Organs on a chip: Applications for drug development and research

Biomed21
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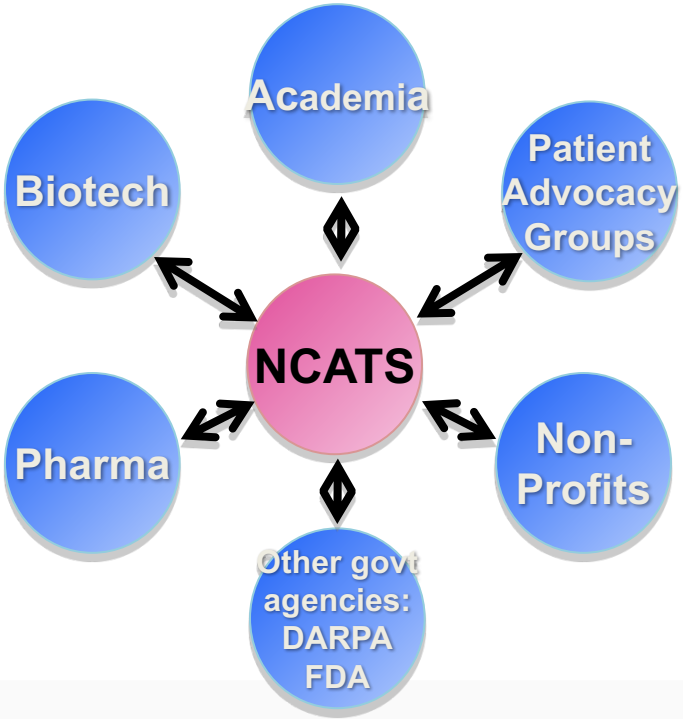
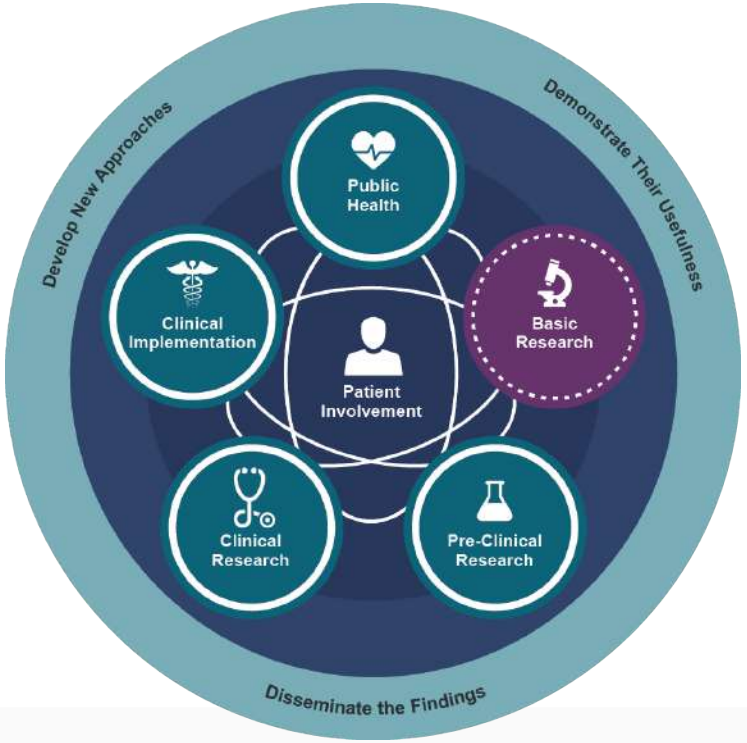
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

NCATS

NIH National Center for Advancing Translational Sciences

NCATS' Mission: To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.





The NIH Tissue Chip 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

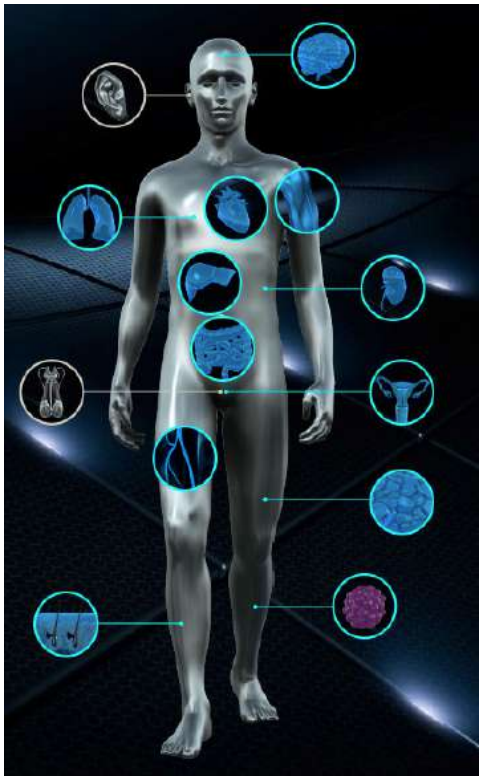
Phase 1: Development

Phase 2: Cell incorporation & organ integration

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

DARPA

DARPA: Organ integration



FDA

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

Current Goals:

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

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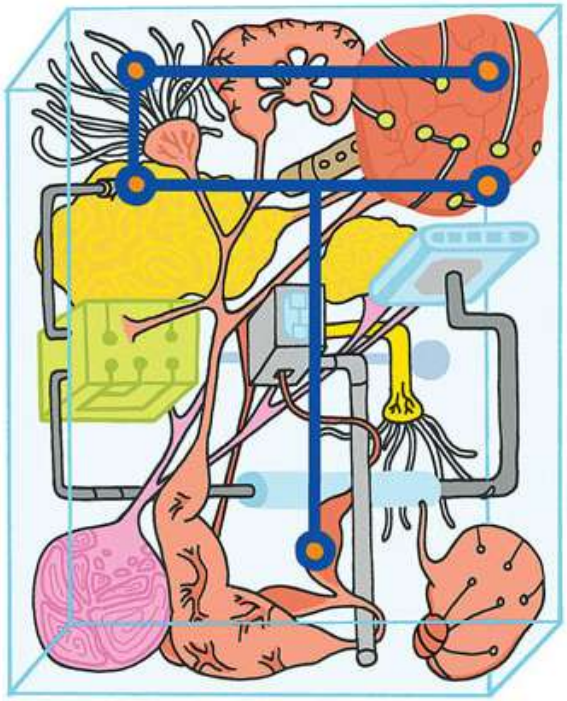
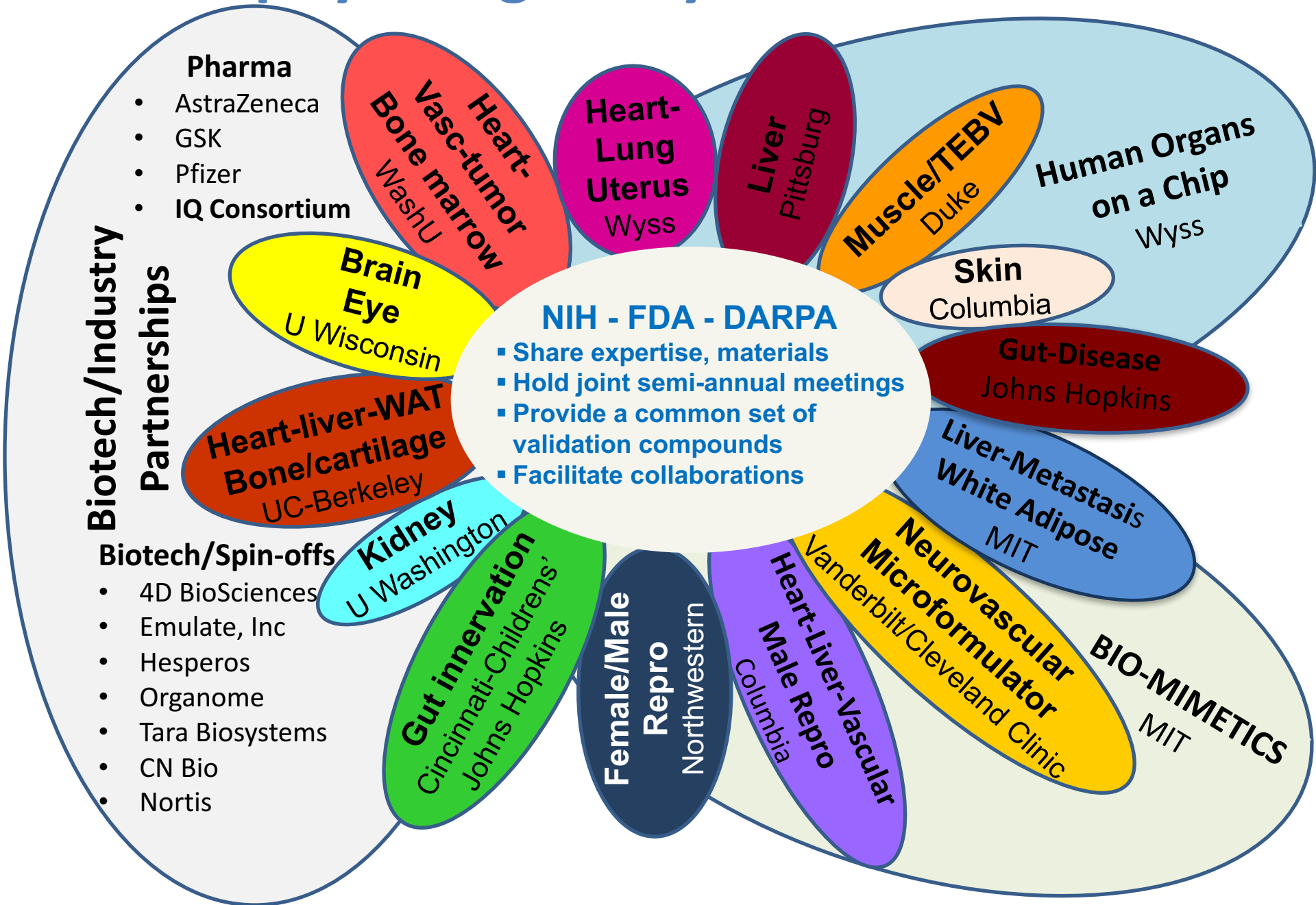
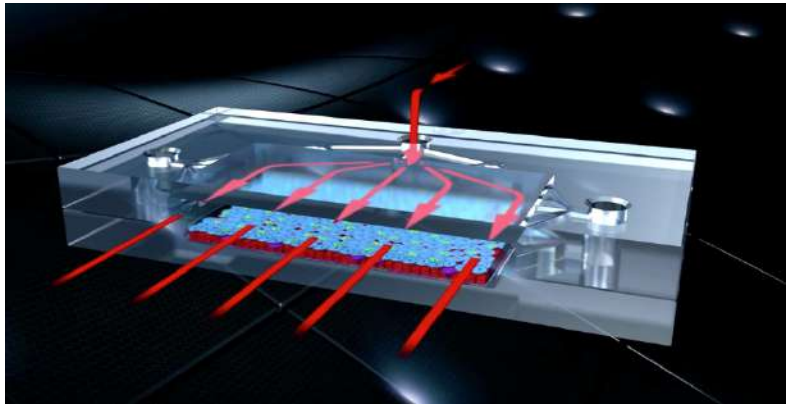


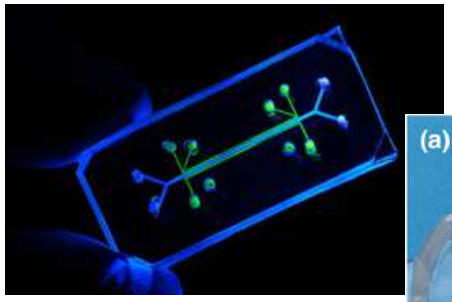
- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Physiologically relevant, genetically diverse, and pathologically meaningful.
- Modular, reconfigurable platform.
- Tissue viability for at least 4 weeks.
- **Community-wide access.**

