NTP Update on Implementing New Approaches to Evaluate the Safety of Chemicals and Medical Products

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Evolving Needs

Growing Opportunity

A Crossroads
“Toxicity testing is under increasing pressure to meet several competing demands:

- Test **large numbers** of existing chemicals, many of which lack basic toxicity data.
- Test the large number of new chemicals and **novel materials**, such as nanomaterials, introduced into commerce each year.
- Evaluate potential adverse effects with respect to all critical end points and **life stages**.
- Minimize animal use.
- Reduce the cost and time required for chemical safety evaluation.
- Acquire detailed **mechanistic and tissue-dosimetry data** needed to assess human risk quantitatively and to aid in regulatory decision-making.
**Opportunity**

**Tox21: Chemical testing in the 21st century**

**Molecular events**

Identification of Compounds That Inhibit Estrogen-Related Receptor Alpha Signaling Using High-Throughput Screening Assays

**Modes of action**

Comprehensive Analyses and Prioritization of Tox21 10K Chemicals Affecting Mitochondrial Function by In-Depth Mechanistic Studies

**Pathways**

A hybrid gene selection approach to create the S1500+ targeted gene sets for use in high-throughput transcriptomics

Identifying Attributes That Influence In Vitro-to-In Vivo Concordance by Comparing In Vitro Tox21 Bioactivity Versus In Vivo DrugMatrix Transcriptomic Responses Across 130 Chemicals
Three-Dimensional (3D) HepaRG Spheroid Model With Physiologically Relevant Xenobiotic Metabolism Competence and Hepatocyte Functionality for Liver Toxicity Screening

Sreenivasa C. Ramaiyahgari, Suramya Waidyanatha, Darlene Dixon, Michael J. DeVito, Richard S. Paules, and Stephen S. Ferguson

TOXICOLOGICAL SCIENCES, 159(1), 2017, 124–136
Enabling Tools

Computer Models of Chemical Activity

Using structural data to generate activity predictions for new or poorly characterized chemicals can help researchers and regulators make decisions about further testing needs.

<table>
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<tr>
<th>Project</th>
<th>Description</th>
<th>Publication</th>
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<td>Quantitative structure-activity relationship (QSAR) models to screen for potential skin sensitizers</td>
<td>NICEATM and collaborators at the University of North Carolina, Chapel Hill (UNC-CH) developed QSAR models of human data that can either be combined with in vivo or in vitro data to screen for potential skin sensitizers.</td>
<td>Alvis, V., et al. &quot;QSAR models of human data: Discrimination of in vivo and in vitro activities for human sensitization.&quot; Green Chem. 2015 Dec 1;17(12):4851-4859.</td>
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In Vitro to In Vivo Extrapolation

A workflow for conducting in vitro to in vivo extrapolation (IVIVE) analyses is now available in the Integrated Chemical Environment.

Key issue with high-throughput in vitro testing methods is how to accurately relate concentrations of substances that induce in vitro responses to in vivo exposure levels that could result in human or animal adverse effects. This relationship is established through IVIVE, the focus of a NICEATM webinar series and follow-up workshop during 2015 and 2016.

Scientists interested in the use of IVIVE for substance screening and risk decision-making met at the 2016 workshop to develop best practices and identify areas for further research. The workshop, co-organized by NICEATM and the U.S. Environmental Protection Agency, was summarized in a 2018 publication in the Journal of Toxicology in Vitro (Bell et al, 2018). NICEATM's computational toxicologists developed methods for conducting IVIVE analyses, described in a publication in the Journal of Applied In Vitro Toxicology (Chao et al, 2014). Subsequent work focused on understanding the impact of various parameters, such as using free plasma concentrations as a surrogate for total plasma concentration, and comparing multiple modeling approaches. This work is described in a publication in Environmental Health Perspectives (Casey et al, 2018).
Key Challenges – Pathobiology Is a Continuum

Magnitude and Duration

Quantitative Biological Measures

Normal physiology  Adaptive physiology  Maladaptive physiology  Pathology

- Transition from normal to abnormal is generally not binomial.
- Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.
- Contextualizing those perturbations in a myriad of possible individual susceptibilities is even more difficult.
Key Challenges – Predictive Toxicology Conundrum

ER pathway to breast cancer

This is the inflection point we need to model since it represents the bridge between observation and prediction.

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92

Appreciation to Cynthia Rider for introducing me to this.
Key Enablers

- Replicate biology
- Demonstrate pharmacology and toxicology
- Test for analytical reproducibility
- Conduct comparative studies
- Evolve use
- Learn to make decisions
- Understand clinical outcomes
- Build experience

Building confidence

Analytical validation

Translational qualification

Key Challenges – Validation-Qualification Continuum
Innovating the Paradigm

Translational Toxicology Pipeline

Hypothesis-driven Research

Data / Knowledge Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Short term in vivo Studies

Chronic in vivo Studies

Knowledge Integration

Communicate

Machine/Deep learning capabilities

Iterative learning

Fully leveraging ‘pre-animal’ capabilities

Human-relevant in vitro systems - e.g., 3D complex

Bespoke and human-relevant animal studies

Human Health Effects
Questions?