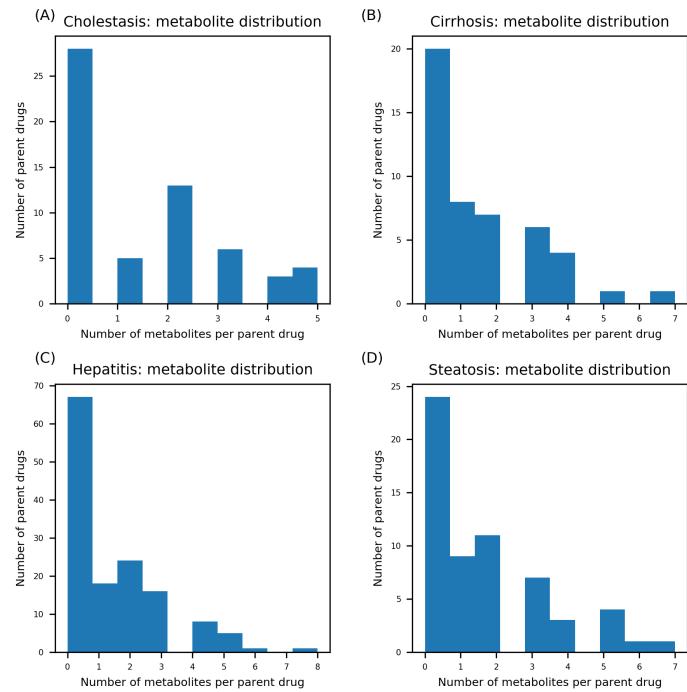
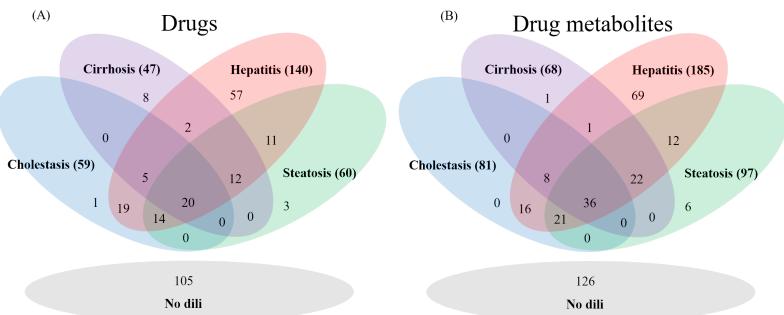


