

# **Drug induced Liver Injury (DILI): What is the Problem?**



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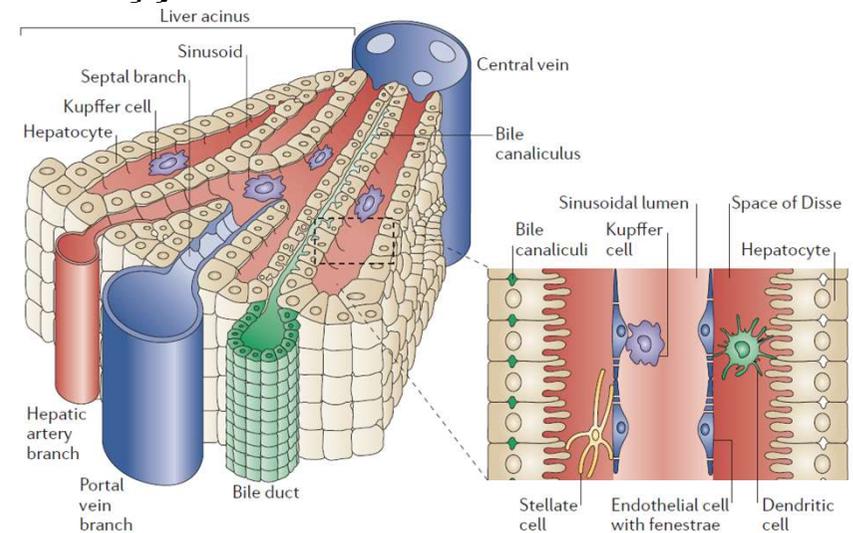
# Presentation outline

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- Liver structure and functions
- Causes of liver injury
- Drug Induced Liver Injury (DILI)
  - Patterns
  - Concordance, animals vs. humans
  - Consequences and impact
  - Assessment (histopathology and clinical chemistry)
  - Tolerance and adaptation
  - Aplaviroc, FDA Guidance, Ximelagatran
  - Predictive screening rationale and challenge
- Summary

# Liver structure and functions

- A complex organ, numerous cell types
- Receives blood from the heart (hepatic artery) and GI tract (hepatic portal vein)
- Key functional unit is the acinus
- Plays essential roles in:
  - Intermediary metabolism - lipid, carbohydrate, protein
  - Whole body homeostasis - blood clotting, albumin synthesis, endocrine & exocrine signalling
  - Digestion - bile formation and release
  - Detoxification - xenobiotic metabolising enzymes, bile
  - Host defence - innate and adaptive immunity



# Liver injury

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- Caused by:
  - Infectious agents (Hep A, B, C, etc.)
  - Foreign compounds (alcohol, **pharmaceuticals**, other chemicals)
  - Vascular changes (portal hypertension)
  - Unknown triggers (“autoimmune”)
- Loss of liver function = liver injury
  - Severe = acute liver failure (high fatality)
  - Less severe = liver disease (hepatocellular, cholestatic or mixed)
- Liver has substantial “functional reserve” and excellent repair capacity
  - Mild liver injury often does not result in impaired liver function
- Drug Induced Liver Injury = DILI

# Two human DILI patterns

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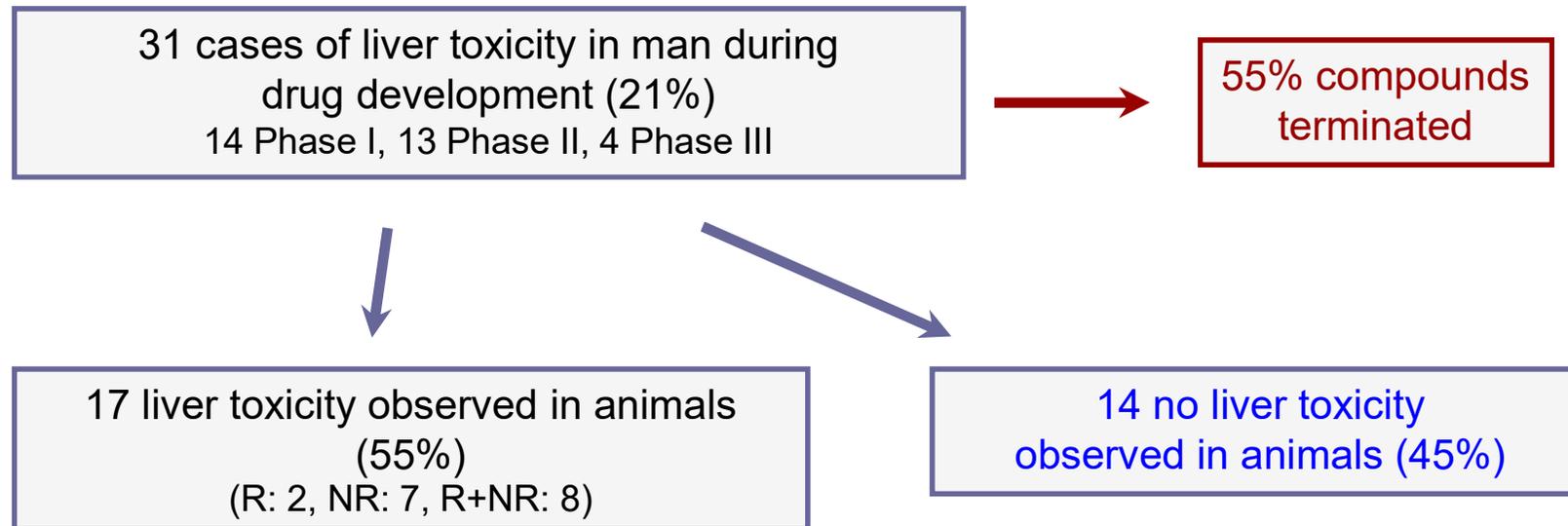
## □ Type A

- Reproducible and dose dependent
- Usually evident from animal safety studies
- Causes:
  - Candidate drug attrition in animal safety studies
  - Attrition in early clinical trials, or dose-capped human exposure

## □ Type B

- Infrequent, not overtly dose dependent (“idiosyncratic”)
- Not evident from animal safety studies
- Causes:
  - Drug attrition in late clinical trials
  - Failed registration
  - Adverse labelling (boxed warnings etc.)
  - Withdrawal of licensed drugs

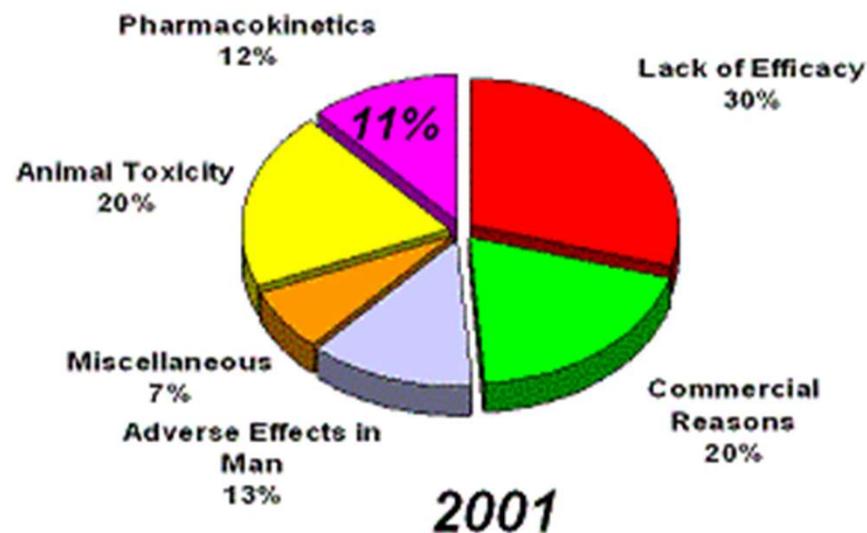
# Poor DILI concordance between preclinical species and humans



