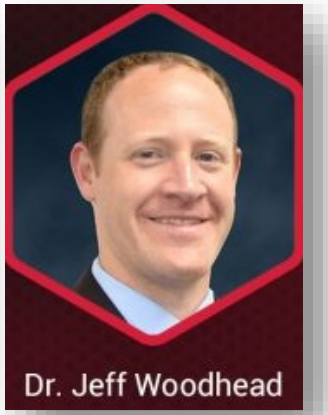
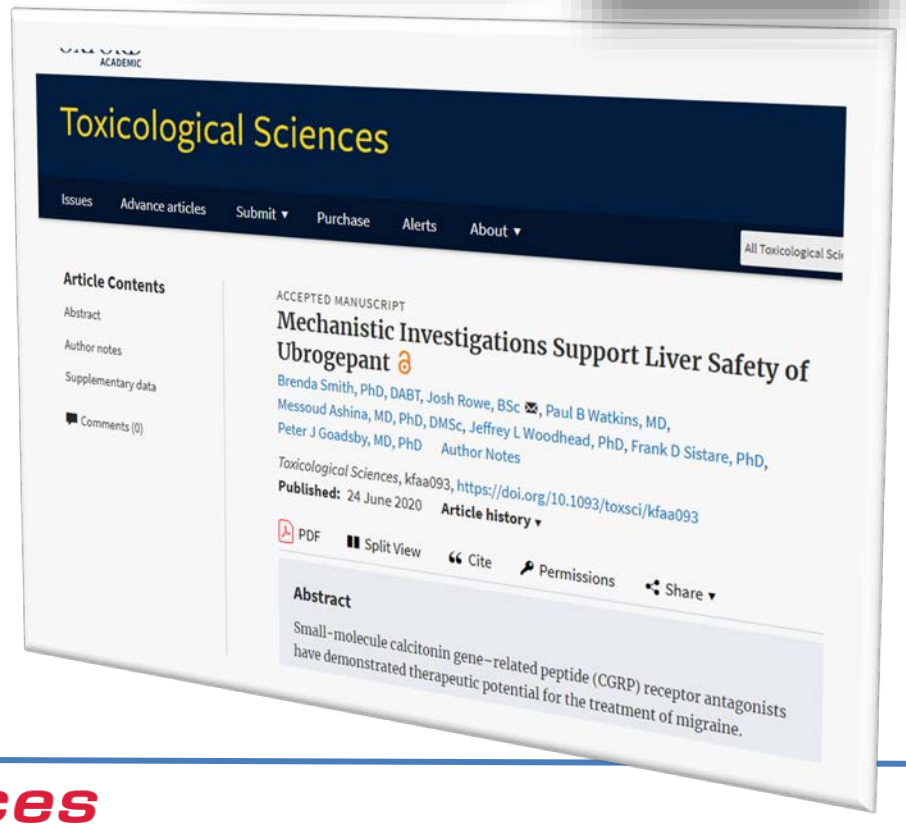
DILIsym Simulations Support the Liver Safety of Ubrogepant in New Toxicological Sciences Publication





