How understanding drug toxicities can aid human chemical safety assessment without using animals

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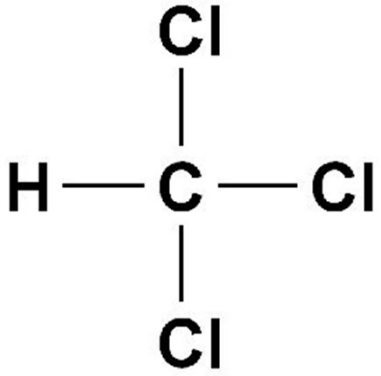
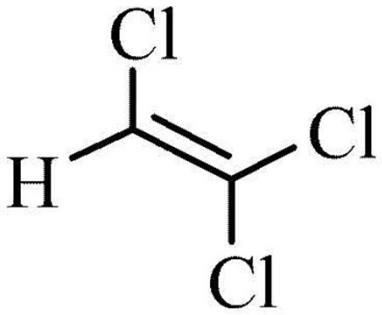
Drugs = prescription medicines

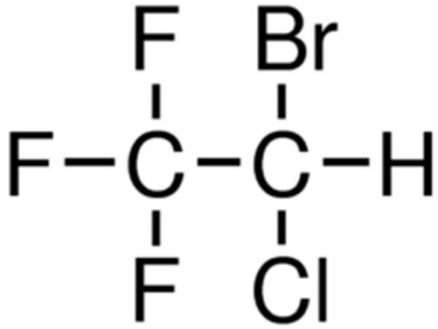
Not drugs of abuse

Drugs are chemicals

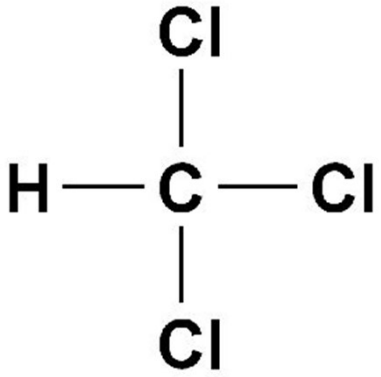


Which of these are drugs?



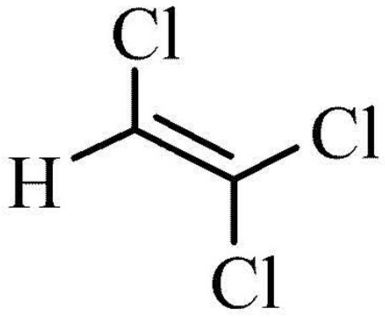


Drugs are chemicals



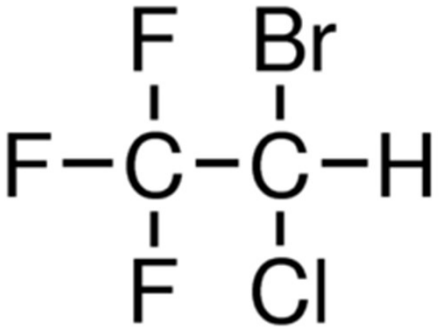
Chloroform

All have been used as drugs
- but two were withdrawn



Trichloroethylene

Halothane
an anaesthetic



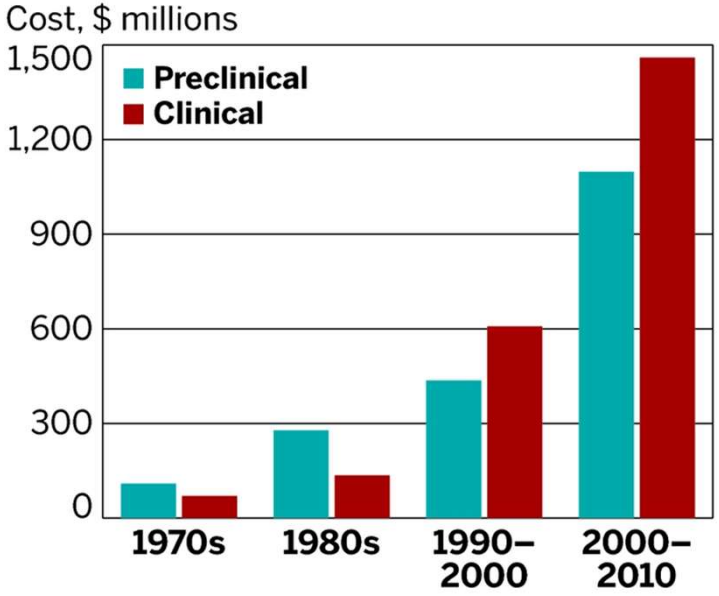
Ex-anaesthetics

Liver and kidney toxicity

Industrial solvents

Consequences of drug toxicity

Inefficient development



Drug withdrawal (1971 - 2010 data)