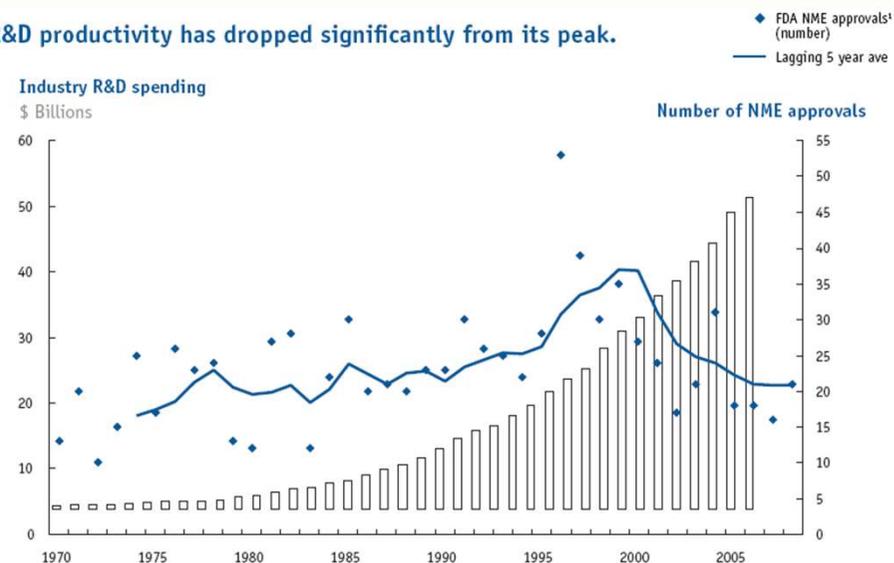
- ❑ DILI was an important adverse event during human drug development and a leading cause of termination
- ❑ Only 55% of compounds that caused DILI in man exhibited evidence of DILI in preclinical species
- ❑ Better concordance in nonrodent (dog) than in rodent (rat)

*Olson et al. 2000, Regul Toxicol Pharmacol 32(1):56-67.*

# Failed drug development



R&D productivity has dropped significantly from its peak.



1 Lagging 5 year average, includes NCEs and BLAs. BLAs included 1986 onward; biologics approvals in prior years assumed negligible.

Source: NME data for 1966 - 1971 from Peltzman, S. (1973) J. of Political Economy 81, no. 5: 1049-91. NME data for 1972-1979 as reported in Hutt, P.B. (1982) Health Affairs 1(2) 624. NME data for 1980-2007 from Parexel's Pharma R&D Statistical Sourcebook. 2009/2010, FDA, and PhRMA. Industry R&D spend data from PhRMA Annual Membership Survey, 2008 and Parexel 2009/2010.

- The leading causes of failed drug development are lack of efficacy and toxicity
- Hence increasing cost and reducing productivity of drug development
- Human Adverse Drug Reactions (ADRs) that occur late in development, or after licensing, are a particular problem

*Kola & Landis (2004) Nature Reviews Drug Discovery 3:711-716*

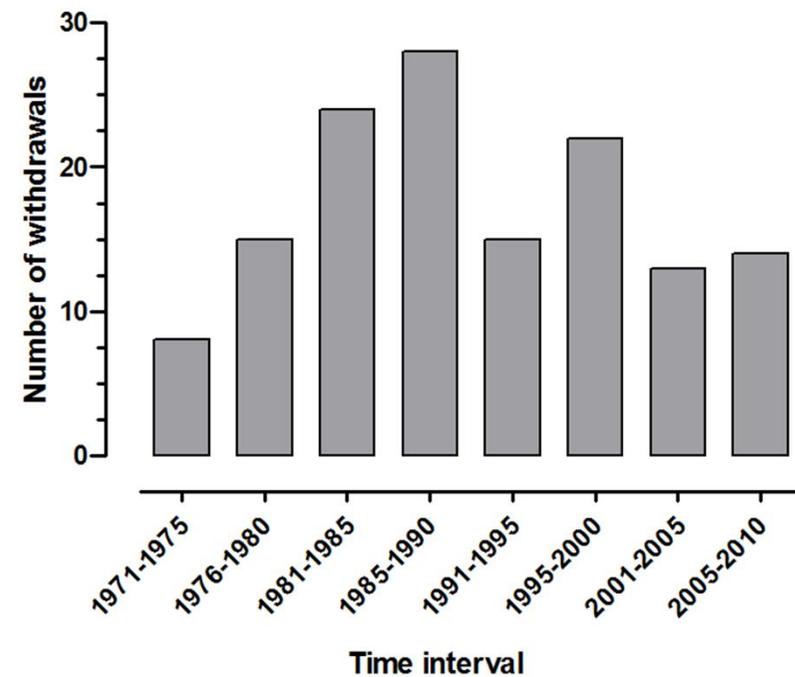
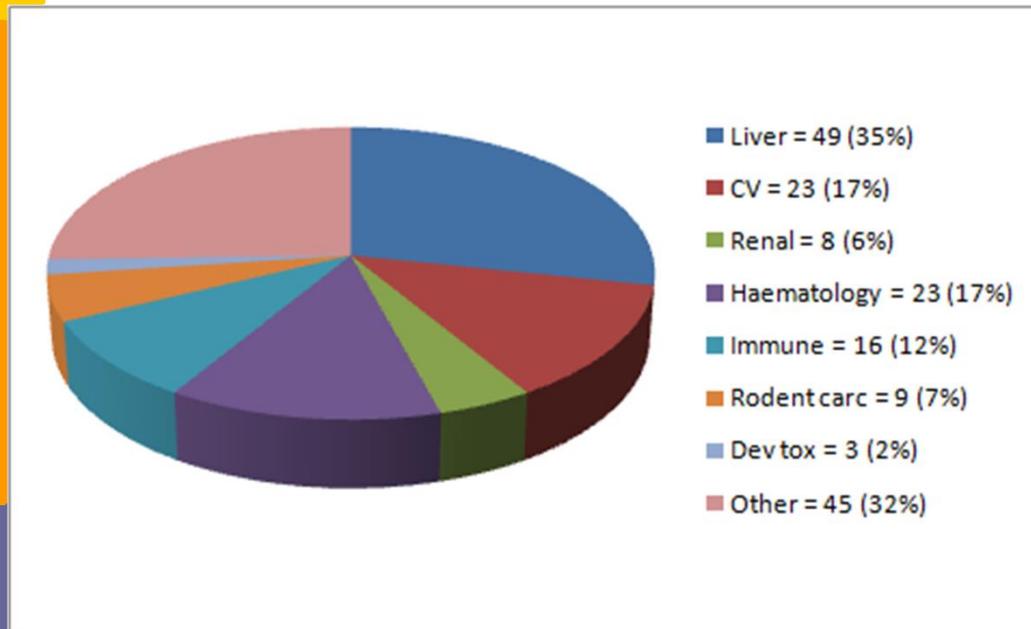
# DILI impact

