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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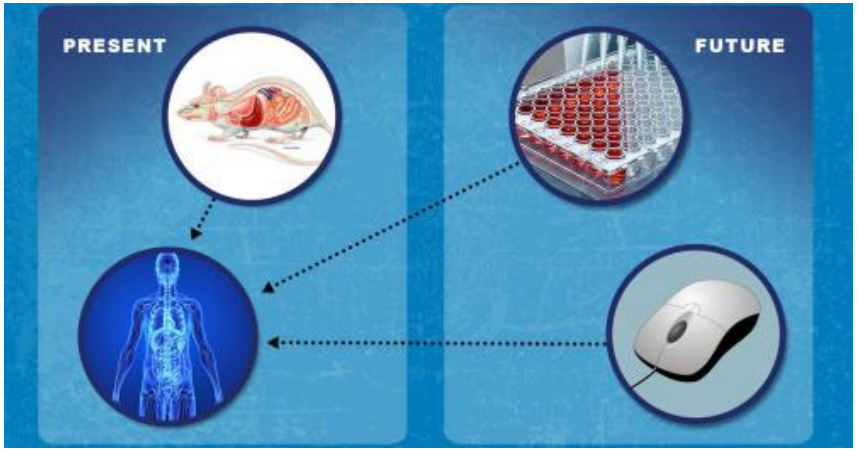
Alternative Methods Working Group (AMWG)

- 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

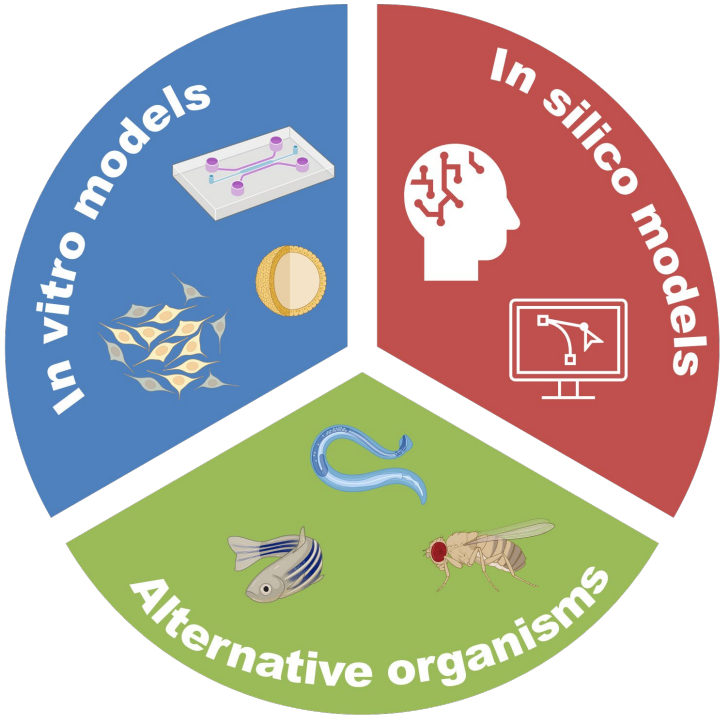


- Website for alternatives at FDA (https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda)
- Inviting developers to showcase their technologies
- Posting FDA-authored peer-reviewed publications and presentations

