SimulationsPlus

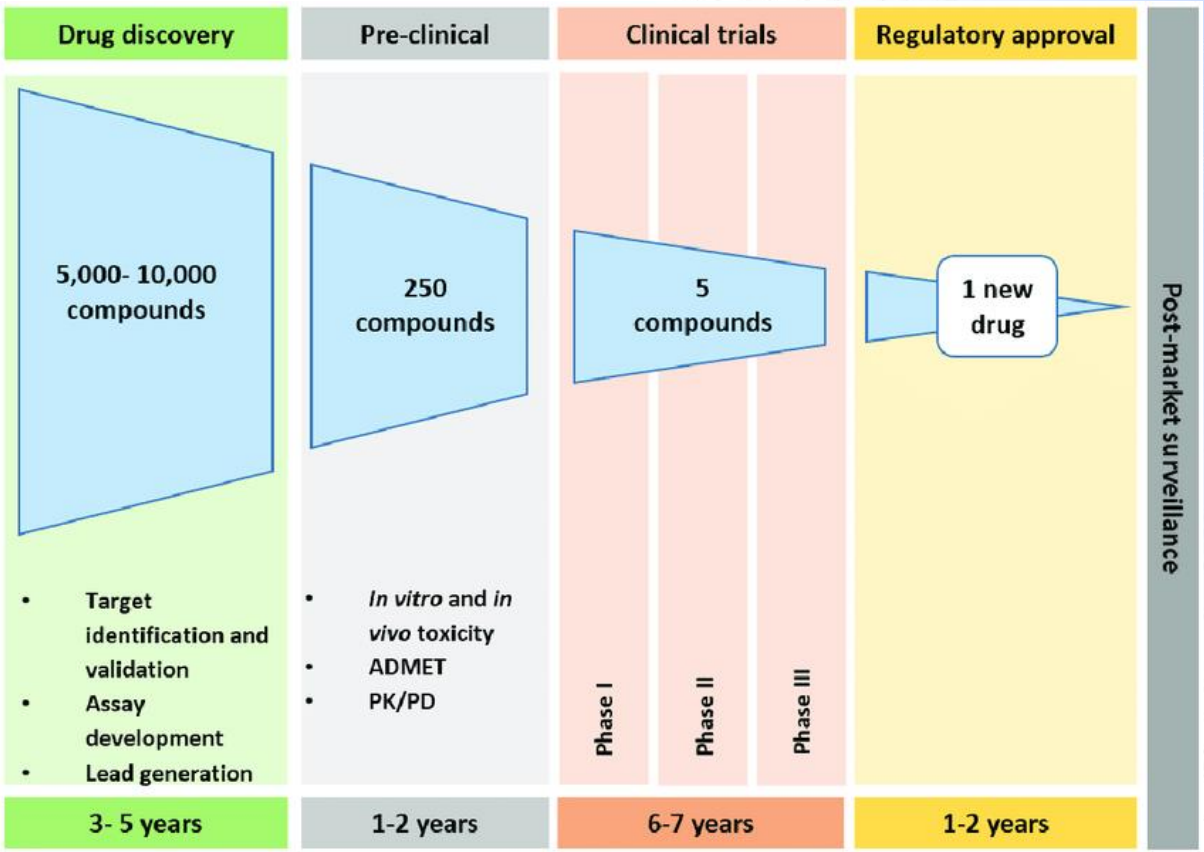
An Introduction to Mathematical Modeling in Drug Development using GastroPlus® and DILIsym®

Celeste Vallejo, Ph.D.

Agenda

- Introduction to drug development
- Introduction to physiologically-based pharmacokinetic (PBPK) modeling
  - GastroPlus Demo
- Introduction to quantitative systems pharmacology/toxicology (QSP/QST) modeling
  - DILIsym Demo

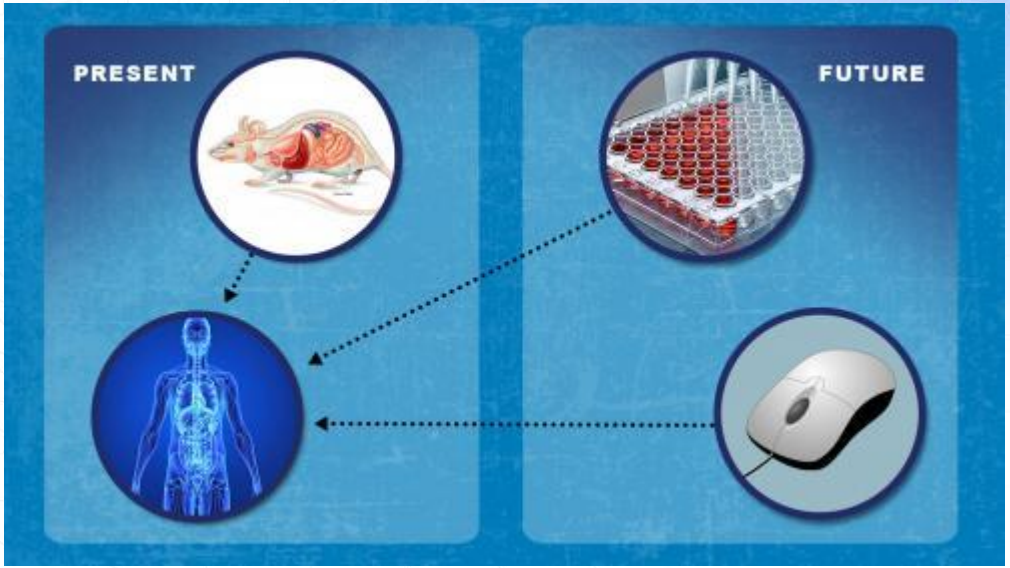
Drug Development Pipeline



Matthews, Holly & Hanison, James & Nirmalan, Niroshini. (2016). "Omics"-Informed Drug and Biomarker Discovery: Opportunities, Challenges and Future Perspectives. Proteomes. 4. 28. 10.3390/proteomes4030028.