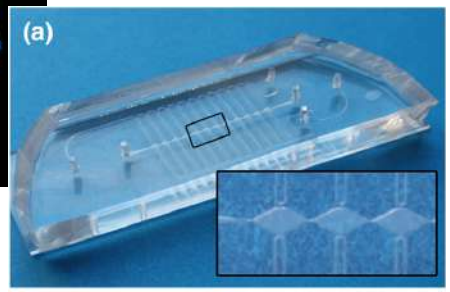
Microphysiological Systems Consortium

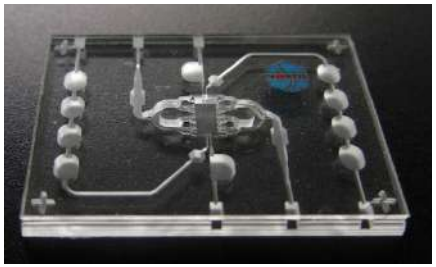


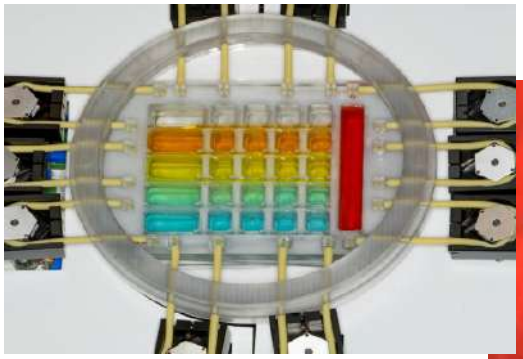
Tissue Chips…a selection

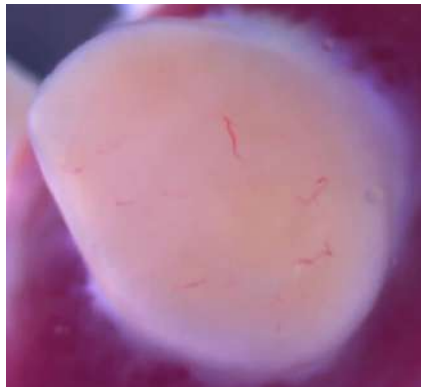


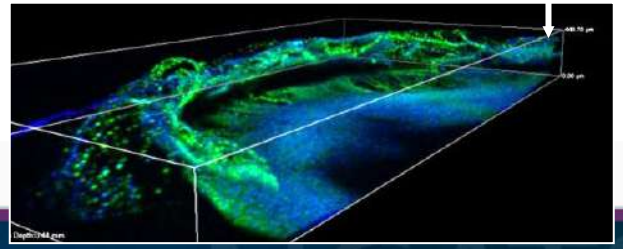




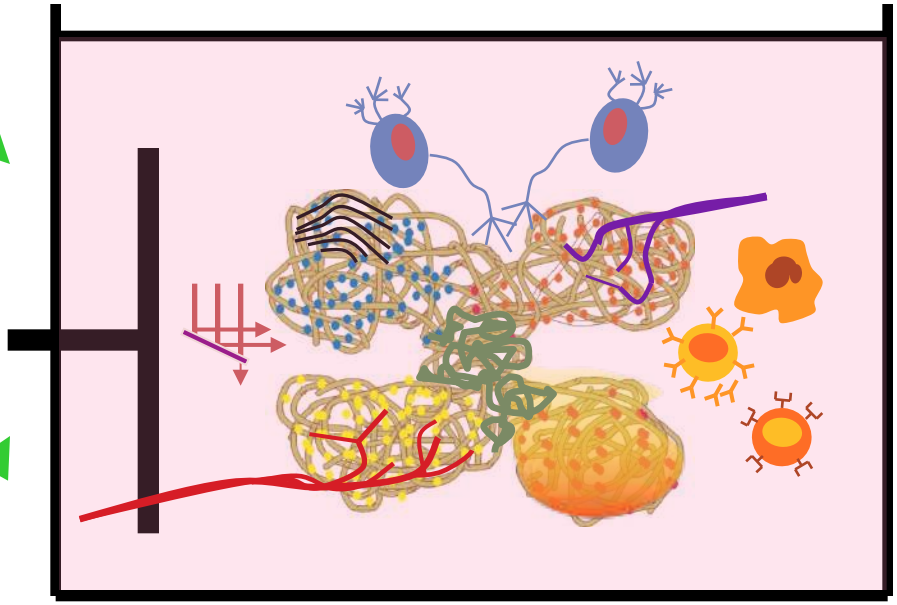




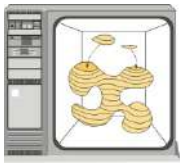




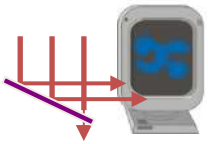
Microphysiological Systems –
A Multidisciplinary, Team-Science Approach



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



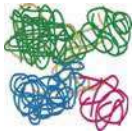
Functional Readout
- real-time, label-free, non-destructive sensing
- imaging

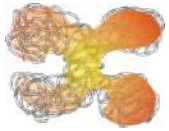


Scaffold
- purified ECM
- synthetic polymers
- composites

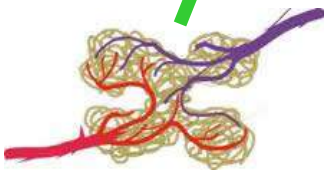
Cells
- stem/progenitor
- differentiated
- mixed cell types
- gene editing

Structure
- porosity
- topography
- stiffness



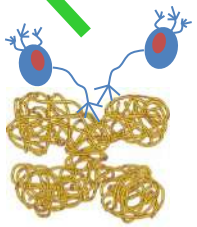


Spatial/Temporal Patterning
- cytokine gradients
- controlled release

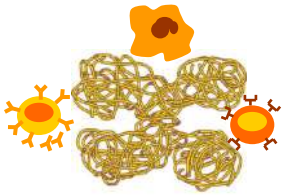


Perfusion
- embedded channels
- vascularization

Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics



Innervation
- signal propagation
- coordinated response



Host Response
- generalized inflammation
- specific immunity

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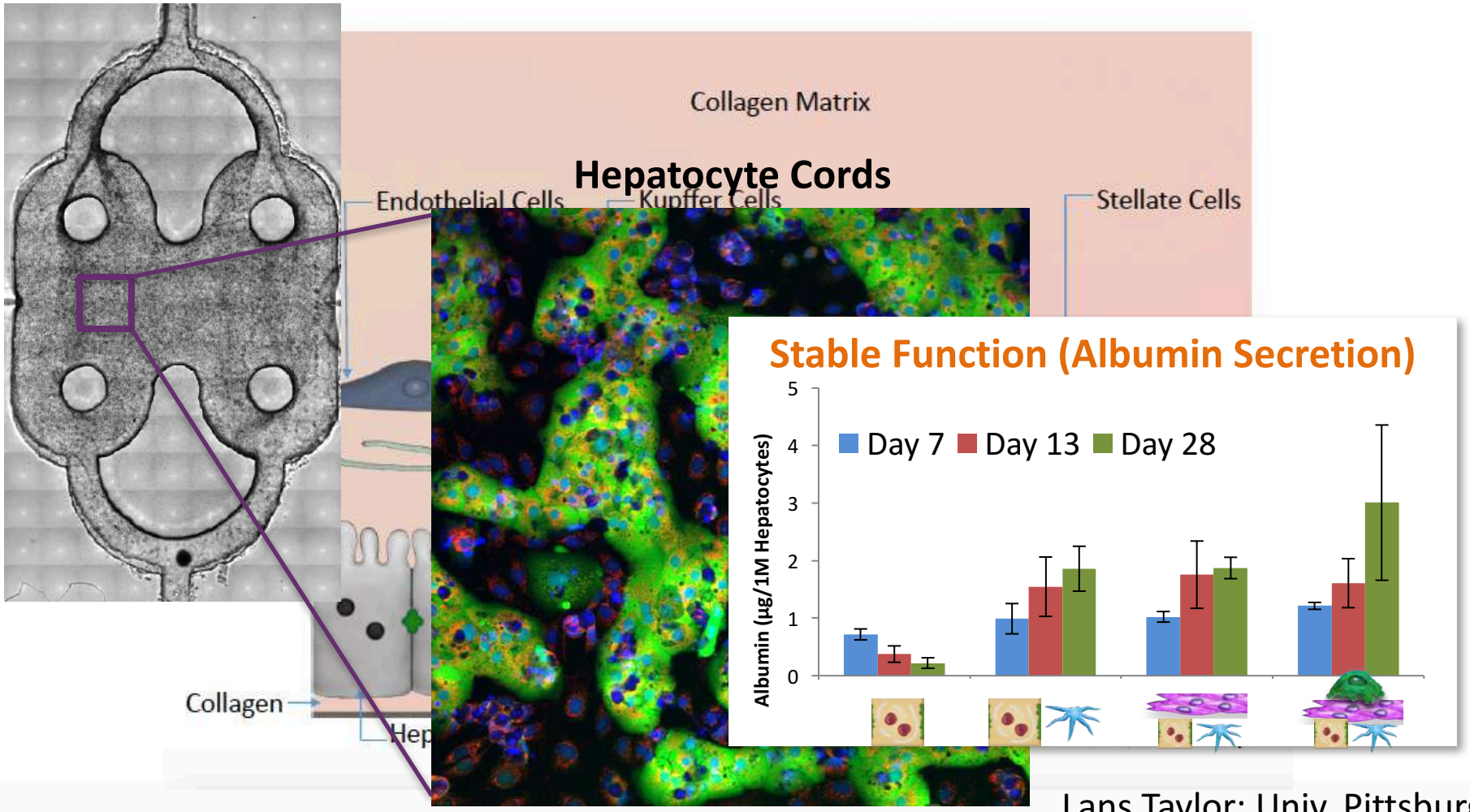
Example: Liver-on-chip

