Humanizing Drug Safety Testing - pragmatic validation

ICCVAM Public Forum

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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 what?
• And how to achieve it?
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- Identify candidate drugs that have been approved for clinical use, but have subsequently been withdrawn due to toxicity in patients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
Alternatively, a Pragmatic Approach

Marketed drugs – pre-clinically ‘clean’

Clinical outcome

toxic

non-toxic

test 1

test 2

test 3

test 4

test 5

test 6
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)

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
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
Study 3
Validation of Integrated Approach to Testing and Assessment

HORIZON 2020 Consortium
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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, \textit{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

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<td>Jack Fowle</td>
<td>Former US EPA</td>
<td>US Regulatory, chemicals</td>
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<td>Anthony Burn</td>
<td>NASA, US</td>
<td>Large aerospace and industrial chemicals industry</td>
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<td>Hiroshi Yamazaki</td>
<td>Showa Pharmaceutical University, Japan</td>
<td>Liver science academic leader</td>
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<td>Weida Tong</td>
<td>US FDA</td>
<td>US regulatory FDA (cosmetics, pharmaceuticals)</td>
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<td>Derek Knight</td>
<td>European Chemicals Agency, EU</td>
<td>EU regulatory, chemicals</td>
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<td>Frank Ackerman</td>
<td>Massachusetts Institute of Technology</td>
<td>Economics of safety testing, REACH</td>
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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 Guidelines 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 (e.g., CV, renal, neuro)