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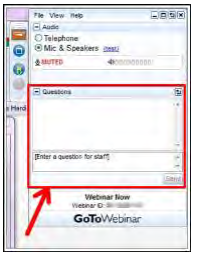

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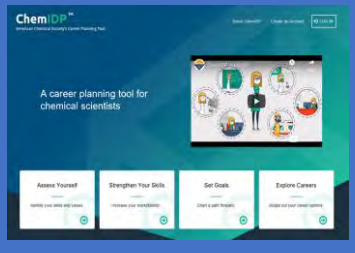

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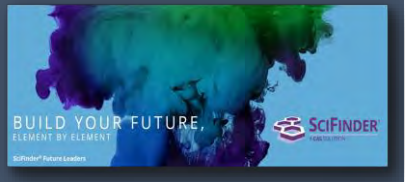

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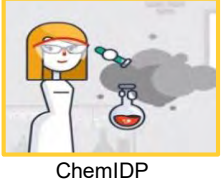
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Upcoming Broadcasts

ACS Chemistry for Life®

Tuesday, December 1, 2020 at 2-3pm ET
Speakers: Jim Skinner, Terregena, Inc. and H.N. Cheng, 2020 ACS President-Elect
Moderator: Diane Grob Schmidt, 2015 ACS President

Register for Free!

What You Will Learn

- The many sources of funding and their impact on ownership
- The importance of milestone achievements for valuation purposes
- The criteria and terms that investors use to make investing decisions

Co-produced with: ACS Industry Member Programs, ACS President-Elect, ACS Board Committee on Corporation Associates, ACS Committee on Technician Affairs, the ACS Division of Small Chemical Businesses, and the ACS Division of Business Development and Management

Wednesday, December 2, 2020 at 2-3pm ET
Speaker: Leah Askarinam, National Journal's Hotline

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What You Will Learn

- What Biden's coalition means for the future of the Democratic Party
- How Trump's coalition differs from that of down-ballot Republicans
- What to look for in Georgia's runoff elections in January

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aaps American Association of Pharmaceutical Scientists

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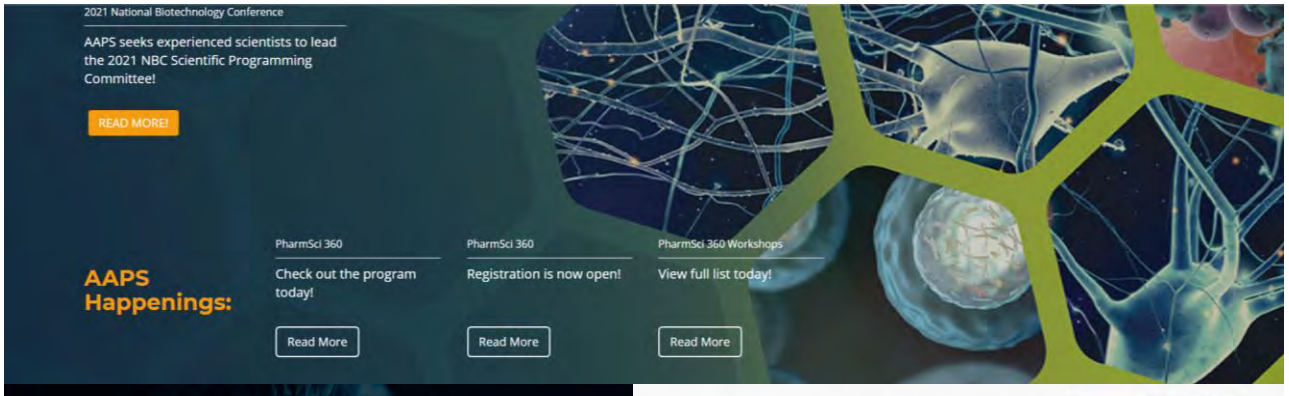

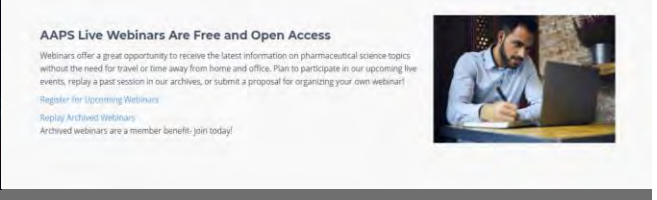

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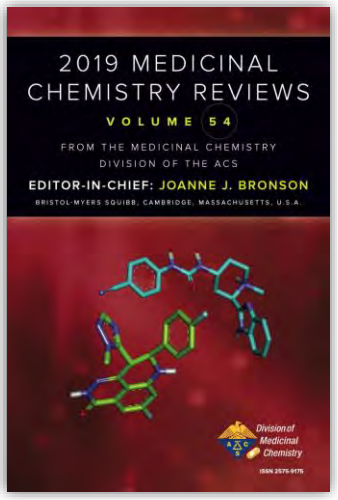

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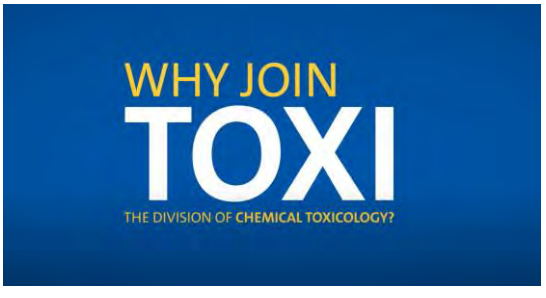

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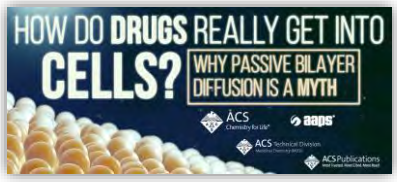
Join Angela Zhou, an Information Scientist at CAS, as she provides an overview of published scientific information relevant to COVID-19 research with an emphasis on patents in the CAS content collection. https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/covid-19.html

Join Research Fellow Li Di of Pfizer as she discusses why design principles that increase passive permeability are effective approaches to increase oral bioavailability, enhance brain penetration, and reduce renal clearance.
https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/passive-permeability.html



Join Douglas Kell, Research Chair in Systems Biology at the University of Liverpool to discover how drugs pass through cell membrane solely by hitchhiking on membrane transporters and why so-called "passive diffusion" through any bilayer in real cells is negligible.
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ACS Chemistry for Life®

Mitigating Drug-Induced Liver Injury 2: Assessing Transporter Liabilities and Bioactivation Transcriptomics

Michael Hafey
Principal Scientist, Merck

Wen Kang
Director of Assay Development, Merck

James Monroe
Senior Principal Scientist, Merck

Kaushik Mitra
Director, Department of Drug Metabolism and Pharmacokinetics; DMPK Therapeutic Area Lead, Cardiovascular and Metabolic Diseases; Head, Biotransformation Sciences, Janssen Research & Development

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This ACS Webinar is co-produced with the ACS Division of Chemical Toxicology, ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications.

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What is your current experience with Drug-Induced Liver Injury (DILI)?

- I'm a medicinal chemist and encounter DILI in my drug discovery and design research
- I'm a clinician and observe DILI in my patients
- I'm a patient and have been personally affected by DILI
- Other (let us know in the questions panel)

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A two-tiered in vitro approach to de-risk drug candidates for potential bile salt export pump inhibition liabilities in drug discovery

Hafey et al. (2020). DMD. 48:1147-1160.

Michael Hafey
Transporters & *In Vitro* Technologies
PPDM
Merck & Co., Inc.

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Learning Objectives

- Identify key hepatic transporters involved in bile acid disposition
- Understand the correlation between BSEP inhibition and DILI risk
- Learn how to utilize a two-tiered in vitro approach to limit compounds that may inhibit BSEP in vivo from reaching the clinic

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Outline

- Hepatic bile salt transport and the DILI BSEP decision tree
- Vesicular Inhibition Assay
  - Experimental background and study design
  - Example data set
- Hepatopac Transporter Inhibition Assay
  - Advantages
  - Experimental background and study design
  - Example data set
- Conclusions

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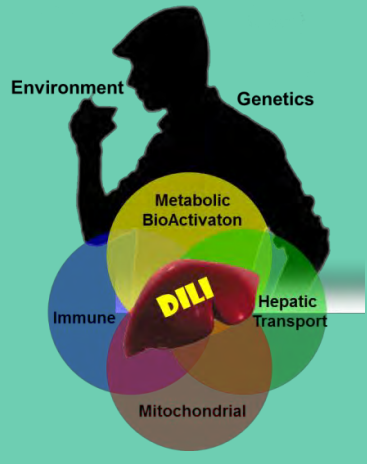
Drug Induced Liver Injury (DILI)

- DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years.
- Evidence for DILI often only emerges in late clinical development or post-marketing.
- The causes of DILI are poorly understood and are potentially multifactorial.
- There is no single assay available to derisk for DILI at the preclinical stage. Instead, a battery of assays is used with a 'weight of evidence' assessment.

Disruption of hepatic transport proteins involved in bile salt transport could contribute to DILI.



Sistare et al. (2016). ILAR J. 57:186-211.

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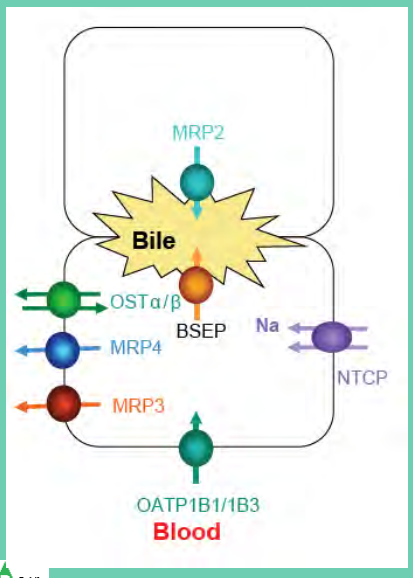
Hepatic Transporters Involved in Bile Salt Transport



- The entero-hepatic circulation of bile salts is complex.
- BSEP mediated efflux represents the driving force for generation of bile flow and is the rate limiting step in overall bile salt transport.
- Interference with the efflux of bile salts from hepatocytes could cause intracellular accumulation of bile salts leading to toxicity.
- Recent studies have shown that several drugs implicated in drug induced liver injury (DILI) inhibit BSEP.

