Advances in the development of tissue chip technologies for toxicity testing

STATE OF THE SCIENCE ON DEVELOPMENT AND USE OF NAMS FOR CHEMICAL SAFETY TESTING

December 17, 2019

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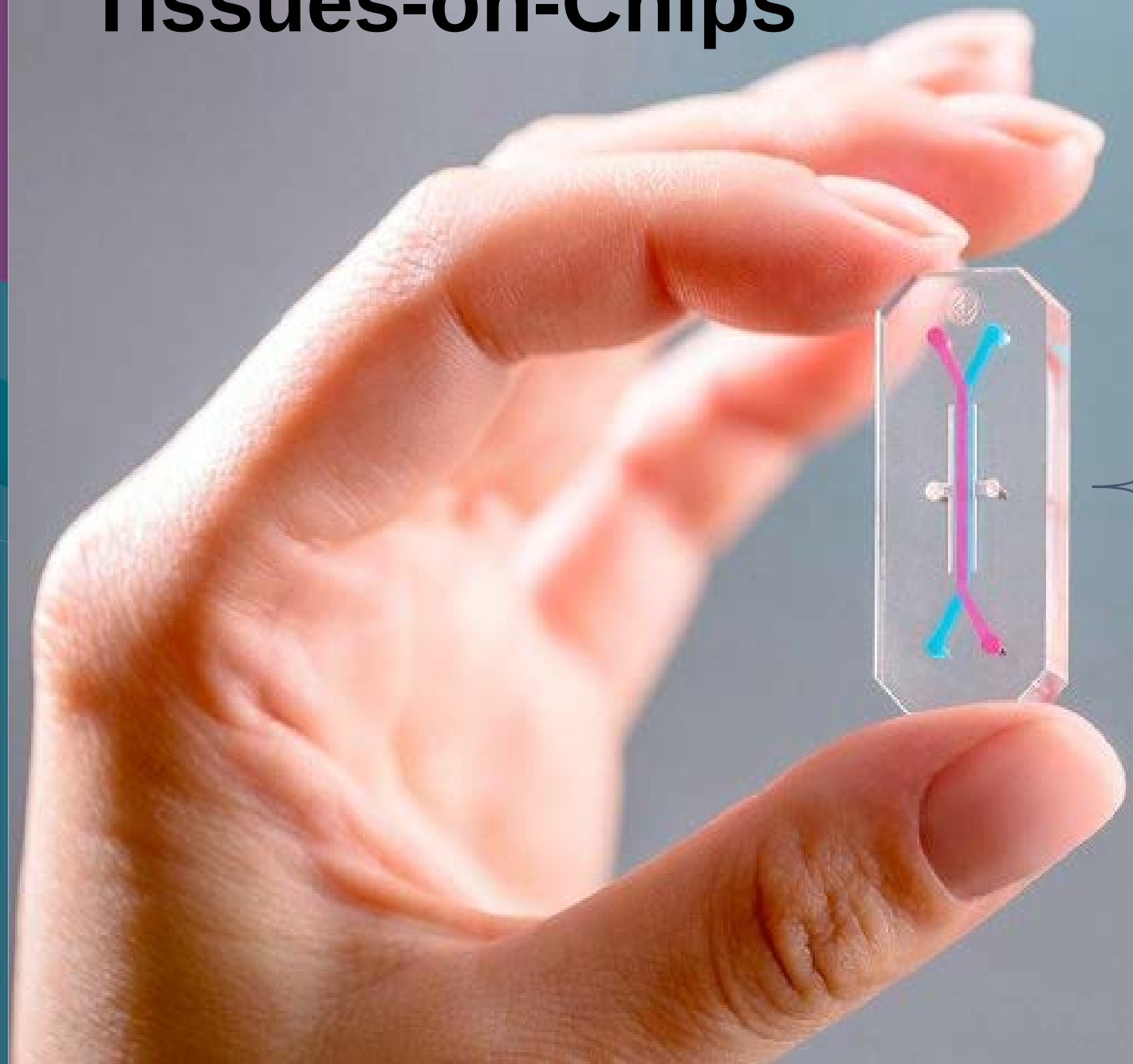
Tissues-on-Chips



Scaffold

Cells

Structure

Spatial and Temporal Patterning

Perfusion

Bioreactor

Innervation

Host Response

Functional Readout

Computational Design

- Microfluidic cell culture devices
- Created with microchip manufacturing methods
- Contains continuously perfused chambers
- Seeded by human-derived cells
- Cytoarchitecture mimics tissue- and organ-level physiology
- High-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities

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Tissue Chips 1.0 to Predict Drug Safety (2012-2017)

- James A. Thomson; Morgridge Institute for Research at the University of Wisconsin-Madison
Human induced pluripotent stem cell and embryonic stem cell-based models for predictive neural toxicity and teratogenicity

- John P. Wikswo; Vanderbilt University
Neurovascular unit on a chip: Chemical communication, drug and toxin responses

- Steven C. George; University of California, Irvine
An integrated in vitro model of perfused tumor and cardiac tissue

- D. Lansing Taylor; University of Pittsburgh
A 3-D biomimetic liver sinusoid construct for predicting physiology and toxicity

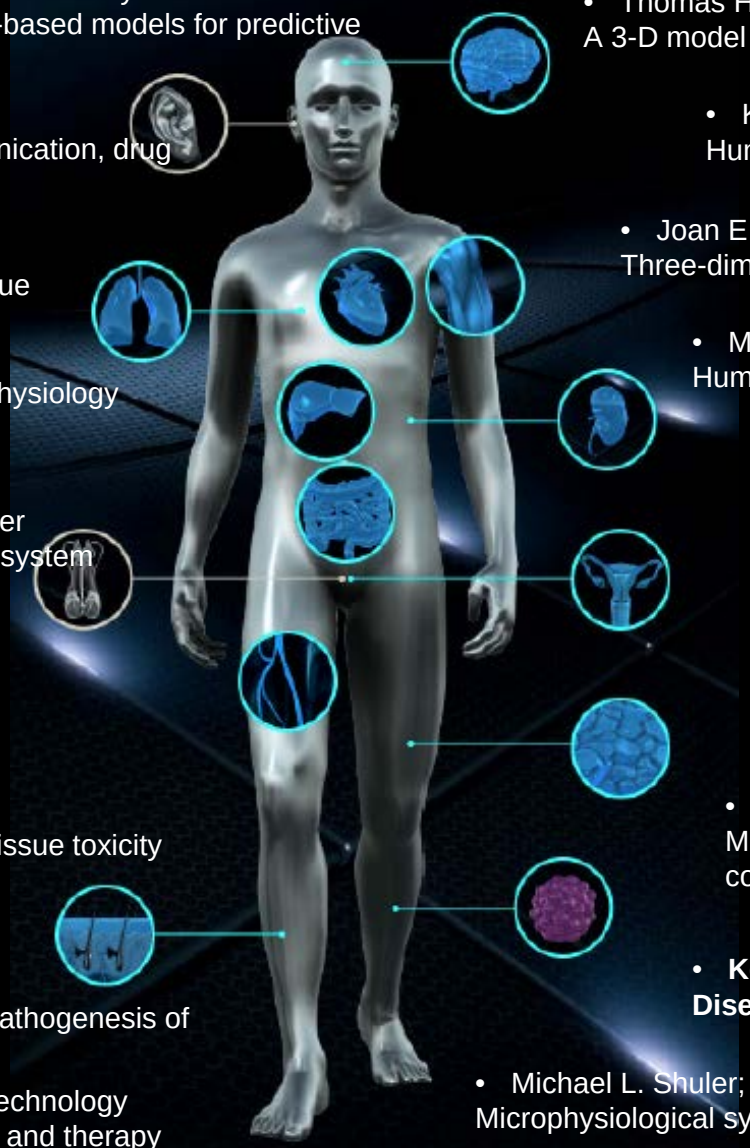
- James M. Wells; Cincinnati Children's Hospital Medical Center
Generating human intestinal organoids with an enteric nervous system

