

# An integrated *in vitro* model of perfused tumor and cardiac tissue

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# CARDIOPULMONARY TRANSPORT AND TISSUE REMODELING

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## Funding

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Fellowships, CIRM training grant

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**Agua Sobrino (2013-present) (Hughes advisor)**  
**Xiaolin Wang (2013-present) (Lee Advisor)**

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Lei Tian (2009-present)  
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**David Tran (2010-present)**  
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**Yosuke Kurokawa (2013-present)**  
**Sandra Lam (2013-present)**  
**Rupsa Datta (2012-present) (Gratton)**  
**Jean Wang (2012-present) (Christman)**

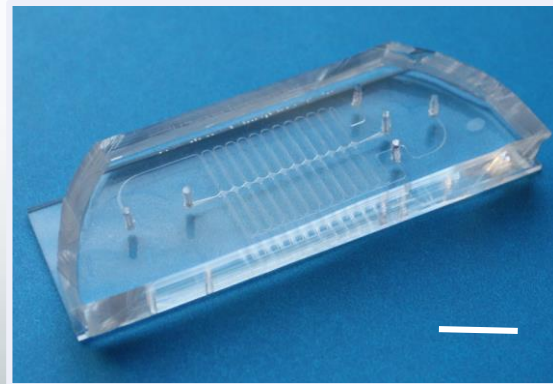
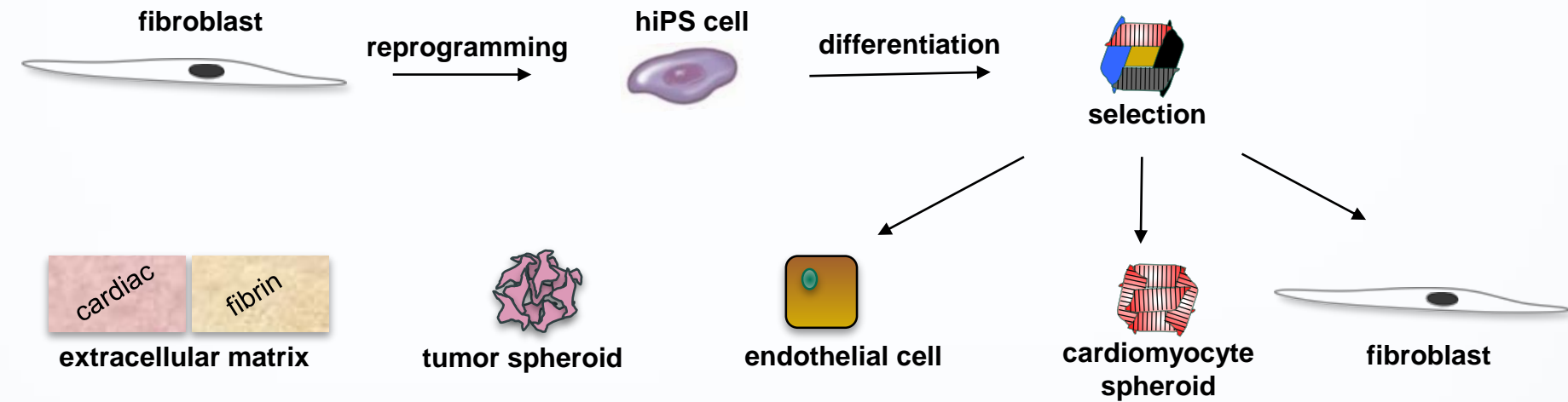


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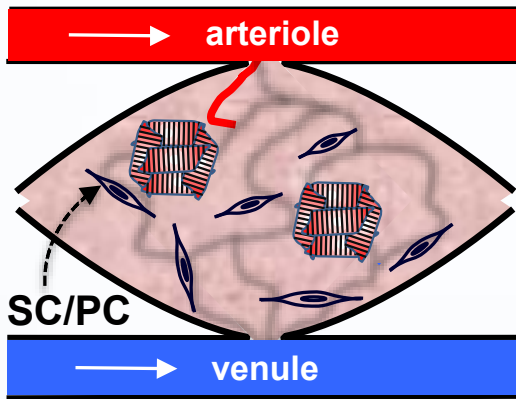
# Overall Strategy



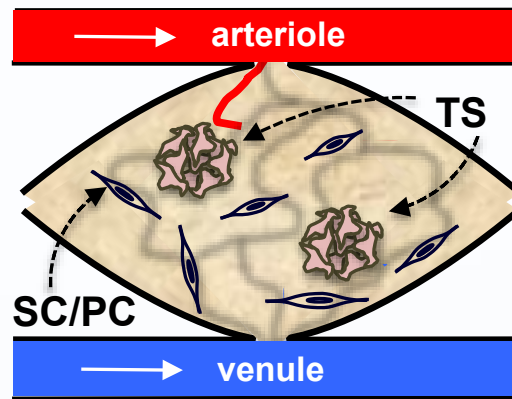
microfabrication

# Integrated micro-organ systems

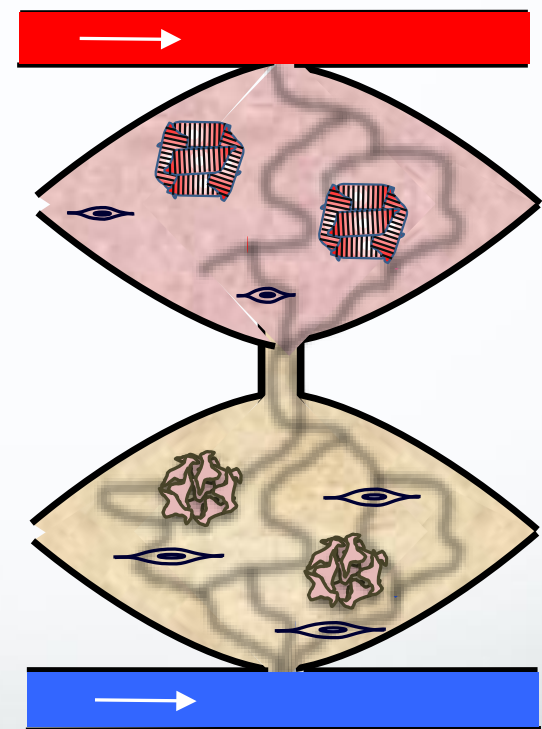
Integrated micro-organ system #1  
(perfused cardiomyocyte spheroids)



Integrated micro-organ system #2  
(perfused tumor spheroids)

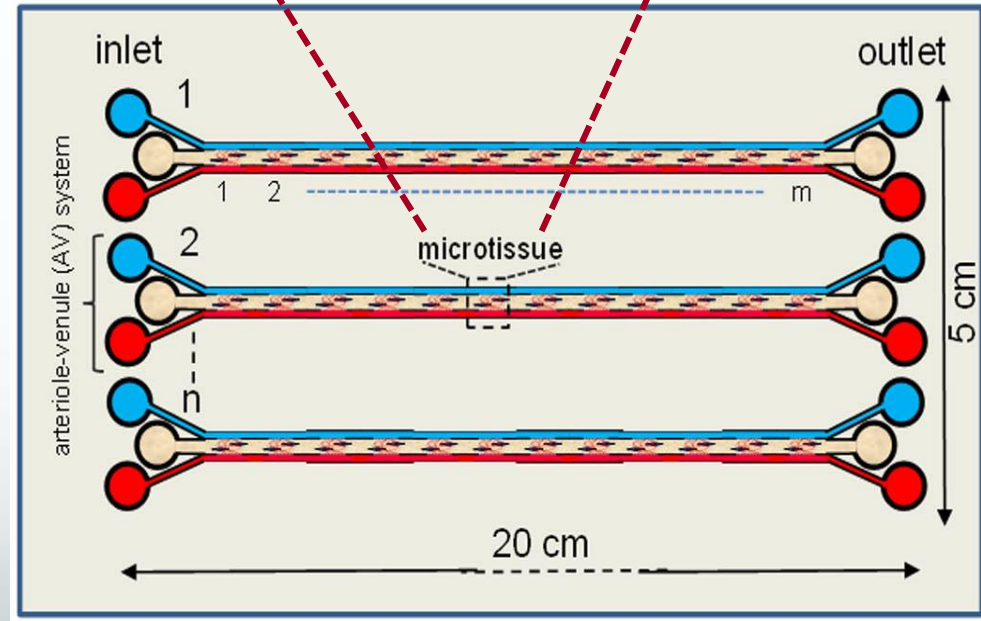
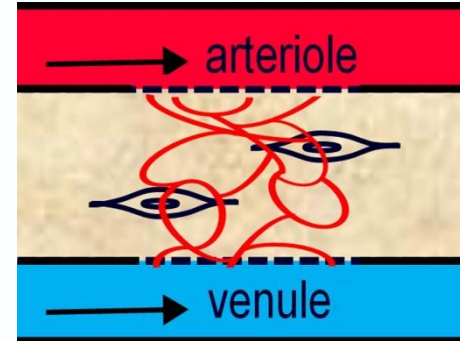
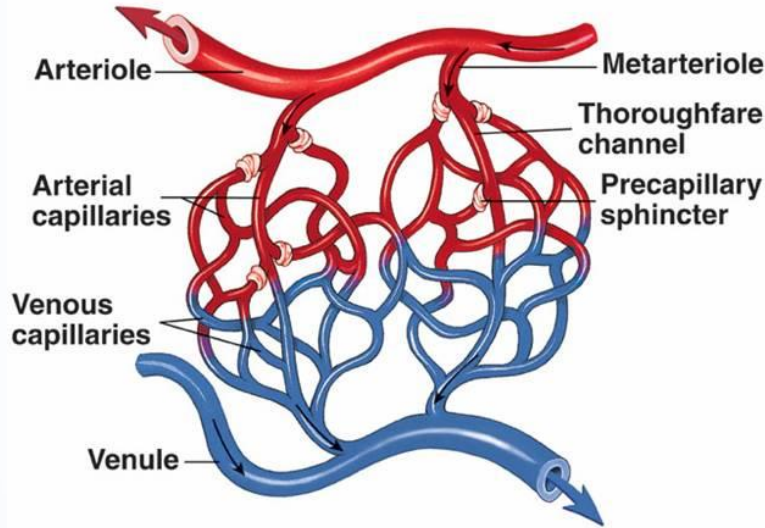


Integrated micro-organ system #3  
(perfused tumor and cardiomyocyte spheroids)