Yang et al. (2013). J Pharm Sci. 102:3037–3057.
Rodrigues et al. (2014). DMD. 42: 566-74.
Kenna et al. (2018). CPT. 104:916–932.

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Bile Salt Transport Inhibition and DILI

- **Objectives**
  - **Understand the correlation between inhibition of liver transporters involved in bile acid transport and human DILI risk.**
  - **Establish *in vitro* assay systems to measure the effect of test compounds on bile salt transport.**
- **Approaches**
  - **Study inhibition of BSEP, MRP2, MRP3, and MRP4 in vesicles by a test set of ~120 DILI+ and DILI- compounds.**
  - **Develop and characterize a holistic TCA transport inhibition model in a long-term human hepatocyte micropatterned co-culture model (Hepatopac).**

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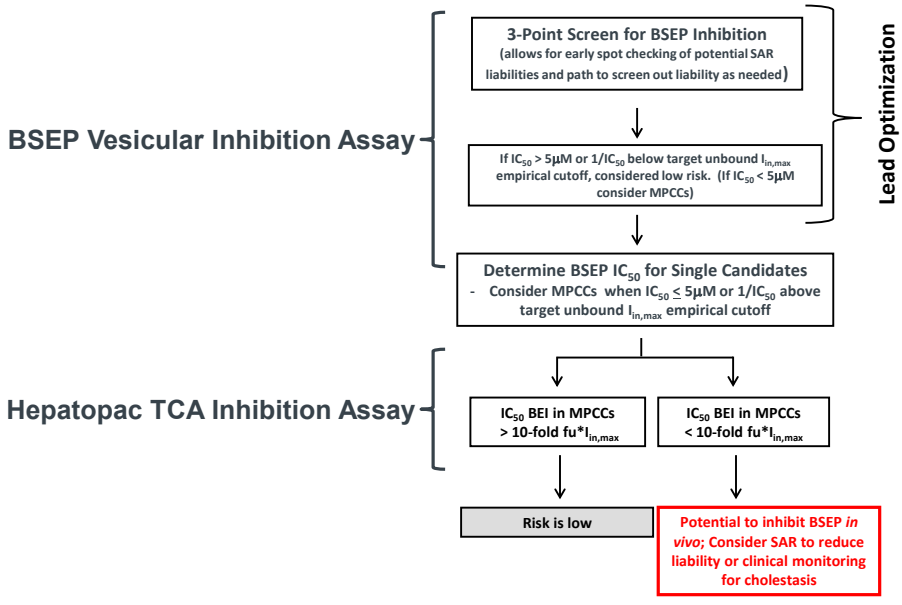
Testing for DILI Potential via Transport Inhibition Mechanisms



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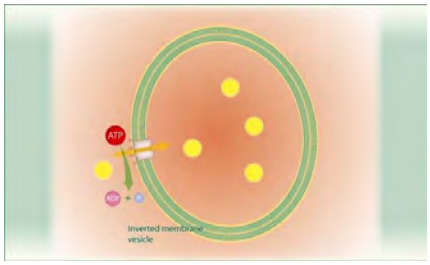
Vesicular Transport Inhibition Assay



- Membrane vesicles isolated from Sf9 cells containing BSEP.
- Uptake transport by inside-out vesicles is driven by ATP.
- For inhibition study, transport of a probe substrate (taurocholic acid) is measured in the presence of potential inhibitors.
- Answers the question: "Does compound X inhibit BSEP *in vitro*?"

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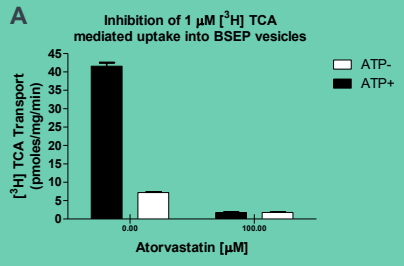
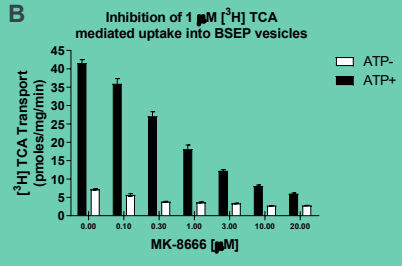
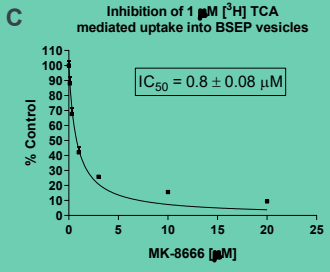
MK-8666 inhibits BSEP in membrane vesicles







- MK-8666 inhibited hBSEP-mediated [^{3}H]TCA uptake with an IC_{50} = 0.79 ± 0.08 µM.
- 100 µM Atorvastatin completely abolished BSEP-mediated [^{3}H] TCA uptake, confirming the functionality of the assay.

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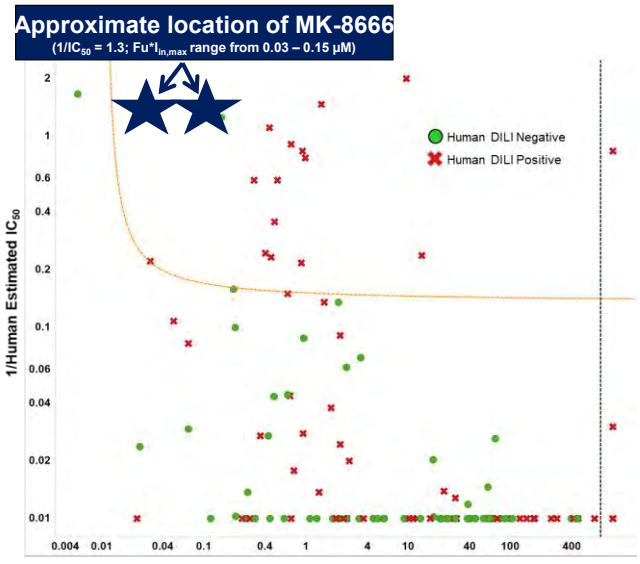
Combining liver inlet drug levels and human BSEP inhibition potency to assess clinical DILI risk potential



- **The orange line represents an empirically drawn cutoff.**
- **Inhibition of BSEP may be predictive of human DILI for compounds that fall above the line.**
- **Inhibition of BSEP is not thought to be predictive of human DILI for compounds that fall below the line.**

		Human BSEP +	Human BSEP -	
Clinical Evidence of DILI	+	True Positive 15	False Negative 49	Sensitivity 23%
	-	False Positive 1	True Negative 56	Specificity 98%
		PPV 94%	NPV 53%	

$Fu^*I_{in,max} = fu * (I_{max} + (Fa * Dose * ka/Qh))$

Combining liver inlet drug levels and human BSEP inhibition potency to assess clinical DILI risk potential

- **The empirical cutoff line for BSEP inhibition is represented by the equation:**

(Log10 (1/[BSEP IC_{50}]) + 0.87) * (2 + Log10 ([Fu* $I_{in,max}$ µM])) = 0.1
where 0.1 is defined as the "BSEP burden"

- **If the BSEP burden for a compound is > 0.1, the compound falls above the empirical cutoff line.**

Fu = 0.002

Dose (mg)	50
Cmax (µM)	10
Fu	0.002
Fu $I_{in,max}$ (µM)	0.03
IC_{50} (µM)	0.79
BSEP Burden	**0.47**

Fu = 0.01

Dose (mg)	50
Cmax (µM)	10
Fu	0.01
Fu $I_{in,max}$ (µM)	0.15
IC_{50} (µM)	0.79
BSEP Burden	**1.15**

Combination of BSEP, MRP2, MRP3, and MRP4 Inhibition Data

Neg Under empirical cut off
Pos Above empirical cut off

Observations

- A compound positive for BSEP, regardless of inhibition of MRPs, may be a DILI risk.
- Inhibition of MRP2-4 alone lowered the positive predictive value of the assay as compared with BSEP alone because it increased the number of false positives.
- MRP2–4 inhibition in addition to inhibition of BSEP decreased the overall specificity of DILI predictions because it also increased the number of false positives.

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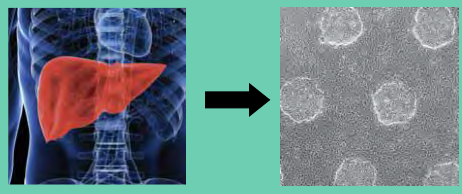
Advantages of a More Holistic Transporter System: Hepatopac



Khetani and Bhatia. (2008). Nature Biotechnology. 26:120-126.

- When assessing the potential for transporter mediated cholestasis, testing inhibition of each transporter in isolation *in vitro* may provide a limited view of what occurs *in vivo*.
- Using a hepatocyte based system may be a more advantageous approach to examine the effects of drugs on bile salt transport.
- Hepatopac is a bioengineered microliver platform which serves as a functional model of the liver *in vivo.* Micropatterned plates contain tiny colonies of organized hepatocytes surrounded by supportive 3T3 fibroblasts.