FDA Modernization Act 2.0

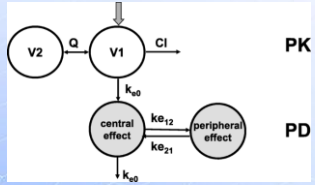
- Signed into law in December 2022
- The Federal Food, Drug, and Cosmetics Act of 1938 mandated animal testing on all new drug products
- With the new law, new drugs are no longer required to be tested on animals before human studies.
- Drug developers may start relying more heavily on modeling and simulation as it uses less resources than an animal study



Advancing Alternative Methods at FDA

Broad Classes of Models Used in Drug Development

Pharmacokinetic (PK)/ Pharmacodynamic (PD)



Blussé van Oud-Alblas et al. 2019

Simplistic representation of the human body into a small number of compartments to model drug disposition and drug action

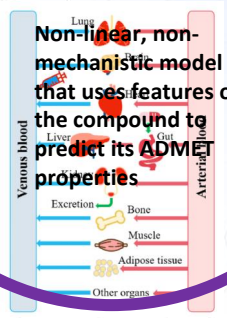
Physiological representation of the human body to model drug disposition

Utilize systems of differential equations

Mechanistic representation of drug action

Quantitative Systems Pharmacology (QSP) or Toxicology (QST)

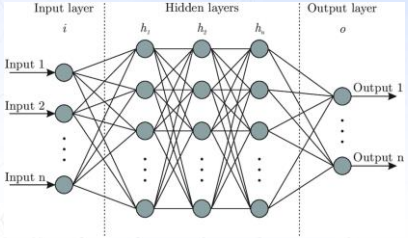
Physiologically Based Pharmacokinetic (PBPK)



Non-linear, non-mechanistic model that uses features of the compound to predict its ADMET properties

Shin, HK et al. 2017

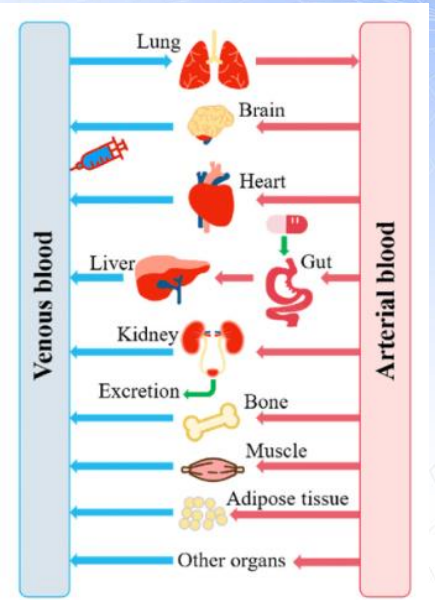
Machine learning



https://blog.knoldus.com/getting-familiar-with-activation-function-and-its-types

What is PBPK?

- A mathematical modeling approach used to understand drug kinetics in the body (human or animal).
- Drug kinetics are described by the acronym **ADMET**
  - **Absorption**
  - **Distribution**
  - **Metabolism**
  - **Elimination**
  - **Toxicity**



How Are PBPK Models Used in Drug Development?

- Predict the first-in-human dose of a drug
- Predict the effect of a change in drug formulation
- Predict drug kinetics in special populations (e.g., pediatrics, hepatic impairment)
- Predict drug interactions (e.g., other drugs, food)
- Predict an appropriate dosing scheme
- Simulate virtual clinical trials

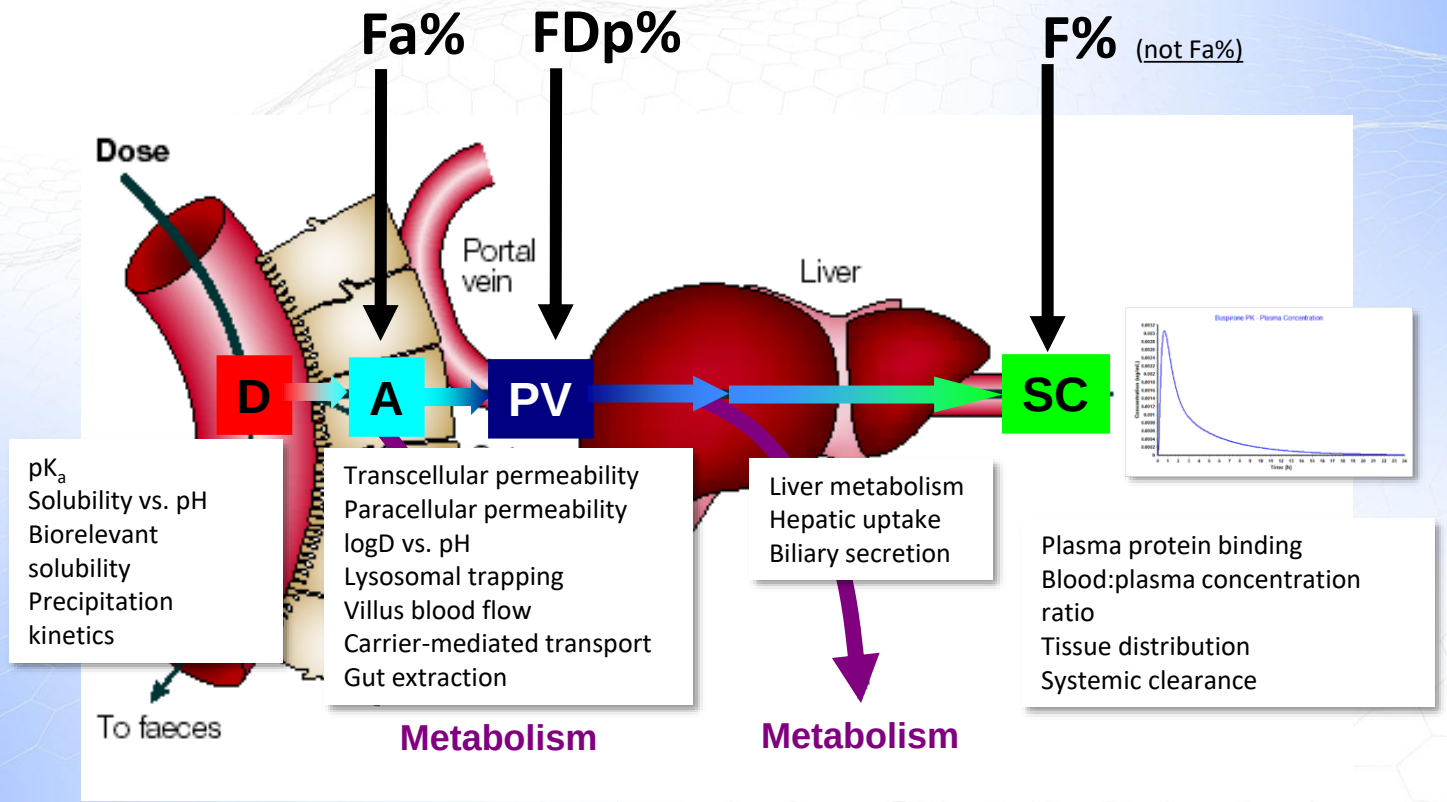
GastroPlus Software

- GastroPlus is a platform for performing PBPK simulations
- Input various physical chemical properties of the drug (e.g., solubility, permeability, lipophilicity)
- Multiple options for simulated physiology (e.g., monkey, dog, rat, human, fed, fasted)
- Population simulations
- Wide range of drug administration routes

  (e.g., oral, IV, IM, SQ, pulmonary, ocular)

Overview of Processes Accounted for in GastroPlus:

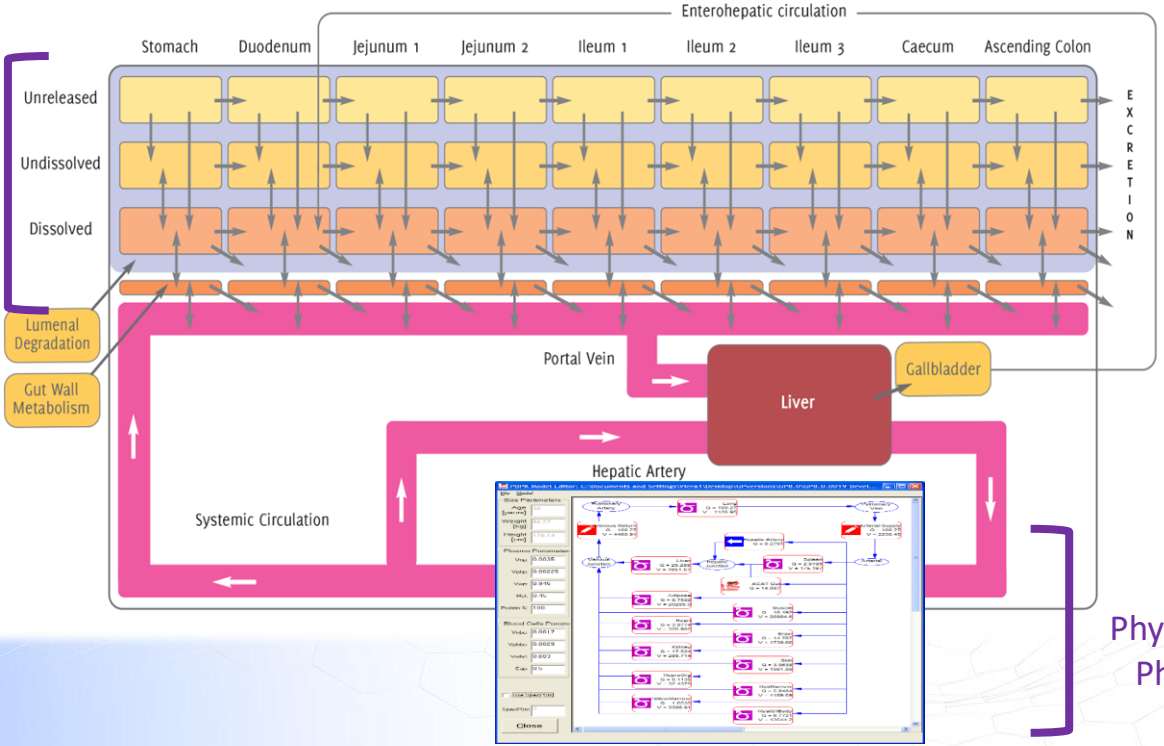
Oral Administration

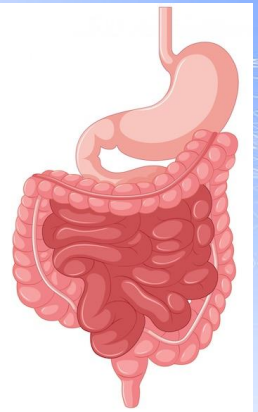


* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

GastroPlus and Mechanistic Oral Absorption: Advanced Compartmental Absorption and Transit (ACAT) Model

Mechanistic Absorption Modeling

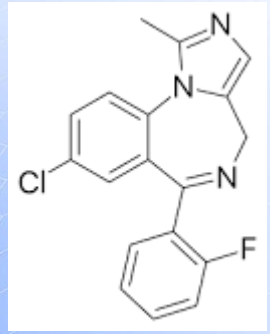




Physiologically based Pharmacokinetics (PBPK)

ADMET Predictor®

- Machine learning platform to predict ADMET of a drug given its chemical structure
- Ensemble of neural networks
- Predictions include uncertainty based on the variance in the neural networks



Midazolam

ADMET Predictor

	Structure	Identifier	S+Acidic_pKa	S+Mixed_pKa	S+Basic_pKa	DiffCoef	MlogP	S+logP	S+logD	logHLC	S+Peff	S+MDCK
1		Midazolam	None	None	4.57; 0.84	0.750	3.864	3.563	3.562	-6.616	7.545	1242.988

	Structure	Identifier	CYP3A4_Inh	CYP3A4_Substr	CYP3A4_Sites	CYP3A4_Km	CYP3A4_Vmax	CYP3A4_CLint
1		Midazolam	No (90%)	Yes (98%)	C1(961); C15(955)	46.268	8.630	20.704

ADMET Predictor Independently Shown to Have High Predictive Performance

Table 4. Predictive abilities of some commercially available software for aqueous solubility prediction, based on 122-compound test-set of drugs.

Software	% Compounds predicted within		r^2	q^2	s	Ref.
	± 0.5 log unit	± 1.0 log unit				
SimulationsPlus	64.8	91.0	0.82	0.82	0.47	[203]
Admensa	72.1	86.9	0.76	0.74	0.65	[205]
Pharma Algorithms ADME Boxes	59.0	86.9	0.74	0.73	0.62	[206]
ChemSilico	59.8	86.0	0.67	0.65	0.73	[202]
ACDLabs	59.0	85.2	0.73	0.72	0.66	[204]
AlogS	51.6	81.1	0.67	0.66	0.73	[207]
PredictionBase	46.7	81.1	0.48	0.46	1.07	[208]
ESOL	54.9	78.7	0.60	0.59	0.84	[209]
MOLPRO	62.3	77.9	0.44	0.42	1.22	[210]
Absolv 2	44.3	74.6	0.53	0.51	0.95	[206]
QikProp	47.6	73.8	0.57	0.57	0.97	[201]
SPARC*	42.9	73.1	0.73	0.72	0.96	[211]
Cerius²ADME	37.7	72.9	0.61	0.60	1.02	[212]
WSKOWWIN	41.0	67.2	0.51	0.49	1.17	[213]
ADMEWORKS Predictor	34.4	66.4	0.42	0.39	1.24	[214]
AlogP98	38.5	62.3	0.42	0.40	0.77	[85,212]
CHEMICALC‡	23.3	45.7	0.35	0.34	1.96	[215]

*Based on 119 compounds; SPARC could not calculate solubilities of 3 compounds.
‡Based on 116 compounds, using log P method with calculated melting point, which was not available for 6 compounds; kindly calculated by Prof. G. Schüürmann.

