Program Update: Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing

Cures Acceleration Network Review Board meeting
December 9, 2016

DANILO A. TAGLE, PH.D.
ASSOCIATE DIRECTOR FOR SPECIAL INITIATIVES
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES
NATIONAL INSTITUTES OF HEALTH

NCATS

NIH National Center for Advancing Translational Sciences

Outline

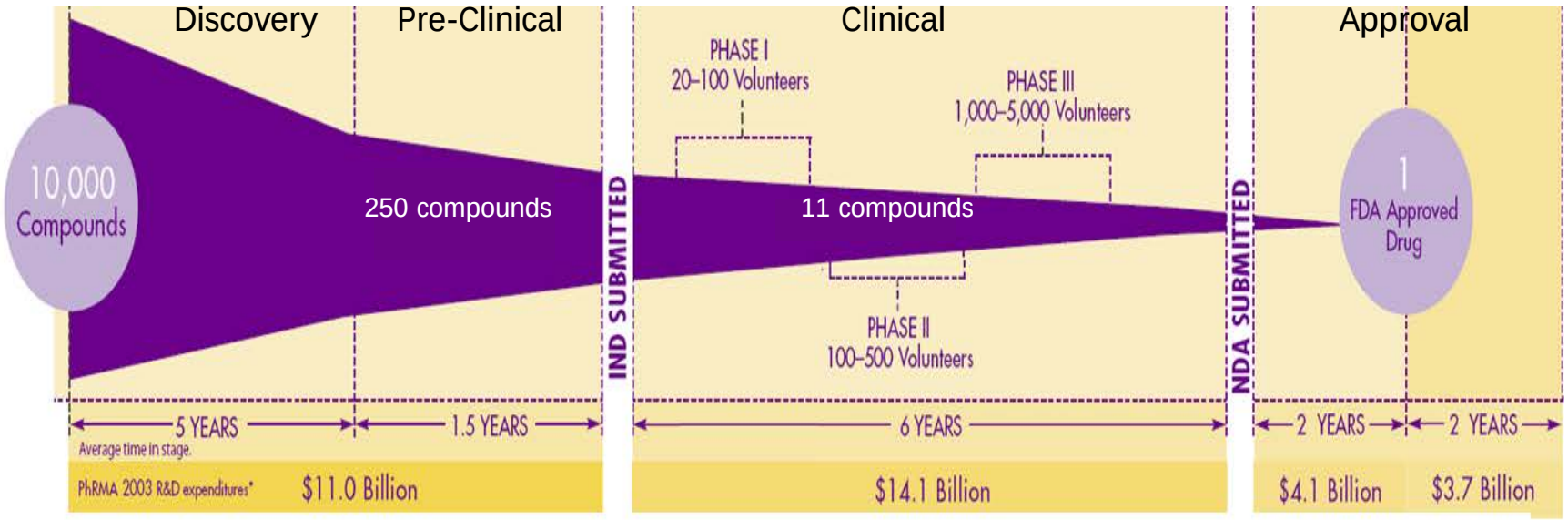
- NIH Microphysiological Systems program
  - » Background
  - » Partnerships and Programmatic Management
  - » CAN RB metrics
- Program Highlights
- Current Initiatives
- Future Directions

NIH – FDA Joint Leadership Council

Advancing Regulatory Science Program

- Started in 2010 through the NIH Common Fund
- RFA-RM-10-006 "Advancing Regulatory Science through Novel Research and Science-Based Technologies (U01) "
- MOU between NIH and FDA; $7M over 3 years
- 4 awards were made that address four distinct, high priority areas of regulatory science which include:
  - Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design
  - Replacement Ocular Battery
  - **Heart-Lung Micromachine for Safety and Efficacy Testing**
  - Characterization/Bioinformatics-modeling of Nanoparticle: Complement Interactions

High Attrition Rate Makes Drug Development a Risky Business



P*h*RMA, 2005

2015 profile
BIOPHARMACEUTICAL RESEARCH INDUSTRY

KEYFACTS 2015

RESEARCH AND DEVELOPMENT (R&D)[1]

Average time to develop a drug = more than 10 years
Percentage of drugs entering clinical trials resulting in an approved medicine = less than 12%

DEVELOPMENT COSTS

Average cost to develop a drug (including the cost of failures):[2]

- 2000s–early 2010s = $2.6 billion
- 1990s–early 2000s = $1.0 billion*
- 1980s = $413 million
- 1970s = $179 million

R&D SPENDING

Year	PhRMA members[3]
2014	$51.2 billion (est.)
2013	$51.6 billion
2012	$49.6 billion
2011	$48.6 billion
2010	$50.7 billion
2009	$46.4 billion
2008	$47.4 billion
2007	$47.9 billion
2006	$43.0 billion
2005	$39.9 billion
2000	$26.0 billion
1990	$8.4 billion
1980	$2.0 billion

SALES

Generic share of prescriptions filled:[4]
2000 = 49%
2013 = 88%

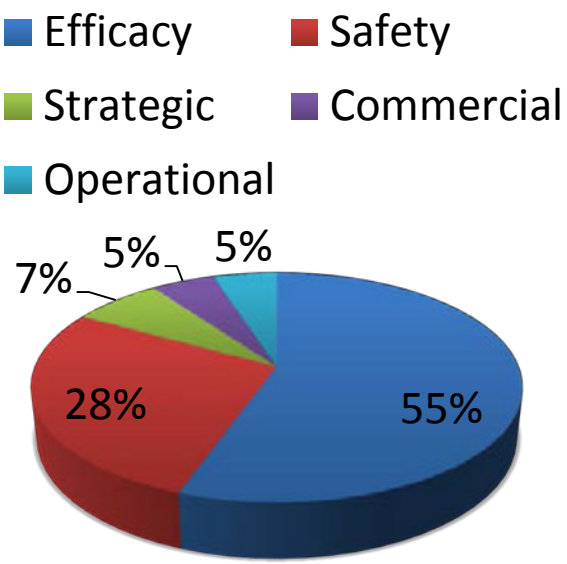
National Center for Advancing Translational Sciences

PhRMA RESEARCH • PROGRESS • HOPE

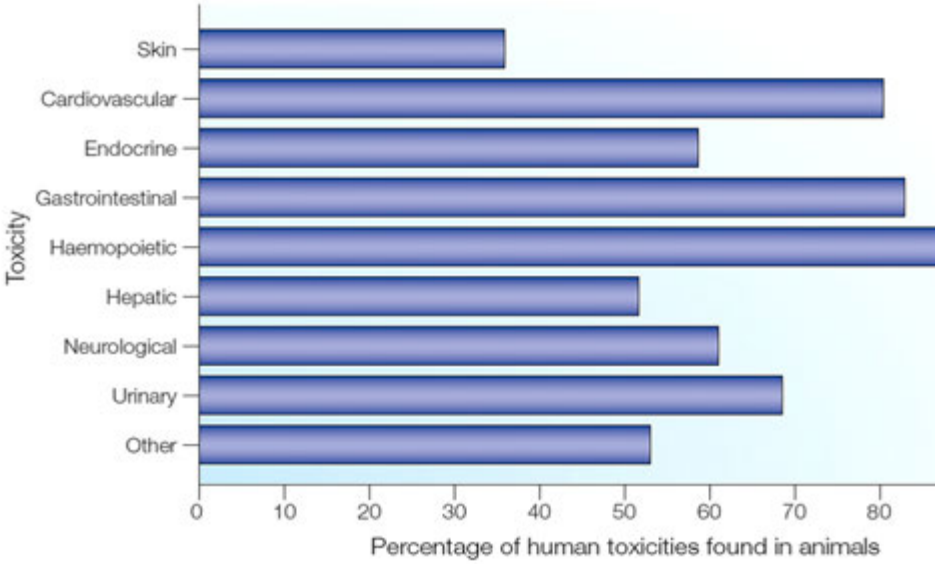
Need for new technologies in risk assessment over current paradigms

Causes of High Attrition Rate in Drug Development

Drug Failure Modes



Human toxicities found in animals



Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)

Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)

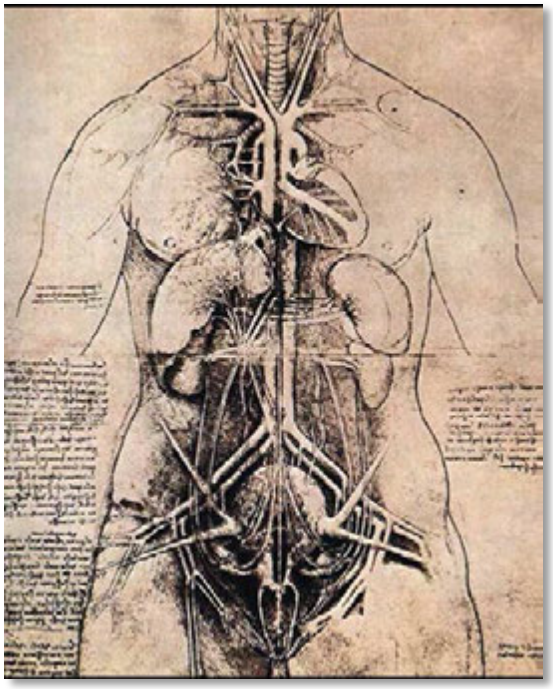
Need for Better Predictive Tools

- 92% of all drugs found safe and therapeutically effective in animal tests fail during human clinical trials due to their toxicity and/or inefficacy, and are therefore not approved.[1]
- Over half of the drugs that gain FDA approval must later be withdrawn or relabeled due to severe, unexpected side effects that animal testing did not predict.[2]
- Adverse drug reactions are the fourth leading cause of death in the United States, killing around 100,000 patients annually and costing up to $4 billion in direct hospital costs alone.[3]
- More than 2 million Americans received emergency hospital treatment in 2009 for an adverse reaction to a prescribed medication.[4]
- "Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies." [5, 6]

1 Innovation or stagnation: Challenge and opportunity on the critical path to new medical products. U.S. Food and Drug Administration Report, March 2004, p. 8.
2 U.S. General Accounting Office. FDA Drug Review: Postapproval Risks 1976-1985. Publication GAO/PEMD-90- 15, Washington, D.C., 1990.
3 JAMA. 1998;279(15):1200-1205. doi:10.1001/jama.279.15.1200
4 The DAWN Report December 28, 2012
5 Mike Leavitt, Secretary of Health and Human Services, U.S. Department of Health and Human Services (Food and Drug Administration press release, FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient, January 12, 2006).
6 Andrew C. von Eschenbach, M.D. then Acting Commissioner of the FDA (prepared statement for FDA Teleconference: Steps to Advance the Earliest Phases of Clinical Research in the Development of Innovative Medical Treatments, January 12, 2006).

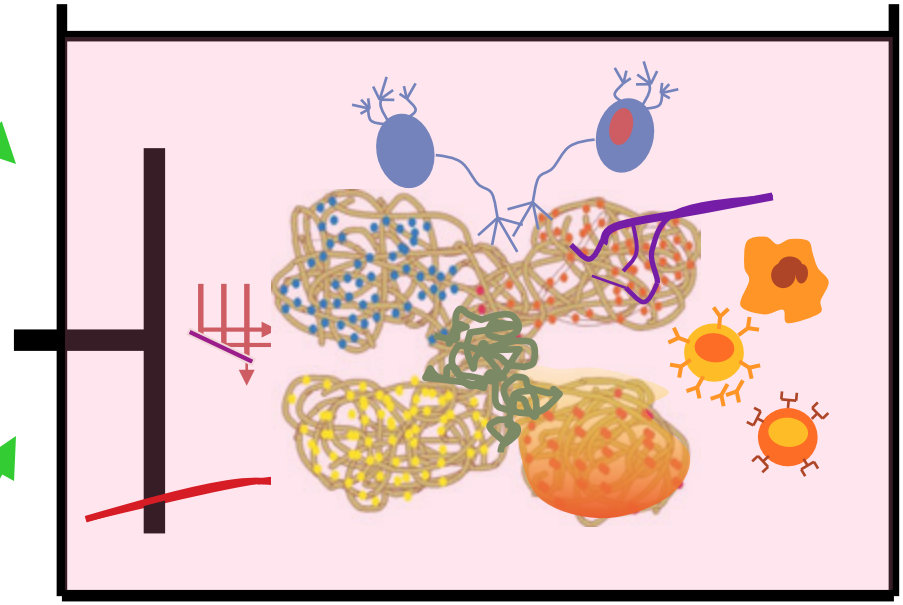
Microphysiological Systems Program "Tissue Chips"

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.



- All ten 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.

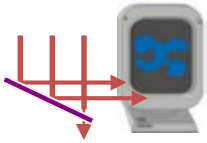
Microphysiological Systems –
A Multidisciplinary, Team-Science Approach



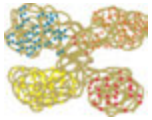
Computational Design
- systems integration
- multi-scale modeling
- simulation
- feedback

Scaffold
- purified ECM
- synthetic polymers
- composites

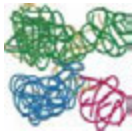
Functional Readout
- real-time, label-free, non-destructive sensing
- imaging

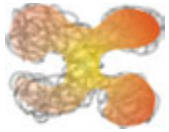


Cells
- stem/progenitor
- differentiated
- mixed cell types
- gene editing

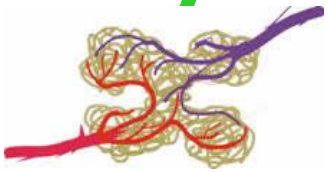


Structure
- porosity
- topography
- stiffness



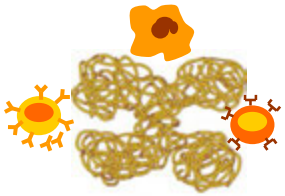


Spatial/Temporal Patterning
- cytokine gradients
- controlled release

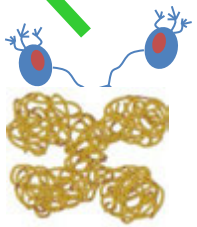


Perfusion
- embedded channels
- vascularization

Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics



Host Response
- generalized inflammation
- specific immunity



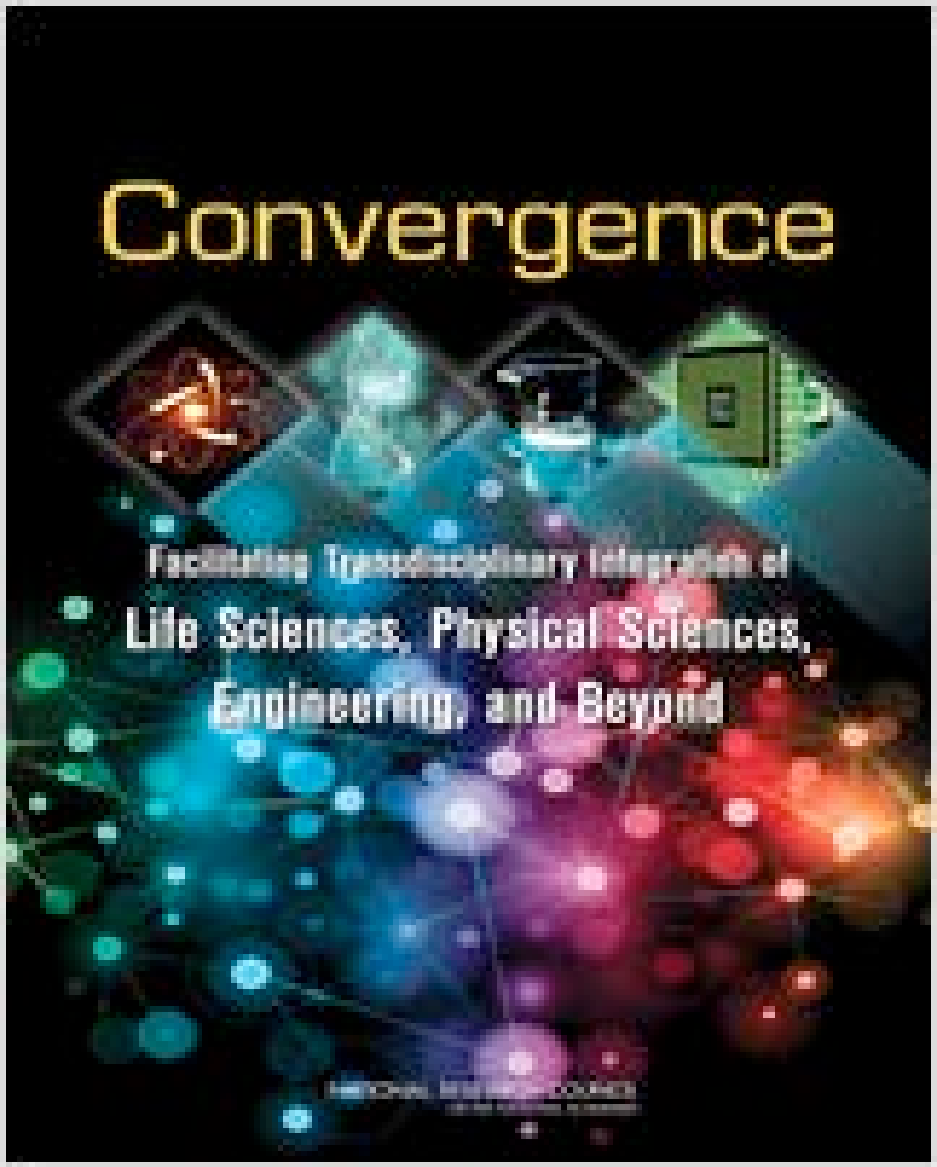
Innervation
- signal propagation
- coordinated response

National Center for Advancing Translational Sciences

Convergence: Facilitating Transdisciplinary Integration of Life Sciences, Physical Sciences, Engineering, and Beyond

- Convergence of the life sciences with fields including physical, chemical, mathematical, computational, engineering, and social sciences is a key strategy to tackle complex challenges and achieve new and innovative solutions.
- Tissues on chips cited as an example of **Convergence**.

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council



Microphysiological System (Tissue Chips) Program

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.