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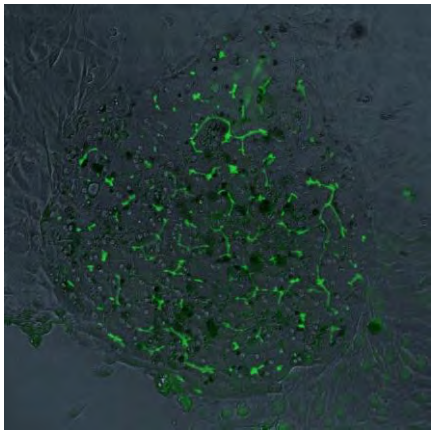
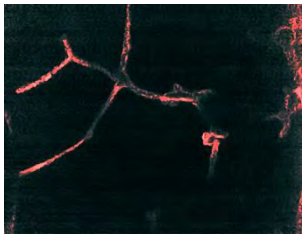
CDF Accumulation in Bile Canaliculi and Localization of MRP2 and BSEP in Hepatopac

CDF* Uptake

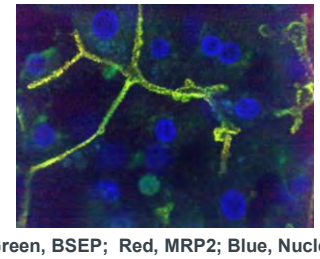


*5(and 6)-carboxy-2', 7'dichlorofluorescein

MRP2 Localization



BSEP Localization



Green, BSEP; Red, MRP2; Blue, Nuclei

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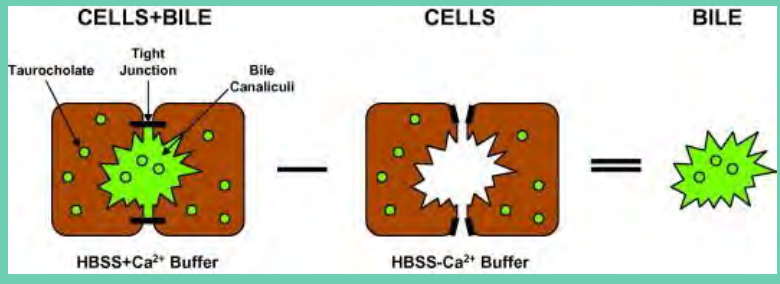
Typical Transporter Experiment in Hepatopac System

Cryopreserved human hepatocytes and stromal cells are plated in co-culture. Hepatocytes form bile canaliculi

Cells are pre-incubated with inhibitors in HBSS buffer +/- calcium for given time

Cells are washed and incubated in HBSS buffer containing radiolabeled substrate (+/- inhibitors)

Cells are washed, lysed, and counted by liquid scintillation counting



Wolf et al. (2010). Toxicology in Vitro. 24: 297-309.

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Calculations and Data Interpretation

$$\text{BEI (Efflux)} = \frac{\text{Accumulation}_{\text{cells+bile}} - \text{Accumulation}_{\text{cells}}}{\text{Accumulation}_{\text{cells+bile}}} \times 100$$

$$\textit{In Vitro}\ \text{CL}_{\text{biliary}} \text{ (Uptake + Efflux)} = \frac{\text{Accumulation}_{\text{cells+bile}} - \text{Accumulation}_{\text{cells}}}{\text{AUC}_{\text{medium}}}$$

In Vitro $CL_{biliary}$	BEI	Data Interpretation
⇩	≠	Sinusoidal uptake pathway affected
⇩	⇩	Sinusoidal uptake and canalicular efflux pathways affected
≠	⇩	Canalicular efflux pathway affected

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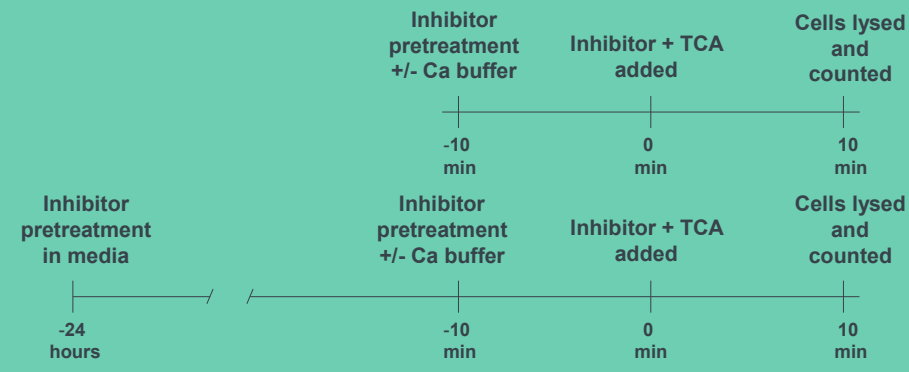
Question

Do known inhibitors of BSEP cause a decrease in BEI in a more holistic system such as Hepatopac?

Experimental Design



- In Vitro $Cl_{biliary}$ and BEI calculated for 10 min and 24 hrs pre-treatments.
- Cells and supernatant collected after 24 hr pretreatment for Met ID analysis.
- To assess cytotoxicity, ATP assay currently included for 24 hr time point.

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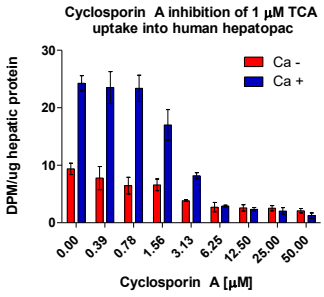
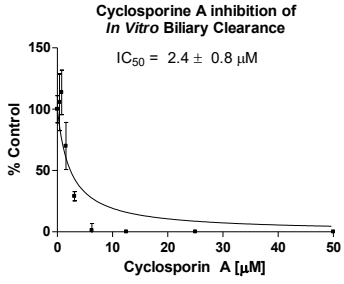
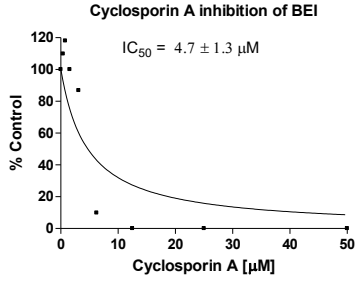
Positive Control: Cyclosporin A







	Hepregen Hepatopac				Vesicles	fu	
	10 min	24 hr	10 min	24 hr	BSEP	I in max	Met ID
Compound	CL [IC_{50}]	CL [IC_{50}]	BEI [IC_{50}]	BEI [IC_{50}]	[IC_{50}]	[µM]	LC/HRMS
Cyclosporin A	2.4 ± 0.8	1.1 ± 0.2	4.7 ± 1.3	2.2 ± 0.4	0.3	4.7	Parent ~93% 3 metabolites

- As expected, cyclosporin A inhibited $CL_{biliary}$ and BEI.
- Cyclosporin A effects sinusoidal uptake and canalicular efflux.

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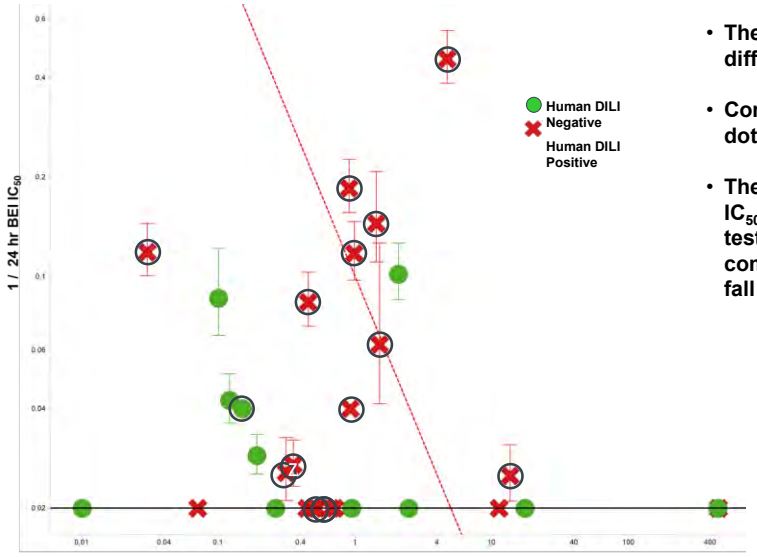
Combining liver inlet drug levels and BEI inhibition potency to assess clinical DILI risk potential



- The red dotted line represents a 10-fold difference between $1/IC_{50}$ and $Fu*I_{in,max}$.
- Compounds that fall to the right of the red dotted line have $1/IC_{50}$ < 10-fold $Fu*I_{in,max}$.
- The black solid line represents cases were the IC_{50} was greater than the highest concentration tested. Since the IC_{50} is unknown it cannot be compared to the $Fu*I_{in,max}$ for compounds that fall to the right of the red dotted line.

		$1/BEI\ IC_{50}$ < 10x $fu*I_{in,max}$		
		+	-	
Clinical Evidence of DILI	+	True Positive 5	False Negative 12	Sensitivity 29%
	-	False Positive 1	True Negative 8	Specificity 89%
		PPV 83%	NPV 40%	

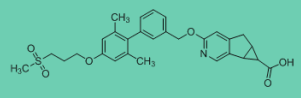
Effect of MK-8666 (L-005090533) on *In Vitro* $CL_{biliary}$ and BEI in Hepatopac

	Hepregen Hepatopac				Vesicles	fu
	10 min	24 hr	10 min	24 hr	BSEP	I in max
Compound	CL [IC_{50}]	CL [IC_{50}]	BEI [IC_{50}]	BEI [IC_{50}]	[IC_{50}]	[µM]
Cyclosporin A	2.9 ± 0.7	1.4 ± 0.7	10.2 ± 1.7	2.5 ± 0.4	0.3	4.70
MK-8666	14.5 ± 4.5	23.6 ± 10.5	> 50	25 - 50	0.79	0.19*

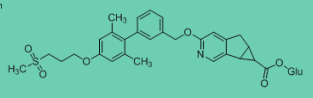
* based on a dose of 500 mg, a Cmax of 20 uM, a fu = 0.0077, and Ka = 0.0067 min^{-1}

- Inhibition of $CL_{biliary}$ was observed at 10 min and 24 hrs with MK-8666. However, IC_{50} > 10 fold of the predicted fu $I_{in,max}$ at a 500 mg dose.
- A decrease in BEI was observed at 24 hrs with MK-8666. However, IC_{50} > 10 fold of the predicted fu $I_{in,max}$ at a 500 mg dose.
- Risk of clinically meaningful *in vivo* interaction with BSEP is low.