Cautionary labelling, e.g. bosentan

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

See full prescribing information for complete boxed warning.

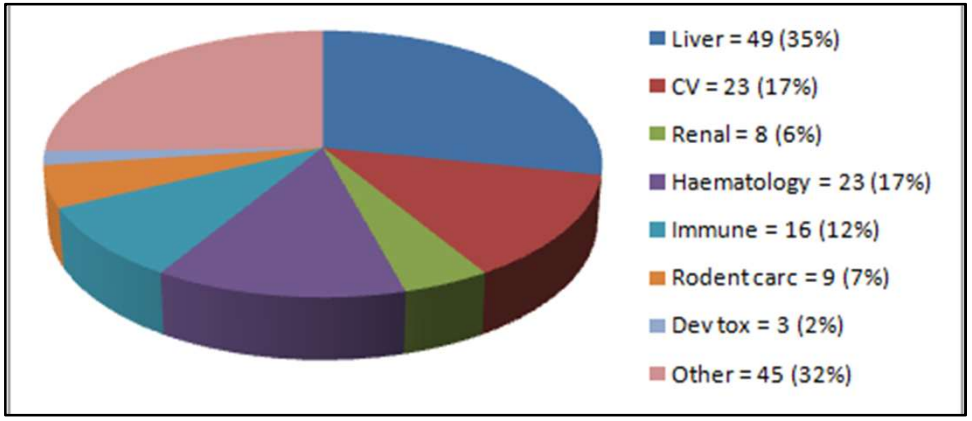
Tracleer can be prescribed and dispensed only through a restricted distribution program (Tracleer Access Program) because of these risks:

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer (5.1).

- Measure liver aminotransferases prior to initiation of treatment and then monthly (5.1).
- Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 x ULN (2.2, 5.1).

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy (4.1, 8.1).

- Must exclude pregnancy before and during treatment (4.1, 8.1) .
- To prevent pregnancy, females of childbearing potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (2.4, 8.1).



Types of drug toxicity

- Type A
  - Dose dependent, common
  - Occur reproducibly in humans and test animals
  - Often, but not always, due to exaggerated pharmacology
- Type B
  - Dose independent, infrequent
  - Occur only in susceptible humans, not in animals
  - Unrelated to drug pharmacology
  - Termed “idiosyncratic”

Toxic and nontoxic drugs

- Many drugs cause serious human toxicities
  - e.g. halothane, troglitazone, sitaxentan, bromfenac etc.
- But many “similar” drugs do not
  - e.g. desflurane, pioglitazone, ambrisentan, ibuprofen etc.

How can safe new drugs be designed and selected?

How drugs cause toxicity

Drug

Step 1 **Drug ADME**

Step 2 **Chemical insult to target cells**

Step 3 **Biological response in cell**

Step 4 **Biological response in tissue**

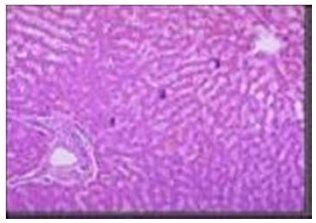
Compound related effects
Can be explored using simplified "*in vitro*" model systems

Patient related effects
Can be explored only *in vivo*

Protection
e.g. stress response

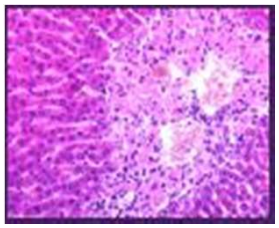
Propagation and amplification
e.g. innate and adaptive immunity

No toxicity:
tolerance & adaptation



Outcome

Preclinical species vs. man



Toxicity

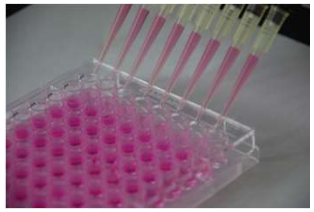
Predictive toxicity challenges

- Which *in vitro* assays and endpoints?
  - Mechanistic relevance?
  - Robustness, throughput, turnaround time, cost?
- How to interpret the data the assays provide?
  - How to evaluate and validate them?

