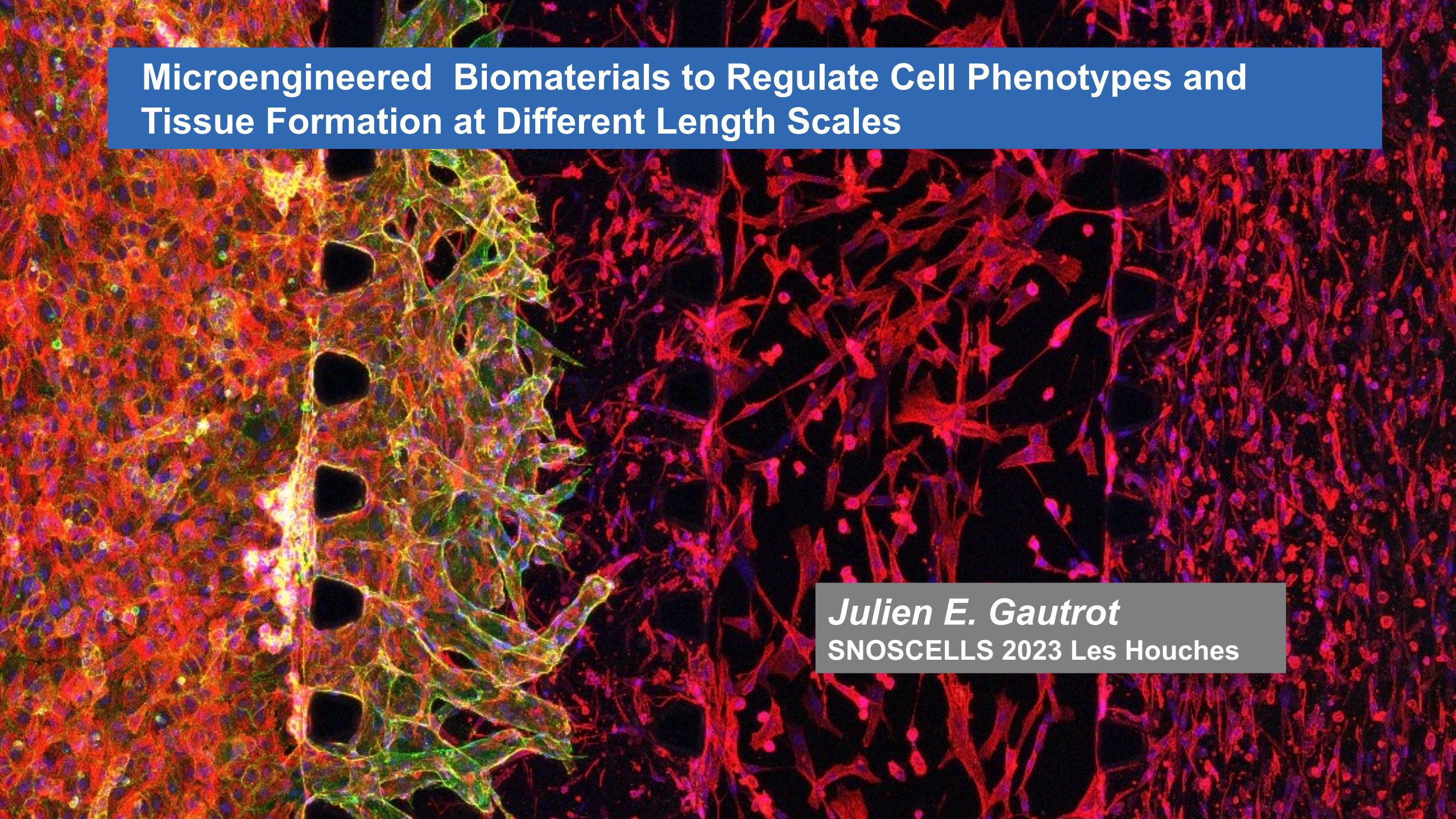
Microengineered Biomaterials to Regulate Cell Phenotypes and Tissue Formation at Different Length Scales