- John P. Lynch; University of Pennsylvania
Modeling oxidative stress and DNA damage using a gastrointestinal organotypic culture system

- George A. Truskey; Duke University
Circulatory system and integrated muscle tissue for drug and tissue toxicity

- Rocky S. Tuan; University of Pittsburgh
Three-dimensional osteochondral micro-tissue to model pathogenesis of osteoarthritis

- Linda Griffith; Massachusetts Institute of Technology
All-human microphysical model of metastasis and therapy



- Thomas Hartung; Johns Hopkins University
A 3-D model of human brain development for studying gene/environment interactions

- Kevin K. Parker; Harvard University
Human cardio-pulmonary system on a chip

- Joan E. Nichols; The University of Texas Medical Branch at Galveston
Three-dimensional human lung model to study lung disease and formation of fibrosis

- Mark Donowitz; Johns Hopkins University, Baltimore
Human intestinal organoids: Pre-clinical models of non-inflammatory diarrhea

- **Teresa Woodruff; Northwestern University**
Ex Vivo Female Reproductive Tract Integration in a 3-D Microphysiologic

- Jonathan Himmelfarb; University of Washington, Seattle
A tissue-engineered human kidney microphysiological system

- Gordana Vunjak-Novakovic; Columbia University Health Sciences
Integrated Heart-Liver-Vascular Systems for Drug Testing in Human Health and Disease

- Angela Christiano; Columbia University Health Sciences
Modeling complex disease using induced pluripotent stem cell-derived skin constructs

- **Kevin E. Healy; University of California, Berkeley**
Disease-specific integrated microphysiological human tissue models

- Michael L. Shuler; Cornell University
Microphysiological systems and low cost microfluidic platform with analytics

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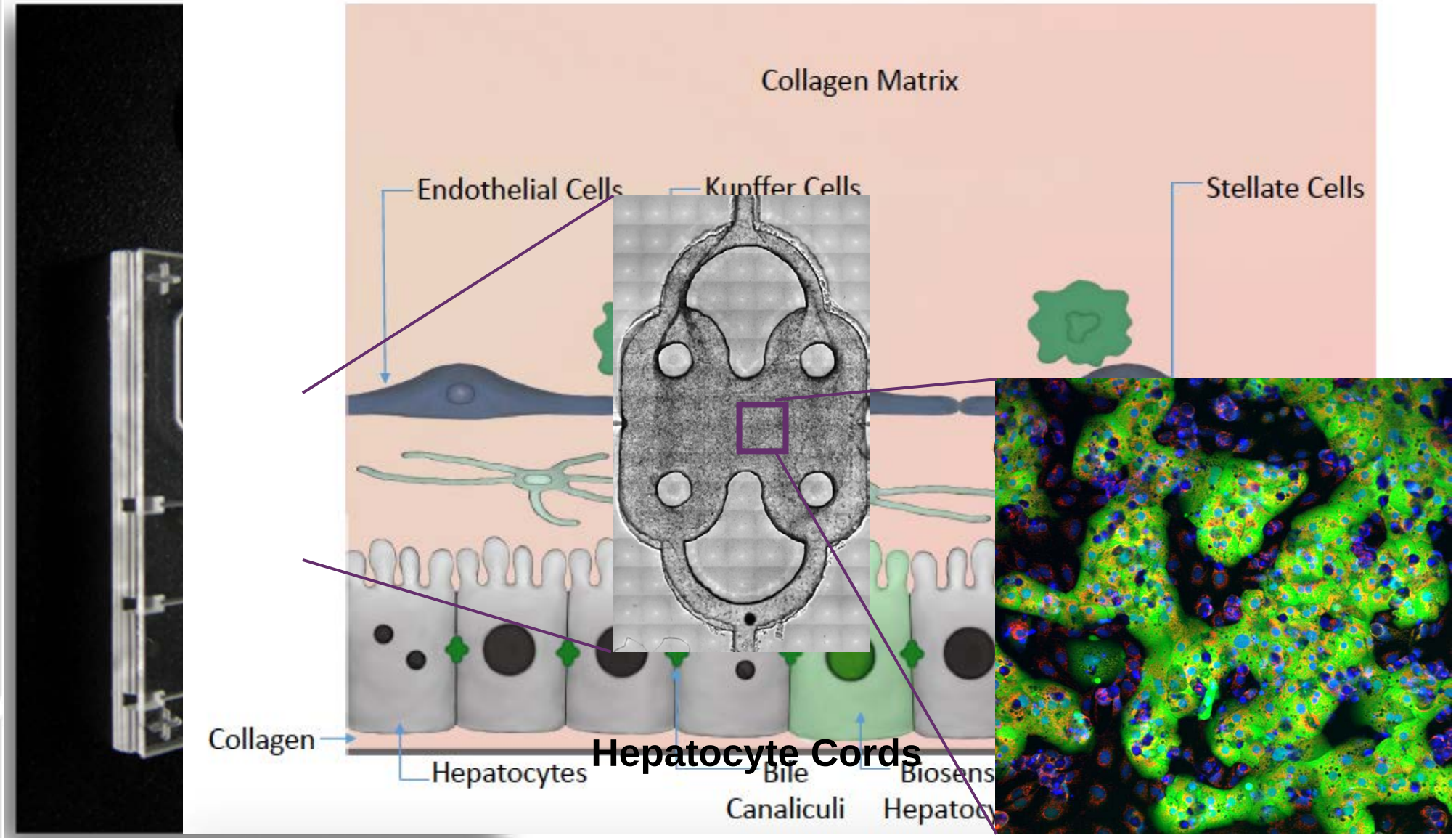
Liver on Chip: Self-assembly of Hepatocytes and NPC



Lans Taylor; Univ. Pittsburgh

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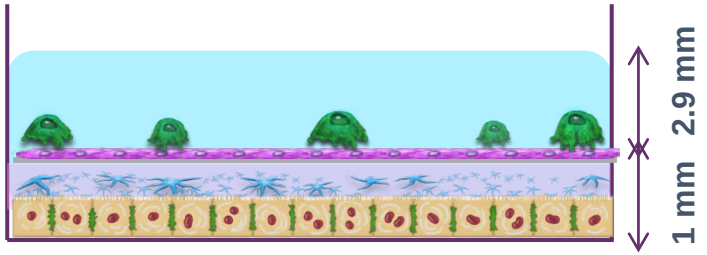
4 Week Co-culture of
Human Hepatocytes and Non-Parenchymal Cells