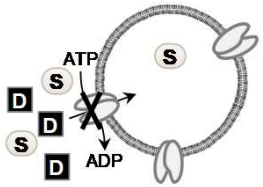
➢ ***Many divergent views, scientific consensus not yet achieved***

Many possible assays

Simple

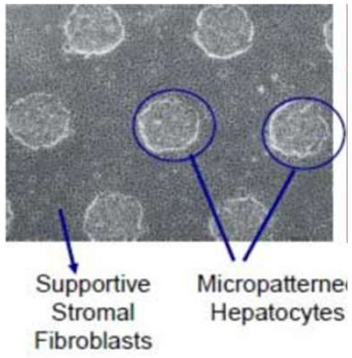


Cultured liver cell lines

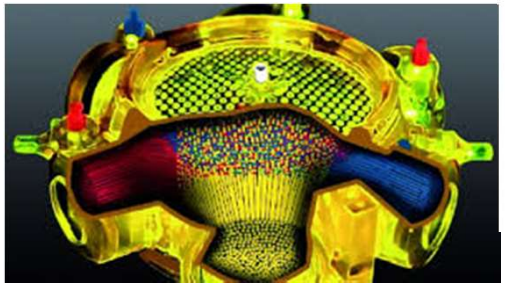


Membrane vesicles

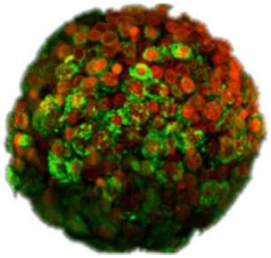
Intermediate



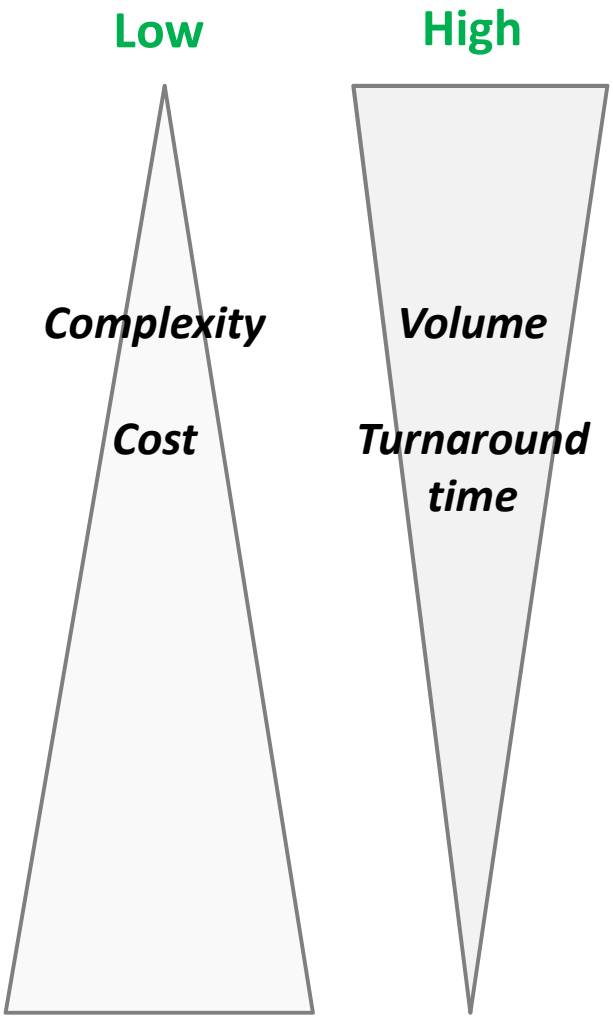
Complex



Bioreactors



Spheroids



A way forwards

- Focus on chemical insults likely to be relevant to human drug toxicity.
- Select robust, high volume, reasonable cost assays that quantify the insults.
- Take account of *in vivo* drug exposure when interpreting assay data.
- Generate validation data using toxic and non-toxic drugs.