Dr. Paul Watkins and Dr. Jeff Woodhead

August 13, 2020

DILIsym Services

A SIMULATIONS PLUS COMPANY

Disclosure

Dr. Watkins chairs the scientific advisory board for the DILI-sim Initiative

Dr. Woodhead is an employee of DILIsym Services Inc., an SLP Company

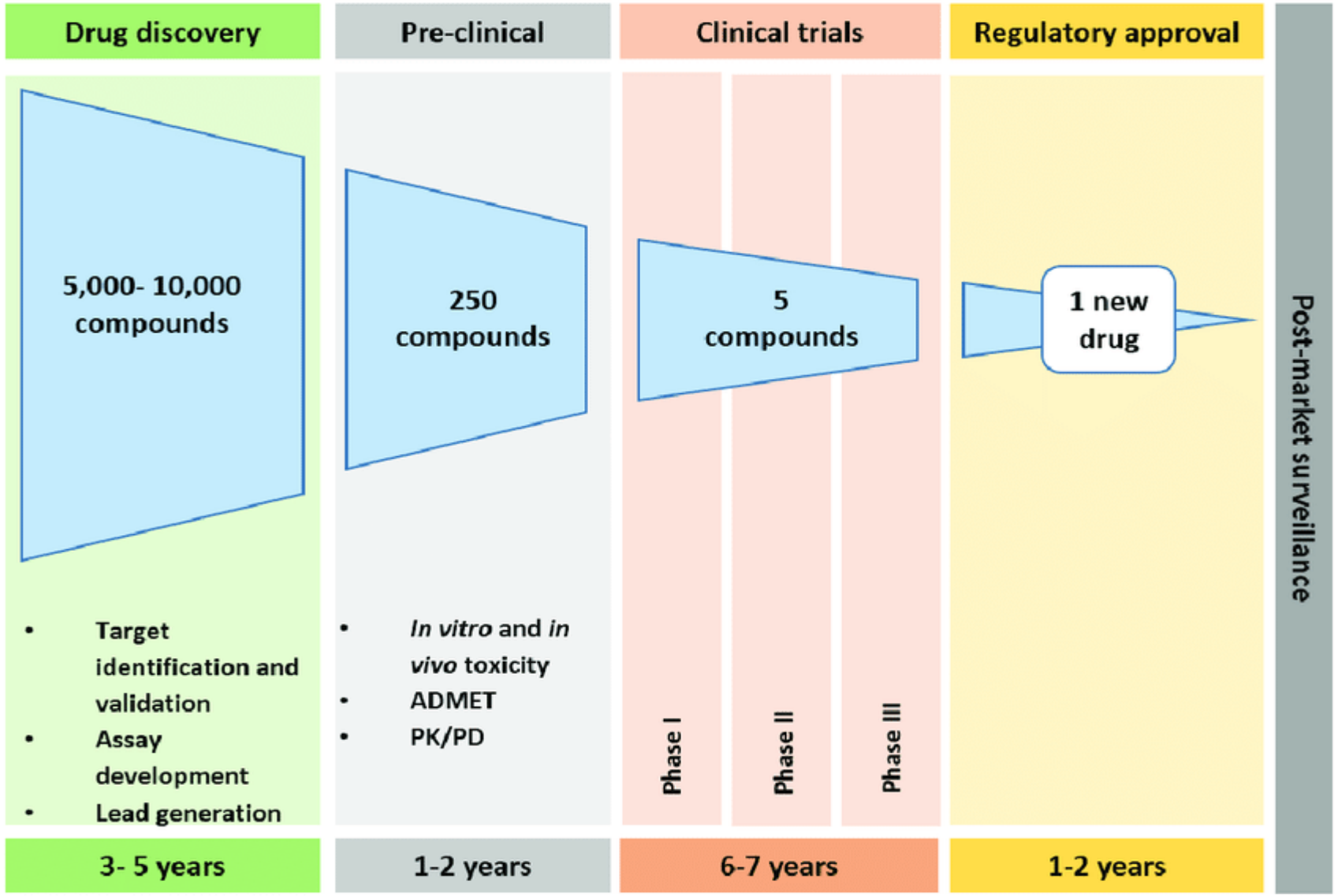
Outline of talk

1). DILI and drug development

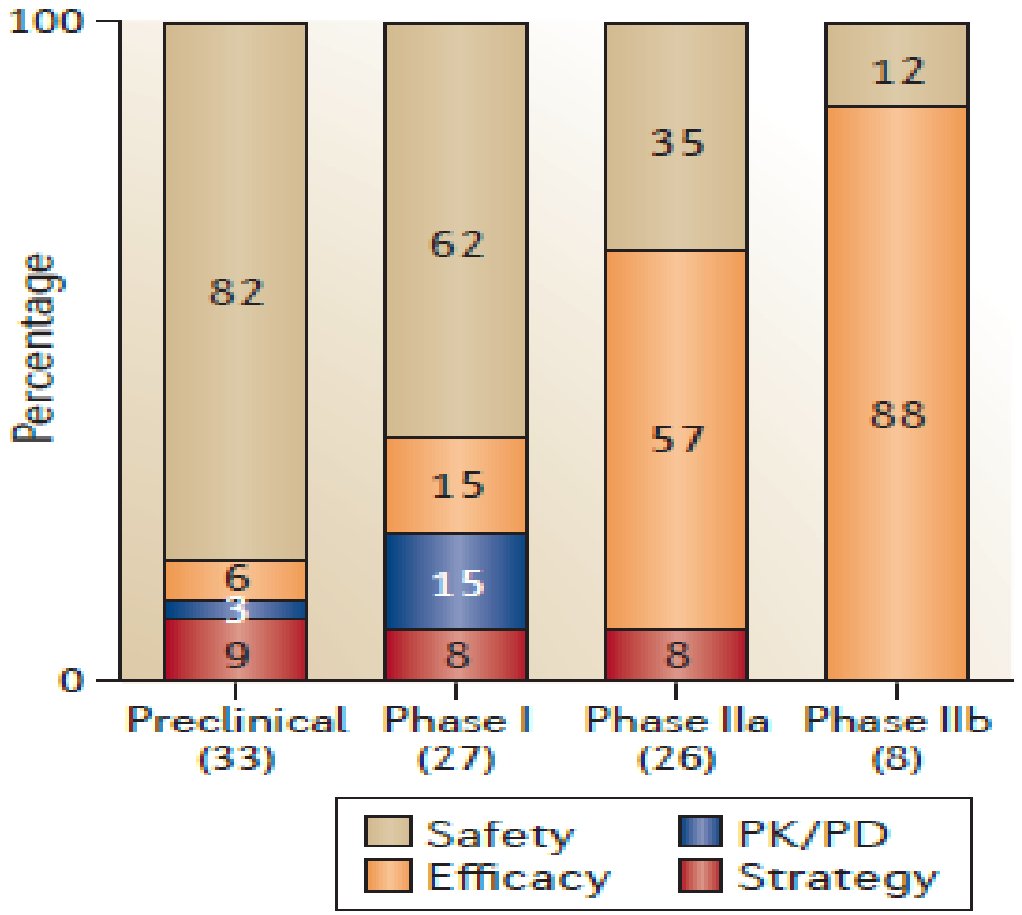
2). DILIsym

3). The Ubrogepant story

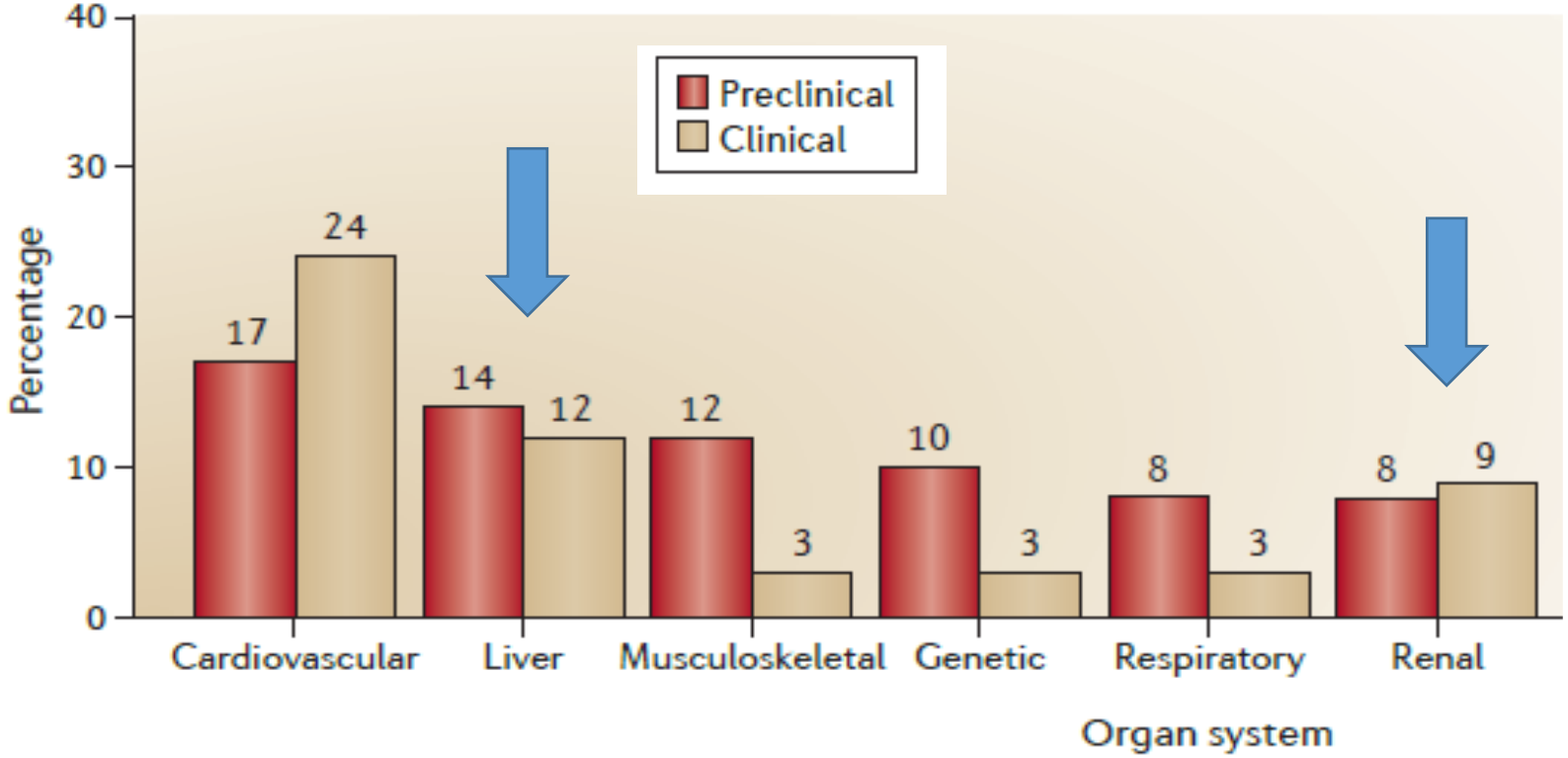
Drug Development Pipeline



Reasons for Termination of Drug Development Programs



Reasons for Termination of Programs due to Safety by Organ System



Is hepatoxicity still a problem?

No drugs approved in the last decade have been withdrawn from the market in the U.S. due to liver safety concerns:

1). Regulators (and drug developers) can better define liver safety signals in clinical trials

but

2). Clinical trials are much bigger and longer now……

Then…and now

The direct acting oral anticoagulants (DOACs)

First in class: Ximelagatran - withdrawn from worldwide markets due to liver toxicity.

Second in class: Rivaroxaban – approved for atrial fibrillation after > 35,000 patients had been exposed to the drug.

FDA rejects Motif Bio's iclaprim for ABSSSI

Feb. 14, 2019 7:36 AM ET| By: Douglas W. House, SA News Editor

Motif Bio (OTCPK:MTFBF) has received a Complete Response Letter (CRL) from the FDA regarding its marketing application seeking approval for iclaprim for the treatment of acute bacterial skin and skin structure infections ((ABSSSI)).

The CRL cited the need for additional data to assess the risk of liver toxicity.

The company plans to meet with FDA as soon as possible to clarify a path forward. It will need to raise additional capital in the near term since it is only financed into next quarter.

Update: Shares are down 78% premarket.