# Microtissue with Perfused Human Capillaries

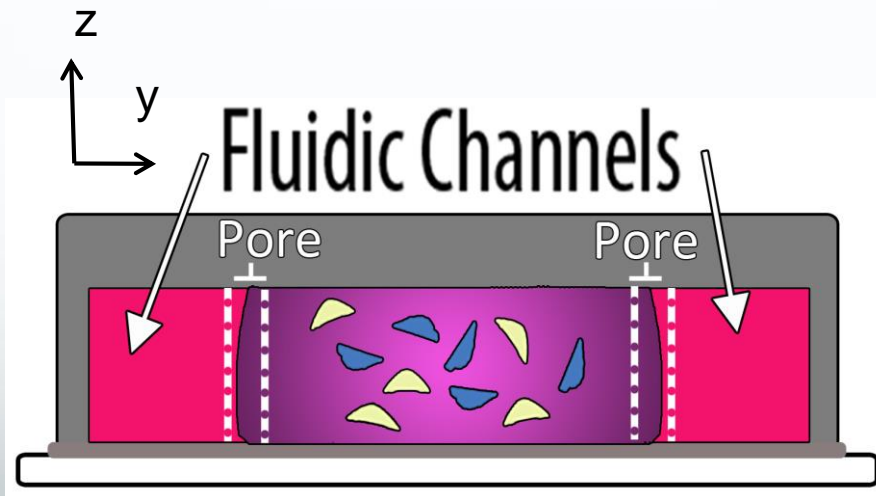
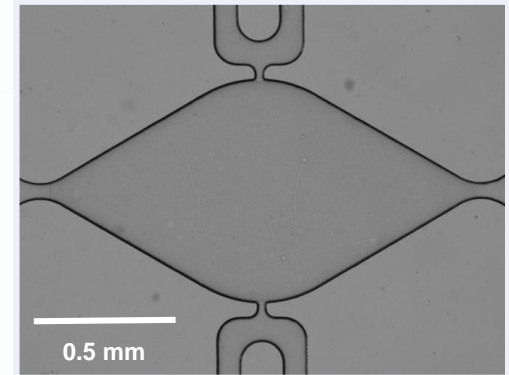
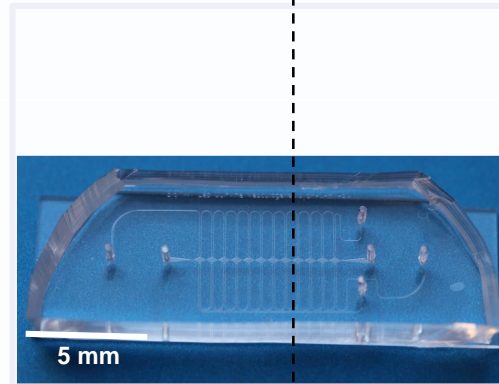
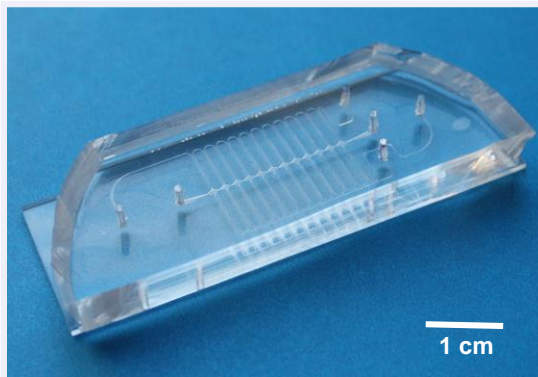
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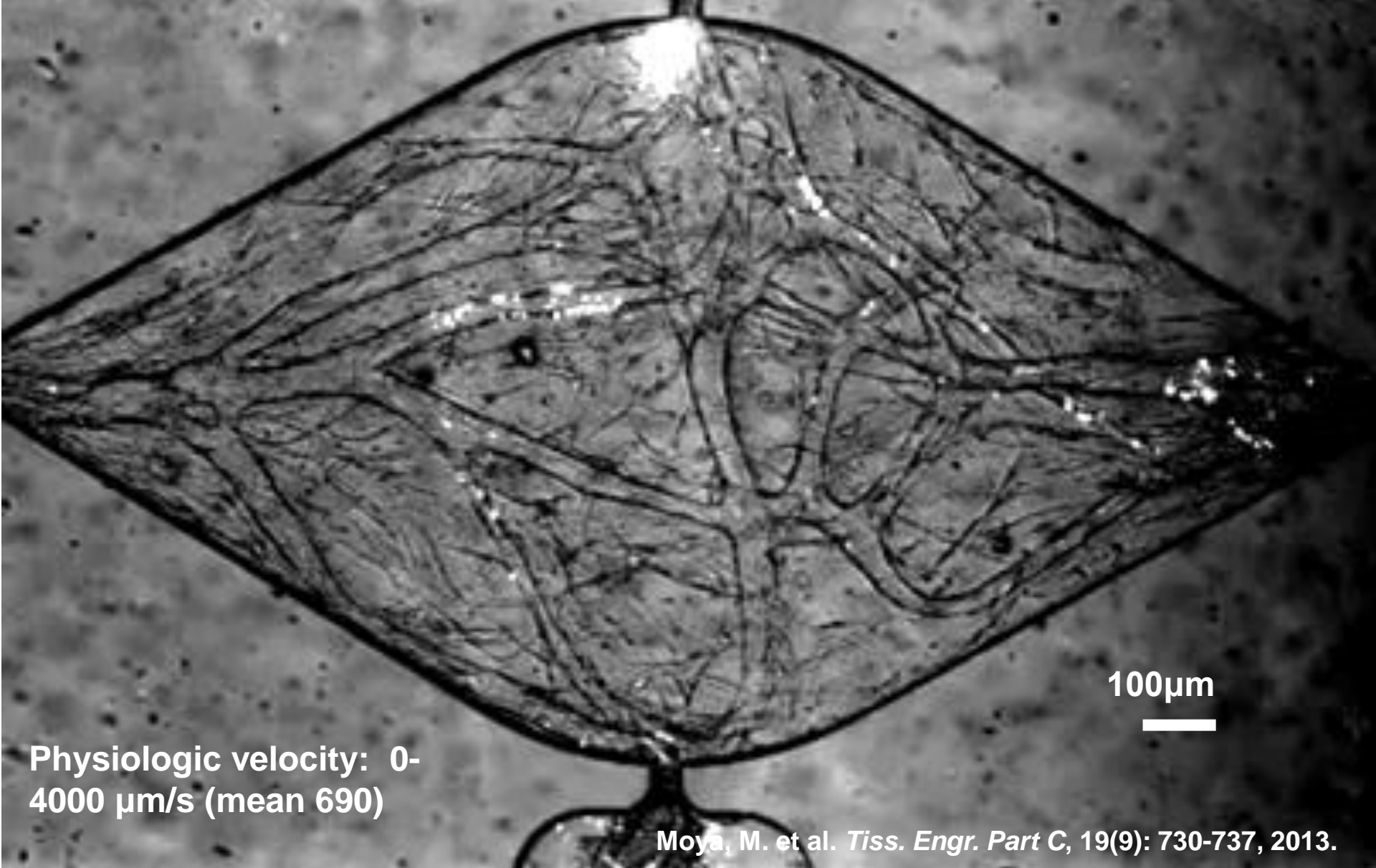
- Biology-directed
- High-throughput design
- Real-time monitoring
- Dynamic model of “tissue microenvironment”



# Soft Lithography



# Perfusion of 21 day Network (1 $\mu\text{m}$ fluorescent beads)

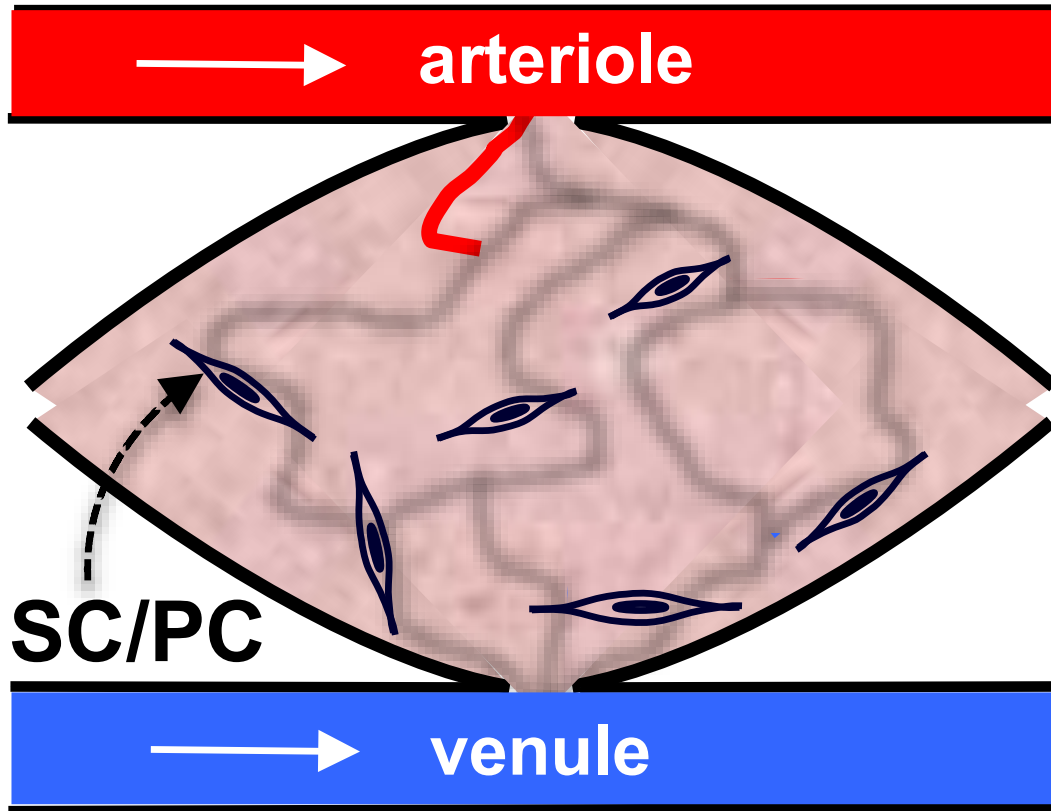


100 $\mu\text{m}$



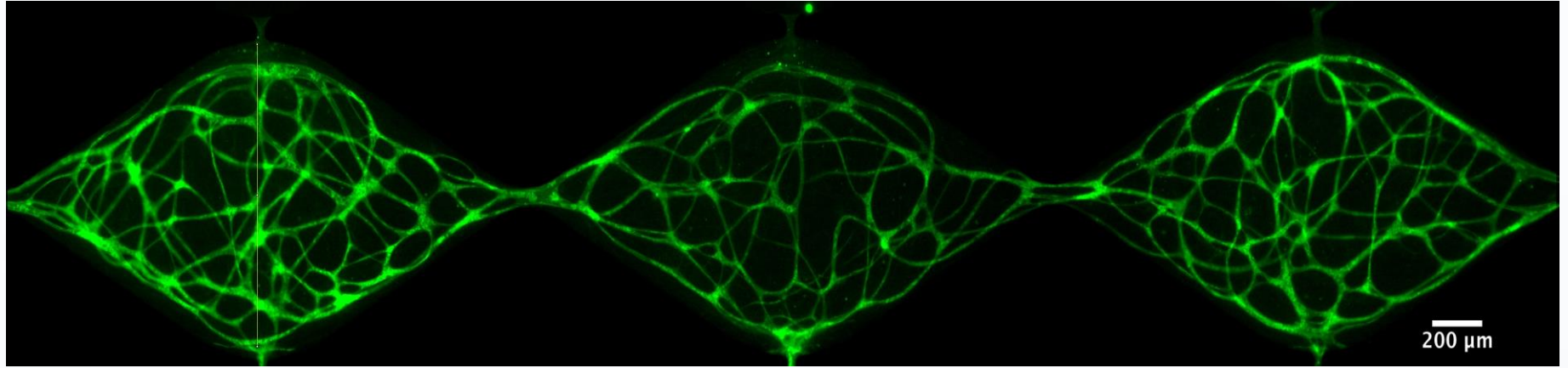
Physiologic velocity: 0-  
4000  $\mu\text{m}/\text{s}$  (mean 690)

