Microphysiological Systems: Tissues-on-Chips for Drug Safety and Efficacy Testing

Deriving Drug Discovery Value from Large-Scale Genetic Bioresources
Institute of Medicine's Roundtable on Translating Genomic-based Research for Health
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NATIONAL INSTITUTES OF HEALTH

NCATS

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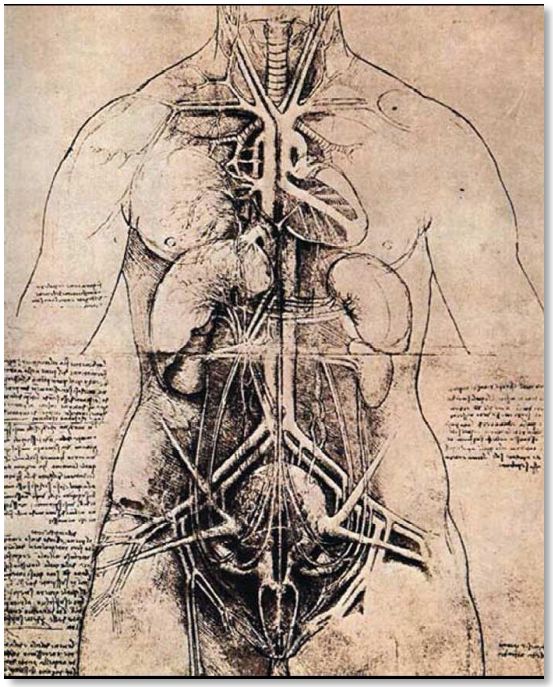
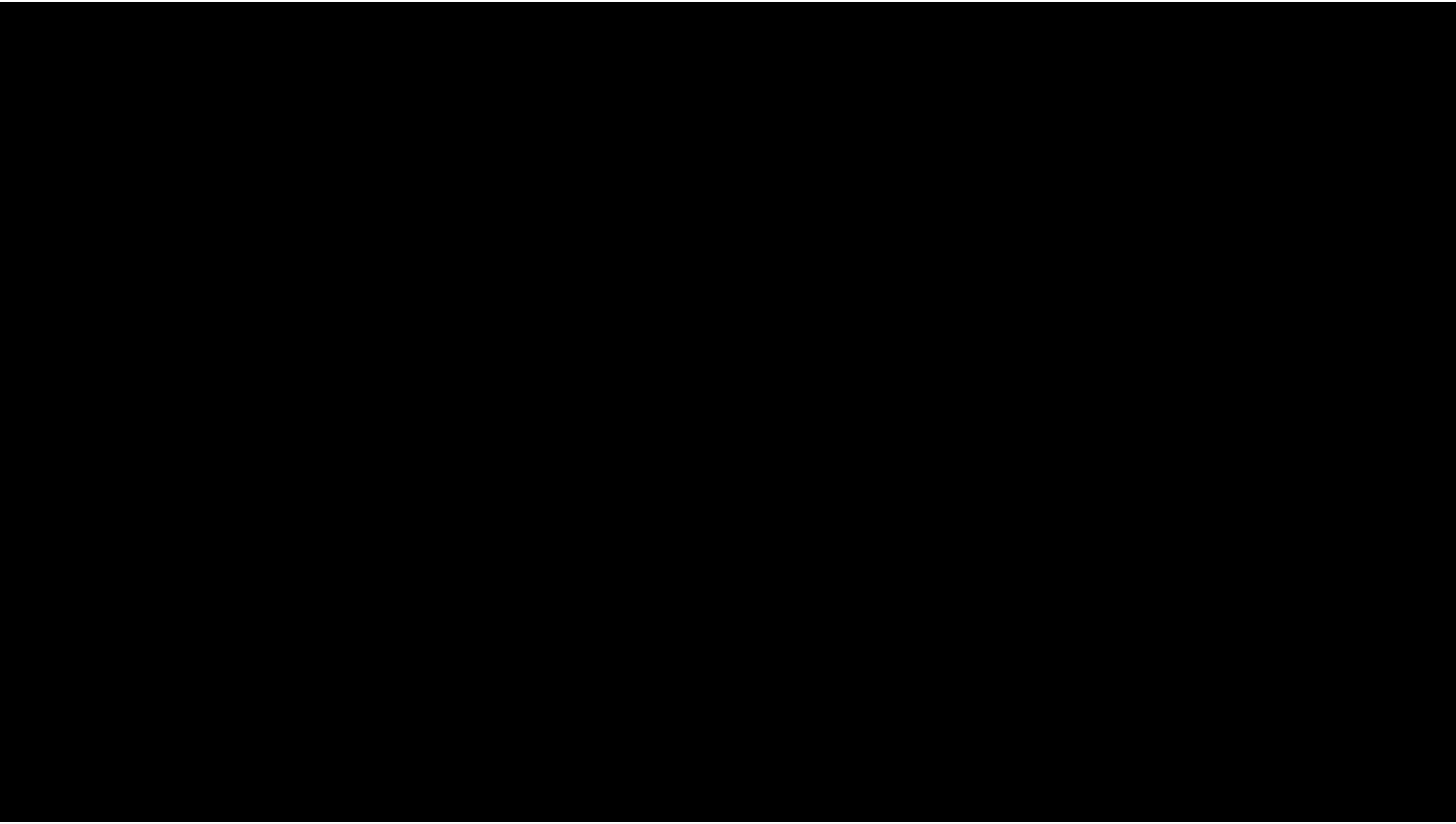
Microphysiological Systems Program "Tissue Chips"