Economics of delay in FDA approval

If drug attains at least $1B/year in sales at the end of patent life

Every day of delay in approval >$2 million

Conclusion

- **Hepatotoxicity remains a major problem in drug development.**

- **Current preclinical testing has not eliminated this problem**

Outline of talk

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Institute for Drug Safety Sciences

DILIsym Services

A SIMULATIONS PLUS COMPANY

The DILI-sim Initiative

janssen

Mitsubishi Tanabe Pharma

GILEAD

DILIsym

Pfizer

abbvie

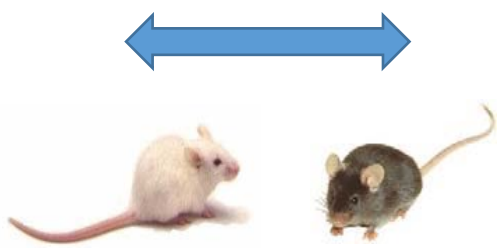
gsk GlaxoSmithKline

FDA

Bristol-Myers Squibb

Patients

Cutting Edge Pre-clinical Models



In Vitro

Quantitative Systems Toxicology

The use of differential equations to recapitulate relevant pathways whereby drugs or other chemicals can cause stress and death to cells, tissues, and organs.

DILI-sim Initiative Approach

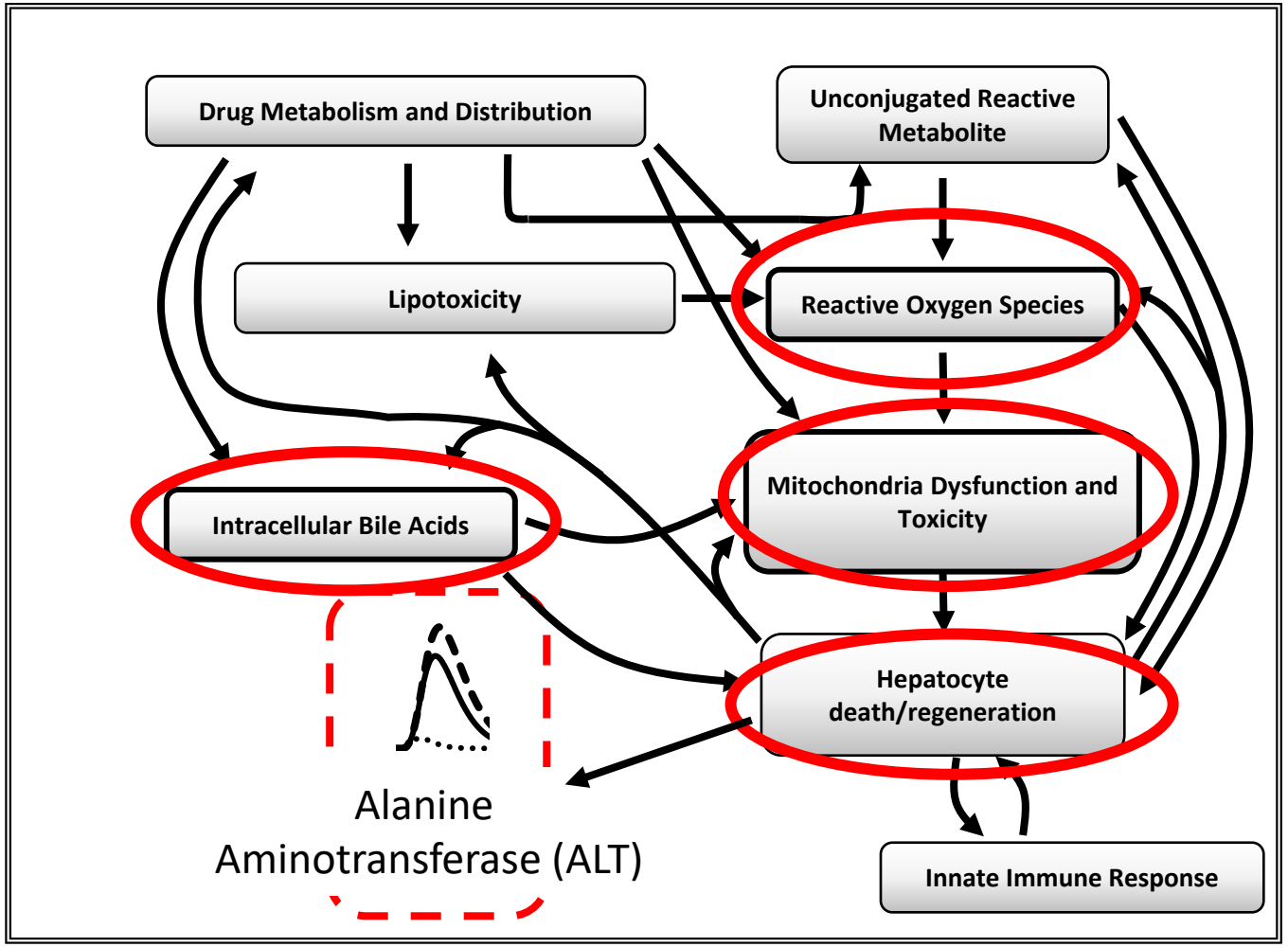
1). Build mechanistic “modules” using differential equations – perform experiments to fill in knowledge gaps.

2). Integrate the modules with the outcome of hepatocyte death and release and clearance of traditional and novel serum biomarkers.

3). Vary model parameters to create simulated patient populations (SimPops™)

4). Refine the aggregate model through incorporating data obtained from successive “exemplar” drugs

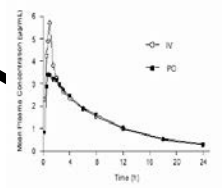
QST software created by the DILI-sim Initiative (DILIsym®)



DILIsym Input Data

Exposure

Pharmacokinetics



Simulated Frequency & Severity of Liver Injury (ALT)

Two Broad Types of Hepatotoxicity

1). Direct or intrinsic toxicity

2). Idiosyncratic toxicity

Two Broad Types of Hepatotoxicity

1). Direct or intrinsic toxicity

2). Idiosyncratic toxicity

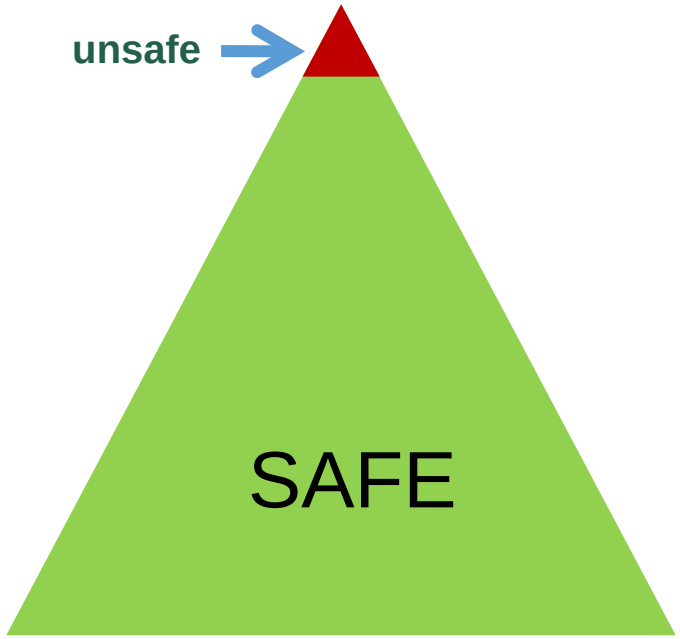
Direct or Intrinsic Hepatotoxicity

- dose dependent
- short latency
- usually, but not always evident in animals
- usually identified in Phase 1 clinical trials
- high DILIsym prediction

