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

- Adrenals
- Aorta
- Bone (femur)
- Bone marrow (sternum)
- Brain (at least 3 different levels)
- Cecum
- Colon
- Corpus and cervix uteri
- Duodenum
- Epididymides
- Esophagus
- Eyes
- Gall bladder (if present)
- Harderian gland
- Heart
- Ileum
- Gall bladder (if present)
- Harderian gland
- Kidneys
- Jejunum
- Liver
- Lung (with main-stem bronchi)
- Lymph nodes
- Mammary glands
- Nasal turbinates
- Ovaries and fallopian tubes
- Pancreas
- Pituitary
- Prostate
- Rectum
- Salivary gland
- Sciatic nerve
- 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

- Any other tissues showing abnormality
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 Wikso, 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

NIH National Center for Advancing Translational Sciences
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
### Select Chemicals

- Acute Dermal Toxicity
- Acute Oral Toxicity
- Acute Inhalation Toxicity
- Primary Skin Irritation
- Primary Eye Irritation
- Dermal Sensitization

#### Enter one CASRN per line.

- 172345-26-5
- 1928-43-4
- 1918-00-9
- 10007-85-9
- 120068-37-3
- 106-24-1
- 1071-83-6

### Formulations

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DNTP Translational Toxicology Pipeline Plan

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Longer-term in vivo Tests

Short-term in vivo Tests

Define Hypotheses & Design a Testing Strategy

Fit for purpose products

Inform Public Health Decisions
NICEATM-ILS Staff