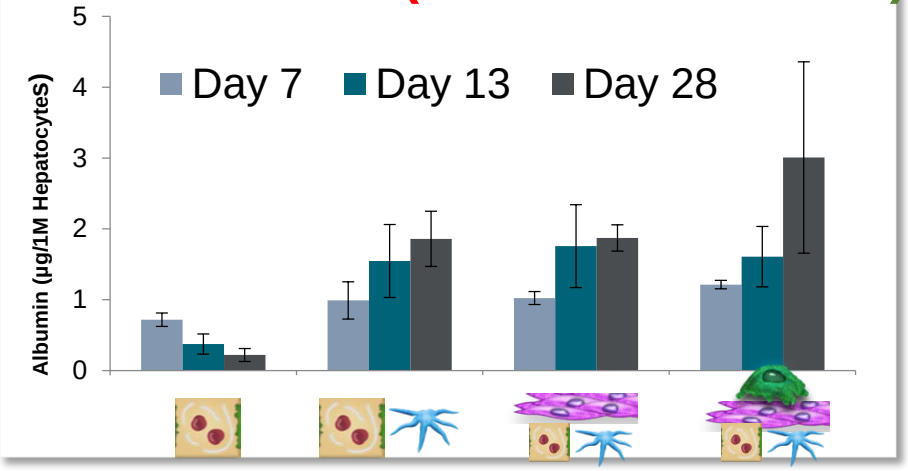
Transwell Culture Format



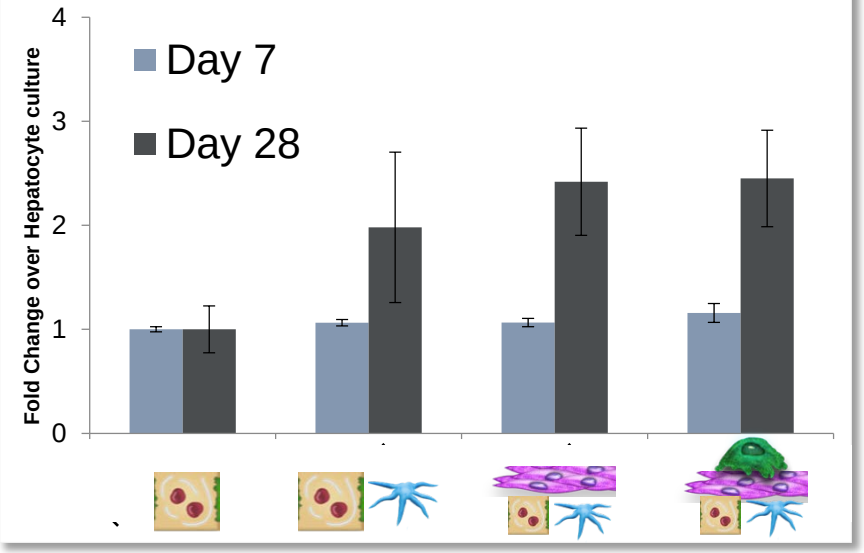
Volume/Cell (nL/cell) = 3

Distance btw cells (mm) = 1

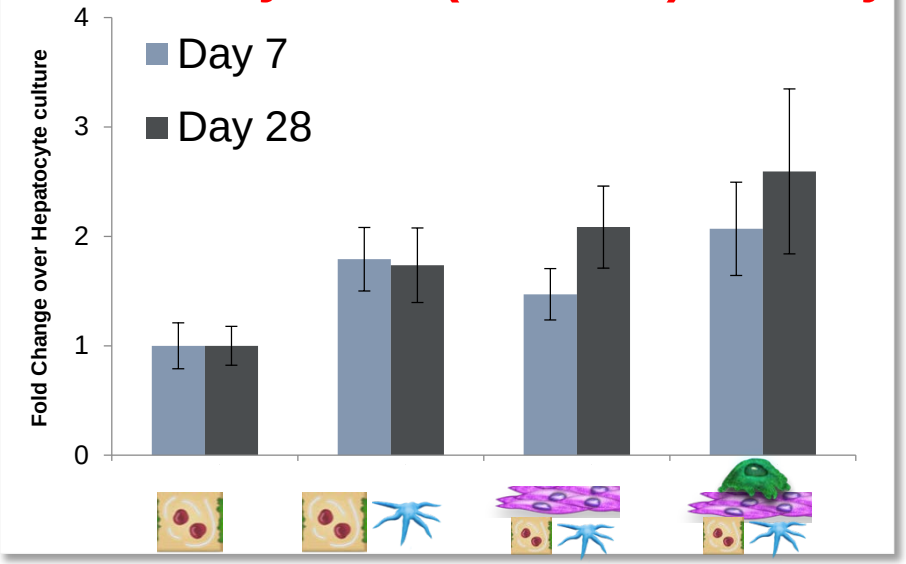
Stable Function (Albumin Secretion)



LDH in cell Lysates (Viable Cultures)



Stable Enzymatic (CYP3A4) Activity



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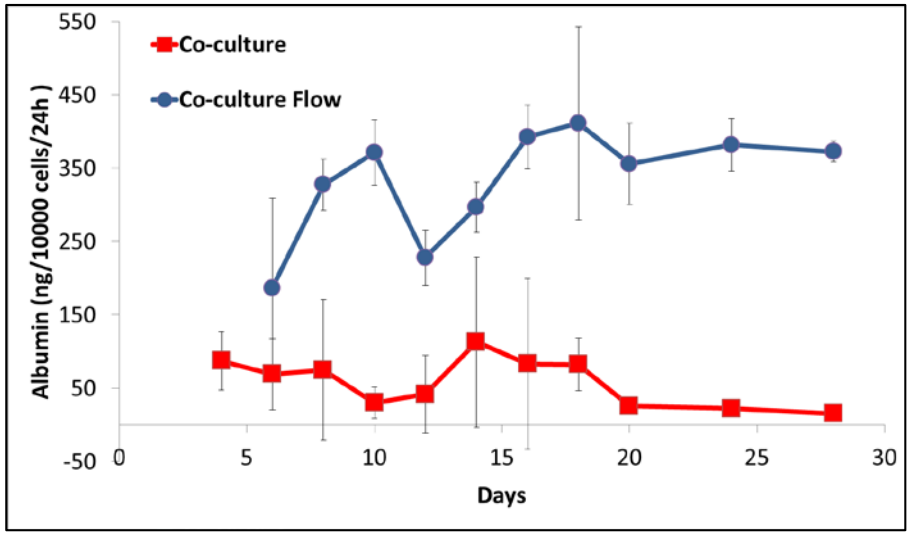
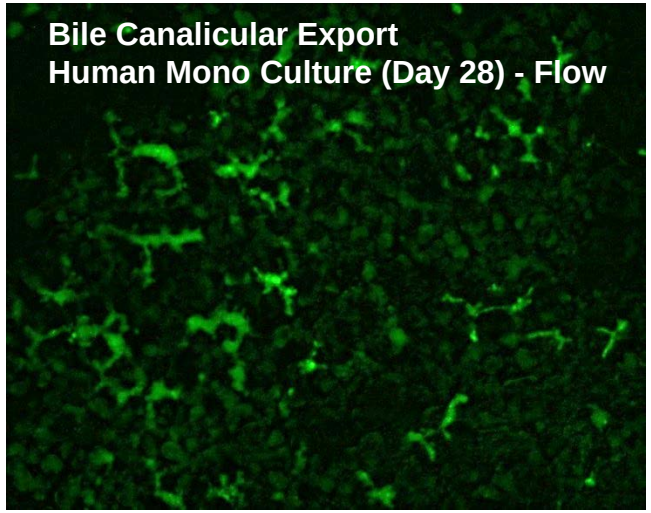
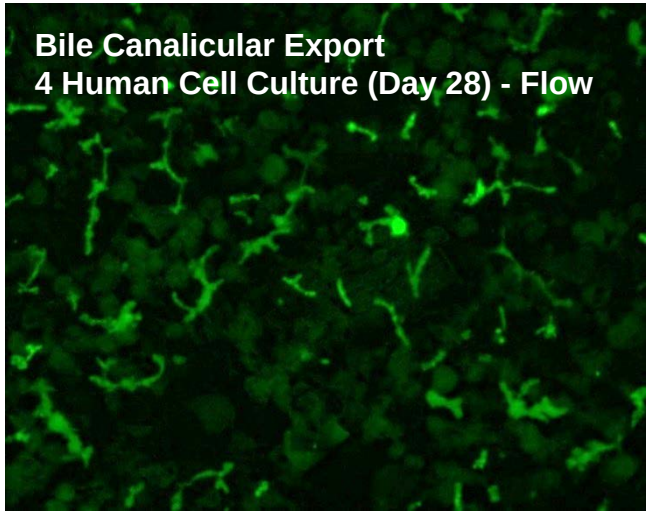
4 Week Culture: Static vs. Flow