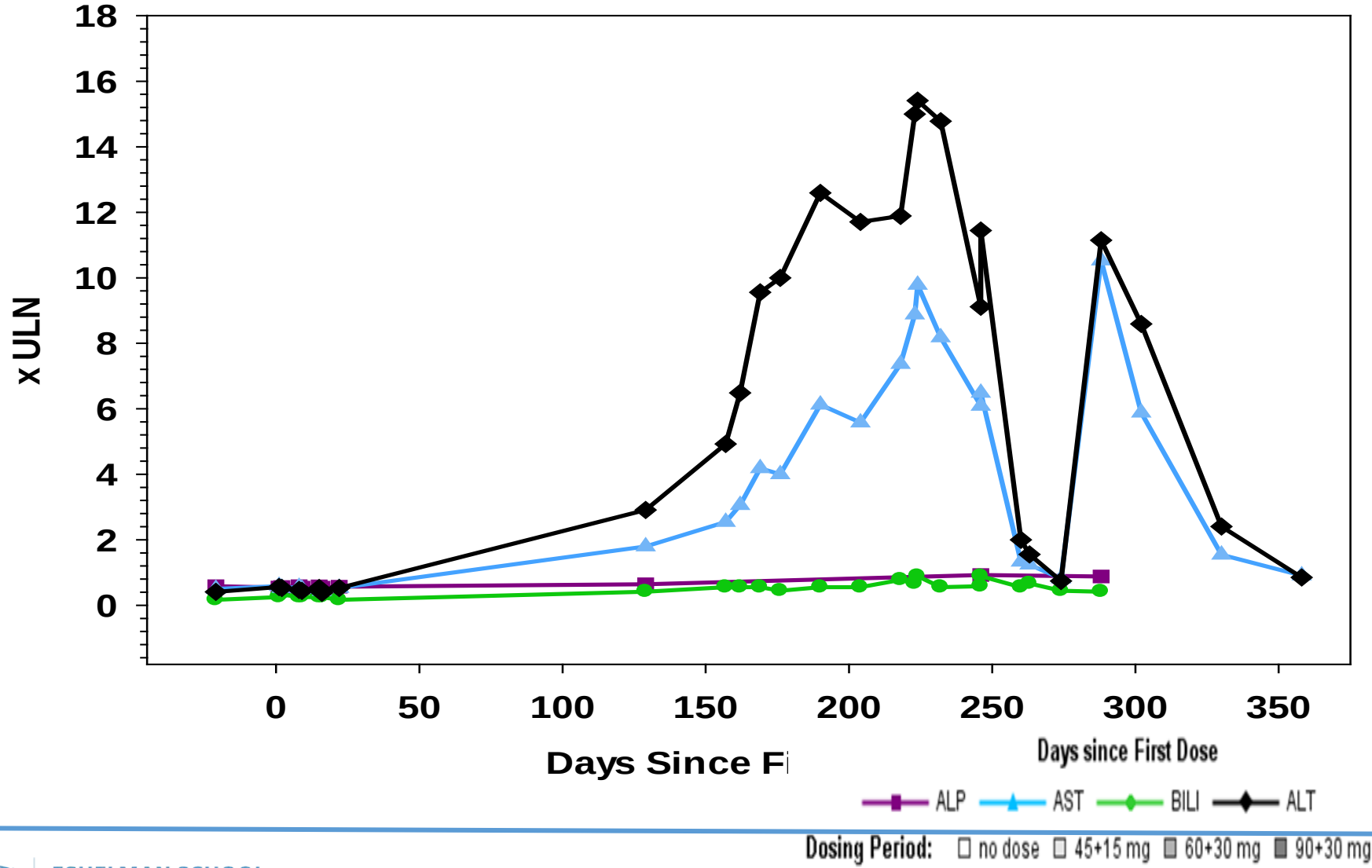
Idiosyncratic Hepatotoxicity

- rare (<1:5,000)
- dose relationship is complex
- longer latency
- no good animal models -
- usually identified late in
  clinical trials or
  post marketing

Concept of Idiosyncrasy



Tolvaptan Idiosyncratic Drug-Induced Liver Injury



Conclusion

- Idiosyncratic DILI usually involves an adaptive immune attack on the liver

Does DILIsym predict this liability in new drug candidates?

Idiosyncratic DILI Liability Predicted by DILIsym

Systems Pharmacology Modeling Predicts Delayed Presentation and Species Differences in Bile Acid–Mediated Troglitazone Hepatotoxicity

K Yang[1], JL Woodhead[2], PB Watkins[1,2], BA Howell[2] and KLR Brouwer[1,3]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 96 NUMBER 5 | NOVEMBER 2014

Quantitative Systems Toxicology Analysis of *In Vitro* Mechanistic Assays Reveals Importance of Bile Acid Accumulation and Mitochondrial Dysfunction in TAK-875-Induced Liver Injury

Diane M. Longo,[*,1] Jeffrey L. Woodhead,[*] Paul Walker,[†] Krisztina Herédi-Szabó,[‡] Károly Mogyorósi,[‡] Francis S. Wolenski,[§] Yvonne P. Dragan,[§] Merrie Mosedale,[¶,‖] Scott Q. Siler,[*] Paul B. Watkins,[*,¶,‖] and Brett A. Howell[*]

TOXICOLOGICAL SCIENCES, 167(2), 2019, 458–467

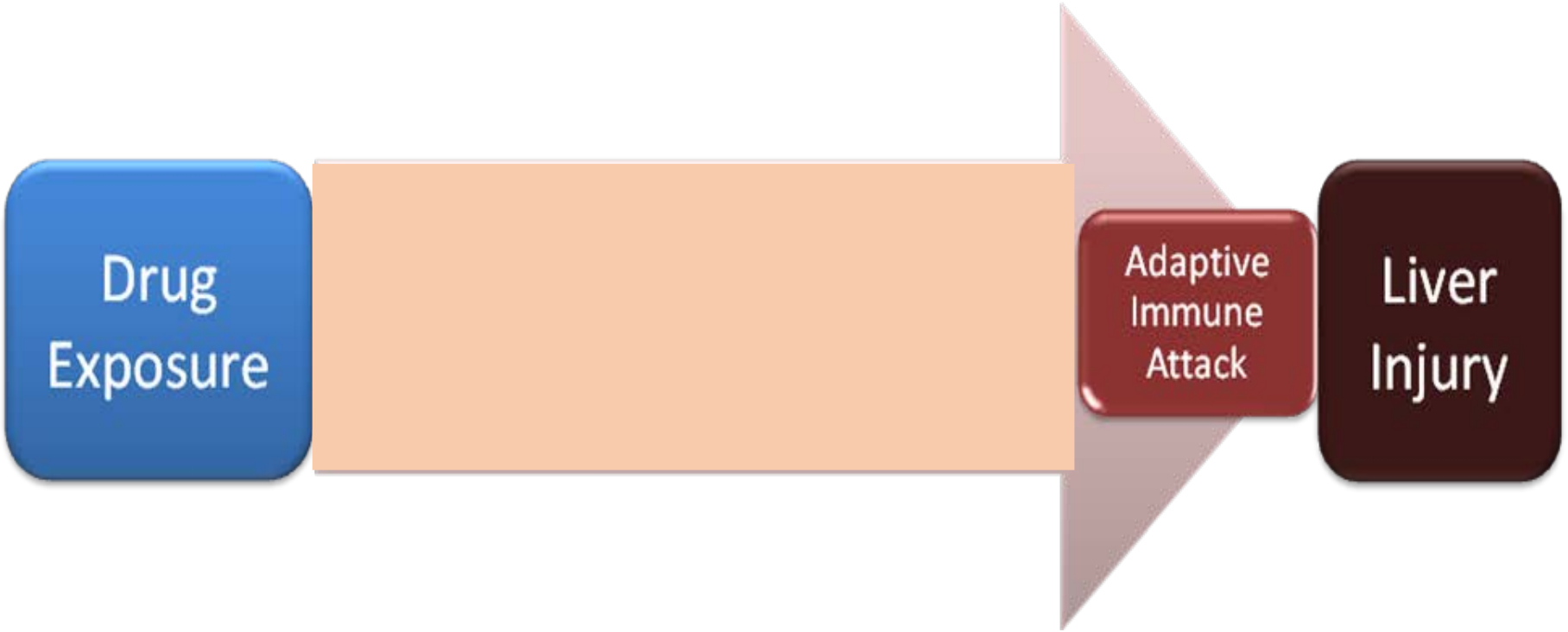
Application of a Mechanistic Model to Evaluate Putative Mechanisms of Tolvaptan Drug-Induced Liver Injury and Identify Patient Susceptibility Factors