Independent comparison of aqueous solubility predictors

(Dearden JC. Exper. Opin. Drug Discovery 2006 1:31)

Table 2. Performance of algorithms

Method	Star (234)		Nostar (50)		Zwitterions (18)		Other (266)
	MAE	Rank	*MAE*	Rank	*MAE*	*AE*	*MAE*
A_S+logP	0.33	I	0.7	I	0.4	-0.01	0.4
ALOGPS[3]	0.39	I	0.7	I	0.64	-0.51	0.44
VLOGP[4]	0.50(0.41)	II	0.95(0.84)	I,III	0.87(0.69)	-0.8(-0.62)	0.56(0.47)
SLIPPER	0.58	II	0.91	I,III	1.2	-1.14	0.6
QikProp	0.58	II	1.01	III	0.83	-0.48	0.64
CSlogP	0.61	II	0.95	I,III	0.54	-0.06	0.68
TLOGP[5]	0.64	II	1.01	III	1.26	-0.97	0.69
Absolv	0.65	II	0.94	I,III	1.98	-1.97	0.61
QuantlogP[3]	0.7	II	1.03	III	1.91	-1.9	0.68
QLOGP	0.72	II	1.19	III	0.9	-0.24	0.79
VEGA[6]	0.8	III	1.07	III	1.53	0.95	0.8
CLIP[7]	0.82	III	1.27	III	1.3	-0.95	0.87
LSER	0.87	III	1.26	III	2.32	-2.31	0.84
MLOGP	0.93	III	1.12	III	1.64	-1.51	0.92
SPARC[8,9]	0.93	III	1.17	III	0.72	0.06	0.99
COSMOFrag[3]	1.13	III	1.38	IV	2.48	-2.47	1.09
LSER UFZ[8]	1.19	IV	2.15	IV	2.32	-1.75	1.29
GBLOGP[7]	1.25	IV	1.76	IV	2.51	2.46	1.26
HINT	1.38	IV	2.14	IV	3.25	-3.24	1.39
AAM	1.37	IV	1.87	IV	2.96		1.36

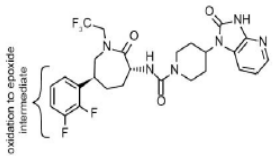
Independent comparison of logP predictors

(Tetko & Poda, 2007)

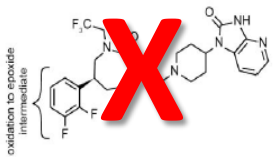
GastroPlus Demo

Introduction to QSP/QST Modeling

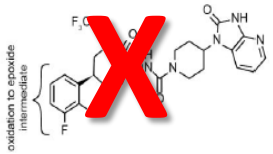
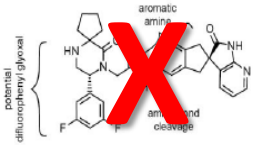
Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]
Structure[d]	
Potency IC_{50}[e]	2.2 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margi 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no live histopathology at 14× margin

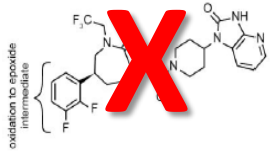
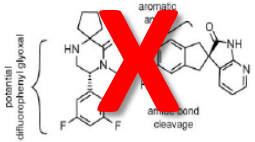
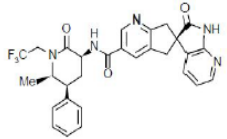
Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]
Structure[d]	
Potency IC_{50}[e]	2.2 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margi 6M rat: no liver safety signal a 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no live histopathology at 14× margin

Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]
Structure[d]		
Potency IC_{50}[e]	2.2 nM	0.12 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin

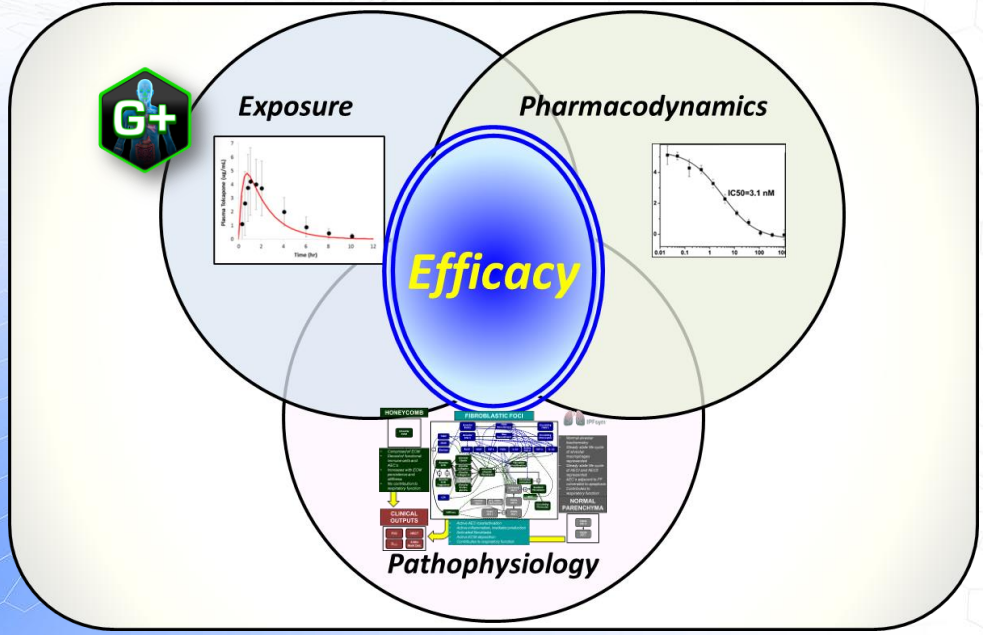
Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]	Ubrogepant[c]
Structure[d]			
Potency IC_{50}[e]	2.2 nM	0.12 nM	0.08 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin	6M rat: <2 × ALT with no liver histopathology at 70× exposure margin 9M NHP: no liver safety signal at 163× margin 3M mouse: no liver safety signal at 80× margin DILIsym

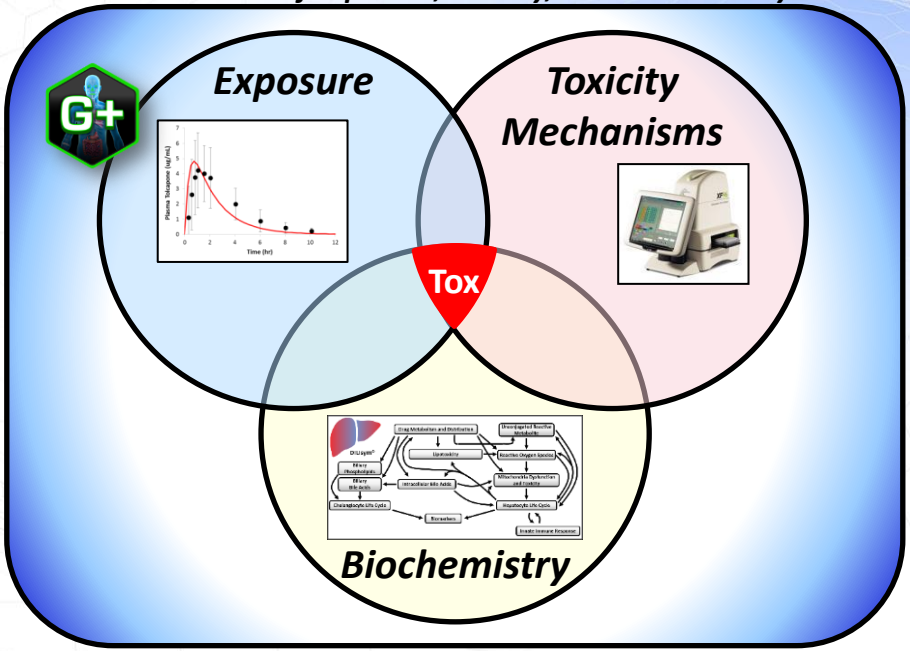
What is QSP/QST?