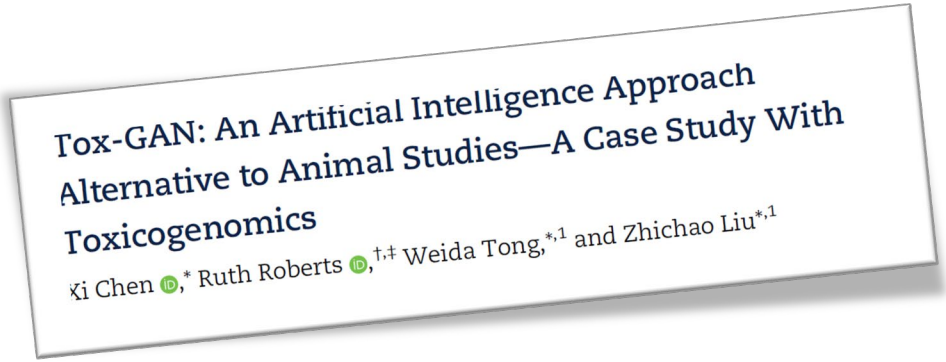
Transparency

Contact information: alternatives@fda.hhs.gov

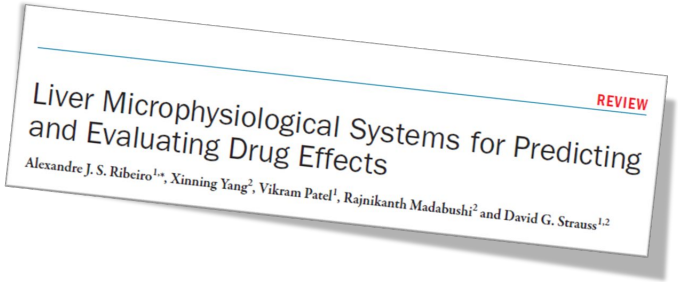
Alternative Methods



Alternative Methods

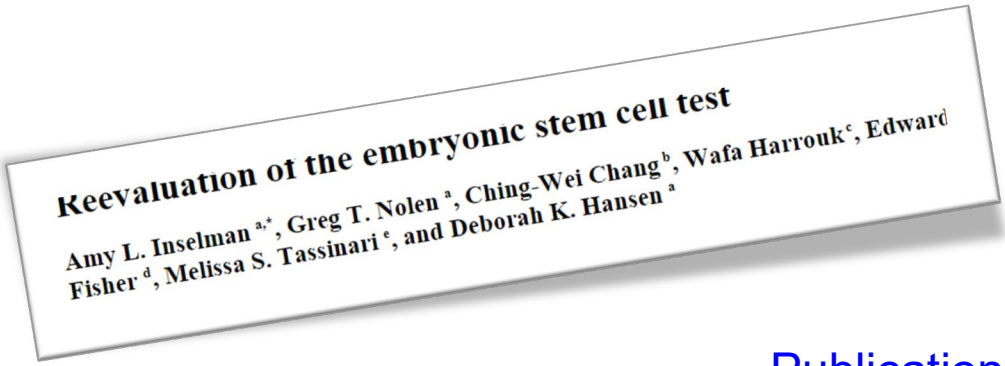

Tox-GAN: An Artificial Intelligence Approach Alternative to Animal Studies—A Case Study With Toxicogenomics

Xi Chen,* Ruth Roberts,†,‡ Weida Tong,*,1 and Zhichao Liu*,1


REVIEW

Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Alexandre J. S. Ribeiro[1,*], Xinning Yang[2], Vikram Patel[1], Rajnikanth Madabushi[2] and David G. Strauss[1,2]


Reevaluation of the embryonic stem cell test

Amy L. Inselman [a,*], Greg T. Nolen [a], Ching-Wei Chang [b], Wafa Harrouk [c], Edward Fisher [d], Melissa S. Tassinari [e], and Deborah K. Hansen [a]


RESEARCH ARTICLE

Effect of ketamine on gene expression in zebrafish embryo

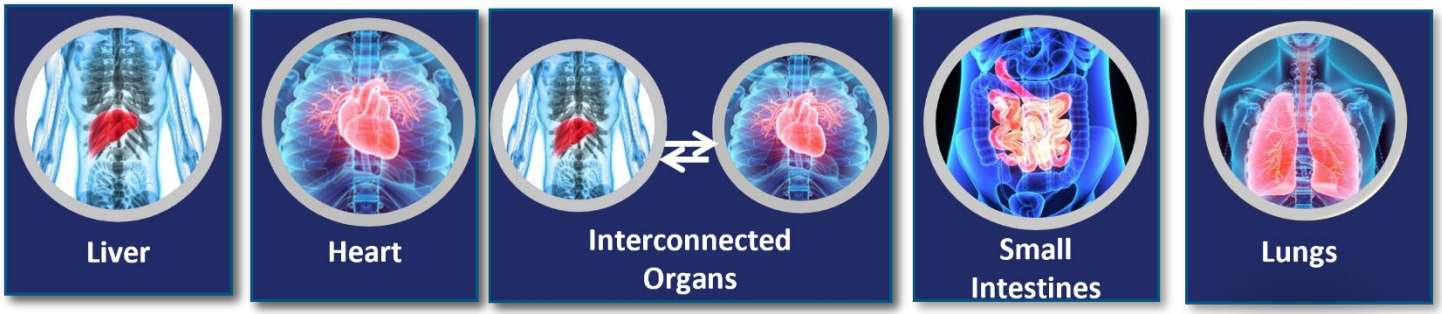
Qiang Gu, Jyotshna Kanungo

First published: 17 May 2021 | https://doi.org/10.1002/jat.4199

Funding information: NCTR/USFDA, Grant/Award Number: E0767501

[Publications Co-authored by FDA on Alternative Methods | FDA]

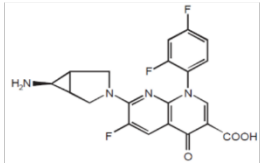
MPS Research in DARS/CDER



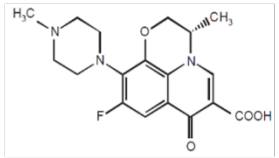
Goals include:

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)

Trovafloxacin (Hepatotoxic)



Levofloxacin (Not Hepatotoxic)



Kevin Ford

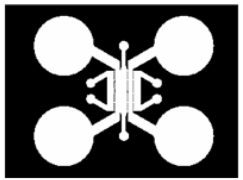
MPS: Assess the Functional Capacity of Regenerative Medicine Cellular Therapy Products

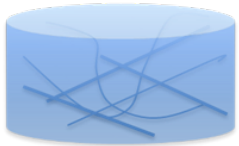
Manufacturing & Regulatory challenges

- 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.