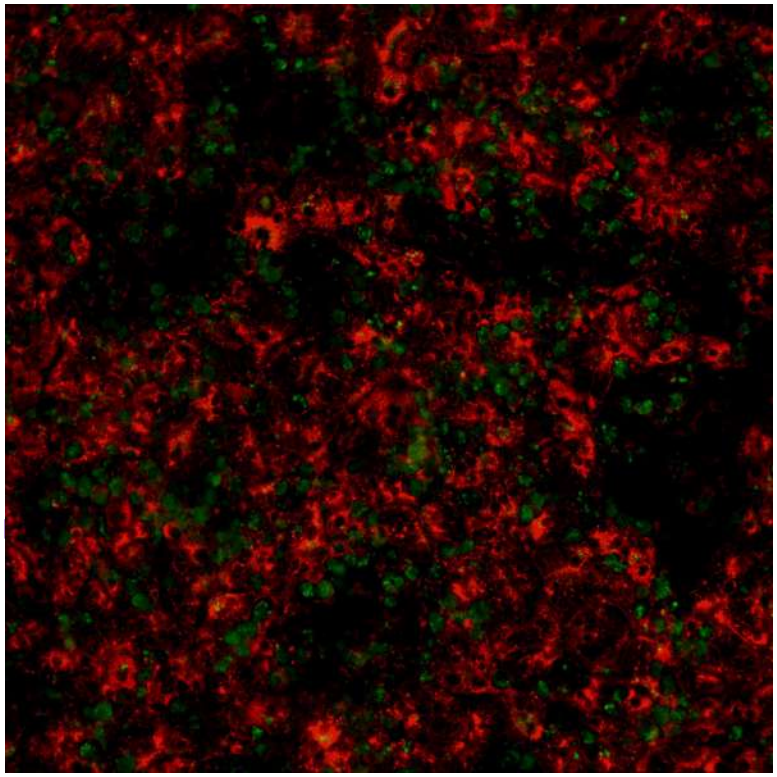


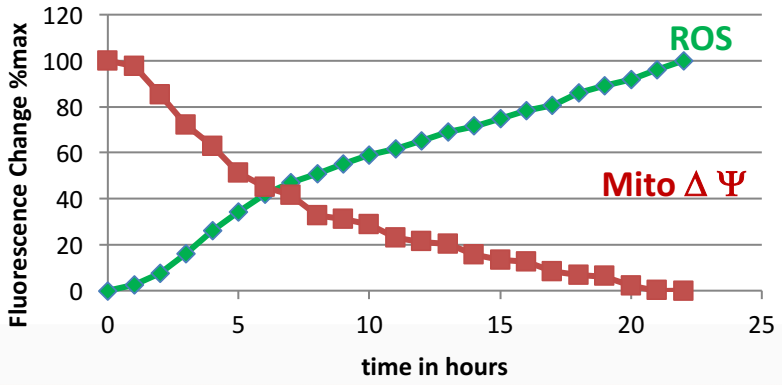
Lans Taylor; Univ. Pittsburgh

Lans Taylor; Univ. Pittsburgh

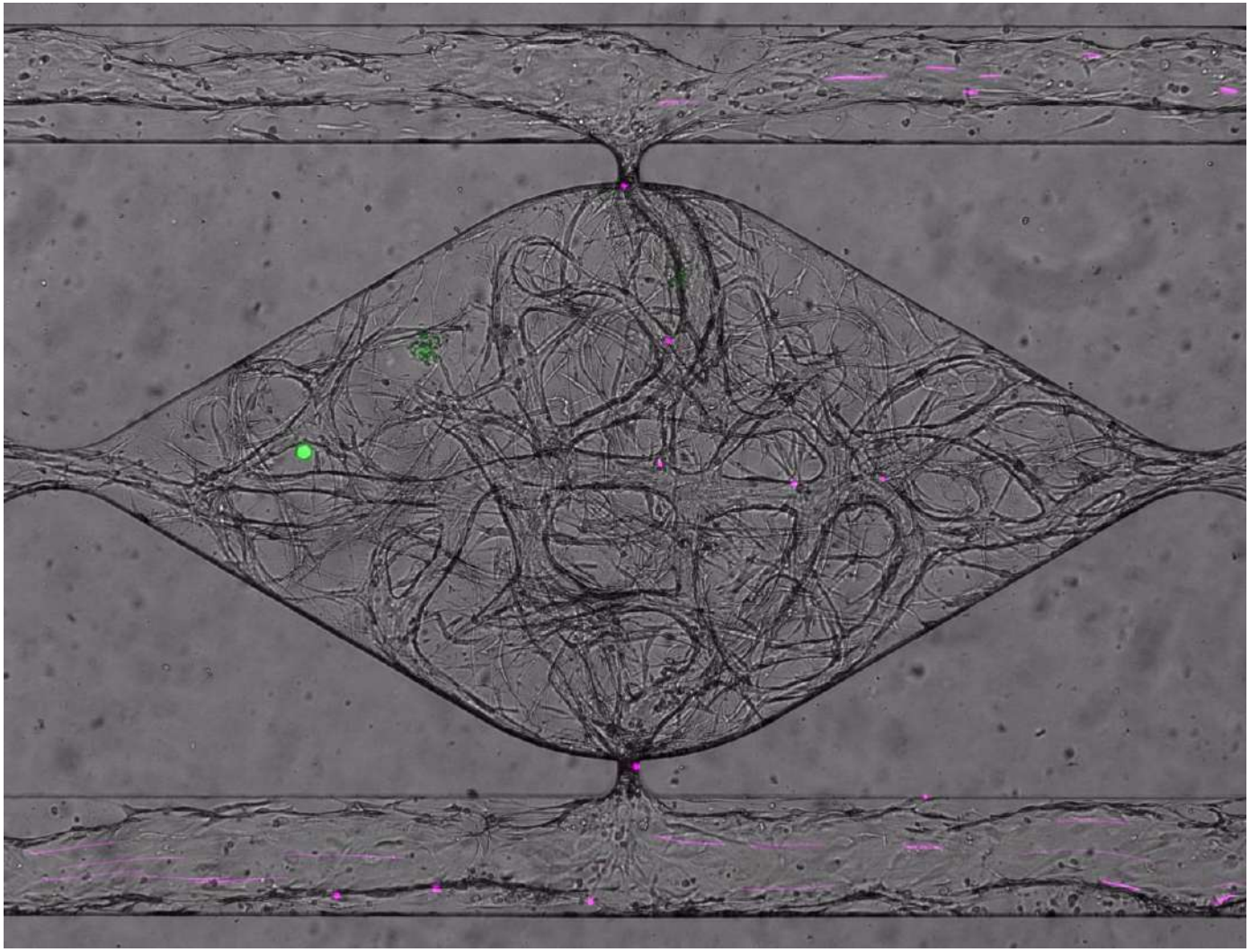
Liver Fluorescent Biosensors

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	





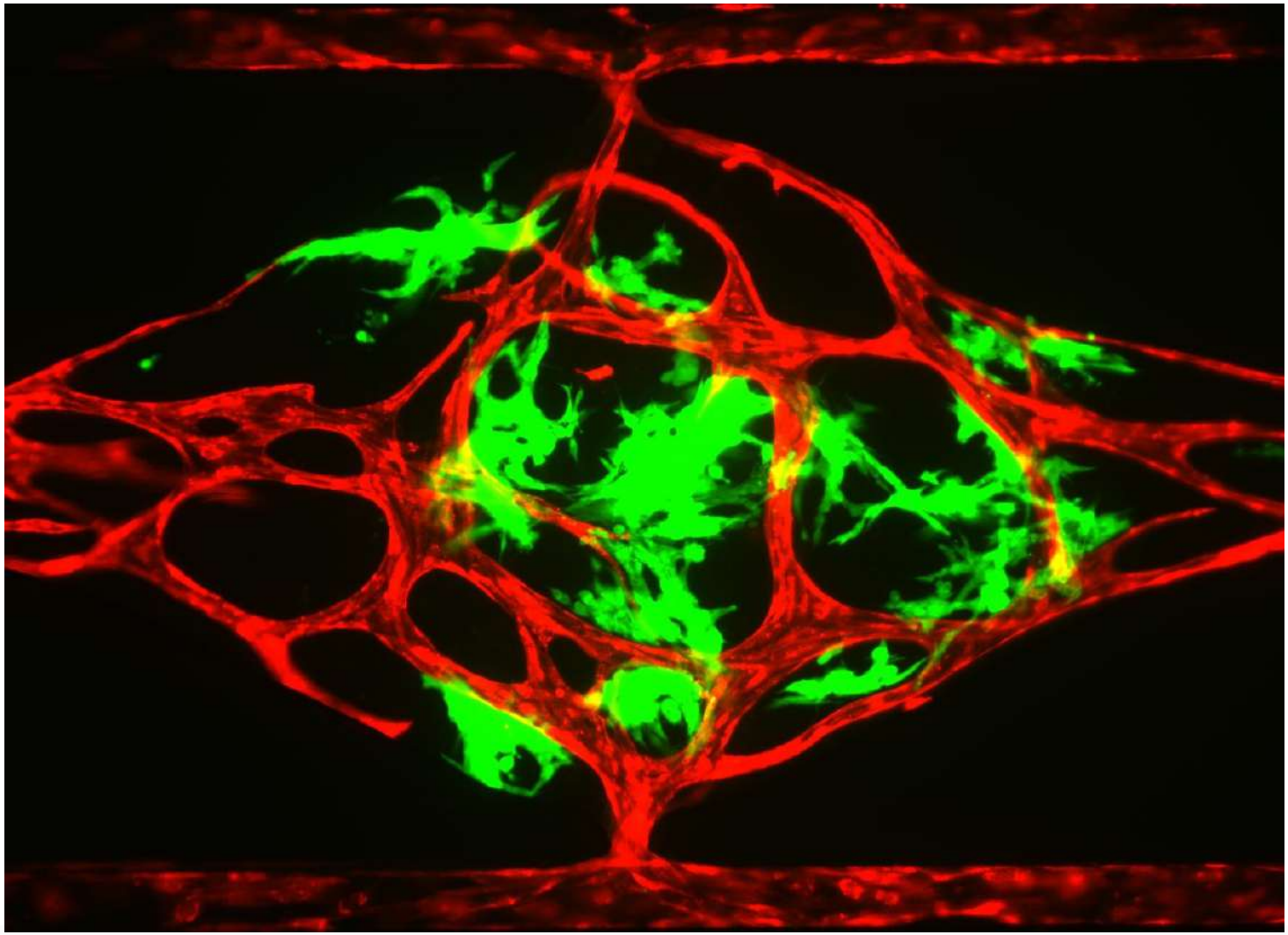