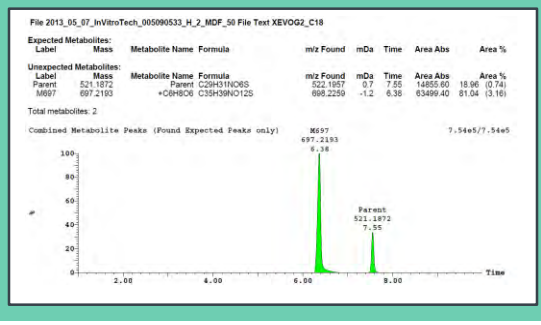
HR-MS Met ID Analysis of MK-8666 Hepatopac samples



MK-8666
M521, 7.55 min



M697
6.38 min
Major



- Approximately 80% of MK-8666 is converted to an acyl glucuronide metabolite following a 24 hr incubation with MK-8666 in Hepatopac.
- MK-8666 acyl glucuronide inhibited BSEP-mediated [^{3}H] TCA uptake with an IC_{50} > 25 µM.
- Thus metabolism of MK-8666 in Hepatopac may explain the discrepancy between potency in the vesicular and Hepatopac inhibition assays.
- In addition, high protein binding (PPB >99%) of MK-8666 could also contribute to the lack of inhibition in hepatocytes.

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In Vitro BSEP Inhibition Summary

DILI Negative

Compound	BSEP Vesicular Inhibition	MPCC BEI Inhibition
Dipyridamole		
Lopinavir		
Ambrisantan		
Atorvastatin		
Buspirone		
Entacapone		
Pioglitazone		
Rosiglitazone		
Valsartan		
Metformin		
Quinidine		

DILI Positive

Compound	BSEP Vesicular Inhibition	MPCC BEI Inhibition
Benzbromarone		
Cyclosporine A		
Ritonovir		
Telithromycin		
Troglitazone		
Almorexant		
Lapatanib		
MK-0773		
Nefazodone		
Sitaxsentan		
Tasosartan		
Verlukast		
Zafirflukast		
MK-3207		
Bosentan		
Cyproterone		
MK-0974		
Tolcapone		
Acetaminophen		

Assay Negative
Assay Positive

Assay Positive:
Vesicular inhibition: < 5 µM
Hepatopac: BEI IC_{50} < 10x fu* $I_{in,max}$

- **Inhibition of BSEP in the vesicular inhibition assay may be predictive of DILI risk, but causality has not been demonstrated.**
- **Inhibition of BSEP in vesicles is not always predictive of inhibition of canalicular efflux of TCA in Hepatopac.**
- **Discrepancies may be explained by metabolism, protein binding / intracellular sequestration, and/or compensatory (transport) mechanisms.**
- **Caution is warranted in the interpretation of vesicular inhibition data in isolation.**

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Conclusions

Clinical Pharmacology & Therapeutics

Review | Full Access

Can BSEP Inhibition Testing In Drug Discovery And Development Reduce Liver Injury Risk? - An International Transporter Consortium Perspective

J Gerry Kenna, Kunal S. Taskar, Christina Battista, David L. Bourdet, Kim L.R. Brouwer, Kenneth R. Brouwer, David Dai, Christoph Funk, Michael J. Hafey, Yurong Lai, ... See all authors

Kenna et al. (2018). CPT. 104:916–932.

- **The International Transporter Consortium's recent BSEP white paper recommends the proactive evaluation and understanding of BSEP inhibition to aid internal decision making on potential human DILI risk.**
- **Our two-tiered in vitro approach can help de-risk drug candidates for potential BSEP inhibition liabilities and limit compounds with major liabilities from reaching the clinic undetected. However, there are caveats to all approaches and gaps in our understanding of BSEP mediated cholestasis remain.**
- **Current efforts are aimed to better understand potential of preclinical models to assess BSEP inhibition as well as explore approaches to translate findings to humans.**

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Acknowledgements

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Keith Tanis

Hepregen

Amanda Moore
Stacy Krzyzewski
Okey Ukario
Onyi Irrechukwu

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THANK YOU

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DEVELOPMENT AND APPLICATION OF A TRANSCRIPTOMIC SIGNATURE OF BIOACTIVATION IN AN ADVANCED IN VITRO LIVER MODEL TO REDUCE DRUG-INDUCED LIVER INJURY RISK EARLY IN THE PHARMACEUTICAL PIPELINE

WEN KANG

MERCK & CO., INC., KENILWORTH, NJ, USA

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Presentation Outline

- Business need
- Rat HEPATOPAC in vitro bioactivation liver response assay (rat in vitro BA-LRA)
- Human HEPATOPAC in vitro bioactivation liver response assay (human in vitro BA-LRA)

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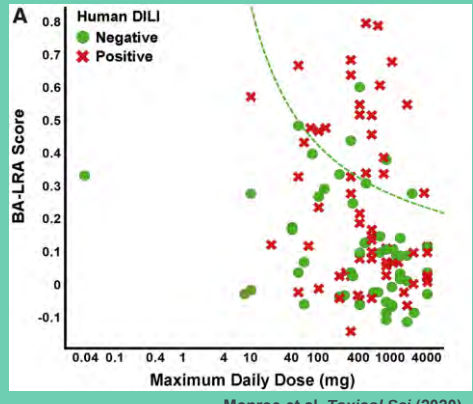
Bioactivation: A Significant Risk Factor for Idiosyncratic Adverse Drug Reactions Including DILI

Methods for Measuring Bioactivation Potential of Drug Candidates

- Covalent protein binding (CPB) assay using radiolabeled compounds
- Trapping assays using GSH, cyanide, semi-carbazide, etc.
- Metabolism dependent inhibition of P450 enzymes
- Rat Liver Gene Expression Biomarkers to inform on bioactivation potential and DILI risk of drug candidates



Monroe et al, *Toxicol Sci* (2020)

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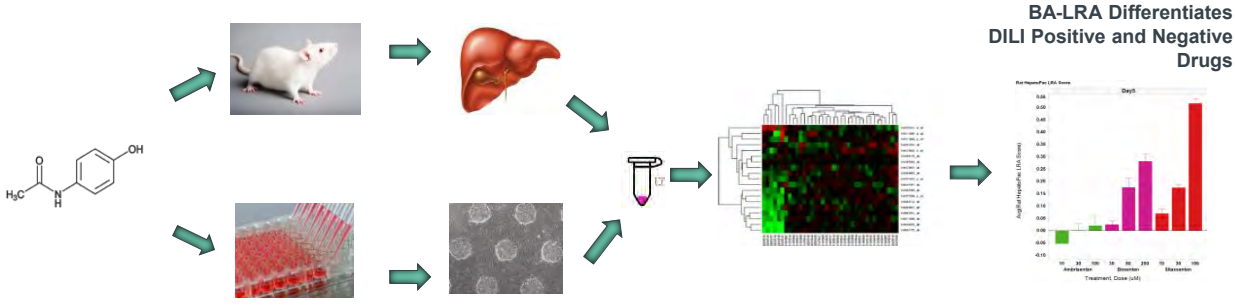
Translation of BA-LRA Biomarker Responses from In Vivo Rat Liver to an In Vitro Assay

Advantages

- **Requires only mg quantity of compounds**
- **Reduces animal use**
- **Higher throughput**
- **Potential for enabling cross-species translation**



BA-LRA Differentiates DILI Positive and Negative Drugs

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In Vitro Liver Model Selection: HEPATOPAC®

Micropatterned coculture of primary hepatocytes

- Robust and stable over time
- Closely mimicking in vivo liver:
  - Drug metabolic activities: Phase I &II enzymes, hepatic transporters, etc.
  - Hepatocyte functions, e.g. albumin and urea production rates
  - Broader gene expression profiles
- Ease for implementation in early drug discovery

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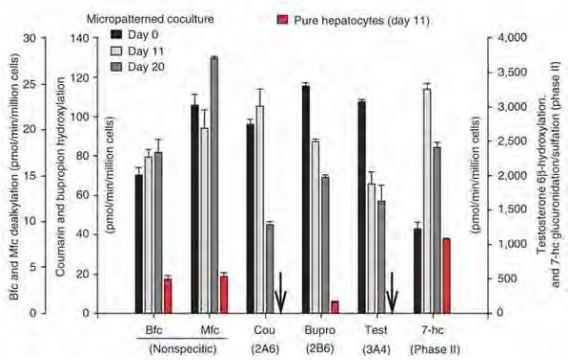
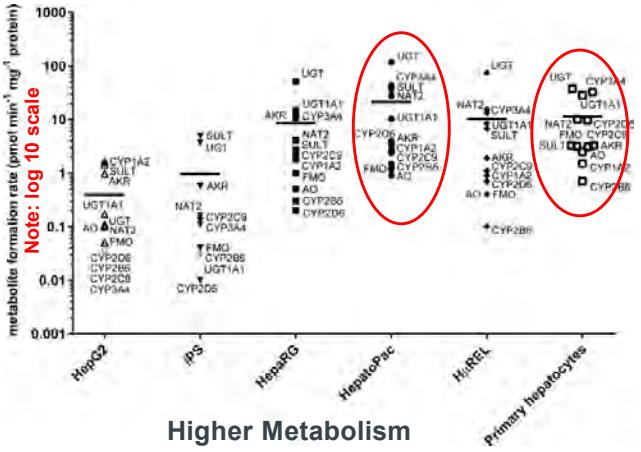
HEPATOPAC® Demonstrates Favorable Drug Metabolism Profiles



Stable Long-term Metabolic Activities

Khetani & Bhatia, *Nat Biotechnol* (2008)