Shin et al., *Front. Pharmacol.* (2020) 11, doi: 10.3389/fphar.2020.00067



In-house *in silico* model

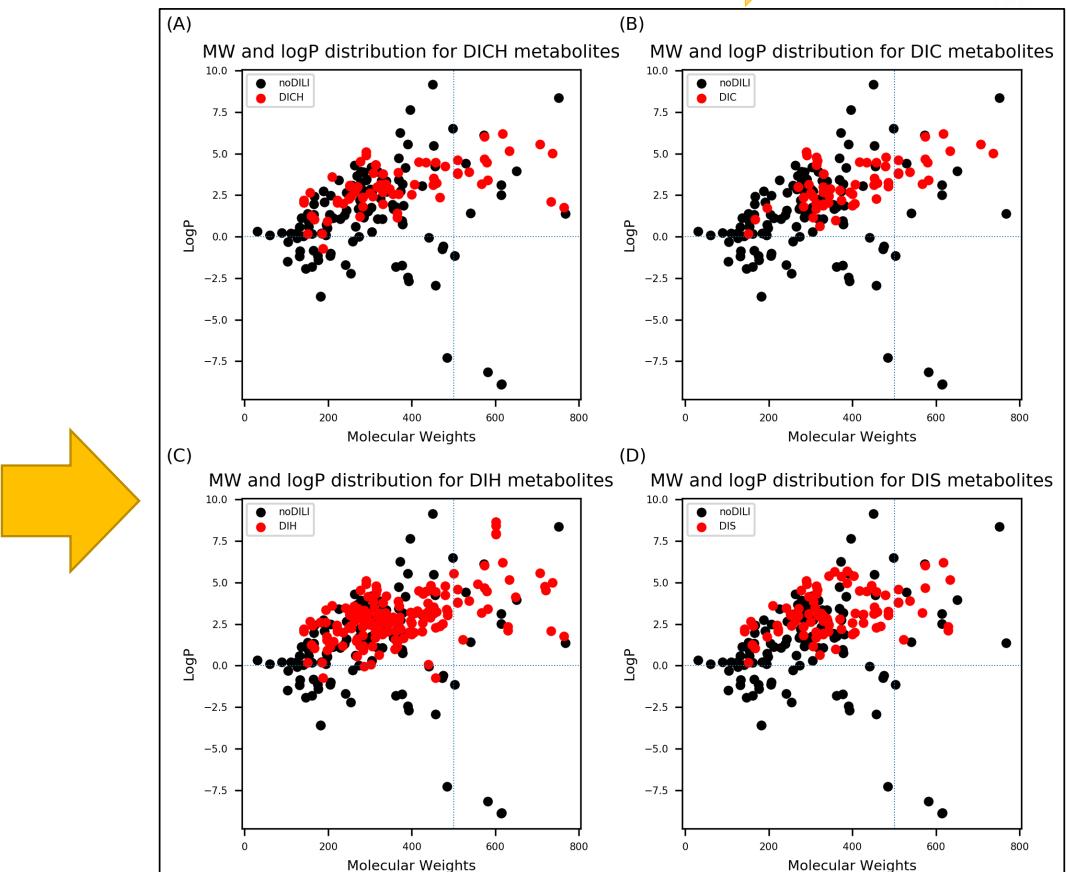
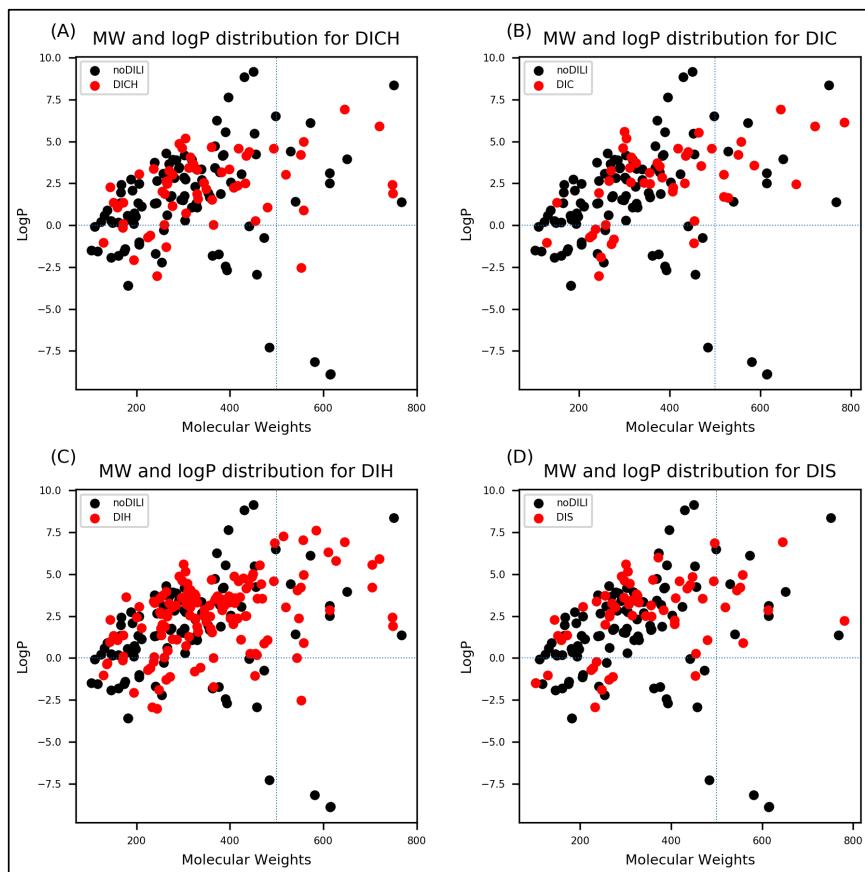
# Data distribution