Jeffrey L. Woodhead,[*] William J. Brock,[†] Sharin E. Roth,[‡] Susan E. Shoaf,[‡] Kim L.R. Brouwer,[§] Rachel Church,[§,¶] Tom N. Grammatopoulos,[‖] Linsey Stiles,[‖] Scott Q. Siler,[*] Brett A. Howell,[*] Merrie Mosedale,[§,¶] Paul B. Watkins,[§,¶] and Lisl K.M. Shoda[*,1]

TOXICOLOGICAL SCIENCES, 155(1), 2017, 61–74

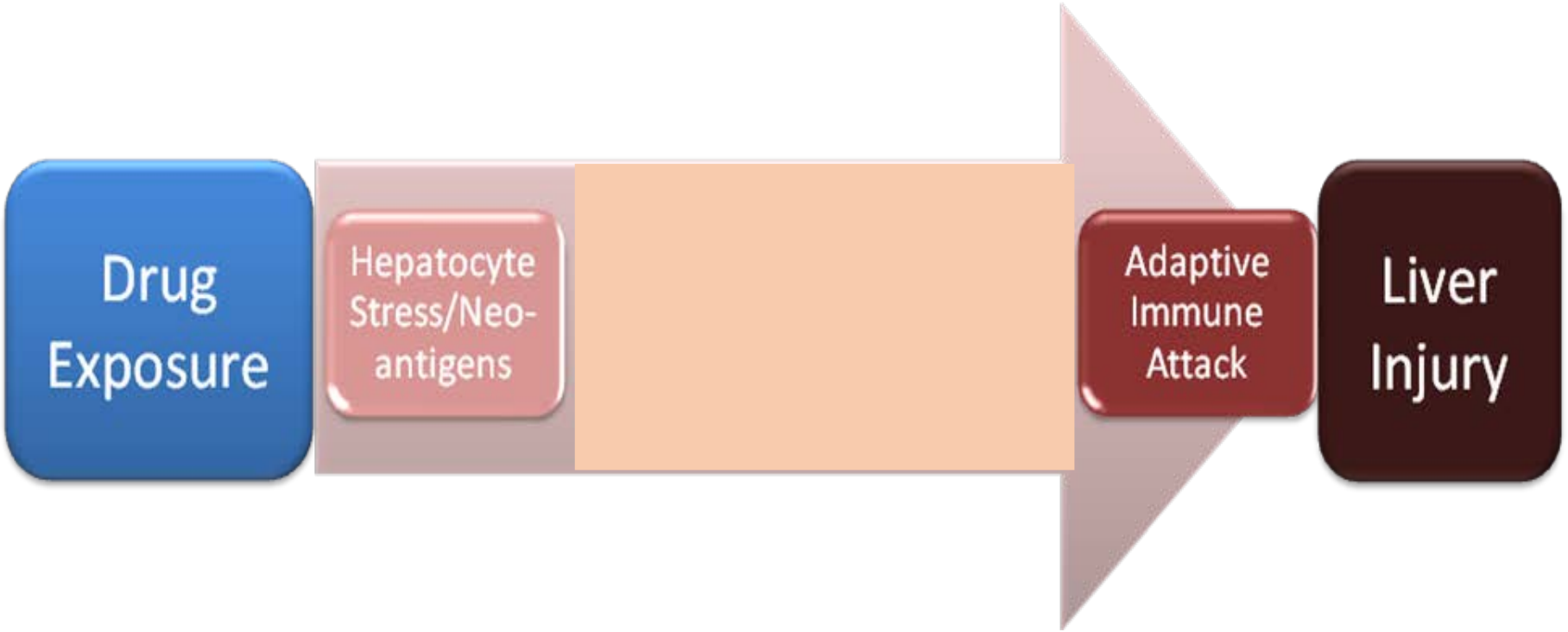
WHY?

Multiple steps involved in idiosyncratic DILI



Mosedale and Watkins Clin Pharmacol Ther. 2017 101(4):469-480.

Multiple steps involved in idiosyncratic DILI



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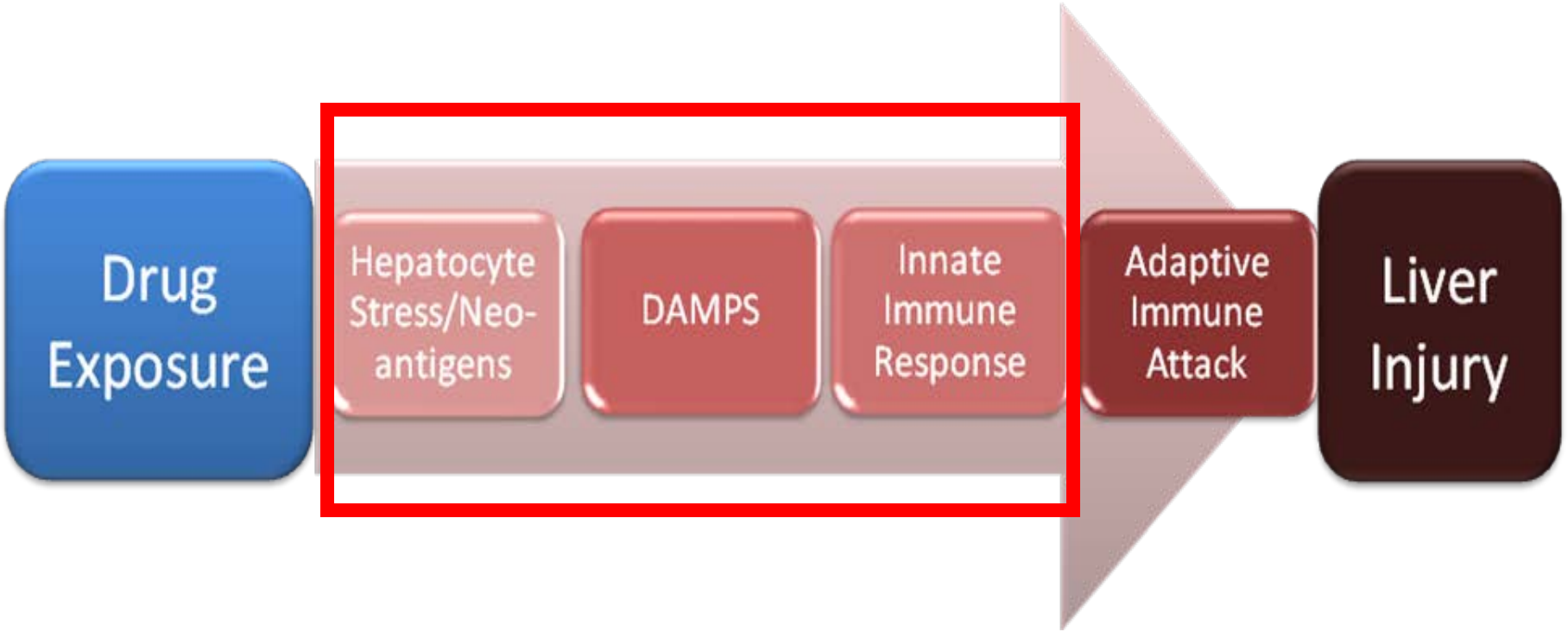

Mosedale and Watkins Clin Pharmacol Ther. 2017 101(4):469-480.