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- More than 1000 drugs listed as possibly hepatotoxic
- An important cause of human illness
  - 10% of apparent “hepatitis cases” (>40% over 50 years of age)
  - Major cause of acute liver failure in U.S.
    - Ostapowicz, *et al.*, Ann Intern Med 2002;137:947
    - W Lee, AASLD DILI Conference, 2005
  - Frequent cause of illness in hospitalized patients
    - Clinically apparent DILI ~14 cases per 100,00 inhabitants
    - Sgro, *et al.* Hepatology 2002;36:451
- Most important single cause of failed drug licensing, limitations on use, and drug withdrawal post marketing

# Drug withdrawals due to toxicity

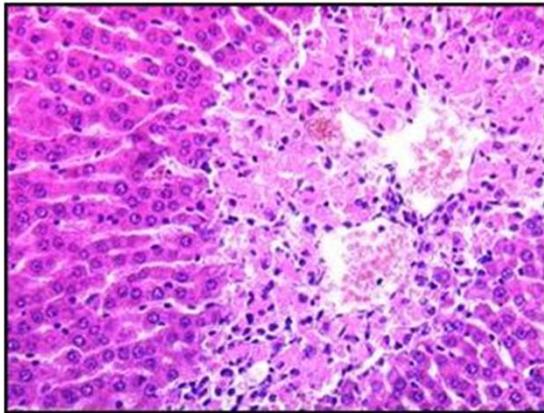
➤ DILI was the most frequent cause, 1970 - 2010



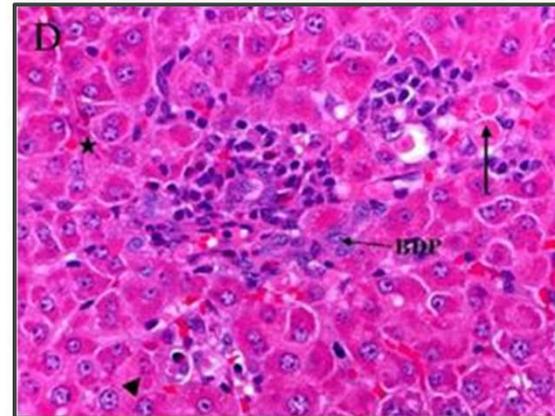
# DILI assessment

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## □ Tissue histopathology



**Paracetamol in the mouse**  
Centrilobular hepatocyte necrosis



**Methapyrilene in the rat**  
Bile duct proliferation (BDP), apoptotic bodies,  
necrotic cell, inflammatory cell infiltration

## □ Serum clinical chemistry

- “Leakage enzymes”, released primarily from damaged hepatocytes
  - ALT, AST: cytosolic
  - AP: canalicular plasma membrane, indicating biliary injury
- Bilirubin, cleared by healthy hepatocytes into bile

# Many different DILI pathologies

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## □ **Hepatocellular injury**

- Hypertrophy (e.g. P450 enzyme induction – an adaptive response)
- **Necrosis**
  - Classical dose-dependent (e.g. *paracetamol*)
  - Idiosyncratic (**Metabolic** e.g. *cocaine* vs. **Immune** e.g. *halothane*)
- Steatosis (microvesicular, macrovesicular)
- Phospholipidosis

## □ Cholestasis (e.g. *estrogens, chlorpromazine*)

## □ **Mixed hepatitis/cholestasis** (e.g. *sulindac*)

- Fibrosis (e.g. *chlorpromazine*)
- Vascular lesions (e.g. *contraceptive steroids*)
- Tumours (e.g. *anabolic steroids*)
- Etc.....

# Serum clinical chemistry

	Control		100 mg/kg		250 mg/kg	
	Mean	SD	Mean	SD	Mean	SD
Glucose	16.95	1.68	17.13	3.60	13.53	2.84
Urea	5.35	0.35	5.43	0.86	6.18	1.14
Albumin	32.75	0.50	33.75	0.50	30.50	1.29
Alk Phos	168.00	25.44	191.50	33.31	209.00	43.54
ALT	60.75	13.00	58.00	12.44	1700.50	2180.50
AST	61.75	6.80	61.25	4.50	2071.50	1956.61
Bile acids	27.25	4.35	30.25	3.30	183.50	172.53
Na	146.00	0.82	145.00	1.15	142.00	1.83
K	4.13	0.40	4.15	0.37	6.40	1.50
Cholesterol	1.58	0.10	1.30	0.08	1.73	0.43
Tryglyceride	1.69	0.50	0.97	0.17	0.99	0.31
GldH	4.50	0.58	5.75	0.96	246.50	187.31
Total Bilirubin	0.25	0.50	1.00	0.00	1.25	0.50

*Cell damage*

*Cell damage*

*Impaired function*

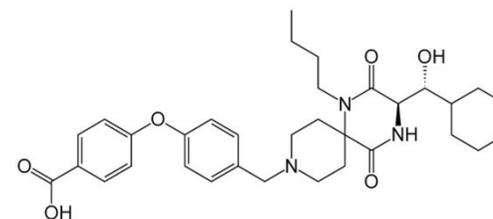
*Cell damage*

*Impaired function*

Elevated transaminases, bilirubin and bile acids in rats doses daily for 6 days with a hepatotoxic compound

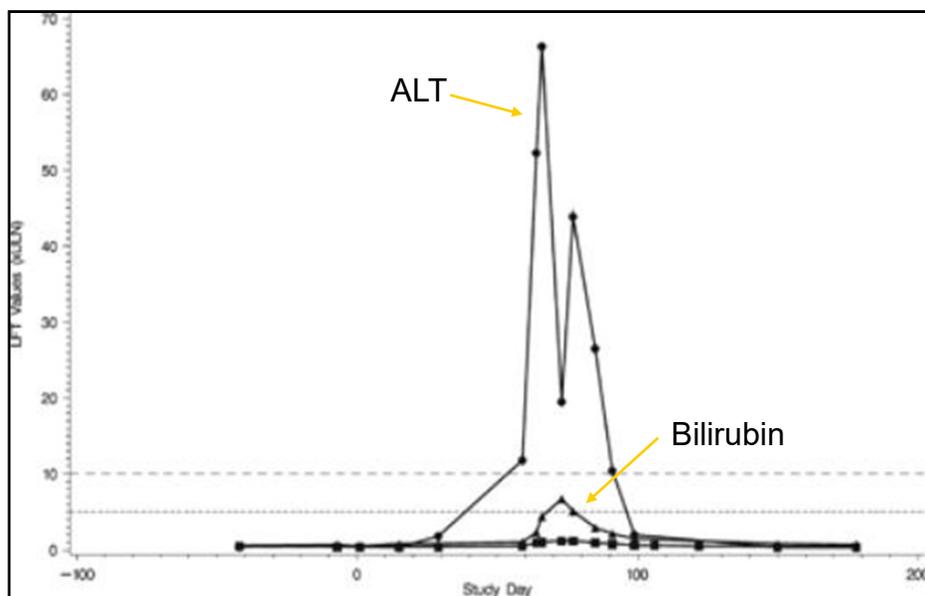
*Data provided by clinical pathology, AstraZeneca*