# Perfused hiPS-derived vessels in cardiac ECM

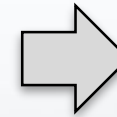
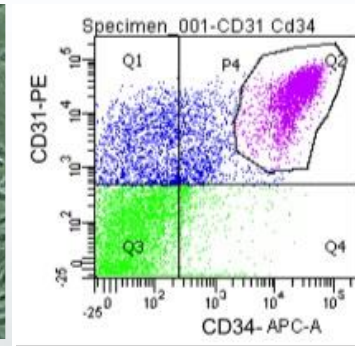
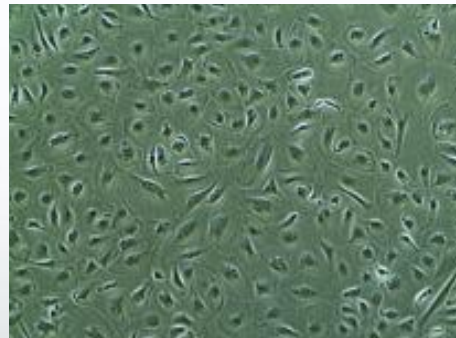




# Network in Cardiac ECM and ECs from human iPS (6 mos)



Human iPS (WTC-11 – B. Conklin)



**>96%**  
(passage 3)

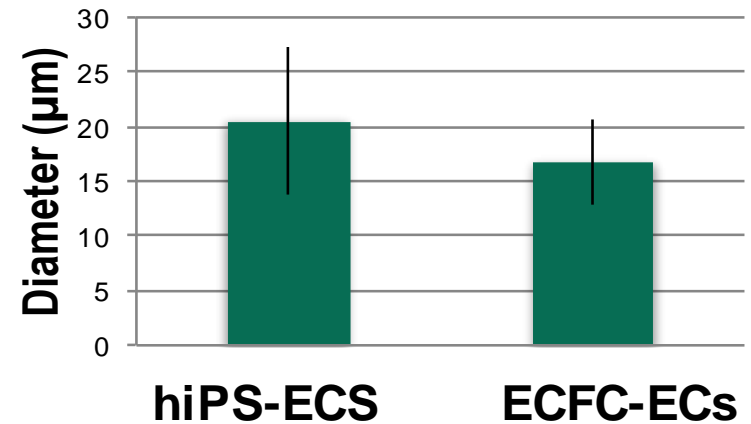
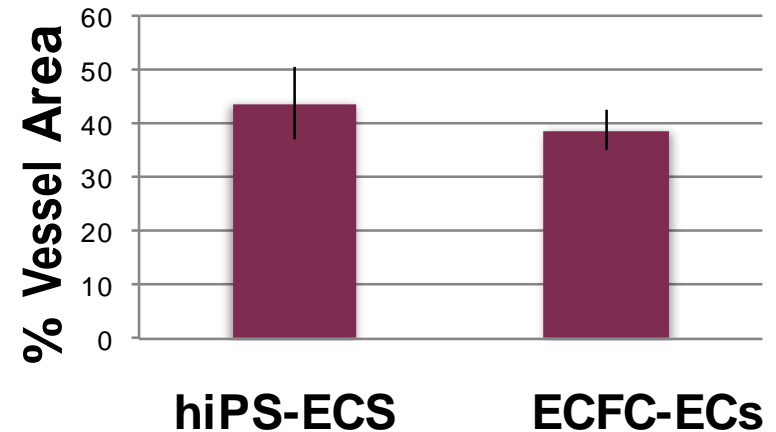
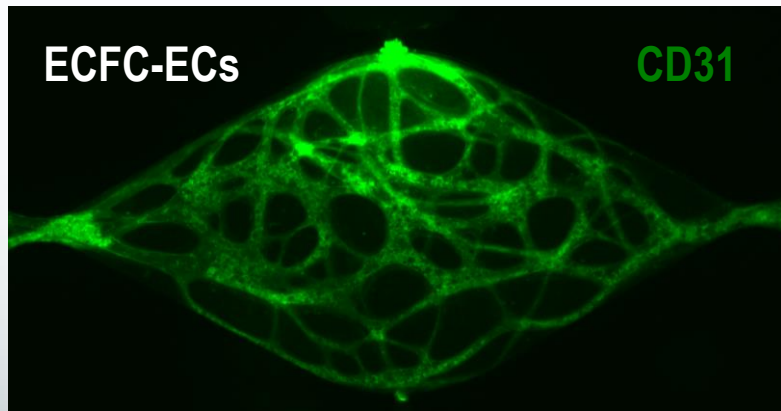
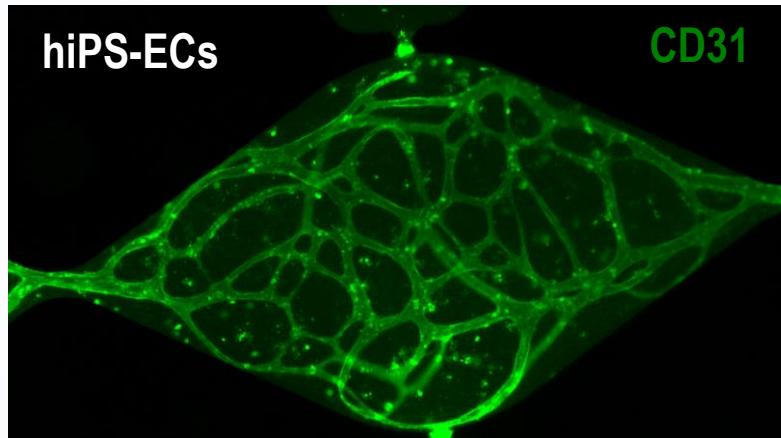
Differentiation protocol from J. Thomson



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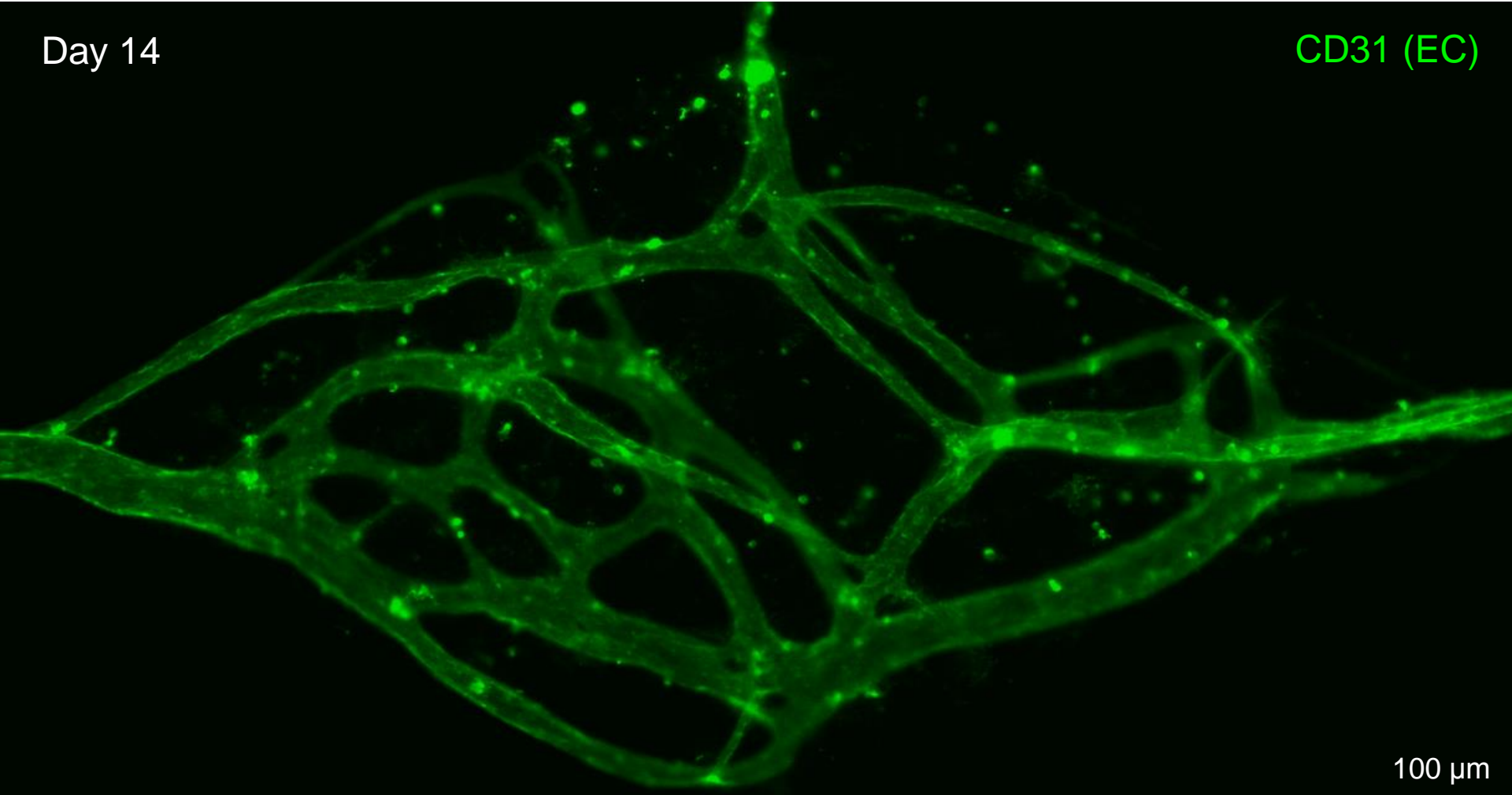
# Human iPS-EC Vessel Network in Fibrin (12 mos)