In-house *in silico* model

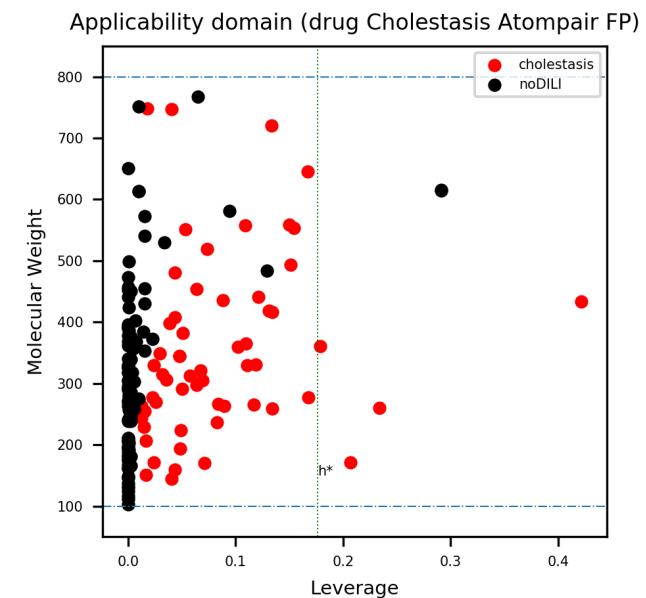
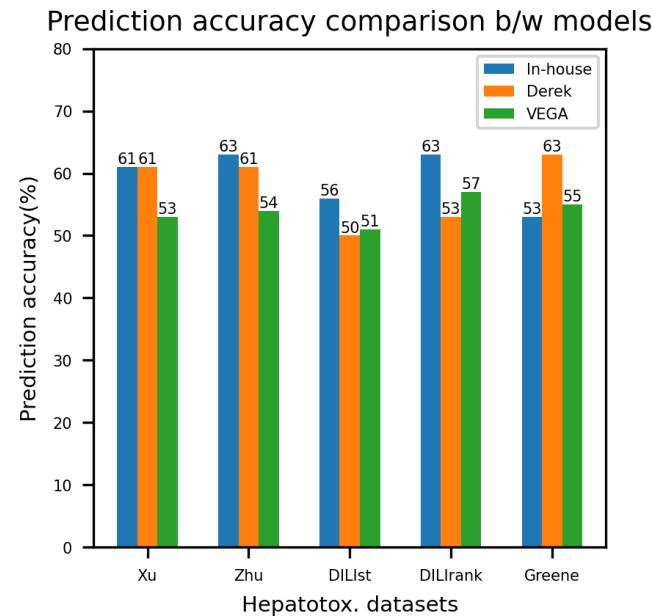
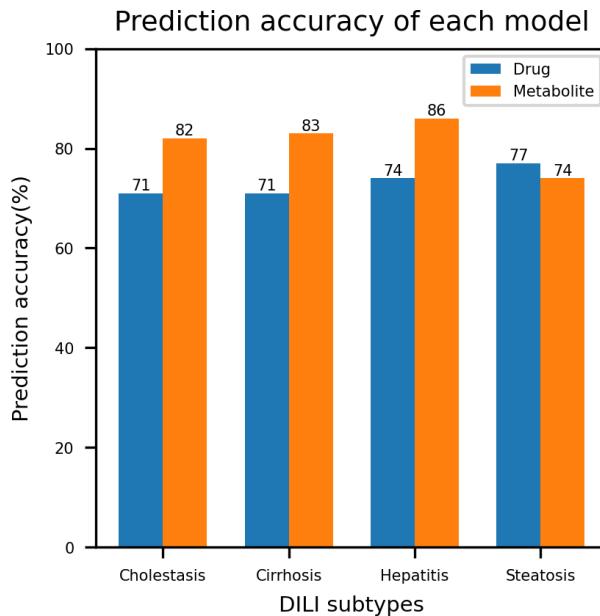
# Chemical space shifting



