US Strategic Roadmap Goal: Encourage the Use and Adoption of New Methods and Approaches by Federal Agencies and Regulated Industry

Microphysiological Systems as an Exemplar

B. R. Berridge, DVM, PhD, DACVP
Associate Director, NTP
• End-user perspective for engagement of a novel technology
• Bridge between pharma and NTP contexts
• A guide to building confidence
• Distinguishing ‘validation’ from ‘qualification’
• I’m going to complicate things
  – toxicology contexts
  – organ systems
  – differentiating validation, qualification and confidence
Engaging a novel technology

Linking platform developers to platform users

IQ Consortium- LGs and WGs

Microphysiological Systems WG

Multi-disciplinary team of pharmaceutical scientists representing expertise and interests in drug metabolism and distribution, safety, and the 3Rs of judicious animal use for research

• Inaugurated late 2014
• NCATS request
• 24 members
• 16 pharma organizations
An analysis of the attrition of drug candidates from four major pharmaceutical companies

Michael J. Waring¹, John Arrowsmith², Andrew R. Leach³, Paul D. Leeson³,⁴, Sam Mandrell², Robert M. Owen⁵, Garry Pairaudeau¹, William D. Pennie⁶,⁷, Stephen D. Pickett³, Jibo Wang⁸, Owen Wallace⁸,⁹ and Alex Weir²

Table 1 | Populations of the primary cause of failure categories for terminated compounds*

<table>
<thead>
<tr>
<th>Termination reason</th>
<th>Overall</th>
<th>Period</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>2000–2005</td>
<td>2006–2010</td>
</tr>
<tr>
<td>Clinical safety</td>
<td>68 (11%)</td>
<td>48 (13%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Commercial</td>
<td>40 (7%)</td>
<td>23 (6%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>55 (9%)</td>
<td>45 (11%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Formulation</td>
<td>9 (1%)</td>
<td>4 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Non-clinical toxicology</td>
<td>240 (40%)</td>
<td>144 (40%)</td>
<td>96 (40%)</td>
</tr>
<tr>
<td>Patent issue</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Pharmacokinetics or bioavailability</td>
<td>29 (5%)</td>
<td>19 (5%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Rationalization of company portfolio</td>
<td>124 (21%)</td>
<td>46 (13%)</td>
<td>78 (32%)</td>
</tr>
<tr>
<td>Regulatory</td>
<td>2 (0.3%)</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Scientific</td>
<td>33 (5%)</td>
<td>26 (8%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Technical</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>605</td>
<td>362</td>
<td>243</td>
</tr>
</tbody>
</table>

*Table entries for each column indicate the total number and the percentage in parentheses.

Over half of terminations are for things we test preclinically.
Tox21: Chemical testing in the 21st century

Tox21 aims to:

- Develop new testing methods that use human cells, called *in vitro* approaches
- Expand the number of chemicals that are tested
- Reduce the time, effort, and costs associated with testing
- Minimize the number of laboratory animals used

Pharma uses secondary pharmacology screening in a lower throughput context.
Current approaches trade human in vivo relevance for throughput and analytical clarity.
Current approaches trade human in vivo relevance for throughput and analytical clarity.

To enable confidence in making in vivo–relevant decisions, we must have confidence in the in vivo relevance of a novel test system. Otherwise, we generally default to the system in which we have most confidence—i.e. the animal system.
Opportunity- Microphysiological Systems

A microfluidics chip positions blood vessels for multiple tests.

Lab Chip, 2014, 14, 869-882

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


Defined Success

1. Partnerships
   Performance/capability development

2. Defining Context of Use
   Mechanistic assays
   Safety screening
   DMPK
   Efficacy

3. Characterization
   Cell/Tissue Composition
   Physiologic Function
   Response to Injury
   Pharmacologic Response

4. Validation
   Throughput capability
   Intra- and inter-laboratory reproducibility
   Platform stability
   Comparative effectiveness

5. Industrialization
   Data and decision management

Future Work

Defined Problems

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

Lorna Ewart, Kristin Fabre, Ananthsrinivas Chakilam, Yvonne Dragan, David Duignan, Jeetu Eswaraka, Jinping Gan, Peggy Guzzie-Peck, Monica Otiene, Claire G Jeong, Douglas A Keller, Sonia M de Morais, Jonathan A Phillips, William Proctor, Radhakrishna Sura, Terry Van Vleet, David Watson, Yvonne Will, Danilo Tagle and Brian Berridge

Defined Success

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Seen by many as a threshold for success

Confidence evolves and is enabled by key elements of the process!
Design compounds by first intent that engage disease-modifying targets at appropriate concentrations without inducing unmanageable liabilities.
Engage decision-makers