Example: Microvasculature-on-chip



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

Steven George, Washington U

Colon tumor (HCT116) supported by microvasculature



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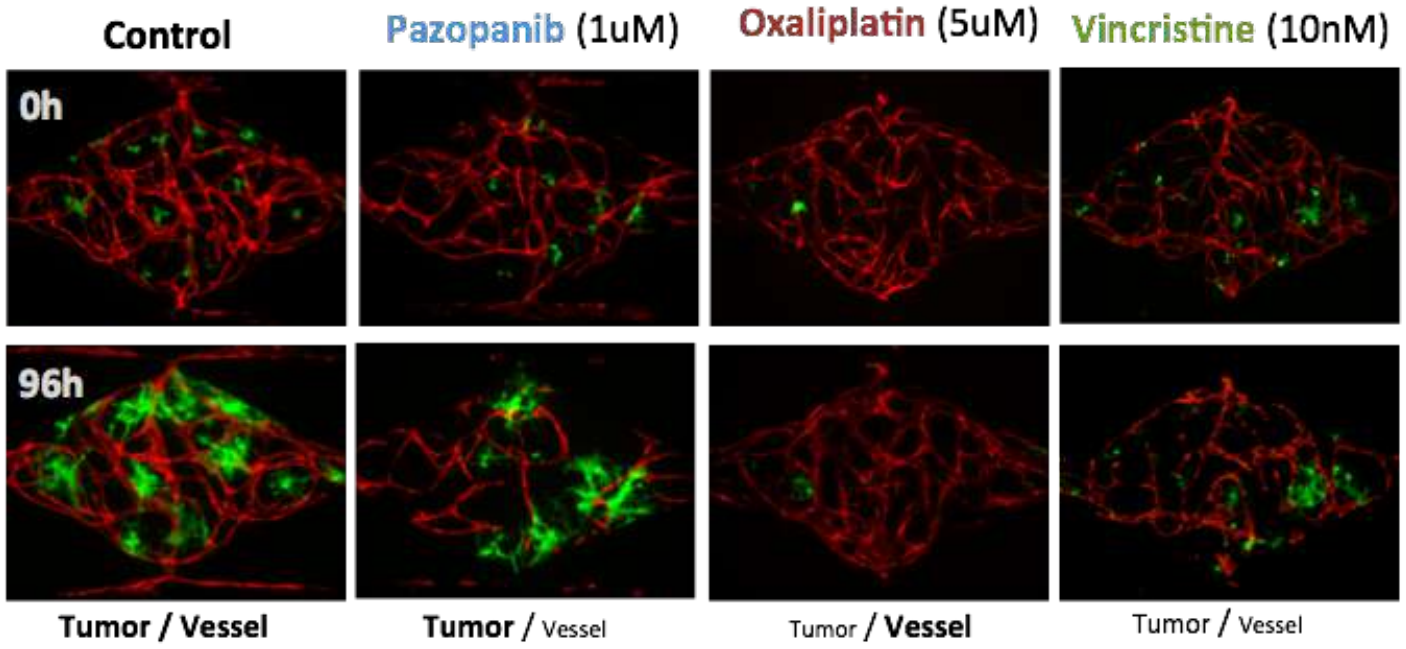
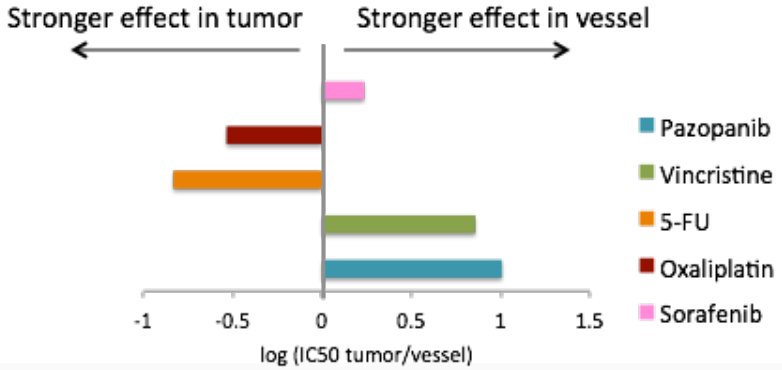