National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

2012-13 | 2013-14 | 2014-15 | 2015-16 | 2016-17

National Institutes of Health

$75 M over 5 years – cell source, platform development, validation and integration

$75 M over 5 years – platform dev

****FDA provides insight and expertise throughout the program**

Current Goals:

- **Integration**
- **Compound testing**
- **Validation**
- **Partnerships**
- **Adoptions of the tech to the community**

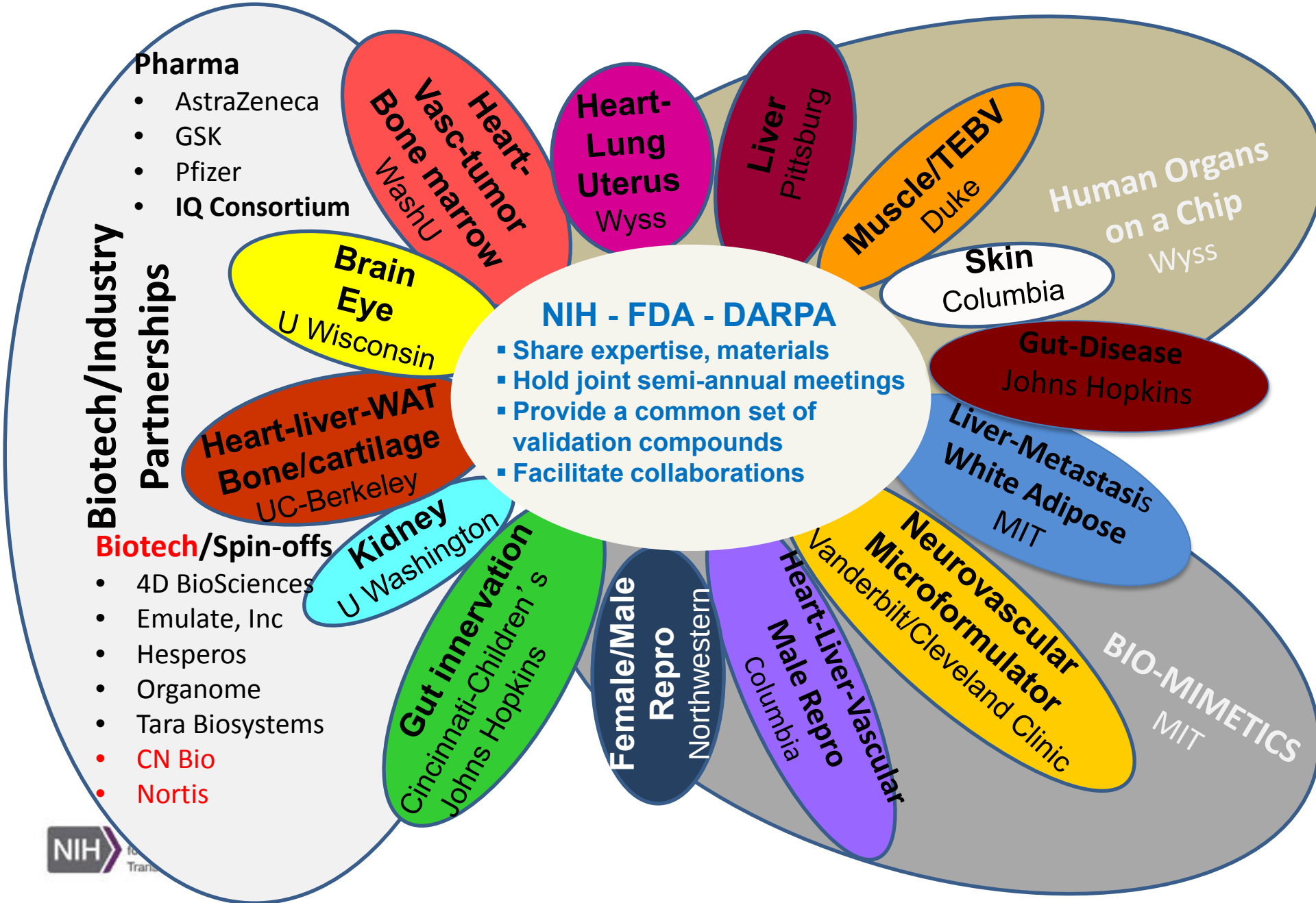
Programmatic Management

- Memorandum of Understanding (MOU)
  - » NIH and DARPA independently manage and fund respective programs
  - » FDA provides regulatory and toxicology expertise
  - » Program coordination between NIH and DARPA
  - » Sharing of scientific expertise, materials, resources
  - » Jointly held semi-annual meetings
- Cooperative Agreement award mechanism
  - » Milestone-driven
  - » Significant government staff involvement and oversight (20 NIH ICs; 41 program staff)
  - » Representatives from major divisions at FDA
  - » Monthly webex-based lab meetings with each awardee
- Microphysiological Systems Consortium
  - » Synergistic interactions and collaborations among NIH and/or DARPA funded investigators
  - » Pre-competitive sharing of resources, platforms, and expertise
  - » Coordinated approach to address challenges and emergent needs
  - » Coordinated publications

CAN RB Metrics for Success

- Administrative outcomes:
  - » Robust number of proposals and prioritization of scientifically meritorious projects
  - » Benchmarking awarded projects to milestones
  - » Follow-on funding to address scientific opportunities
  - » Collaborations within consortia and with industry to advance findings
- Project outcomes:
  - » Publications, IP-generated
  - » Number of distinct organ models developed
  - » Proof of concept that organ-on-chip technology predicts adverse drug reactions (ADR) from compounds known to cause them
  - » Demonstration of safety for FDA-approved and "safe" compounds
  - » Defined regulatory path for use in the approval process
  - » Technology transferred
- Transformative outcomes (longer term):
  - » Therapeutic areas of Investigational New Drug applications containing chip data
  - » Identification of compounds with high likelihood of ADRs and compounds that are designated as safe
  - » Establishment of a standard for quality of predictability and reproducibility compared with animal models and human studies
  - » Predicted percent reduction of speed of medicine development or failure in areas of unmet need
  - » Integration and use of organ or tissue chip technology as part of compound selection in pharmaceutical development programs
  - » Reduction of serious adverse events in human studies and clinical use
  - » Reduction of animal testing
  - » Industry and regulatory adoption of technology

Microphysiological Systems Consortium



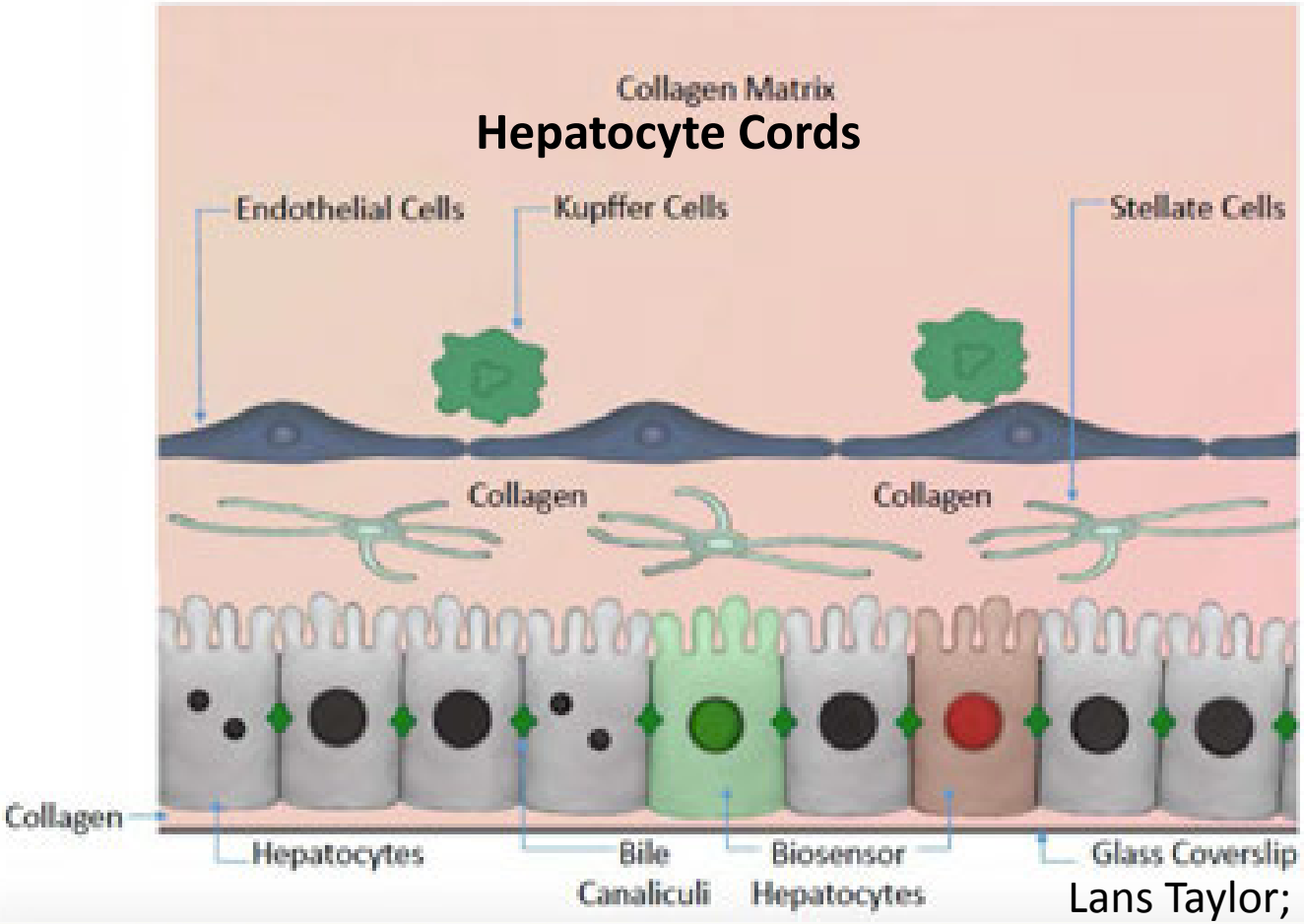
Program Highlights:

- Liver
- Functional readouts
  - Biosensors
  - RNAseq
  - Histology
- Perfusion
- Innervation

NCATS

Example: Liver-on-chip

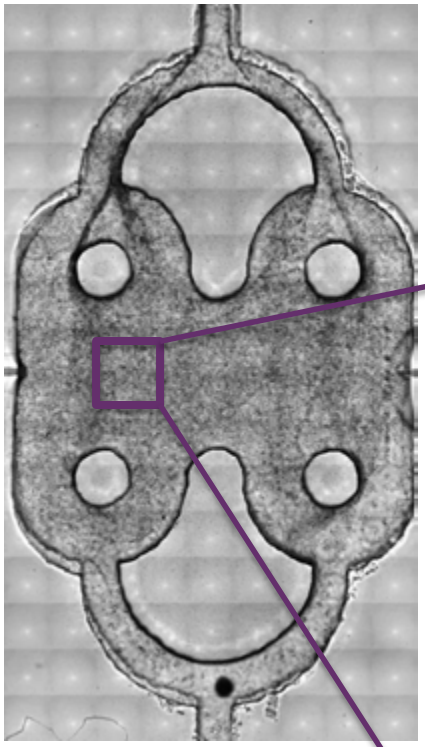
Self-assembly of Hepatocytes and NPC in Nortis MPS



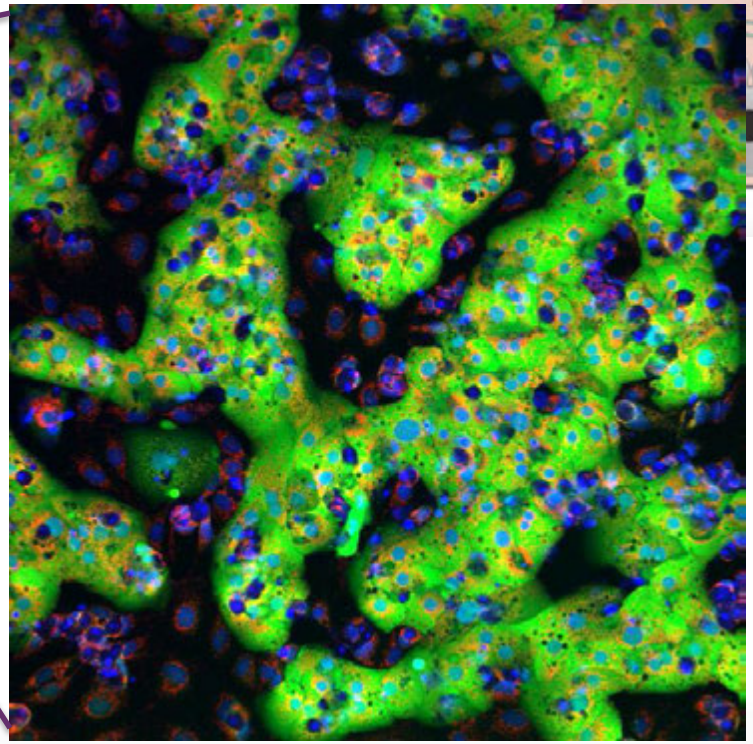
Lans Taylor; Univ. Pittsburgh

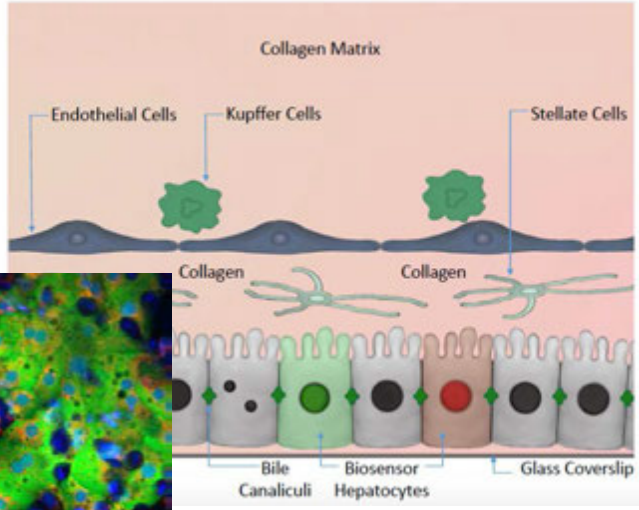
Example: Liver-on-chip

Self-assembly of Hepatocytes and NPC in Nortis MPS



Hepatocyte Cords

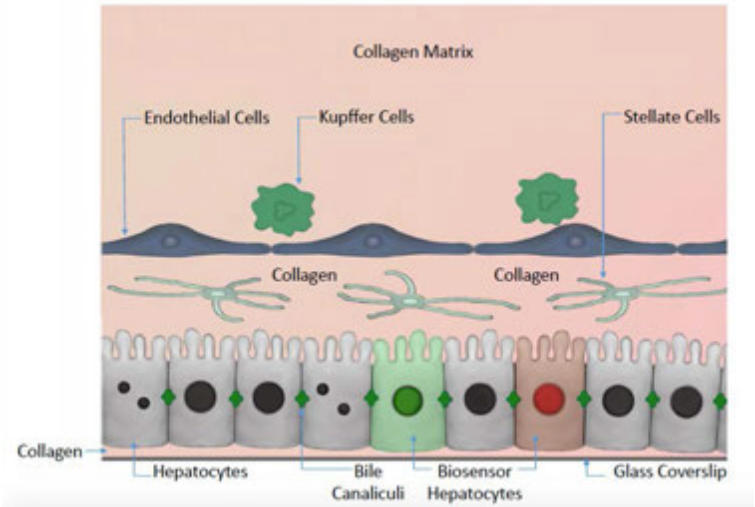


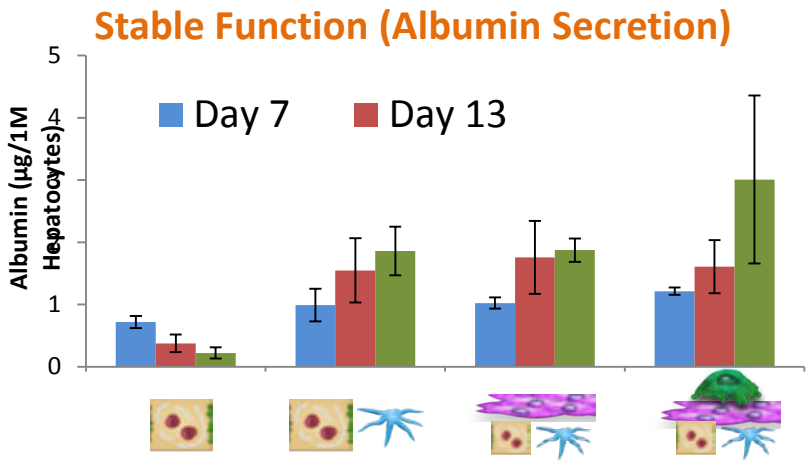


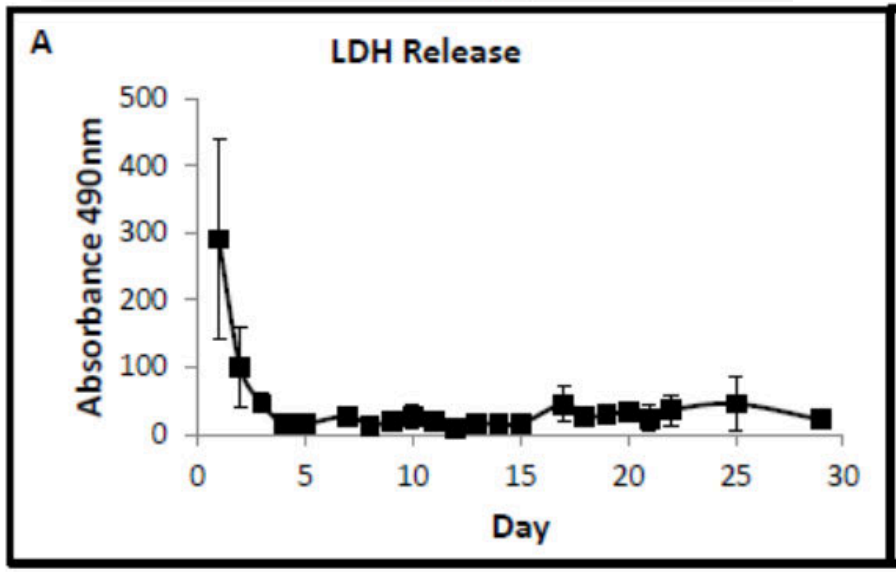
Lans Taylor; Univ. Pittsburgh

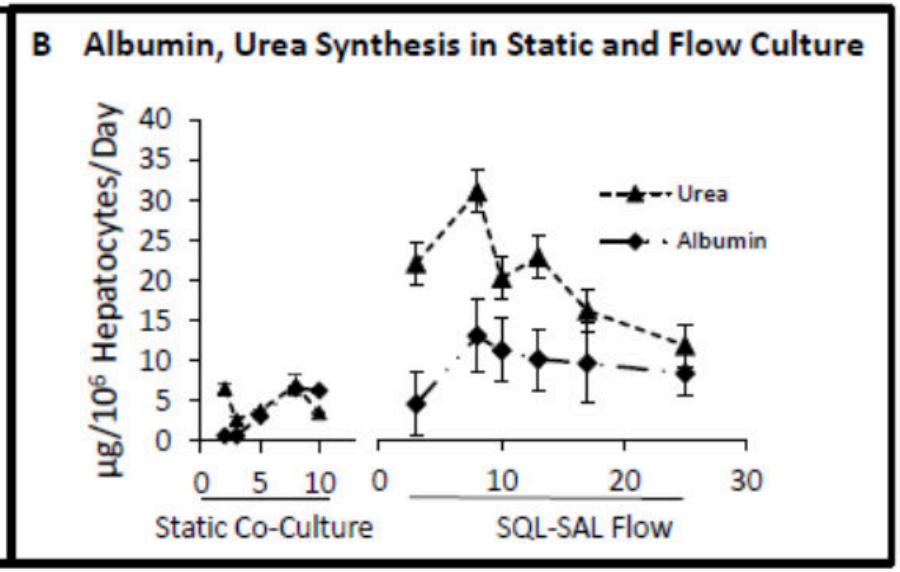
4 week co-culture with NPC and with fluidic flow

Vernetti et al (2016) A human liver microphysiology platform for investigating physiology, drug safety, and disease models. *Exp. Biol. Med.* 241:101-114