# Aplaviroc

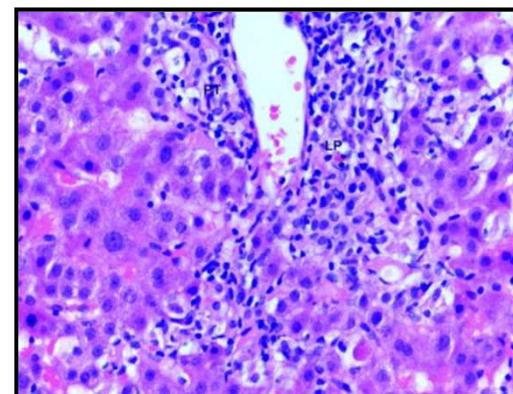


- Antiretroviral CCR5 antagonists
- Development terminated due to infrequent liver toxicity observed in clinical phase 2

Serum liver marker elevations



Liver portal tract inflammation

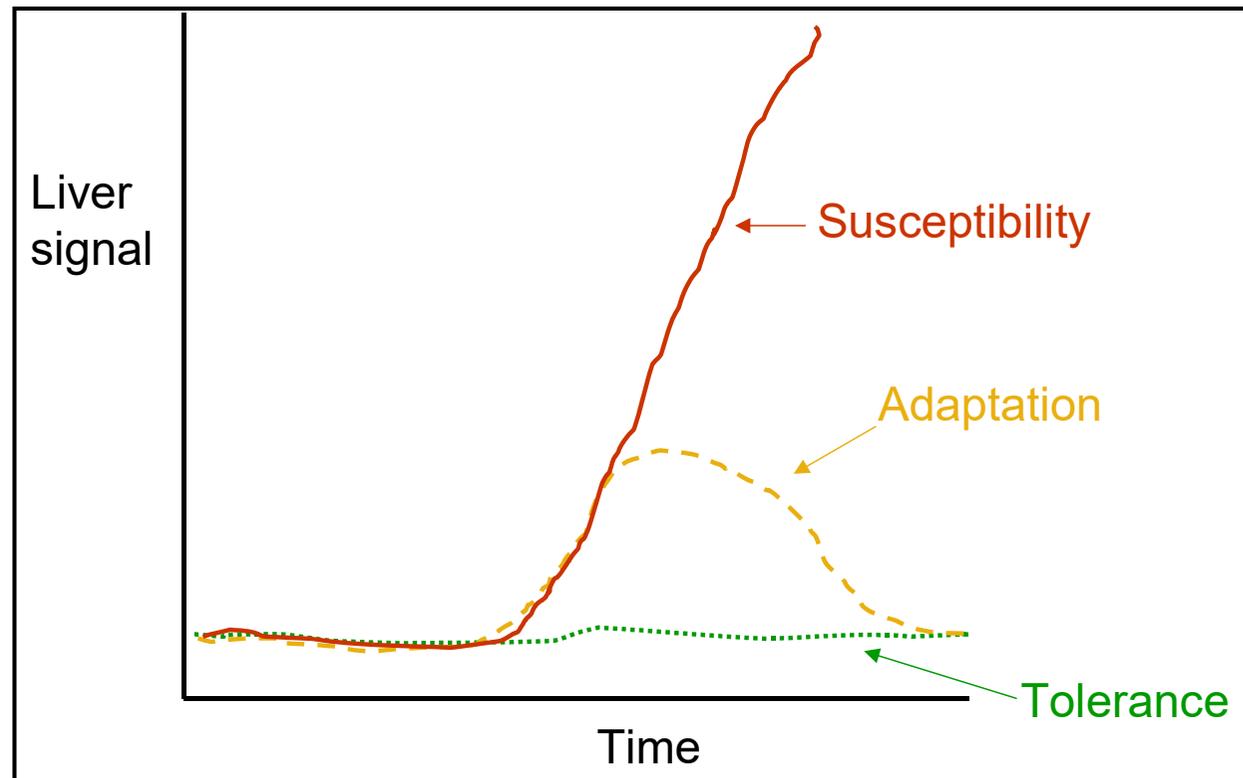


*Nichols et al., Antimicrob. Agents. Chemother. 52: 858–865, 2008*

# DILI tolerance and adaptation

When treated with drugs that cause human idiosyncratic DILI:

- ❑ Most individuals “tolerate” the drug (typically  $\geq 90\%$ )
- ❑ A small proportion sustain initial injury and then adapt
- ❑ Relatively few fail to adapt (typically  $\leq 1\%$ ) – these may progress to acute liver failure



# FDA Guidance

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- ❑ Pragmatic advice on how best to detect and interpret DILI signals in clinical trials
- ❑ ALT >3 x ULN a possible signal
- ❑ Focus on low frequency “outliers” (eDISH)
- ❑ ALT >3 xULN plus bilirubin >2xULN = a possible index DILI case (“Hy’s Law”)
- ❑ Importance of causality assessment highlighted

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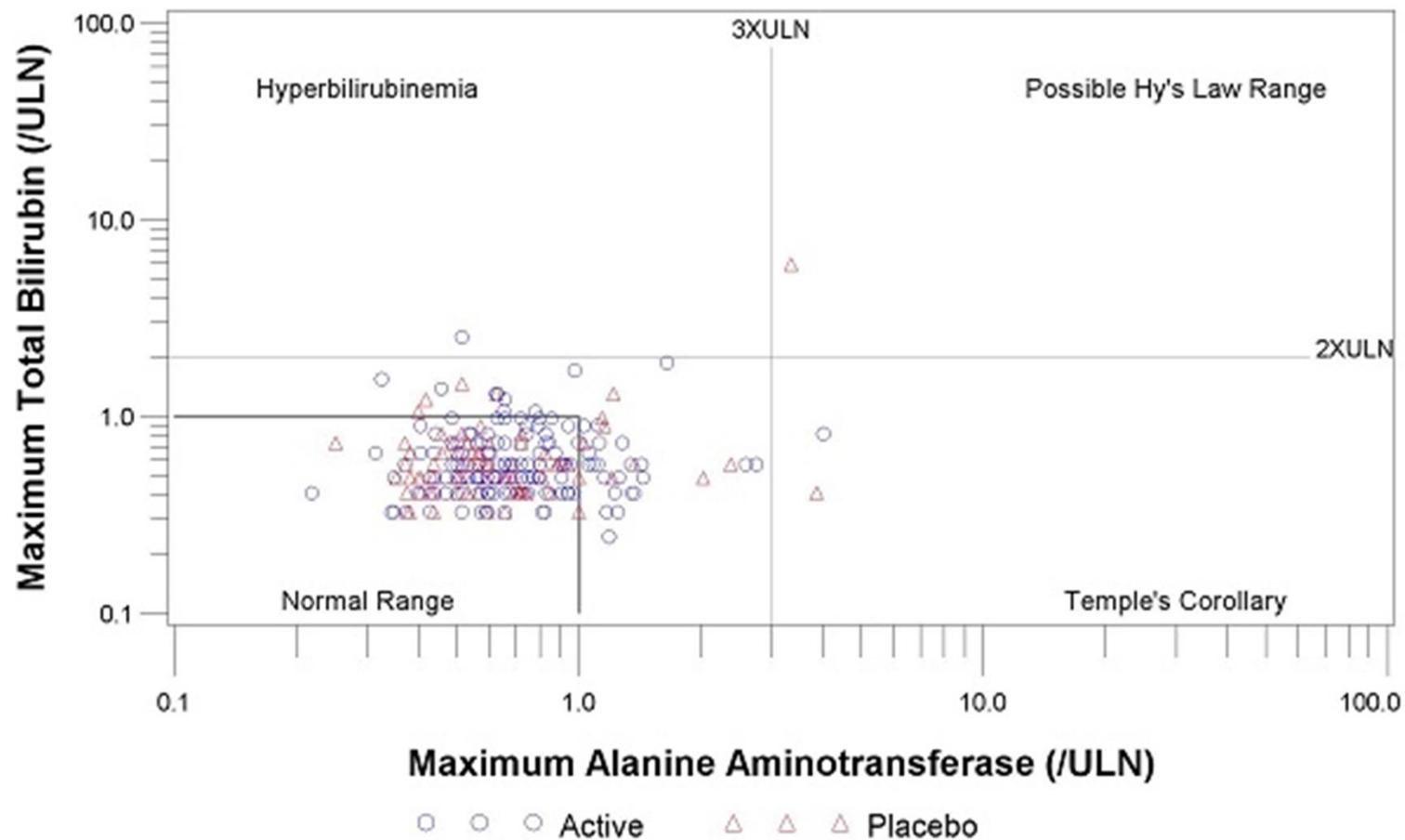
## **Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation**

