Engineering Microvascular Networks for Therapeutic and *in vitro* Applications

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IEEE Life Sciences Grand Challenges
Thursday October 4, 2012

BioSym BIOSYSTEMS AND MICROMECHANICS

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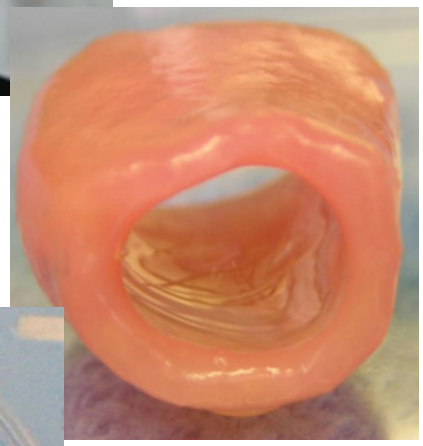
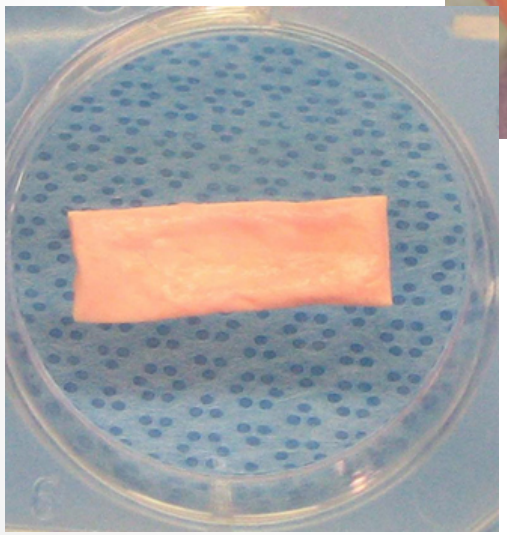
EBKS

NSF

There have been many attempts, and some significant advances, in engineered tissues





childrenshospital.org

But the successes have been limited to avascular tissues such as skin, cartilage, bone, urethra, bladder

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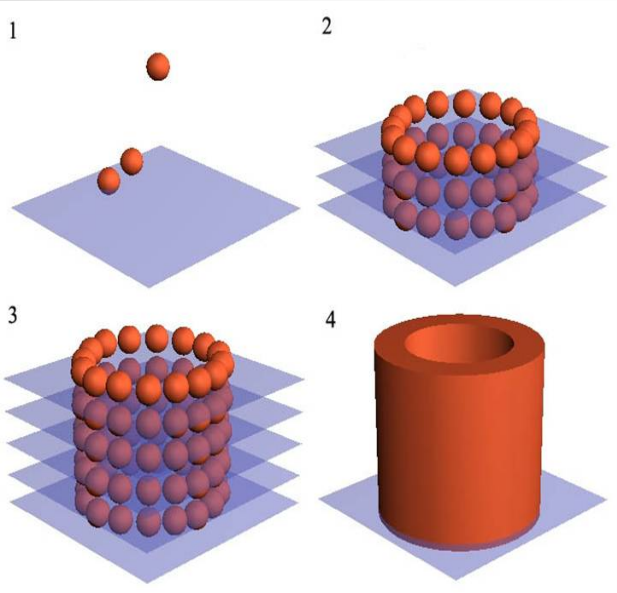

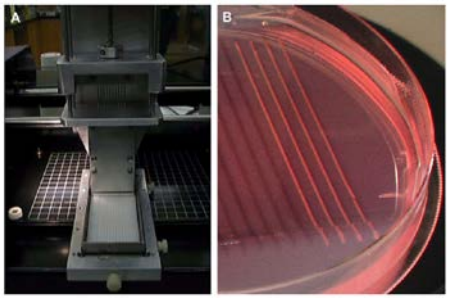

There are promising approaches to creating large vessels

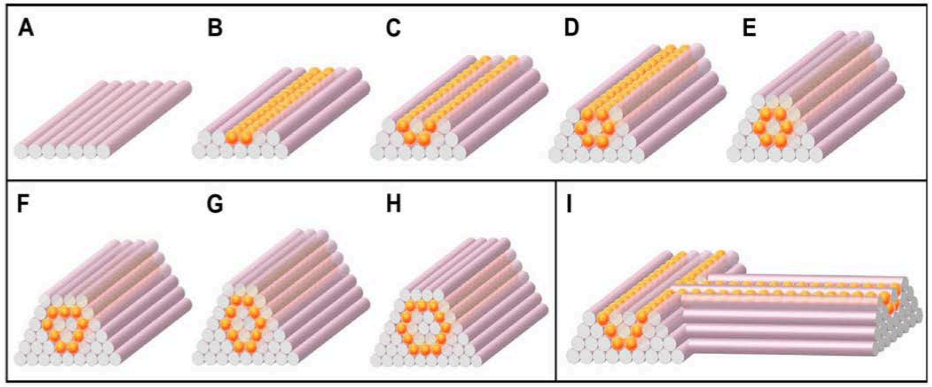

Fig. 3. Design template for tubular structures. (A–E) Deposition scheme for the smallest diameter tube that can be built of agarose rods (pink) and multicellular spheroids (orange) of the same diameter. (F–H) More complex tubular structures. (I) Scheme for a branching structure.

But few of these are applicable to the microcirculation.

Niklason and Forgacs Labs

Biomaterials, 2009

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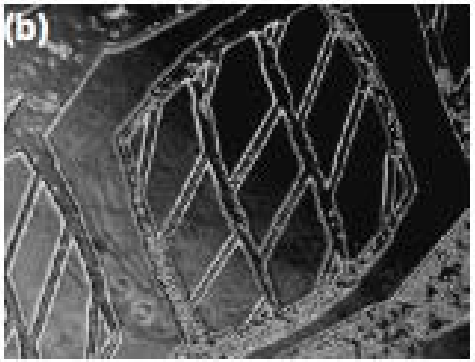

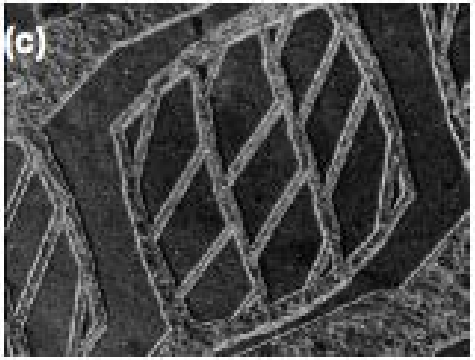

Engineered networks on 2D

Systems in PDMS can be patterned, lined with endothelial cells, and perfused.

Borenstein and co-workers, Draper Laboratories

Biomed Microdevices, 2004

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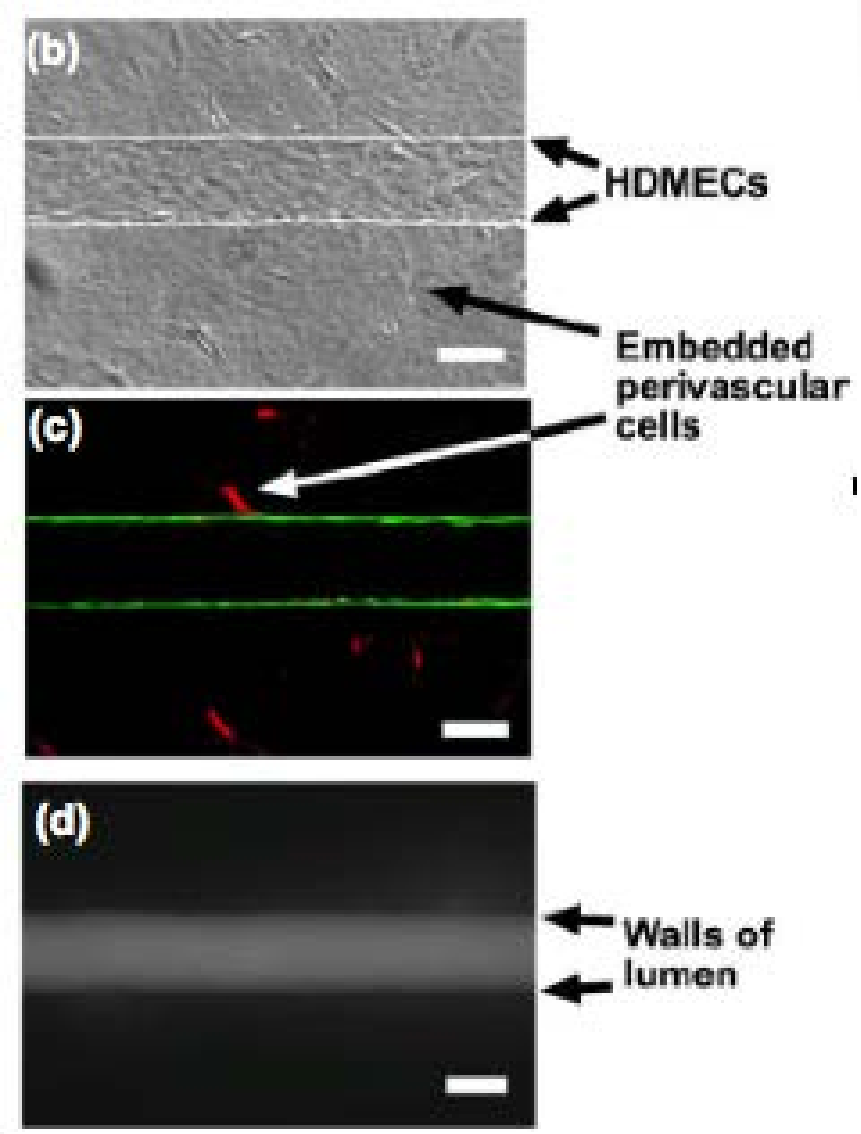