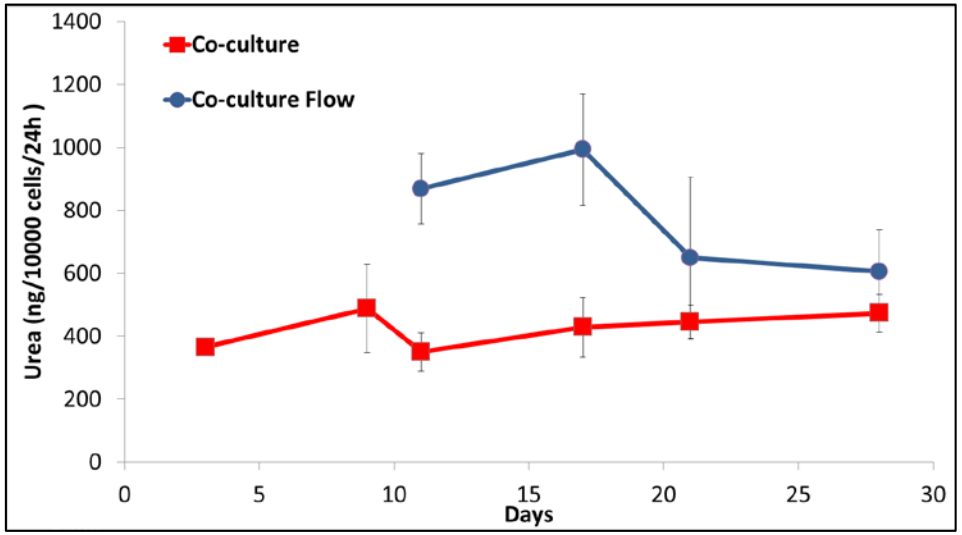
Albumin Secretion in Flow vs Static Culture







Urea Secretion in Flow vs Static Culture



Vernetti et. al. 2016. A human liver microphysiology platform for investigating physiology, drug safety and disease models. Expt Biol Med 241: 101

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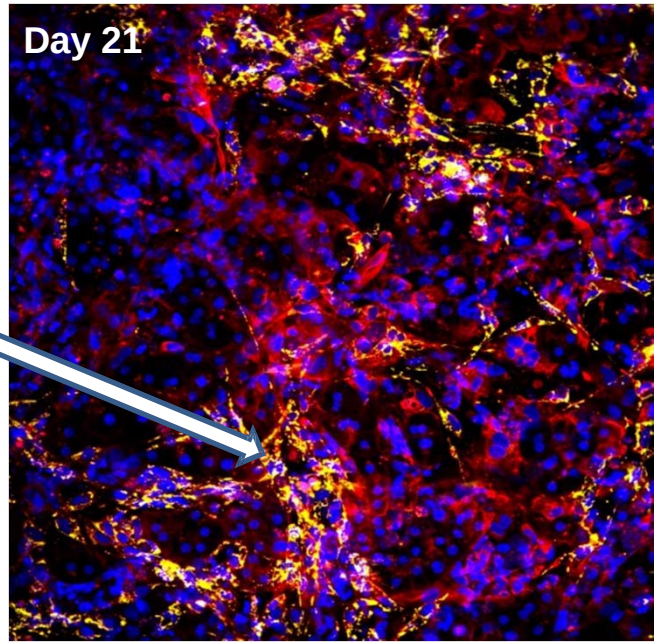
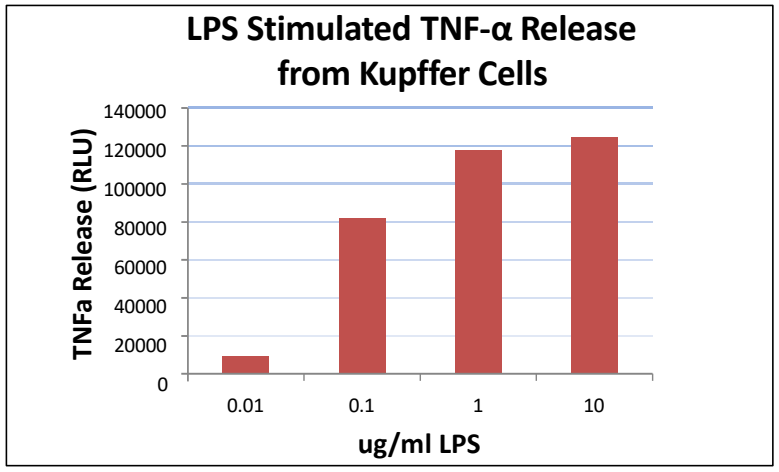
Methotrexate induced fibrosis and LPS Immune-mediated hepatotoxicity