U.S. Department of Health and Human Services  
Food and Drug Administration

[http://www.fda.gov/downloads/Drugs/.../  
Guidances/UCM174090.pdf](http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf)

# eDISH plot

Maximum Total Bilirubin versus Maximum Alanine Aminotransferase (ALT)



• Maximum values are those maximum values that occur post-baseline (no time constraints and not necessarily concurrent events)

# Ximelagatran

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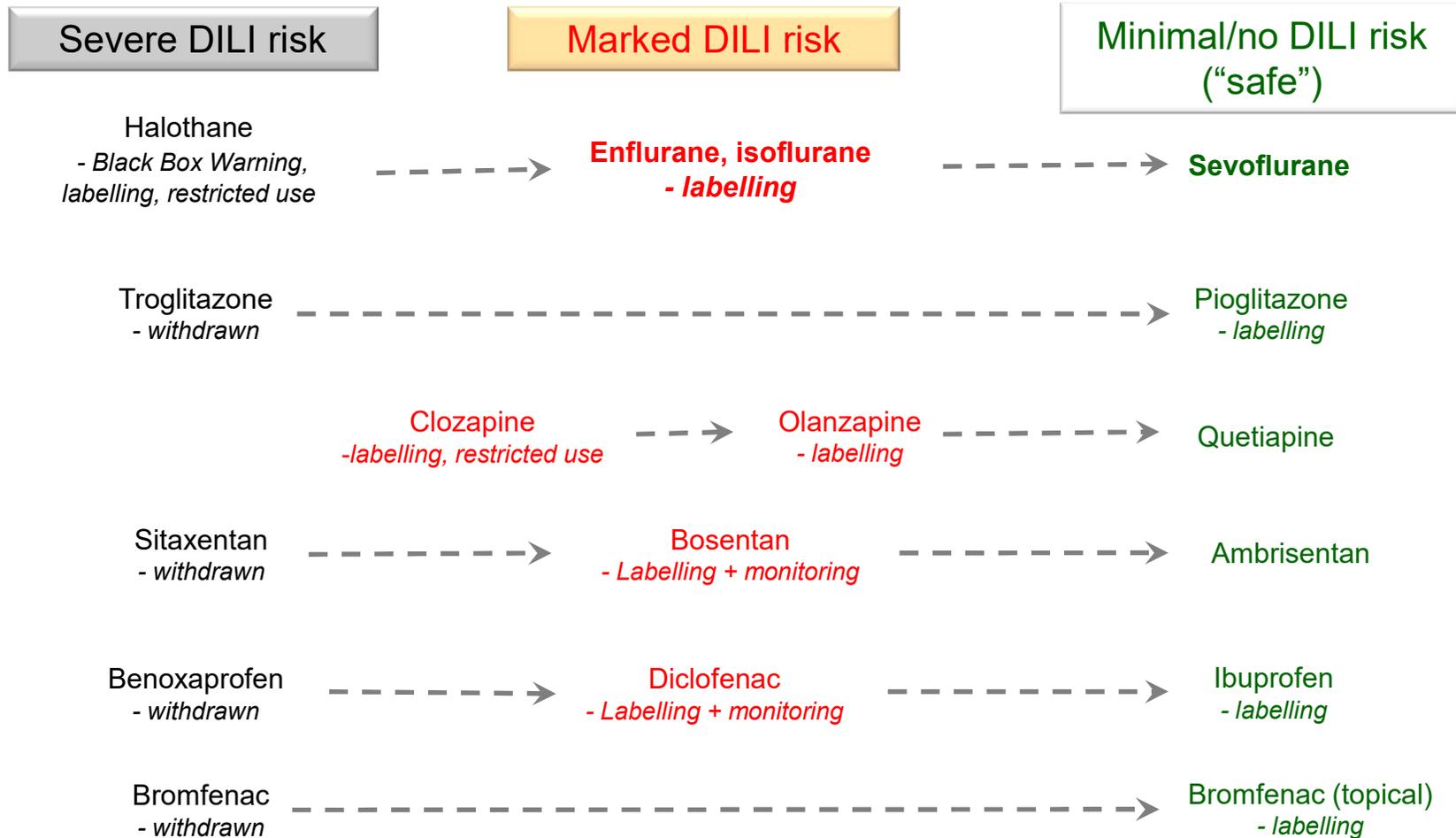
- First in class oral direct thrombin inhibitor, for venous thromboembolism (VTE) prevention and treatment
- No evidence of liver injury:
  - In preclinical safety studies undertaken in rat, dog and cynomolgus monkey
  - In short-term use in humans (7-12 days)
- Elevated serum ALT levels when administered >35 days in humans
  - 7.9% patients affected; 93% between 1-6 months after start of treatment
  - Marked (ALT >3x ULN) but relatively transient ALT elevations
  - In 96% of patients, ALT elevations returned to normal within 6 months whether or not treatment was continued
- Very few symptomatic liver injury cases
- RUCAM: 65% of liver injury cases judged 'possible' or 'probable' causality

*Keisu & Andersson 2010, Handb Exp Pharmacol 196:407-18*

*Lee et al., 2005, Drug Safety 28:351-370*

*Petersen et al. 2003, J Am Coll Cardiol 41:1445-51*

# Unsafe vs. safe drugs



# DILI annotation

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**Chen M, Vijay V, Shi Q, Liu Z, Fang H, Tong W. FDA-approved drug labeling for the study of drug-induced liver injury. Drug Discov Today. 2011 Aug;16(15-16):697-703.**

Drug-induced liver injury (DILI) is a leading cause of drugs failing during clinical trials and being withdrawn from the market. Comparative analysis of drugs based on their DILI potential is an effective approach to discover key DILI mechanisms and risk factors. However, assessing the DILI potential of a drug is a challenge with no existing consensus methods. **We proposed a systematic classification scheme using FDA-approved drug labeling to assess the DILI potential of drugs, which yielded a benchmark dataset with 287 drugs representing a wide range of therapeutic categories and daily dosage amounts.** The method is transparent and reproducible with a potential to serve as a common practice to study the DILI of marketed drugs for supporting drug discovery and biomarker development.