100 µm

Engineered single vessels in 3D

Another approach is to cast cylindrical holes in gels and line these with endothelial cells, co-cultured with other cell types.

Tien Laboratory, Boston University

Microvascular Res, 2006

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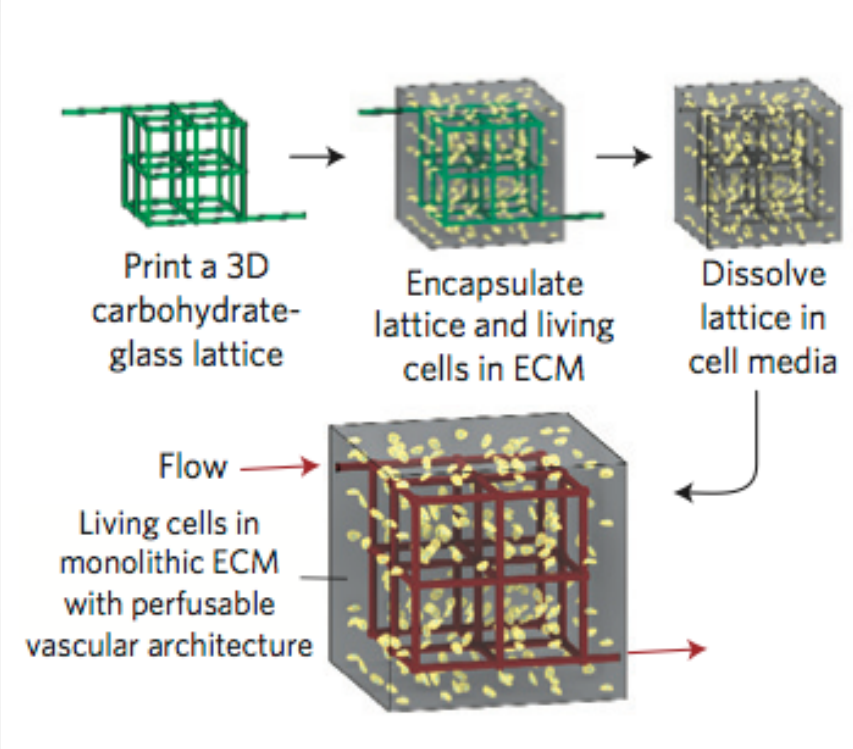
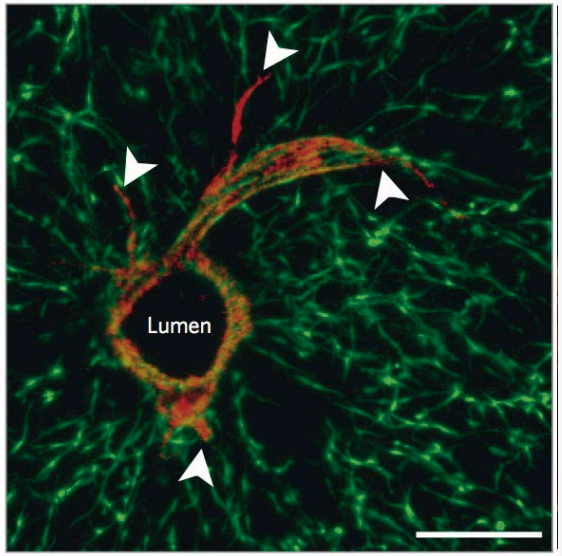
Engineered networks in 3D





200 µm

C. Chen and S. Bhatia Laboratories
Nat Mat, 2012

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Grand Challenge #1

Building Microvascular Networks for Applications in Regenerative Medicine and Biological Machines

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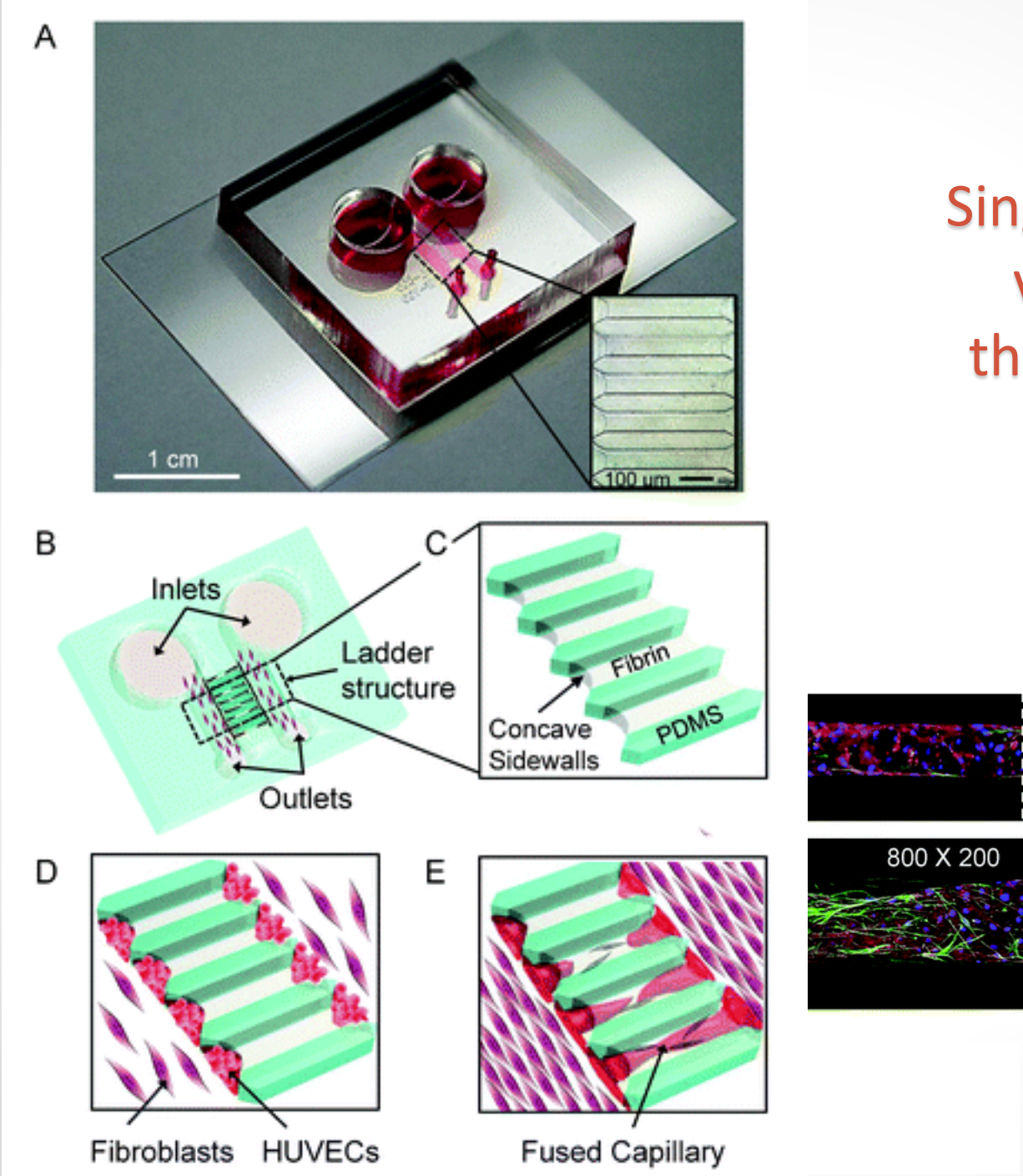
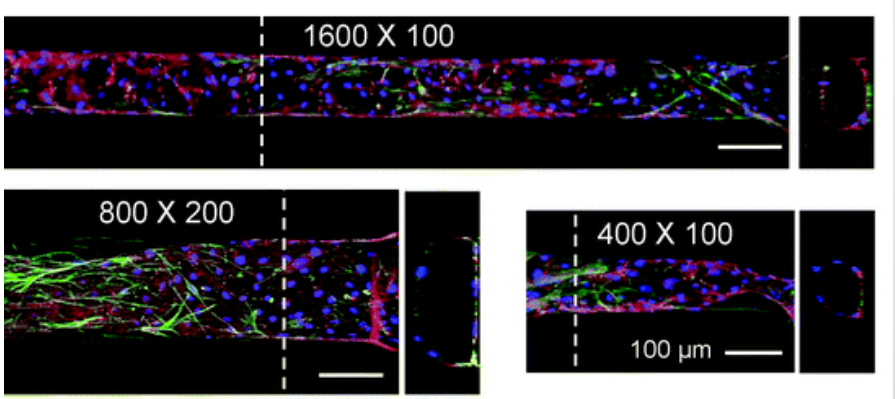
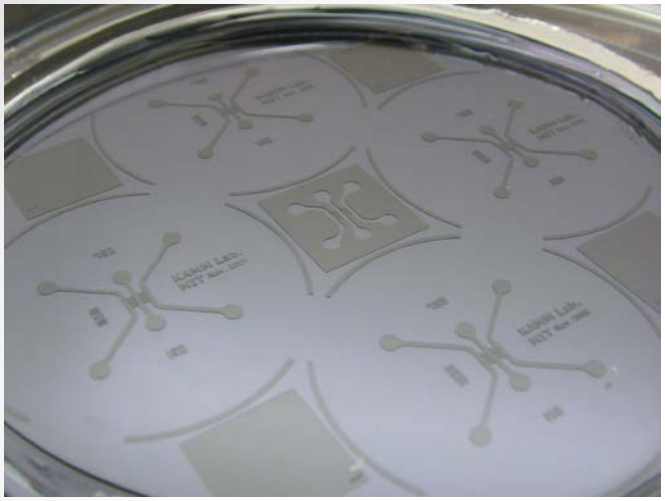
Single small-caliber vessels grown through fibrin gel