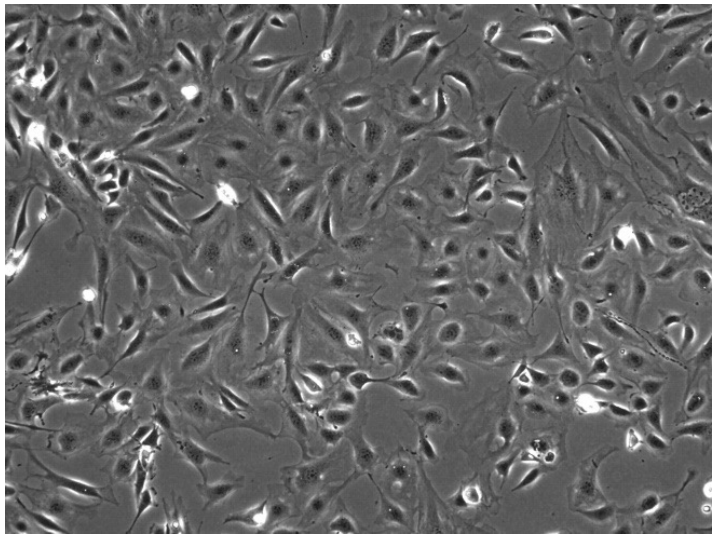


Julien E. Gautrot

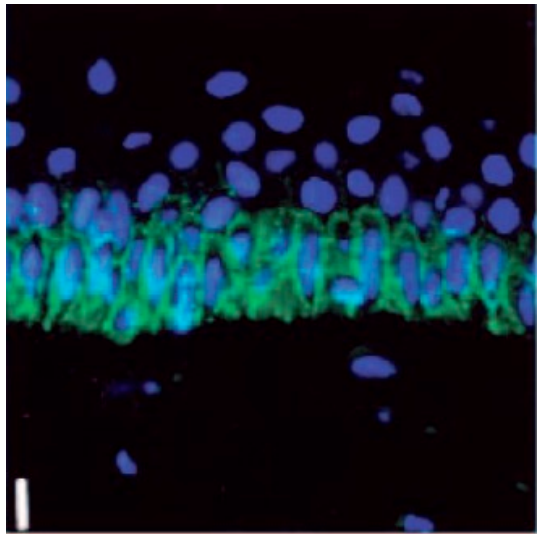
SNOSCELLS 2023 Les Houches

Cells in Culture Do not Look Like Cells *in Vivo*

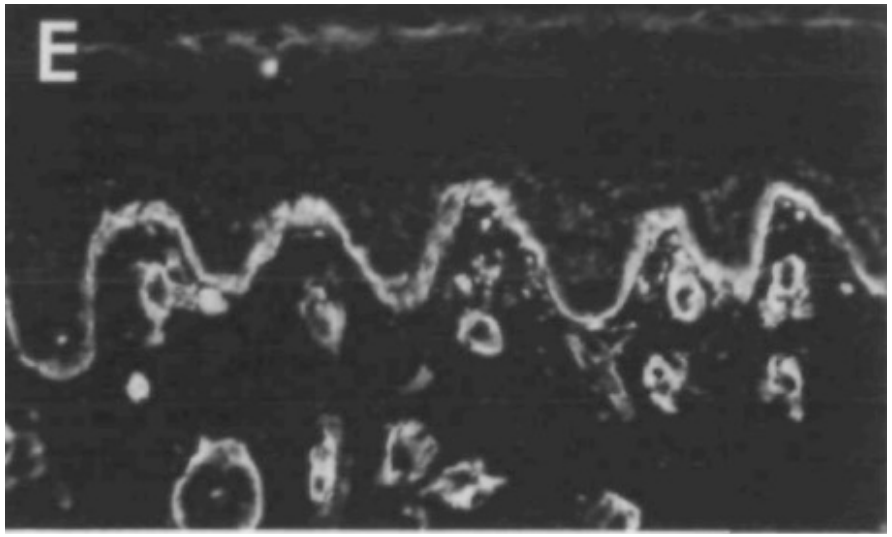
2D In Vitro Culture



In Vivo



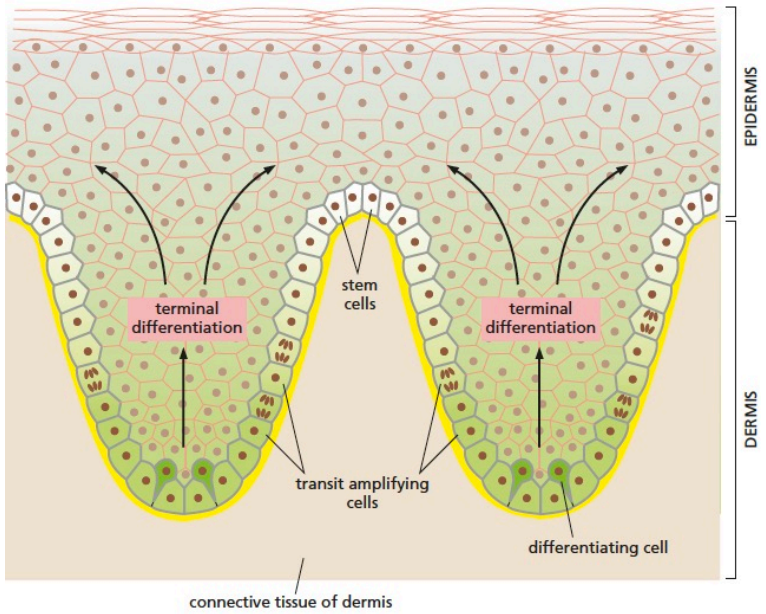
Niessen et al. J. Cell Sci (1996), *109*, 1695.