Microtumor responses to chemotherapeutics





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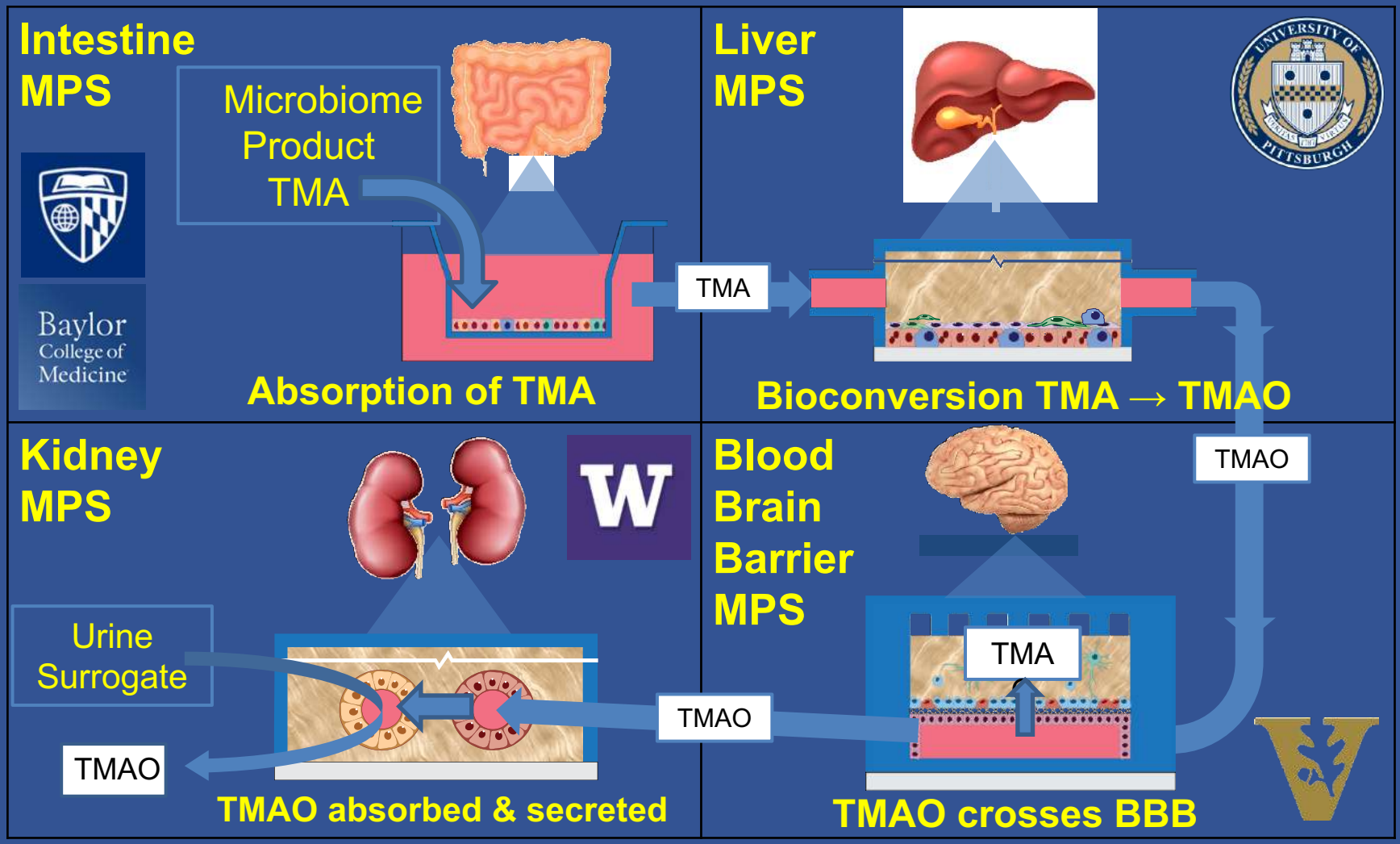
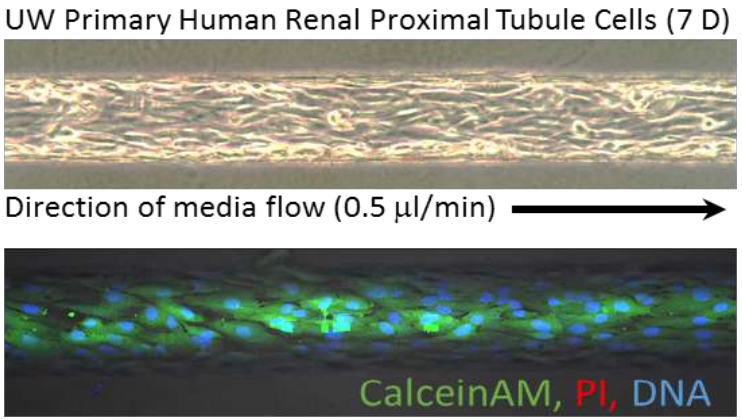
Functional coupling of four chips demonstrates physiological processing of the microbiome product trimethylamine (TMA)