**Table 1. DILI indication prediction model (Drugs / Drug metabolites)**

Endpoint		Cholestasis		Cirrhosis		Hepatitis		Steatosis	
FP	Avalon	Avalon	MACCS	Avalon	Avalon	MACCS	Avalon	Layer	
ML	SVM	RF	SVM	RF	RF	RF	SVM	RF	
Type	Drug	Metabolites	Drug	Metabolites	Drug	Metabolites	Drug	Metabolites	
SEN	5-fold CV	0.89	0.78	0.83	0.89	0.73	0.86	0.76	0.75
	External	0.83	0.94	0.80	0.93	0.70	0.86	0.75	0.83
SPE	5-fold CV	0.89	0.78	0.70	0.92	0.74	0.80	0.91	0.75
	External	0.69	0.79	0.70	0.81	0.86	0.88	0.78	0.72
ACC	5-fold CV	0.89	0.78	0.75	0.91	0.74	0.83	0.81	0.75
	External	0.71	0.82	0.71	0.83	0.74	0.86	0.77	0.74
MCC	5-fold CV	0.78	0.53	0.52	0.81	0.47	0.66	0.64	0.49
	External	0.40	0.63	0.35	0.60	0.50	0.68	0.50	0.44
AUC	5-fold CV	0.89	0.78	0.77	0.91	0.74	0.83	0.84	0.75
	External	0.76	0.87	0.75	0.87	0.78	0.87	0.76	0.78

# Prediction accuracy



Drug-induced liver injury	Prediction	Applicability domain
Cholestasis	Toxic	In-domain
Cirrhosis	Non-Toxic	In-domain
Hepatitis	Toxic	In-domain
Steatosis	Toxic	In-domain