# Human iPS-EC Vessel Network in cECM (18 mos)

Day 14

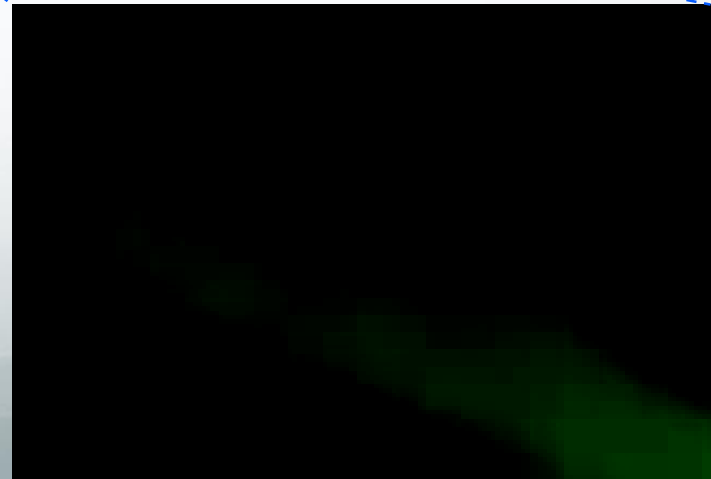
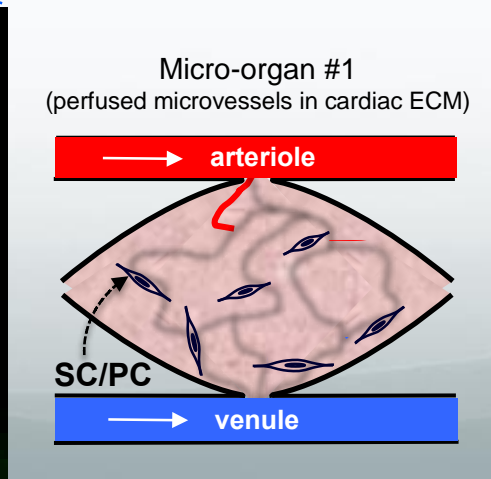
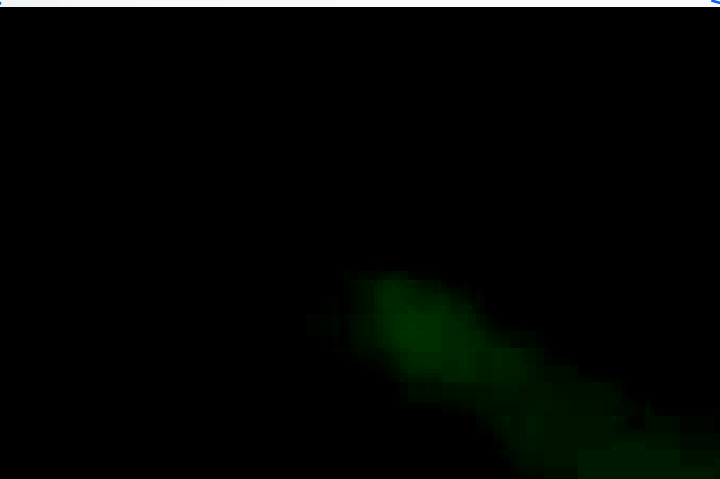
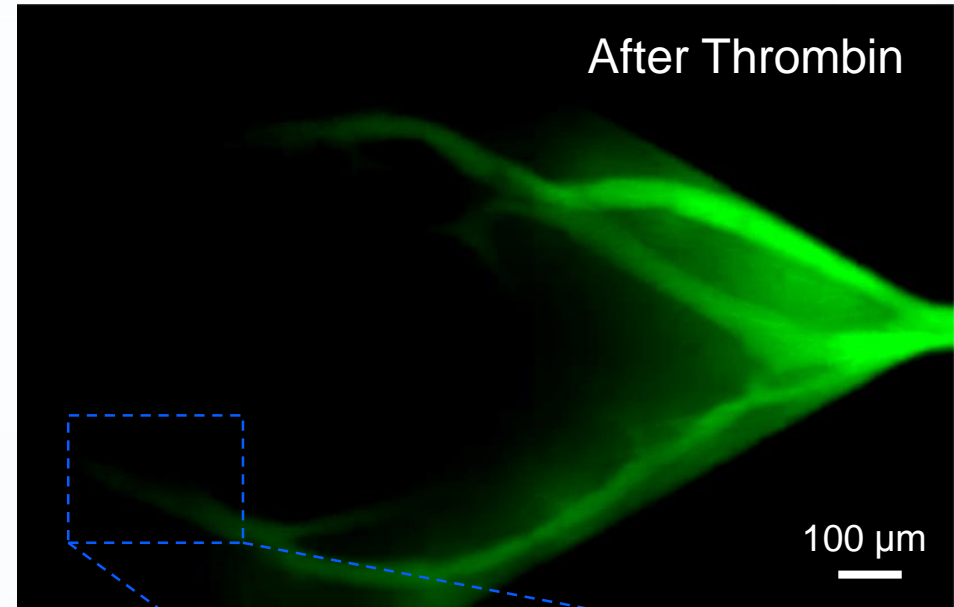
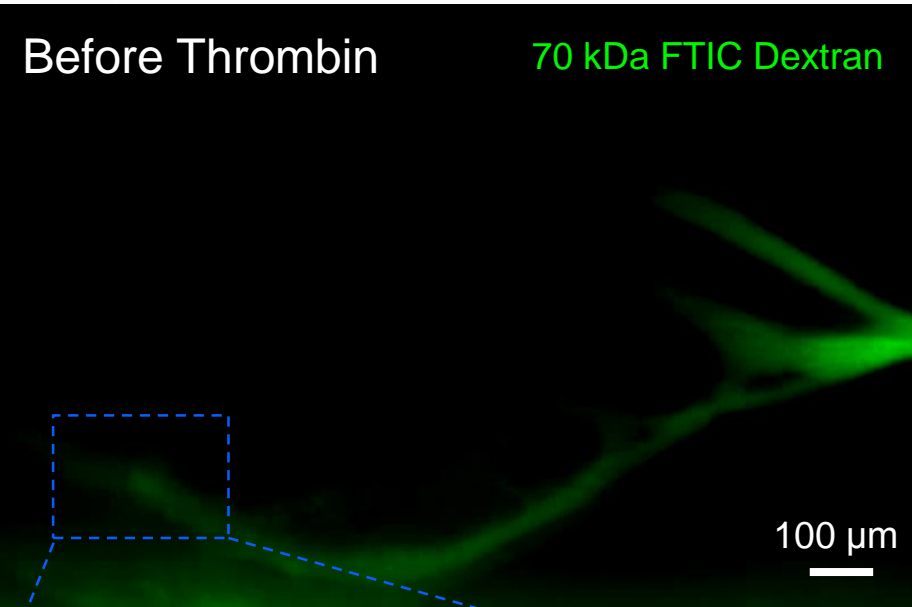
CD31 (EC)