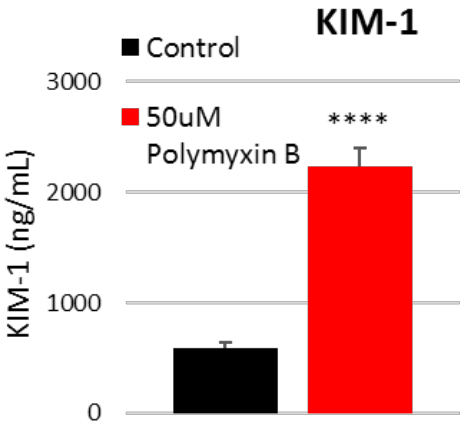


Vernetti L et al (2017) *'Functional Coupling of Human Microphysiology Systems: Intestine, Liver, Kidney Proximal Tubule, Blood-Brain Barrier and Skeletal Muscle'.* Sci Rep 7:42296).

Tissue Chip Testing Centers

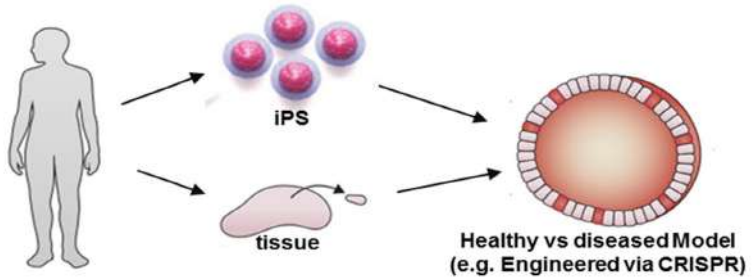
Massachusetts Institute of Technology





- FDA and IQ provides expert guidance on reference set of validation compounds, assays, biomarkers

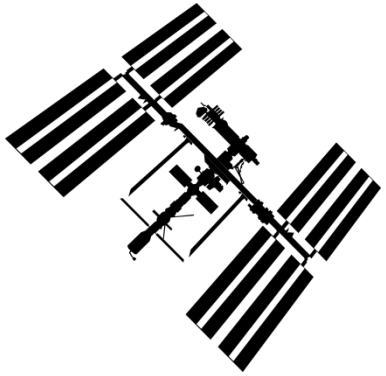
"TC2.0" for Disease Modeling
2017-2022



- 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 joined by NIEHS, NINDS, NIAMS, NIDDK, NICHD, ORWH, NIDCR, NIBIB, NHLBI
- NIH support: approximately $75M over five years

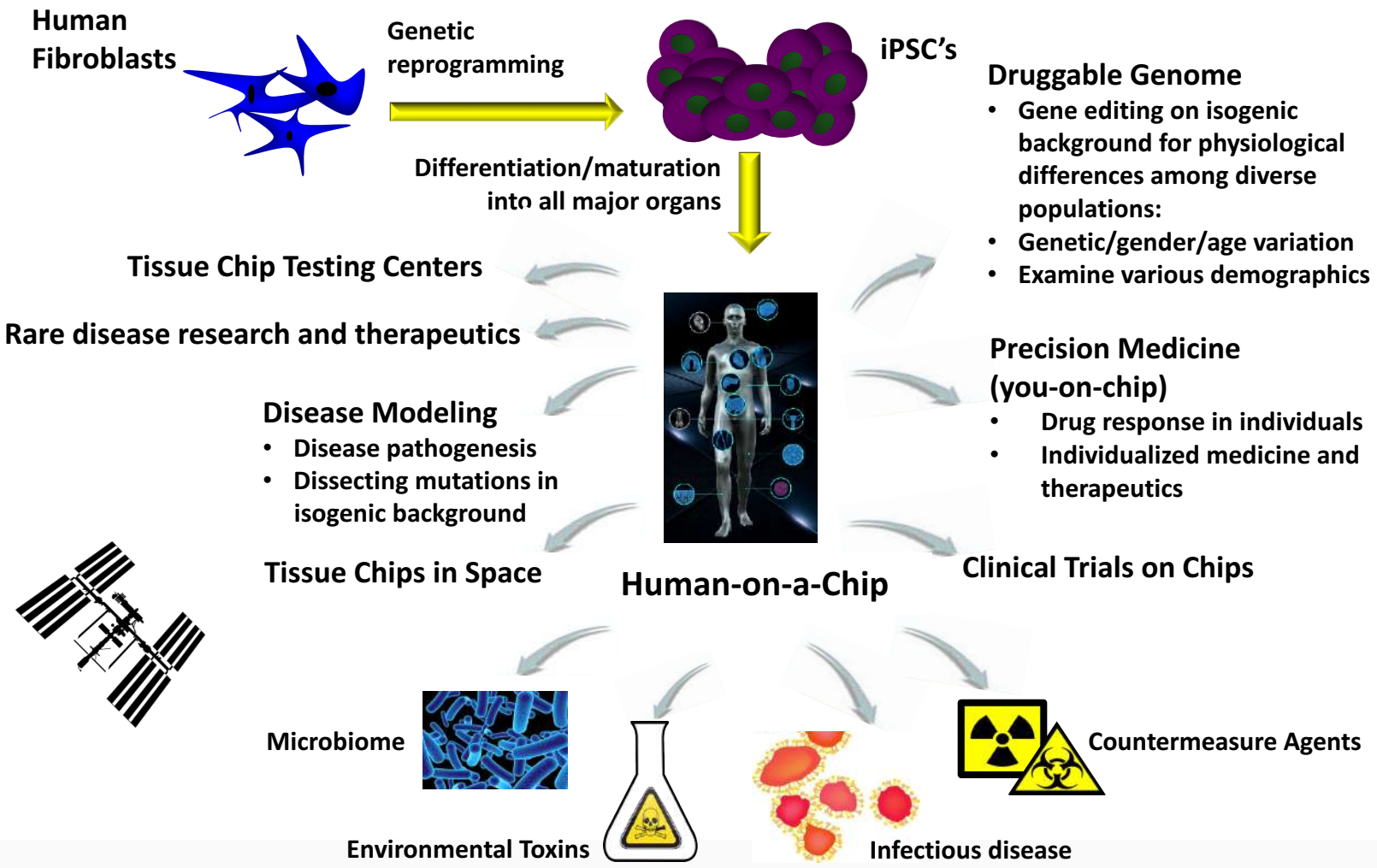
Chips in Space

2017-2021



- Partnership between NCATS and Center for Advancement of Science in Space (CASIS)
- 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
- NCATS support: approximately $12M over four years
- NASA support: $3M over four years; CASIS: $8M in-kind support