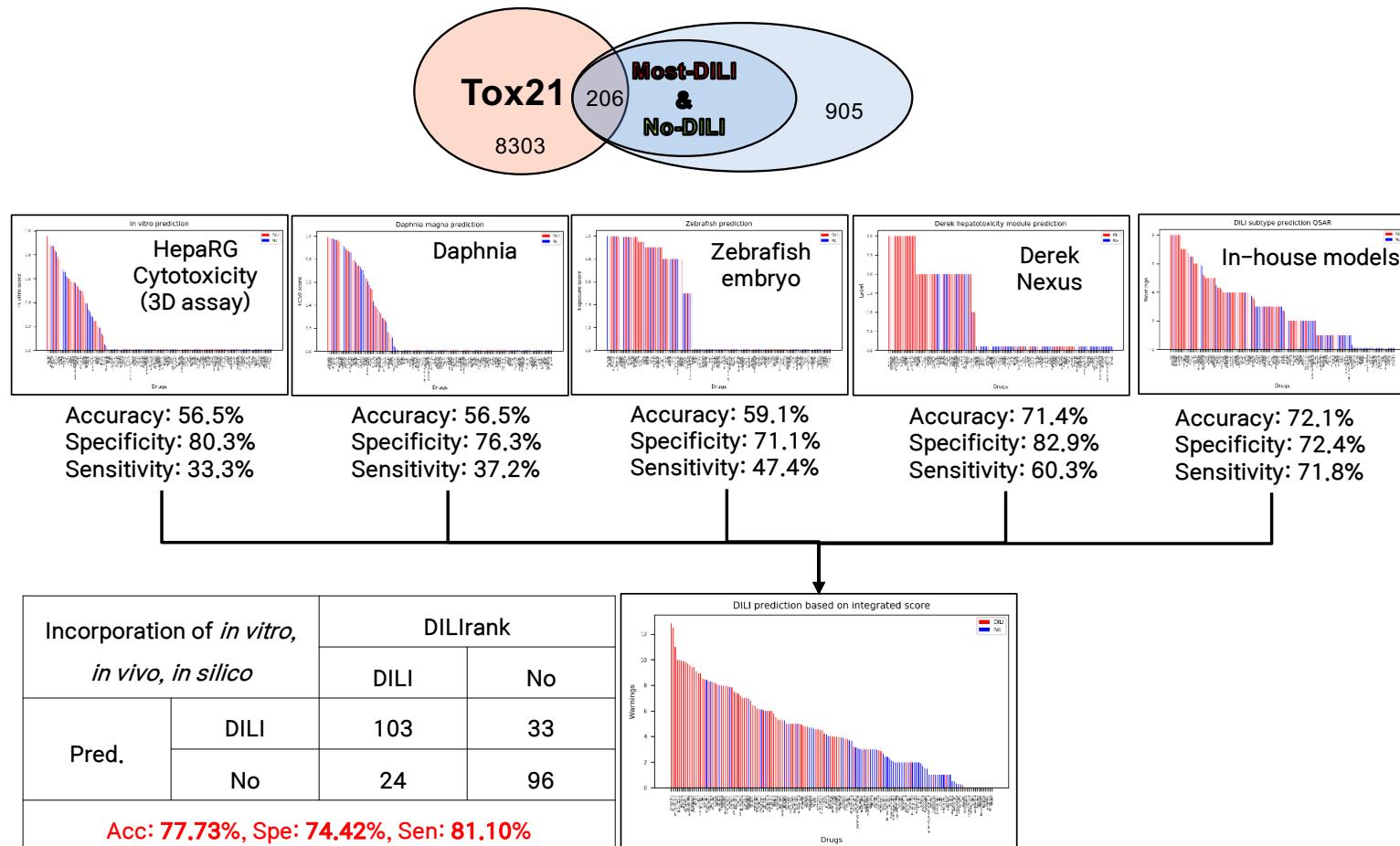
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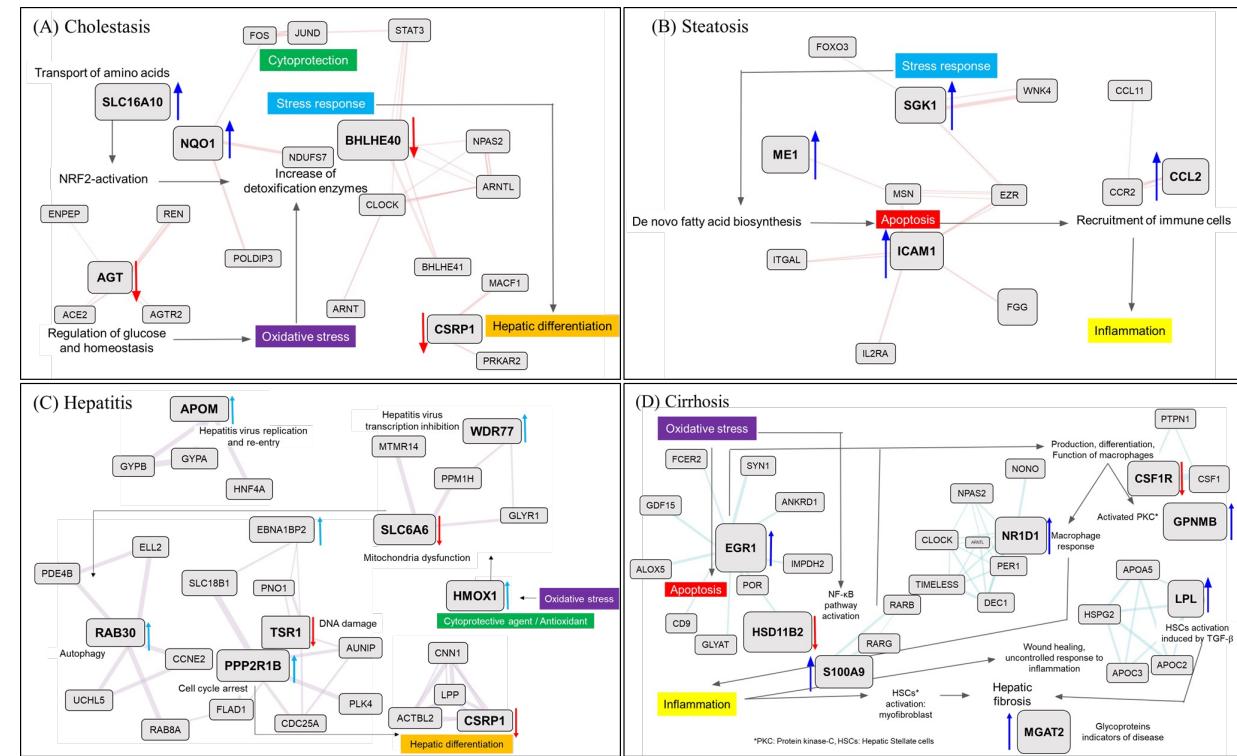
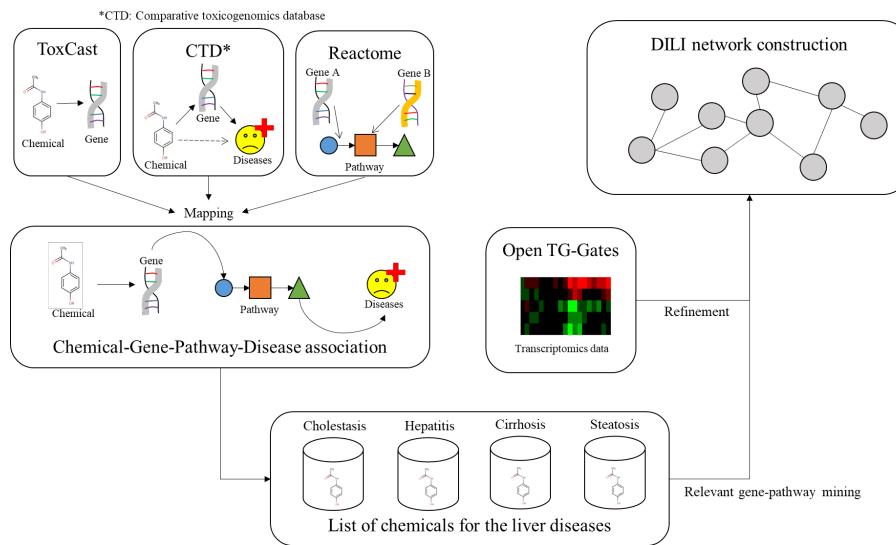
## Alternative testing based prediction