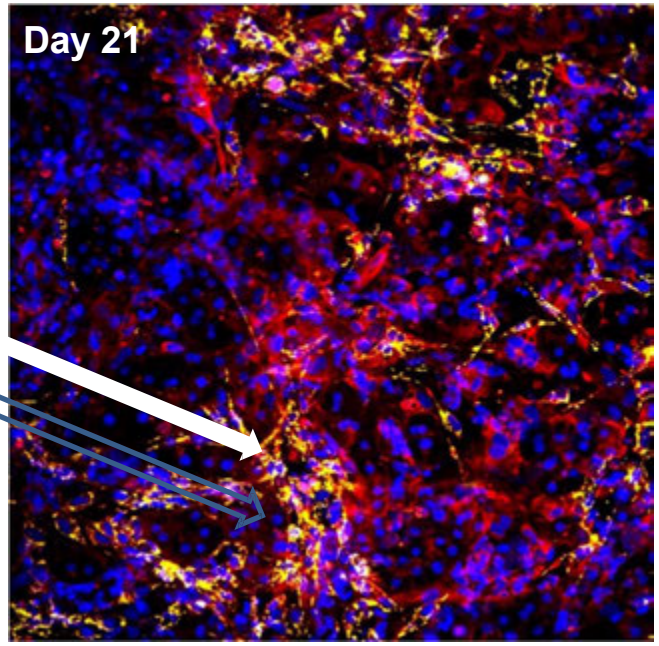
Example: Liver Chip

Lans Taylor; Univ. Pittsburgh

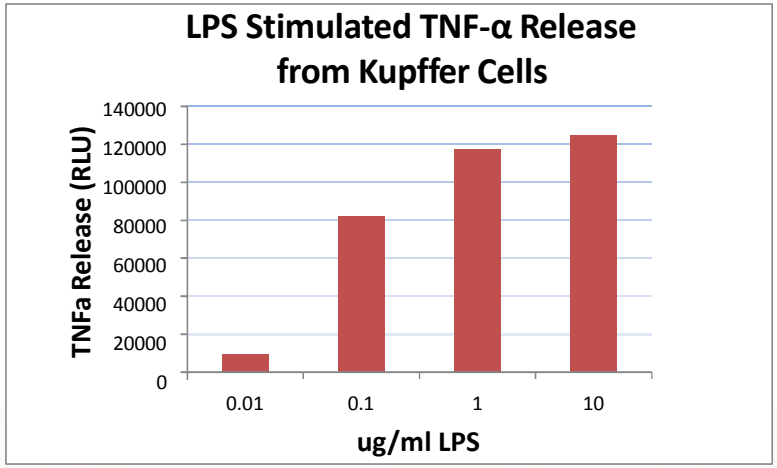
Demonstration of Fibrotic Response

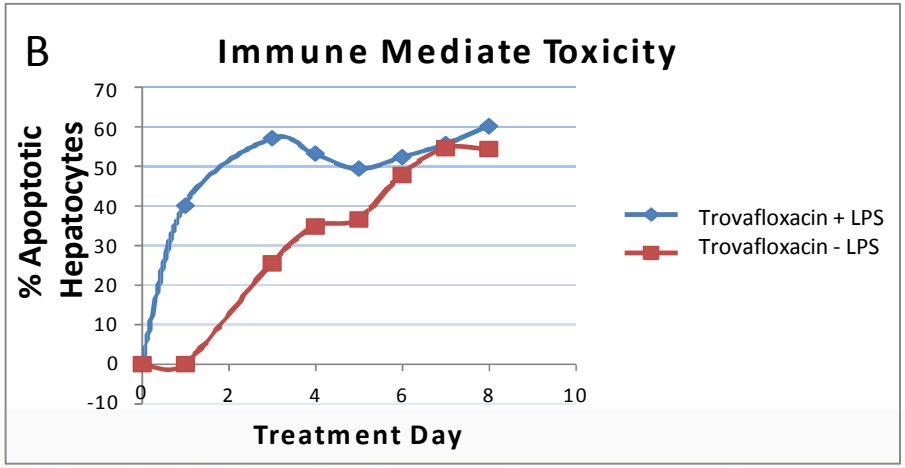
Stellate cell activation
in response to methotrexate

Stellate cells
Express
Collagen 1A2

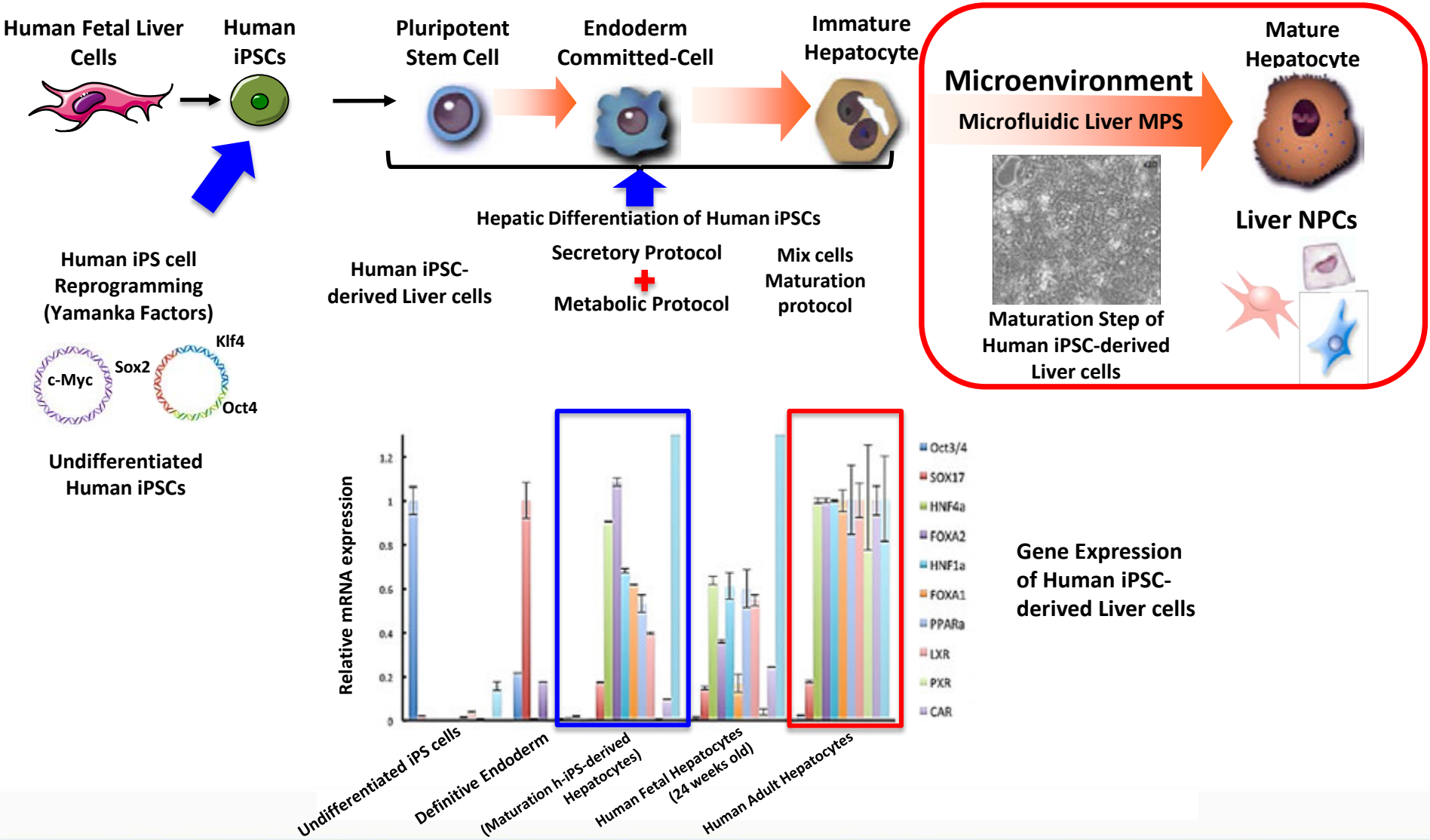


Immune-Mediated Hepatotoxicity by LPS





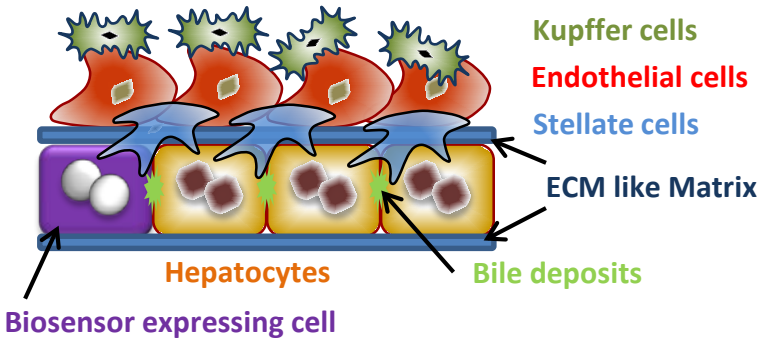
Role of Microenvironment in Maturation of iPSC derived Hepatocytes



Lans Taylor; Univ. Pittsburgh

Optogenetic Biosensors

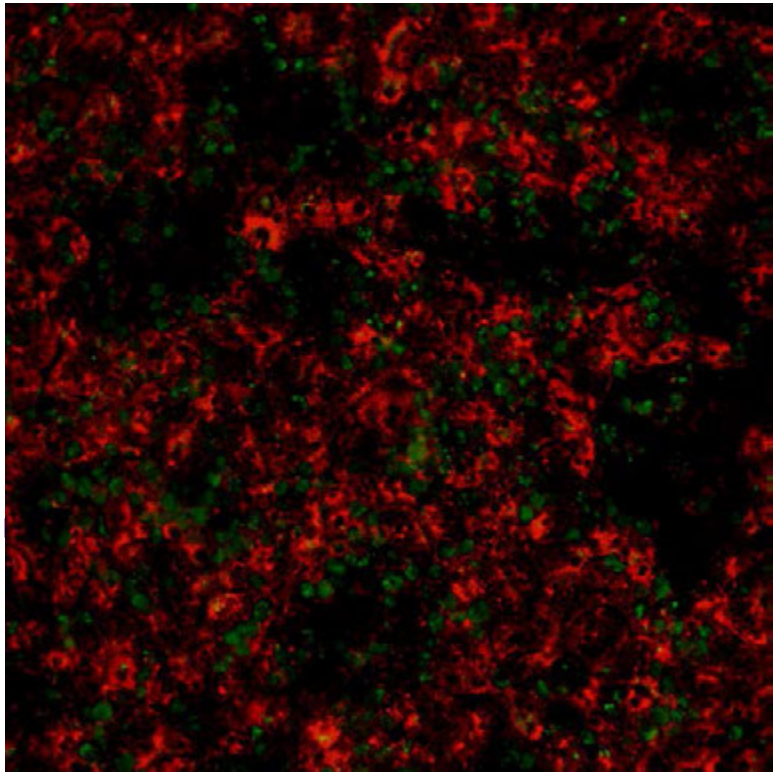
Biosensor	Biosensor Color Options
Nuclear/cell position (Histone H2B)	■ ■ ■
Cytochrome C Release: Apoptosis	■ ■
Reactive Oxygen Species in Mito. (H_2O_2)	■
Mitochondrial Calcium Uptake	■
Steatosis (Label-Free)	□
Bile canalicular efflux (CMFDA)	■
Oxidative Stress in Mito.& Cytoplasm	■ ■ ■

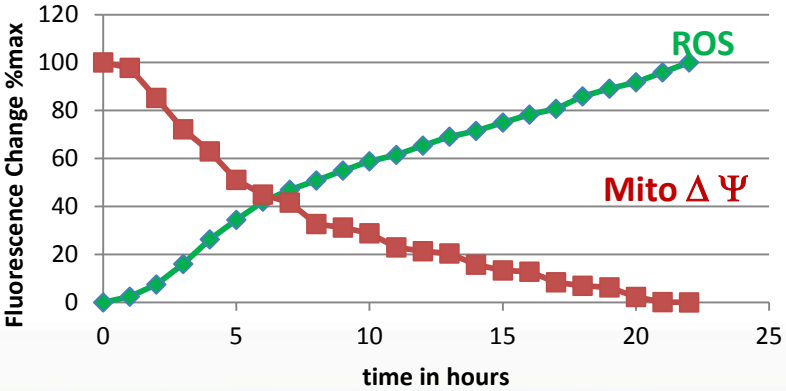


Lans Taylor; Univ. Pittsburgh

Optogenetic Biosensors

Biosensor	Biosensor Color Options
Nuclear/cell position (Histone H2B)	
Cytochrome C Release: Apoptosis	
Reactive Oxygen Species in Mito. (H_2O_2)	
Mitochondrial Calcium Uptake	
Steatosis (Label-Free)	
Bile canalicular efflux (CMFDA)	
Oxidative Stress in Mito.& Cytoplasm	



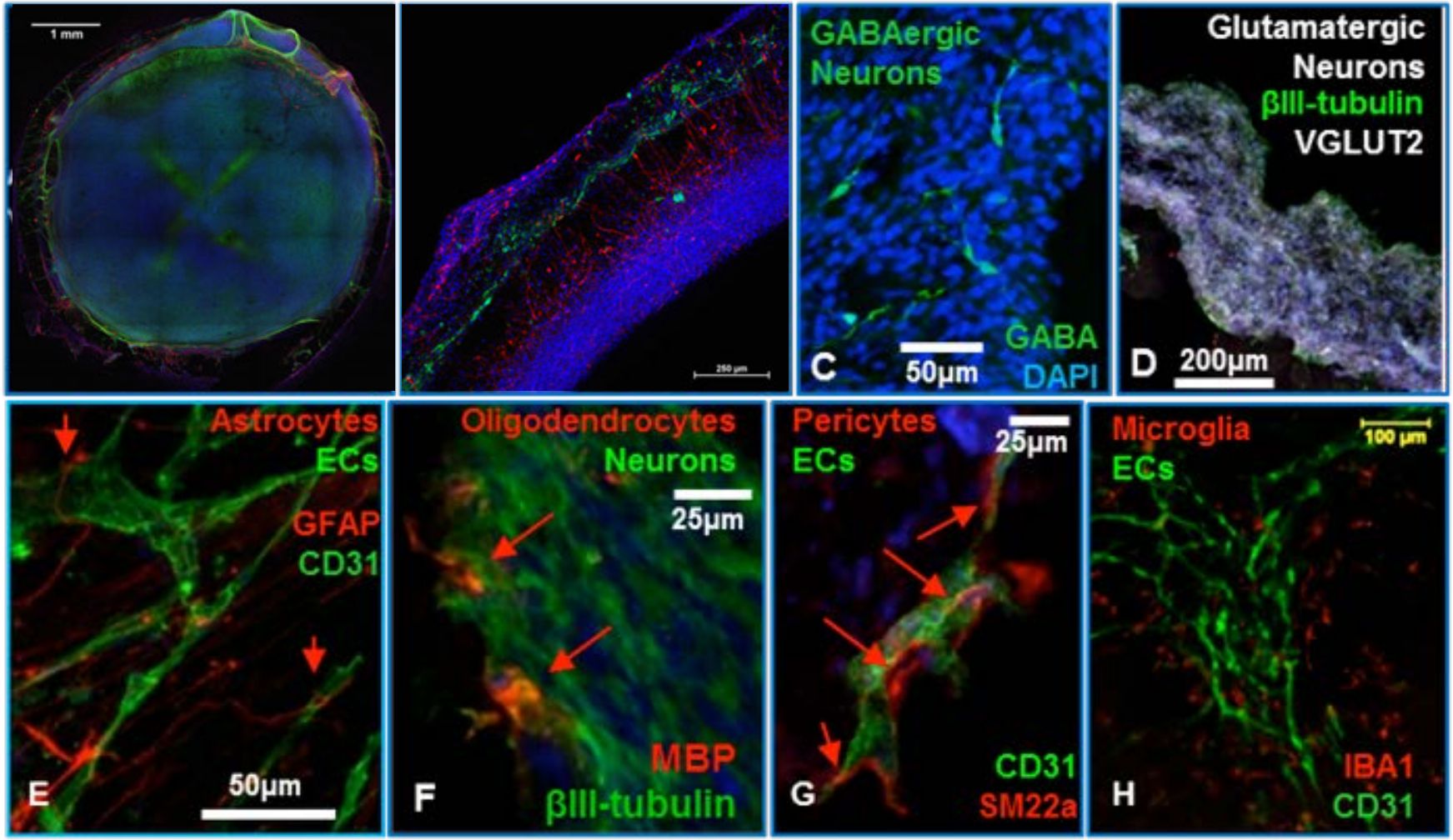


Compounds Tested Using Biosensors

Drug	Cmax	Human/Animal Toxicology	Metabolism dependence	Suggested MOT	Our Results Negative Weak or late positive Strong Positive
Trazodone (in use)	5 uM	extremely rare liver injury Mild ↑transaminases, self eliminating 0.21 incidents/million prescriptions	High clearance drug	No known liver tox	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Nefazodone (withdrawn US)	0.9 uM	Acute hepatitis Centrilobular (zone 3) necrosis Cholestasis , apoptosis 105 incidents/million prescriptions	High clearance drug, toxic intermediates	Mitochondrial Inhibitor ROS Generation Bile Efflux Inhibition	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Troglitazone (Withdrawn)	1.8 uM	Moderate to severe ↑ALT,AST Variable necrosis, hepatocellular damage, cholestasis, inflammatory response Up to 1000 incidents/million prescriptions	Impaired clearance	Mitochondrial dysfunction BSEP inhibitor (bile efflux inhibition)	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux
Menadione (lead compound-cancer)	Rat 100 mg/kg	Infants: menadione injections produce liver toxicity with hyperbilirubinemia Rat Toxicity (Kidney, Heart, Liver, Lung) IV infusion: Liver: inflammation, degeneration, vacuolization and necrosis MOT identified ROS in liver, calcium uptake into hepatocytes massive liver necrosis in GSH depleted rats	No toxic intermediates known	ROS Mitochondrial Inhibition Calcium uptake	ROS Calcium uptake Mito. membrane potent. Apoptosis bile efflux

Lans Taylor; Univ. Pittsburgh

Example: RNAseq Neurotoxicity Testing



Thomson J, Morgridge Institute

PNAS 2016

Neurotoxins and RNAseq Analyses

Schwartz et al (2015) - Human pluripotent stem cell-derived neural constructs for predicting neural toxicity. *PNAS* 112:12516-21.

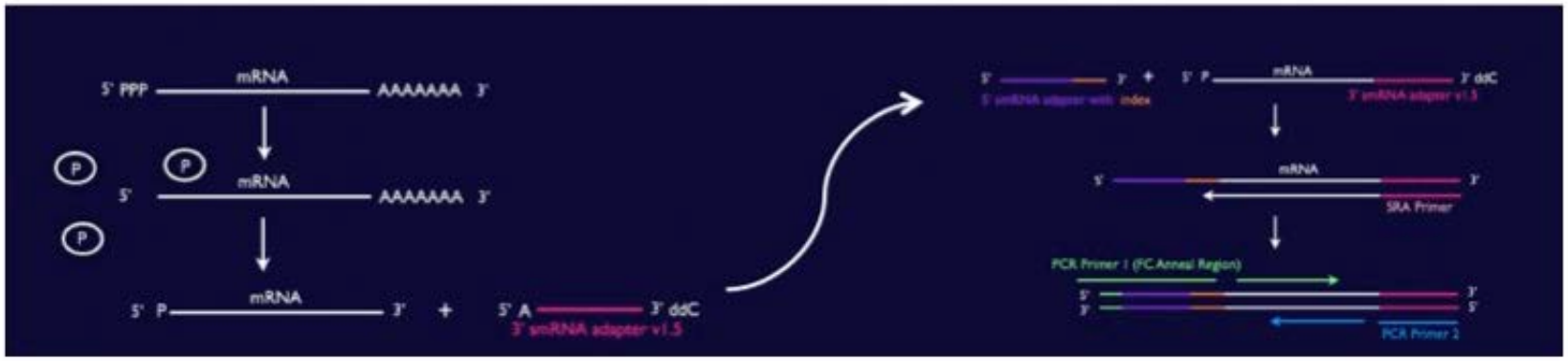


Table 2. Compounds for neurotoxicity screening.									
1	benzene	15	5-Fluorouracil	29	Dexamethasone	43	saccharin	57	Cefepime
2	bioallethrin	16	Busulfan	30	GDC-0449	44	sorbitol	58	glycogen
3	diazinon	17	(*trans*) Retinoic acid	31	cyclopamine	45	sucrose	59	Meropenem
4	hydroxyurea	18	Thalidomide	32	amprolium	46	fructose	60	Doxycycline
5	maneb	19	Amiodarone	33	BMAA	47	PVP	61	Carbenicillin
6	monosodium glutamate	20	Carbamazepine	34	LDE225	48	PEG 3350	62	tamoxifen
7	permethrin	21	Isotretinoin	35	kainate	49	ibuprofen	63	4-hydroxy-tamoxifen
8	L-phenylalanine	22	lead acetate	36	PD0325901	50	glycerol	64	17 beta-estradiol
9	propylthiouracil	23	Bis-I	37	GBR 12909	51	glucosamine	65	hCG
10	PD166866	24	K252a	38	L-741,626	52	aspirin	66	lactose
11	Cytosine β-D-arabinofuranoside	25	Okadaic acid	39	Ouabain	53	ficoll 400	67	maltose
12	Dioxin	26	U0126	40	Acetaminophen	54	Naproxen sodium	68	PenStrep (1x)
13	Arsenic	27	Vincristine	41	amoxicillin	55	DMSO	69	Oleic acid
14	Cadmium	28	2-Imidazolidinethione	42	glyphosate	56	Resveratrol	70	arabinose
70 drugs were tested using final 3D neural construct (1-39 neurotoxic; 40-70 nontoxic)									

Thomson J, Morgridge Institute

Neuro Chip for Predictive Neurotoxicity

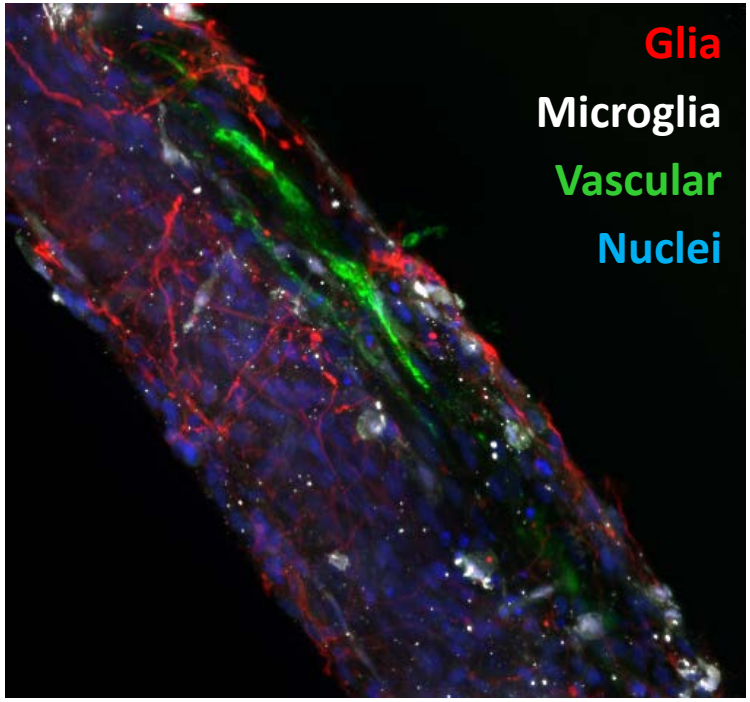
1. **Model key neurodevelopmental processes *in vitro*.**
2. **Cell-based endpoint amenable to high throughput testing.**

Human neurotoxicity:

- Mechanisms of action poorly understood.
- Cellular targets are often unknown.
- **Neurons, glia, microglia, vasculature all implicated in neurotoxicity mechanisms**.