3D aggregates | Co-culture | Biomaterials





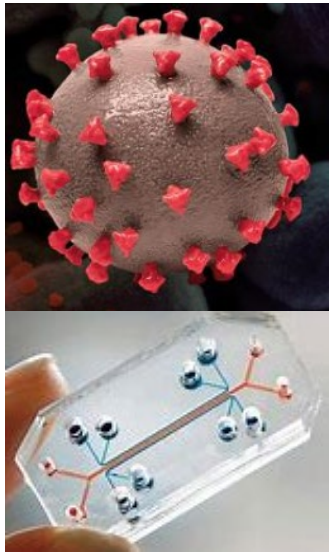
Kyung Sung

Current MPS research

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

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

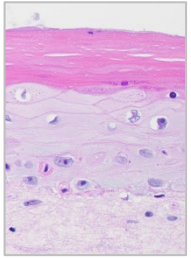


PI Tony Wang

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

Rationale

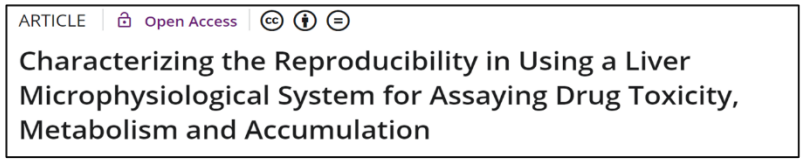
- In vitro, excised human skin = the 'gold standard' to quantify skin permeation
  - Limited supply, high cost and variability of human skin explants
- Need a reliable, non-animal, human-relevant skin equivalent model for in vitro
- The increased availability and reduced cost of bioprinted skin would 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

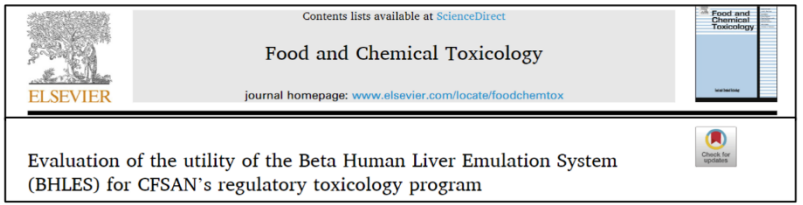
Cross-Cutting FDA Applied Research: Liver MPS

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


ARTICLE Open Access

Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

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


Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

ELSEVIER

Evaluation of the utility of the Beta Human Liver Emulation System (BHLES) for CFSAN's regulatory toxicology program

[Food and Chemical Toxicology, 2022,161:112828]

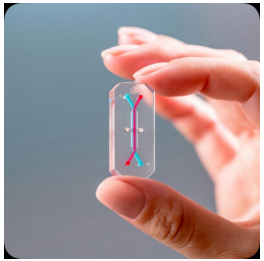
Precision Medicine

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

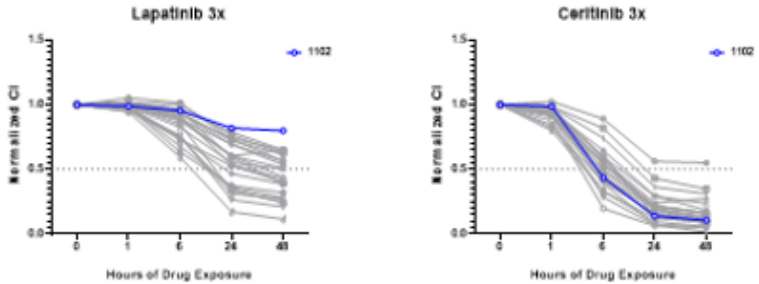
PI Qiang Shi



Evaluation of Drug-Induced Cardiotoxicity with Patient-Specific iPSC-CMs

Rationale

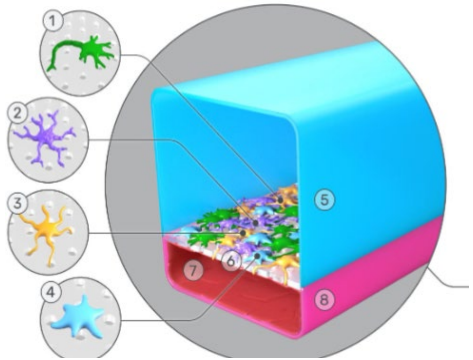
- 250 lines of iPSC derived cardiomyocytes generated from donors with diverse genetic backgrounds (HyperGEN Cohort); do not respond the same to different drugs
- Individual cell lines showed some were more susceptible to doxorubicin (DOX)- and tyrosine kinase inhibitor (TKI)-induced cardiotoxicity
- 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