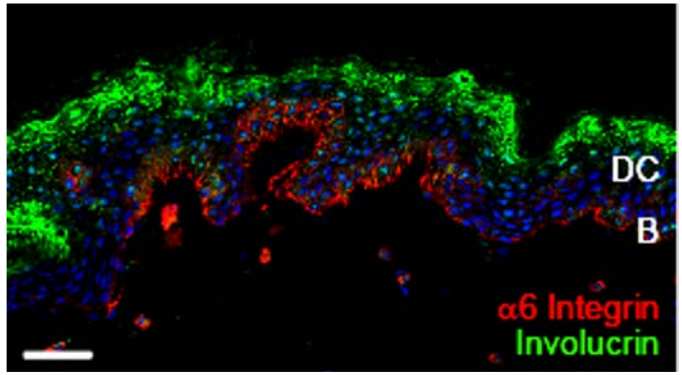
Herle et al. Development (1991), *112*, 193.

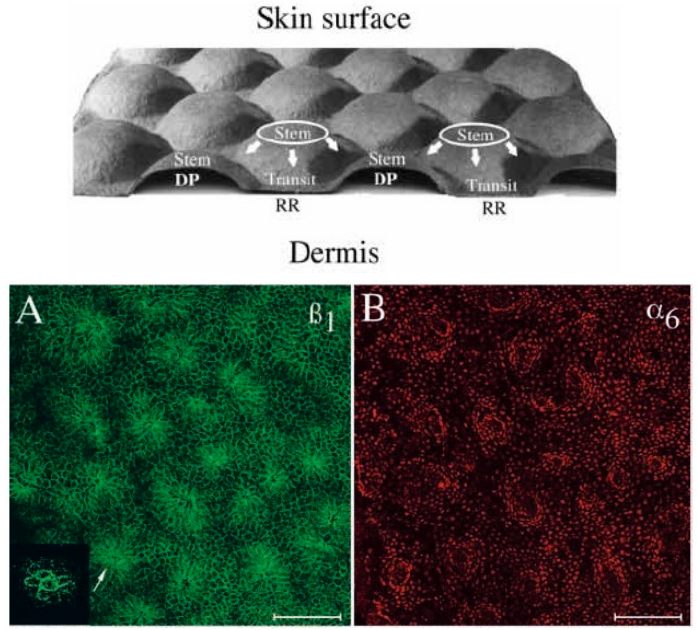
- Cells and tissues in vivo have reproducible shapes, size and geometries.
- In 2D cultures, cell shape is unconstrained.