Jeon Laboratory

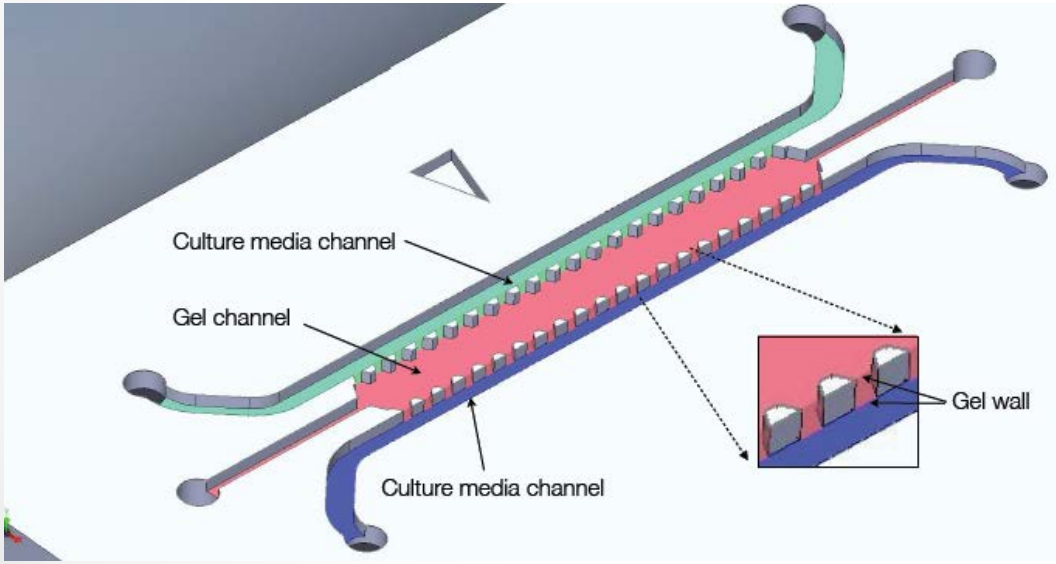
LoC, 2012







Using Microfluidics to create 3D microvascular beds



Shin et al., Nat Prot, 2012

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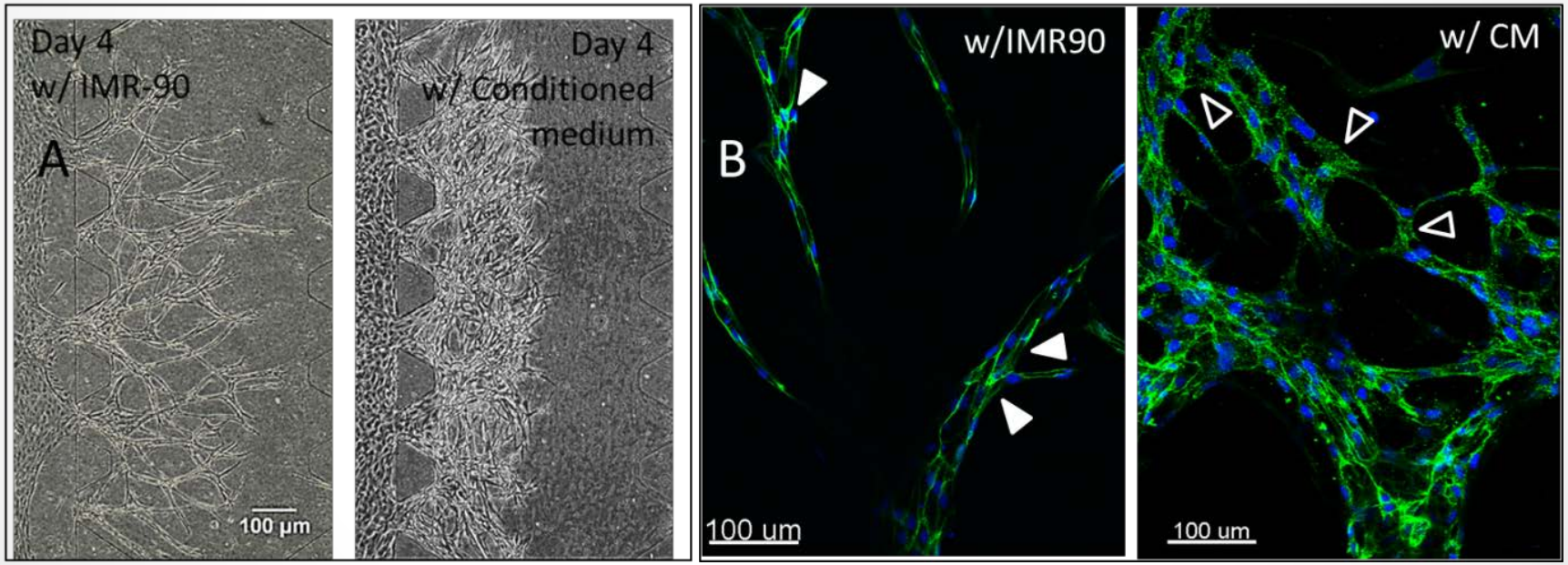
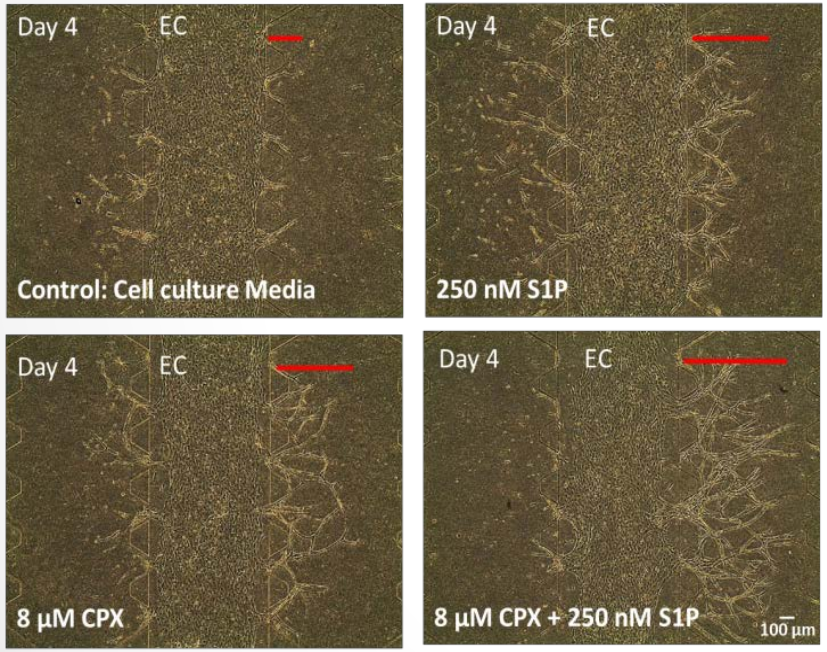
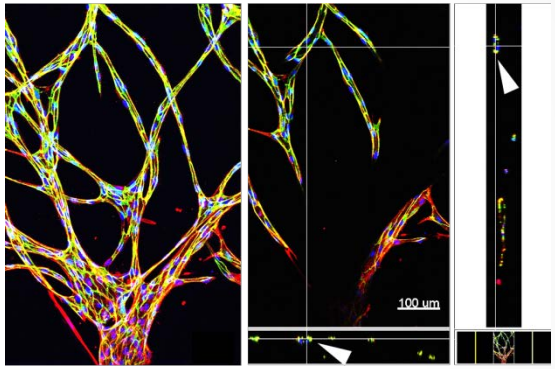
Controlling structure by co-culture with a second cell type