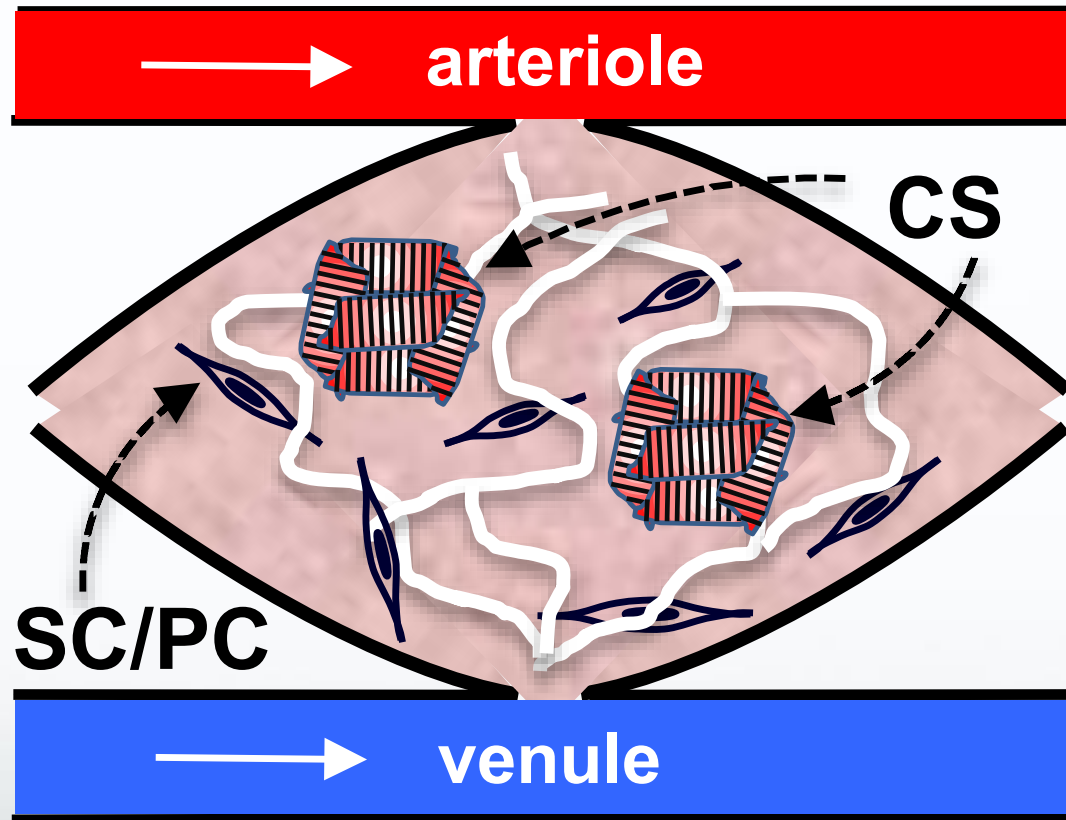
100  $\mu$ m



# Perfused/Functional Human iPS-EC Vessel Network in cECM (24 mos)

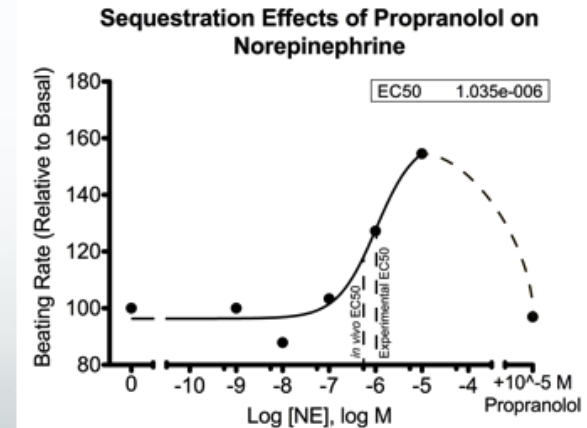
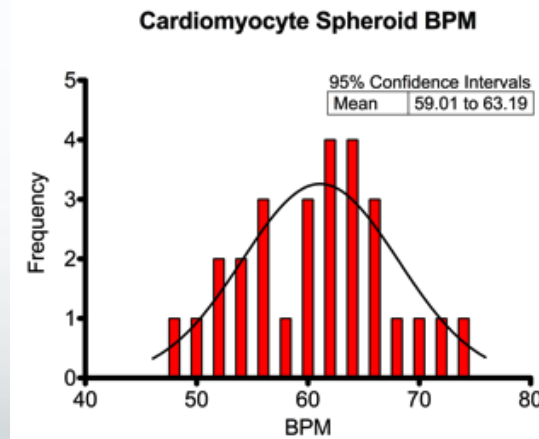
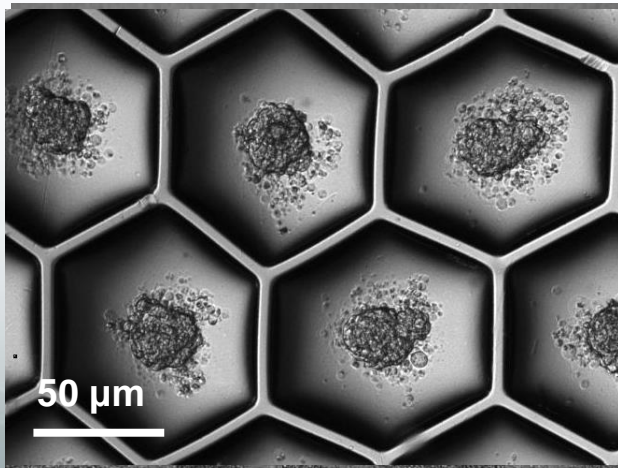
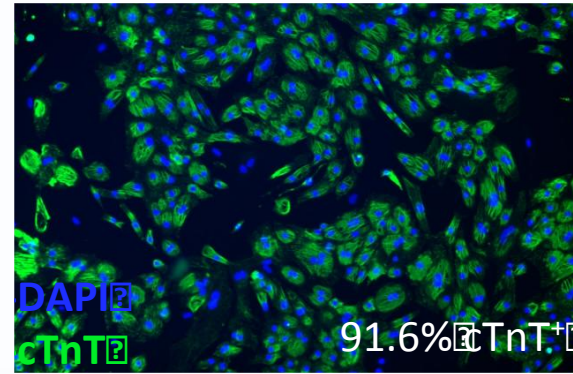
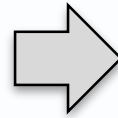
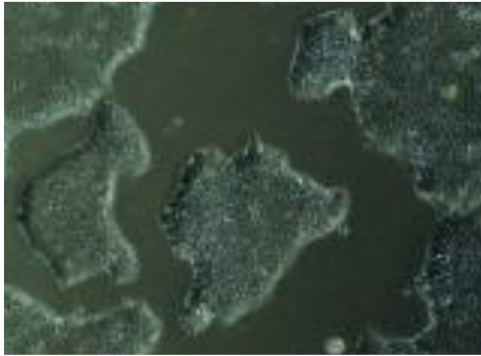


# hiPS-CM spheroids with hiPS-EC network

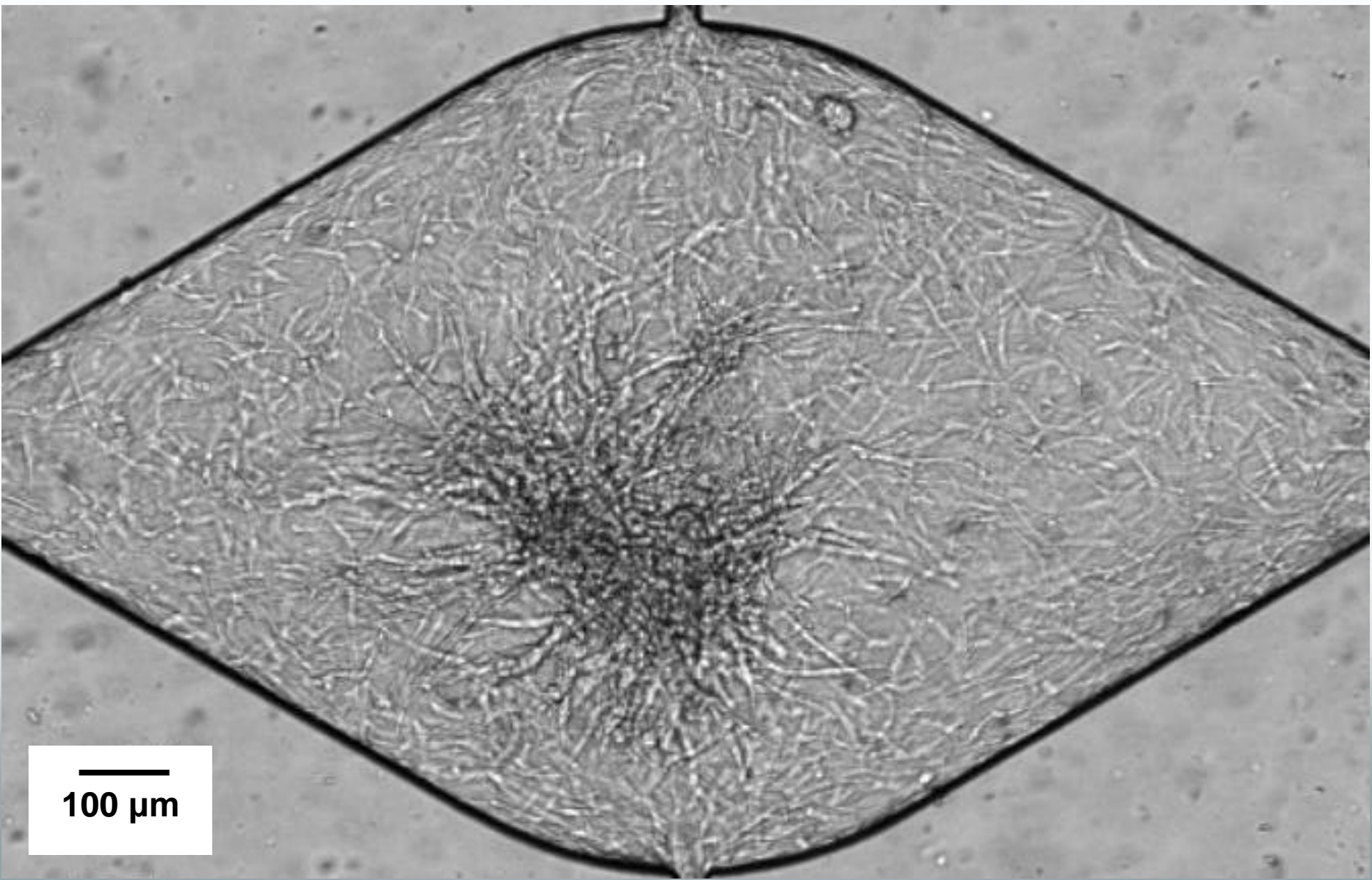


# Human iPS-CM with physiologic drug response

Human iPS (WTC-11 – B. Conklin)

