Humanizing Drug Safety Testing - pragmatic validation

ICCVAM Public Forum

May 27, 2015

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Background

- Current approach to identifying safe and effective new medicines is failing
- There is an urgent need for change
- But a change to to what?
- And how to achieve it?

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Importance of Human Focus

- It *has* to involve a more human-based approach
- Possibilities include human *in vitro*, human-based *in silico* and/or human *in vivo*
- There is nothing else

Alternatively, a Pragmatic Approach

Assess ability of human-based *in vitro* tests to detect toxicities missed by *in vivo* animal testing

- **Identify candidate drugs that have been approved for clinical use, but have subsequently been withdrawn due to toxicity in patients**
- **For each of the above, identify a structurally and/or functionally similar drug that does not exhibit the same clinical toxicity**
- **Submit pairs to testing in a range of human-based *in vitro* alternatives**

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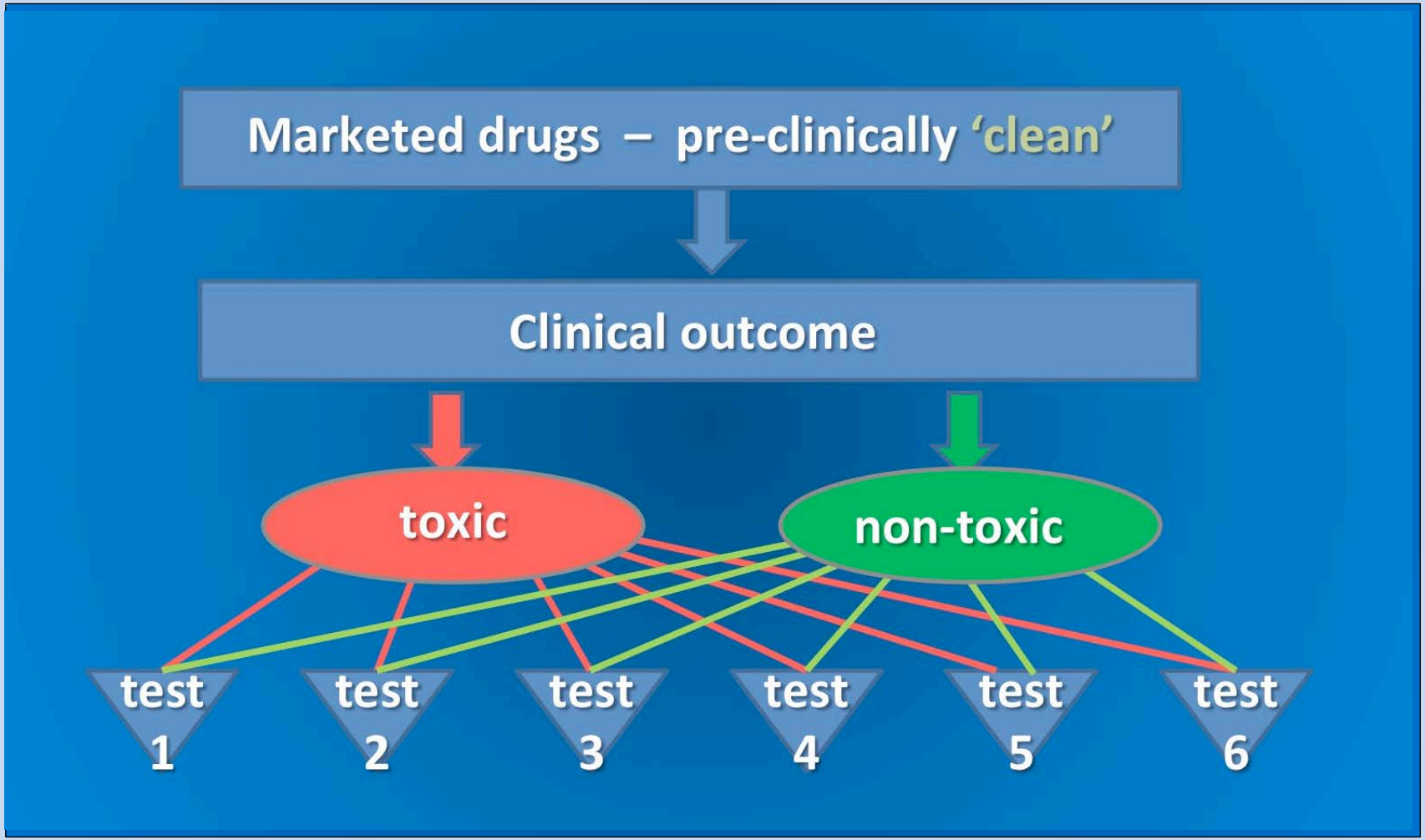
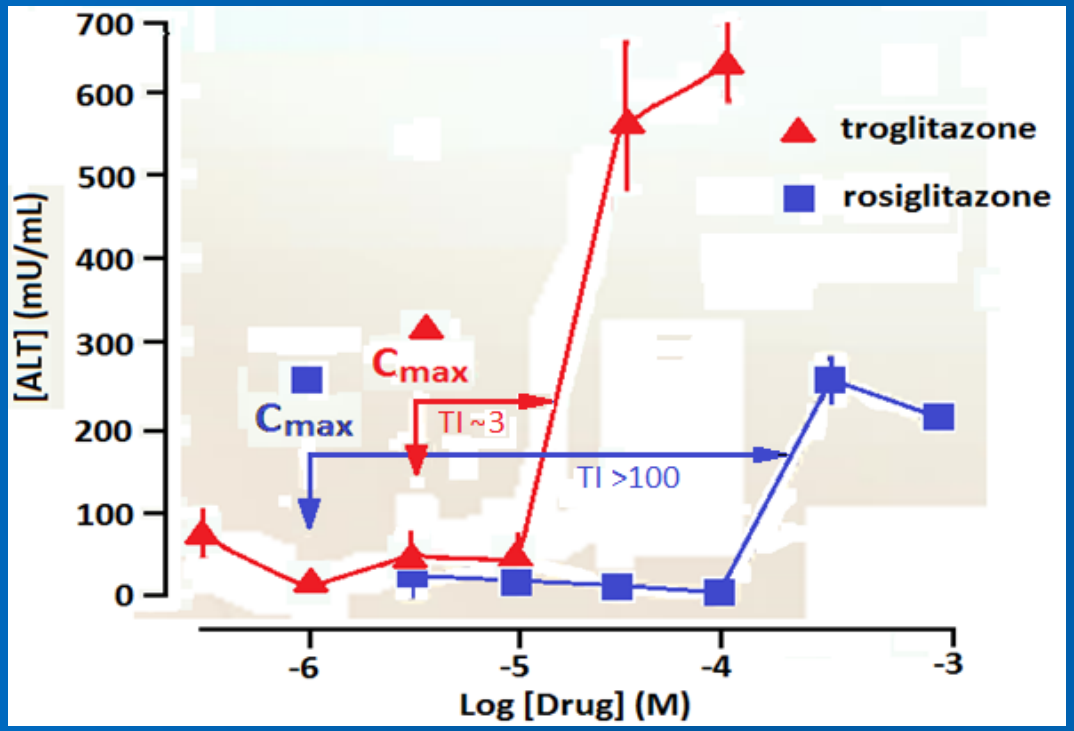
Alternatively, a Pragmatic Approach