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

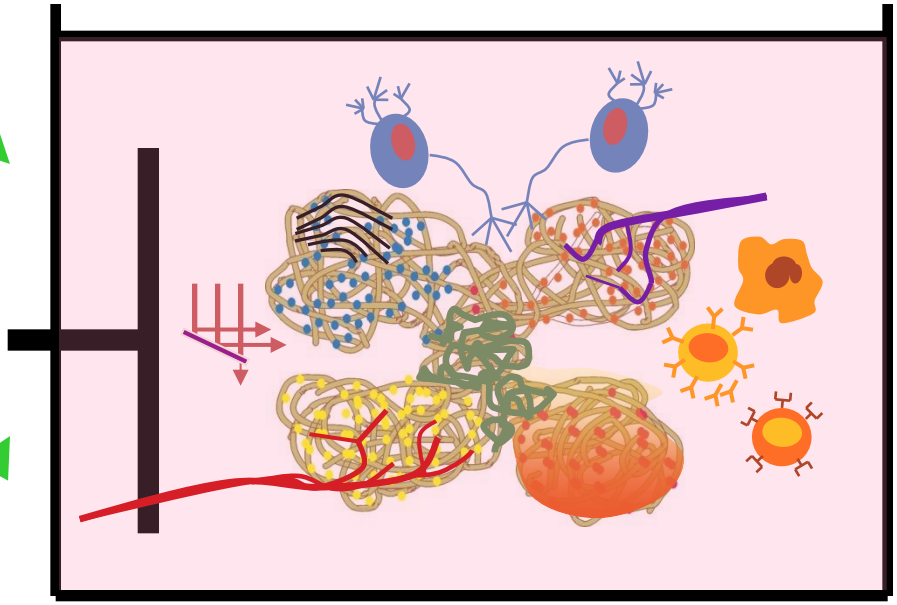


- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Physiologically relevant, genetically diverse,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

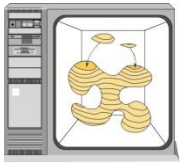
NIH Tissues-on-Chips Program



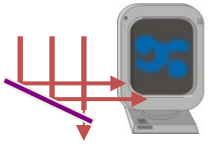
Microphysiological Systems –
A Multidisciplinary, Team-Science Approach