Hazard and Risk

Hazard = any source of potential adverse health effect, harm or damage

Risk = the likelihood that a person exposed to a hazard will be harmed

Exposure = the extent to which someone is subjected to a hazard

HAZARD + EXPOSURE = RISK

Some useful assays

Chemical insult	Assay
Cell cytotoxicity	THLE-Null cell toxicity
Reactive metabolite toxicity	THLE-3A4 cell toxicity
	Covalent binding to human hepatocyte proteins
Mitochondrial injury	HepG2 cell toxicity in glucose vs. galactose media
	Seahorse® analyzer
Membrane transporter inhibition	Bile Salt Export Pump (BSEP) inhibition

Chem. Res. Toxicol. 2012: 25;1616
Drug Metab Dispos 2012; 40:130
Toxicol Sci 2014;137:189

Chemical Research in Toxicology

Article

pubs.acs.org/crt

In Vitro Approach to Assess the Potential for Risk of Idiosyncratic Adverse Reactions Caused by Candidate Drugs

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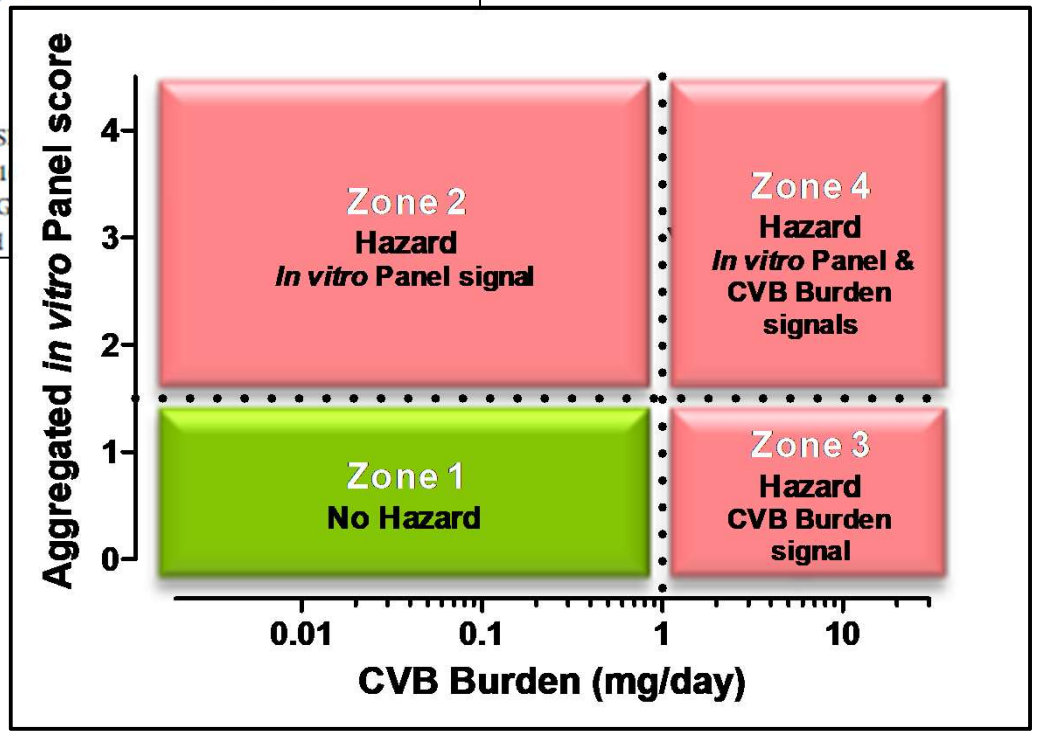
Chem Res Toxicol 2012; 25:1616.

See also: J Pharmacol Exp Ther. 2015; 352:281.

