Perspectives on Evaluating New Tools for Regulatory Use

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DIA 2022 session: The Translational Value of Animal Models in Rare Diseases

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Alternative Methods Working Group (AMWG)

- Office of Chief Scientist (OCS), Office of Commissioner
  - Chaired by Drs. Fitzpatrick (CFSAN) and Mendrick (NCTR), includes members from each Center, Office of Regulatory Affairs, and OCS
- Leadership Group consisting of researchers and regulators
- Starting with Microphysiology Systems (MPS)
- Research group comprised of individuals working with MPS
- Educational function
- Example of external outreach is interaction with the IQ MPS Affiliate

Report available on the FDA webpage
Advancing Alternative Methods at FDA

- Inviting developers to showcase their technologies
- Posting FDA-authored peer-reviewed publications and presentations

Transparency
Contact information: alternatives@fda.hhs.gov
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Tox-GAN: An Artificial Intelligence Approach Alternative to Animal Studies—A Case Study With Toxicogenomics
Xi Chen ⊕, Ruth Roberts ⊕,†,‡ Weida Tong,*,† and Zhichao Liu*,†

Reevaluation of the embryonic stem cell test
Amy L. Inselman*, Greg T. Nolen †, Ching-Wei Chang*, Wafa Harrouk*, Edward Fisher †, Melissa S. Tassinari*, and Deborah K. Hansen *

Publications Co-authored by FDA on Alternative Methods | FDA
MPS Research in DARS/CDER

Goals include:

1. **Predict patient safety**  
   Examples: (i) distinguishing toxic vs. non-toxic drugs; (ii) predicting drug permeability

2. **Reduce timing and need for clinical drug-interaction studies**

3. **Predict efficacy in patients**  
   e.g., expanding drug approvals based on increasing the number of genetic variants that a drug can treat (rare diseases)

Kevin Ford
MPS: Assess the Functional Capacity of Regenerative Medicine Cellular Therapy Products

Manufacturing & Regulatory challenges
- Cellular heterogeneity
- Patient to patient variability
- Limited shelf life/limited sample volume
- Limited availability of starting material for test method development
- A wide range of manufacturing protocols

New methods and quality attributes are necessary to reliably predict biological functions of manufactured products.

Current MPS research
- Develop and improve test methods for cell product characterization
- Identify product attributes that are predictive of safety and effectiveness

Kyung Sung
COVID-19 Organ-Chip Models

• Project: Understanding the protective immunity against SARS-CoV-2 and testing vaccine safety and efficacy using Lung-chip

• Highlights
  – Delineate the initial innate immune response toward the virus to explore susceptibility to SARS-CoV-2 infection
  – Evaluate effects of antibodies on SARS-CoV-2 infection
  – Knowledge obtained from the study will provide insights into antibody-dependent enhancement (ADE), which is relevant to evaluating the safety of vaccines for COVID-19

PI Tony Wang
Performance of 3D-Bioprinted Human Skin for In Vitro Permeation Studies

Rationale

• In vitro, excised human skin = the ‘gold standard’ to quantify skin permeation
  • Limited supply, high cost and variability of human skin explants

• Need a reliable, non-animal, human-relevant skin equivalent model for in vitro

• The increased availability and reduced cost of bioprinted skin would enable larger and continued studies, ultimately offering an opportunity to be used as a tool to support regulatory decision-making at FDA.

PI Luísa Camacho
Cross-Cutting FDA Applied Research: Liver MPS

- Liver toxicity = major reason for discontinuation of drugs in development
- Chemical contaminants in food and dietary supplements can also cause liver toxicity

**Clinical & Translational Science, 2021,14(3):1049-1061**

**Food and Chemical Toxicology, 2022,161:112828**
Precision Medicine
Predict Individual Susceptibility and Adaptation to DILI

Rationale

• Use Emulate Human Quad-Culture Liver Chip with primary human cells (hepatocytes, LSECs, stellate cells, and Kupffer cells) from 10-20 donors

• Characterize transient, adaptive (i.e., benign) hepatic responses in primary human hepatocytes to acetaminophen (APAP)

• Identify biomarkers that would distinguish between benign and serious outcomes that can be used in the clinic

PI Qiang Shi
Evaluation of Drug-Induced Cardiotoxicity with Patient-Specific iPSC-CMs

Rationale

• 250 lines of iPSC derived cardiomyocytes generated from donors with diverse genetic backgrounds (HyperGEN Cohort); do not respond the same to different drugs
• Individual cell lines showed some were more susceptible to doxorubicin (DOX)- and tyrosine kinase inhibitor (TKI)-induced cardiotoxicity
• Suggests the importance of addressing heterogeneity
• May identify markers that will enable patient stratification prior to drug treatment and dose selection

PI Li Pang
Modeling Alzheimer’s Disease (AD)-on-a-Chip Using hiPSCs

- Construct chips using hiPSC-derived brain cells from a healthy individual (APOE ε3/3) and an AD patient (APOE ε4/4)
- Standardize a battery of neurovascular associated assays
- Compare AD-chip pathology to human pathology
- Can help assess pharmacologic activity of potential therapies

PI Hector Rosas-Hernandez
In Silico (Computational) Approaches
AI4TOX consists of 4 Initiatives

1. Animal GAN: AI approaches as alternatives to animal models
2. safetAI: AI models for toxicity endpoints critical to drug safety
3. BERTox: AI powered NLP to support toxicity assessment of FDA documents
4. PathologAI: Preclinical digital pathology with AI

PI Weida Tong
Computational Repositioning of Drugs for Rare Disease

- **Hypothesis:** Some existing marketed drugs can be repurposed for the treatment of rare diseases

- **Approach:** Systematically match marketed drugs with rare diseases using computational methods
  - Drug similarity – two similar drugs can treat the same disease
  - Disease similarity – two similar diseases can be treated with the same drugs

- **Completed Projects include:**
  - LEOPARD syndrome (Zhu et al. PMID: 32676024)
  - Cancer drugs for treatment of rare diseases (Cheng et al. PMID: 31375661)

- **On-going:** Developing AI approaches for drug repositioning for rare diseases with CDER and NCATS/NIH collaborators

PI Weida Tong
CDER’s Article on Data Gaps and Animal Use

Slide courtesy of Dr. Janet Woodcock, Principal Deputy Commissioner

• “An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies,” Regulatory Toxicology and Pharmacology: 114 (2020)
  – Review of strengths and gaps in current primarily empirical approach to nonclinical safety testing for drugs
  – Highlights areas where in vitro methods have replaced animal studies
  – Mentions areas where current prediction is less than satisfactory with “Statements of Need”
  – Discusses new emerging paradigms such as Comprehensive In Vitro Proarrhythmia Assay (CiPA) for certain cardiac toxicities
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• Li Pang, NCTR, Precision medicine, cardiotoxicity
• Hector Rosas–Hernandez, NCTR, Alzheimer’s research
• Weida Tong, NCTR, Computational work