Outline of talk

1). DILI and drug development

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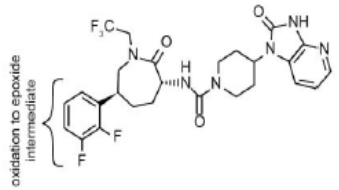
3). The Ubrogepant story

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 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

Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention

Tony W. Ho, MD
Kathryn M. Connor, MD
Ying Zhang, PhD
Eric Pearlman, MD, PhD
Janelle Koppenhaver, MA
Xiaoyin Fan, PhD
Christopher Lines, PhD
Lars Edvinsson, MD
Peter J. Goadsby, MD
David Michelson, MD

Randomized to telcagepant 140 mg, telcagepant 280 mg, or placebo twice daily for 12 weeks.

Neurology® 2014;83:958-966

Table 3 Summary of adverse events

	Telcagepant 140 mg (n = 263)	Telcagepant 280 mg (n = 265)	Placebo (n = 128)
Any adverse event	138 (52.5)	143 (54.0)	74 (57.8)
Drug-related adverse event[a]	81 (30.8)	74 (27.9)	38 (29.7)
Serious adverse event	3 (1.1)	2 (0.8)	1 (0.8)
ALT increased	6 (2.3)	12 (4.5)	0 (0.0)

Two patients with severe and symptomatic liver injury

1). patient was a 25-year-old obese woman. After 2 weeks of treatment with telcagepant 140 mg, her laboratory results were within normal limits. After 4 weeks of treatment, her ALT level was 39× ULN and her AST was 19× ULN, without concomitant elevation of bilirubin. The patient also complained of abdominal pain and nausea of 2 weeks' duration. Following dis-

2). patient was a 45-year-old woman. After 2 weeks of treatment with telcagepant 280 mg, her ALT level was 1.2× ULN, but her other laboratory tests were within normal limits. She experienced severe influenza-like symptoms from days 17 to 24, and severe nausea, anorexia, and dyspepsia starting on day 24. After 4 weeks of treatment, her ALT level was 33× ULN and her AST was 21× ULN. Total

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine

Cephalalgia
2016, Vol. 36(2) 148–161

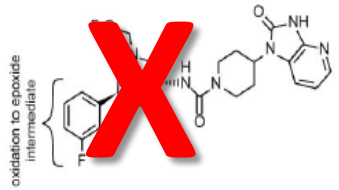
DOI: 10.1177/0333102415584308
cep.sagepub.com
SAGE

Tony W Ho[1,a], Andrew P Ho[1,b], Yang (Joy) Ge[1], Christopher Assaid[1], Regina Gottwald[1], E Anne MacGregor[2], Lisa K Mannix[3], Willebrordus PJ van Oosterhout[4], Janelle Koppenhaver[1], Christopher Lines[1], Michel D Ferrari[4] and David Michelson[1]

n = 2660 on 140 mg qd X 7d each month vs n = 1336 on placebo

“In three patients, all in the telcagepant group, ALT elevations > 8 ULN were reported and were considered to be a serious laboratory adverse event.”

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

Parameter	Telcagepant[a]
Structure[d]	
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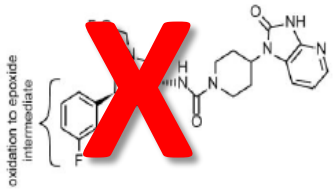
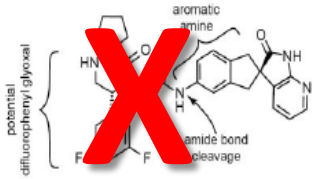
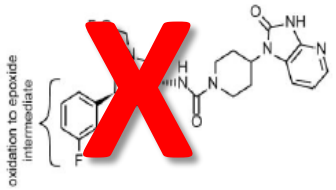
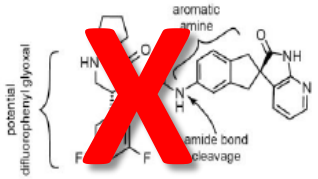
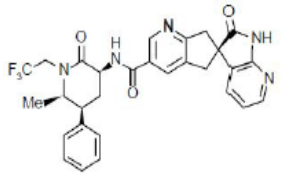
Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

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

Ubrogepant Simulation Project Overview

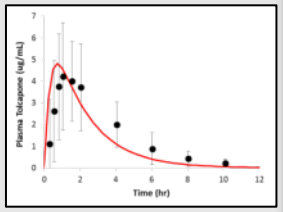
- *In vitro* experiments performed on three represented mechanisms of DILI for telcagepant, MK-3207, and Ubrogepant
  - Mitochondrial dysfunction: Seahorse XF Analyzer
  - Bile acid transporter inhibition: vesicle assays
  - Oxidative stress: high-content screening with DHE
- Simulations performed with telcagepant and MK-3207 using clinical trial dosing protocols
  - Goal is to **recapitulate clinically observed toxicity**
- Simulations performed with Ubrogepant
  - Goal is to **predict likelihood of toxicity**

DILIsym Utilizes Various Data Types to Inform Decisions

Exposure Data

PBPK Modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*



In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP*
- **Bilirubin transport/metabolism**
  - ***OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3***

Modeling & Simulation

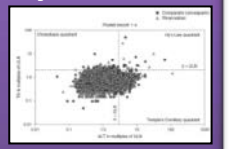
DILIsym®

Simulations and Assays inform:

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

Clinical Data

- **Biomarkers**
  - **Timing and magnitude of injury**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**



DILIsym Services

A SIMULATIONS PLUS COMPANY

Clinical Dosing Protocols Simulated for MK-3207, Telcagepant, and Ubrogepant

Smith et al., *Tox Sci* 2020

	Compound	Dosing Protocol	Clinical ALT > 3X ULN***
MK-3207	MK-3207, Competitive BSEP Inhibition	200 mg, 2 daily doses 2 hours apart (400 mg daily dose), for 14 days	42% (5/12) amongst individuals dosed for more than 1 week; most responding were given 600 – 900 mg per day
		300 mg, 2 daily doses 2 hours apart (600 mg daily dose), for 14 days	
		450 mg, 2 daily doses 2 hours apart (900 mg daily dose), for 14 days	
Telcagepant	Telcagepant	280 mg BID 12 weeks	3.2% (8/265)
		140 mg BID 12 weeks	1.9% (5/263)
Ubrogepant	Ubrogepant	100 mg q.d. for 8 days	Not known at time of simulation
		100 mg q2h (200 mg per day), 2 daily doses, for 4 days	
		100 mg q.d. for 2 days, 2 days off, 56 days total of dosing with 28 total doses	

*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used; DILIsym v5A was used for MK-0974 and MK-8031, while v7A was used for MK-1602 and MK-3207

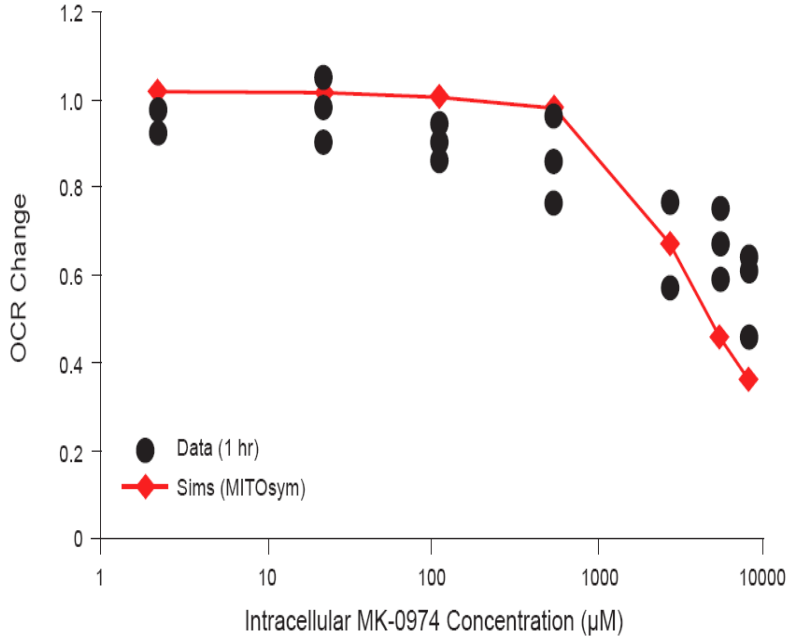
**Upper limit of normal (ULN) in DILIsym is 40 U/L