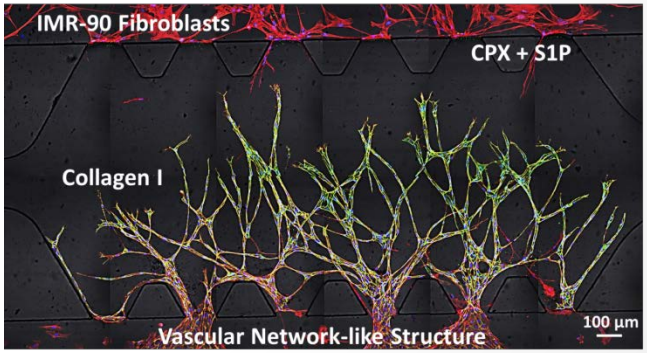


Co-culture with stimulatory factors

Fibroblasts w/ factors to stimulate production of growth factors







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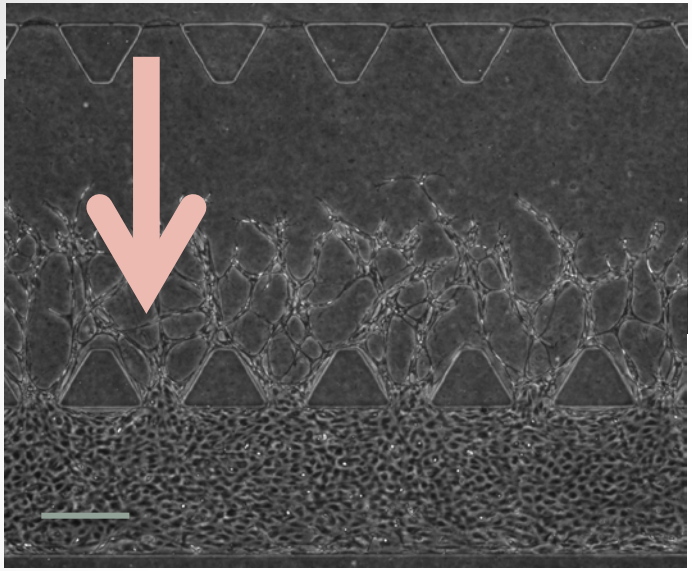
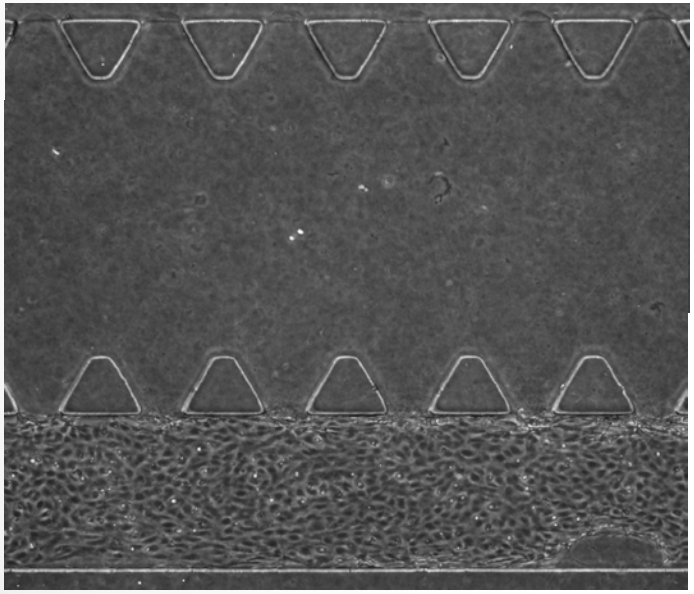
Harnessing nature's ability to create vascular beds