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

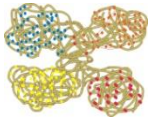


Functional Readout
- real-time, label-free, non-destructive sensing
- imaging



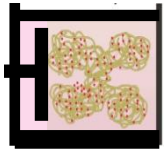
Scaffold
- purified ECM
- synthetic polymers
- composites

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

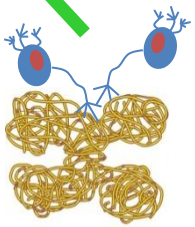


Structure
- porosity
- topography
- stiffness

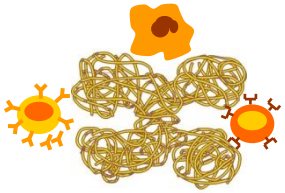
Perfusion
- embedded channels
- vascularization



Bioreactors
- optimized culture conditions
- biomechanical properties
- blood mimetics



Innervation
- signal propagation
- coordinated response



Host Response
- generalized inflammation
- specific immunity

Spatial/Temporal Patterning
- cytokine gradients
- controlled release

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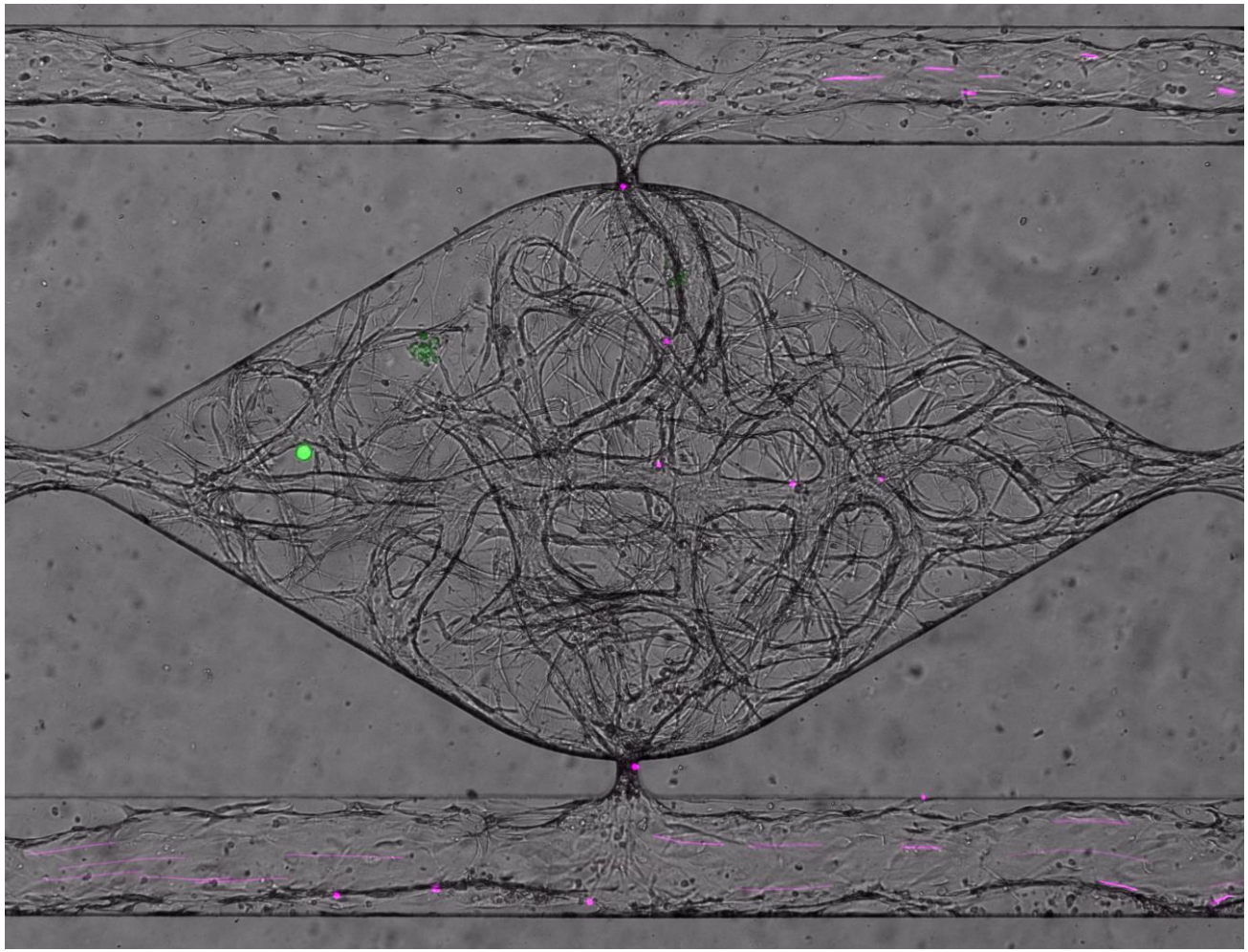
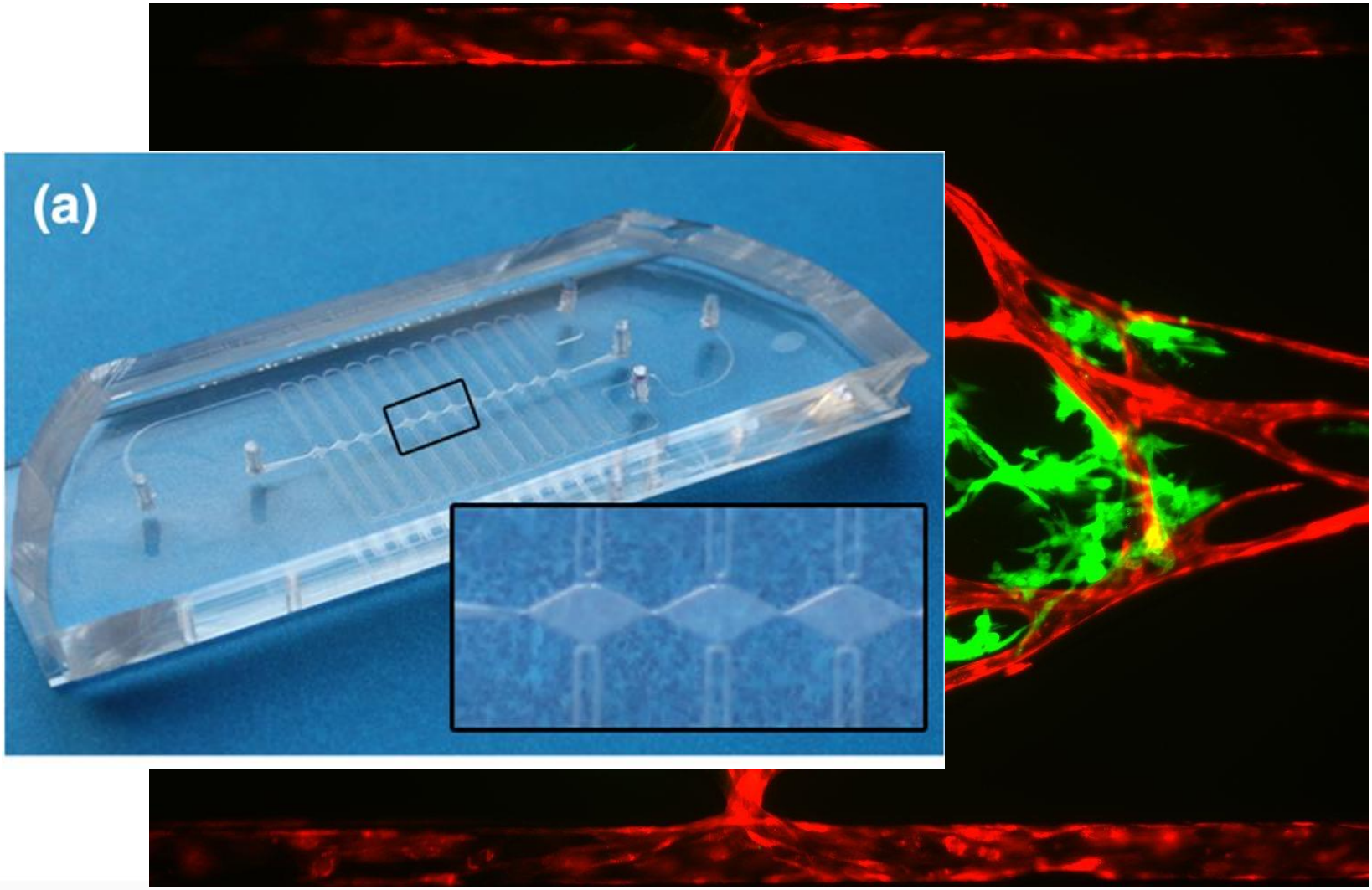
Microvasculature