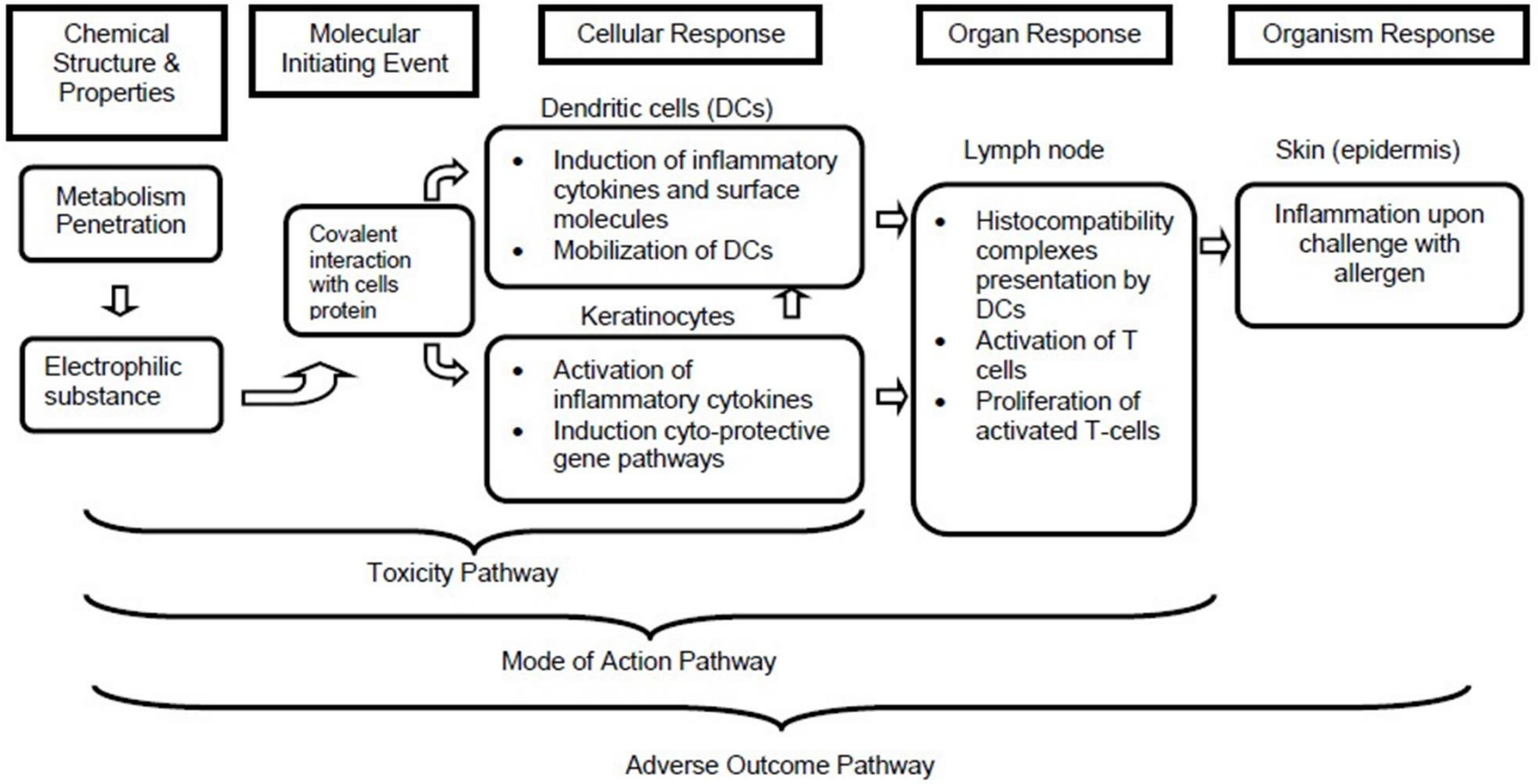


➢ **Excellent discrimination between 27 toxic drugs and 9 non-toxic drugs (100% sensitivity, 78% specificity)**

Conclusions

- Mechanistically relevant *in vitro* assays can discriminate between non-toxic drugs and drugs that cause idiosyncratic human toxicities.
- These assays have the potential to aid selection of safe new drugs.
- In principle, the same approaches could be used to support human risk assessment of other chemicals.