RNA-Seq as a readout:

- Leverage cellular complexity.
- Evaluate 19,000+ genes.
- ~$25 / sample (Hou et. al., submitted).



National Center for Advancing Translational Sciences

Machine Learning: David Page, Collin Engstrom, Vitor Santos Costa

Neuro Chip for Predictive Neurotoxicity

1. **Model key neurodevelopmental processes *in vitro*.**
2. **Cell-based endpoint amenable to high throughput testing.**
3. **Evaluate detection of key event using a "training set".**
4. **Assessment of cell health/viability (cytotoxicity assays).**

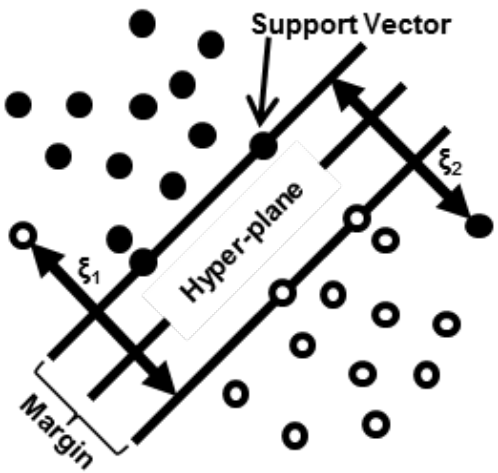
Machine Learning to build the predictive model.

- 60 Training compounds (34 toxin / 26 control).
- 10 blinded compounds (5 toxin / 5 control).
- Duplicate samples.
- Two time points.

280 individual neural constructs for this experiment!

RNA-Seq as a readout:

- Leverage cellular complexity.
- Evaluate 19,000+ genes.
- ~$25 / sample (Hou et. al., submitted).



Machine Learning: David Page, Collin Engstrom, Vitor Santos Costa

Neuro Chip for Predictive Neurotoxicity

1. **Model key neurodevelopmental processes *in vitro*.**
2. **Cell-based endpoint amenable to high throughput testing.**
3. **Evaluate detection of key event using a "training set".**
4. **Assessment of cell health/viability (cytotoxicity assays).**

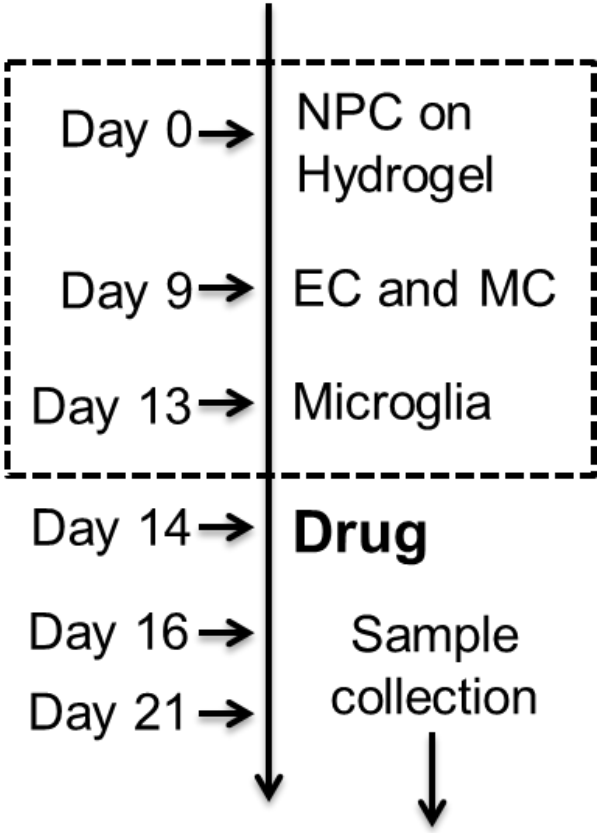
Machine Learning to build the predictive model.

- 60 Training compounds (34 toxin / 26 control).
- 10 blinded compounds (5 toxin / 5 control).
- Duplicate samples.
- Two time points.

280 individual neural constructs for this experiment!

RNA-Seq as a readout:

- Leverage cellular complexity.
- Evaluate 19,000+ genes.
- ~$25 / sample (Hou et. al., submitted).



NIH National Center for Advancing Translational Sciences

Machine Learning: David Page, Collin Engstrom, Vitor Santos Costa

Neuro Chip for Predictive Neurotoxicity

1. **Model key neurodevelopmental processes *in vitro*.**
2. **Cell-based endpoint amenable to high throughput testing.**
3. **Evaluate detection of key event using a "training set".**
4. **Assessment of cell health/viability (cytotoxicity assays).**

Machine Learning to build the predictive model.

- 60 Training compounds (34 toxin / 26 control).
- 10 blinded compounds (5 toxin / 5 control).
- Duplicate samples.
- Two time points.

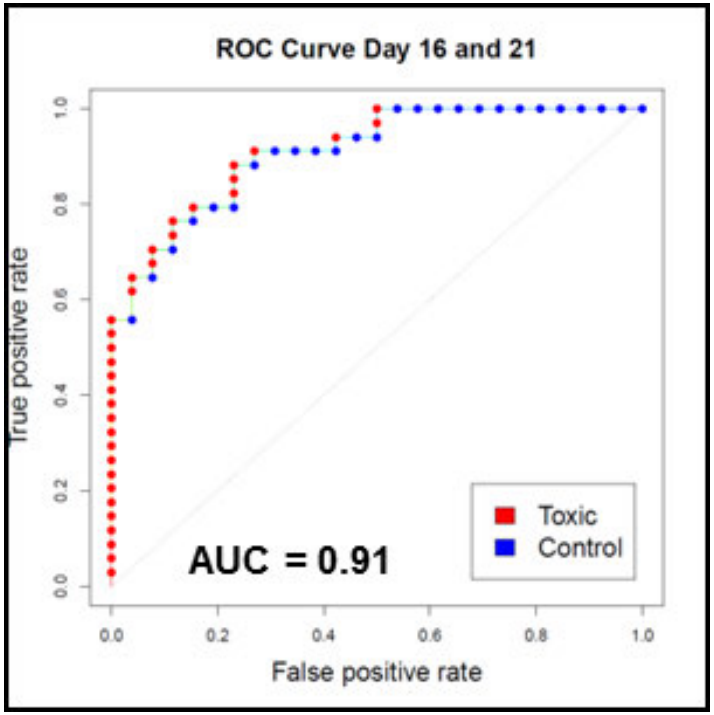
280 individual neural constructs for this experiment!

Training set:

- >80% accuracy each time point.
- ~90% accuracy for combined data.

Blinded set:

- **9 / 10 correctly predicted.**
- 1 miss was a false positive.



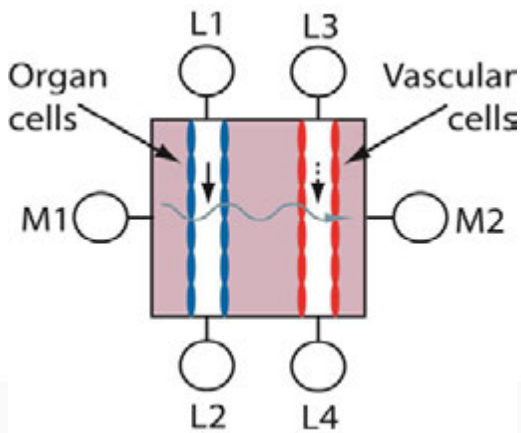
National Center for Advancing Translational Sciences

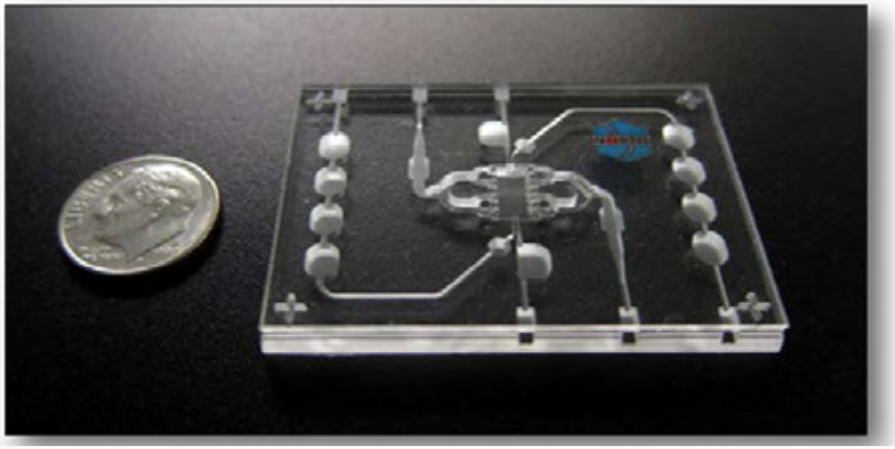
Machine Learning: David Page, Collin Engstrom, Vitor Santos Costa

Kidney Proximal Tubule on Nortis 3-D Chip Technology

Weber et al (2016) Development of a microphysiological model of human kidney proximal tubule function. *Kidney Int*.90:627-37

- Disposable microfluidic chips containing 3D micro-environments traversed by tubular cell structures
- Allows for creation of compartmentalized tissue models: luminal versus extracellular matrix (ECM) compartment
- Luminal and ECM compartments can be independently perfused. There are no artificial material surfaces to which cells must attach
- Luminal fluid flow leads to controlled shear force and other mechanical stimuli
- Septa for injection/extraction of fluids directly on the chip, and insertion of sensors
- Integrated bubble-traps

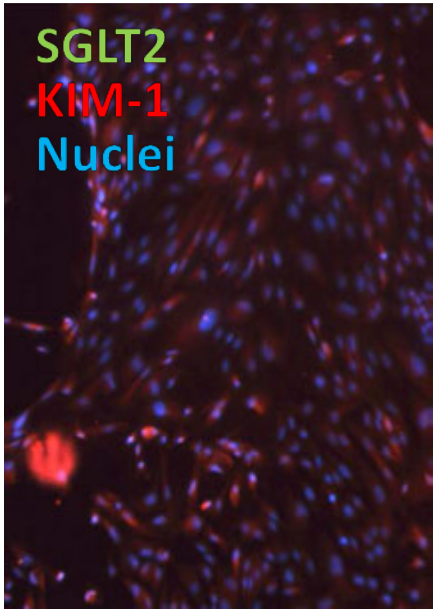


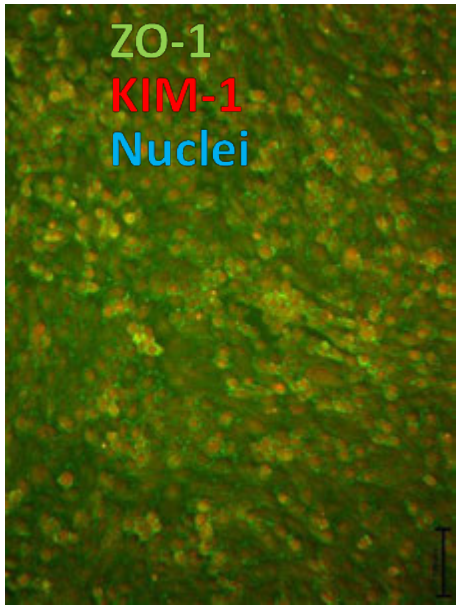


Jonathan Himmelfarb, U Washington

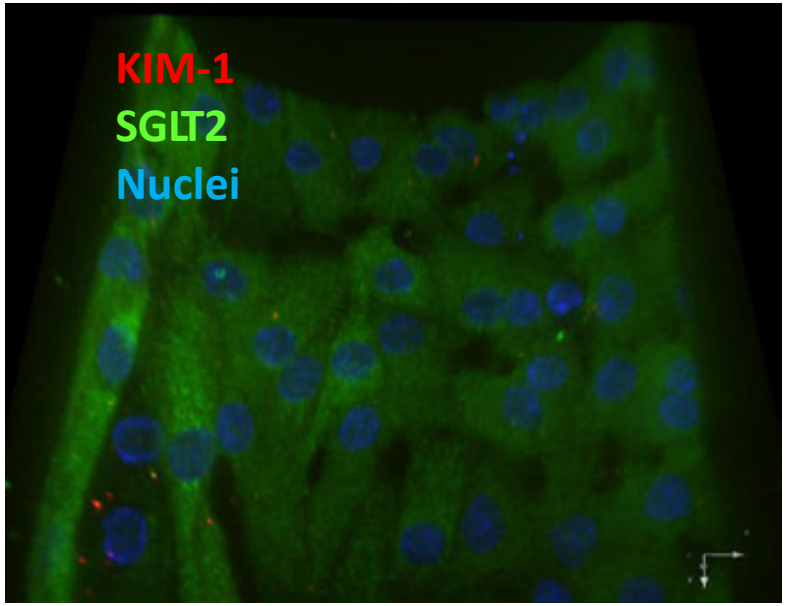
Phenotypic changes for kidney tubules in 2D vs 3D