# Managing DILI

## Drug discovery

- Proactive prediction and avoidance during compound selection
- “Picking likely winners”
  - Flagging and deselecting problem compounds when there is chemical choice and the cost of terminating them is low



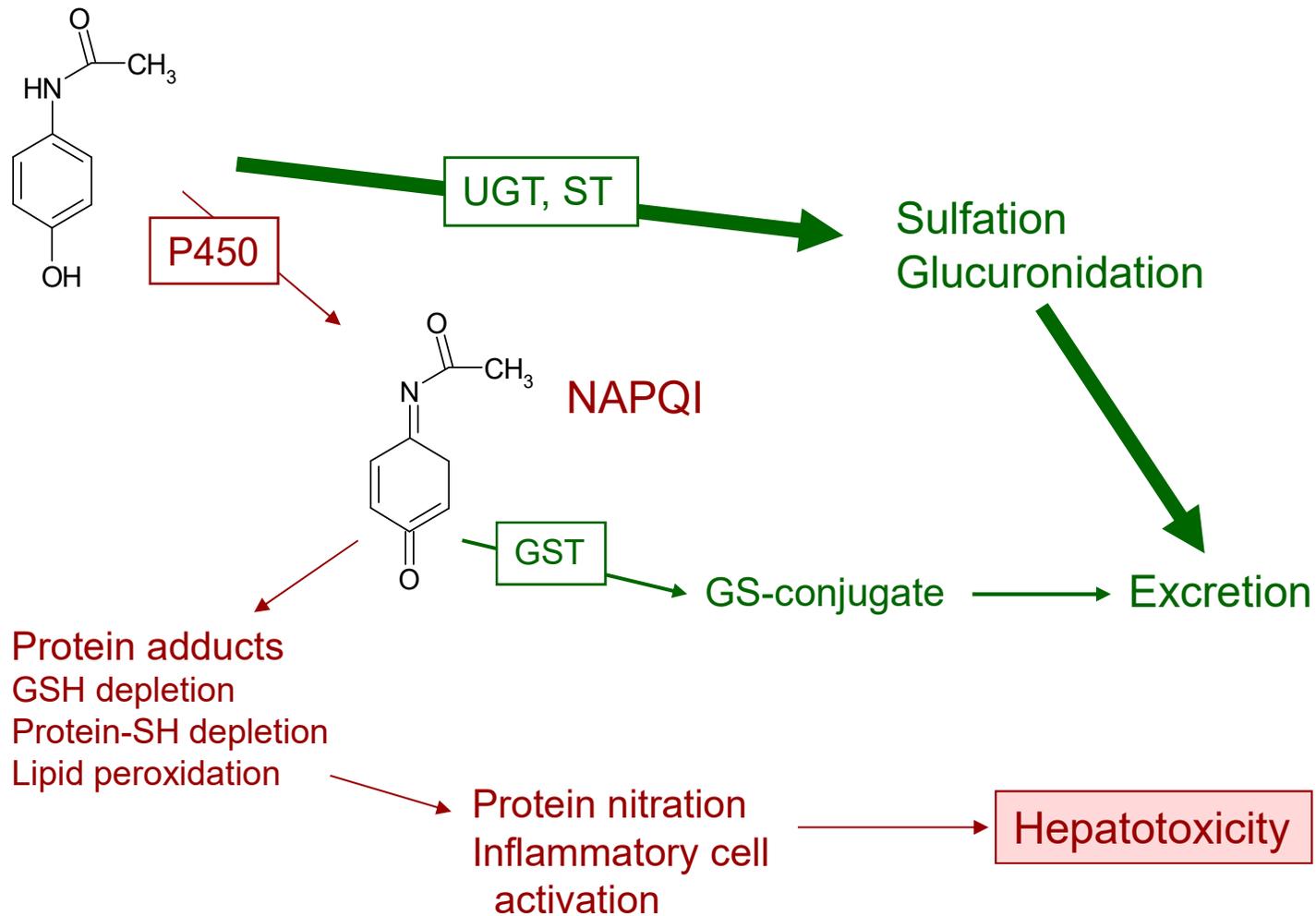
## Drug development

- Monitoring biomarkers of susceptibility or toxicity
- “Personalised healthcare”:
  - Proactive detection of patients at high risk of ADRs
  - Early identification of patients who sustain ADRs, prior to onset of serious illness



**Drugs with good safety profiles have a big competitive advantage**

# Paracetamol (acetaminophen)

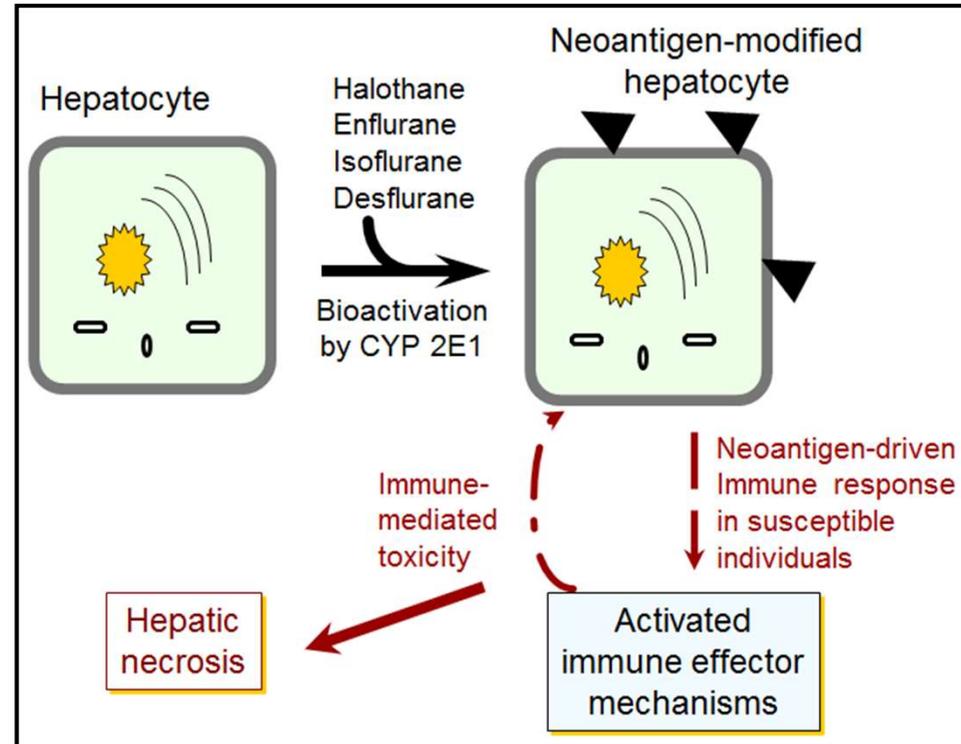
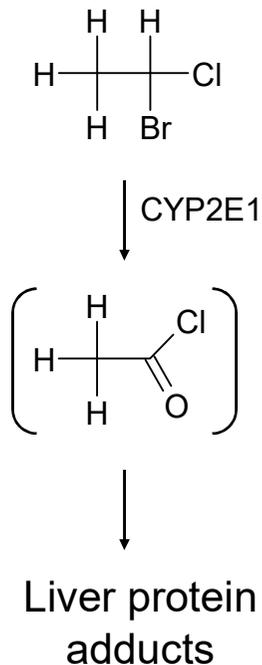