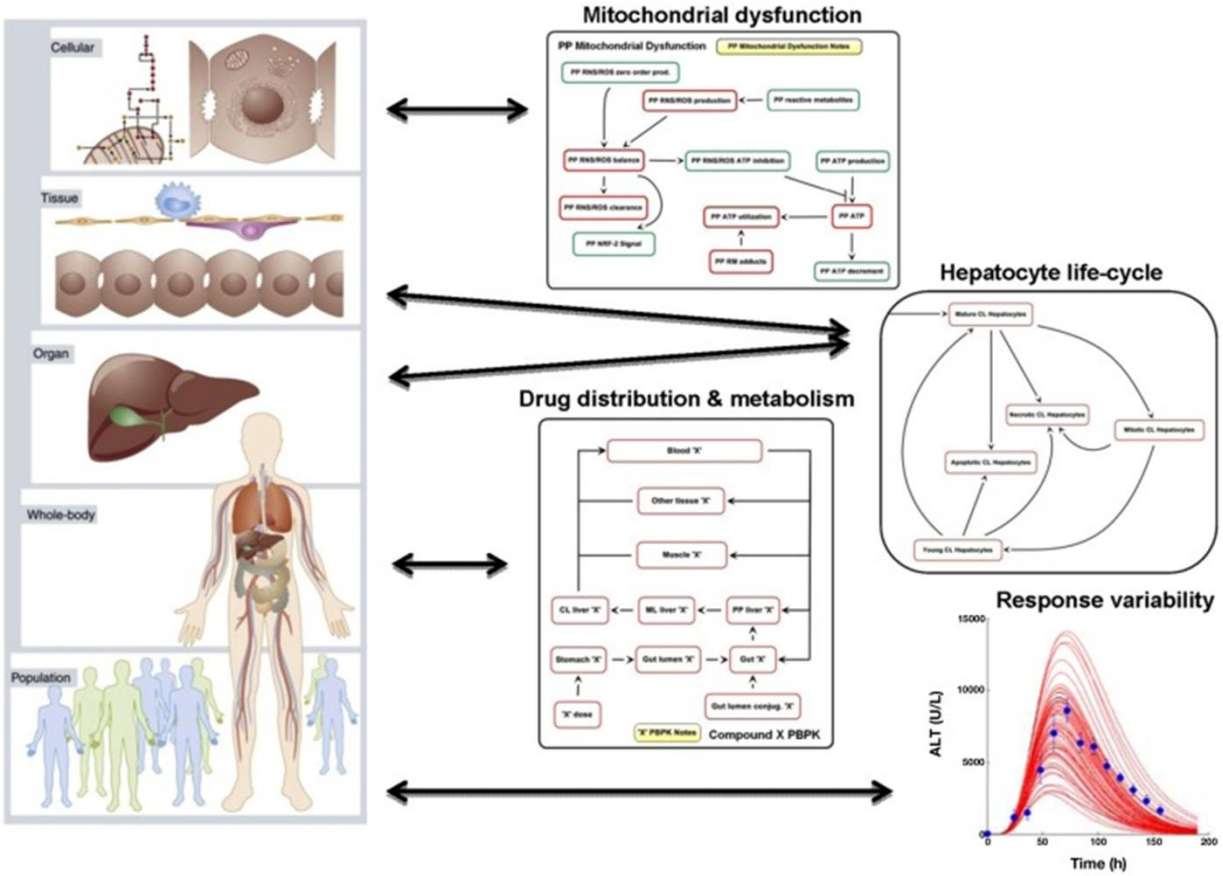
The future: Adverse Outcome Pathways



OECD. (2012). The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence. [Series on Testing and Assessment No.168 ENV/JM/MONO(2012)10/PART1].

The future: Systems Modelling

e.g. Hamner DILI-sim consortium: http://www.dilisym.com/



➢ **Drug exposure based simulation of population variability**

Bottlenecks to progress

- Underpinning science is still emerging.
- No consensus on which assays to select, or how.
- Limited scientific funding.
- Innovation largely driven from industry, not academia.
- Toxicologists are conservative.
- Lack of regulatory pressure to change.
- It’s much easier to criticise than to be constructive.


THAT WHEEL THING...WE TRIED IT ONCE BEFORE AND IT DIDN'T WORK!
NEANDERTHAL MAN'S LACK OF CURIOSITY DOOMED HIM TO EXTINCTION
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Safer Medicines Trust

- An independent charity.
- Our goal is to replace poorly performing animal studies with more predictive human biology-based methods, for human efficacy and safety testing of pharmaceuticals and other chemicals.
- See: www.SaferMedicines.org