Fibrotic response after stellate cell activation in response to methotrexate

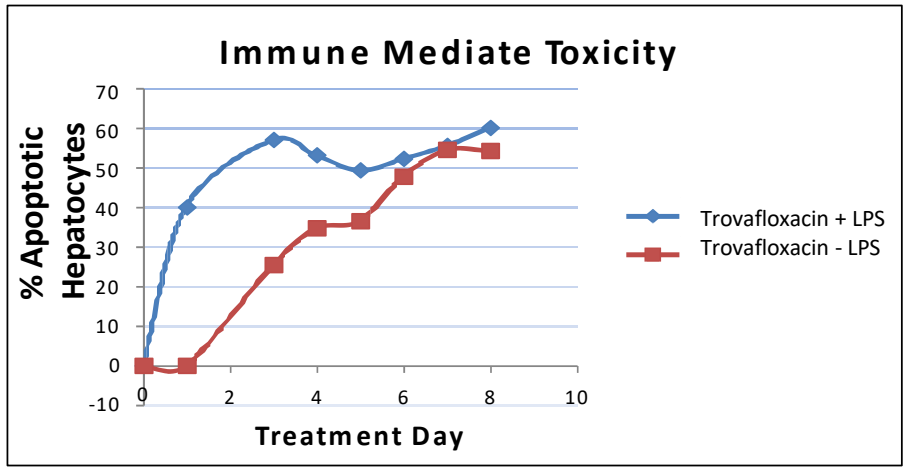
Stellate cells Express Collagen 1A2



Immune-Mediated Hepatotoxicity by LPS



LPS + Trovafloxacin induces apoptosis



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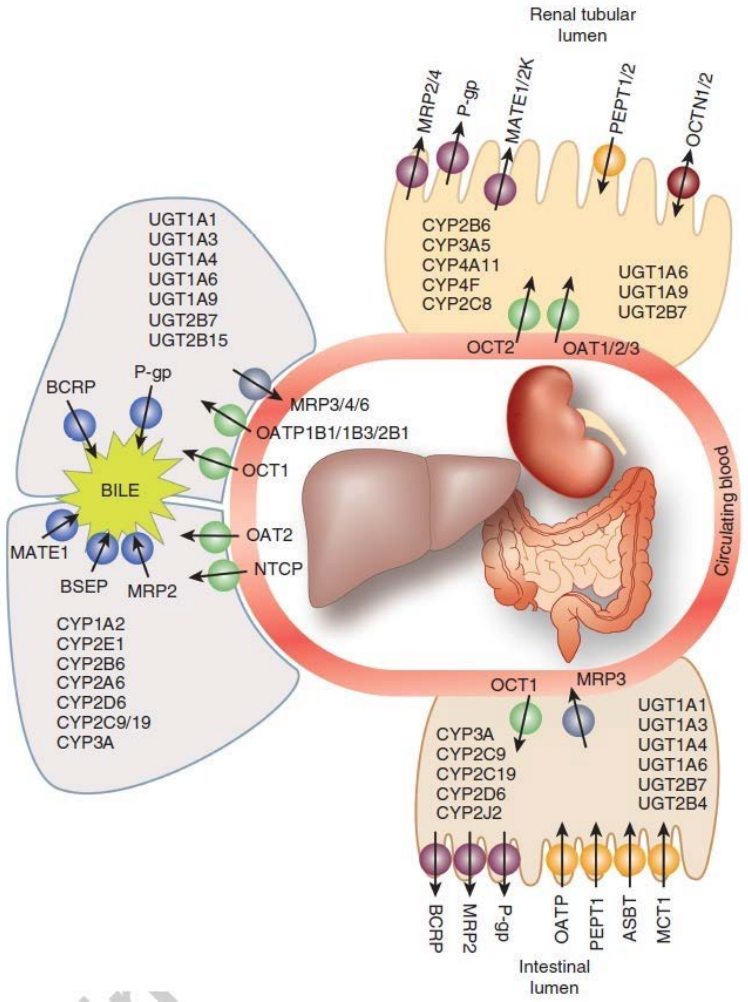
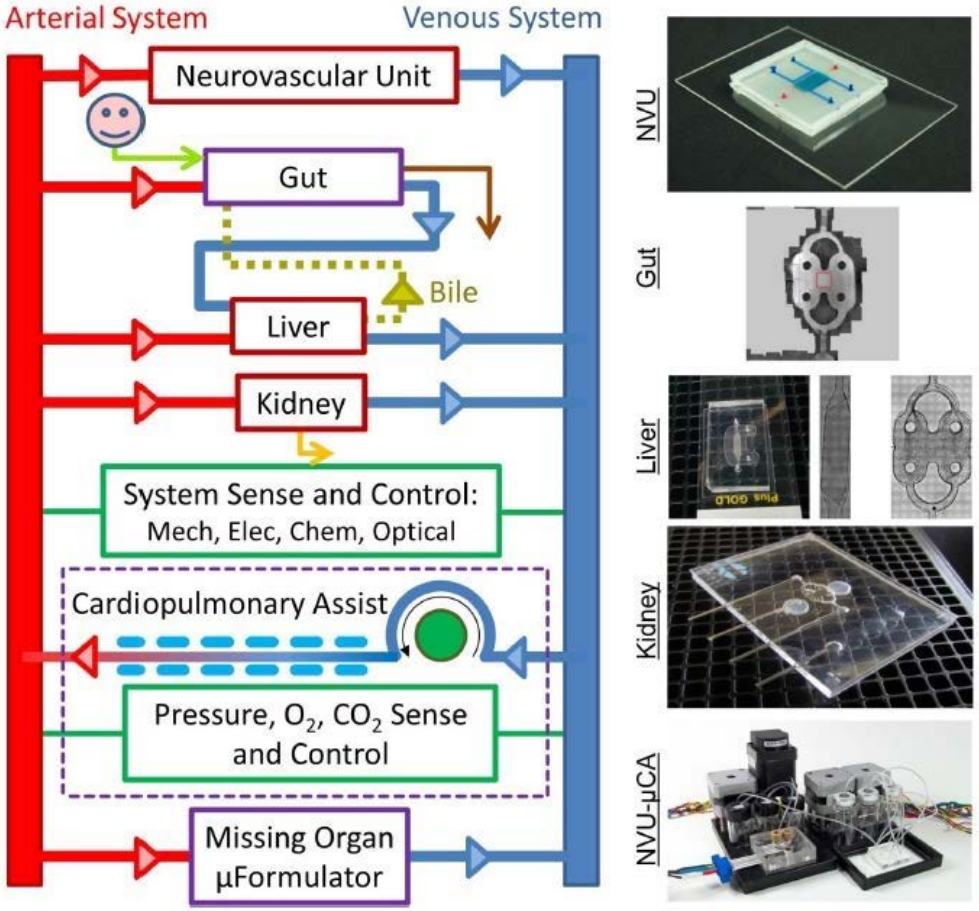
Integration of Multiple Tissue Chips



Yeung et al, Kidney International



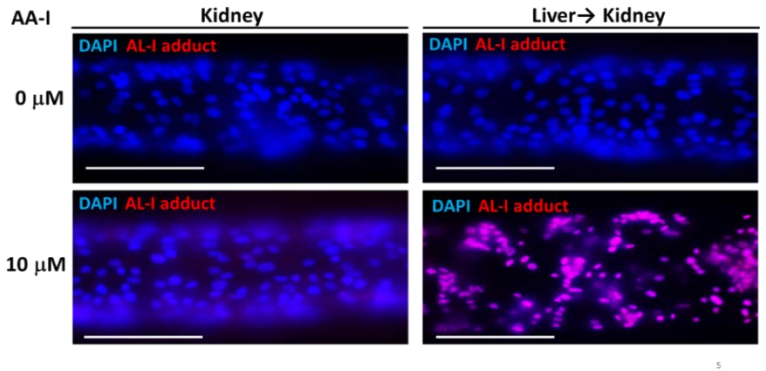
Vernetti et al, Scientific Reports 2017

Functional and Physical Coupling

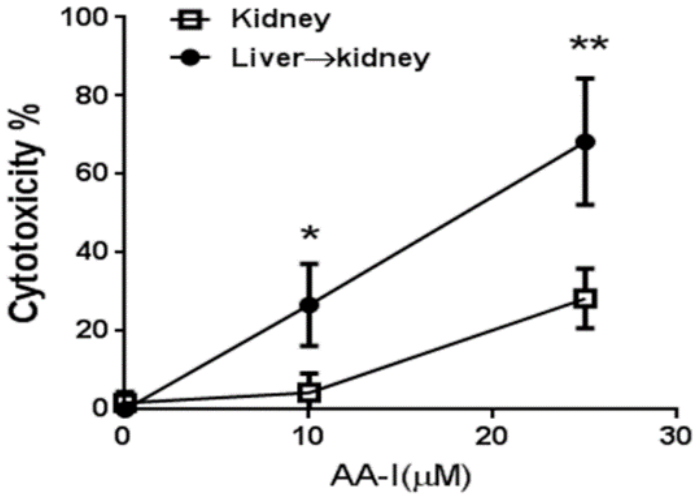
Human Mechanism of Aristolochic Acid (AA) Nephropathy Elucidated by Coupled Liver-Kidney MPS