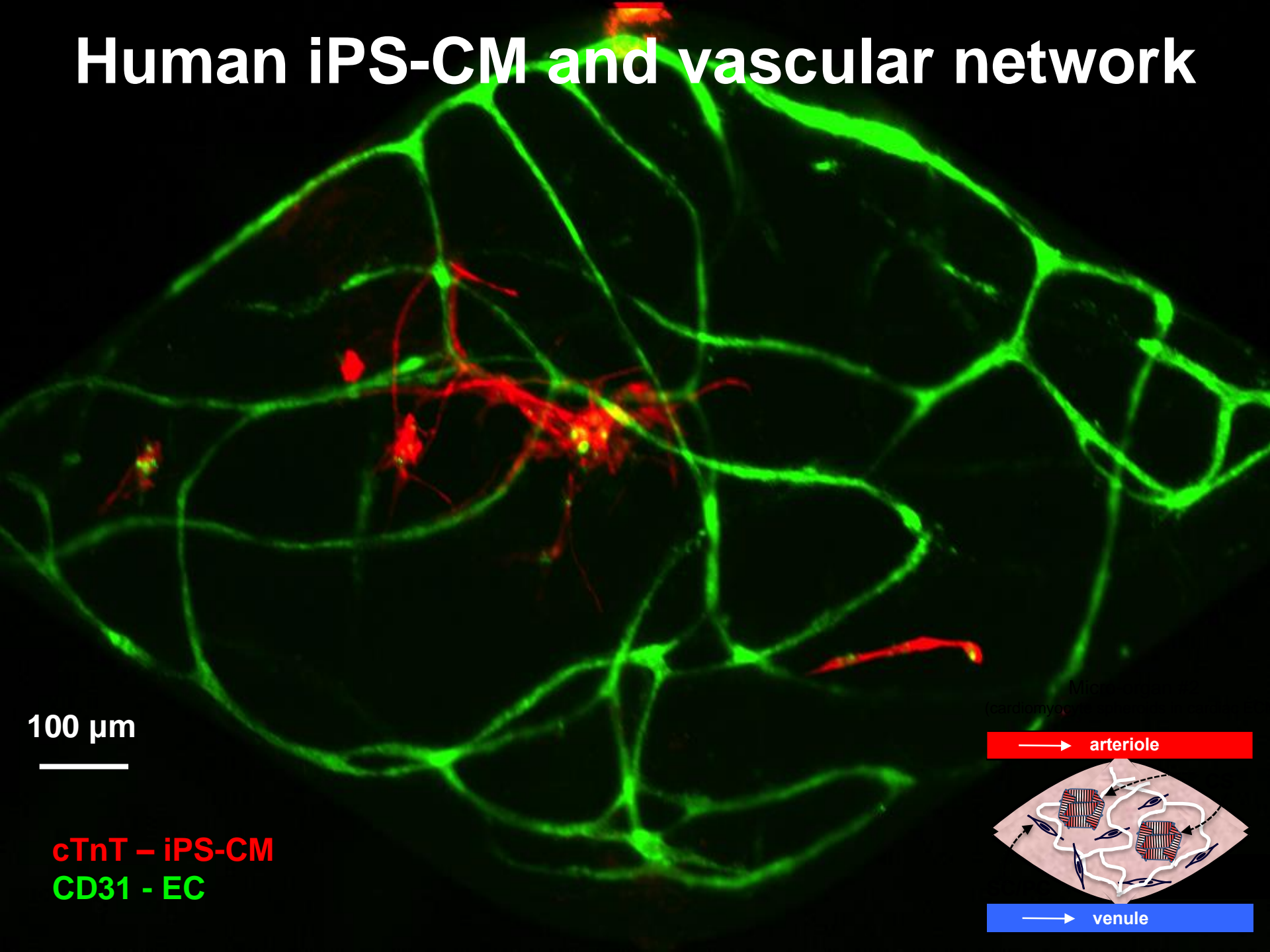


# hiPS-CM, fibroblast, and EC in cECM within the Microdevice



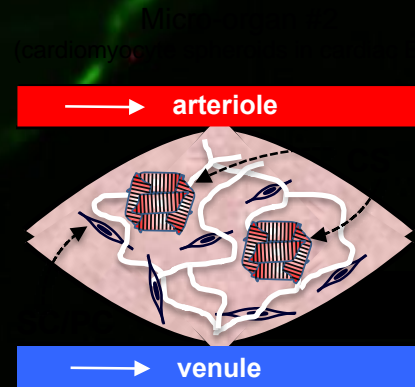
—  
100  $\mu\text{m}$

# Human iPS-CM and vascular network



100 μm

cTnT - iPS-CM  
CD31 - EC



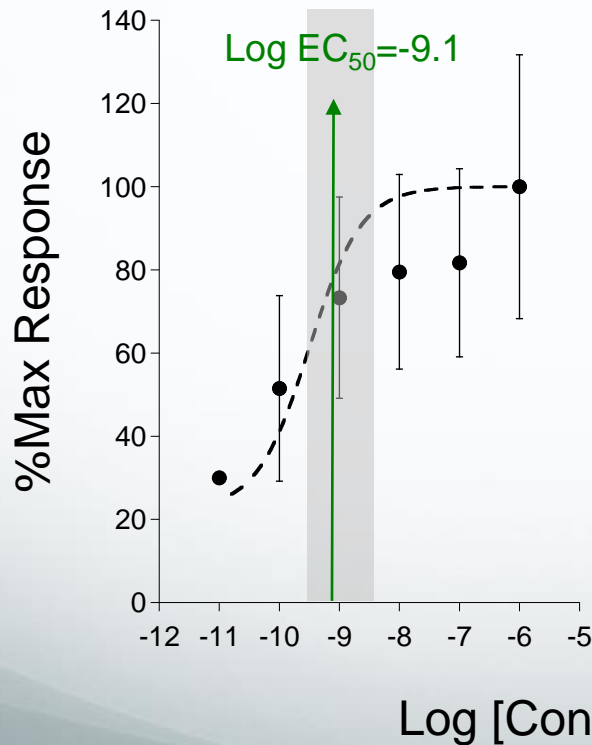


# Drug response of human iPS-CM in device

*In vivo* therapeutic plasma concentration

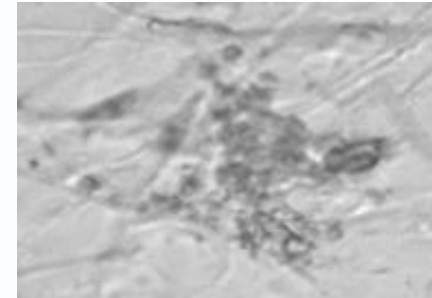
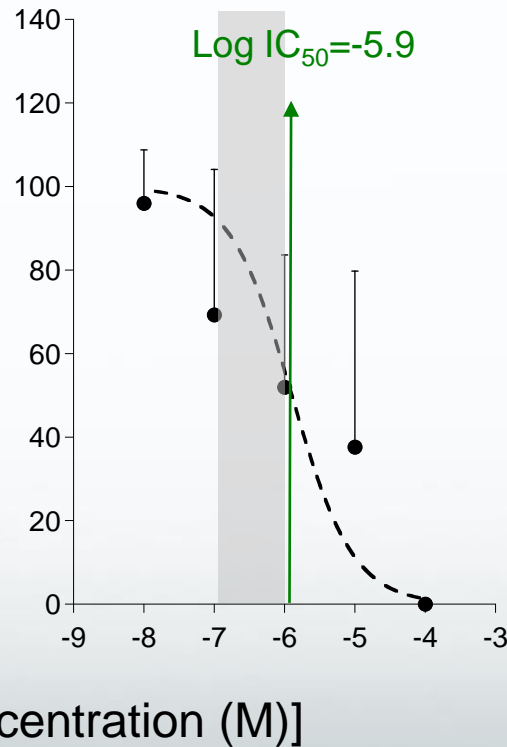
Isoproterenol

Log EC<sub>50</sub> = -9.1

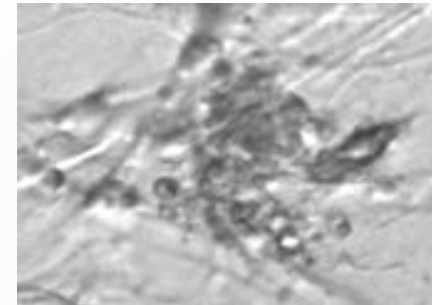


Propranolol

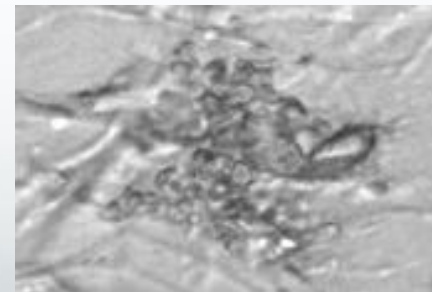
Log IC<sub>50</sub> = -5.9



Control  
(52 bpm)



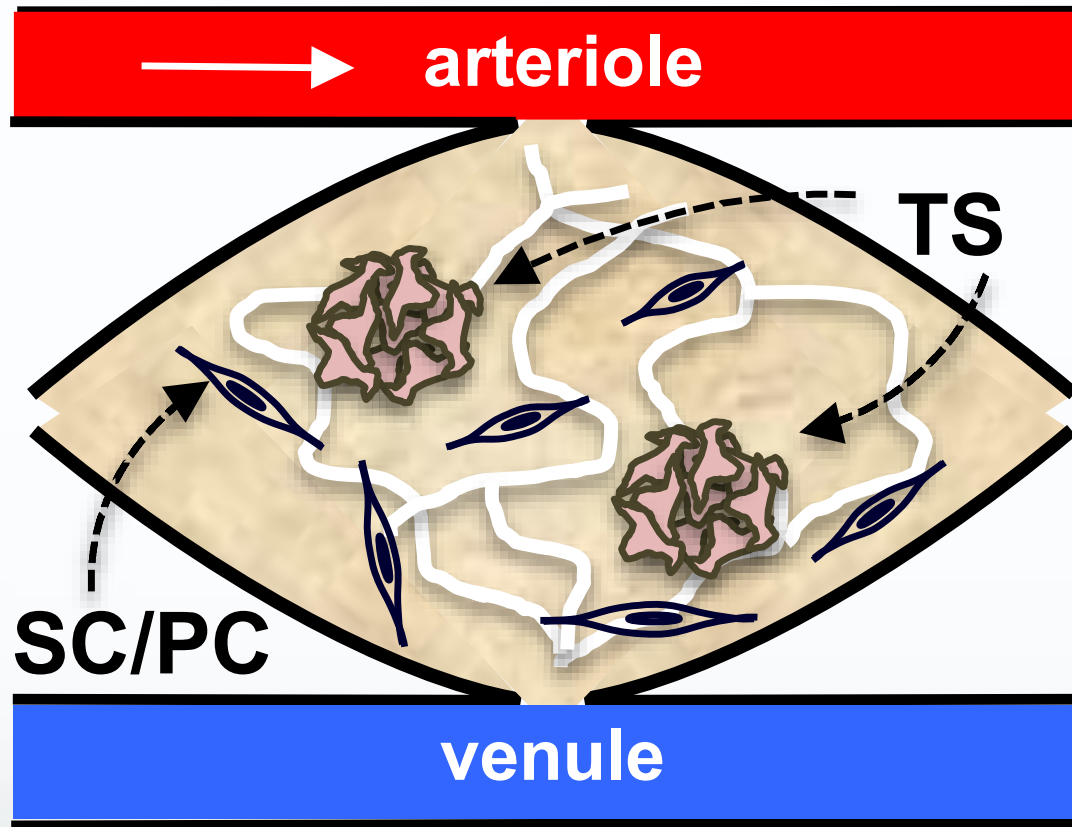
10<sup>-7</sup> M  
Isoproterenol  
(160 bpm)



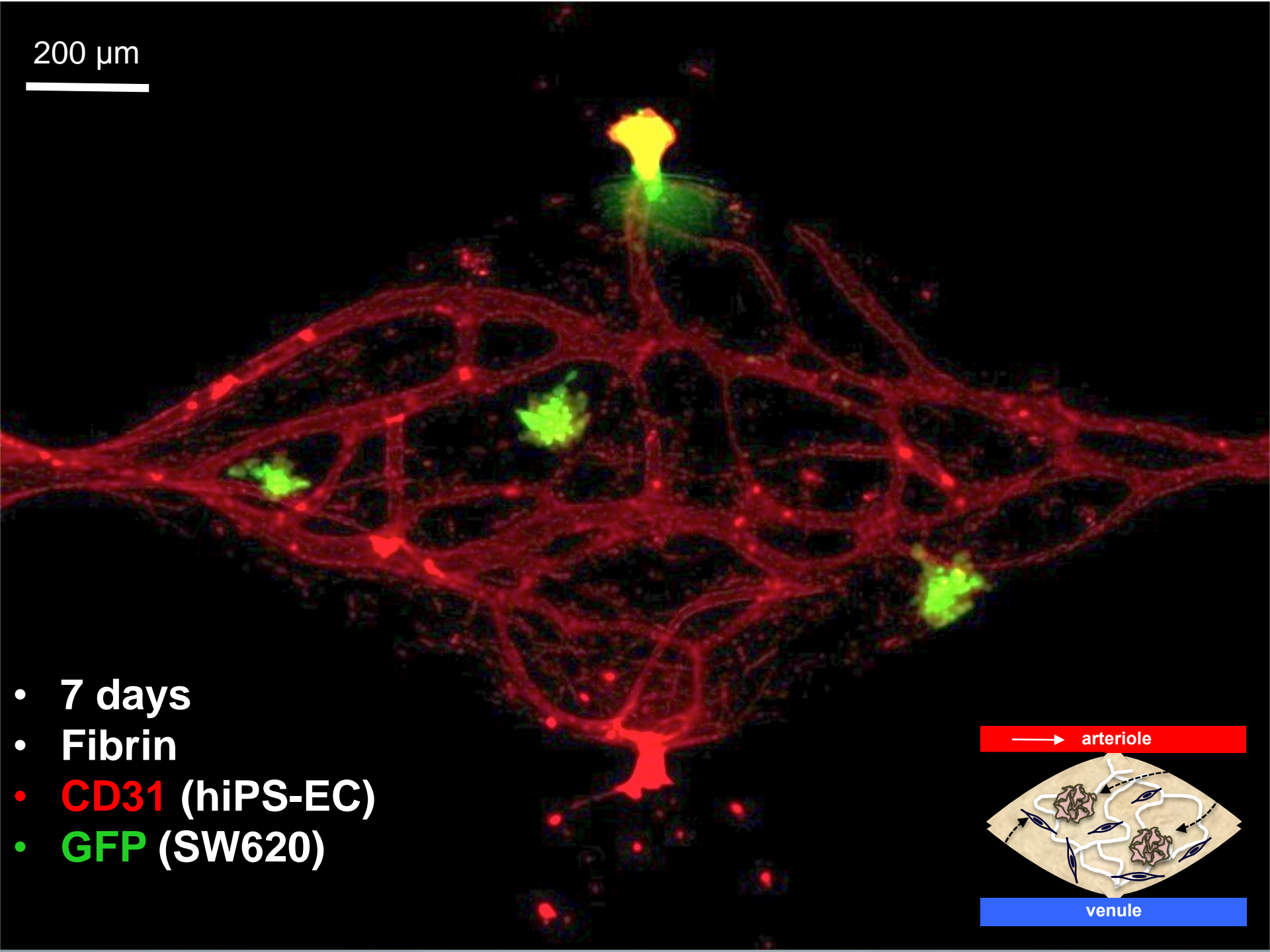
10<sup>-6</sup> M  
Propranolol  
(76 bpm)