Define a problem statement

Mine current knowledge
- Literature analysis

QSAR/read-across profiling
- In silico analytics
- Medium-high throughput screen

Bioactivity screening profile

Develop hypotheses, strategy and priority

Mechanistic in vitro-simple, complex
- Medium-low throughput

Short duration, integrative in vivo testing
- IVIVE

Sub-chronic to chronic in vivo outcomes
- IVIVE

Consider use of the outcomes

Fit-for-purpose product with human contextualization

Building bridges from simple in vitro screening to complex in vivo assessments

NTP Context of Use
Define Hypotheses & Design a Testing Strategy

Process of iterative learning and knowledge building that will enable greater confidence in non-animal approaches in the future

Fully leveraging available knowledge and in vitro assessments prior to animal studies

In vitro Studies

Bioactivity Screening

Data Mining

QSAR Profiling

Fit for purpose products

Longer-term in vivo Tests

Short-term in vivo Tests

In the current state, animal studies are important places for understanding IVIVE

We intend to have well-defined questions to ensure we’re doing the right experiments

In the current state, animal studies are important places for understanding IVIVE

Broad portfolio of products that can emerge from any stage of the pipeline

The ultimate species of interest is the human species. Accordingly, all assessments are designed to give human insights

Inform Public Health Decisions
Understand the biology you need to represent

ER pathway to breast cancer

A critical inflection point not generally modeled in simple in vitro systems

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

Appreciation to Cynthia Rider for introducing me to this.
Ensure that biology is translatable
Consult relevant guidelines or engage your local XVAM!
‘Qualification’ is larger contextualization exercise

Qualification of a novel test or modeling system requires-
- an understanding of the how the new system compares to the traditional system
- an understanding of how the pathobiology of interest manifests in the species of interest
- an understanding of how the pathobiology of interest manifests in traditional model species.

cf. Human toxicity
  • Tubular toxicity

• cf. Animal assessment
• Tubule cell injury
• Urinary Kim-1, NAG
Common Presentations

- Acute interstitial nephritis
- Chronic interstitial nephritis
- Rhabdomyolysis
- Tubular cell toxicity
- Crystal nephropathy
- Altered glomerular hemodynamics
- Glomerulonephritis

But, not in every patient!

Table 2. Patient-Related Risk Factors for Drug-Induced Nephrotoxicity

<table>
<thead>
<tr>
<th>Risk Factor (continued)</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute or &quot;effective&quot; intravascular volume depletion</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Age older than 60 years</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>Exposure to multiple nephrotoxins</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>Underlying renal insufficiency (glomerular filtration rate &lt; 60 ml per minute per 1.73 m²)</td>
<td>Acute interstitial nephritis</td>
</tr>
</tbody>
</table>

Information from references 1 through 3, 7, 34, and 35.
Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System

KENDALL S. FRAZIER, JOHN CURTIS SEELEY, GORDON C. HARD, GRAHAM BETTON, ROGER BURNE TT, SHUNJI NAKATSUJI, AKIYOSHI NISHIKAWA, BEATE DURCHFELD-MEYER, AND AXEL BUBE

Renal responses to injury

• Degeneration, tubule
• Necrosis, proximal and distal tubules
• Necrosis, papillary
• Infarct, cortex
• Hemorrhage
• Vacuolation, proximal and distal tubules
• Accumulation, glycogen
• Accumulation, hyaline droplets
• Accumulation, pigment
• Cast, hyaline
• Cast, granular
• Crystals, proximal and distal tubules
• Mineralization, tubule
• Mineralization, interstitial

• Hypertrophy, tubule
• Glomerulonephritis
• Glomerulosclerosis
• Infiltrate, inflammatory cell, interstitial
• Edema, interstitial
• Fibrosis, interstitial
• Hyperplasia, tubule
• Hyperplasia, juxtaglomerular
• Adenoma, kidney
• Carcinoma, kidney

Renal biomarkers

• Serum- BUN, Cr
• Urine- Total protein, albumin, sp. gravity, Kim-1, osteopontin, lipocalin-2, NAG

Contextualizing the opportunity- How do we characterize it in animals?
Challenges of Qualification

• Qualifying the *in vivo* relevance of a modeling system (novel or traditional) requires a fundamental understanding of what you’re modeling.

• Need to understand how the pathobiology manifests in both the species of interest and the species that has been traditionally used to model that pathobiology.

• Qualifying a novel test system for its *in vivo* relevance to a species of interest is a bit more challenging than validating one but just as important.

• Given the challenges of doing the ‘human experiment’, *in vivo* experiments in the alternative species may be a component of building confidence in the *in vivo* relevance of a novel system.
• Engaging end-users and stakeholders of a novel test system or alternative approach is critical to their adoption.

• End-users have a responsibility to guide developers in the construction, validation and qualification of a novel system.

• Building confidence is an evolutionary process with many elements including working the paradigm and seeing the outcomes.

• Acceptance of a novel approach requires a clear line of sight from a problem to a strategy for enabling confidence.
Questions?