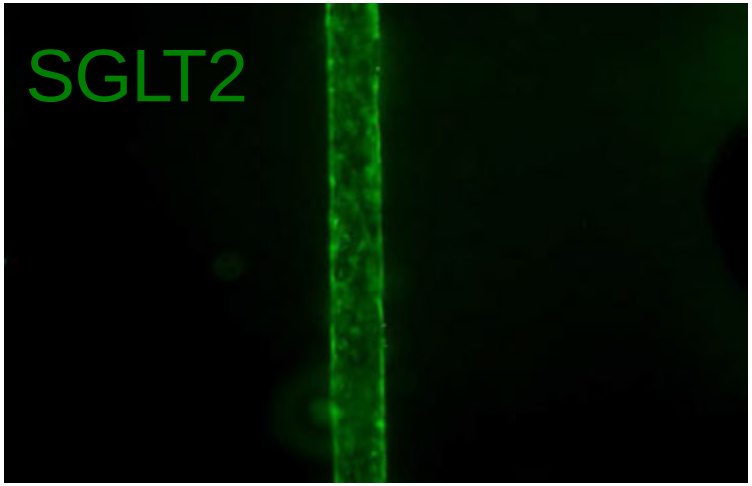
2D

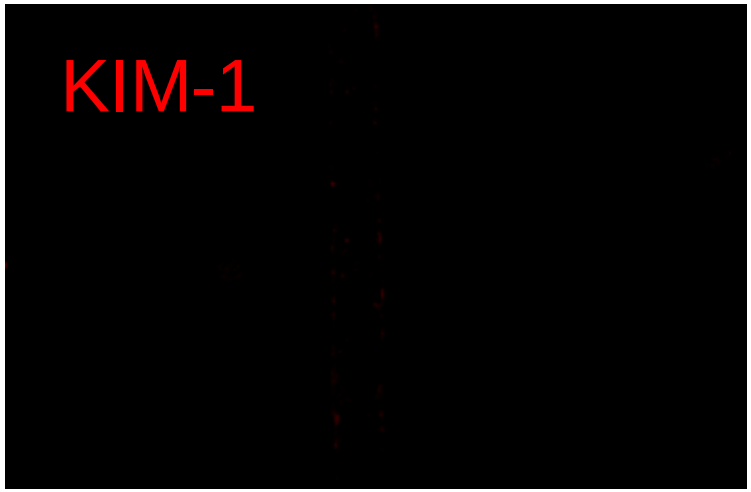




3D MPS



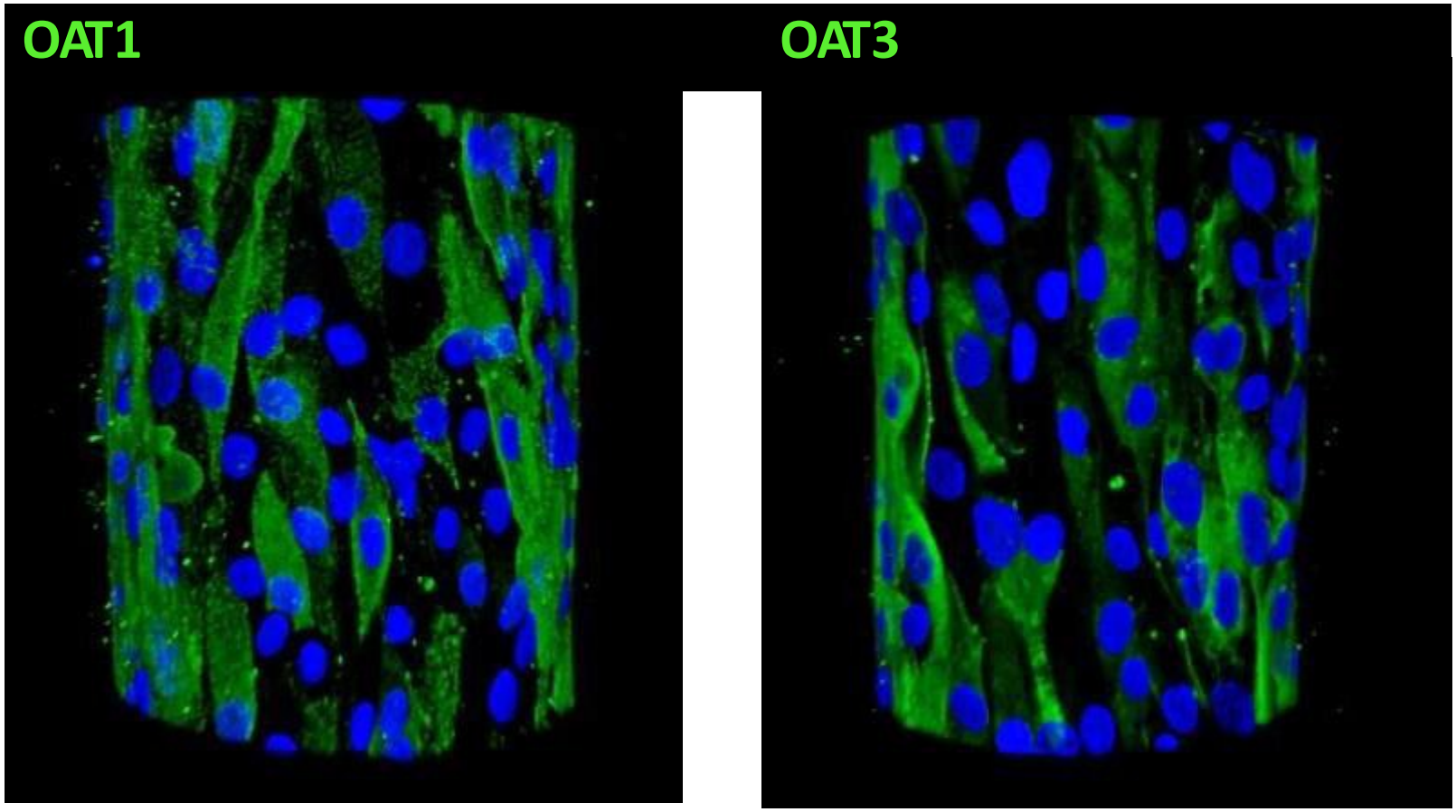




Jonathan Himmelfarb, U Washington

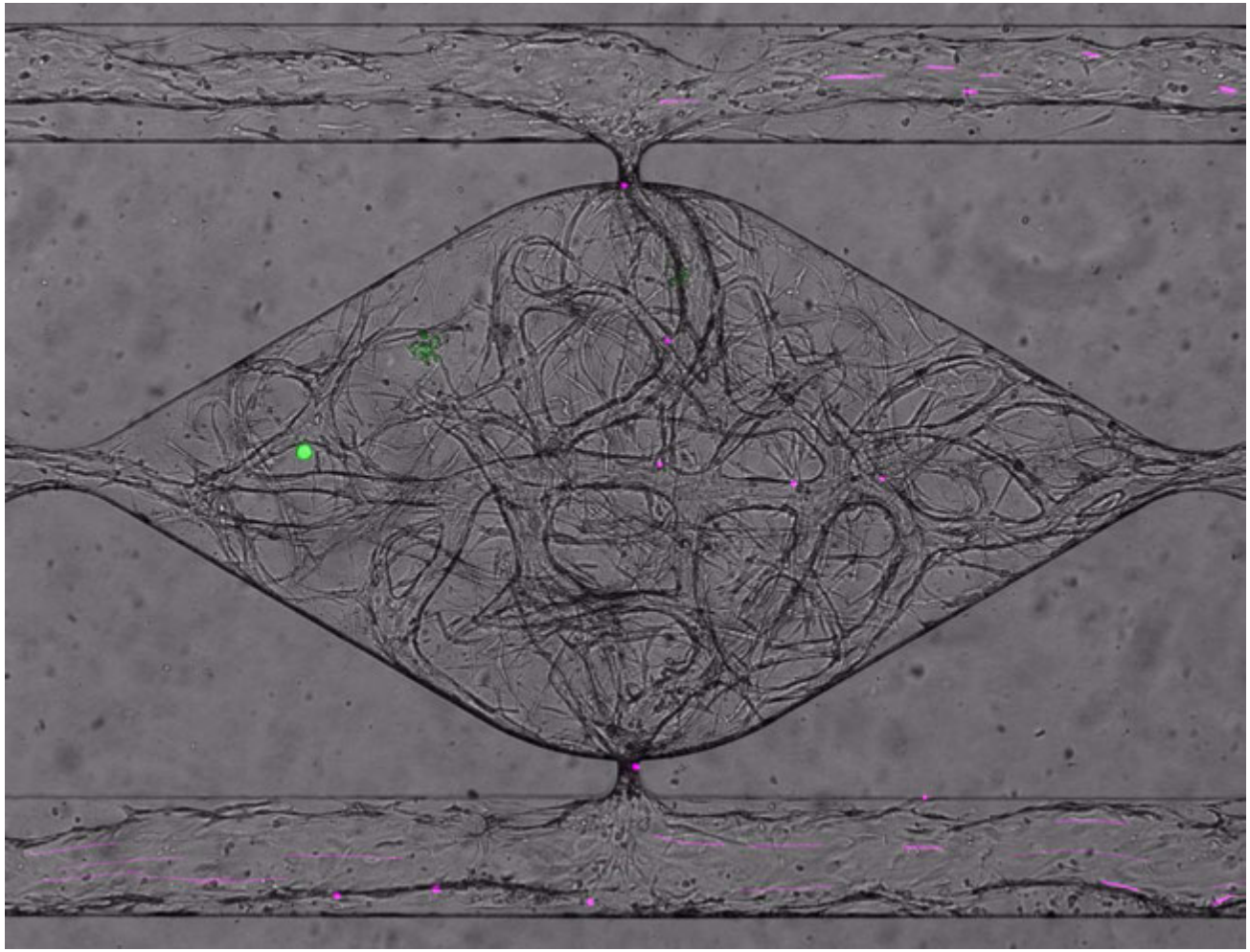
Transporter Expression in Proximal Tubule Epithelial Cells

- Proximal tubule epithelial cells (PTEC) express OAT1 and OAT3 transporters after 7-14 days in MPS



Jonathan Himmelfarb, U Washington

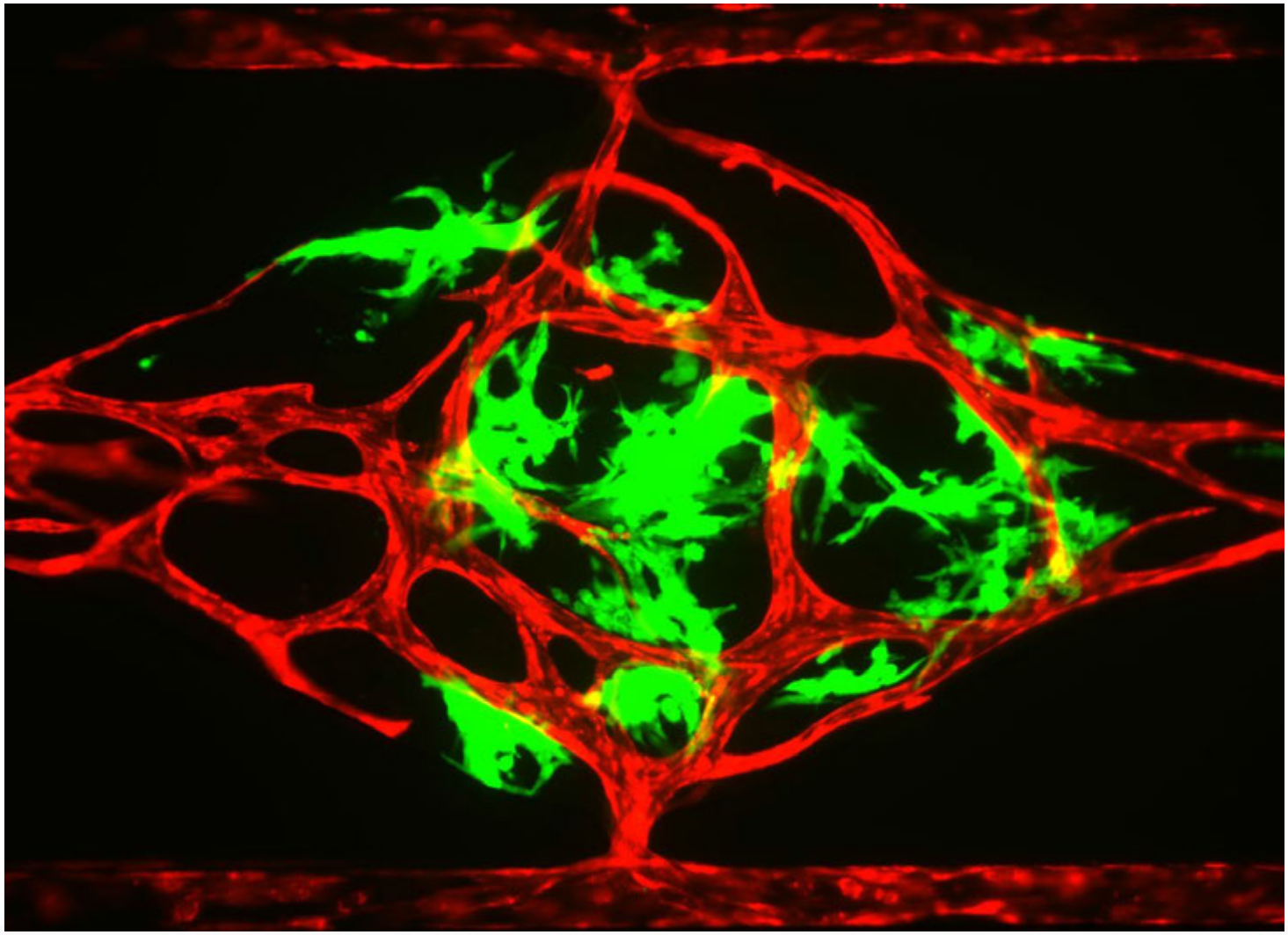
Perfusion - Microvasculature-on-chip



- **7 days**
- **hiPS-EC**
- **1 µm beads**

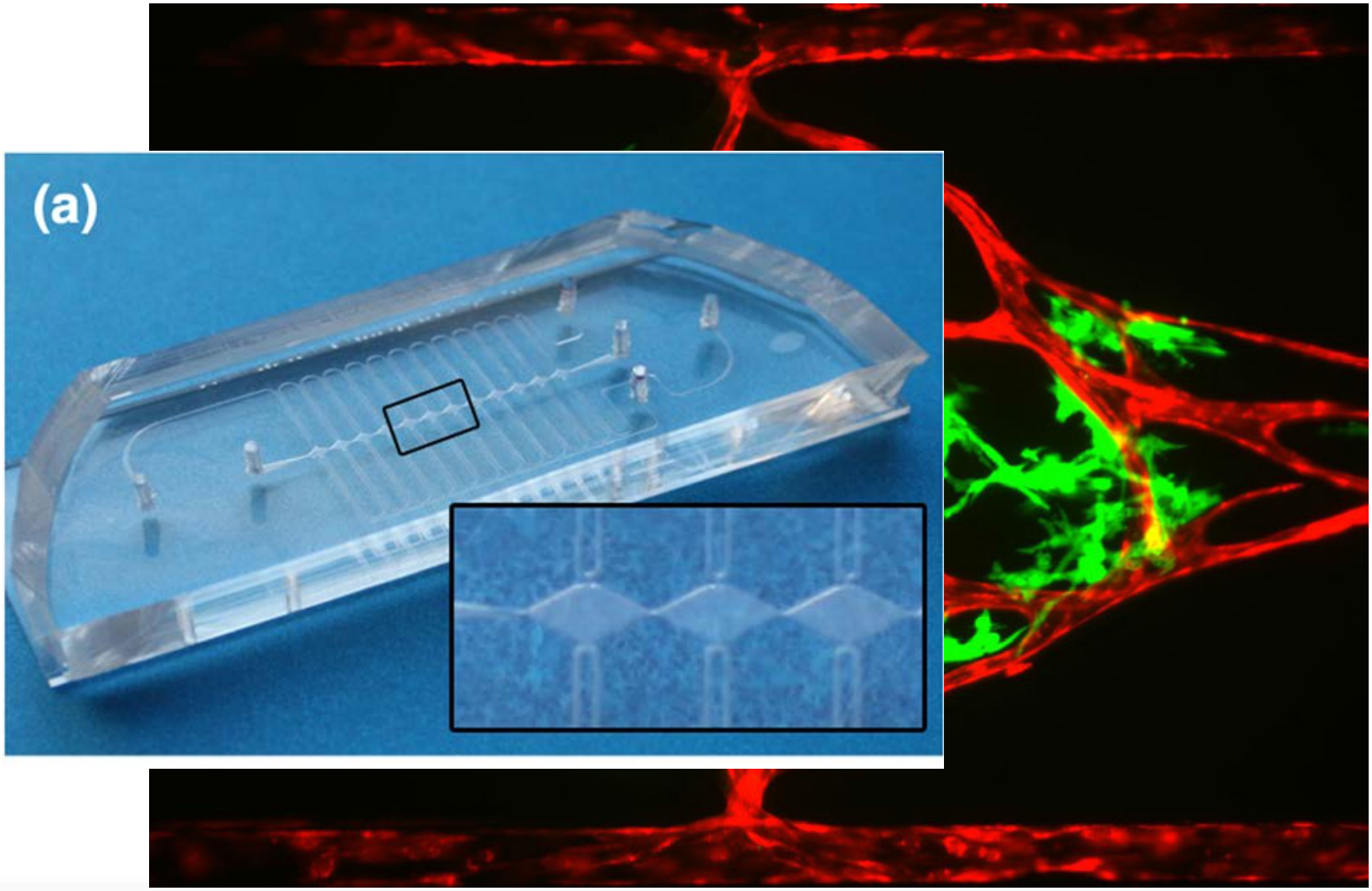
Steven George, Washington U

Colon tumor (HCT116) supported by microvasculature



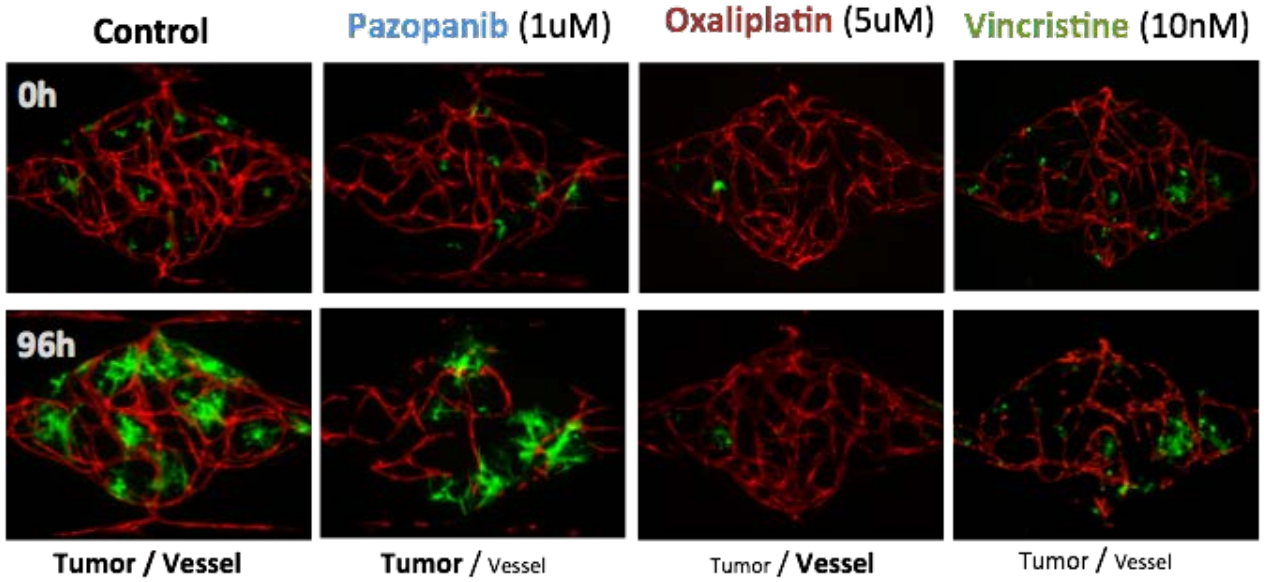
Steven George, Washington U

Colon tumor (HCT116) supported by microvasculature

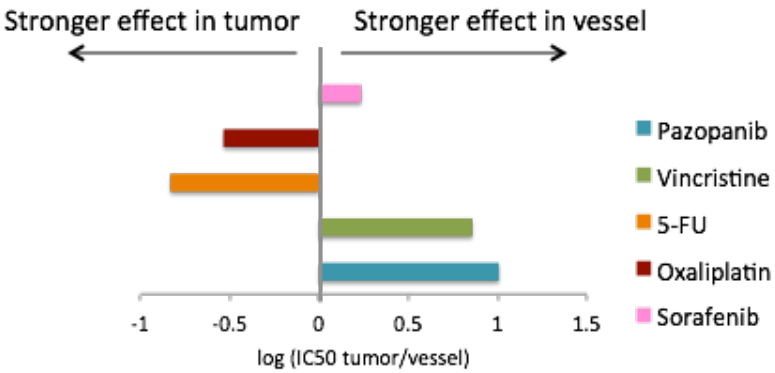


Steven George, Washington U

Different responses to drugs in 2D vs 3D



HCT116
Vessels

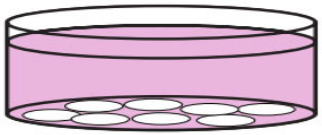


	HCT116 – IC50 (48h)		
	2D (XTT assay)	3D (VMT)	Plasma concentration range
5-FU	3.1 µM	> 200 µM	≈140 to 425 µM
Oxaliplatin	8.6 µM	32 µM	≈5.3 µM
Vincristine	10 nM	> 100 nM	≈170 to 265nM
Bortezomib	9 nM	57 nM	≈10 to 100nM
Sorafenib	9.5 µM	17 µM	≈6.5 to 22 µM
Pazopanib	> 10 µM	> 10 µM	103 µM

Steven George, Washington U

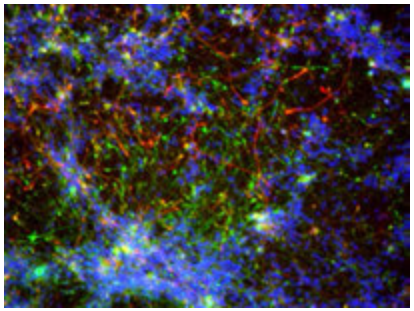
Innervation of Gut Enteroids

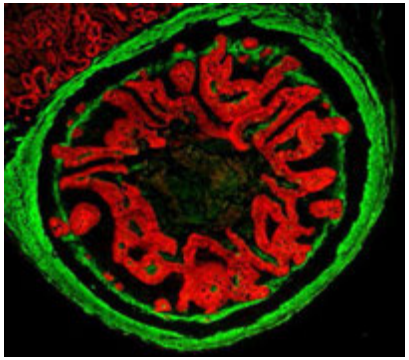
Workman et al. (2016) Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system
Nature Medicine



Pluripotent Stem Cells: renewable human cell source

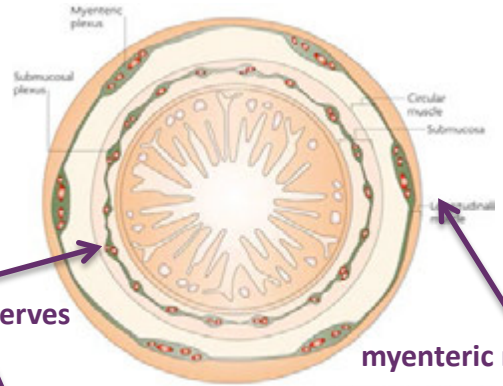
Vagal Neural Crest Cells: peripheral nerve cells