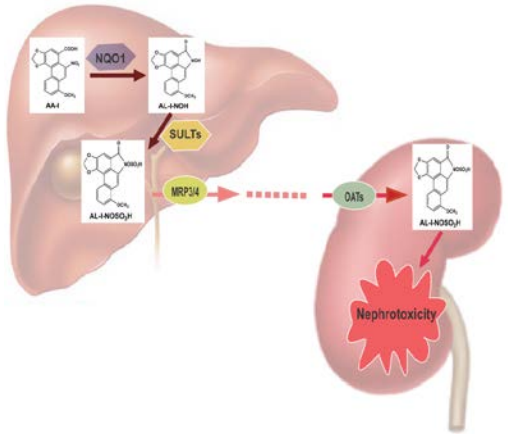
Vernetti et al, Scientific Reports 2017

- AA is highly nephrotoxic and a Class I carcinogen for the lower urinary tract
- Identified as etiological agent for Chinese Herbs Nephropathy and Balkan Endemic Nephropathy
- Mode of action via adducting to DNA and proteins
- Pathways of human bioactivation not fully elucidated



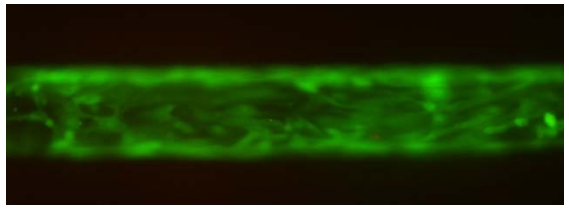
Hepatocyte AA bioactivation required



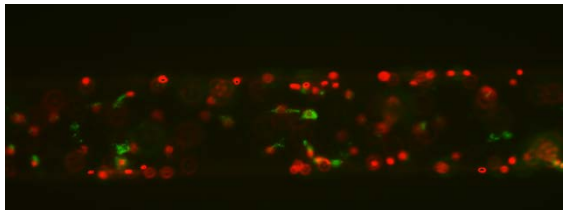


Multistep model

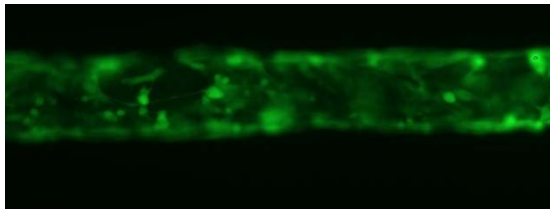
Vehicle control



AL-I-NOSO3 25 uM



AL-I-NOSO3 25 uM + Pro 2mM



(AL-I-NOSO3 as causative agent: Live/Dead staining following direct kidney 24 h exposure)

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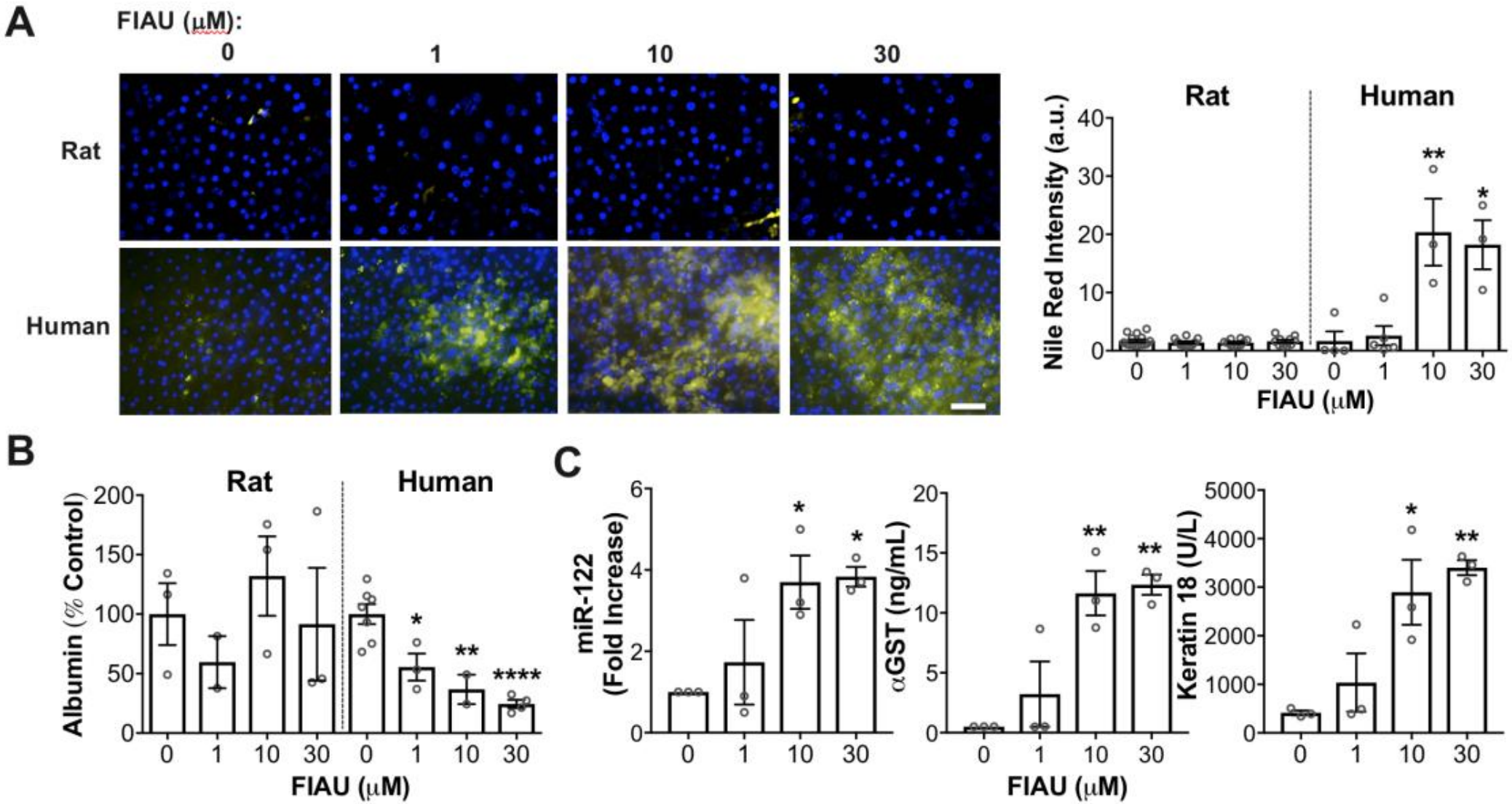
Species Differences in Steatosis using Rat and Human Liver-Chips following Fialuridine (FIAU) Treatment