- **7 days**
- **SW620 tumor spheroids**
- **hiPS-EC**
- **1 µm beads**

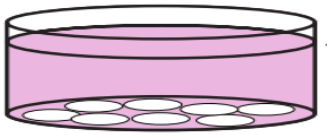
Steven George, Univ. Washington

Colon tumor (HCT116) supported by microvasculature



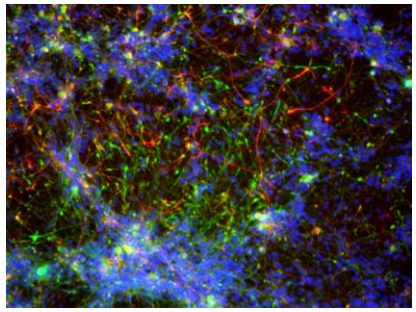
Steven George, Univ. Washington

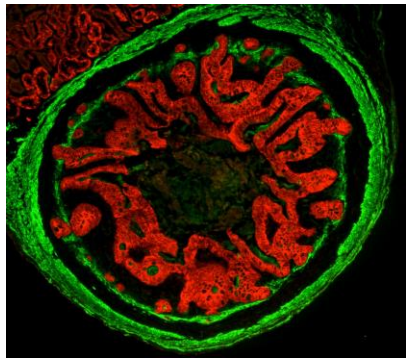
Innervation of Gut Enteroids



Pluripotent Stem Cells: renewable human cell source

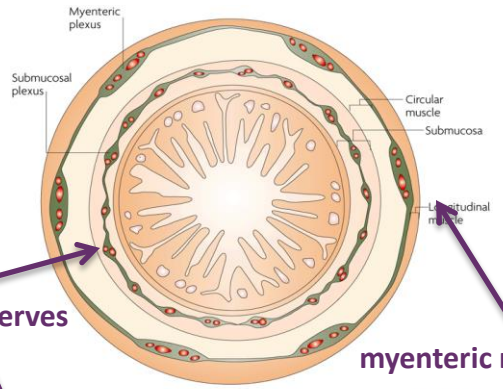
Vagal Neural Crest Cells: peripheral nerve cells