Future Directions for Tissue Chip technology



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Announce Listserv: https://bit.ly/1sdOI5w

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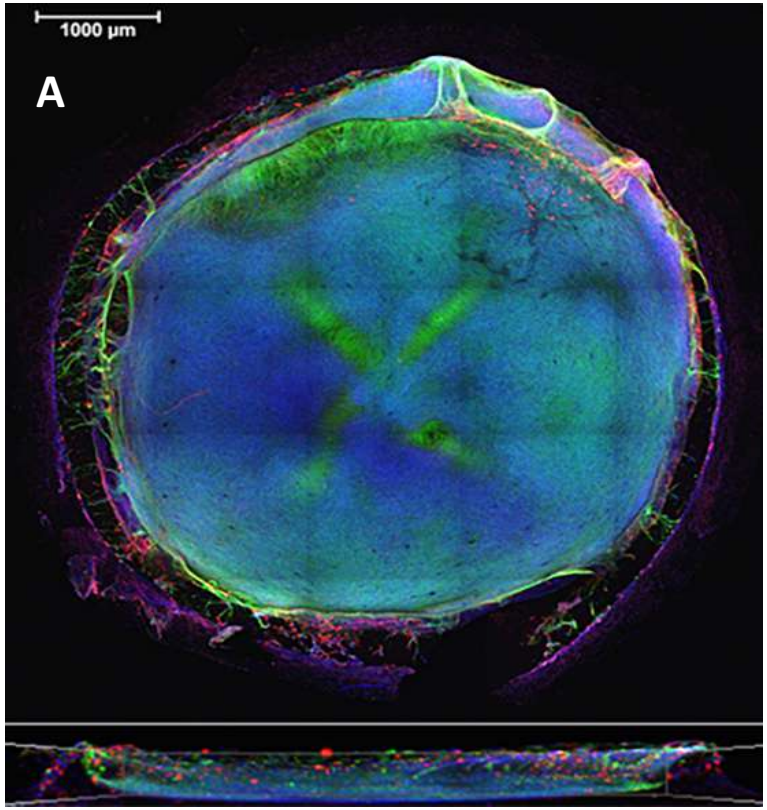
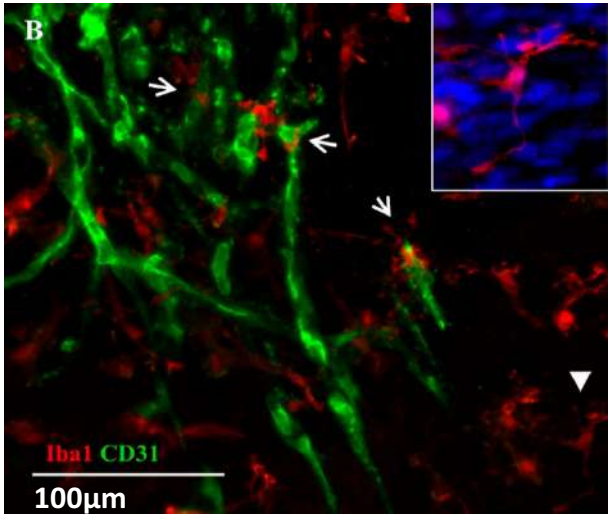
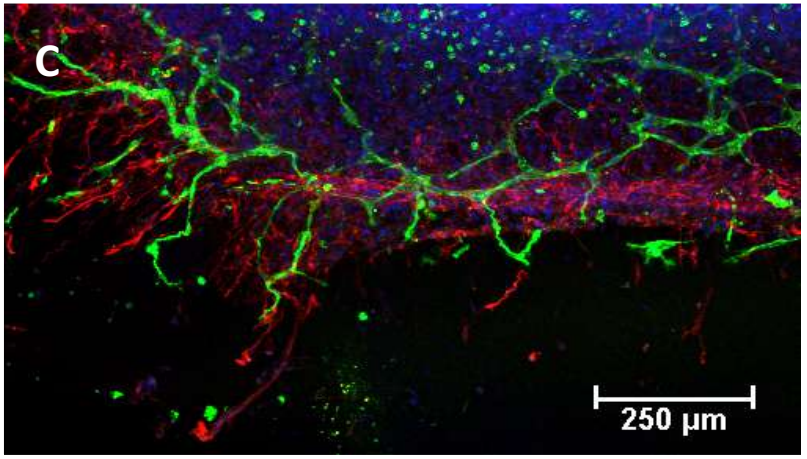
Human ESC-derived neural constructs for predictive neurotoxicity



Neurons = green; glia = red; nuclei = blue



Endothelial = green;
microglia = red;
nuclei = blue



Endothelial cells = green; glia = red; nuclei = blue

Schwartz (2015) *PNAS 112:12516-21.*

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.

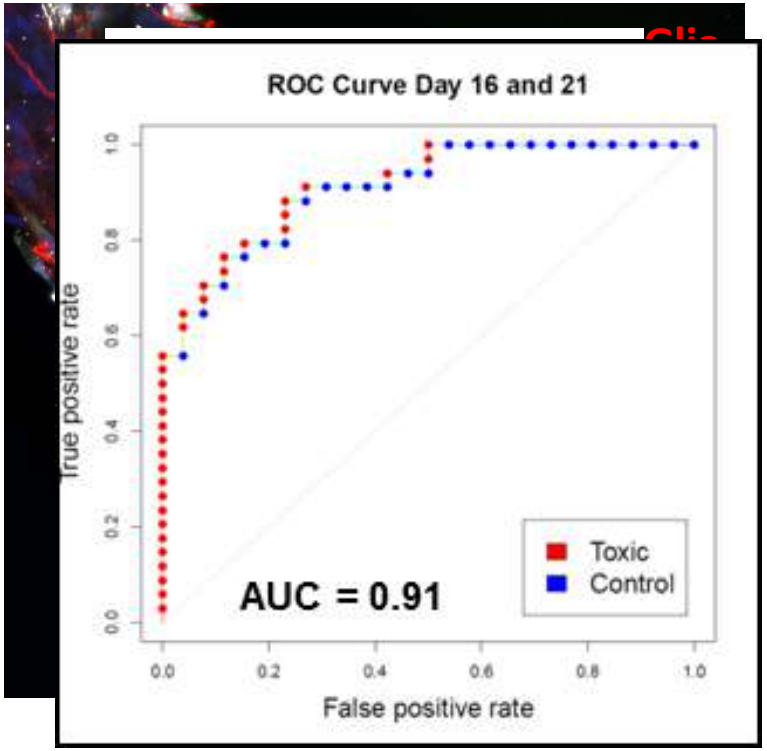
280 individual neural constructs for this experiment!

Training set:

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

Blinded set:

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



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