Hinson et al. 2010, *Handb Exp Pharmacol* 196:369-405

# Halothane

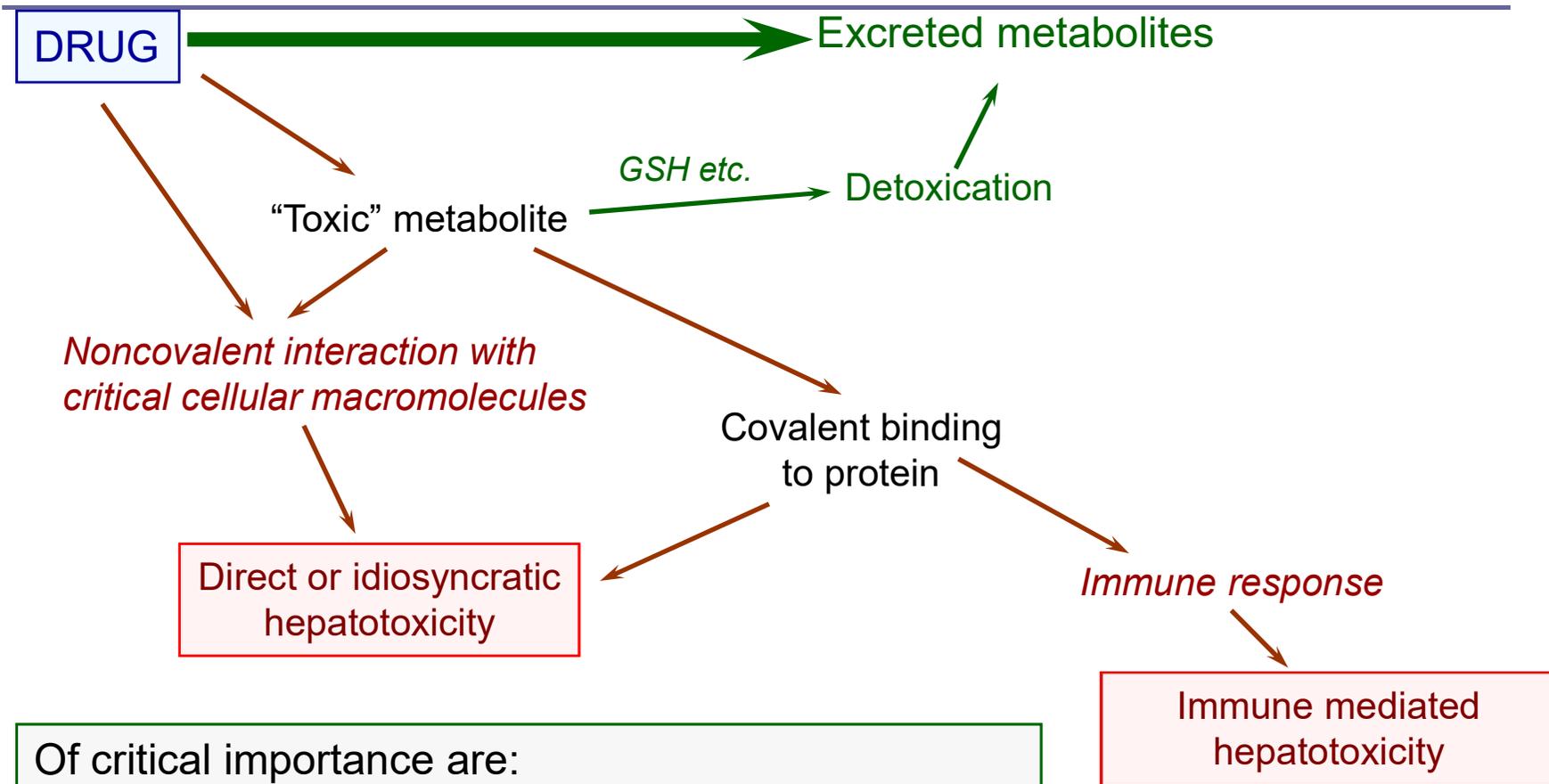
Kenna & Jones 1995, *Anesth Analg.* 81(6 Suppl):S51-66

Halothane etc.



- ❑ Patients with halothane hepatitis have:
  - serum antibodies to TFA-modified liver proteins
  - serum autoantibodies to CYP2E1 and other liver proteins
- ❑ The lower frequencies of DILI caused by other anesthetics correlates with their reduced extents of bioactivation