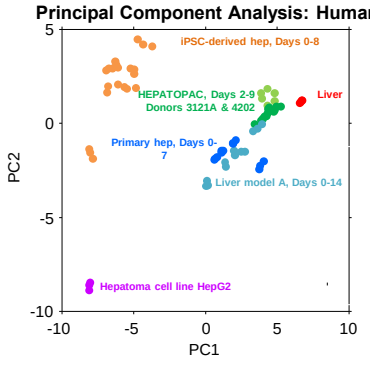
Higher Metabolism Activities

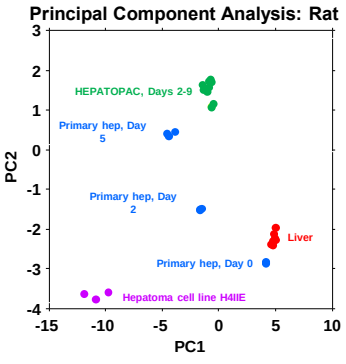
Kratochwil et al, *AAPS J* (2017)

Stable and In Vivo-like Albumin and Urea Production Rates in HEPATOPAC®

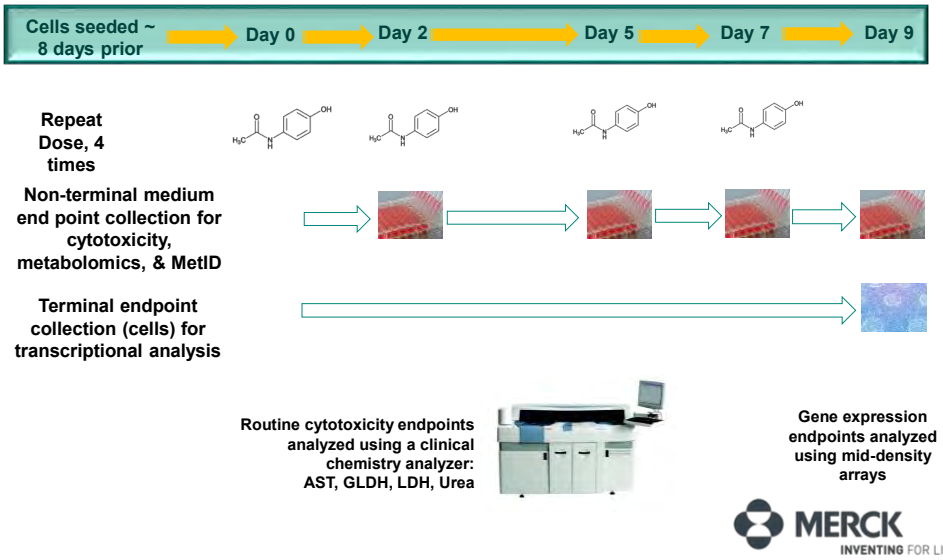
Average Daily Production Rate		HEPATOPAC Study Day 2	HEPATOPAC Study Day 5	HEPATOPAC Study Day 7	HEPATOPAC Study Day 9	Estimated In Vivo Liver
Albumin (ug/day/million cells)	Rat (pooled WH)	214.3 ± 49.1	264.9 ± 14.3	198.2 ± 17	273.2 ± 14.3	~ 200
	Human (donor 3121A)	15.9 ± 0	15 ± 1.3	10.3 ± 0.9	15 ± 0.9	37-105
	Human donor (3121B)	18.8 ± 1.9	19.4 ± 4.4	14.1 ± 1.9	20.6 ± 2.8	
	Human donor (4202)	50.6 ± 6.6	26.3 ± 6.9	16.9 ± 1.9	16.9 ± 1.9	
Urea (ug/day/million cells)	Rat (pooled WH)	1178.6 ± 10.7	928.6 ± 12.9	1039.3 ± 8.6	1307.1 ± 13.9	~ 500 - 1500
	Human donor (3121A)	281.3 ± 25.3	282.5 ± 12.5	345.9 ± 27.2	319.7 ± 21.6	56-159
	Human donor (3121B)	266.3 ± 25.3	281.3 ± 13.8	360 ± 21.6	352.5 ± 11.3	
	Human donor (4202)	180 ± 26.3	237.5 ± 30.6	274.7 ± 26.3	261.6 ± 22.5	

Transcriptional Profiles of HEPATOPAC® Show a Closer Resemblance to Human Liver

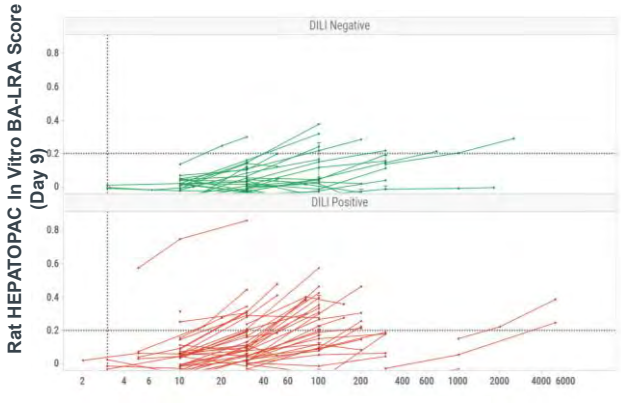


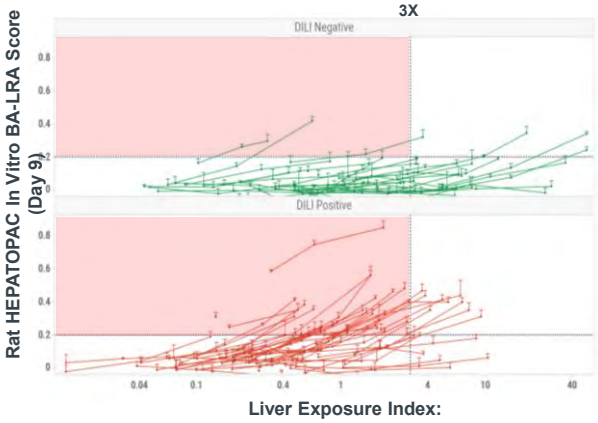


HEPATOPAC Study Design



A 90+ Test Set of DILI Positive and Negative Drugs Were Evaluated in Rat HEPATOPAC for BA-LRA Responses





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Rat HEPATOPAC In Vitro BA-LRA Assay Shows Good Performance in Detecting DILI Positive Drugs

True Positive	False Negative	Sensitivity
False Positive	True Negative	Specificity
Positive Predictive Value	Negative Predictive Value	

Rat HEPATOPAC In Vitro BA-LRA[a]

Human DILI	+	-	
+	34	8	81%
-	3	26	90%
	92%	76%	

[a] Assay outcomes not determined for
1) 8 of 93 compounds due to limited solubility
2) 14 of 93 compounds due to significant cytotoxicity

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Application Case 1: Differentiation of Structurally Diverse Chemical Series Within Same Pharmacological Class

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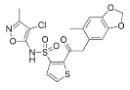
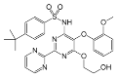
Endothelin Receptor Antagonists

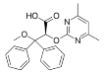
Sitaxsentan **Withdrawn due to DILI**



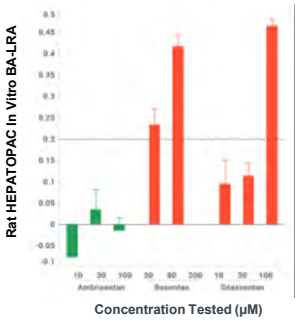
Bosentan **Black Box Warning for DILI**

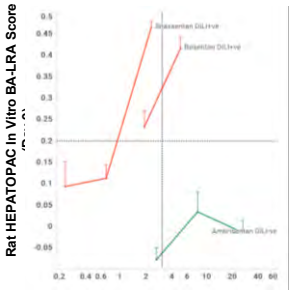


Ambrisentan **Low DILI Concerns**



	Sitaxsentan	Bosentan	Ambrisentan
Max Human Daily Dose (mg)	100	250 (125 BID)	10
Human Therapeutic Cmax (μM)	30	2	2
Calculated Human Liver Inlet Max (μM)	44	16	4





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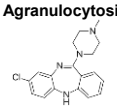
Application Case 2: Differentiation of Close Structure Analogs

In Vitro LRA Differentiates DILI Risk of Close Structure Analogs

Clozapine

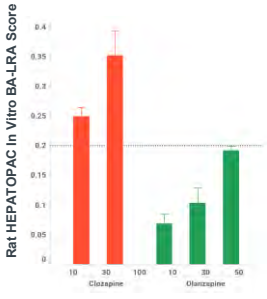
High Risk for DILI & Agranulocytosis



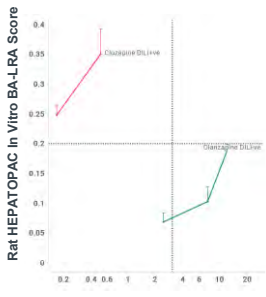
Olanzapine

Low DILI Concerns

	Clozapine	Olanzapine
Max Human Daily Dose (mg)	900 (450 BID)	10
Human Therapeutic Cmax (μM)	1	0.26
Calculated Human Liver Inlet Max (μM)	60	4



Concentration Tested (μM)



Liver Exposure Index: [Total Conc Tested]/[Calculated Total Human Liver Inlet Cmax]

Drug	Extent of Covalent Binding	Formation Rate of GSH Adducts	Time-dependent Inhibition
Clozapine	44.7 pmol/mg protein	14.7 pmol/ml /mg protein	1A1 & 3A4 inactivation
Olanzapine	138.9 pmol/mg protein	11.3 pmol/ml /mg protein	2D6 inactivation

Adapted from Nakayama et al, *Drug Metab Dispos* (2011)

Application Case 3: Drugs Differentiated by Exposure Margins

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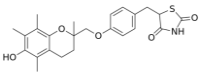
Differentiation by Exposure Margins for Drugs Displayed Similar Profiles