A Pragmatic Approach

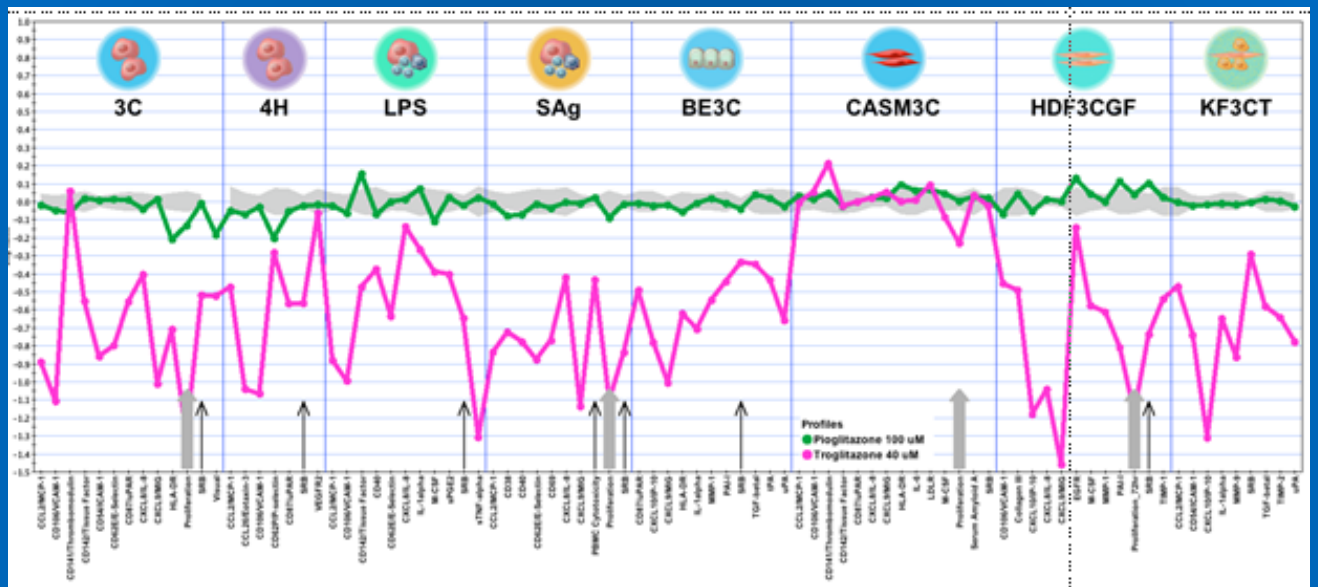
Toxicity testing in human primary hepatocytes



Coleman *et al* (2001) *DDT*, 6, 1116-1126

A Pragmatic Approach 1.