Science Translational Medicine, 11: 2019

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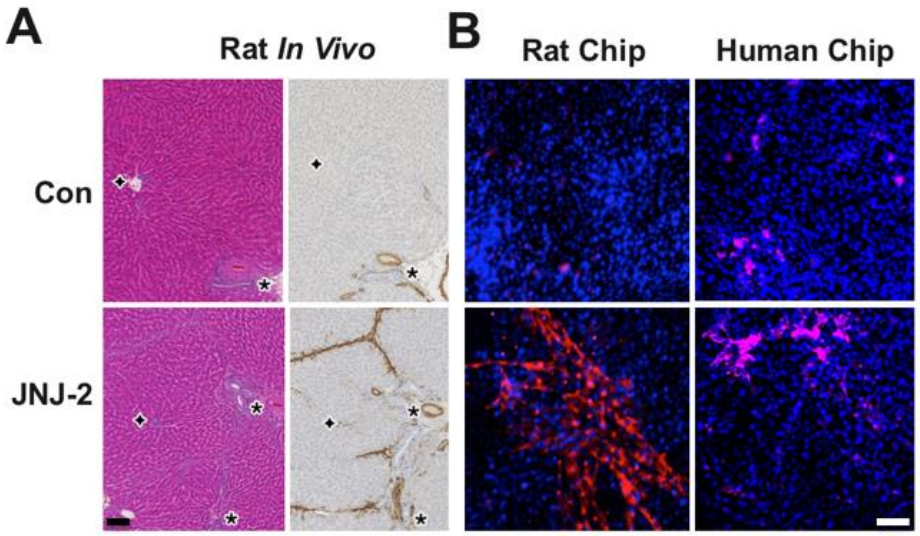
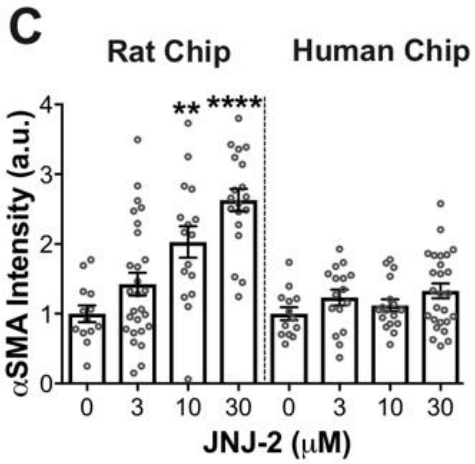
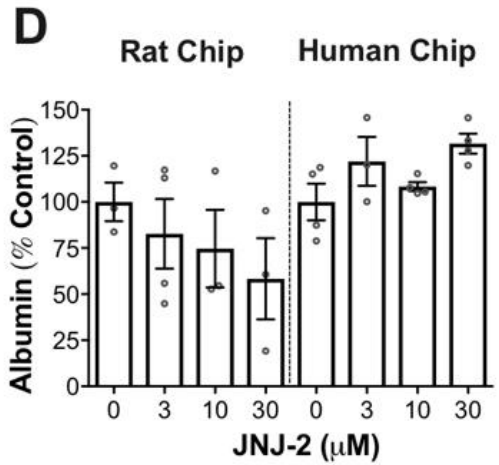
Species Differences in Fibrosis using Rat and Human Liver-Chips







Science Translational Medicine, 11: 2019

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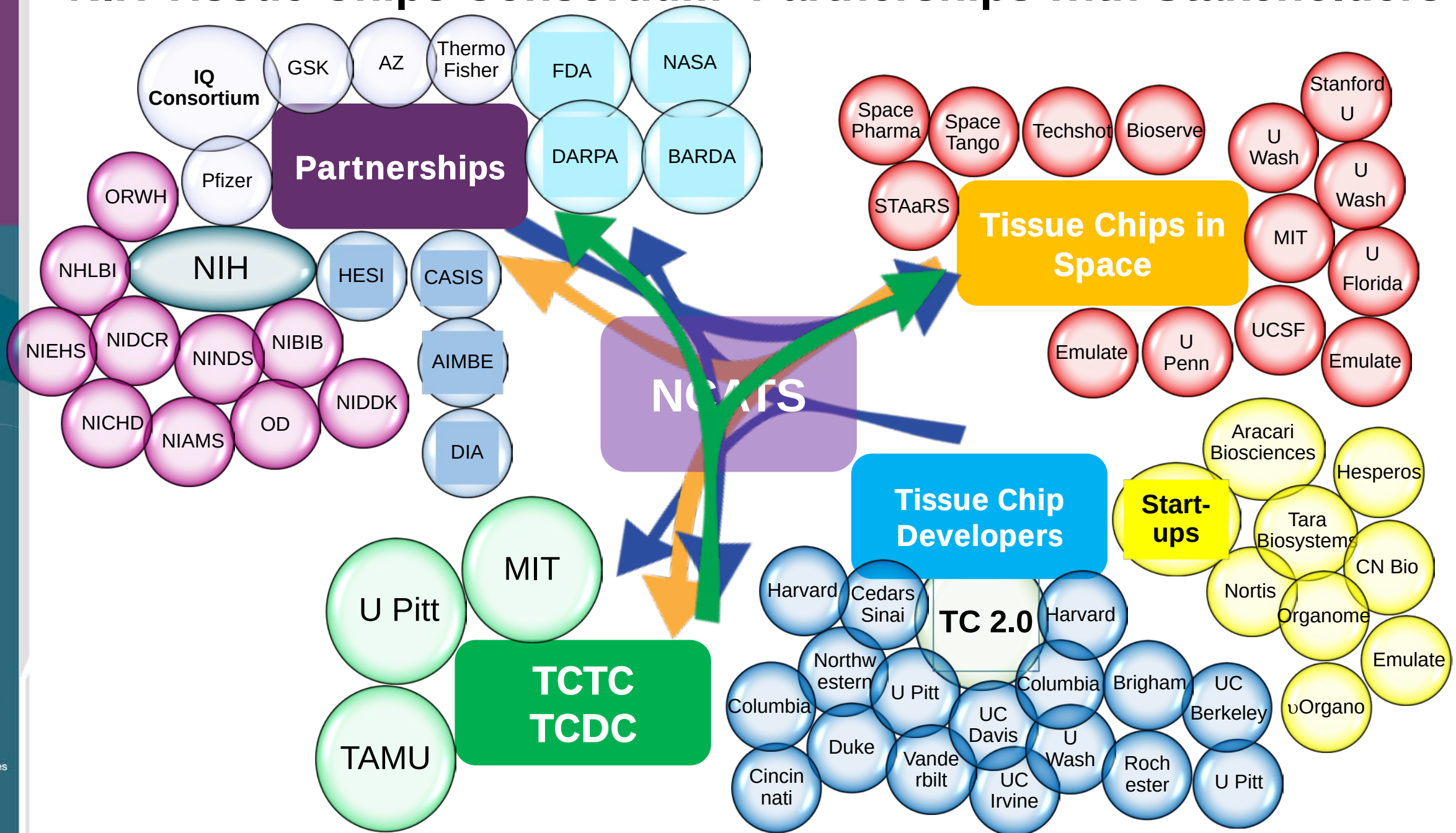
NIH Tissue Chips Consortium- Partnerships with Stakeholders



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NIH Tissue Chips 2.0 for Disease Modeling and Efficacy Testing 2018 to 2022)

Kam Leong, Columbia U
Proteus Syndrome and DiGeorge Syndrome

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

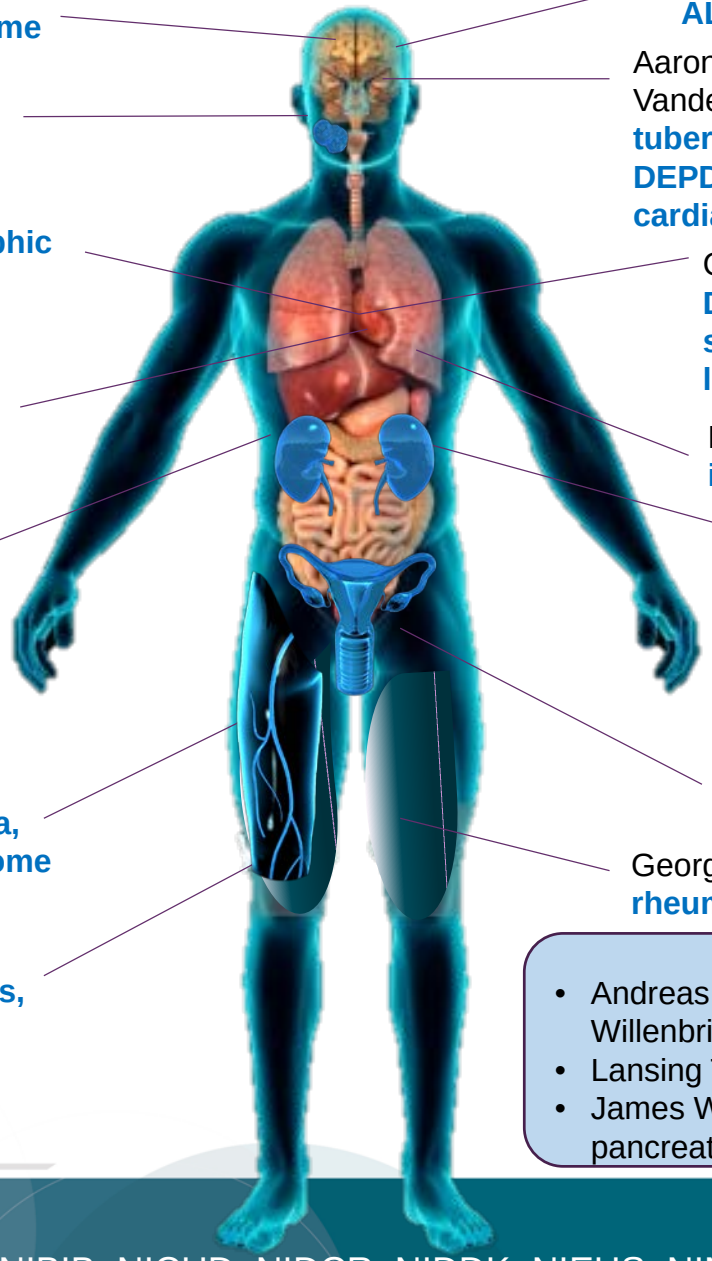
Kevin Kit Parker, William Pu, Harvard U
Barth syndrome, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy

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 Wikswo, 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

Type-2 Diabetes Mellitus

- Andreas Stahl, Kevin Healy, Matthias Hebrok, Edward Hsiao, Holger Willenbring, UC Berkeley - Pancreatic islet, liver, adipose
- Lansing Taylor, U Pittsburgh – Vascularized liver and pancreatic islets
- James Wells, Moo-Yeal Lee, Cincinnati Children's Hospital - Liver, pancreatic islet and intestine

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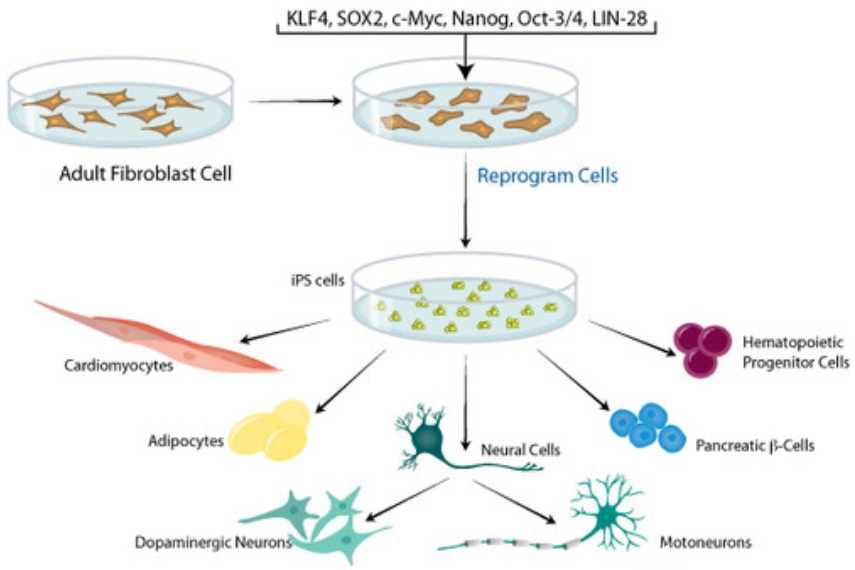
Current NIH Initiatives for Tissue Chips



Human body on Chip

- Co-culture of many differentiated iPSC-derived cell types per tissue architecture and composition
- Integration of different tissue chips to form human body on chip
- Genome editing to introduce various polymorphisms on isogenic iPSC lines
- Developmental/pediatric response to drugs/toxins
- Rare diseases

Just awarded:

- **Nociception-on-chip RFA-TR-19-003** (*5 awards*)
- **Immune system-on chip PAR-19-138** (*3 awards*)
- **ADRD on chip RFA-NS-19-027** (*1 award*)

To be reviewed:

- **"Clinical Trials-on-chips" for Precision Medicine (You-on-chip) RFA-TR-19-014**

New or ongoing Initiatives:

- **Nervous system MPS PAR-16-398**

(Standard dates until January 8, 2020)

- **Cancer Biomimetics PAR-19-113**

(Standard dates until January 8, 2022)

- **BBB interface on chip RFA-HL-20-21**

(December 2, 2019; October 19, 2020)

- **Biomimetics for Infectious diseases RFA-AI-20-009** *(to be released)*

NIH National Center for Advancing Translational Sciences

Tissue Chips Consortium – Lead: Danilo A. Tagle

Program Managers: **Lucie Low, Ph.D. and Passley Hargrove-Grimes**

Trans-NIH Microphysiological Systems Working Group

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- Guillermo Arreaza-Rubin (NIDDK)
- David Balshaw (NIEHS)
- Steven Becker (NEI)
- Lisa Begg (OD)
- Bonnie Burgess-Beusse (NIDDK)
- Warren Casey (NIEHS)
- Preethi Chander (NIDCR)
- Ricardo Cibotti (NIAMS)
- Ki-Cha Flash (NCATS)
- Nancy Freeman (NIDCD)
- Daniel Gossett (NIDDK)
- Halonna Kelly (NIAID)
- Anthony Kirilusha (NIAMS)
- Lillian Kuo (NIAID)
- Timothy Lavaute (NINDS)
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- Vicky Whittemore (NINDS)
- Bradley Wise (NIA)
- Da-Yu Wu (NIDA)
- Nastaran Zahir (NCI)

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  - Paul Brown, Ph.D., CDER
  - Tracy Chen, Ph.D., DABT, OC
  - Karen Davis-Bruno, Ph.D., CDER
  - Suzanne Fitzpatrick, Ph.D., CFSAN
  - Timothy McGovern, Ph.D., CDER
  - Donna Mendrick, Ph.D., NCTR
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  - Bill McLamb, Ph.D.
  - Melissa Rhodes, Ph.D.
  - Liz Warren, Ph.D.
  - Patrick O'Neill
- **IQ MPS Affiliate**
  - IQ MPS Executive Committee (EC): IQ MPS Chair (Will Proctor, Genentech), Vice Chair (Monicah Otieno, Janssen) and Vice Chair-Elect (Terry van Vleet, AbbVie); IQ-NCATS engagement workstream POC (Jason Ekert GSK)
  - Szczepan Baran, Ph.D., Novartis
  - Ananthsrinivas Chakilam, Ph.D., Vertex
  - Yvonne Dragan, Ph.D., Takeda
  - David Duignan, Ph.D., AbbVie
  - Jeetendra Eswaraka, DVM, Ph.D., Amgen
  - Jason Ekert, Ph.D., GSK
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  - Jinping Gan, Ph.D., BMS
  - Peggy Guzzie-Peck, Ph.D., DABT, J & J
  - Claire Jeong, Ph.D., GSK
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  - William Proctor, Ph.D., DABT, Genentech
  - Terry Van Vleet, Ph.D., DABT, AbbVie
  - Rahda Sura, Ph.D., AbbVie
  - Matthew Wagoner, Ph.D., Takeda
  - David Watson, Ph.D., Eli Lilly
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- **E-Newsletter:** https://ncats.nih.gov/enews
- **Announce Listserv:** https://bit.ly/1sdOI5w

Thank you!

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