Using interstitial flow to regulate network growth

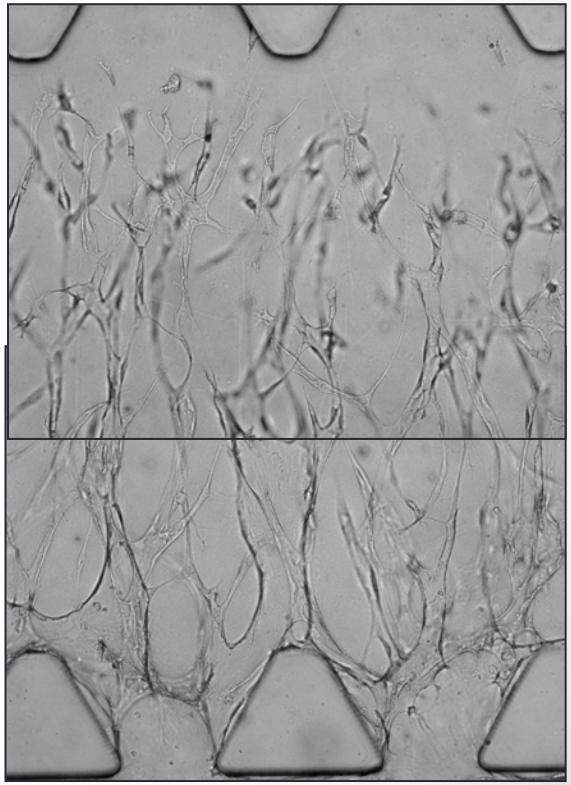


150 µm

With flow



Static



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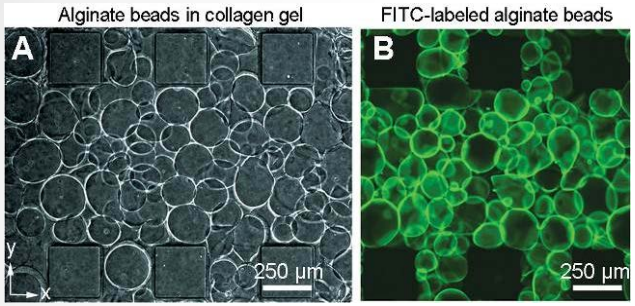
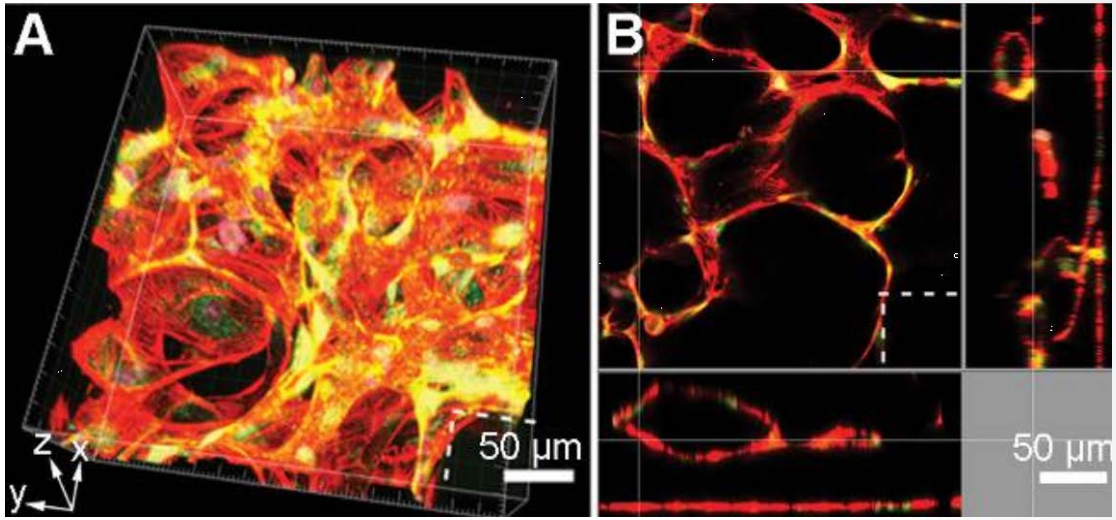
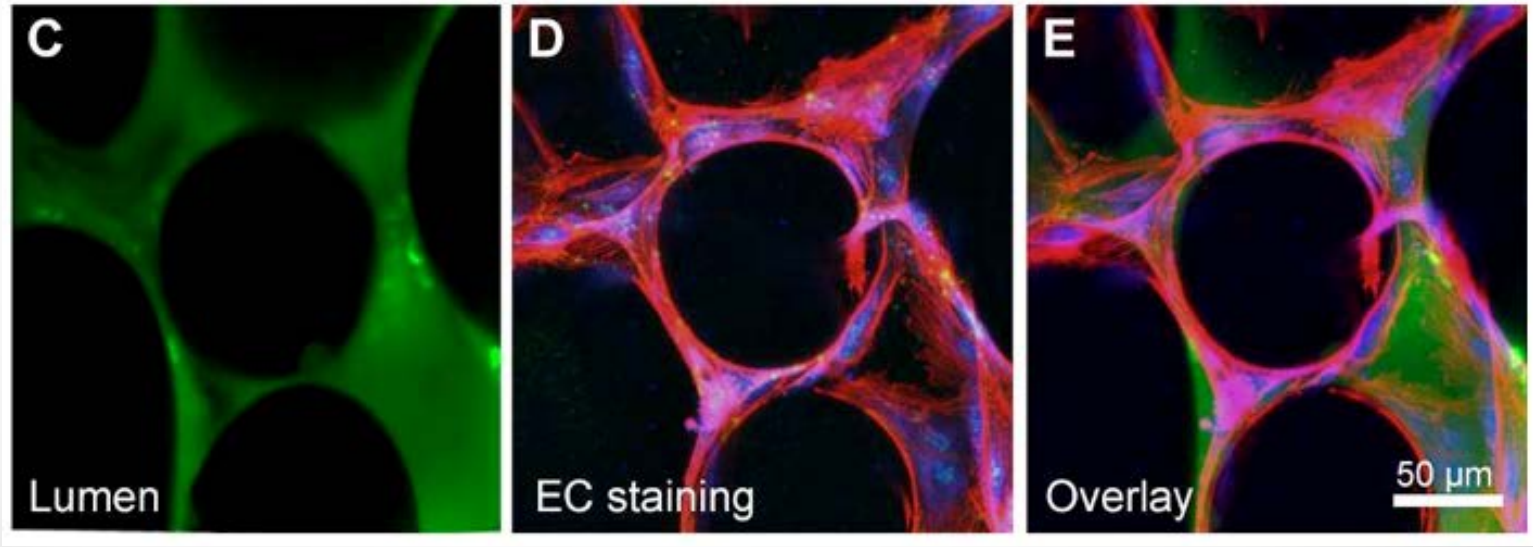
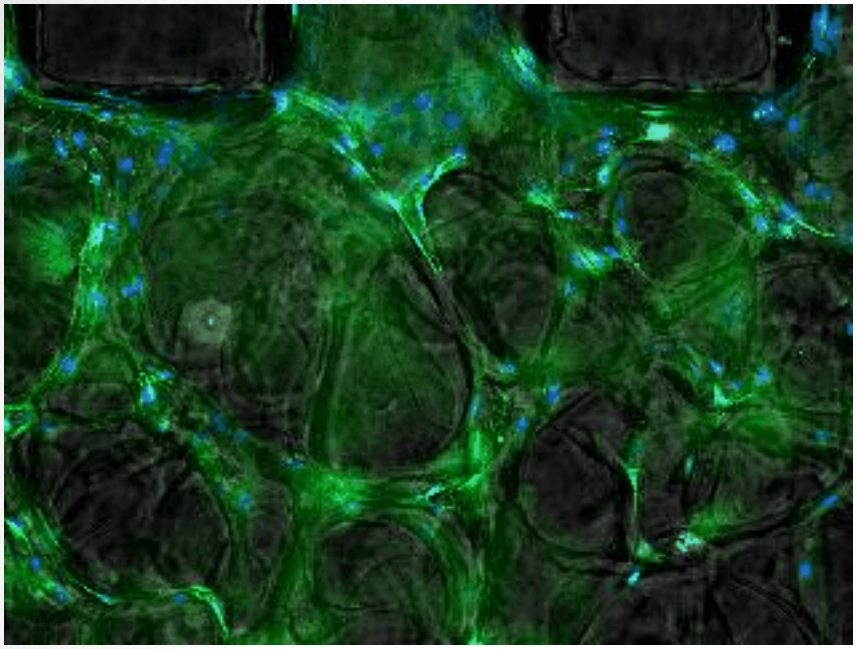
Controlling microvascular structure by gradients in stiffness

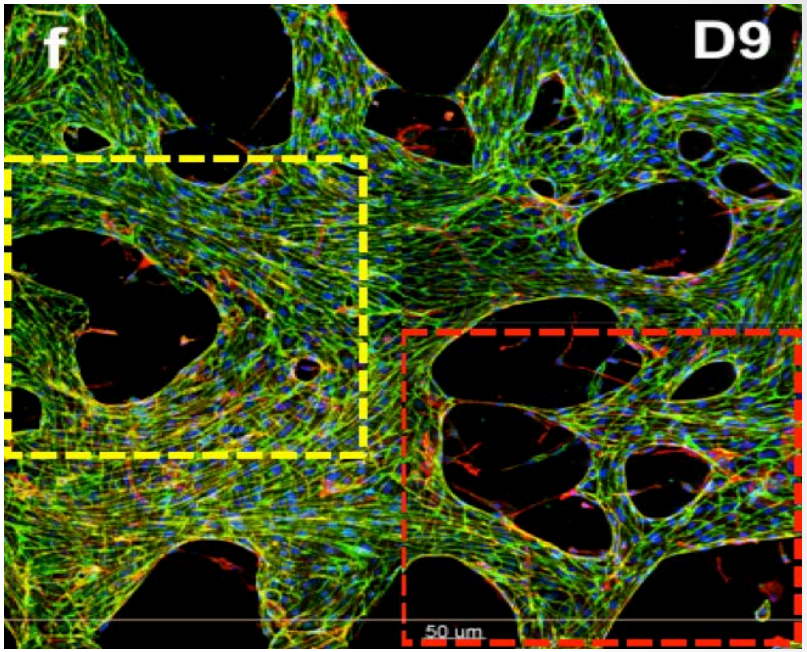


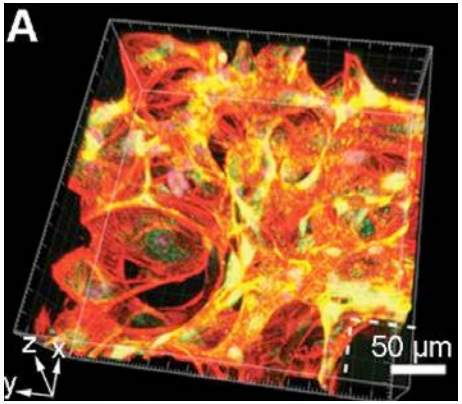


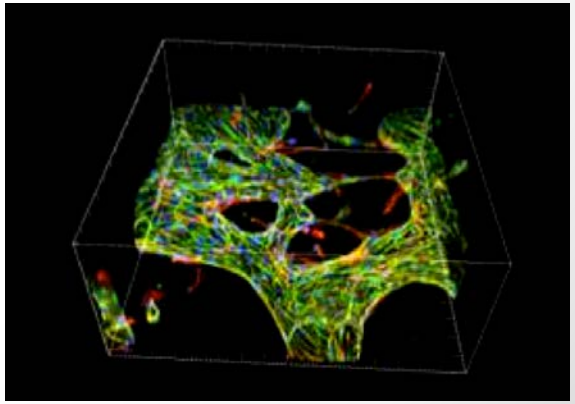


Angiogenesis or Vasculogenesis?