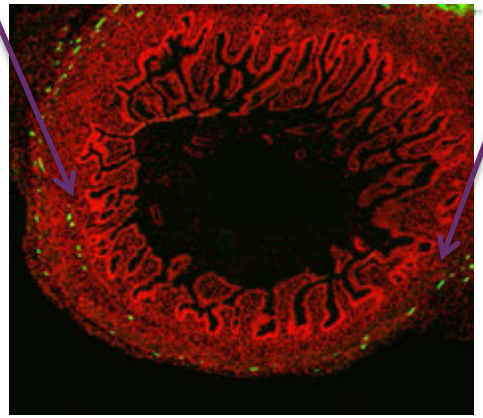
Gut enteroid: 3D mulitcellular mini gut

Gut Lumen



submucosal nerves

myenteric nerves

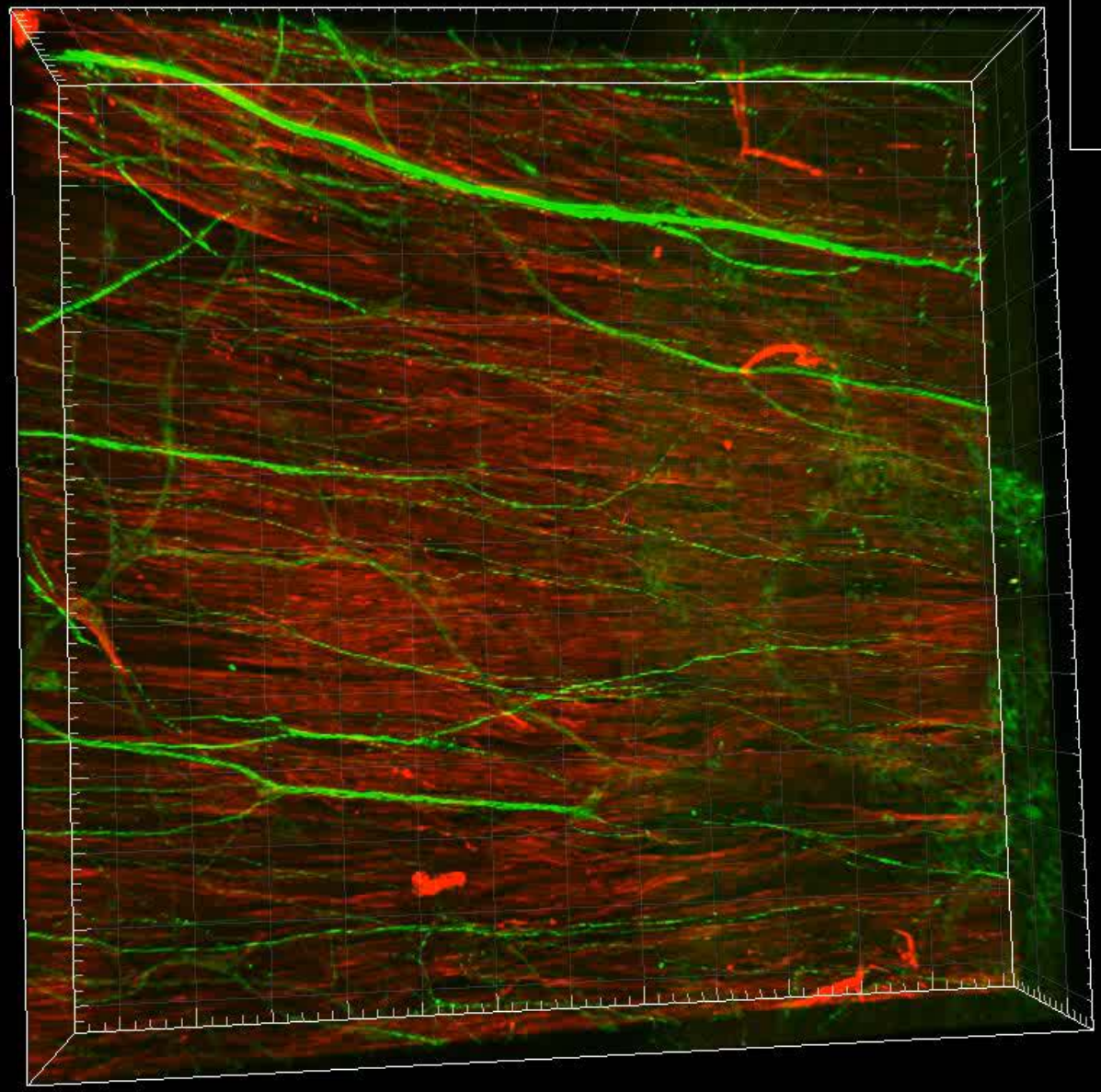


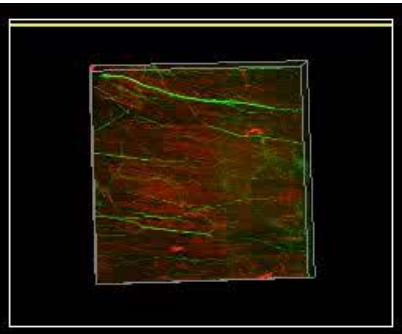
The nervous system in the gut plays a critical role in GI function, including peristalsis (gut contraction). Both nerve and gut tissue can be engineered using renewable human cell sources

As these systems begin to mature, the nerve tissues are added to the GI, creating physiological-like innervated structures

James Wells, Univ. Cincinnati

HIO+NCCs B3-tubulin Desmin



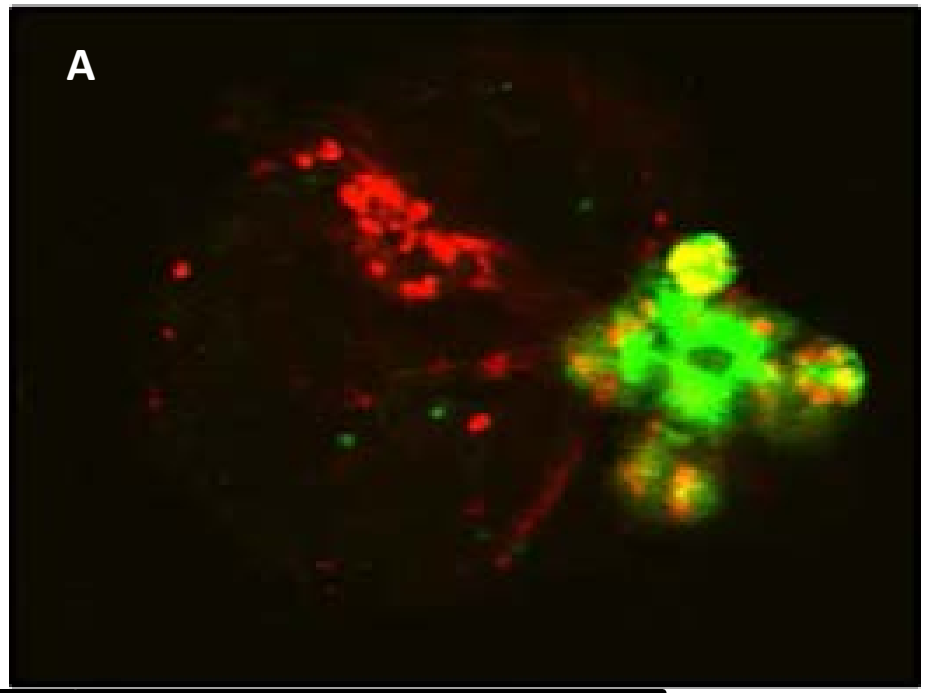


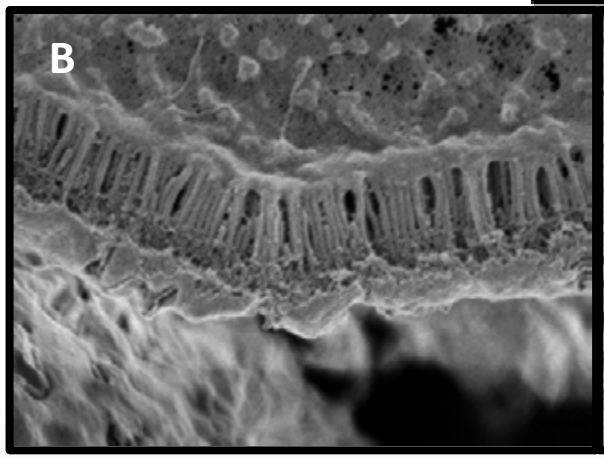
Mimicking Peristalsis on Gut Enteroid

National Center for Advancing Translational Sciences

James Wells, Univ. Cincinnati

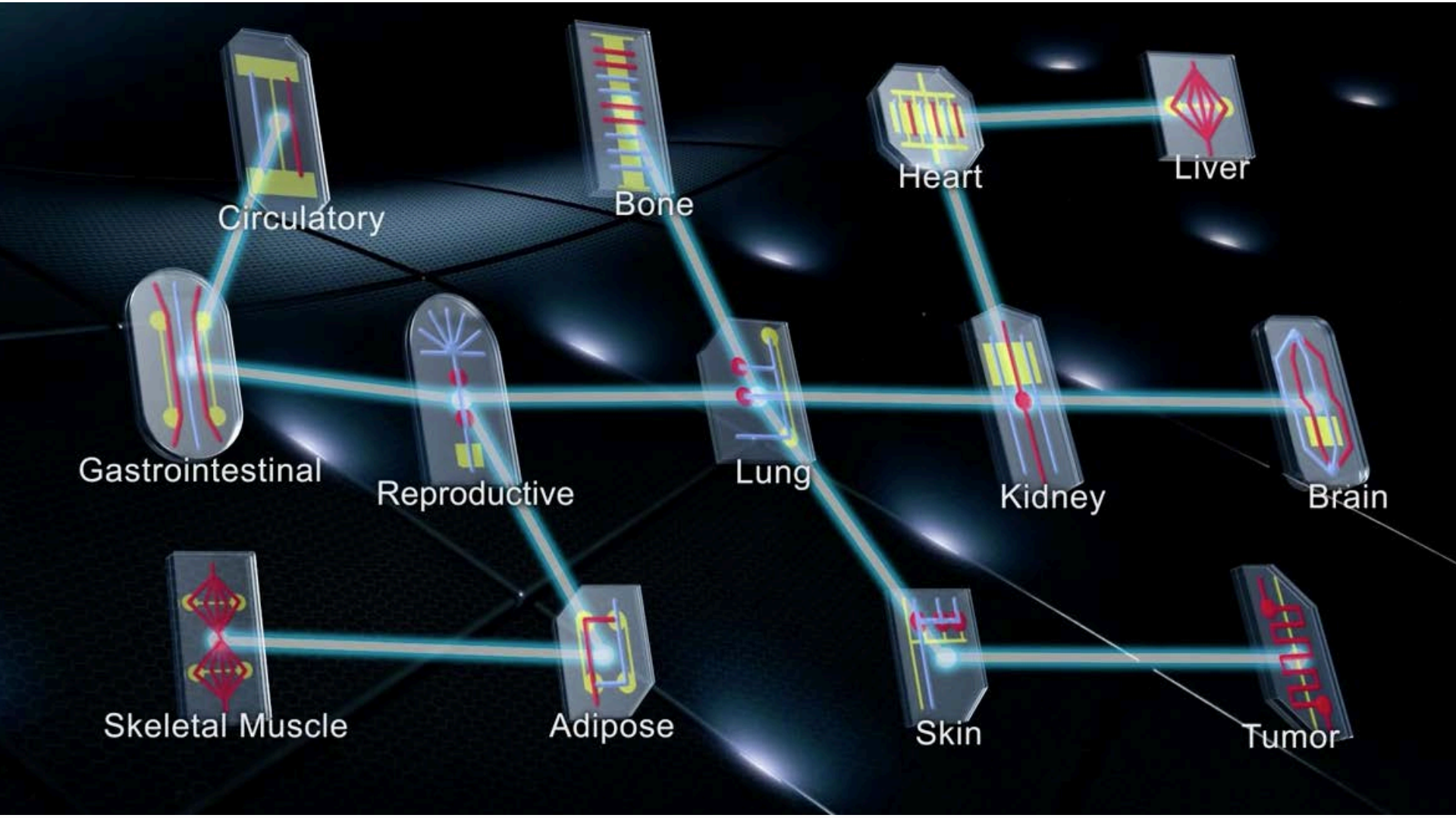
Enteroids mimic gut structure and function