Geometry, Structure and Function: Regulation of Epidermal Homeostasis



Alberts B. et al. The Molecular Biology of the Cell, 5th Edition

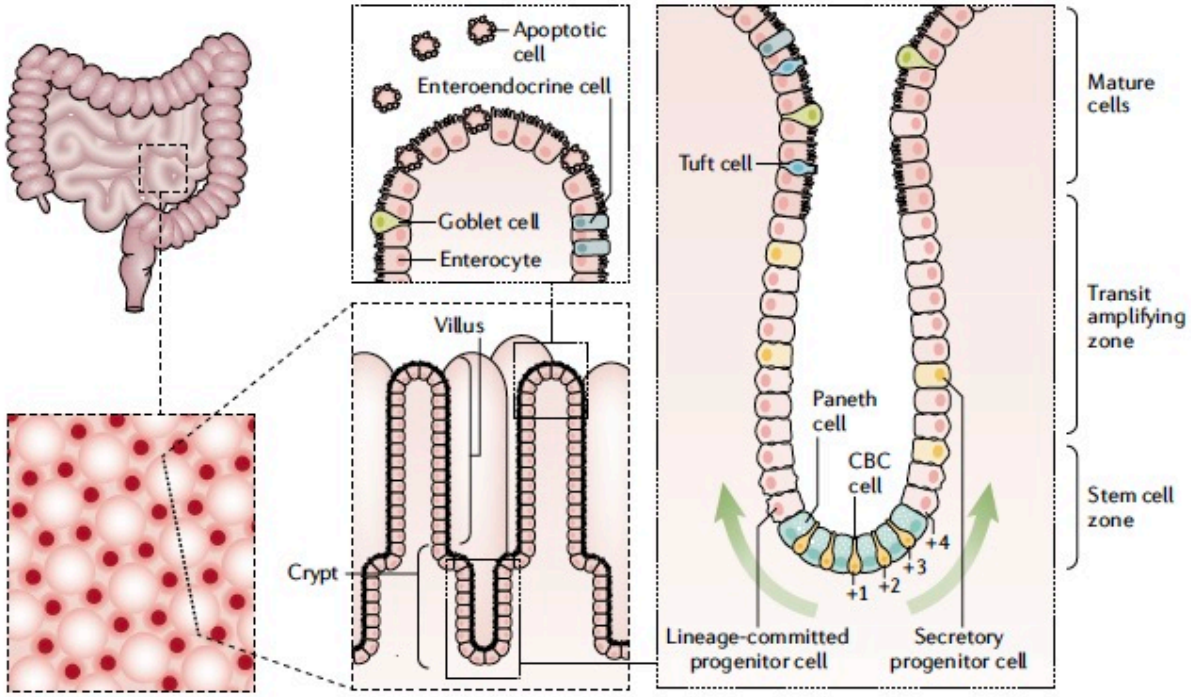




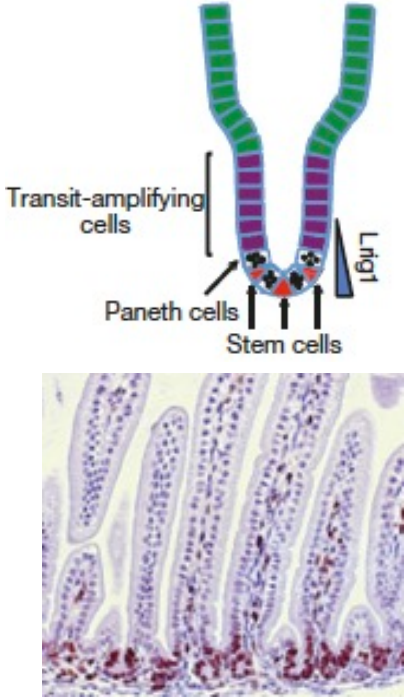
Jensen, U. et al. *Development* 126, 2409-2418 (1999)

- Stem cells in the interfollicular epidermis reside at the tip of ridges, directly adhering to the basement membrane (extra-cellular matrix) that separate the dermis from the epidermis.
- Integrin expression ensures adhesion of the epidermis to the basement membrane and tissue cohesion.
- Upon differentiation, cells migrate towards the bottom of the ridge, proliferate and lower integrin expression, ensuring their detachment and migration upward.

Stem Cell Niches Everywhere: Regulation of the Fastest Cycling Tissue, the Small Intestine