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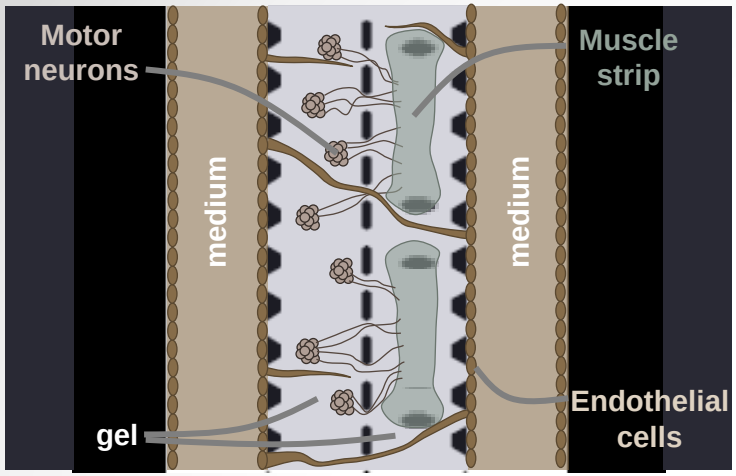
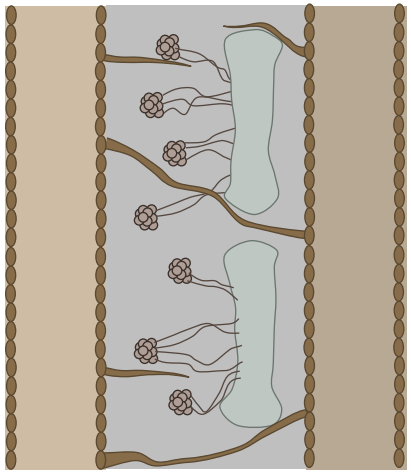
Creating artificial muscle with vascular perfusion

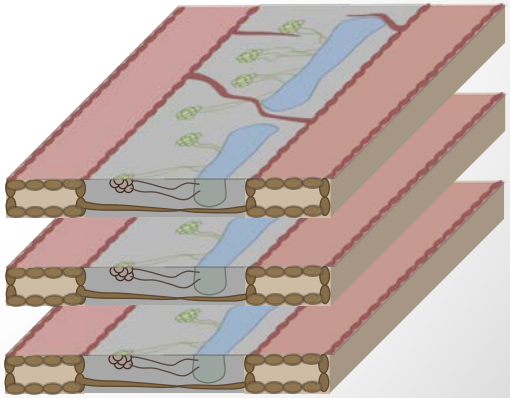


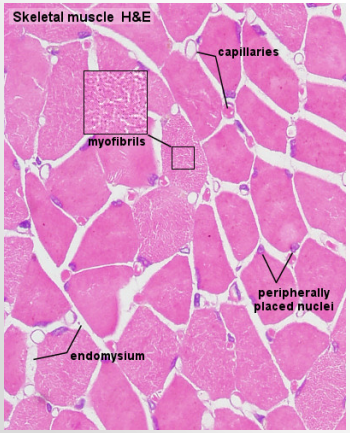
Heterotypic cellular tissue formation in microfluidic device

Tissue extraction from the synthetic cast



Stacking up several layers of tissue to form a functional 3D machine





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Where we are, and where we need to head

- Microvascular networks can be grown from endothelial monolayers and their morphology can be controlled
- Co-culture is not only useful, but it is also essential if we hope to form complex organs or other “biological machines”

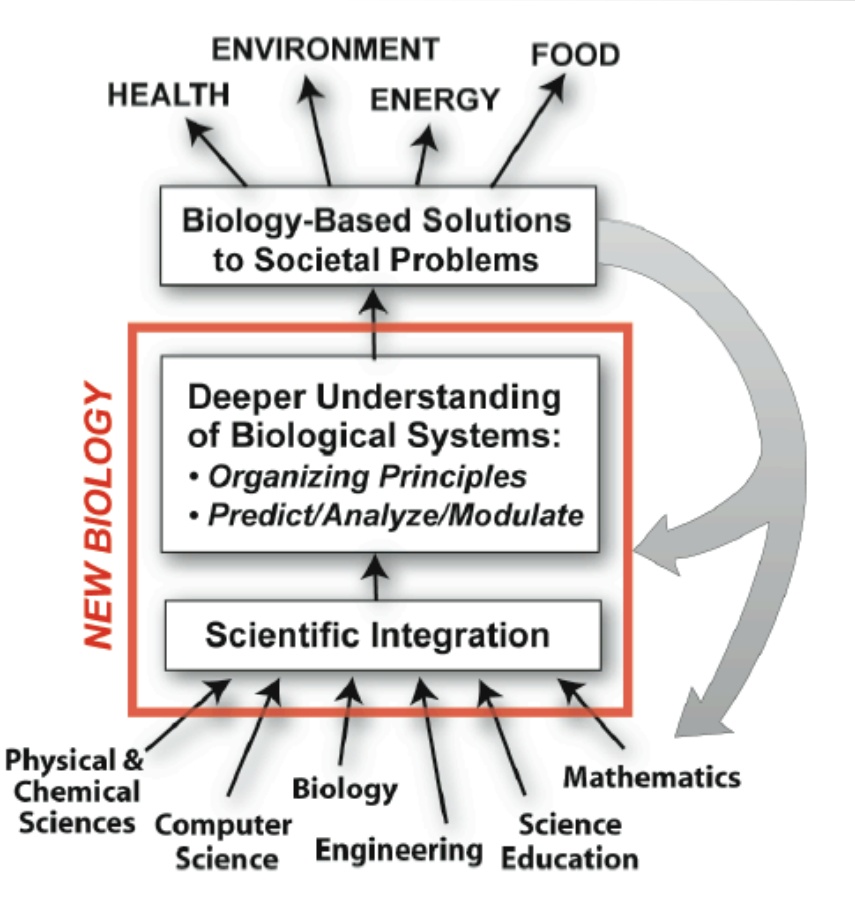
But:

- Need to establish long-term stability
- We lack the ability to form complex tissues
- We lack the understanding, to harness natural self assembly

The Grander Challenge

A New Biology for the 21st Century.
Report from the NAS, NAE, IOM, NRC

Despite the potential of .. recent advances, *there is still much to be done to move from identifying parts to defining complex biological systems*. Furthermore, the systems design, manipulation, and prediction needed for practical applications such as ecosystem repair or individualized medicine, are still well beyond current capabilities. The report's authoring committee has developed the idea of *the New Biology to provide a framework to connect biological research with advances in other branches of science and engineering*.



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Some critical questions

From the *National Academies Keck Futures Initiative*

How can one engineer self-synchronizing populations, that behave coherently, despite cell-cell variability?

How do we achieve effective cell communication over multiple length and time scales? For example, what are strategies for cell communication to nearest neighbors, over several cell layers and across an entire culture?

How do we design cells to self organize into defined three-dimensional structures (Example: organs)?

What applications might exist for controlled multi-population systems?