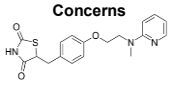
Troglitazone

Withdrawn due to DILI

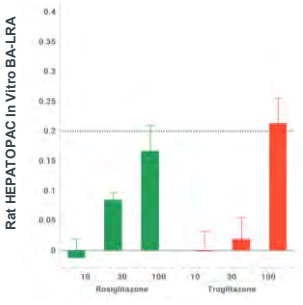


Rosiglitazone

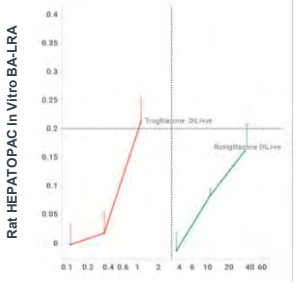
Low DILI Concerns



	Troglitazone	Rosiglitazone
Max Human Daily Dose (mg)	600	8
Human Therapeutic Cmax (μM)	6.4	1.4
Calculated Human Liver Inlet Max (μM)	90	2.8



Concentration Tested (μM)



Liver Exposure Index: [Total Conc Tested]/[Calculated Total Human Liver Inlet Cmax]

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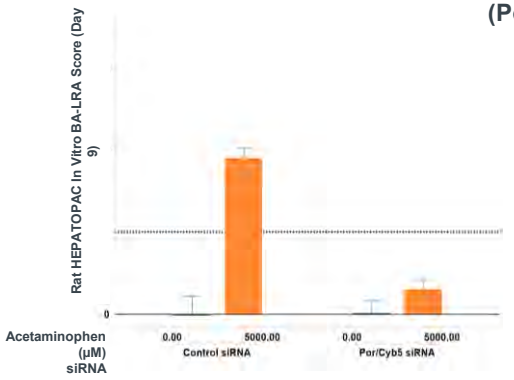
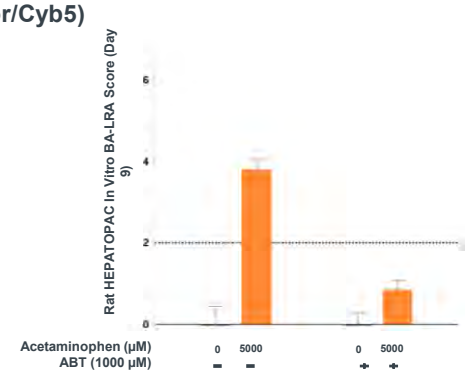
Mechanistic Studies Confirm Involvement of Cytochrome P450 in Mediating In Vitro BA-LRA Responses

Acetaminophen-induced BA-LRA response in rat HEPATOPAC blocked by co-administration of a pan P450 inhibitor (ABT) or knocking down of P450 co-factors (Por/Cyb5)





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Human HEPATOPAC In Vitro BA-LRA

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Development of Human HEPATOPAC In Vitro BA-LRA

True Positive	False Negative	Sensitivity
False Positive	True Negative	Specificity
Positive Predictive Value	Negative Predictive Value	

Rat HEPATOPAC In Vitro BA-LRA +(pooled donor lot)

Human DILI				
	+	34	8	81%
	-	3	26	90%
		92%	76%	

Human HEPATOPAC In Vitro BA-LRA +(single donor lot)

Human DILI				
	+	24	12	67%
	-	4	23	86%
		66%	76%	

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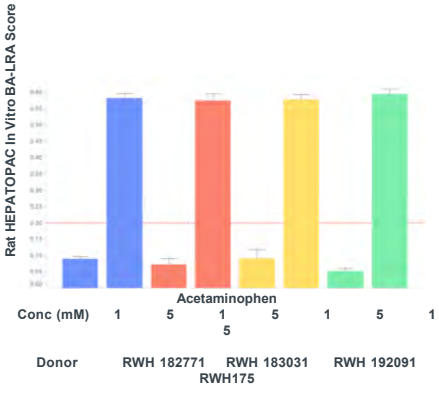
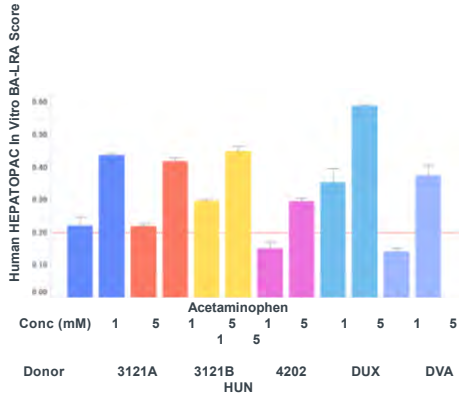
Variability of BA-LRA Responses in Human HEPATOPAC Among Individual Donors



BA-LRA responses in RAT HEPATOPAC from 4 pooled donor lots



BA-LRA responses in HUMAN HEPATOPAC from 6 single donor lots

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Application of Human HEPATOPAC BA-LRA: a Case Example

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Clopidogrel a.k.a. Plavix

- A widely prescribed antiplatelet agent used to prevent heart attack and stroke
- Given at 75 mg daily dose following 300 mg loading dose in the clinic
- In vitro studies (CPB, trapping, TDI) indicated formation of reactive metabolites [a]
- Results from rat in vivo BA-LRA study suggested an increased risk for DILI at the current clinical daily dose of 75 mg [b]

Why is clopidogrel not associated with a high incidence of DILI despite having reactive metabolite liability and a moderate clinical dose?

[a] Nakayama et al, *Drug Metab Dispos* (2011)

[b] Monroe et al, *Toxicol Sci* (2020)

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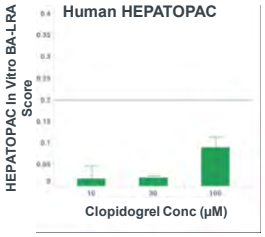
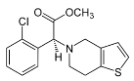
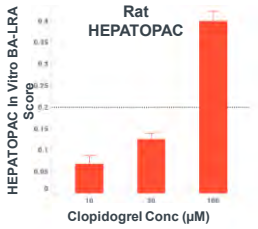
Species Differences in HEPATOPAC BA-LRA Responses and Metabolite Profiles

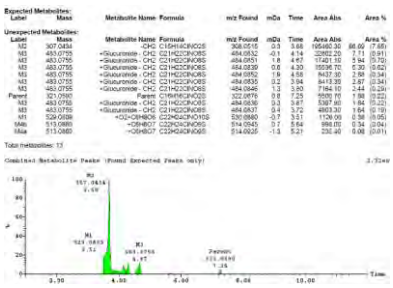


Clopidogrel

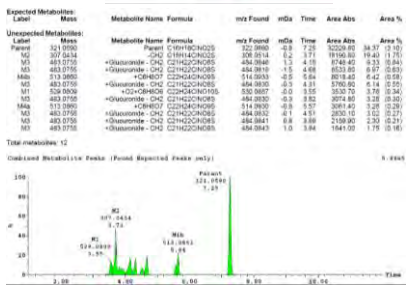




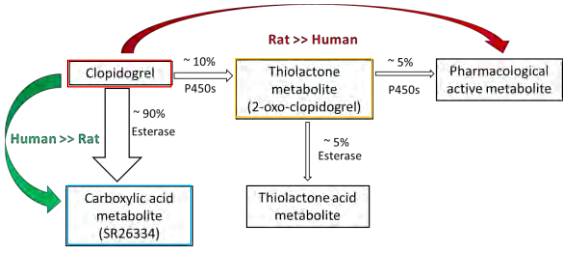
MetID profiles in Human HEPATOPAC

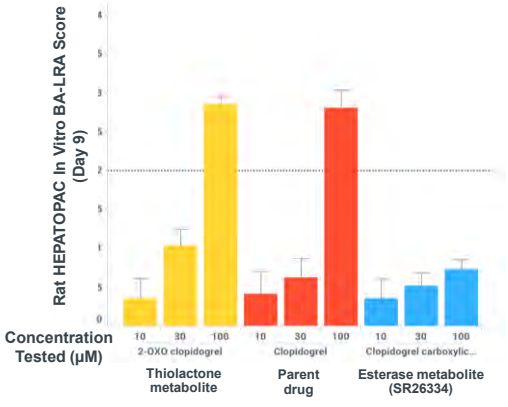


MetID profiles in Rat HEPATOPAC



Species Differences in Clopidogrel-induced HEPATOPAC BA-LRA Responses Are Likely Driven by Differential Metabolism





Summary

- A resource-sparing and higher throughput in vitro BA-LRA was developed to help identify new chemical entities with lower reactive metabolite-forming potential and associated DILI risk.
- Using 93 DILI positive and negative drugs, the rat HEPATOPAC in vitro BA-LRA-based model demonstrated greater than 80% sensitivity and specificity in detecting hepatotoxicants
- Using human HEPATOPAC from a single donor, the in vitro BA-LRA model yielded 68% sensitivity and 86% specificity in detecting DILI positive drugs.
- Routine use of the rat model has been adopted with deployment of the human model as warranted on a case-by-case basis.
- This in vitro transcriptomic signature-based strategy can be used early in drug discovery to de-risk DILI potential from chemically reactive metabolites by guiding structure activity relationship hypotheses and candidate selection.

