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

All have been used as drugs - but two were withdrawn

Ex-anaesthetics
Liver and kidney toxicity
Industrial solvents
Consequences of drug toxicity

**Inefficient development**

<table>
<thead>
<tr>
<th>Cost, $ millions</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1980s</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1990–2000</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>2000–2010</td>
<td>1,200</td>
<td>1,500</td>
</tr>
</tbody>
</table>

**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).

**Drug withdrawal**

(1971 - 2010 data)
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 ADME

Drug ADME

Chemical insult to target cells

Biological response in cell

Biological response in tissue

Protection
e.g. stress response

Propagation and amplification
e.g. innate and adaptive immunity

Outcome
Preclinical species vs. man

No toxicity:
tolerance & adaptation

Compound related effects
Can be explored using simplified “in vitro” model systems

Patient related effects
Can be explored only in vivo

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**
  - Supportive Stromal Fibroblasts
  - Micropatterned Hepatocytes

- **Complex**
  - Bioreactors
  - Spheroids

Diagram shows:
- Complexity: Low → High
- Cost: Low → High
- Volume: Low → High
- Turnaround time: Low → High
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

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

Drug Metab Dispos 2012; 40:130
Toxicol Sci 2014;137:189

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

**Excellente 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

The future: Systems Modelling

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