Gehart, H et al. *Nature Reviews* (2019) 16, 19-34

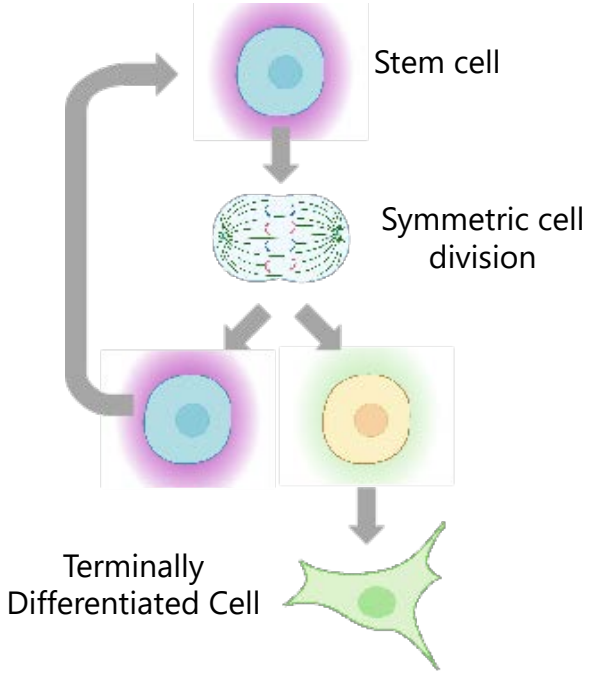


Wong, V et al. *Nature Cell Biol.* (2012) 14, 401

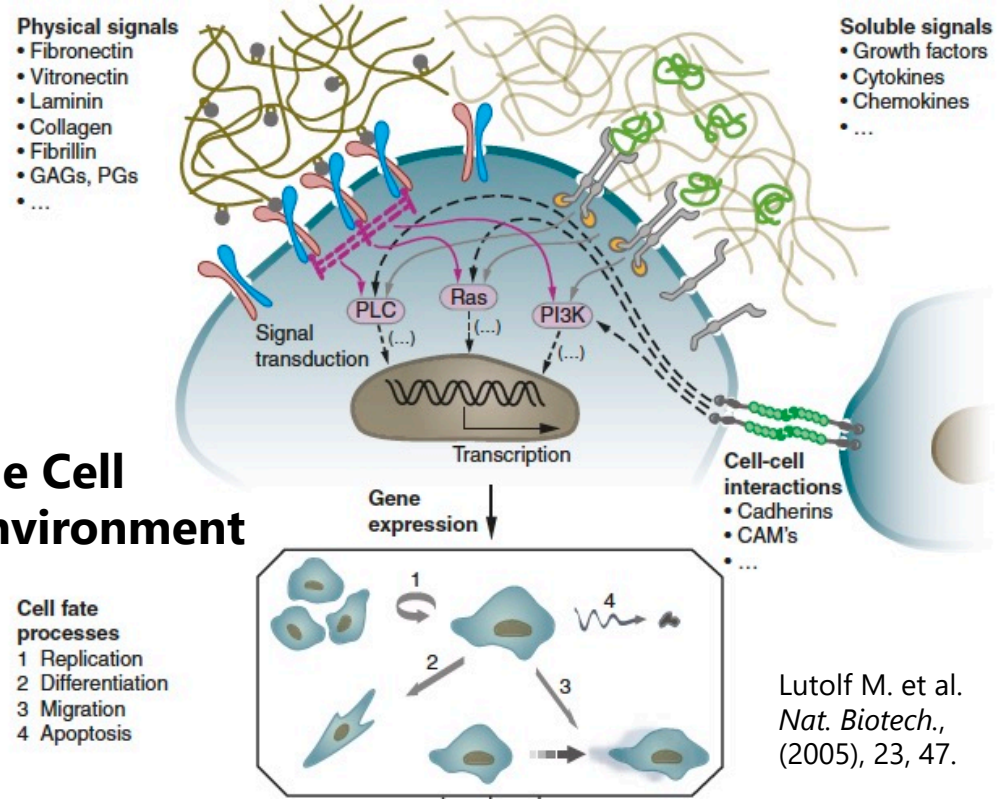
- The small intestine is highly patterned and Lrig1^{+} stem cells reside at the bottom of intestinal crypt.
- Their differentiation, followed by round of divisions (transit-amplifying) and migration upwards towards the top of villi, regulates intestinal homeostasis.

Stem Cell Niches and the Cell Microenvironment

Environmental asymmetry and stem cell fate decision



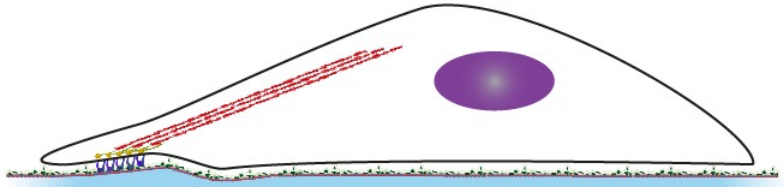
The Cell Microenvironment



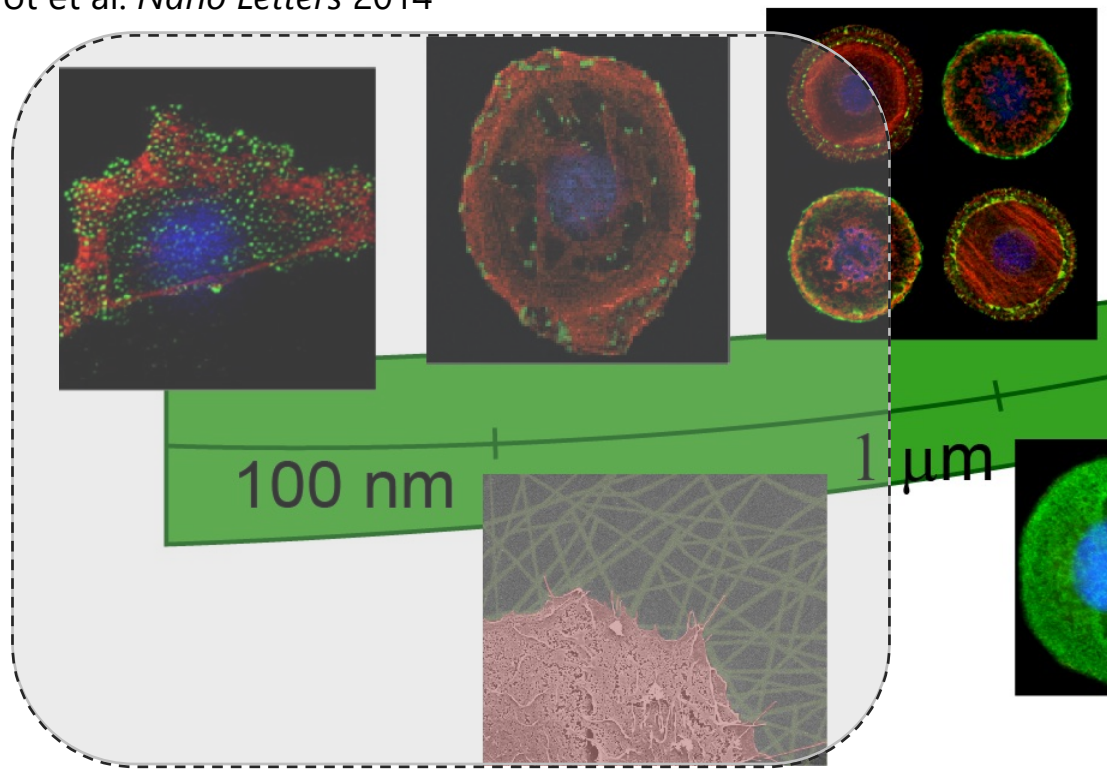
Lutolf M. et al. *Nat. Biotech.*, (2005), 23, 47.