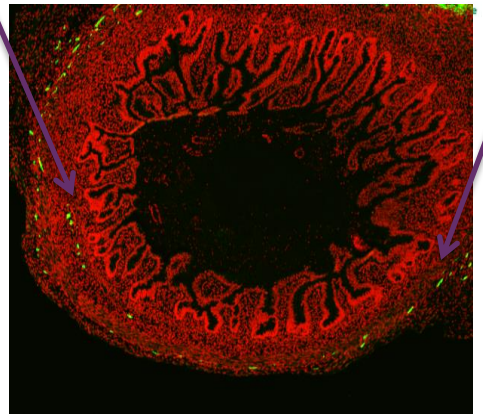
Gut enteroid: 3D mulitcellular mini gut

Gut Lumen



submucosal nerves

myenteric nerves

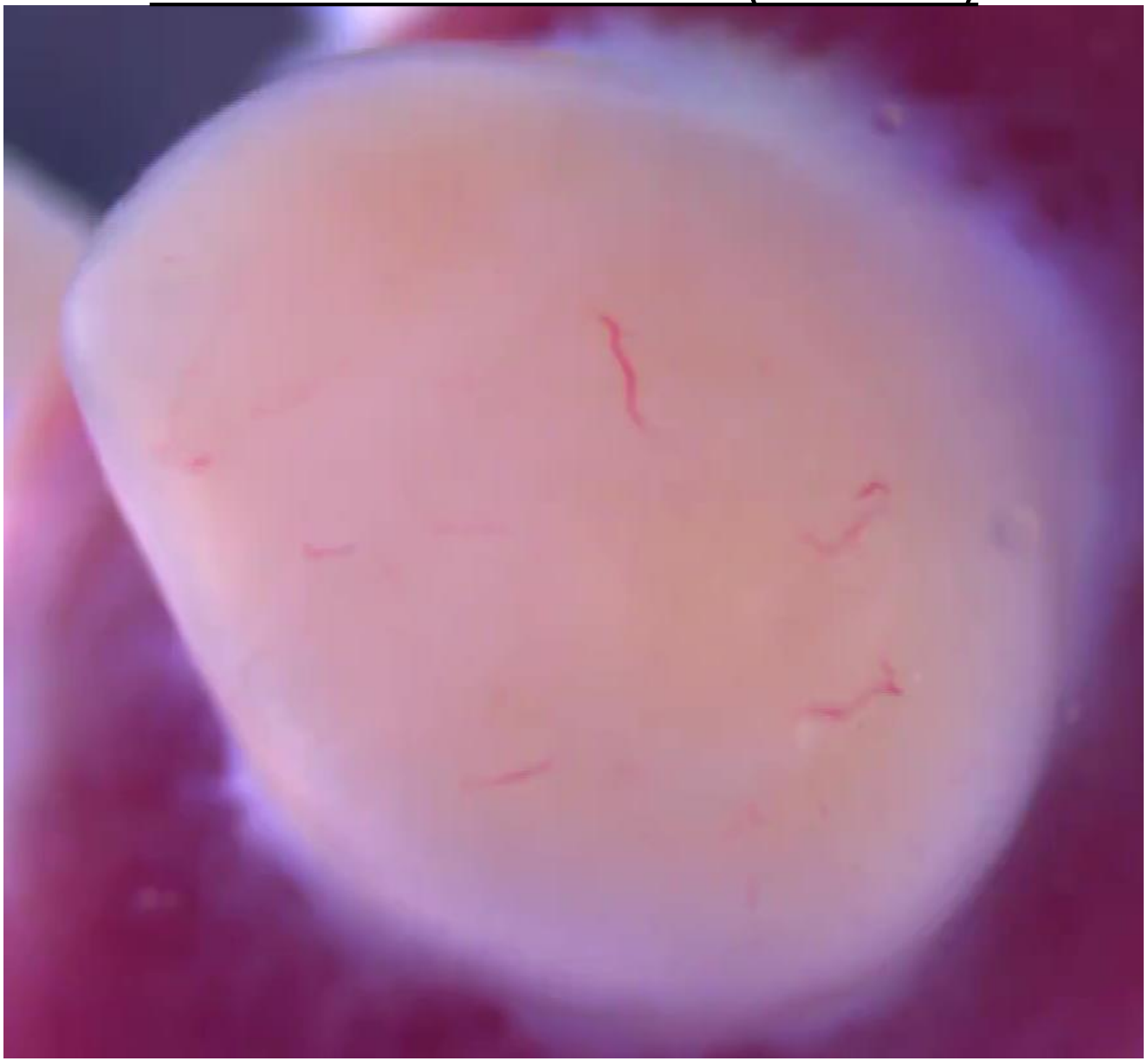


As these systems begin to mature, the nerve tissues are added to the GI, creating physiological-like innervated structures

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

James Wells, Univ. Cincinnati

Electrical field stimulation (with ENS)