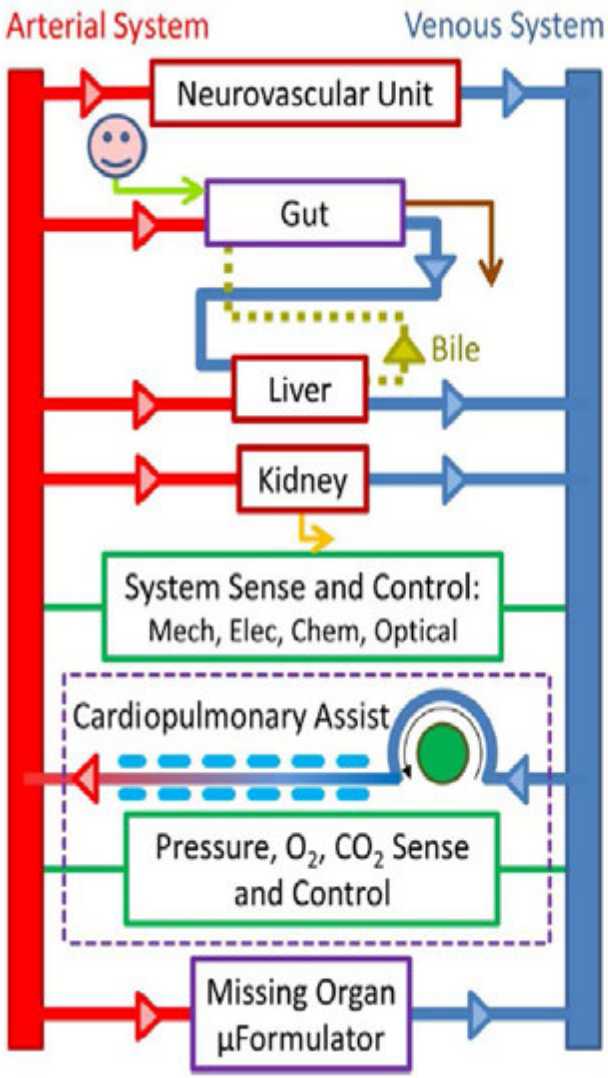


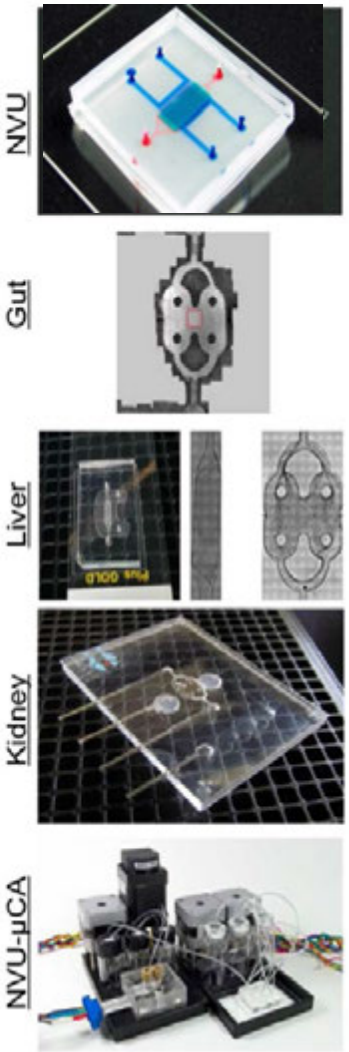
Mark Donowitz, Johns Hopkins

Connecting Multiple Organ-on-Chips –> Human-on-Chip



Collaborative Approach towards Multi-Organ Integration

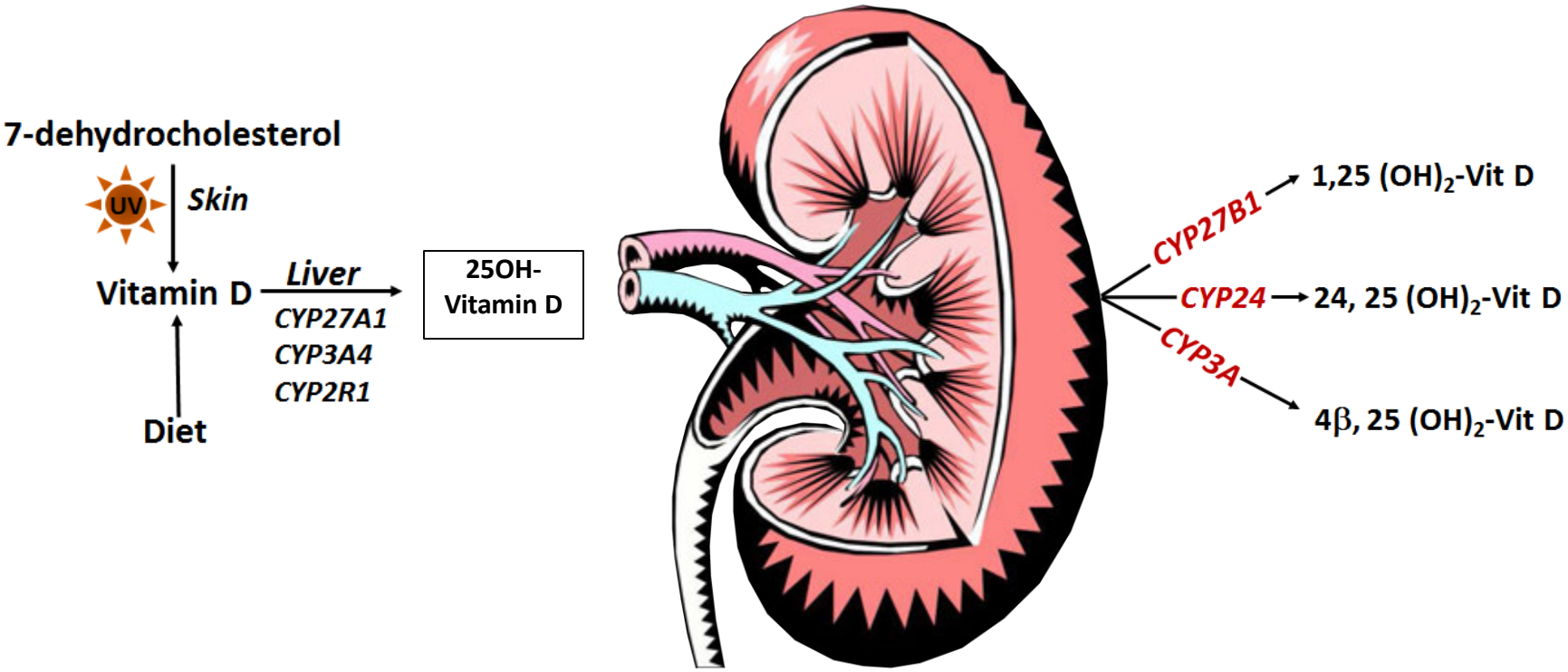




Baylor College of Medicine

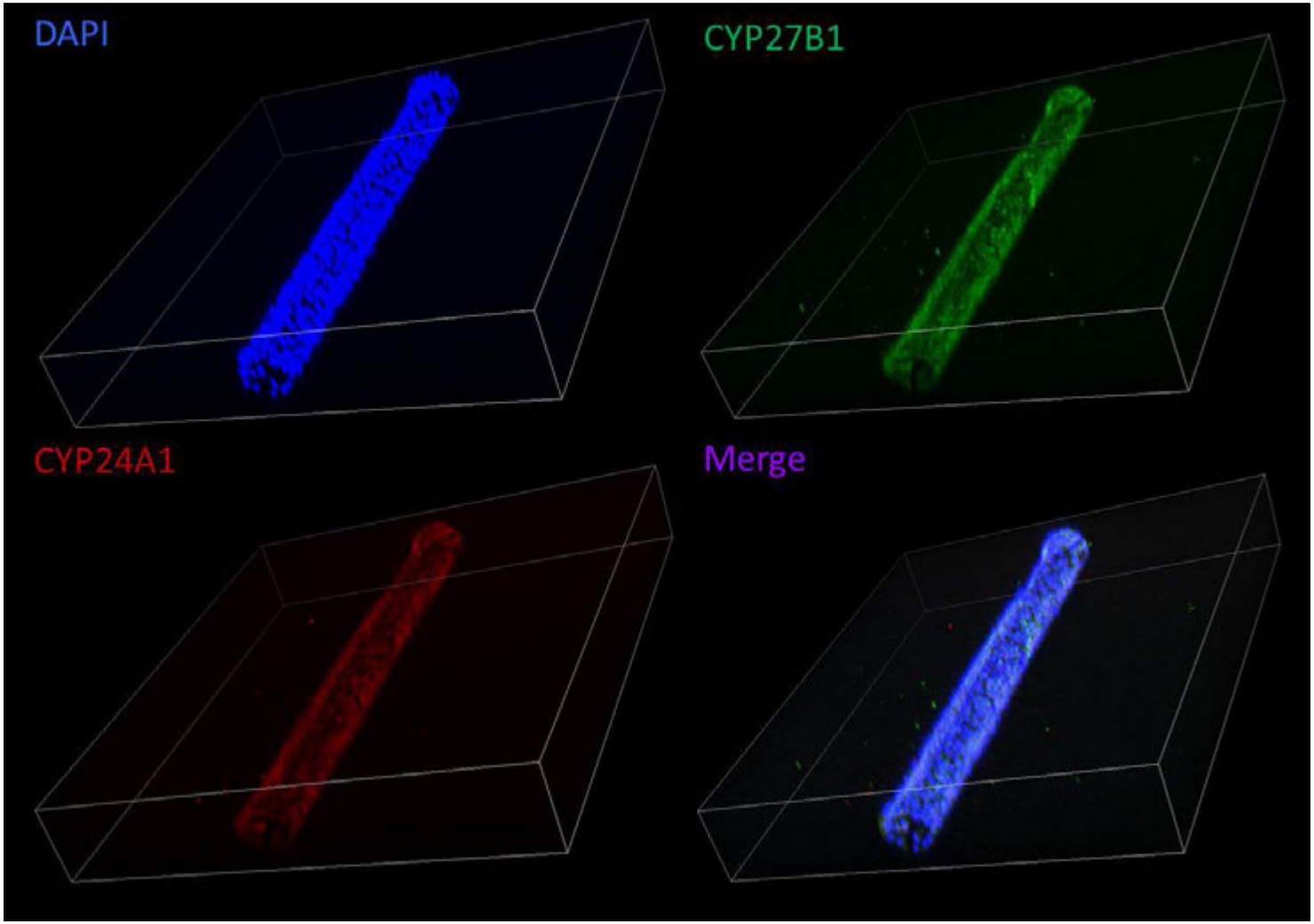
KIDNEY RESEARCH INSTITUTE

Vitamin D Metabolic Pathway



Jonathan Himmelfarb, U Washington

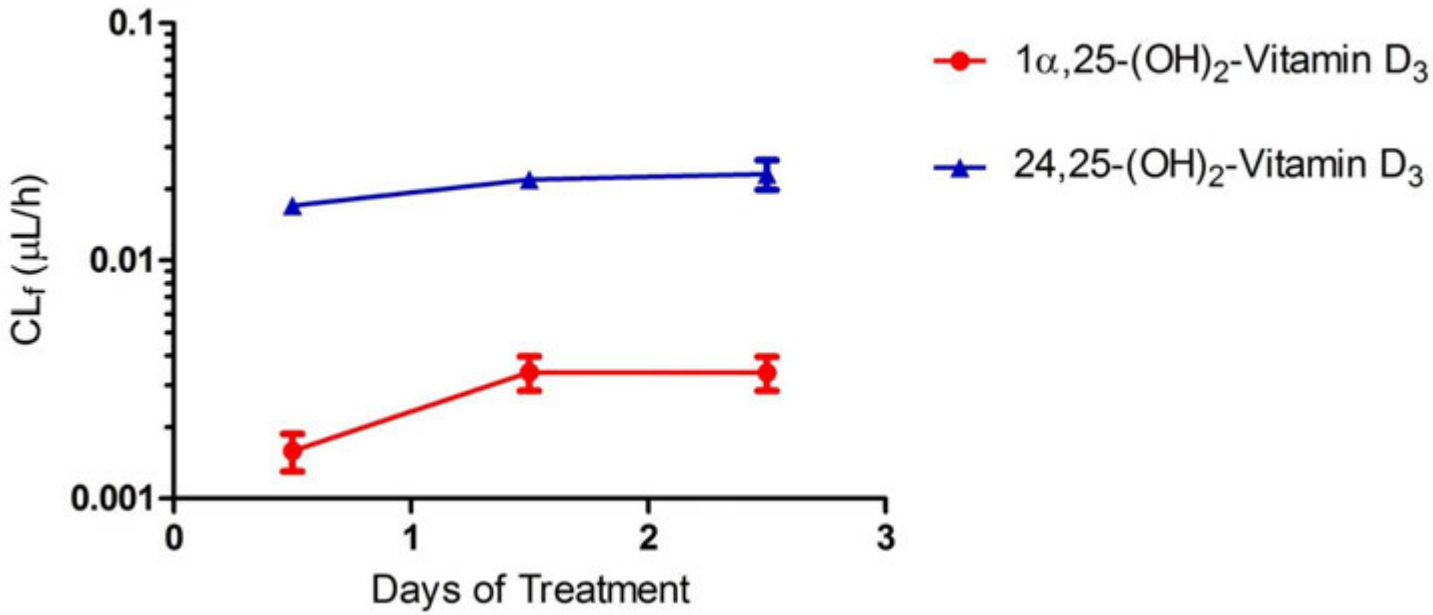
Renal 25OHD$_3$-Metabolizing P450s

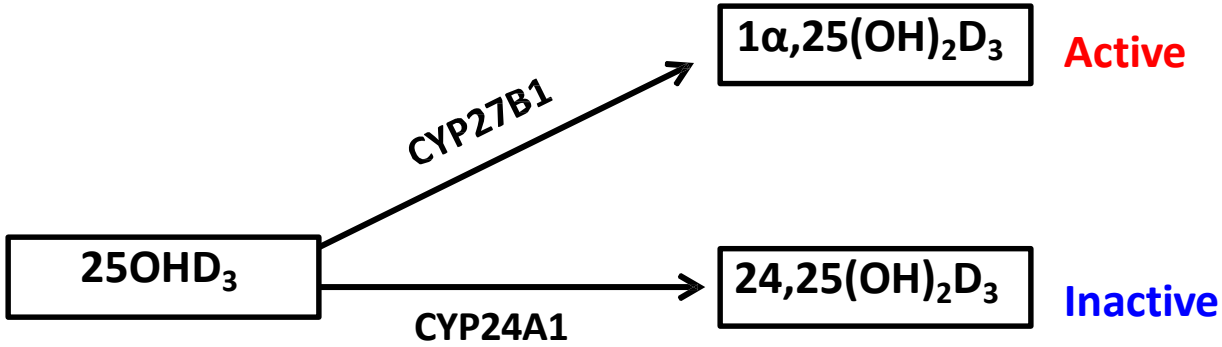


National Center for Advancing Translational Sciences

Jonathan Himmelfarb, U Washington

Metabolic Activity of PTECs in 3D MPS

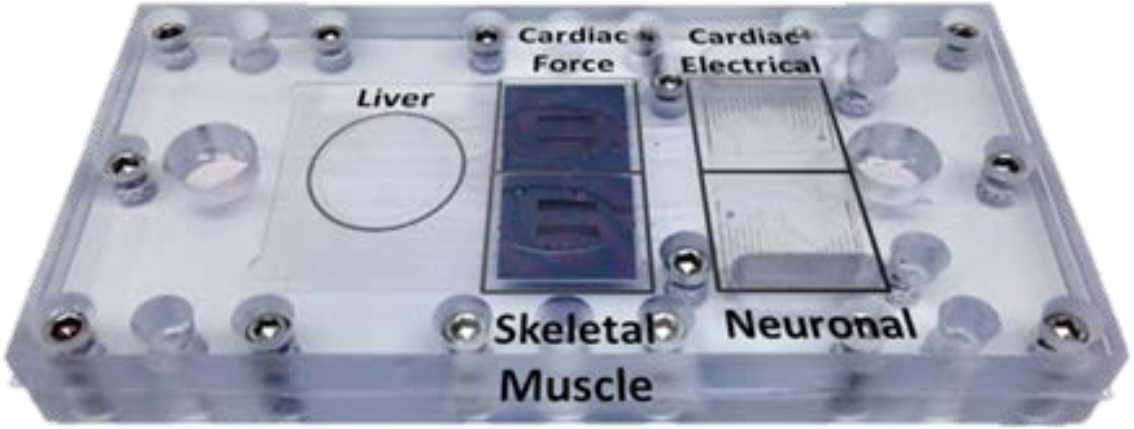




Jonathan Himmelfarb, U Washington

Functional Multi-organ System

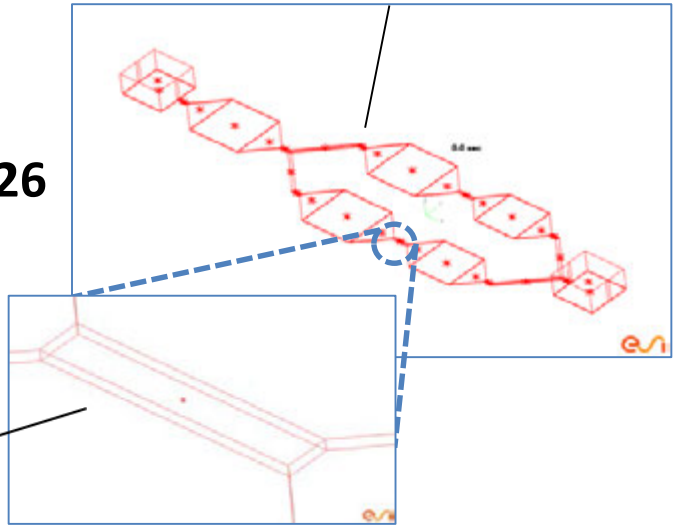
HESPEROS INC



- ✓ Pumpless
- ✓ Serum-free medium
- ✓ Integrated
- ✓ Functional readouts
- ✓ Recirculating system
- ✓ Low cost

Oleaga, et al., Multi-Organ Toxicity Demonstration in a Functional Human in Vitro System Composed of Four Organs. *Nature Scientific Reports* 6:20030 (2016).

Animation showing the bi-directional flow represented by velocity vectors



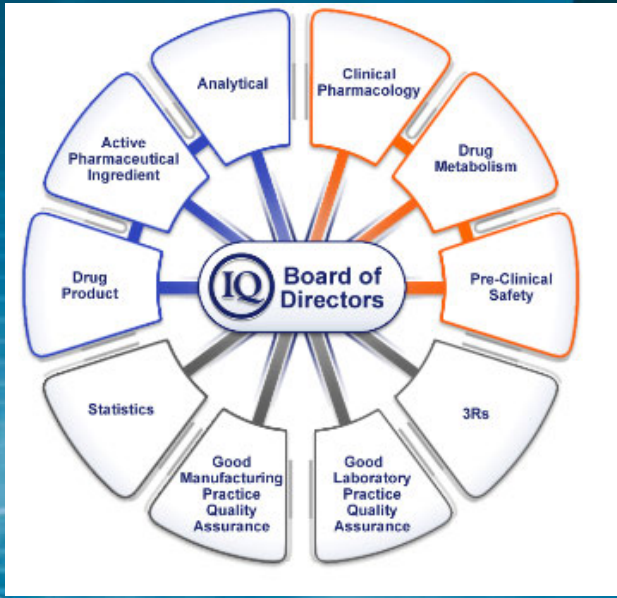
NCATS 2016 direct to Phase II Awardee R44TR001326

Zoomed in view of the flow within an interconnecting channel

National Center for Advancing Translational Sciences

Michael Shuler – President and CEO, also Cornell
James Hickman – Chief Scientist, also UCF

Tissue Chip Testing Centers



NCATS

Building a Tissue Chip Validation Framework

Adoption and Commercialization

3) Industrial

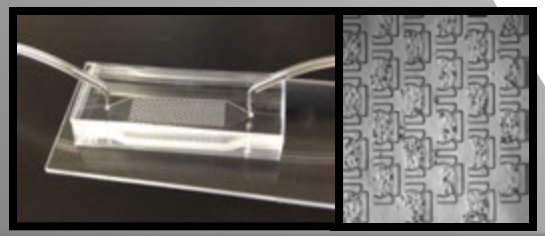
- Adoption by industry
- Proprietary set of compounds
- CRO-type environment

2) Analytical

- Independent: robustness, reproducibility, rigor
- Validation set of compounds
- Conducted TCTC

1) Physiological

- Organ function and structure
- Training set of compounds
- TC developers



NCATS 3 Ds

- Develop
- Demonstrate
- Disseminate

Comput Struct Biotechnol J.(2016) 14: 207–210. Facilitating the commercialization and use of organ platforms generated by the microphysiological systems (Tissue Chip) program through public–private partnerships

Building a Tissue Chip Validation Framework

- Physiological
  - » Mimics organ cytoarchitecture and function
  - » Training set of compounds (AstraZeneca, GSK, Pfizer)
  - » Performed by MPS developers (UH2/UH3 awards)
- Analytical
  - » Portability, reproducibility, sensitivity, specificity, dosing paradigm, cellular vs. organ toxicity, toxicity readouts, etc
  - » Reference set of validation compounds, assays, biomarkers with input from IQ consortium and FDA based on technical specifications of each platform from MPS developers
  - » Independently conducted by testing centers (U24 awards – TCTC)
- Industrial (future partnership opportunities?)
  - » Adaptation by pharma for a specific "context-of-use" in drug development
  - » Likely proprietary set of compounds from pharma
  - » CRO-type environment?

Comput Struct Biotechnol J.(2016) 14: 207–210. Facilitating the commercialization and use of organ platforms generated by the microphysiological systems (Tissue Chip) program through public–private partnerships

Tissue Chips Available for Validation

https://ncats.nih.gov/files/specs-tissue-chip-validation.xlsx

- Skin
- GI
- microvascular-endothelial
- vascular: endothelial cells, pericytes
- engineered blood vessels
- heart-cardiomyocytes
- cardiomyocytes, HUVEC
- liver-hepatocytes
- liver-hepatocytes plus nonparenchymal cells (endothelial cells, Kupffer cells, stellate cells, fibroblasts and immune cells)
- tumor-breast cancer metastasis in liver (can be any tumor type - have used breast, prostate, and melanoma)
- heart-cardiomyocytes
- fat-white, adipocytes
- bone – tumor
- kidney-proximal tubule,
- kidney-derived microvascular
- "brain: neural progenitor cells, microglia
- blood brain barrier-pericytes, astrocytes, neuron, endothlial cells
- myofibers-muscle bundle
- Ovarian Follicle/Ovary
- Fallopian Tube
- Uterus
- Cervix

- Technical specifications (Cell Source; EC Matrix; Online Measurements; End point measurements; Media used when when testing drug response in system; Fluidics (ex: microfludic)
- IQ Consortium, FDA to propose appropriate assays, biomarkers and validation set of compounds

Building a Tissue Chip Validation Framework

- Physiological
  - » Mimics organ cytoarchitecture and function
  - » Training set of compounds (AstraZeneca, GSK, Pfizer)
  - » Performed by MPS developers (UH2/UH3 awards)
- Analytical
  - » Portability, reproducibility, sensitivity, specificity, dosing paradigm, cellular vs. organ toxicity, toxicity readouts, etc
  - » Reference set of validation compounds, assays, biomarkers with input from IQ consortium and FDA based on technical specifications of each platform from MPS developers
  - » Independently conducted by testing centers (U24 awards – TCTC)
- Industrial (future partnership opportunities?)
  - » Adaptation by pharma for a specific "context-of-use" in drug development
  - » Likely proprietary set of compounds from pharma
  - » CRO-type environment?

Comput Struct Biotechnol J.(2016) 14: 207–210. Facilitating the commercialization and use of organ platforms generated by the microphysiological systems (Tissue Chip) program through public–private partnerships

Principles for Validation

(adapted from OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment)

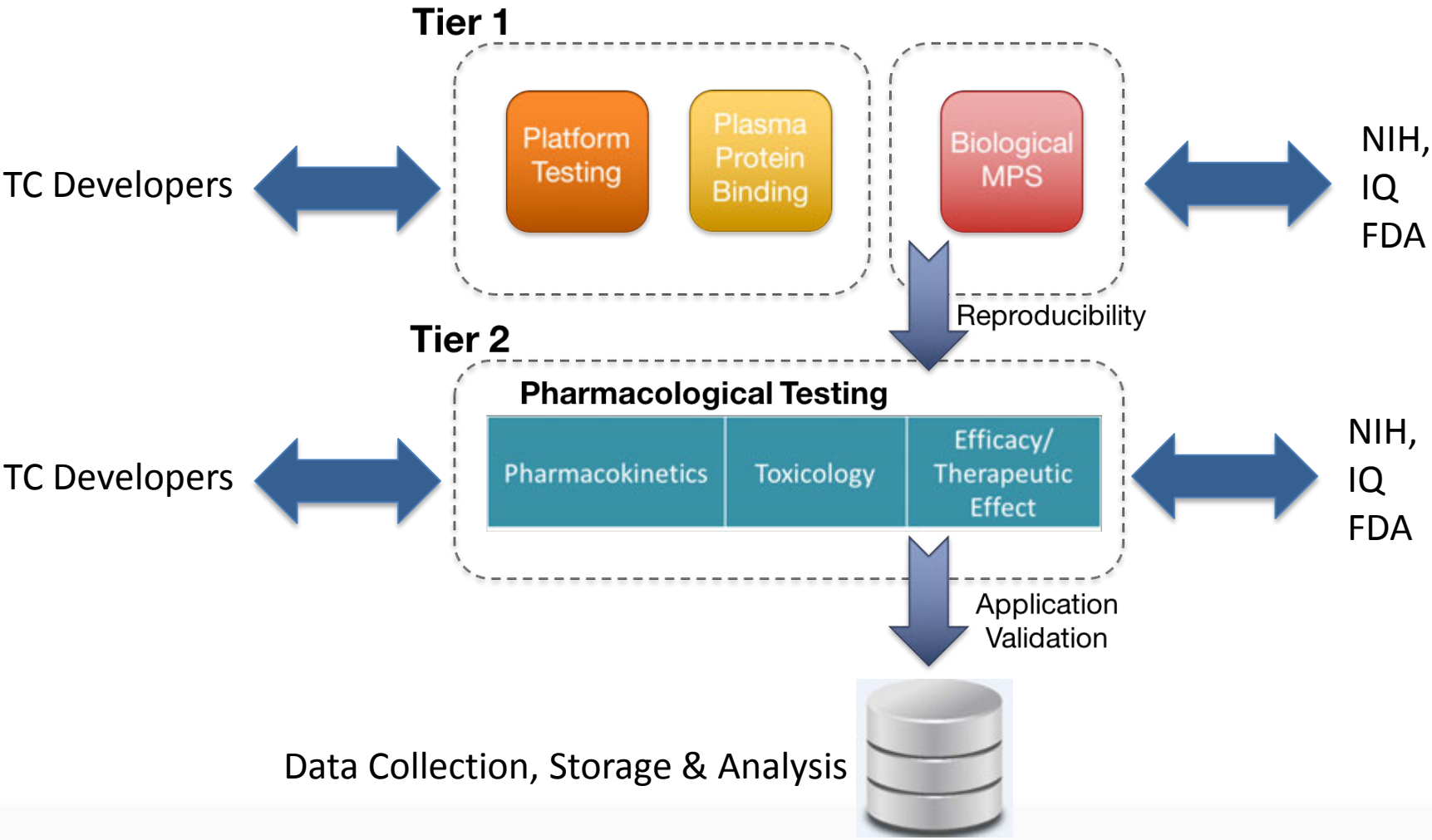
1. Rationale for assay – need and purpose
2. Relationship of endpoint to in vivo effect of interest, also limitations
3. Detailed protocol
4. Intra-test variability, repeatability and reproducibility of the test method within and amongst laboratories
5. Test method's performance must have been demonstrated using a series of reference chemicals
6. Performance of a test method should be evaluated in relation to existing relevant toxicity data
7. Data supporting the validity must be available for review
8. Data should be obtained in accordance with GLPs