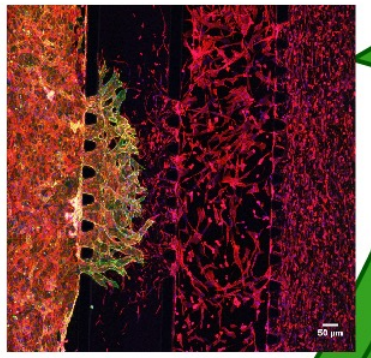
- The geometry and anisotropy of the cell microenvironment regulates stem cell phenotype and stem cell fate decision (retention of stemness versus differentiation).
- The microenvironment is a collection of factors (soluble, matrix, cell-cell adhesion) that modulate transcriptional activity, and in turn regulate cell phenotype.

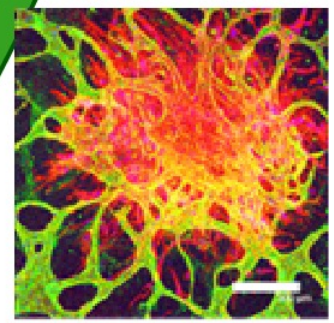
Engineering the Cell Microenvironment at Multiple Scales

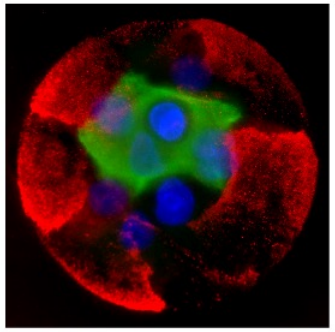


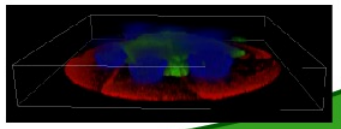
Kong et al. *ACS Nano* 2018
Kong et al. *Nano Letters* 2018
Trappmann, Gautrot et al. *Nat. Mater.* 2012
Costa et al. Acta Biomater. 2014
Gautrot et al. *Nano Letters* 2014