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Additional details
https://academic.oup.com/toxsci/article/177/1/121/5860031

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Acknowledgements

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Discovery pGx

Keith Tanis, Alexei Podtelezhnikov

Clinical Pathology

PPDM

Ian Knemeyer, Jackie Shang, Qing Chen

BioIVT

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APPLICATION OF A RAT LIVER DRUG BIOACTIVATION TRANSCRIPTIONAL RESPONSE ASSAY EARLY IN DRUG DEVELOPMENT THAT INFORMS CHEMICALLY REACTIVE METABOLITE FORMATION AND POTENTIAL FOR DRUG-INDUCED LIVER INJURY

DOI: 10.1093/TOXSCI/KFAA088

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James Monroe

ACS/AAPS Webinar

November 19, 2020

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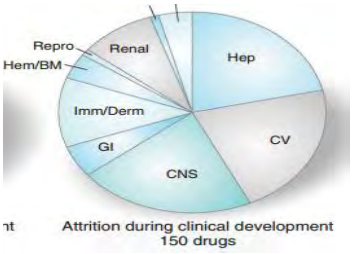
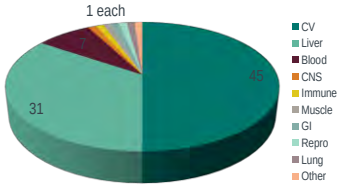
Heart and Liver are Dominant Organs Where Toxicity Results in Development Attritions, &/or Market Withdrawals



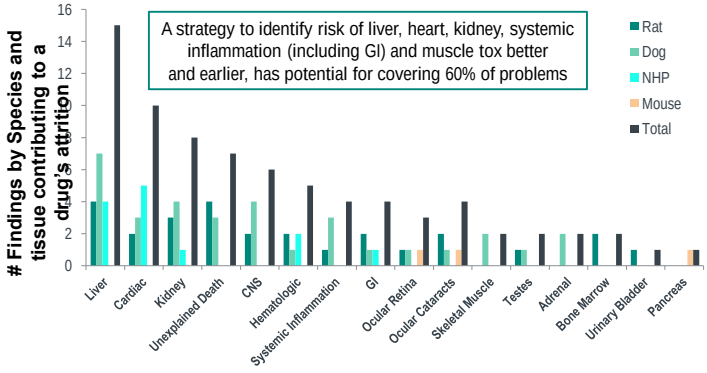
Hornberg, et al. (2014) Drug Disc. Today 19, 1131-1136

Target Organ Contributions to drug withdrawals 1975-2007



Stevens, JL and Baker TK, (2009) Drug Disc. Today 14, 162-166

Analysis of the Target Organ Toxicities Underlying Merck Attritions 2000-2014



And importantly ~45% of human hepatotoxicity is NOT seen in animal studies

(Olson H, et al (2000) Regul Toxicol Pharmacol 32, 56-67)

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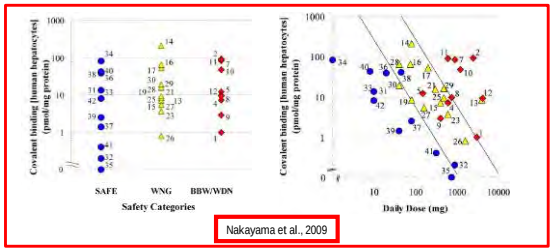
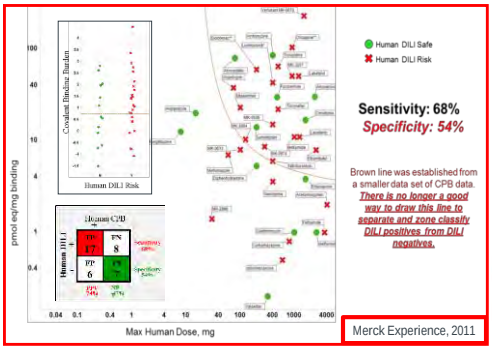
Bioactivation to Reactive Intermediates is Frequently Associated with Molecules Causing Clinical DILI

- Published literature indicates LIVER MICROSOME based covalent binding is poorly correlated to organ tox, hypersensitivity or idiosyncratic AEs
  Bauman, J.N., *et al.* (2009) *CRT* 22, 332-340,
  Obach, R.S. et al., (2008) *CRT* 21, 1814-1822
  Usui, T. et al., (2009) *DMD* 37, 2383-2392
- Radiolabeled drug and microsome based covalent binding studies at Merck were eliminated in 2009
- Covalent binding data in HEPATOCYTES together with the daily dose claims better correlation to liver safety (Nakayama, S et al., (2009) DMD.37:1970-7)
- Merck experience with 38 additional ^{14}C-labeled compounds in HUMAN HEPATOCYTES showed poor test performance
- Reduction of the *body burden* of reactive intermediate formation is still considered advantageous.



Nakayama et al., 2009



Merck Experience, 2011

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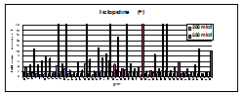
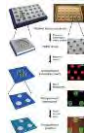
An Assortment of Tools Is Needed to Address Multiple Mechanisms of DILI

(1) Response to reactive metabolite formation:

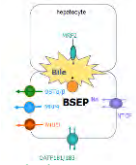
In vivo rat
Liver Response Assay
from rat SLO study



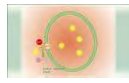
In vitro MPCC **Hep's**
Liver Response Assay



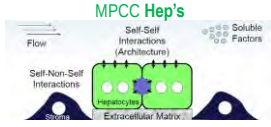
(2) Disruption of bile acid homeostasis:



Vesicular transport

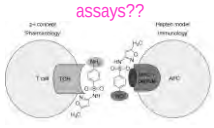


MPCC **Hep's**

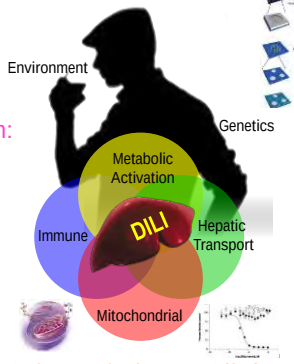


(4) Acquired and innate immune activation:

HLA matched APC-T cell assays??



Genetically engineered humanized mice??



Seahorse Technology, MPCC **Hep's**
HepG2 Glucose/Galactose Media Shift

(3) Mitochondrial toxicity:

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Rat Safety Lead Optimization (SLO) Study Allows for Early Derisking of Toxicities in 4 Organs Based on Transcriptomics Response

- SLO study is conducted very early in lead-optimization to de-risk new structural motifs or later to help select a lead compound from a series of potential candidates to move into the development

5-day SLO Study

- 2 dose levels
  - 30 mg/kg
  - 600-750 mg/kg
- In-life endpoints
  - Toxicokinetics
  - Physical signs
  - Hematology
  - Coagulation
  - Lipid assessments
  - Others as needed

Collect Tissues

Liver

Heart

Kidney

Skeletal Muscle

Isolate RNA & Analyze Gene Sets

- Tox gene sets each tissue
- Liver gene sets:
  - ADME (AhR, CAR, PXR, etc.)
  - AGP, A2M, etc.

➢ Is there a Liver Transcriptional Response (LRA) to the formation of reactive metabolites that inform on human DILI?

Interpret Results

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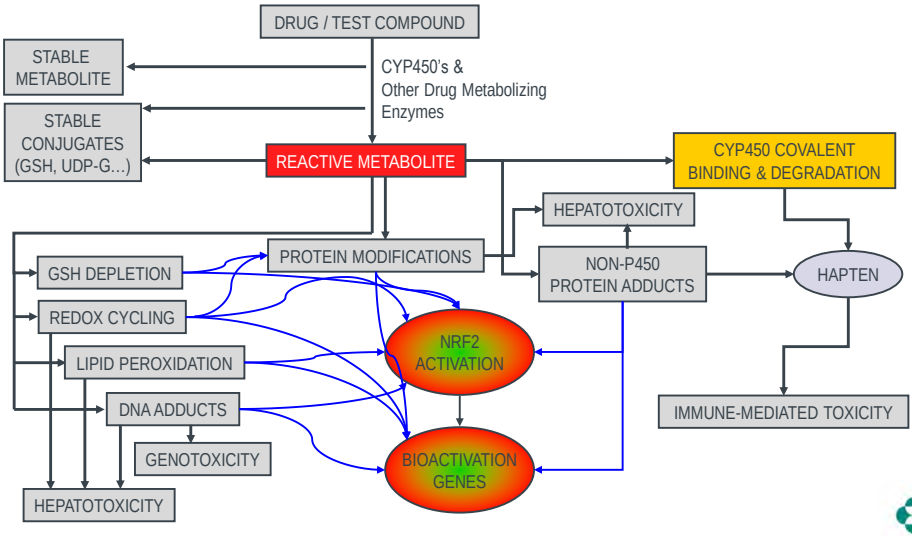
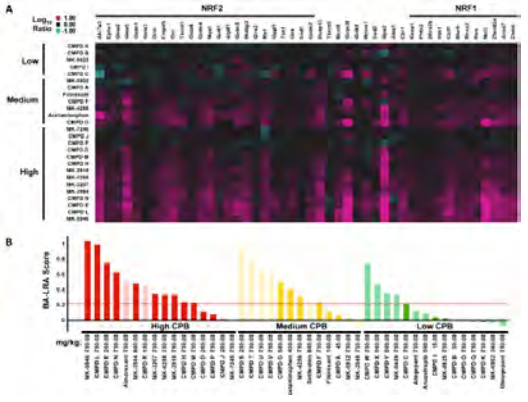
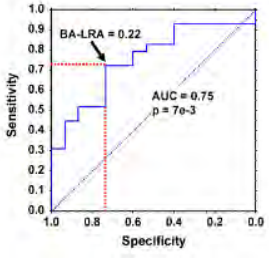
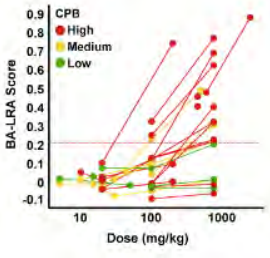
The Biological Response to Reactive Metabolites Is Complex



Development & Qualification of the Liver Response Assay (LRA)

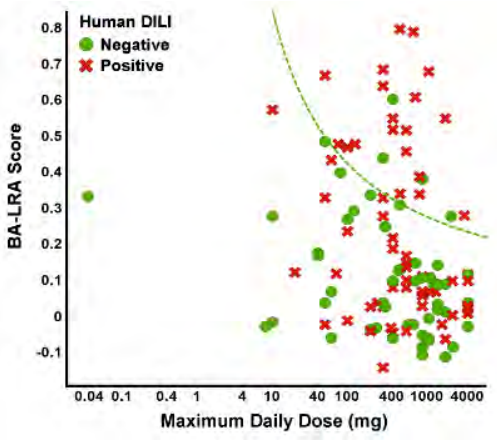


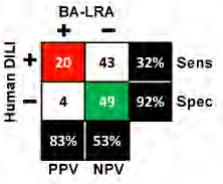




- Internal MRL profiling data anchored in covalent binding endpoints were combined with large external DILI transcriptomics databases (NiBio, ICONIX) to identify a signature.
- LRA score defined as average of fold-change across the genes
- Started to optimize the rat study design: doses < 300 mkd were considered inadequate test
- LRA signature and performance was established using training set of 40 DILI +/- compounds, and tested further with a larger test set of 90 more

Correlation of Rat Liver BA-LRA Score with Expanded Test Set for Human DILI Risk after Correction for Human Dose





- ✓ ~130 Rat SLO studies with doses 400-750 mg/kg/day
- ✓ Consideration of clinical dose for DILI +/- cmpds improved assay performance for determining risk of clinical DILI
- ✓ Low False Positive Rate
- ✓ Inflammatory response suppresses LRA scores
- ✓ False Negatives?
  - alternative mechanism
  - alterative metabolism
  - poor exposure in rat liver?

