New Approach Methodologies: Translational Impact and Human Relevance of Microphysiological Systems

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Microphysiological Systems

Need  ⟷  Opportunity

Strategy  ⟷  Confidence

Application
Need

Mission
To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology.

http://ntp.niehs.nih.gov; April 2015

21st Century Vision
To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004
NRC Committee on Toxicity Testing and Assessment of Environmental Agents

“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.

i.e. “Translational Impact and Human Relevance…”

National Academies Press, 2007
Blood vessels conduct blood to the heart itself as well as the rest of the body.

Rhythmic waves of electrical activity ensure coordinated contraction of different regions of the heart.

Cardiomyocytes are contractile cells with immense energy needs.

A muscular pump and its delivery system.

Heart valves ensure unidirectional flow of blood.

Rationalizing the current paradigm

Biological conservation
Rationalizing the current paradigm

Pathobiological conservation

- Structural injuries
  - Cardiomyocyte injury
  - Vascular injury
  - Valvulopathy
  - Ultrastructural injury
  - \( \Delta \) cardiac mass

- Functional changes
  - Arrhythmia
  - \( \Delta \) BP
  - \( \Delta \) HR
  - \( \Delta \) contractility

- Changes in disease
  - Ischemic events
  - Coronary artery dz
  - Heart failure
  - Cerebrovascular events
  - Hypertension
  - Metabolic disease

Neoplasia
Rationalizing the current paradigm

**Mechanistic conservation**

- Calcium is primary mediator
- Excitation-contraction coupling is “energy-requiring”
- Mitochondria critical as stores of calcium and producers of ATP
- Myocardial relaxation is more sensitive to ATP depletion than is the process of myocardial contraction (cf. diastolic dysfunction)


Excitation-Contraction Coupling
“For all that, current approaches to safety or hazard assessment are imprecise.”
Interagency Coordinating Committee on the Validation of Alternative Methods

Tox21: Chemical testing in the 21st century

Molecular events

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

Pathways

Predictive extrapolation

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

Comprehensive Analyses and Prioritization of Tox21 10K Chemicals Affecting Mitochondrial Function by In-Depth Mechanistic Studies
Interagency Coordinating Committee on the Validation of Alternative Methods

Supporting in silico tools

In Vitro to In Vivo Extrapolation

A framework for conducting in vitro to in vivo nonparametric IVIVE analyses is now available in the "Integrative Toxicology" journal.
Throughput comes at a price!

Current approaches trade human in vivo relevance for throughput and analytical clarity.
Gap = Linking Mechanisms to Phenotypes

Need

E.g. Calcium handling, contractility and heart failure

Screen this

Model this

Predict this

Secondary pharmacology

iPSC cardiomyocytes?
“Current approaches to ‘predictive’ safety or hazard assessment are even more imprecise.”
Definition of precision in English:

**precision**

**NOUN**

[mass noun]

1. The quality, condition, or fact of being exact and accurate.

‘the deal was planned and executed with military precision’
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Uncertainty

Uncertainty factors

Margin of safety

https://www.lexico.com/en/definition/precision

https://www.edvardmunch.org/the-scream.jsp
Opportunity

For the purposes of this presentation, MPS are defined as small scale *in vitro* devices that recreate the dynamic *in vivo* cellular environment by incorporating components of 3-dimensional tissue architecture, extracellular matrix, cellular interactions and in vivo physiologic function.
Strategy

Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective

Lorna Ewart¹, Kristin Fabre², Anantharvinivas Chakilam³, Yvonne Dragan⁴, David B Duignan⁵, Jeetu Eswaraka⁶, Jinping Gan⁷, Peggy Gazzle-Peck⁸, Monica Otieno⁹, Claire G Jeong⁩, Douglas A Keller¹⁰, Sonta M de Morais¹¹, Jonathan A Phillips¹², William Proctor¹³, Radhakrishna Sura¹⁴, Terry Van Vleet¹⁵, David Watson¹⁶, Yvonne Wilt¹⁵, Danilo Tagle¹⁵ and Brian Berridge⁹

A roadmap from Point A to Point B
NTP Translational Toxicology Pipeline

Strategy

Define a problem statement

Engage decision-makers

Consider use of the outcomes

Mine current knowledge

- Literature analysis

Develop hypotheses, strategy and priority

Complex in silico and in vitro modeling

- Medium-low throughput

Short duration, integrative in vivo testing

- IVIVE

Sub-chronic to chronic in vivo outcomes

Microphysiological systems

Consider use of the outcomes

Bioactivity screening profile

- In silico analytics

Bioactivity screening profile

- Medium-high throughput screen

Bioactivity screening profile

- Medium-high throughput screen

Bioactivity screening profile

- Medium-high throughput screen

Fit-for-purpose product with human contextualization

Fit-for-purpose product with human contextualization

Fit-for-purpose product with human contextualization

Defining a context of use

Building bridges from simple *in vitro* screening to complex *in vivo* assessments
Confidence evolves and is enabled by key elements of the process!
Reconstituting Organ-Level Lung Functions on a Chip

Dongeun Huh,1,2 Benjamin D. Matthews,2,3 Akiko Mammoto,2 Martín Montoya-Zavala,1,2 Hong Yuan Hsin,2 Donald E. Ingber1,2,4*

Application
An Orally Active TRPV4 Channel Blocker Prevents and Resolves Pulmonary Edema Induced by Heart Failure

Kevin S. Thorneloe,¹ Mui Cheung,¹ Weike Bao,¹ Hasan Alsaid,¹ Stephen Lenhard,¹ Ming-Yuan Jian,² Melissa Costelli,³ Kristen Maniscalco-Hauk,³ John A. Krawiec,³ Alan Olzinski,¹ Earl Gordon,¹ Irina Lozinskaya,¹ Lou Elefante,² Pu Qin,¹ Daniel S. Matusic,¹ Chris James,¹ James Tunstead,¹ Brian Donovan,¹ Lorena Kallal,¹ Anna Waszkiewicz,¹ Kalindi Vaidya,¹ Elizabeth A. Davenport,⁶ Jonathan Larkin,⁷ Mark Burgert,⁷ Linda N. Casillas,⁸ Robert W. Marquis,⁸ Guoisen Ye,¹ Hilary S. Eidam,¹ Krista B. Goodman,¹ John R. Toomey,¹ Theresa J. Roethke,¹ Beat M. Jucker,¹ Christine G. Schnackenberg,¹ Mary I. Townsley,² John J. Lepore,¹ Robert N. Willette¹

Aortic-banded mouse HF
The Microphysiological Systems (MPS) program supports military readiness by enabling timely evaluation of the safety and efficacy of novel medical countermeasures against a wide range of natural and man-made health threats, including emerging infectious disease and chemical or biological attack.
Confidence

• We’re building humanized systems to model human outcomes

• But, the current approach and experience in environmental hazard assessment and drug development make the human outcome a challenging qualifying measure
  – Low ‘n’
  – Mixed and variable exposures
  – Co-morbidities
  – Acute vs. chronic progressive effects

• Animal studies are likely a necessary surrogate measure for informing approaches and building confidence in phenotypic outcomes
A Human Disease Model of Drug Toxicity–Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice

Dongeun Huh,1,2,3 Daniel C. Leslie,1,2 Benjamin D. Matthews,2,4 Jacob P. Fraser,1 Samuel Jurek,2 Geraldine A. Hamilton,1 Kevin S. Thorpe,5 Michael Allen McAlexander,6 Donald E. Ingber1,2,7*

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How do we decrease the depth of this trough?

Altering the usual trajectory
Thank you!

Questions?