# Alternative testing integration

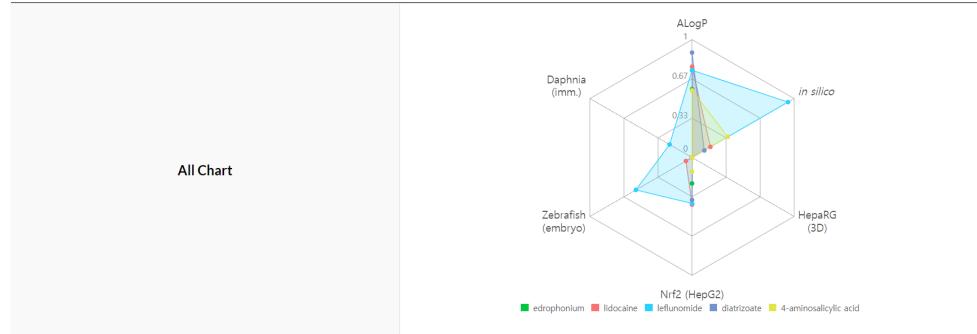


# Biological network analysis



# Web implementation

## Similarity Data



Name	Structure	Similarity Index	DILIrank label	DILI score	Radar plot
edrophonium		0.67	vNo-DILI-Concern	0.31	
lidocaine		0.56	vNo-DILI-Concern	0.41	

## *in silico*

- ALogP (PaDEL)
  - Well known property for DILI prediction
- In-house models (Statistical)
  - 0~8 (Drug: 4 / Drug metabolite: 4)
- Structural alert (Rule-based)
  - Derek Nexus
  - The number of alerts for each molecule