BioMAP® high content profiling in human cell systems



- **Troglitazone (40 uM)** but not **pioglitazone (100 uM)** is overtly cytotoxic in the 3C, 4H, LPS, SAG, BE3C and HDF3CGF systems (thin black arrows) and antiproliferative to EC, T cells, SMC and fibroblasts (thick grey arrows)

DiscoveRx

Ellen Berg, DiscoveRx - *personal communication*

Study 1

- 5 toxic/non-toxic pairs (ie total of 10 compounds)
- Toxicities - heart, liver, kidney & muscle
- All drugs included in US EPA's Phase 3 ToxCast *in vitro* profiling platform
- Data to be available within 2015, and submitted for detailed analysis to compare the performance of human *in vitro* tests with original regulatory animal-based *in vivo* tests
- Outcome to be published

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Study 2

- As Study 1, but focus on liver and cardiovascular toxicities
- Wider range of toxic/non-toxic drug/compound pairs
- Multiple mechanisms of toxicity of liver and cardiovascular system explored
- Analysis performed blind
- Results to be published and developed into FDA Guidance

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Study 3

Validation of Integrated Approach to Testing and Assessment

HORIZON 2020 Consortium

HORIZON 2020 Consortium Members

Participant No	Participant organisation name	Type	Country
01	FRAME	Charity	UK
02	Safer Medicines Trust	Charity	UK
03	Kirkstall	SME	UK
04	Biopredic	SME	France
05	HMGU	Academic	Germany
06	DiscoveRx	SME	USA
07	GE Healthcare	Large Enterprise	UK
08	INSTEM	SME	UK
09	L'Oreal	Large Enterprise	France
10	Oxford University	Academic	UK
11	NMI TT	SME	Germany
12	Parker Hannifin	Large Enterprise	UK
13	Selvita	SME	Poland
14	Quretec	SME	Estonia
15	UKK	Academic	Germany
16	LNE Group	SME	Belgium
17	AXANOMICS	SME	Spain
18	Critical Path Institute	Non-profit	USA
19	Protoqsar	SME	Spain
20	Eurofins	Large Enterprise	Belgium
21	University of Nottingham	Academic	UK

Major Partners of the Consortium

- **Regulatory**
  - **FDA Critical Path Institute** (leadership in regulatory interactions and submission, connection to FDA and EMA)
  - European Chemicals Agency and US EPA
  - US FDA National Center for Toxicology Research (SAB)
- **Technology**
  - Systems Biology, Cheminformatics, *in vitro* biology, systems toxicology thought leaders
- **Large Industry**
  - GE Healthcare, L'Oreal, Predictive Safety Testing Consortium (18 major pharma companies), Eurofins, Parker Hannifin
- **Economic Impact Assessment**
  - MIT economics of chemicals safety assessment (SAB)

Scientific Advisory Board

Name	Organisation	Sector
Jack Fowle	Former US EPA	US Regulatory, chemicals
Anthony Burn	NASA, US	Large aerospace and industrial chemicals industry
Hiroshi Yamazaki	Showa Pharmaceutical University, Japan	Liver science academic leader
Weida Tong	US FDA	US regulatory FDA (cosmetics, pharmaceuticals)
Derek Knight	European Chemicals Agency, EU	EU regulatory, chemicals
Frank Ackerman	Massachusetts Institute of Technology	Economics of safety testing, REACH

HORIZON 2020 project

- Designed to fill the gap between science and regulatory requirements
- Based on the methodology developed by Safer Medicines Trust and accepted by the Consortium members and SAB as a platform for comparative testing of new technologies
- Focused on 2 major organ toxicities that underlie the largest human health and monetary losses in all industries: liver and heart
- The most mature and validated tests available were selected
- The aim of the Consortium is to develop a mechanism-based safety assessment strategy, in collaboration with regulatory agencies, who will then issue Guidances on the use of this approach to assess human safety across the chemical, cosmetic and pharmaceutical industries

Immediate Goals

- **Analyse and publish outcomes of Studies 1 and 2**
- **Integrate data with those from other programmes: *e.g.* IMI's Safe-T Project, SEURAT-1**
- **Fund and conduct consortium-led Study 3 (HORIZON 2020 project) to validate an integrated strategy for safety assessment for liver, heart and systemic toxicity**
- **Refine the pragmatic validation approach and apply to similar studies for other toxicities (eg CV, renal, neuro)**

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