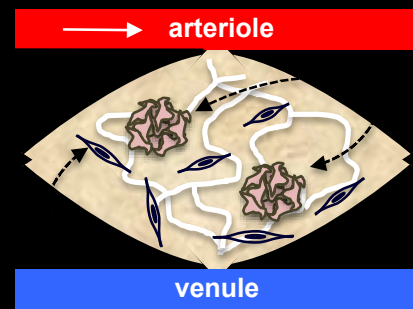
# Tumor spheroids with hiPS-EC network

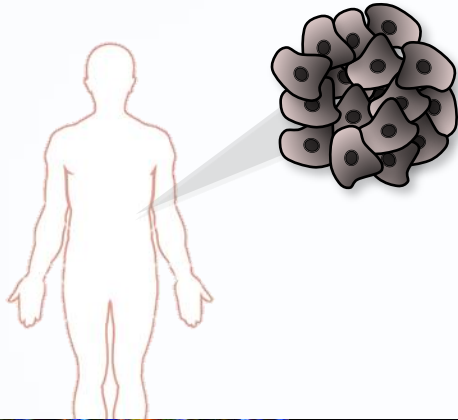


200  $\mu\text{m}$



- 7 days
- Fibrin
- **CD31** (hiPS-EC)
- **GFP** (SW620)

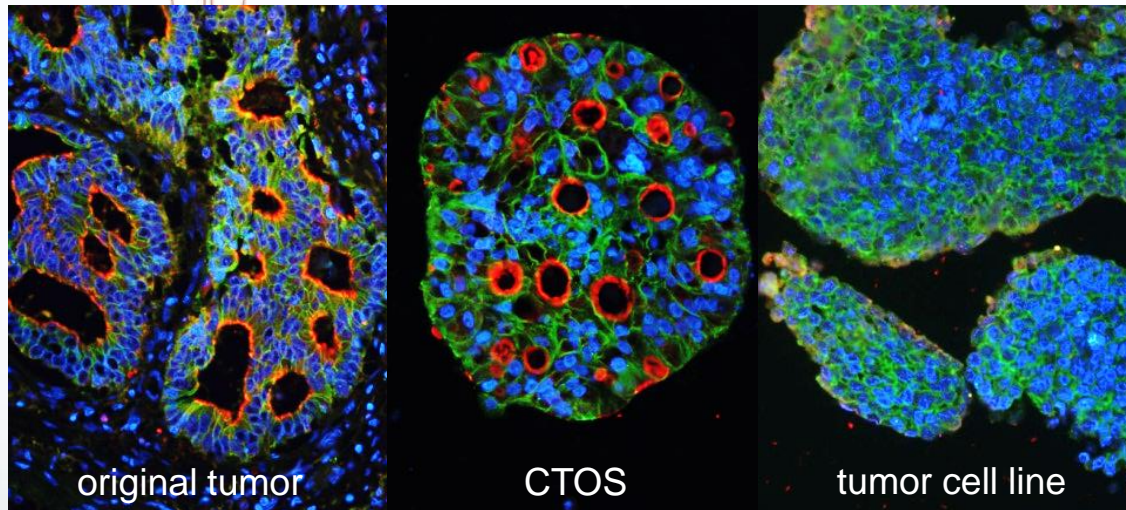




# Cancer Tissue-Originated Spheroids (CTOS)

## Key Features:

- ✓ Inexpensive and efficient methods of preparation
- ✓ Easy to culture *in vitro*
- ✓ Retains three dimensionality
- ✓ Preserves biochemical and mechanical characteristics of original tumor



★ Significant potential for personalized therapy

Professor Masahiro Inoue

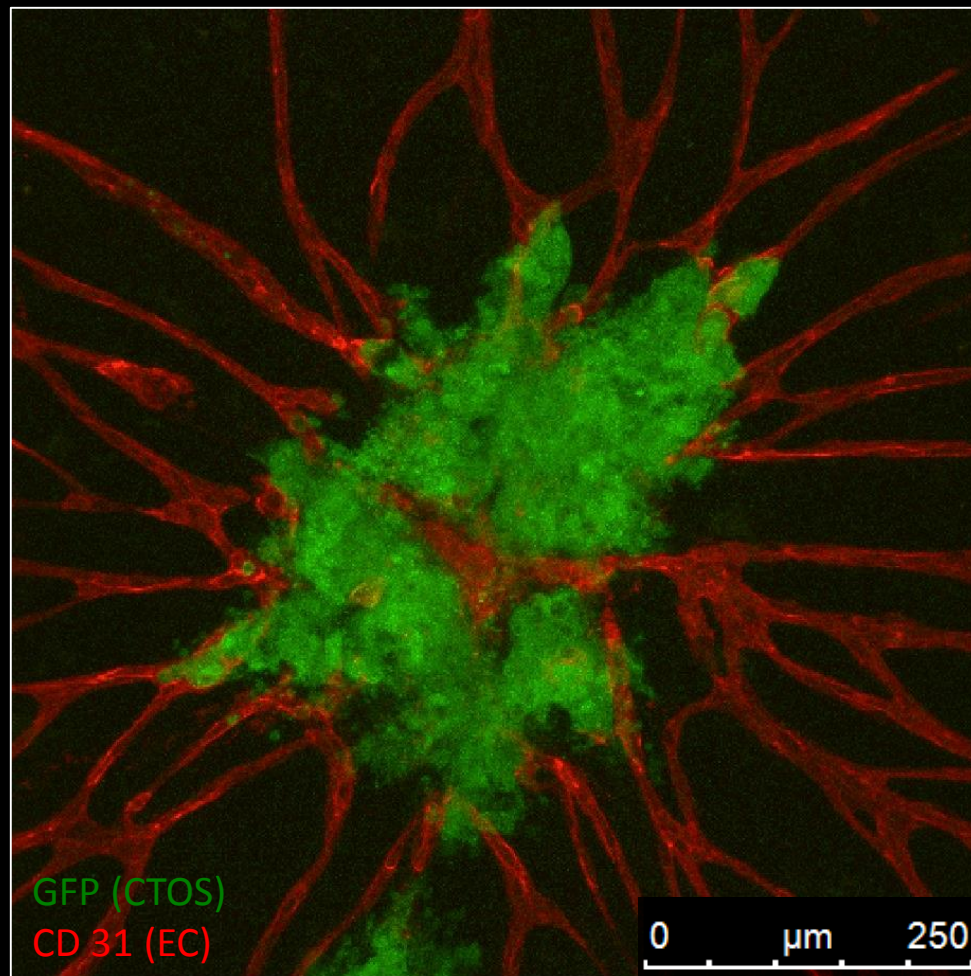
Osaka Medical Center for Cancer and Cardiovascular Diseases Research Institute