***Single dose study (006) and study with max of 3 doses (007) up to 100 mg showed no ALT elevations for MK-1602

Parameters Identified for Telcagepant Mediated Mitochondrial Dysfunction and Oxidative Stress

OCR

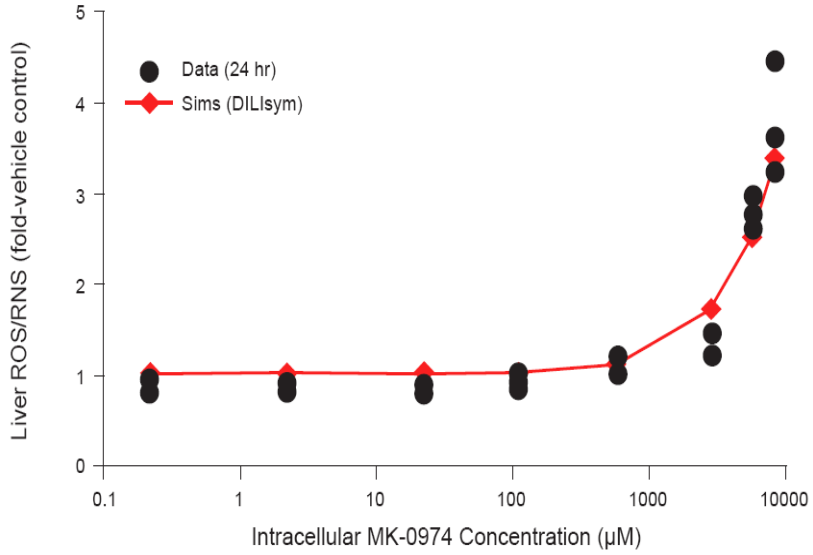
HepG2 cells, 1h incubation



Telcagepant

ROS/RNS

HepG2 cells, 24h incubation



DILIsym Parameter	Value	Units
Coefficient for ETC Inhibition 1	17400	µM
RNS/ROS production rate constant 1	2e5	mL/mol/h

Smith et al., *Tox Sci* 2020

Preclinical Data and Simulation Results

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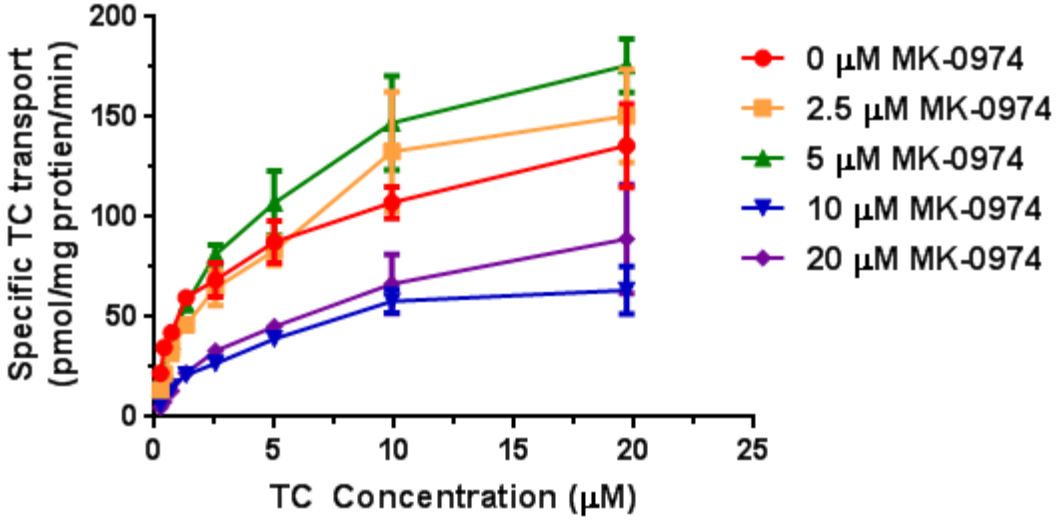
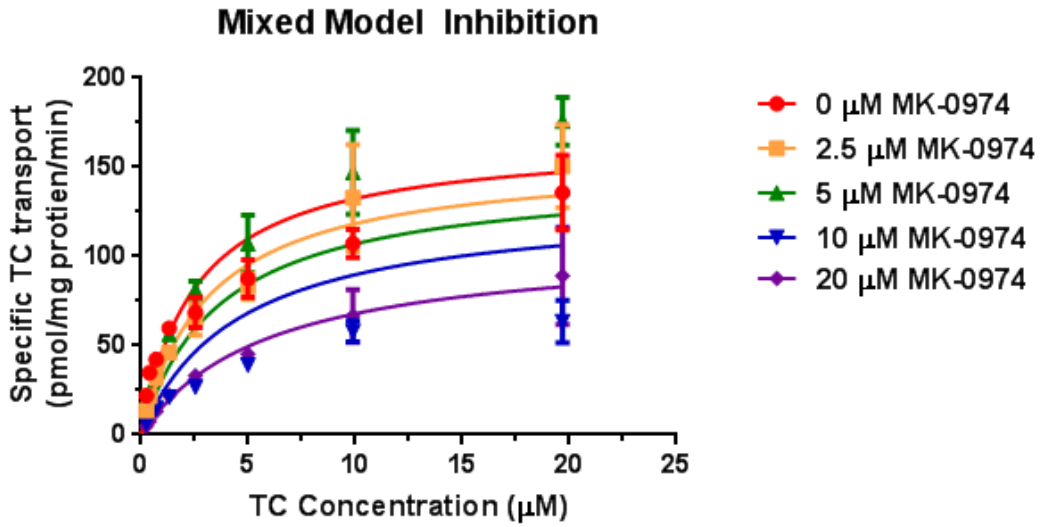
Telcagepant Alters Km and Vmax of BSEP-Mediated Taurocholate Transport

Telcagepant





Telcagepant concentration (µM)	0	2.5	5	10	20
V_{max} (pmol/mg protein/min)	135.8	186.3	208.1	77.52	119.7
K_m (µM)	1.786	4.388	3.756	3.844	6.946

$$\frac{d[BA]}{dt} = \frac{V_{max}[BA]}{K_m(1+\frac{[I]}{K_i}) + [BA](1+\frac{[I]}{\alpha K_i})}$$

Smith et al., *Tox Sci* 2020

Preclinical Data

DILIsym Services

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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

**IC_{50} values calculated from experiment; mixed inhibition with alpha = 5 assumed

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DILIsym Recapitulates MK-3207 and Telcagepant Clinical Hepatotoxicity and Suggests that Ubrogepant Is Safe

	Compound	Dosing Protocol	Simulated* ALT > 3X ULN**	Clinical ALT > 3X ULN***
MK-3207	MK-3207, Competitive BSEP Inhibition, no RM	200 mg, 2 daily doses 2 hours apart (400 mg daily dose), for 14 days	3.5% (10/285)	42% (5/12) amongst individuals dosed for more than 1 week; most responding were given 600 – 900 mg per day
		300 mg, 2 daily doses 2 hours apart (600 mg daily dose), for 14 days	7% (20/285)	
		450 mg, 2 daily doses 2 hours apart (900 mg daily dose), for 14 days	10.2% (29/285)	
Telcagepant	Telcagepant	280 mg BID 12 weeks	12.6% (36/285)	3.2% (8/265)
		140 mg BID 12 weeks	0% 0/285	1.9% (5/263)
Ubrogepant	Ubrogepant	100 mg q.d. for 8 days	0% (0/285)	Not known at time of simulation
		100 mg q2h (200 mg per day), 2 daily doses, for 4 days	0% (0/285)	
		100 mg q.d. for 2 days, 2 days off, 56 days total of dosing with 28 total doses	0% (0/285)	