- QSP/QST applies a systems-level, mechanistic representation of drug interaction with normal or disease physiology to retrospectively interpret clinical data and to prospectively predict efficacy (QSP) or safety (QST)

IPFsym, a QSP model, simulates efficacy at the intersection of exposure, pharmacodynamics, and pathophysiology



DILIsym, a QST model, simulates toxicity at the intersection of exposure, toxicity, and biochemistry



How Are QSP/QST Models Used in Drug Development?

QSP

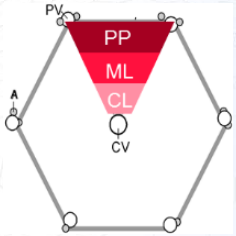
- Predict treatment efficacy
- Predict comparative efficacy against standards of care
- Predict clinical efficacy of combination therapies
- Predict optimal dosing regimen
- Predict mechanistic underpinnings of response / non-response
- Predict biomarkers of response
- Predict potential response variability in human populations

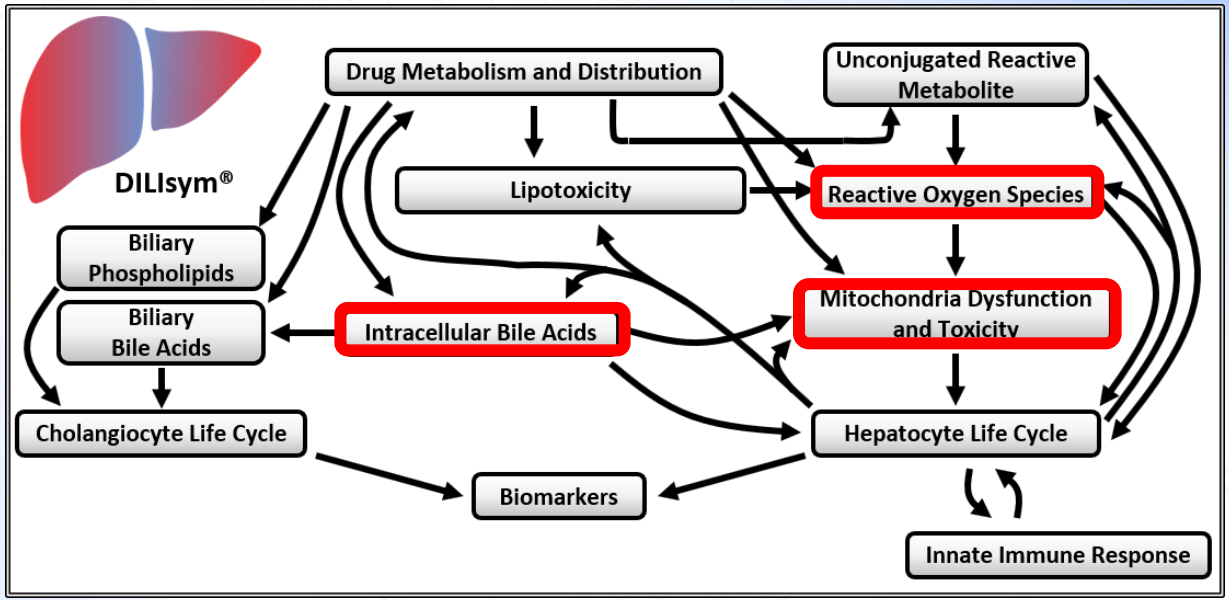
QST

- Retrospectively identify key mechanistic drivers of clinically observed toxicity
- Predict treatment toxicity
- Prospectively identify key mechanistic drivers of predicted toxicity
- Predict safe dosing regimen
- Predict biomarkers of toxicity response
- Predict response variability in human populations

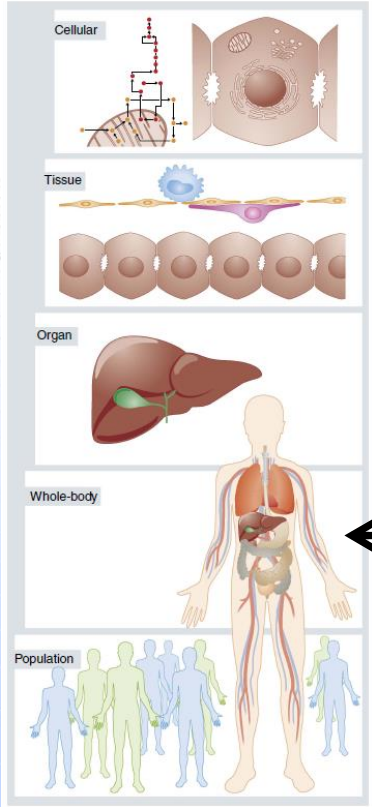
DILIsym Software Overview

- Multiple species: human, rat, mouse, and dog
  - Population variability
- The three primary acinar zones of liver represented
- Essential cellular processes represented to multiple scales in interacting sub-models
- Over 80 detailed representations of optimization or validation compounds with ~80% prediction success
- Single and combination drug therapies