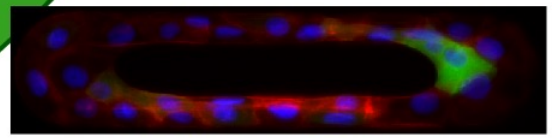


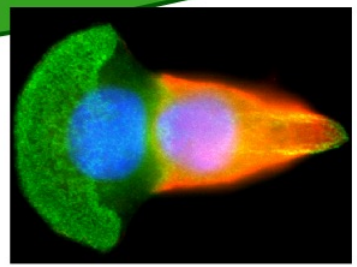


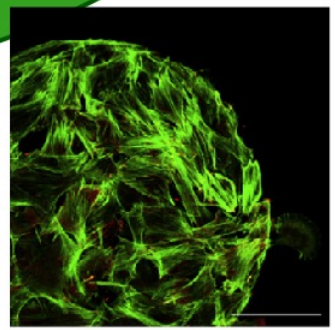










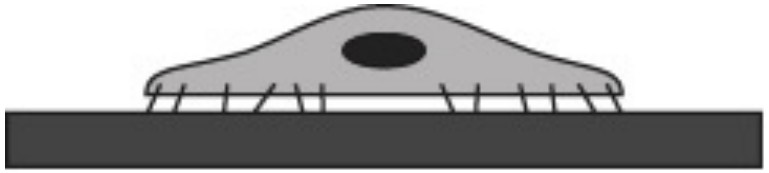


100 µm

1 mm

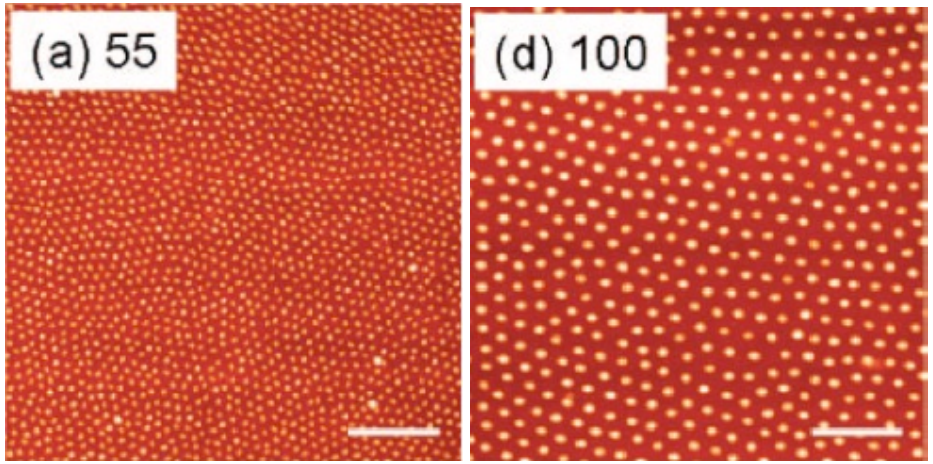
Colak et al. Biomacromolecules 2018
Di Cio et al. *Acta Biomat.* 2016
Di Cio et al. *Acta Biomat.* 2017
Tan et al. Integ. Biol. 2013
Connelly et al. *Nat. Cell Biol.* 2010
Gautrot et al. *Biomaterials* 2012

1. Multiple Physical Signals Control Integrin-Mediated Adhesions



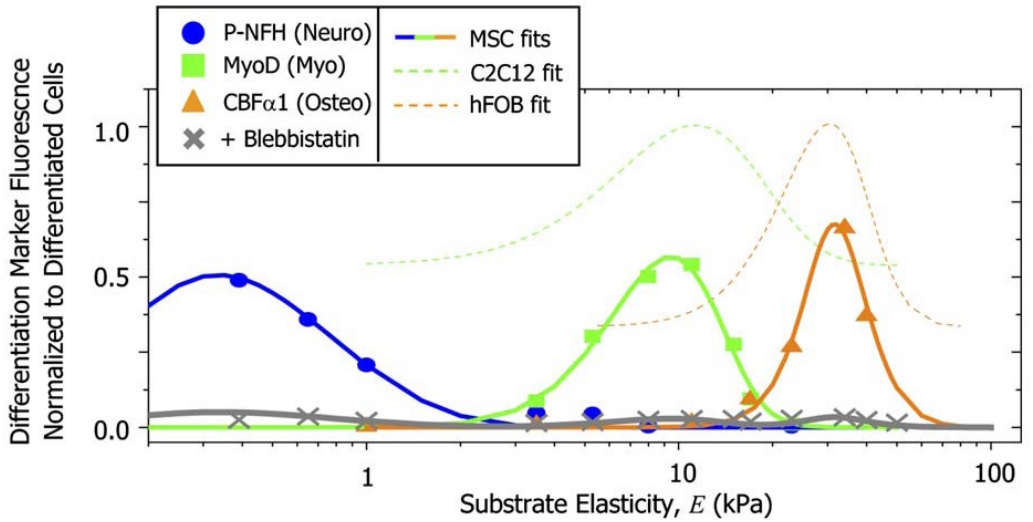
Integrins anchor cells to the extra-cellular matrix (ECM)