## *in vitro*

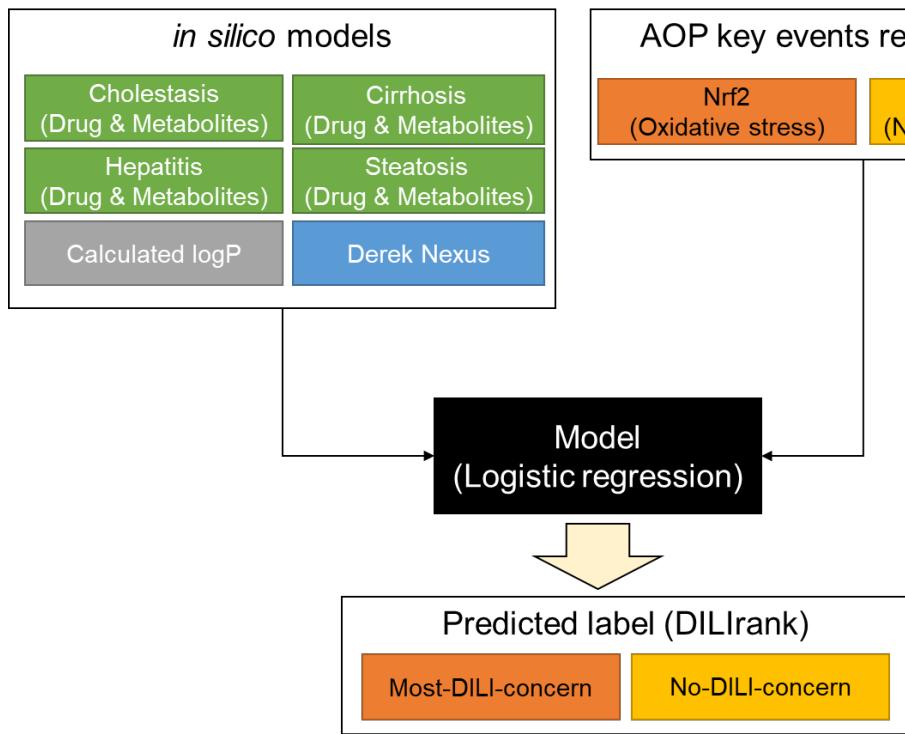
- Cytotoxicity
  - HepaRG 3D assay
- Nrf2 assay
  - HepG2
- BMD (Bench mark dose)

## *in vivo*

- Zebrafish embryo test
  - Similar gene change in human hepatocyte
  - Driessens et al., Toxicol Lett, 232, 403–412
- Daphnia magna test
  - Expression of DMEs
  - Tkaczyk et al., Drug Discov., 25, 201–208

\* DME: Drug metabolizing enzyme

# Update alternative testing



<b>in silico models</b>	<b>AOP related assays</b>	<b>5-fold CV accuracy</b>	<b>Available data size (Most-DILI/No-DILI)</b>
Cholestasis, Cirrhosis, Hepatitis, Steatosis, Derek Nexus, AlogP	-	76.56%	401 (176/225)
Cholestasis, Cirrhosis, Hepatitis, Steatosis, Derek Nexus, AlogP	Nrf2	81.04%	211 (111/100)
Cholestasis, Cirrhosis, Hepatitis, Steatosis, Derek Nexus, AlogP	Zebrafish	84.44%	45 (23/22)
Cholestasis, Cirrhosis, Hepatitis, Steatosis, Derek Nexus, AlogP	Nrf2, Zebrafish	92.31%	39 (19/20)



# Acknowledgements

I

## Funding

KIT (1711159817)

NRF(MSIT)-2019R1F1A1061955



National Research  
Foundation of Korea



Ministry of Science, ICT  
and Future Planning

II

## KIT

Jung-Hwa Oh (Ph.D.), Hyoung-Yun Han (Ph.D.), Se-Myo Park,  
Soojin Kim, Woo-Keun Kim (Ph.D.), Hang-Suk Chun (Ph.D.),  
Sangwoo Lee (Ph.D.), Myung-Gyun Kang (Ph.D.), Daeui Park (Ph.D.),  
Sungbo Hwang (Ph.D.), Seokjoo Yoon (Ph.D.)

II

## Edelweiss Connect

Tatyana Doktorova, Barry Hardy



# Thank you

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