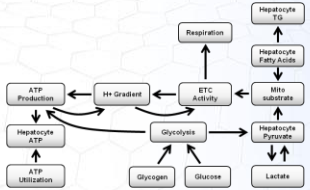


DILIsym: Quantitative Systems Toxicology

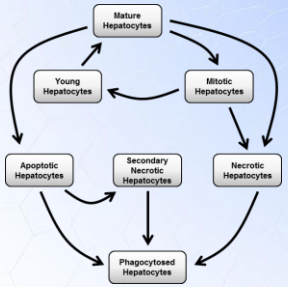


Kuepfer 2010, Molecular Systems Biology

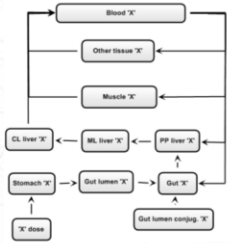
Mitochondrial dysfunction

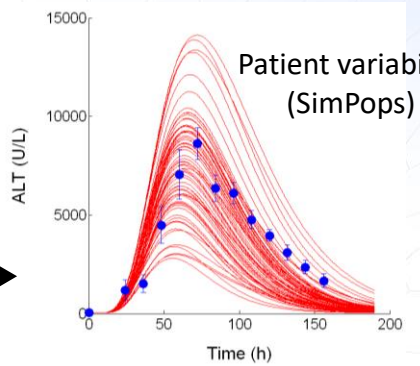


Cellular life-cycle



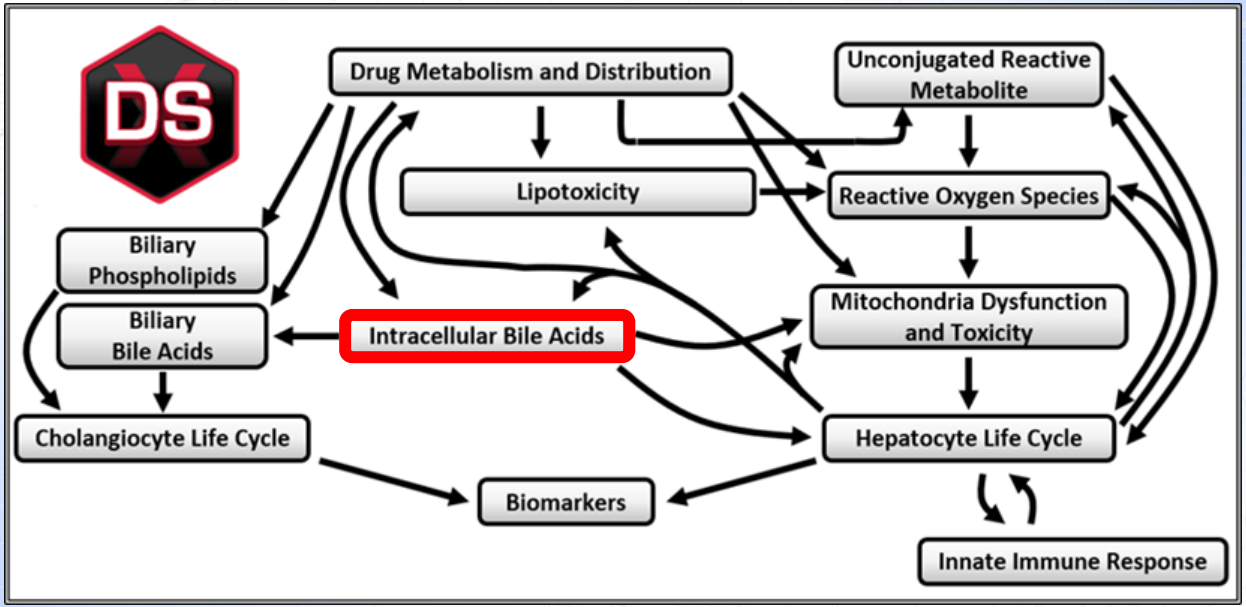
Drug distribution & metabolism



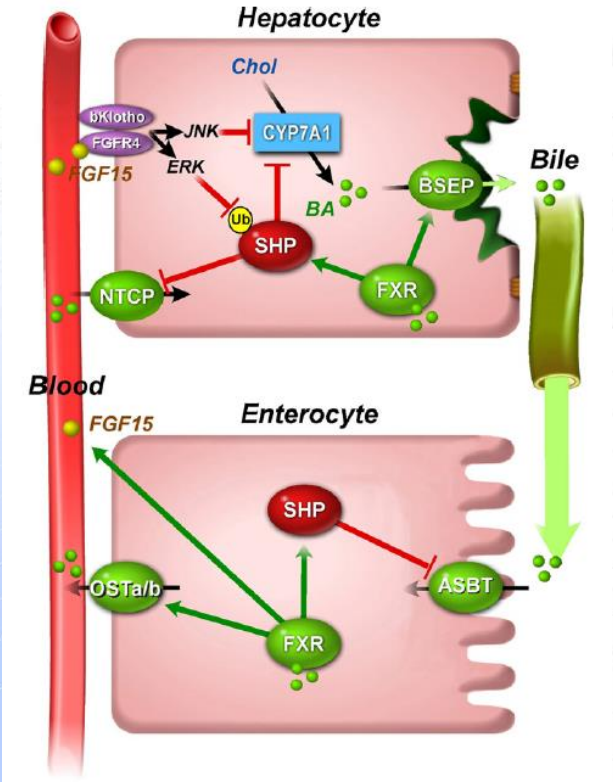


Patient variability (SimPops)

Toxicity Mechanism: Bile Acid Transporter Inhibition



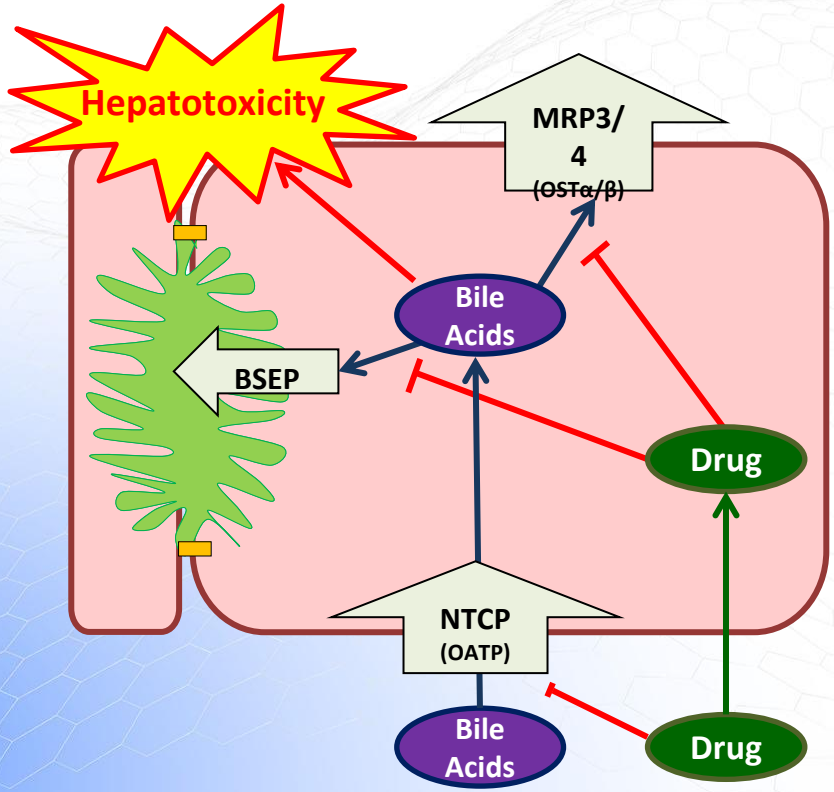
Bile Acids Undergo Efficient Enterohepatic Recirculation Mediated by Transporters



