3D-Tissue Microsystems for Tumor Microenvironments Designs for Basic and Translational Research

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Outline

A Program Project Grant

Hughes Group

The Tumor Microenvironment in Colon Cancer

- Chris Hughes, Marian Waterman, Steve George, John Lowengrub
- Cellular cross-talk among tumor, stroma, and vasculature
- Wnts, HGF, TNF_{α} signaling pathways, hypoxia
- Tumor progression, growth, angiogenesis, invasiveness

A Novel 3D-Tumor Model

- Advances in microfabrication, microfluidics, and microscopy
- 3D biological constructs for studying tissues and cells
- New kinds of experiments and measurements
- Bridging gaps to animal models...with translational potential

Selected Literature & Funding Avenues

Special Issue—3D Cell Biology

- Huh, et al. From 3D cell culture to organs-on-chips, *Cell Biology*, 21, 745-53, 2011.
- Fischer, et al. Microscopy in 3D: a biologist's toolbox, *Cell Biology*, 21, 682-91, 2011.

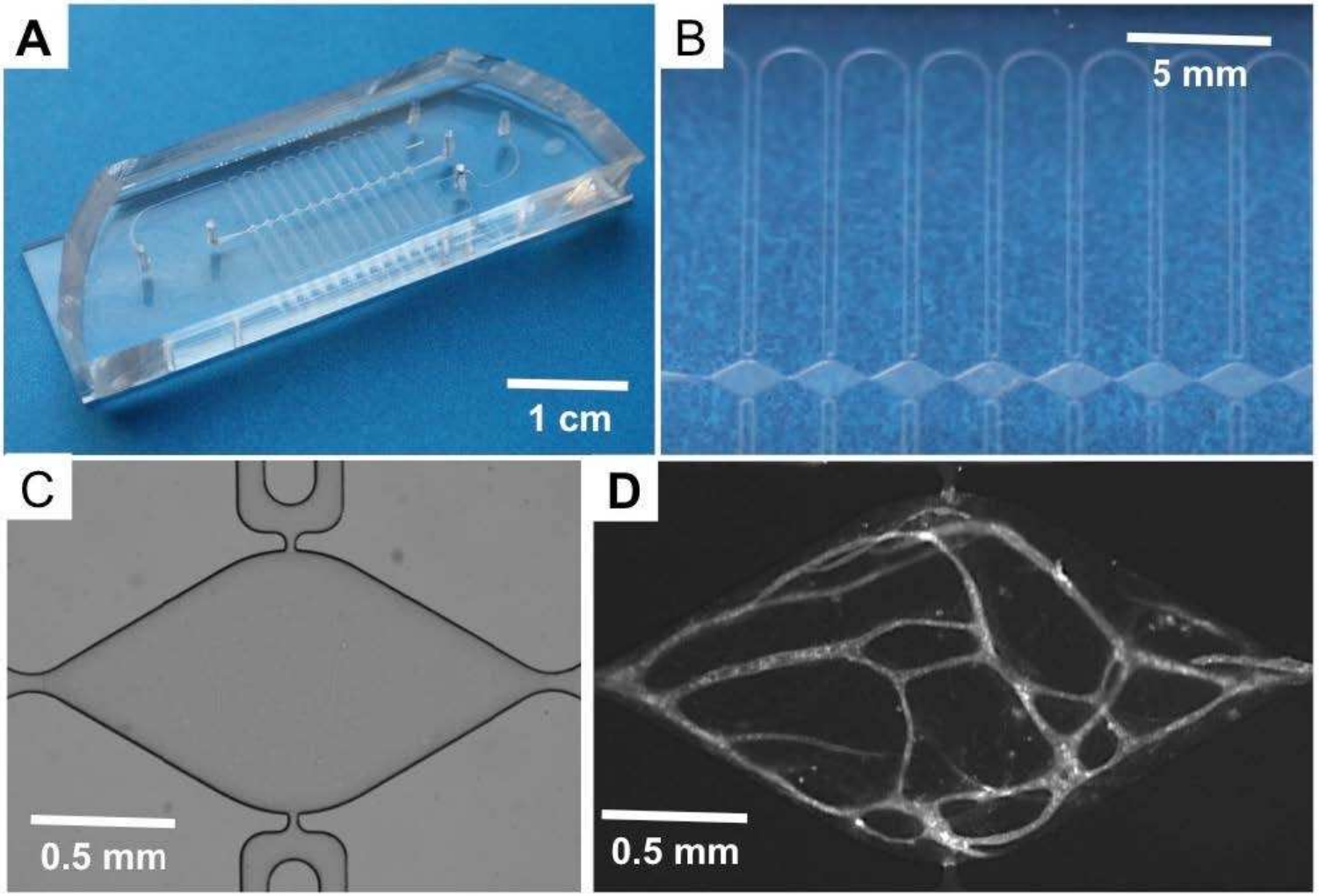
Cancer Related—emphasizing perfused tissue