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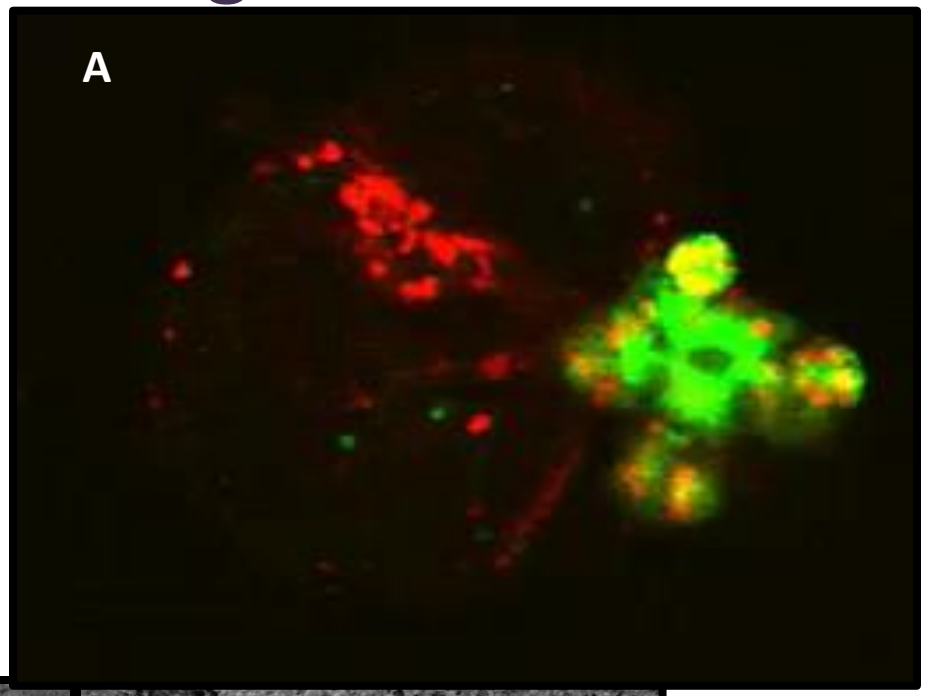
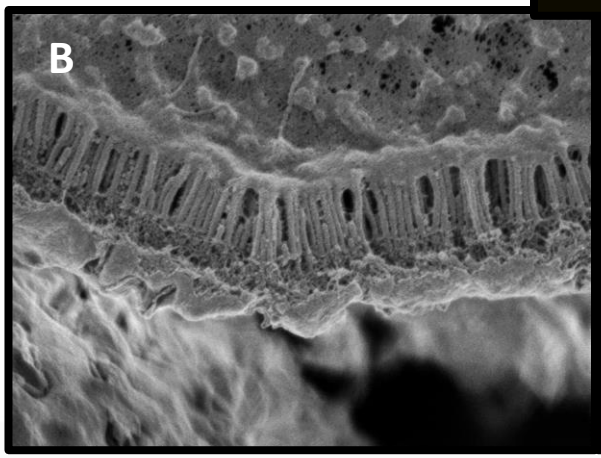
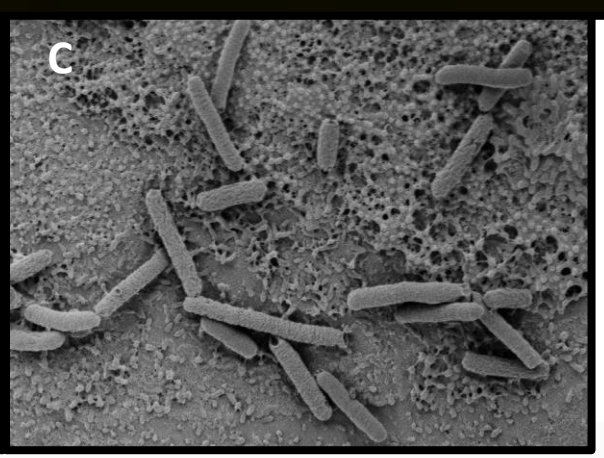
Enteroids mimic gut structure and function







Mark Donowitz, Johns Hopkins

Future Applications of Tissues-on- chips