- Bile acids are synthesized in the liver and transported into the bile by BSEP
- In humans, bile acids are stored in the gall bladder until meal time
  - Rats do not have a gall bladder
- Bile acids are taken up by enterocytes and return to the portal blood
- Hepatocytes take up bile acids, mediated by NTCP
- MRP3/4 can transport bile acids from hepatocyte to blood
- Bile acids are presumed to be concentrated in the periportal region of the liver

Jonker 2011

Drugs Can Inhibit Bile Acid Transporters

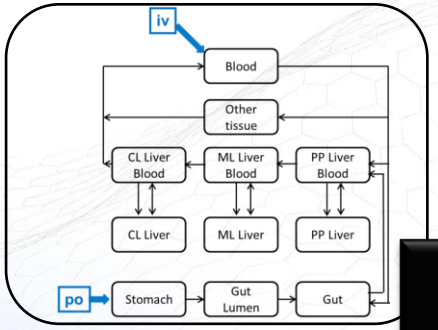


- Drugs can interfere with multiple bile acid transport processes such as uptake, canalicular efflux, and basolateral efflux
- Research has shown a relationship between bile acid efflux transporter inhibition and toxicity ‡
- **Drug effects on hepatobiliary bile acid disposition can be simulated using data from in vitro transport assays**
  - **Inhibition constants (e.g., IC50, Ki)**
  - **Type of inhibition (e.g., competitive, noncompetitive)**

‡ *Morgan 2013, Pedersen 2013, Dawson 2010, Morgan 2010*

Bile Acid Transport Inhibition Model Overview

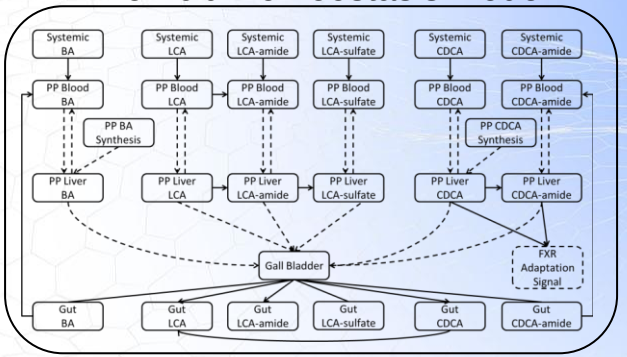
Drug PBPK model



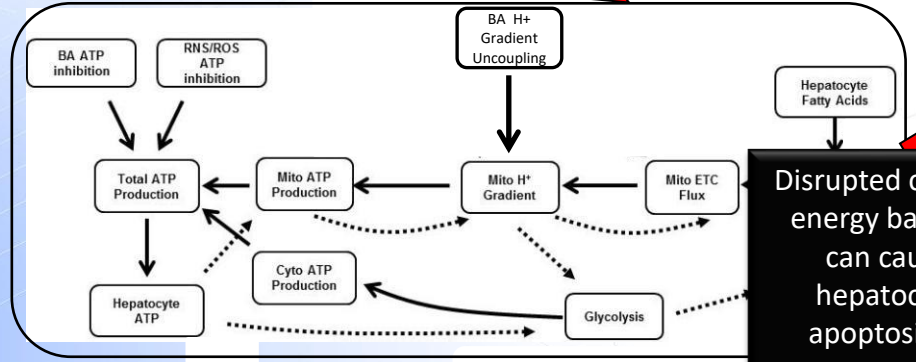
Drug inhibits BA transport

Bile acid accumulation disrupts cellular energy balance

Bile Acid Homeostasis Model

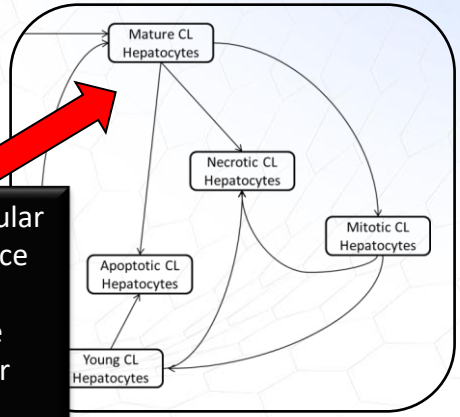


Cellular ATP Model

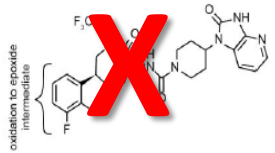
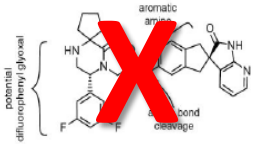
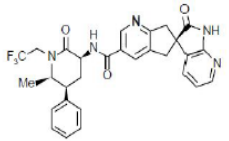


Disrupted cellular energy balance can cause hepatocyte apoptosis or necrosis

Hepatocyte Life-Cycle



Calcitonin Gene-related Peptide (CGRP) Antagonists for Treatment of Migraines

Parameter	Telcagepant[a]	MK-3207[b]	Ubrogepant[c]
Structure[d]			
Potency IC_{50}[e]	2.2 nM	0.12 nM	0.08 nM
Pivotal conventional nonclinical toxicology study liver findings	3M rat: <3 × ALT/AST with no liver histopathology at 15× exposure margin 6M rat: no liver safety signal at 7x margin 9M NHP: no liver safety signal at 7× margin 6M mouse: <2 × ALT/AST with no liver histopathology at 14× margin	6M rat: no liver safety signal at 25× exposure margin 9M NHP: no liver safety signal at 4× margin 6M mouse: no liver safety signal at 12× margin 1M dog: slight periportal vacuolation with <4 × ALT/AST associated with excessive body weight loss at 17x margin	6M rat: <2 × ALT with no liver histopathology at 70× exposure margin 9M NHP: no liver safety signal at 163× margin 3M mouse: no liver safety signal at 80× margin