Grand Challenge #2

Creating Biological Machines by Harnessing the Power of Nature

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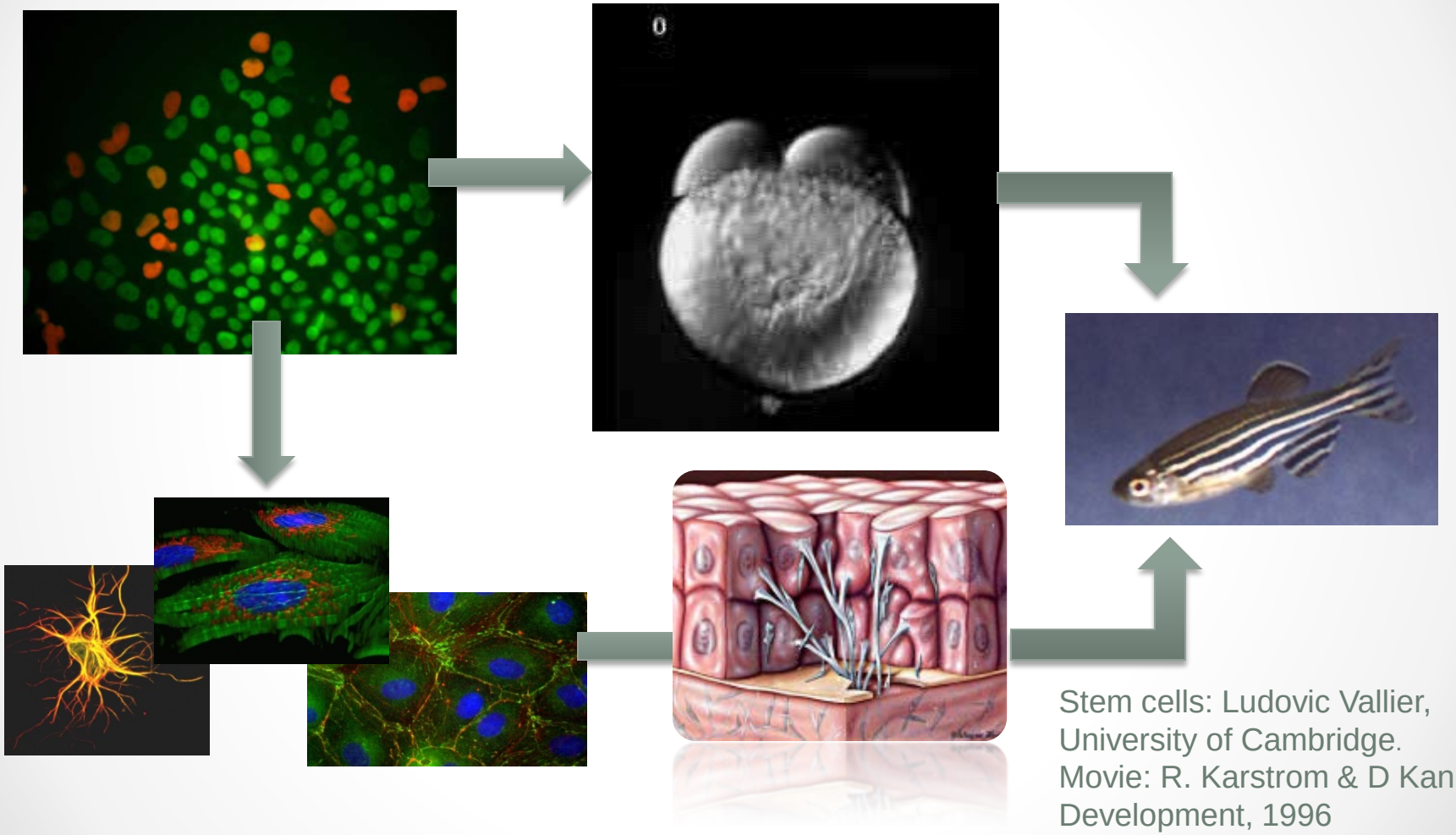
Two pathways to a “machine”: Engineered vs. Emergent



Stem cells: Ludovic Vallier, University of Cambridge.
Movie: R. Karstrom & D Kane, Development, 1996
http://www.depauw.edu/news/index.asp?id=17734

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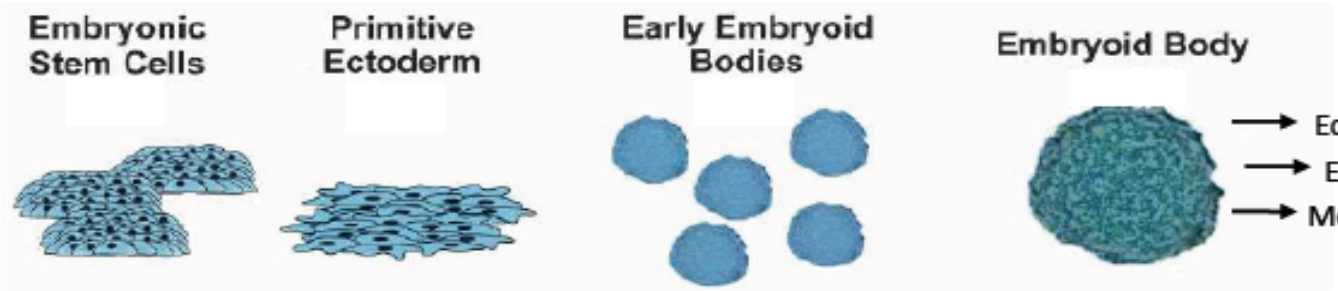
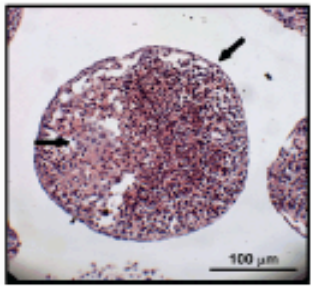
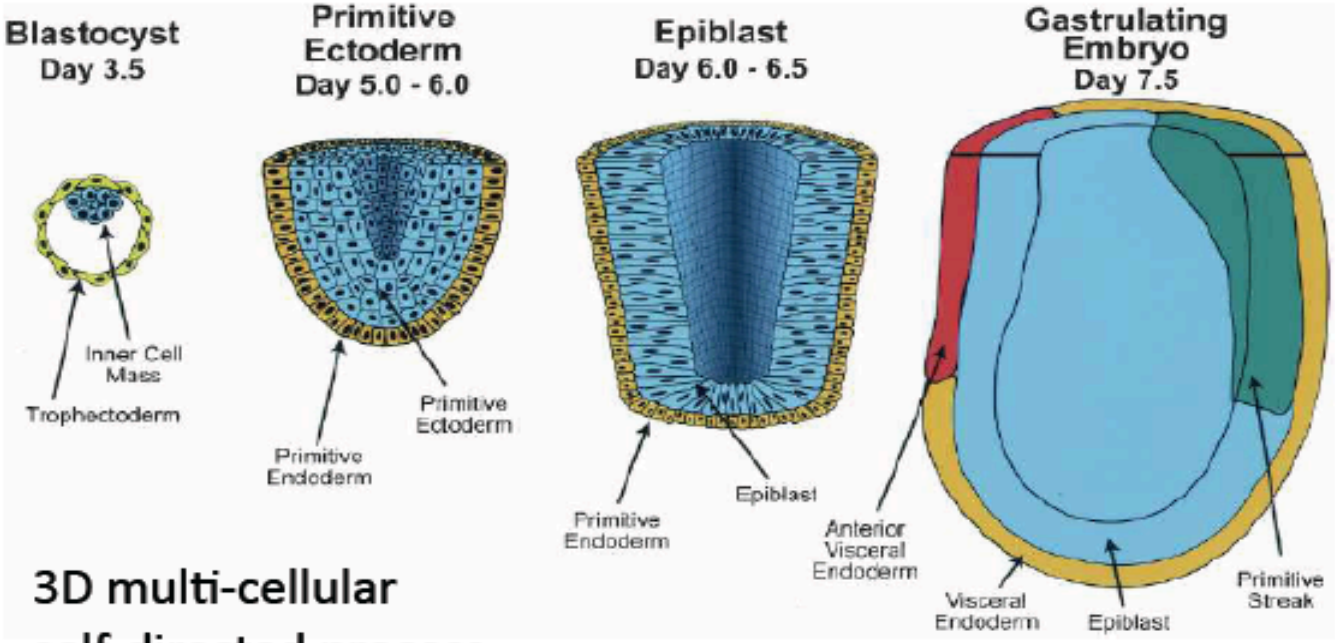
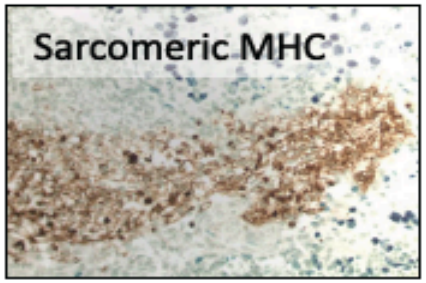
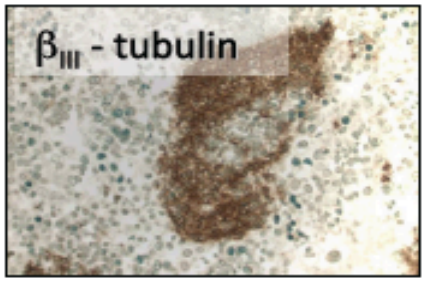
The Challenge: to Recreate and Control the Process of Development