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*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used; DILIsym v5A was used for MK-0974 and MK-8031, while v7A was used for MK-1602 and MK-3207

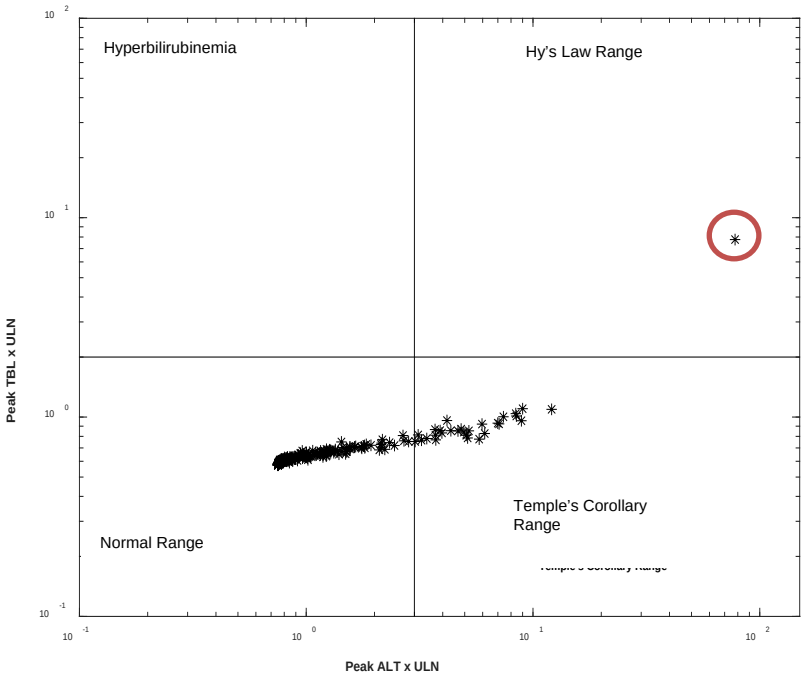
**Upper limit of normal (ULN) in DILIsym is 40 U/L

***Single dose study (006) and study with max of 3 doses (007) up to 100 mg showed no ALT elevations for MK-1602

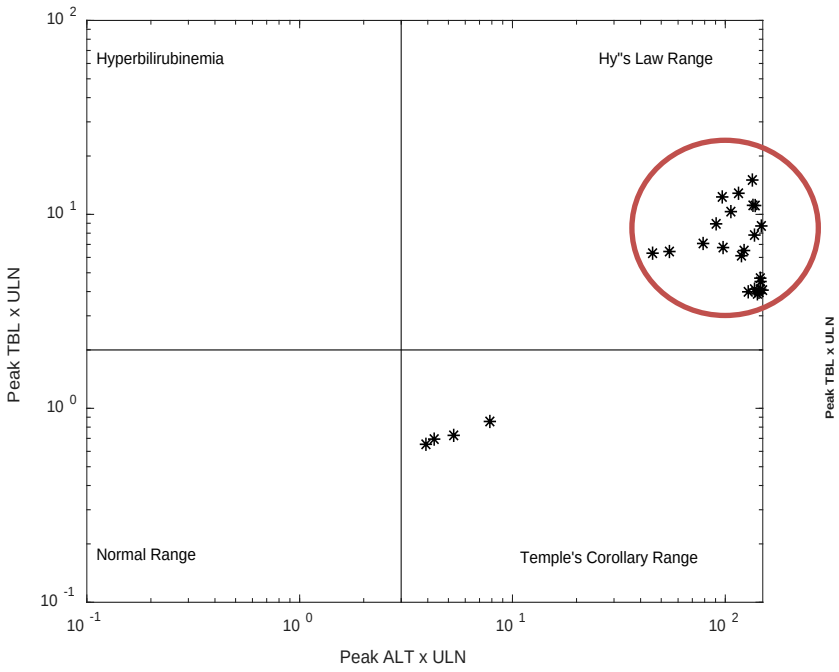
Simulation Results and Clinical Data

eDISH Plots Show Predicted Hy's Law Cases for MK-3207 and Telcagepant but None for Ubrogepant

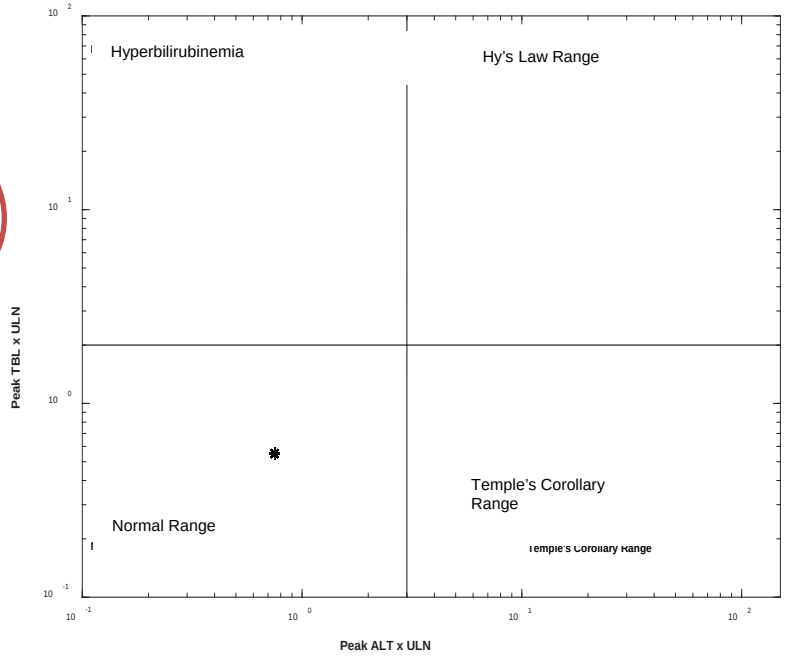
MK-3207 450 mg 14 days



Telcagepant 280 mg 12 weeks



Ubrogepant 100 mg q2h 4 days



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Simulation Results

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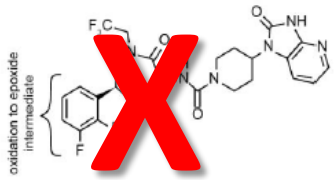
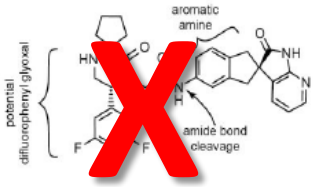
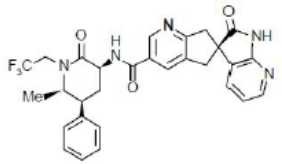
CGRP Modeling Project Conclusions

- DILIsym modeling predicted liver toxicity for telcagepant and MK-3207
  - Consistent with clinical experience

- DILIsym **prospectively** predicted liver safety for ubrogepant

Calcitonin gene-related peptide (CGRP) antagonists for treatment of migraines

Parameter	Telcagepant[a]	MK-3207[b]	Ubrogepant[c]
Structure[d]	 X	 X	
Potency IC_{50}[e]	2.2 nM	0.12 nM	0.08 nM
Pivotal DILIsym	X	X	

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Original Article

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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)

For Immediate Release:
December 23, 2019

Food and Drug Administration today approved Ubrelvy (ubrogepant) tablets for the acute (immediate) treatment of migraine with or without aura (a sensory phenomenon or visual disturbance) in adults.

No liver safety warning in package insert!

Conclusion

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

Application of Systems Pharmacology to Explore Mechanisms of Hepatotoxicity

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We look forward to future efforts to apply this model for prediction of hepatotoxicity that has not been clinically observed.

Clin Pharmacol Ther 2014 Nov;96(5):536-7.

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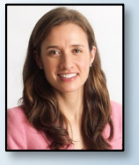

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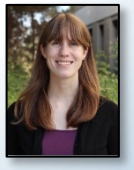

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Questions?