NIH Update
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Director, NICEATM

ICCVAM Public Forum
May 24, 2018
Microphysiological Systems Program
“Tissue Chips for Drug Screening”

GOAL: Develop an *in vitro* platform that uses human tissues to evaluate the safety and toxicity of promising therapies.

- All 10 human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Skin
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary

- Physiologically relevant, genetically diverse, and pathologically meaningful
- Modular, reconfigurable platform
- Tissue viability for at least 4 weeks
- Community-wide access

Slide courtesy of Dan Tagle, NCATS
Microphysiological Systems Consortium 2012-2020
“Tissue Chips for Drug Screening”

- Platform and cell resources development
- Functional Validation, training set of compounds, multi-organ integration

$75 M over 5 years – cell source, platform development, validation and integration (NCATS, CF, NIBIB, NIEHS, NICHD, ORWH, NCI)

$75 M over 5 years - development of 10-organ platforms

**FDA provides insight and expertise throughout the program

Publications: (as of Oct 2017; cited over 5600 times)
A total of 506 original and review articles published in top tier journals, including Nature Medicine, Nature Communications, Nature Materials, PNAS, Science, Science Translational Medicine, etc.
**Tissues Typically Collected and Examined in a Pharma GLP Tox Study**

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Tissues</th>
<th>Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>•Adrenals •Aorta •Bone (femur) •Bone marrow (sternum) •Brain (at least 3 different levels) •Cecum •Colon •Corpus and cervix uteri •Duodenum •Epididymides •Esophagus •EyesGall bladder (if present) •Harderian gland •Heart •Ileum •Gall bladder (if present) •Kidneys •Kidneys •Heart</td>
<td>•Kidneys •Gall bladder (if present) •Harderian gland •Heart •Ileum •Jejunum •Kidneys •Liver •Lung (with main-stem bronchi) •Lymph nodes •Mammary glands •Nasal turbinates •Ovaries and fallopian tubes •Pancreas •Pituitary •Prostate •Rectum •Salivary gland •Sciatic nerve</td>
<td>•Seminal vesicle (if present) •Skeletal muscle •Skin •Spinal cord (3 locations) •Spleen •Stomach •Testes •Thymus (if present) •Thyroid/parathyroid •Trachea •Urinary bladder •Vagina •Zymbal's gland</td>
</tr>
<tr>
<td>•Any other tissues showing abnormality</td>
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</table>
Microphysiological Systems (MPS) for Disease Modeling and Efficacy Testing (2017-2022)

GOAL:

- Develop highly reproducible and translatable in vitro models for preclinical efficacy studies using MPS
  
  • discovery and validation of translatable biomarkers
  
  • development of standardized methods for preclinical efficacy testing and definitive efficacy testing of candidate therapeutics using best practices and rigorous study design
  
- 5-year UG3/UH3 program; $75 M Funding partnerships between NCATS and other NIH ICs (NIAMS, NICHD, NIDCR, NIDDK, NIEHS, NINDS, NIBIB, NHLBI, ORWH)

- Non-funding partnerships with FDA and IQ Consortium
Kam Leong, Columbia U
Proteus Syndrome and DiGeorge Syndrome

Danielle Benoit, Lisa Delouise, Catherine Ovitt, U Rochester
Radiation-induced xerostomia

Kevin Kit Parker, William Pu, Harvard U
Barth syndrome, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy

Steven George, David Curiel, Stacey Rentschler, UC Davis and WashU atrial fibrillation

Joseph Vincent Bonventre, Luke Lee, Brigham and Women’s autosomal dominant/recessive models of polycystic kidney disease, Focal segmental glomerulosclerosis

Christopher Hughes, UC Irvine Hereditary hemorrhagic telangiectasia, Port Wine stain, Sturge-Weber syndrome

Rocky Tuan, U Pittsburgh Osteoarthritis, inflammatory arthritis, adipose-mediated diabetic joint complications

Clive Svendsen, Cedars-Sinai
ALS; Parkinson’s Disease

Aaron Bowman, Kevin Ess, John Wiksoo, Vanderbilt U tuberous sclerosis complex (TSC) epilepsy, DEPDC5-associated epilepsy, & associated cardiac dysfunction

Gordana Vunjak-Novakovic, Columbia U
Dox induced cardiomyopathy; multi-system pathologies involving heart, liver, skin, bone and vasculature

Donald Ingber, Harvard U influenza infection, COPD

Jonathan Himmelfarb, U Washington apolipoprotein L1 mediated kidney disease, drug induced and host-pathogen interaction induced renal thrombotic microangiopathies

Teresa Woodruff, Northwestern U Polycystic Ovarian Syndrome

George Truskey, Duke U rheumatoid arthritis, atherosclerosis

Dan Tagle, NCATS
Integrated Chemical Environment: ICE

• Uphold FAIR principles for ICCVAM Data

• Provide intuitive access to high quality (curated) data and tools to support:
  – chemical evaluations,
  – data integration, and
  – model development

• Enable wider community to engage in the use of alternative and computational approaches for assessing chemical safety
### Latest Release: Formulations

**Select Chemicals**
- Acute Dermal Toxicity
- Acute Oral Toxicity
- Acute Inhalation Toxicity
- Primary Skin Irritation
- Primary Eye Irritation
- Dermal Sensitization

**Enter one CASRN per line.**

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**Download**

**Send the CASRNs to the Integrator**
Brian Berridge - NTP Associate Director
DNTP Translational Toxicology Pipeline Plan

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Define Hypotheses & Design a Testing Strategy

Short-term in vivo Tests

Longer-term in vivo Tests

Fit for purpose products

Inform Public Health Decisions