# DILI initiating mechanisms

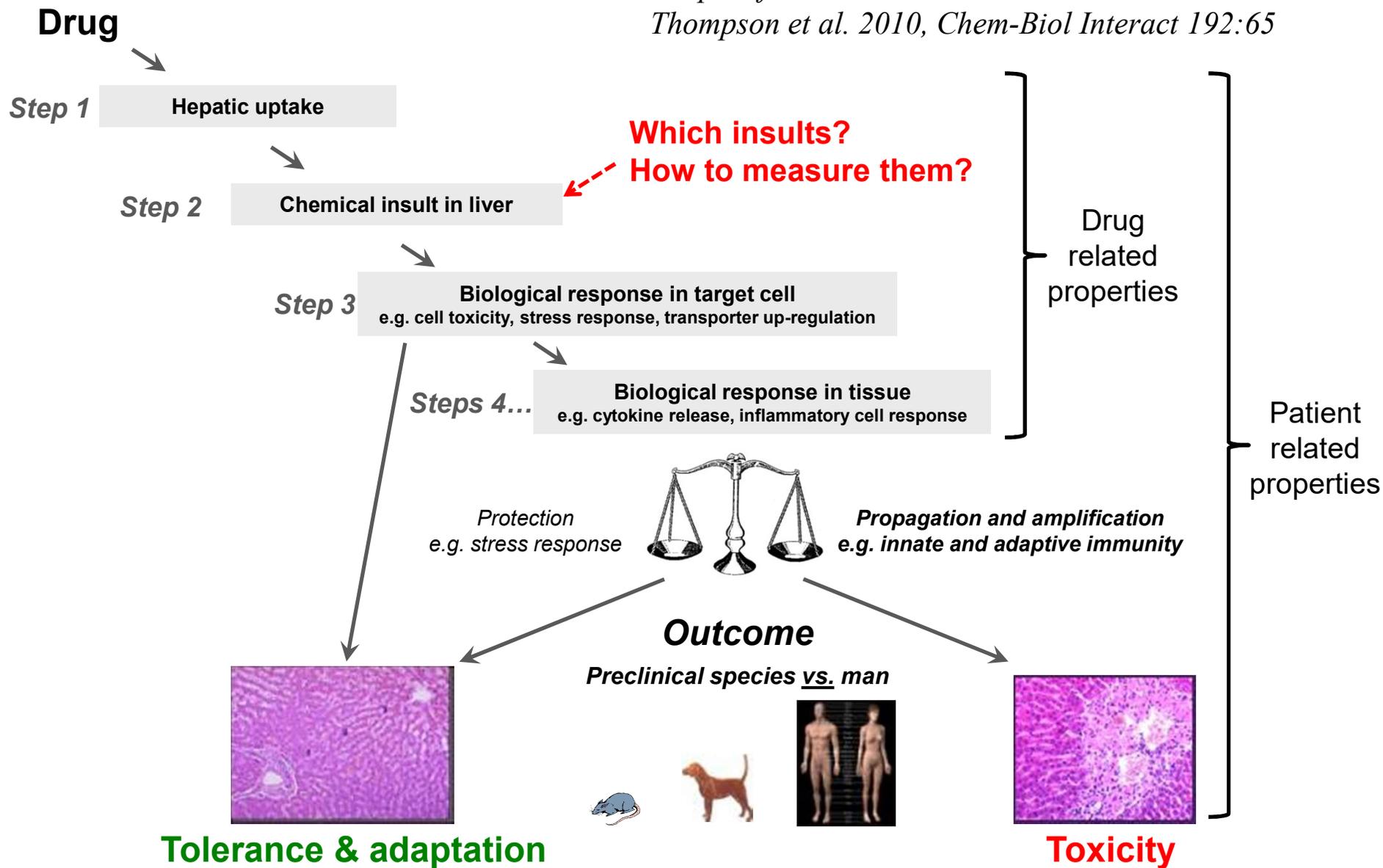


Of critical importance are:

- Metabolism (toxication and detoxication)
- Disposition (transporters!)
- Molecular and cellular events leading to toxicity

# Predictive DILI screening rationale

Adapted from: Ulrich 2007, *Annu Rev Med* 58:17  
Thompson et al. 2010, *Chem-Biol Interact* 192:65

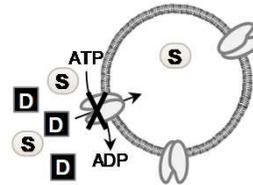


# Many possible *in vitro* tools.....

**Simple**



Cultured liver cell lines

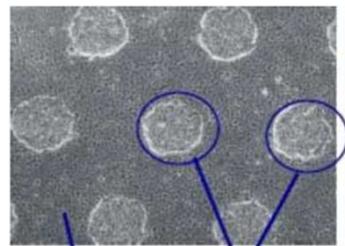


Membrane vesicles

**Low**

**High**

**Intermediate**



Supportive  
Stromal  
Fibroblasts

Micropatterned  
Hepatocytes

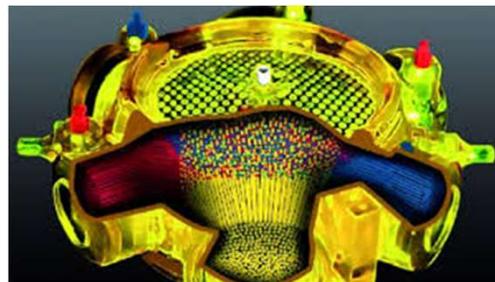
**Complexity**

**Volume**

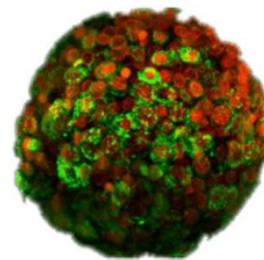
**Cost**

**Turnaround  
time**

**Complex**



Bioreactors



Spheroids

**High**

**Low**

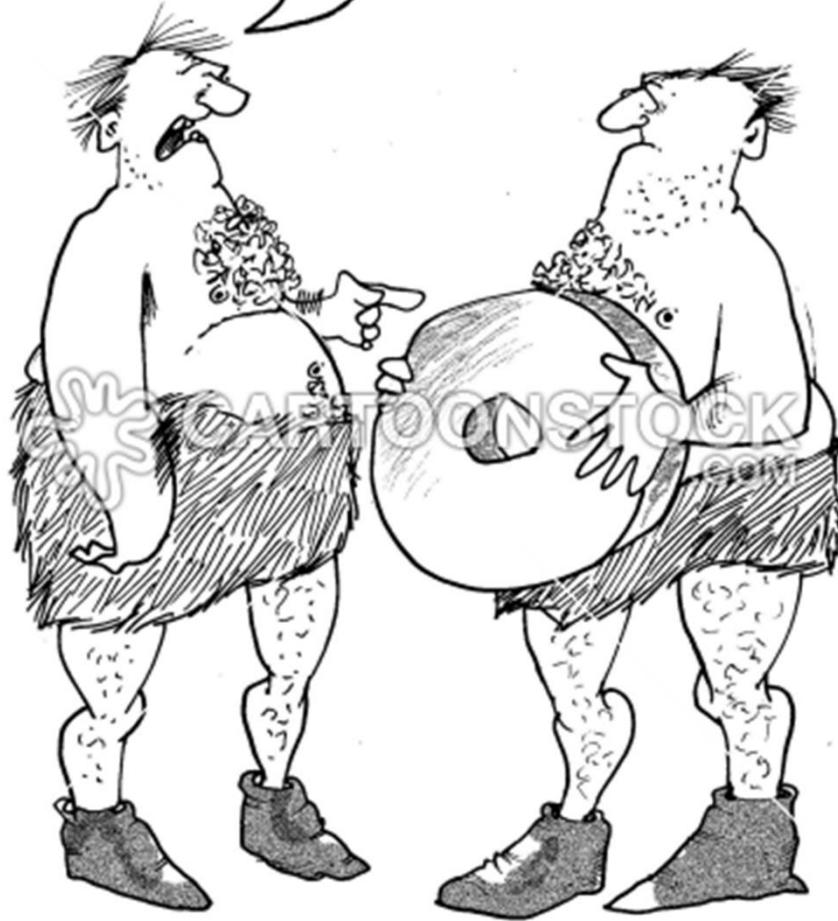
# The Challenge

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- ❑ Which *in vitro* assays and endpoints?
  - DILI mechanistic relevance?
  - Robustness, throughput, turnaround time, cost?
- ❑ How to evaluate and validate them?
- ❑ When to run them?
- ❑ How to interpret the data and use them to take better decisions in drug Discovery?
- ❑ How to use *in vitro* data to enhance preclinical and clinical hazard identification and risk assessment, not hinder it?

➤ *Many divergent views, scientific consensus only now emerging....*

THAT WHEEL THING... WE TRIED IT ONCE  
BEFORE AND IT DIDN'T WORK!



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frdh

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NEANDERTHAL MAN'S LACK OF CURIOSITY  
DOOMED HIM TO EXTINCTION

# Summary so far

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- ❑ Preclinical safety studies in animals are valuable for detection of dose dependent DILI, and protect patients in early clinical trials from significant liver dysfunction.
- ❑ But they cannot detect idiosyncratic DILI.
- ❑ Tools which can detect both idiosyncratic and dose dependent DILI are needed during drug discovery.
- ❑ How can we identify, validate and use such tools to aid the design of safe drugs?

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