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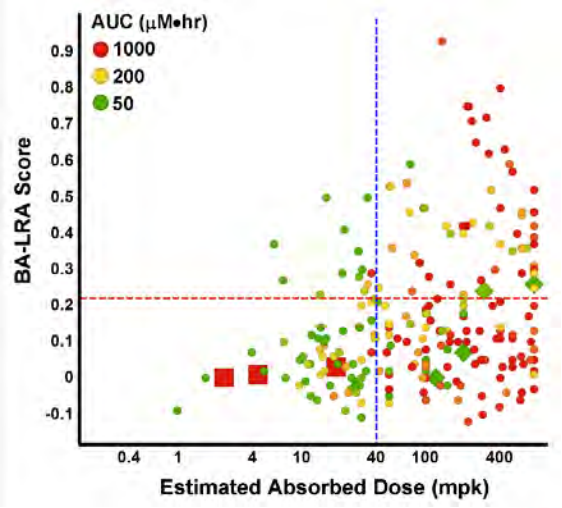
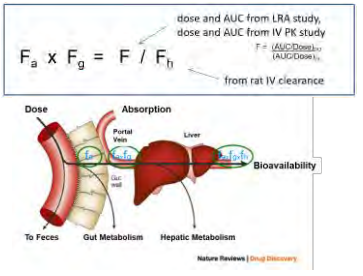
Empirical Approach to Assess Liver Exposure: "Hepatic Absorbed Dose" (HAD)



the fraction of dose delivered to the liver
= dose x (F_a x F_g)



Assumptions of the approach:
- Cl is linear from low dose IV study to high oral dose in LRA study
- Cl is linear after multiple dosing

Refinement in progress:
- Dose response studies with DILI +/- compounds

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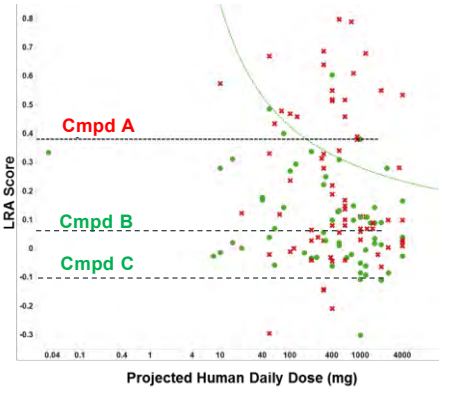
Case 1: A Recent Internal Merck Example

Clinical Study Findings:

Frequency of ALT >3X ULN in repeat-dose clinical studies
- Overall: 2.8% (9/319):
- ≤100 mg (daily dose) 1.0% (2/197)
- >100 mg 5.7% (7/122)
- >500 mg x 2 weeks 42% (5/12)
- 3 SAEs with >20X ULN ALT, 1 symptomatic w/ Hy's Law

Generally delayed onset (as long as 2-3 months)
Slow resolution (12 weeks or longer)



Positive LRA signal for Cmpd A predicts low risk at projected clinical doses of <100 mg, but higher risk at daily doses > 300 mg.

- ✓ Reduce animal use, lower resource costs and cycle time than in vivo studies → less API required
- ✓ Option when rat tolerability poor
- ✓ Option when formulation poor
- ✓ Inflammatory responses suppress LRA

→ In vitro assay (?)

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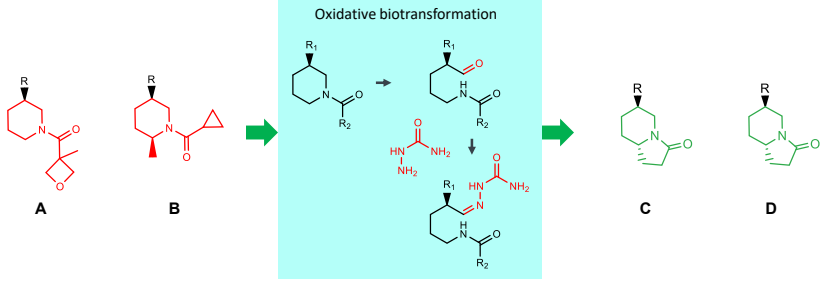
Case 2: LRA & Metabolite Identification Studies To Address SAR of Potential DILI Risk



Integration of BA-LRA data with metabolite identification tools such as exogenous trapping or protein adduct analysis allows a view into reactive metabolite hotspots that could be leveraged to help chemists make improved molecules

	A		B		C		D	
Rat in vivo LRA	Positive		Positive		Negative		Negative	
	human	rat	human	rat	human	rat	human	rat
% Semicarbazide	62%	66%	56%	32%	0%	0%	0%	0%
% Glutathione	2%	6%	1.0%	1.4%	0.6%	3.7%	0.3%	0.8%
% Cyanide	0%	0%	0%	0%	0%	0%	0%	0%

% pathway X = AUC of metabolite X/Total AUC of all metabolites, assumes that all metabolites have equal ionization efficiency

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Summary and Conclusions

- DILI is a major contributor to attrition in development and to market withdrawal; risk should be addressed as early as possible
- SLO studies include assessment of tissue toxicity endpoints as well as provide LRA findings informing potential for reactive metabolite formation
- Our goal mechanism-based strategy for improving prediction of unsafe doses for drugs associated with high DILI potential resulting from: 1) reactive metabolite formation; 2) alteration of bile acid homeostasis; 3) mitochondrial toxicity; 4) innate and/or acquired immune system activation
- Several new in vivo and in vitro liver models, novel endpoints, and biomarkers are being benchmarked for these DILI mechanisms (e.g., drug metabolism, transport, gene expression)

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- Merck Toxicological Sciences, Clinical Pathology, & Pathology Groups

THANK YOU

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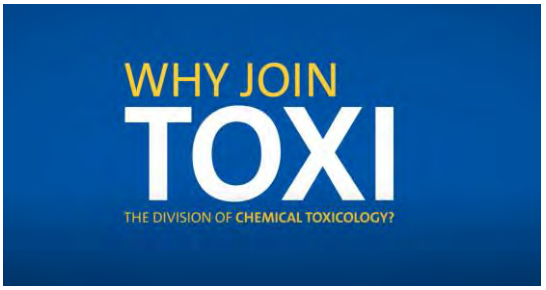

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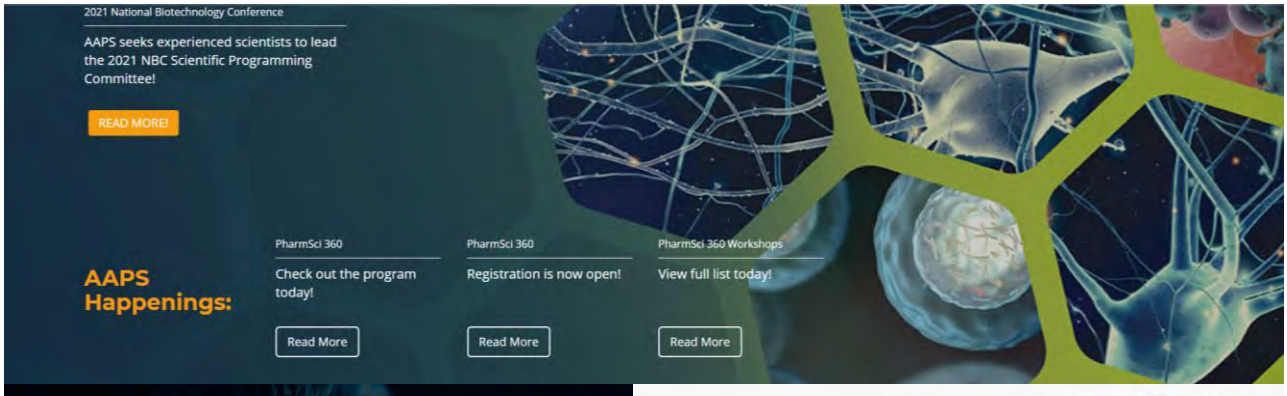

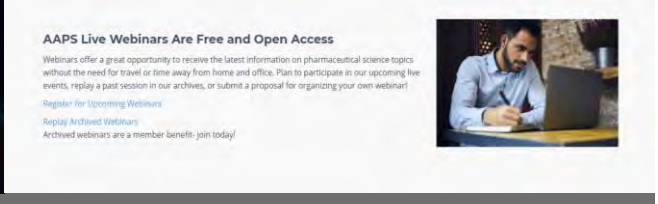

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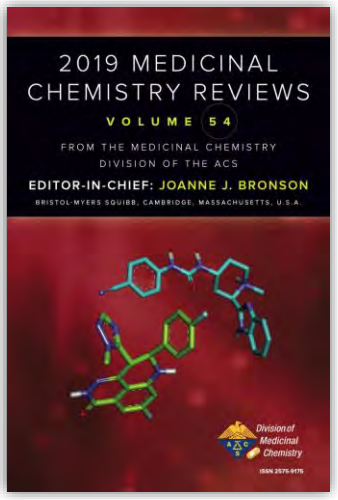

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