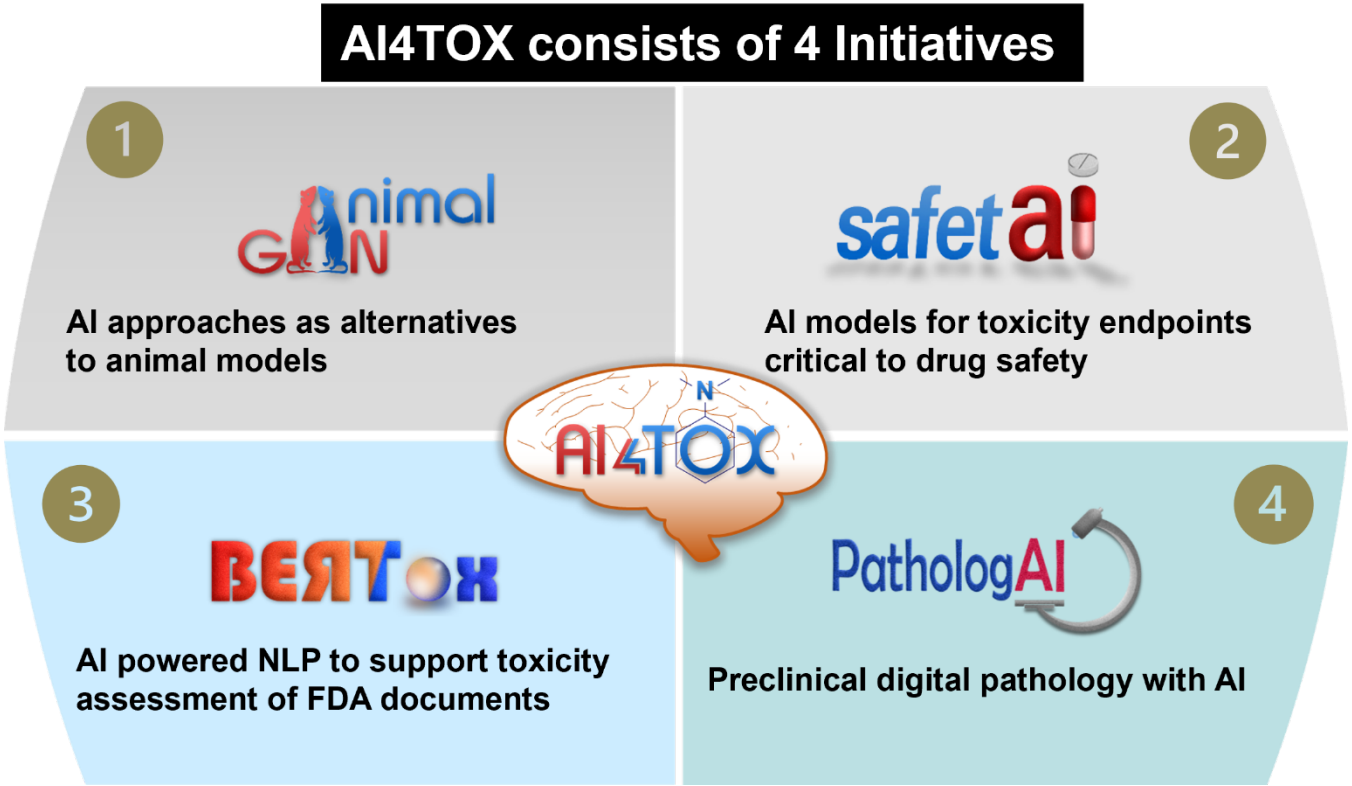


PI Hector Rosas-Hernandez

FDA U.S. FOOD & DRUG ADMINISTRATION

In Silico (Computational) Approaches

AI4TOX



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

Acknowledgments

- Kevin Ford, CDER, DARS/CDER
- Kyung Sung, CBER, Regenerative medicine
- Tony Wang, CBER, COVID research
- Luísa Camacho, NCTR, Skin
- Qiang Shi, NCTR, Precision medicine, DILI
- Li Pang, NCTR, Precision medicine, cardiotoxicity
- Hector Rosas–Hernandez, NCTR, Alzheimer’s research
- Weida Tong, NCTR, Computational work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