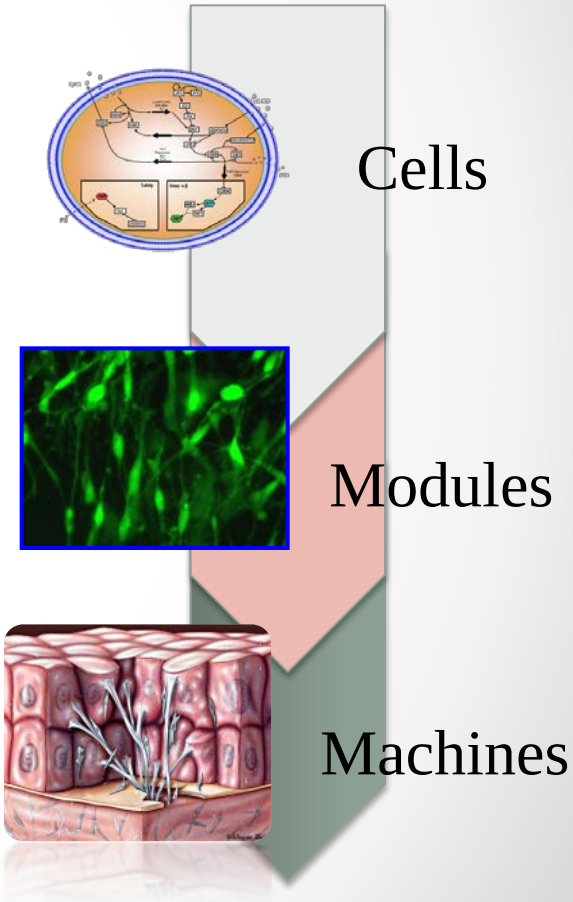
3D multi-cellular self-directed process

Keller, Genes Dev, 2005.

To *harness* development requires a series of essential steps

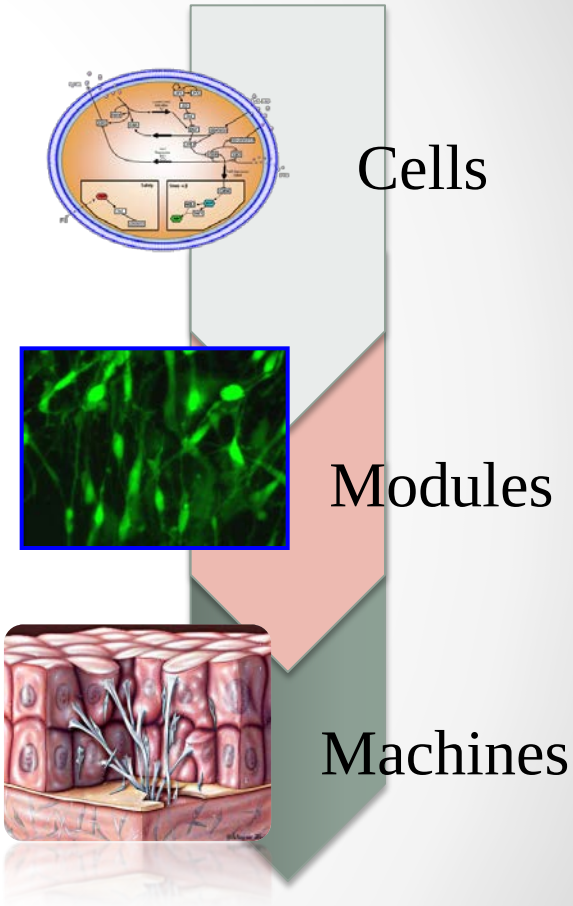
We need to understand:

- how to control cell differentiation both in isolation and as part of a population of cells
- how cells communicate with their environment and neighboring cells to develop coordinated behavior (the modules of the machine)
- how to assemble the modules to produce functionality of the biological machine



… and new technologies

- New imaging modalites: deep imaging of signaling events, real-time, super resolution
- New ways of controlling and measuring forces & signaling in the local microenvironment
- New ways of regulating the external (global, macroscale) environment (e.g., growth factors, O_2, pH, temperature, electric fields)

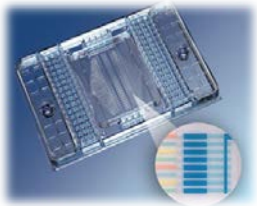


Creating a biological machine

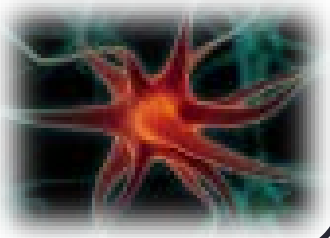
System integration

Modeling

Matrix & microfluidics

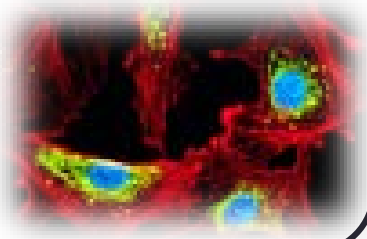


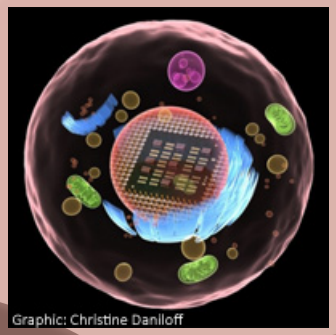
Neuronal circuits

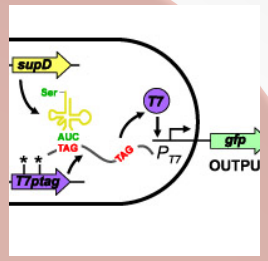


Muscle actuators

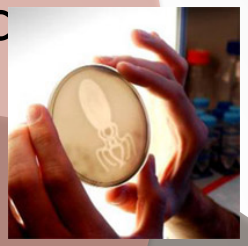
Vascular networks



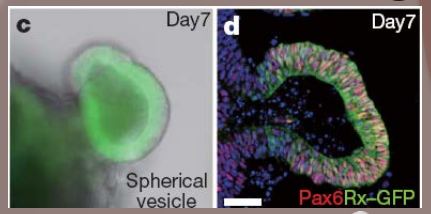


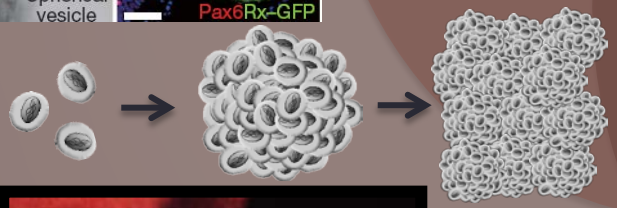


Synthetic Biology

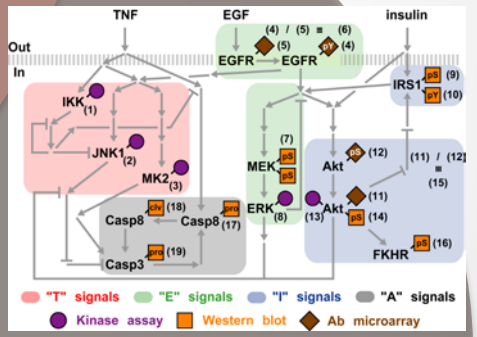


MicroNano Technology
Tissue Engineering

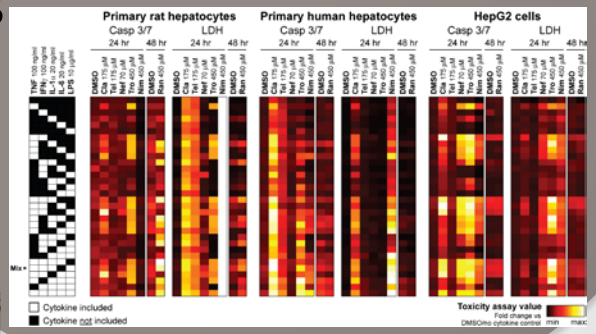




Integrated Cellular Systems



Systems Biology



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