DILIsym Toxicity Parameters for Telcagepant, MK-3207 and Ubrogepant

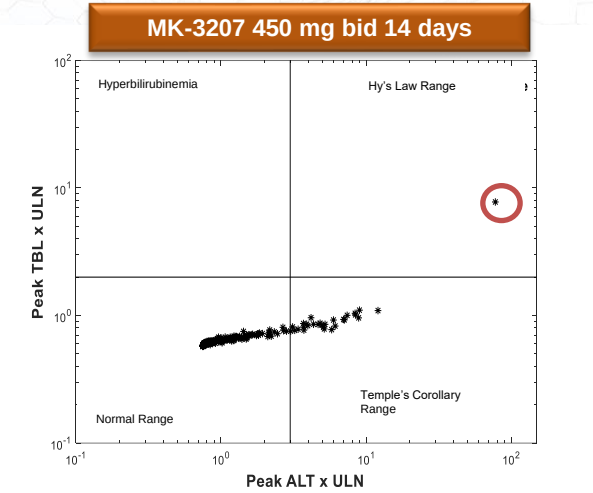
Mechanism	DILIsym Parameter	Unit	DILIsym Parameter Value***		
			telcagepant	MK-3207	Ubrogepant
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	µM	17,400	N/A	472
	Coefficient for ETC inhibition 3	µM	N/A	0.347	N/A
	Max inhibitory effect for ETC inhibition 3	dimensionless	N/A	0.35	N/A
Oxidative Stress	RNS/ROS production rate constant 1	mL/nmol/hr	2.0×10^{-5}	2.2×10^{-4}	1.6×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	7.9	7.62	38.1
	BSEP inhibition alpha value	dimensionless	4.6	Competitive	8.39
	NTCP inhibition constant	µM	19.4	No Inhibition	No Inhibition
	MRP3/4 inhibition constant**	µM	16.6	49.9	85.9

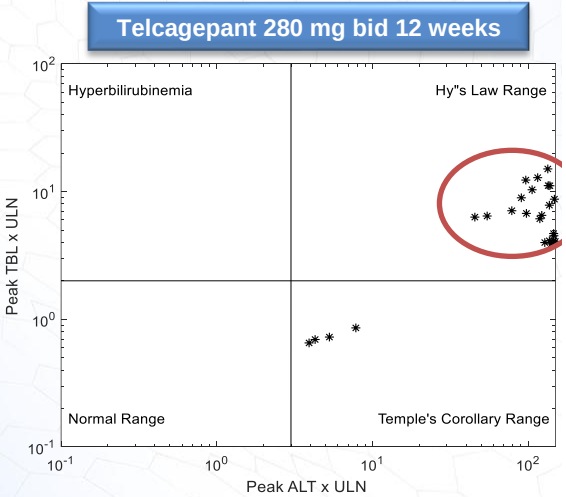
*Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

**Mixed inhibition with alpha = 5 assumed

Smith et al., *Tox Sci* 2020

eDISH Plots Simulated by DILIsym Show Predicted Hy's Law Cases for MK-3207 and Telcagepant





Smith et al., *Tox Sci* 2020

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2019, Vol. 39(14) 1753–1761

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0333102419869918
journals.sagepub.com/home/cep
SAGE

Safety and tolerability of ubrogepant following intermittent, high-frequency dosing: Randomized, placebo-controlled trial in healthy adults

Peter J Goadsby[1], Stewart J Tepper[2], Paul B Watkins[3], Girma Ayele[4], Rosa Miceli[4], Matthew Butler[4], Lawrence Severt[4], Michelle Finnegan[4], Armin Szegedi[4], Joel M Trugman[4] and Abhijeet Jakate[4]

Table 3. Hepatic laboratory parameters.

	Placebo (n = 260)	Ubrogepant 100 mg (n = 256)
ALT, U/L	n = 258	n = 256
Baseline, mean (SD)	20.5 (7.2)	21.1 (9.1)
End of trial, mean (SD)	21.7 (7.7)	21.3 (8.7)
Change from baseline, mean (SD)	1.2 (7.4)	0.1 (8.4)
Post baseline ≥ 3 × ULN, n (%)	3 (1.2)	2 (0.8)

Conclusion

DILIsym modeling was part of the weight of evidence that *supported FDA approval* of Ubrogepant for the treatment of acute migraine headaches.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

NON-CLINICAL REVIEW(S)

In the investigative hepatotoxicity assays using HepG2 (human hepatocellular carcinoma) cells and HepaRG spheroids (a metabolically active system) and a proprietary in silico analysis system, the effects of ubrogepant were compared to those of two other CGRP receptor antagonists, for which development was discontinued because of hepatotoxicity. The results indicated that ubrogepant inhibited bile acid transporters, inhibited HepG2 oxygen consumption rate in a concentration-dependent manner (suggesting the potential to induce mitochondrial toxicity), and exhibited "a modest induction of oxidative stress in HEPG2 cells," considered an effect of ubrogepant itself rather than metabolite(s). Based on "Eight different clinical protocols of ubrogepant…investigated in SimPops," the sponsor concluded that …despite in vitro results, no ALT elevations were predicted for any of the protocols tested…indicating that ubrogepant would be safe at doses up to 10-fold higher than the clinical dose in the hepatic safety clinical study (dosing 100 mg 2 days on, 2 days off for 56 days, 28 total doses)." The maximum recommended clinical dose for the proposed indication (acute migraine) is 200 mg/day, suggesting a 5-fold safety margin with a similar dosing regimen.

DILIsym Services QSP/QST Platforms

	Model	Disease area	Key References	Primary biomarkers included:	Number of compounds/ targets evaluated
QSP	NAFLDsym	Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis	Kenz 2020, Kenz 2019, Longo 2018, Siler 2018, Siler 2022	Histologic NAS, histologic fibrosis score Liver fat (MRI), plasma ALT	25-30
QSP	IPFsym	Idiopathic pulmonary fibrosis	Siler 2021	Forced vital capacity; high resolution computed tomography	6
QSP	ILDsym	Interstitial lung disease	Kenz 2022	Forced vital capacity; high resolution computed tomography	5
QSP	CARDIOsym	Cardiac recovery following myocardial infarction	Kenz 2021	Cardiomyocytes, myofibroblasts, collagen	2
QSP	KIDNEYsym	Kidney diuresis	--	Urine volume; urinary sodium loss	3
QSP	GOUTsym	Gout Emphasis on hyperuricemia	--	Uric acid	5
QSP	MITOsym	Hepatocyte bioenergetics	Yang 2015	Oxygen consumption rate; ATP concentrations	>70
QST	DILIsym	Drug induced liver injury	Shoda 2017, Battista 2020, Eichenbaum 2020	Plasma ALT, plasma AST, plasma bilirubin	>70
QST	RENAsym	Drug induced kidney injury	Gebremichael 2020	Urine KIM-1, urine αGST, serum creatinine	10

DILIsym Demo

University+

Modeling and simulation (M&S) education today to set the next generation of scientists up for success tomorrow.

One-year access
to Simulations Plus software to students and educators at accredited universities worldwide

Training and Workshops
Simulations Plus hosts a variety of learning opportunities to help further your modeling and simulation research

User Support
Free videos, webinars, and open-source publications – highlighting best practices, case studies, and step-by-step tutorials

Utilized by Educators Worldwide
Providing accredited university professors with free access to the software, we are able to drive M&S learning and understanding prior to entering the workforce.

Apply Today

Free & paid courses

Membership pricing to government agencies

Internship+

Postdoc+