Courtesy of Paul Brown, FDA

Tissue Chip Testing Centers: Validating Microphysiological Systems

- Resource Centers (U24)
- GOAL: Independent validation of tissue chip platforms
- Partnerships between NCATS, FDA and IQ Consortium
- NCATS support: $12 M over two years; awarded 9/28/16
- FDA and IQ provides expert guidance on reference set of validation compounds, assays, biomarkers
- Testing Centers:
  - » MIT (Murat Cirit and Alan Grudzinsky)
  - » TAMU (Ivan Rusyn)
- MPS Database:
  - » U Pittsburgh (Mark Schurdak)

General Testing Strategy



Implementation Of Database And Analytics Based On OECD And FDA Guidelines

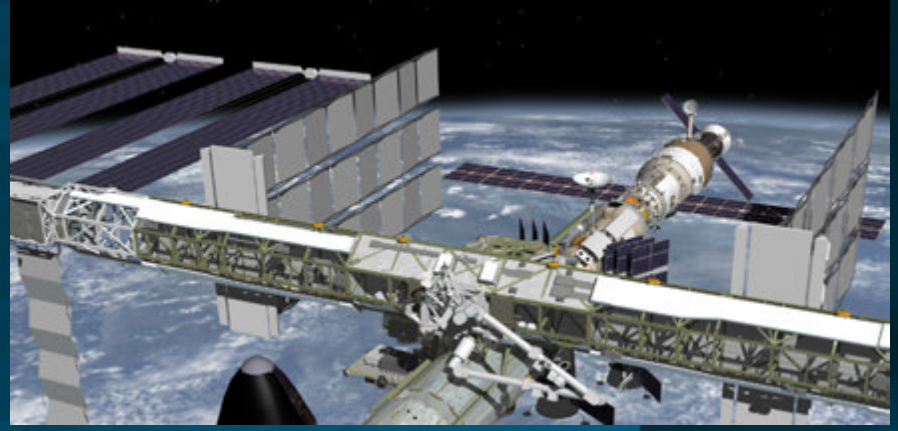
- Statistical analyses to rigorously describe reproducibility
  - Intra-test variability (chip-to-chip)
  - Day-to-day variability
  - Comparison of reproducibility across testing sites
- Acquisition of organ relevant clinical reference data for all test compounds
- Enable evaluation of concordance with in vivo reference data
- Develop computational models to predict in vivo response
  - Determination of in vitro data requirements for in vitro-to-in vivo extrapolation
  - Enable in vitro-to-in vivo extrapolation
- Enable a standardized Method Description for each assay according to OECD Guidance:
  - General information, Test method definition, Data interpretation and prediction model, Test method performance, Potential regulatory applications

Contact: Dan Tagle
Danilo.Tagle@nih.gov
Lucie Low
Lucie.Low@nih.gov

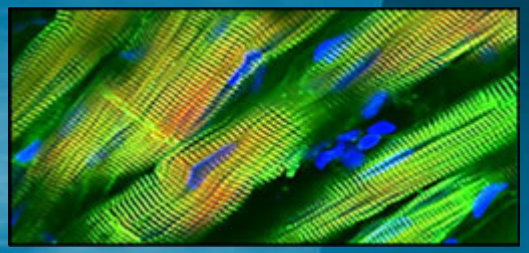
For acknowledgements and more information: on funded projects, participants, resources please see http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html

or search:
NCATS Tissue Chips

NCATS



NEW Tissue Chips Initiatives – Leveraging NCATS/CAN Investment through Partnerships



NCATS

The New Reality

~~BigPharma Pipeline Model~~

Distributed Partnership Model

~~Economic Competition~~

PreCompetitive Collaborations

~~Profit-Centered Goals~~

Patient-Centered Goals

~~Patenting Early-Stage Innovations~~

Patenting Developed Products

~~Basic vs. Applied Research~~

Team-Based Research

NCATS Office of Strategic Alliances

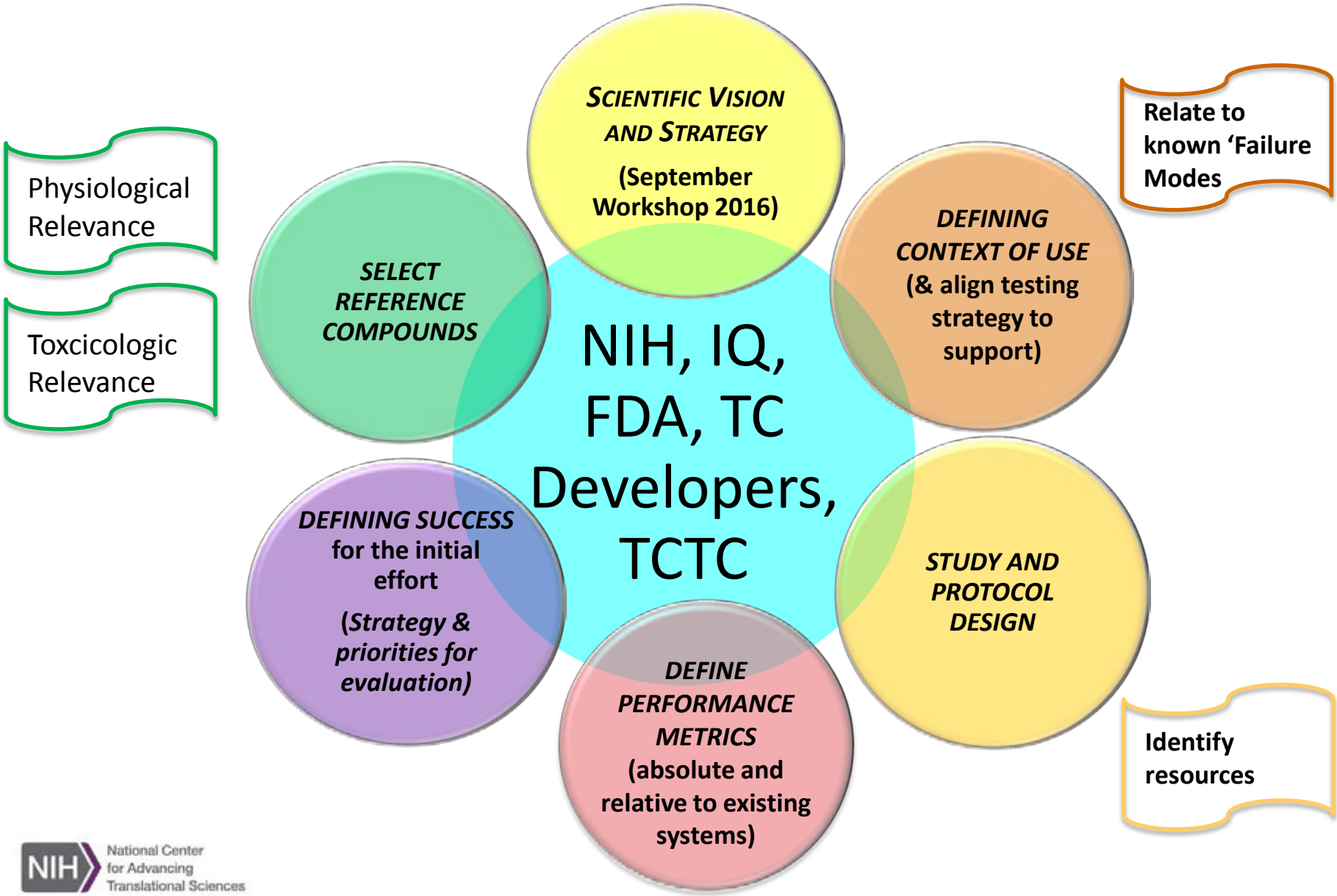
- Focused on exploring new collaborative approaches
- Facilitating PPP using Template Agreements
  - » Memorandum of Understanding (MOU)
  - » Confidential Disclosure Agreement (CDA)
  - » Material Transfer Agreement (MTA)
  - » Collaborative Research Agreement (CRA)
  - » Clinical Trials Agreement (CTA)
  - » Cooperative Research and Development Agreement (CRADAs)
- Lessens transaction time

- Lili M. Portilla, MPA - Director, Office of Strategic Alliances

NCATS Partnerships: Tissue Chips Program for Drug Screening

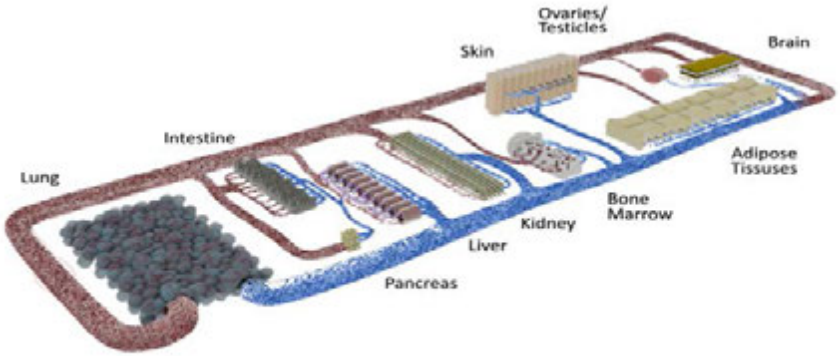
- MOU with DARPA and FDA
- MTA with AstraZeneca, GSK and Pfizer for reference set of training compounds
- NCATS/CAN ($10 M/year) Funding partners with other NIH IC's
  - Common Fund ($4 M/year)
  - NIBIB, NIEHS, NCI, ORWH, NICHD ($3.5 M/year)
  - Administrative supplements
    - NCI - $2 M to develop cancer models
    - ORWH – women's health
- NCATS SBIR/STTR program
- NCATS RDCRN program
- Co-organized series of workshops focused on Validation and Qualification of New In Vitro Tools and Models for the Pre-clinical Drug Discovery Process with American Institute for Medical and Biological Engineering (AIMBE), NIBIB, FDA and EMeA

Tissue Chip Testing Centers



National Center for Advancing Translational Sciences

Human Relevance of a Model Starts with the Disease

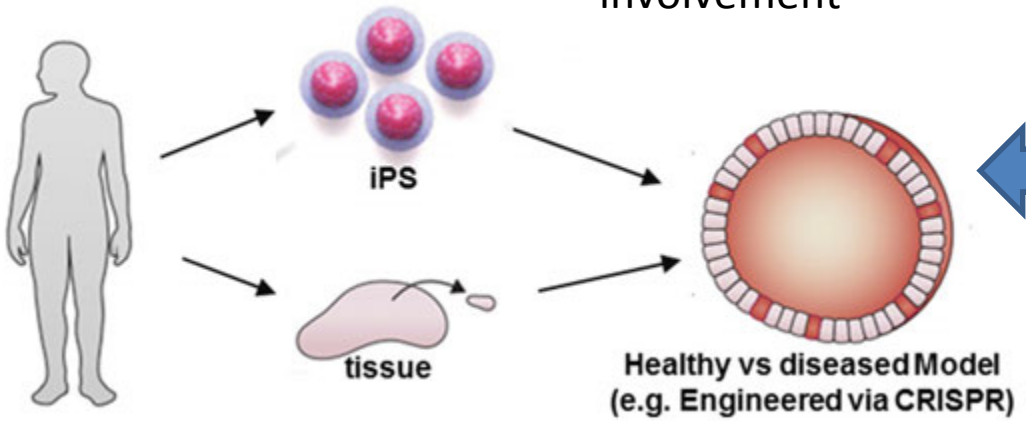


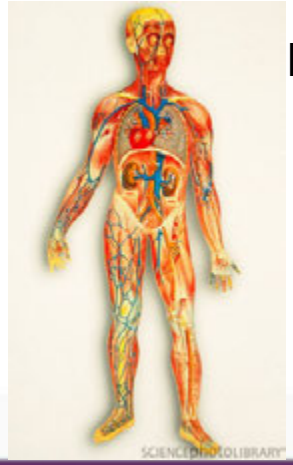
Courtesy of TISSUSE

Readouts

- Human biology
- Tissue/organ structure
- Cell histology
- Cell viability
- Mechanical properties
- Electrical properties
- Signaling pathways
- Cell metabolism
- Protein synthesis
- Gene expression
- Enzyme activities
- Ion channel properties

- Monogenic or polygenic
- Mendelian or multifactorial
- Single organ or multi-system involvement





In vivo Correlation

- Absorption
- Distribution
- Metabolism
- Excretion
- Concentration
- Effect
- Toxicity
- Rare toxicities

Tissue-on-chips Disease Models for Efficacy Testing

- RFA-TR-16-017
- GOAL: Develop models for a wide range of human diseases for efficacy testing, assessment of candidate therapies and establishing the pre-clinical foundation that will inform clinical trial design
  - » NCATS ($5 M/year) joined by NCI, NEI, NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINDS, ORWH as funding partners
  - » NIH support: approximately $ 80 M over five years
  - » Bi-phasic:
    - o Develop and characterize models of diseases
    - o Testing for efficacy of candidate therapeutics
- Application Receipt Date: December 13, 2016

Aging-like Physiological Changes under Prolonged Microgravity Environment

- **Early response (<3 weeks)**
  - » Upper body fluid shift
  - » Neurovestibular disturbances
  - » Sleep disturbances
  - » Bone demineralization

- **Intermediate (3 weeks to 6 months)**
  - » Radiation exposure
  - » Bone resorption
  - » Muscle atrophy
  - » Cardiovascular deconditioning
  - » GI disturbances
  - » Hematological changes

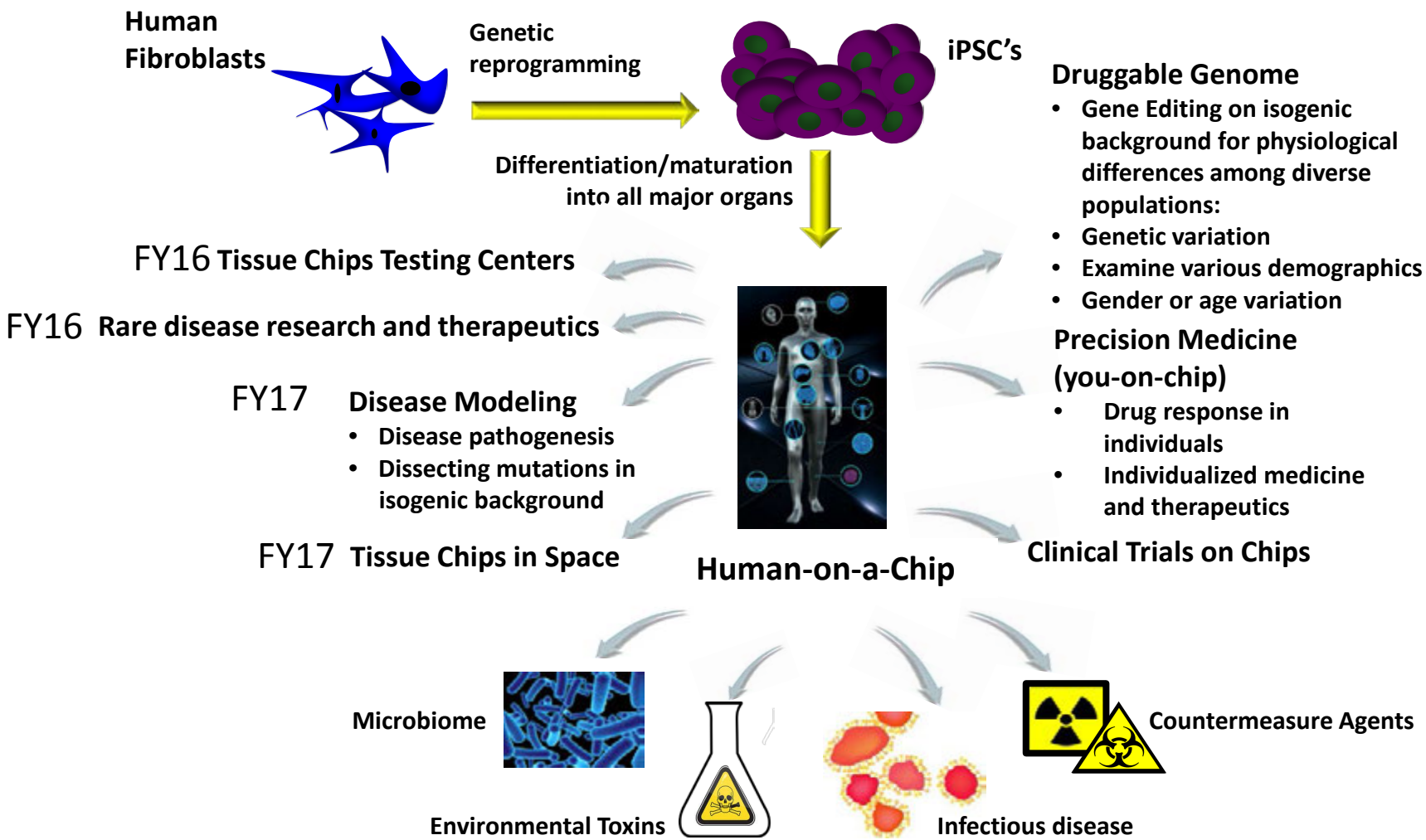
- **Long Duration (greater than 6 months)**
  - » Radiation exposure
  - » Muscle atrophy
  - » Cardiovascular deconditioning
  - » GI disturbances
  - » Hematological changes
  - » Declining immunity
  - » Renal stone formation

- **Reverts to normal on return to Earth**

NIH-CASIS Coordinated Program in Tissue Chip Systems Translational Research in Space

- RFA-TR-16-019
- Partnership between NCATS, NASA and CASIS (Center for Advancement of Science in Space)
  - » GOAL: Utilize tissue-on-chips technology towards biomedical research at the International Space Station that will lead to a better understanding of the molecular basis of human disease and effectiveness of diagnostic markers and therapeutic interventions
  - » Potential impact: Understanding of the effects of microgravity on human organ systems. It could provide better insight into the molecular basis, including epigenome changes for many human conditions in space and provide information for novel drug targets for use on Earth
  - » NCATS support: approximately $12 M over four years
  - » NASA support: $ 3 M over four years; CASIS: $ 8 M in-kind support
  - » Application Receipt Date: December 15, 2016
  - » http://www.casistissuechip.blogspot.com

Future Directions in Tissue-on-chips Technology



Contact: Dan Tagle
Danilo.Tagle@nih.gov
Lucie Low
Lucie.Low@nih.gov

For acknowledgements and more information: on funded projects, participants, resources please see http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html

or search:
NCATS Tissue Chips

NCATS

Tissue-on-Chips

- Administrative Supplements
  - » Missing organs towards a Homunculus PA-TR-16-178; $773,044
    - o Subchondral Bone and Articular Cartilage System (Berkeley)
    - o Microformulator (Vanderbilt)
    - o Male Reproductive System (Columbia and Northwestern)
    - o White Adipose Tissue (MIT and Berkeley)
    - o Uterine Muscle-on-Chip (Wyss)
    - o Vascularized Retina (Eye)-on-chip (Morgridge)
    - o Bone Marrow-on-Chip (Washington U)
  - » Rare Disease Modeling in collaboration with RDCRN PA-TR-16-173; $1,299,044
    - o Hereditary Hemorrhagic Telangiectasia (Washington U and UC Irvine)
    - o Glycogen Storage Disease III (Duke University)
    - o Timothy Syndrome (Columbia University)
    - o Tuberous Sclerosis (Vanderbilt University)
    - o Nephrotic Syndrome (U Washington)
    - o Alpers Huttenlocher syndrome (Pittsburgh)
    - o Congenital Central Hypoventilation Syndrome (Berkeley and Gladstone)
    - o Rett Syndrome (Morgridge)