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

Nat Rev Drug Disc 14: 475, 2015

Over half of terminations are for things we test preclinically.

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**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>Clinical safety</td>
<td>68 (11%)</td>
<td>48 (13%)</td>
<td>20 (8%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Candidate nomination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td>Commercial</td>
<td>40 (7%)</td>
<td>23 (6%)</td>
<td>17 (7%)</td>
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<td></td>
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<td></td>
<td>Phase I</td>
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<td></td>
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<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>Efficacy</td>
<td>55 (9%)</td>
<td>45 (11%)</td>
<td>10 (4%)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Phase I</td>
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<td></td>
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<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>Formulation</td>
<td>9 (1%)</td>
<td>4 (1%)</td>
<td>5 (2%)</td>
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<td></td>
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<td></td>
<td>Phase I</td>
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<td></td>
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<td>Phase II</td>
</tr>
<tr>
<td>Non-clinical toxicology</td>
<td>240 (40%)</td>
<td>144 (40%)</td>
<td>96 (40%)</td>
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<td></td>
<td></td>
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<td>Phase I</td>
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<td>Phase I</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>Patent issue</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
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<td></td>
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<td></td>
<td>Phase I</td>
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<td></td>
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<td>Phase II</td>
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<tr>
<td>Pharmacokinetics or bioavailability</td>
<td>29 (5%)</td>
<td>19 (5%)</td>
<td>10 (4%)</td>
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<td></td>
<td></td>
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<td>Phase I</td>
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<td>Phase II</td>
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<td></td>
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<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>Rationalization of company portfolio</td>
<td>124 (21%)</td>
<td>46 (13%)</td>
<td>78 (32%)</td>
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<td></td>
<td></td>
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<td>Phase I</td>
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<td>Phase II</td>
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<td></td>
<td></td>
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<td>Phase II</td>
</tr>
<tr>
<td>Regulatory</td>
<td>2 (0.3%)</td>
<td>2 (0.6%)</td>
<td>0</td>
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<td>Phase II</td>
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<td>Phase II</td>
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<tr>
<td>Scientific</td>
<td>33 (5%)</td>
<td>26 (8%)</td>
<td>5 (2%)</td>
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<td></td>
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<td></td>
<td>Phase I</td>
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<td>Phase II</td>
</tr>
<tr>
<td>Technical</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
<td>0</td>
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<td>Phase II</td>
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<td></td>
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<td>Phase II</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1 (0.4%)</td>
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<td>Phase I</td>
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<td>Phase II</td>
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<tr>
<td>Total</td>
<td>605</td>
<td>362</td>
<td>243</td>
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<td>356</td>
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<td>157</td>
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<td></td>
<td></td>
<td></td>
<td>89</td>
</tr>
</tbody>
</table>

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

Integr. Biol., 2013, 5, 1119-1129

Lab Chip, 2012

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

Lorna Ewart¹, Kristin Fabre², Ananthsrinivas Chakilam³, Yvonne Dragan⁴, David B Duignan⁵, Jeetu Eswaraka⁶, Jainping Gan⁷, Peggy Guzzie-Peck⁸, Monica Otieno⁸, Claire G Jeong⁹, Douglas A Keller¹⁰, Sonia M de Morais¹¹, Jonathan A Phillips¹², Willian Proctor¹³, Radhakrishna Sura¹¹, Terry Van Vleet¹¹, David Watson¹⁴, Yvonne Will¹⁵, Danilo Tagle¹⁶ and Brian Berridge⁹

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

Defined Problems

Defined Success

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Defined Success

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Defined Problems

Seen by many as a threshold for success

Confidence evolves and is enabled by key elements of the process!
Pharma Context of Use

**Capabilities**

- Bioinformatics
- Phenotypic assays
- Activity assays
- Binding assays
- Animal studies

**Pharmacological Context of Use**

1. **Target ID & validation**
2. **Hit/lead discovery**
3. **Lead optimisation**
4. **Candidate selection**
5. **Preclinical safety**
6. **Clinical assessment**

**#compounds**

- 1000's
- 100's
- 10's
- 1-3

**Design compounds by first intent that engage disease-modifying targets at appropriate concentrations without inducing unmanageable liabilities**
Building bridges from simple in vitro screening to complex in vivo assessments

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

Sub-chronic to chronic in vivo outcomes

Fit-for-purpose product with human contextualization

NTP Context of Use
**DNTP Translational Toxicology Pipeline Plan**

**Define Hypotheses & Design a Testing Strategy**

- **Bioactivity Screening**
- **QSAR Profiling**
- **Data Mining**

**Fit for purpose products**

- **In vitro Studies**
- **Short-term in vivo Tests**
- **Longer-term in vivo Tests**

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

**Inform Public Health Decisions**

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

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

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

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

**Broad portfolio of products that can emerge from any stage of the pipeline**
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
Ensure that biology is translatable

- Microanatomy and physiology
- Response to injury
- Mechanisms, Biomarkers, Efficacy, Safety
- Omics
- Biochemistry
- Comparative Pathobiology
- High content imaging
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 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
Adecoxib (Hepsera), celecoxib (Vioxx), ibuprofen (Vioxx) (Vivid), indomethacin (Indocin), benzodiazepines, calcineurin inhibitors, cyclosporine (Neoral), tacrolimus (Prograf), cardiovascular agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clopidogrel (Plavix), ticlopidine (Ticlid), statins, chemotherapeutics, Carmustine (Gliadel), semustine (investigational), cisplatin (Platinol), interferon-alpha (Intron A), methotrexate, mitomycin-C (Mutamycin), contrast dye, diuretics, loops, thiazides, trimethamidine (Dynemur), drugs of abuse, cocaine, heroin, ketamine (Ketalar), methadone, methamphetamine, Chinese herbs with aristolochic acid, proton pump inhibitors, Lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), allopurinol (Zyloprim), gold therapy, haloperidol (Haldol), pimobendane (Aries), penicillin antibiotics, phenytoin (Dilantin), quinine (Qualarin), ramipril (Altace), zoledronate (Zometa)

Tubular cell toxicity
Acute interstitial nephritis, crystal nephropathy
Rhabdomyolysis
Rhabdomyolysis
Rhabdomyolysis
Increased intraglomerular hemodynamics, chronic interstitial nephritis, thrombotic microangiopathy

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

<table>
<thead>
<tr>
<th>Drug class/drug(s)</th>
<th>Pathophysiologic mechanism of renal injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age older than 60 years</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Tubular cell toxicity</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Acute interstitial nephritis, crystal nephropathy</td>
</tr>
<tr>
<td>Renal insufficiency (glomerular filtration rate &lt; 60 ml/minute per 1.73 m²)</td>
<td>Acute interstitial nephritis</td>
</tr>
</tbody>
</table>

Information from references 1 through 3, 7, 34, and 35.

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

But, not in every patient!
Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System

Kendall S. Frazier 1, John Curtis Seely 2, Gordon C. Hard 3, Graham Betton 4, Roger Burnett 5, Shunji Nakatsuji 6, Akiyoshi Nishikawa 7, Beate Durchfeld-Meyer 8, and Axel Bube 8

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?