- Barkefors, et al. A fluid device to study directional angiogenesis...*Lab Chip*, 9, 529-35, 2009.
- Kim, et al. Breast cancer diagnosis using...*PLoS ONE*, 5(5), e10441, 2010.

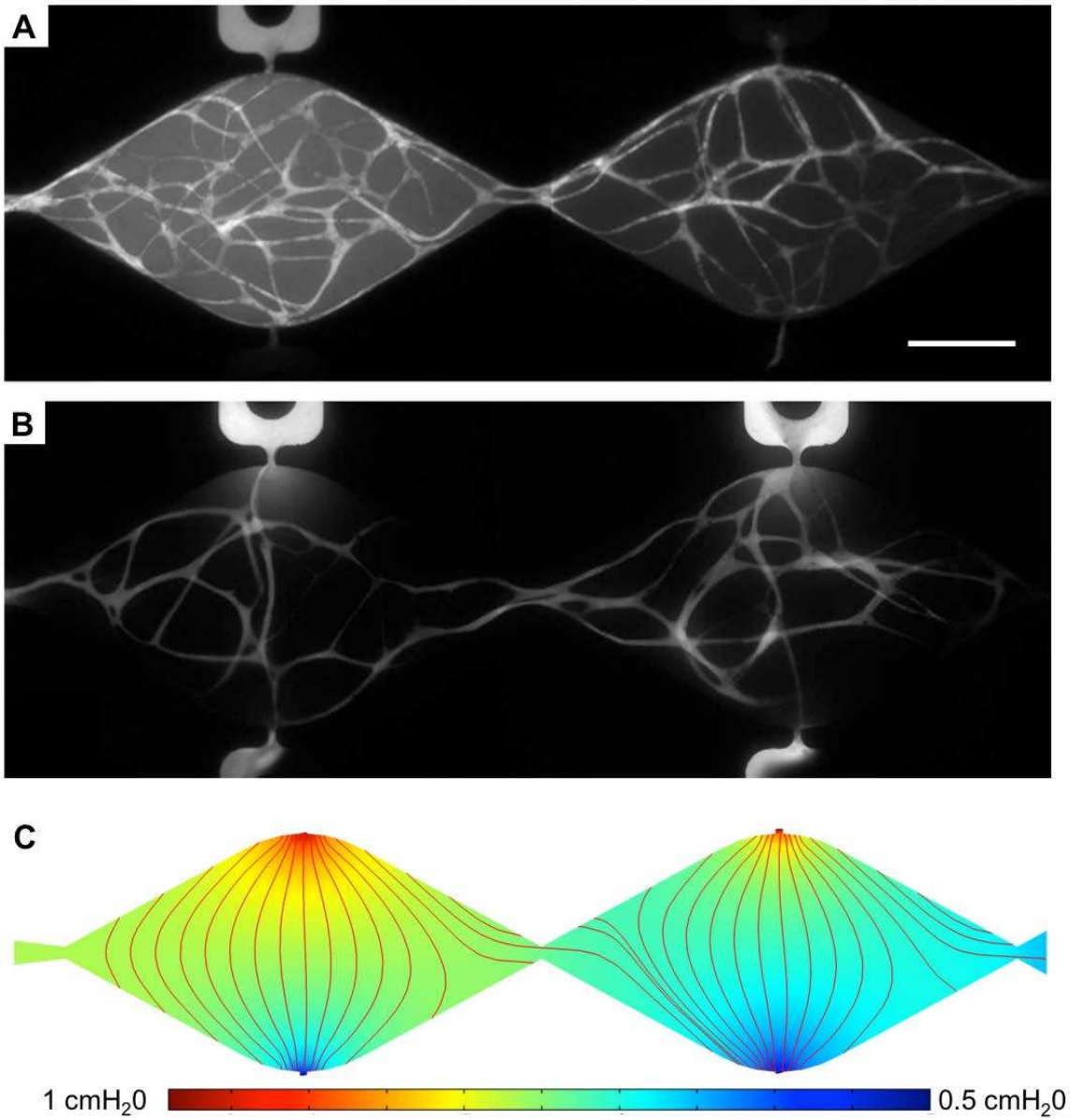
Funding Avenues

- NIH Common Fund on human microsystems in translational research.
- NCI "Provocative Questions" program—e.g. models of metastasis.