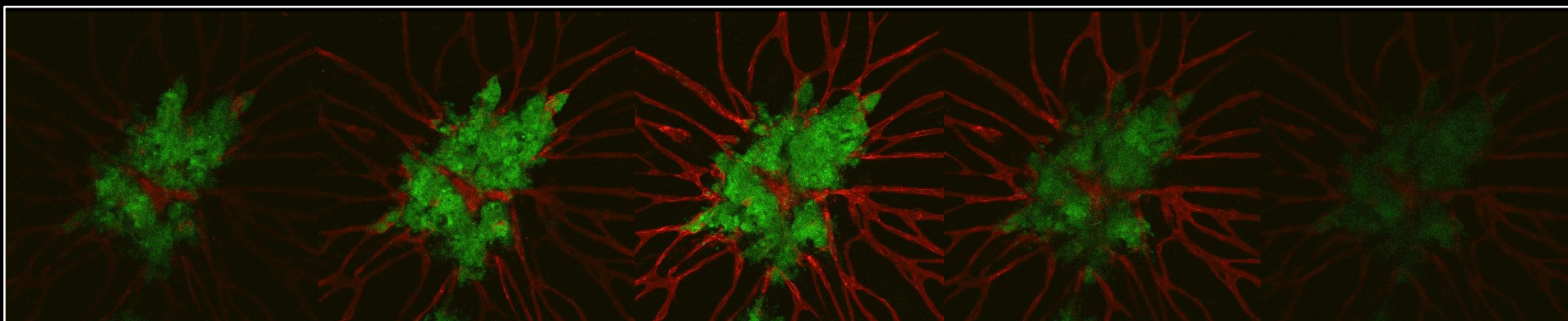
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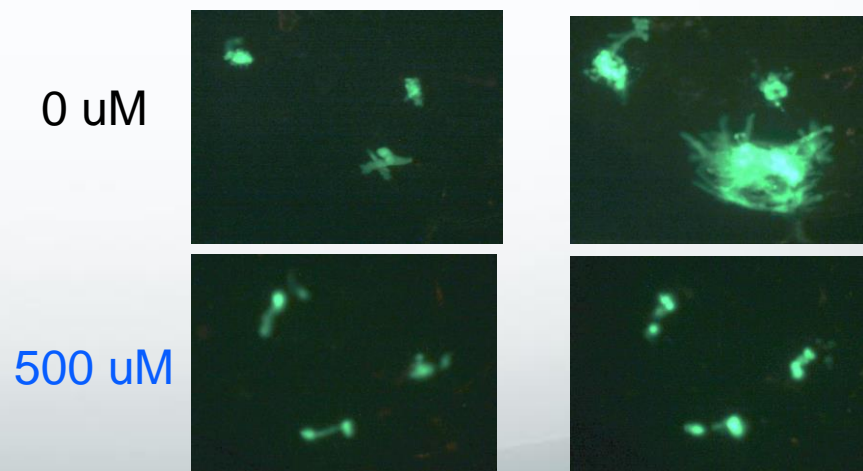
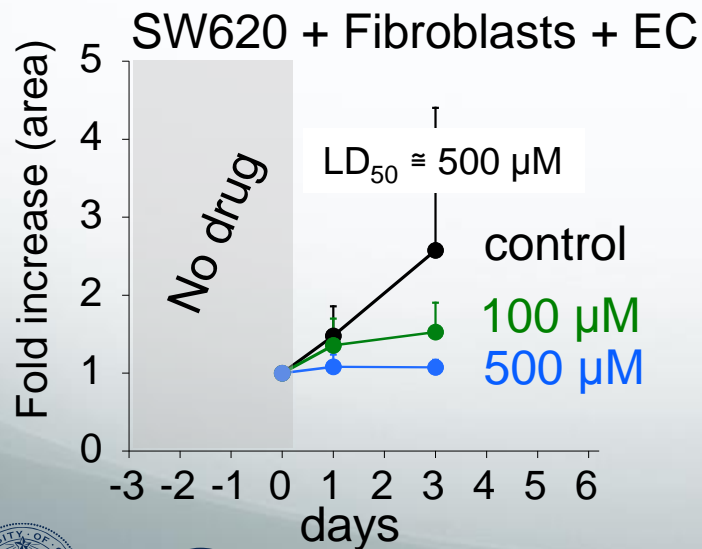
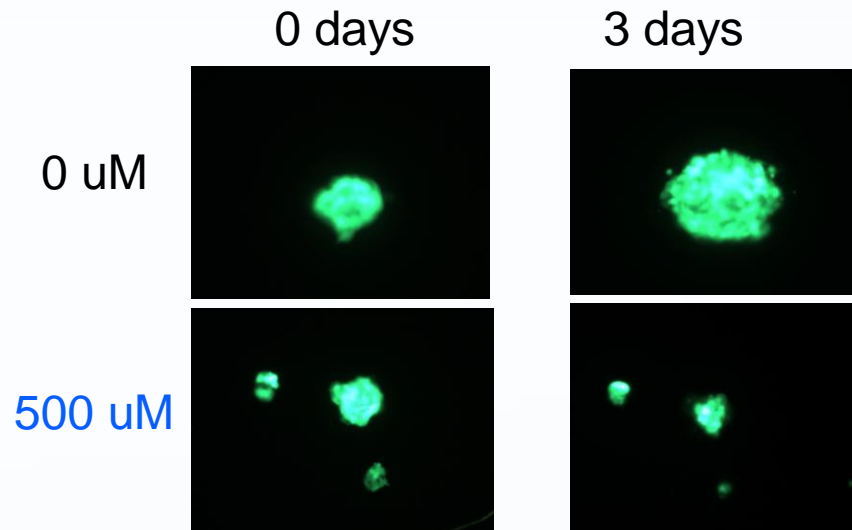
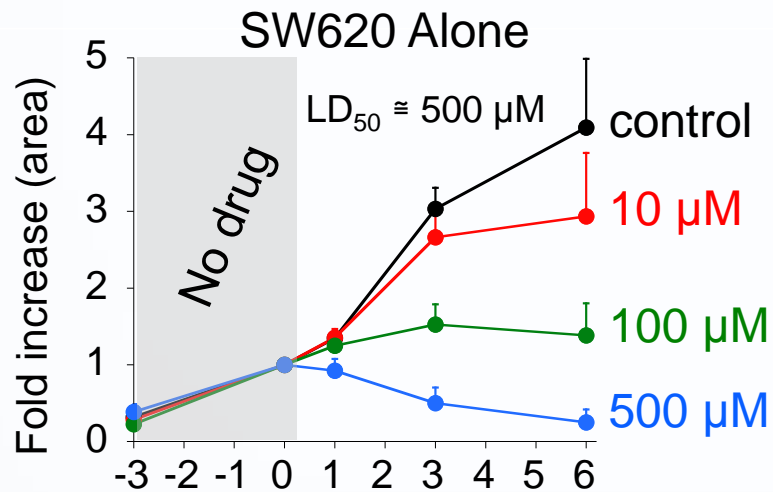
Angiogenesis  
model

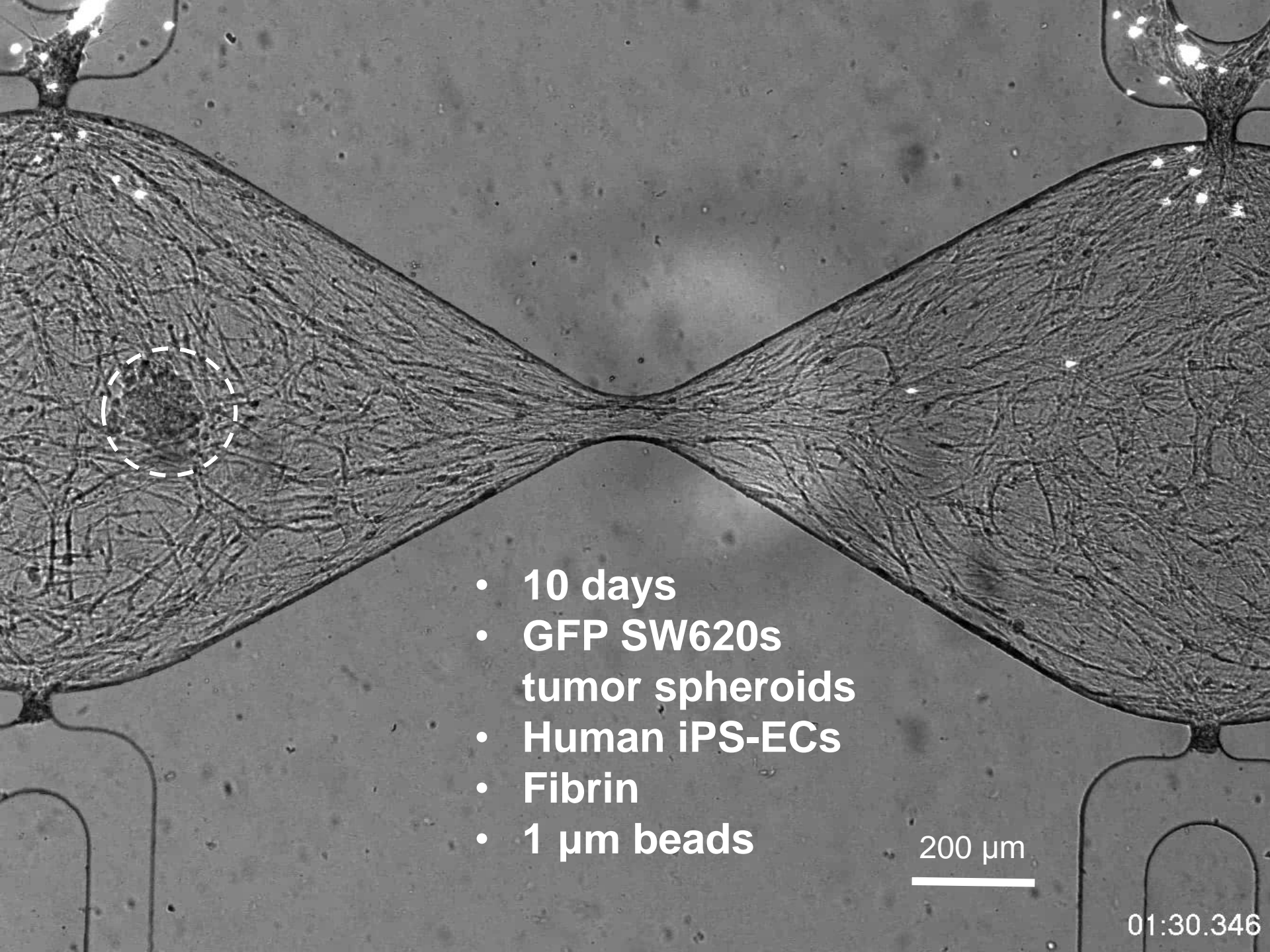


z  $\rightarrow$




# Drug (5FU) sensitivity of human tumor spheroids in device





- 10 days
- GFP SW620s tumor spheroids
- Human iPS-ECs
- Fibrin
- 1  $\mu\text{m}$  beads

200  $\mu\text{m}$



# Commercialization

## Licensing

- License technology to pharma for drug discovery
- License technology for personalized drug screening

## Service

- Manufacture and sell microtissue platform
- Perform heart toxicity screens
- Perform compound library screens for anti-tumor drug discovery
- Determine optimal combination personalized drug therapy

## Discovery

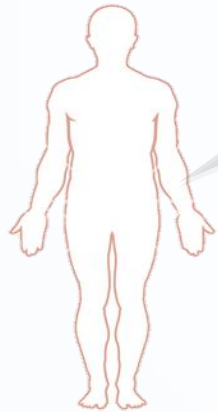
- Perform library screens “in house” and license lead compounds





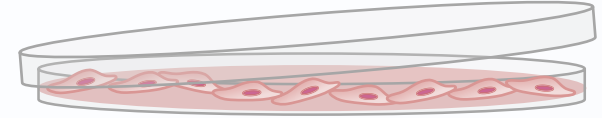
# Personalized Anti-cancer Therapy

1. Isolate cells from body



Stromal cells (fibroblasts)  
Cancer cells

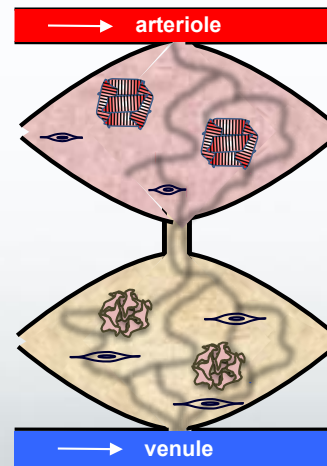
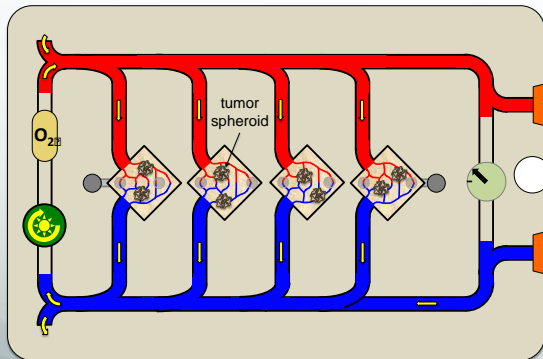
2. Create and expand iPS cells



3. Create EC, CM, Fib



4. Test drug susceptibility



4. Add matrix and create 3D array of tissues



# Conclusions and Future Work

## Summary

- Tumor and Cardiac “microenvironments” with perfused human capillaries
- Control of flow, dimensions, matrix, cell, and gradients
- Patient-specific models (primary tumor, iPS cells)

## Questions/Future

- Drug interaction with PDMS
- Vessel remodeling (pruning, arterioles, venules)
- Red blood cells, white blood cells, platelets
- Reproducibility and validation