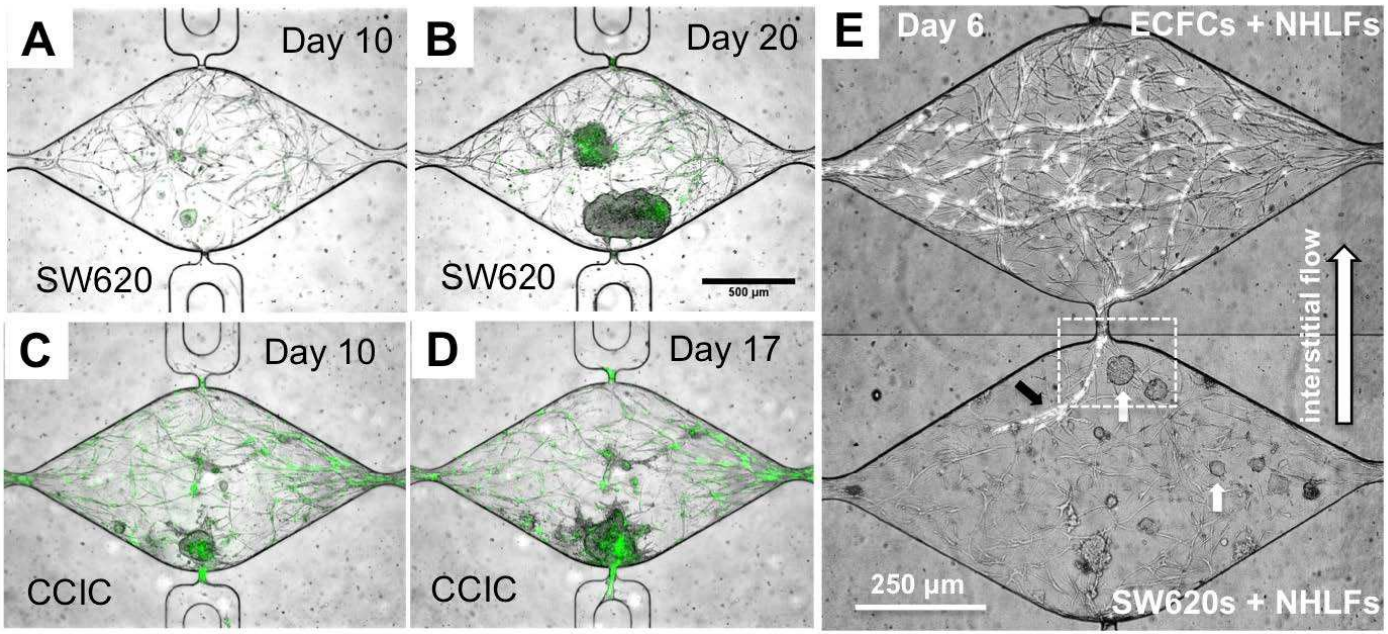
A Basic System



Microfluidic Control

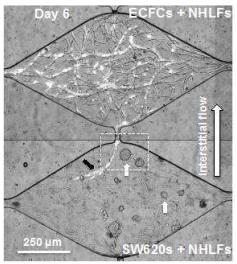


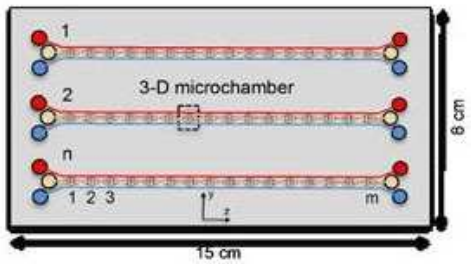
Tumor growth, Wnt-signaling, directional angiogenesis



An experiment on directional angiogenesis

Microtissue consists of co-cultures of fibrin, endothelial cells, stromal cells and tumor spheroids. There are two sources each of stromal cells and tumor spheroids, and there are two oxygen conditions for hypoxia versus normoxia. Of particular interest is the combined effects of phosphorylation ratios, lactate and VEGF on a total vessel network length.





Treatments to the Whole microarray

- 2 stromal cells $\times$ 2 tumor spheroids $\times$ 2 hypoxic conditions

Treatments to Angiostatic units nested within arrays

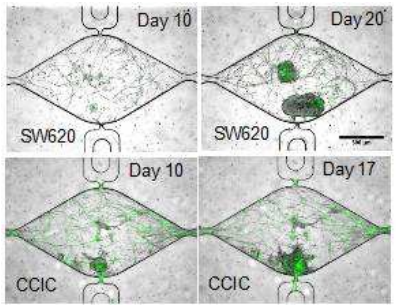
- 3 levels phosphorylation ratios $\times$ 3 levels lactate $\times$ 3 levels VEGF

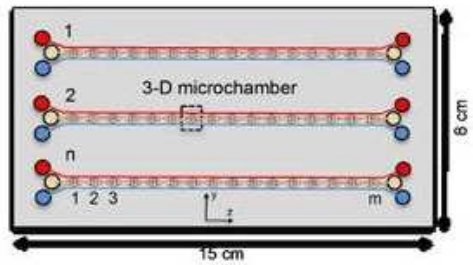
Split-unit principle

On choosing factors

i. *main* factors of direct interest, e.g. lactate gradients or profusion of small molecule inhibitors

ii. *special* factors which may modify the action of the main factors or may throw light on how the main factors works, e.g. hypoxia or cell lines





Assigning treatments[1]

- assign *special* factors to all angiostatic units in any one array
- assign *main* factors to angiostatic units within an array

[1] Advice on when to do it, next slide.

Split-unit principle *continued*

Effects on precision

- decreased for comparisons connected to *special* factors
- increased for comparisons connected to *main* factors and for their modifications by *special* factors

When to do it

- there is a factor of little direct importance, but it clearly plays the role of a *special* factor, e.g. different cell lines
- technical reasons, e.g. hypoxia

Notes

i. prepare homogeneous co-cultures for all tissue on a given array

ii. replicate arrays, the equivalent here of biological replication

Applications to Translational Research

Robust Therapeutic Design

Our problem is the development and preclinical testing of promising therapies of high value in the clinic. We aim to...

- investigate combination therapies.
- establish performance parameters over diverse patient populations under a range of clinical applications.

An Approach using Human Microsystems

- there are therapies and 'environments'
- one set of factors for the active ingredients of combination therapies, and another for the environments
- one design option takes therapies as *main* factors and environments as *special*...

Summary

- Novel 3D-Tumor Models
- Split-unit Principal of Design
- Robust Therapeutic Design...
  ...Or, ask what works? for whom? and in whose hands? i.e. a *critical mix.*
- Biostatistics Shared Resource

`http://www.cancer.uci.edu/biostatistics/`

...follow the links to Consultation Requests