Geometry



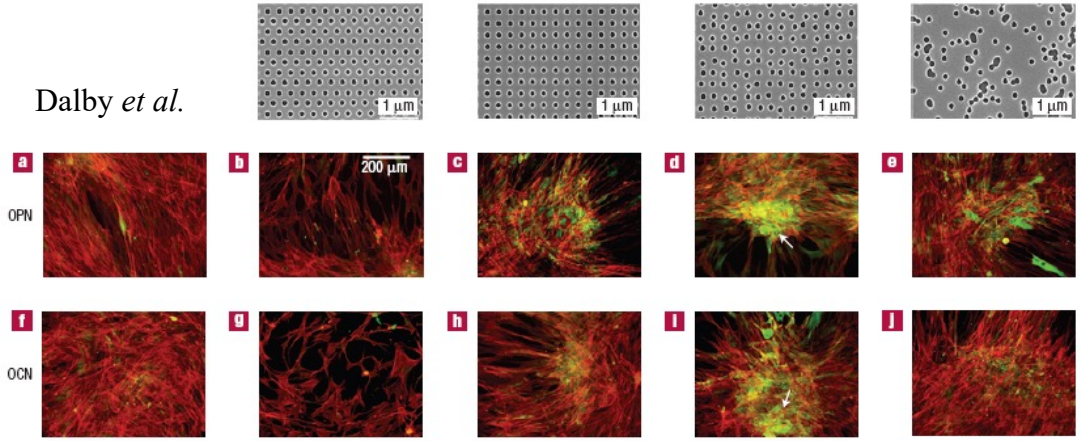
Spatz *et al.*

Mechanical Properties

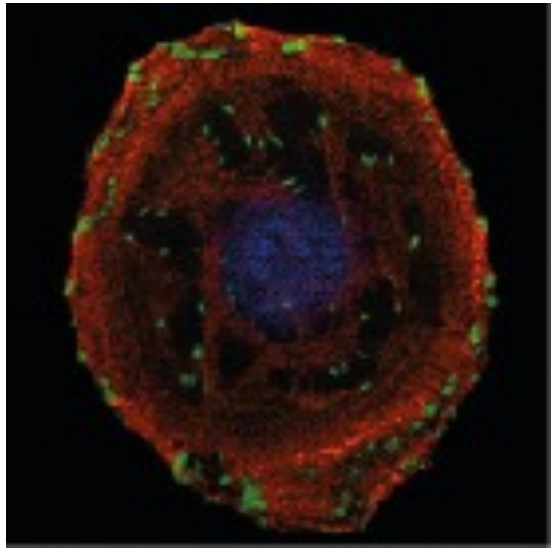


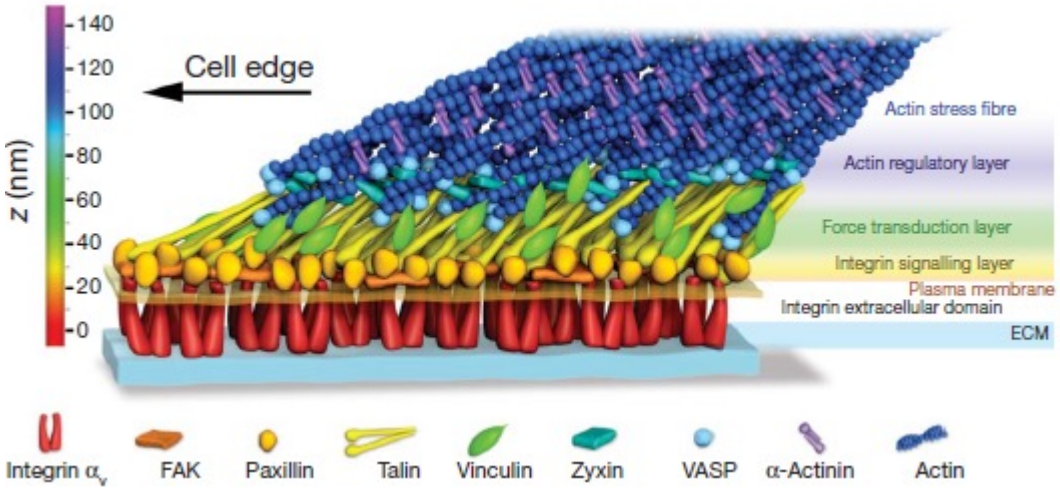
Topography (3D Geometry)

Dalby *et al.*



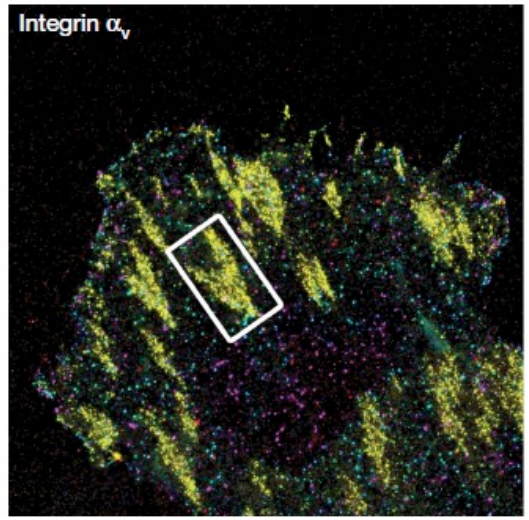
1. Mechanisms of Nano-Scale Topography and Geometry Sensing ?



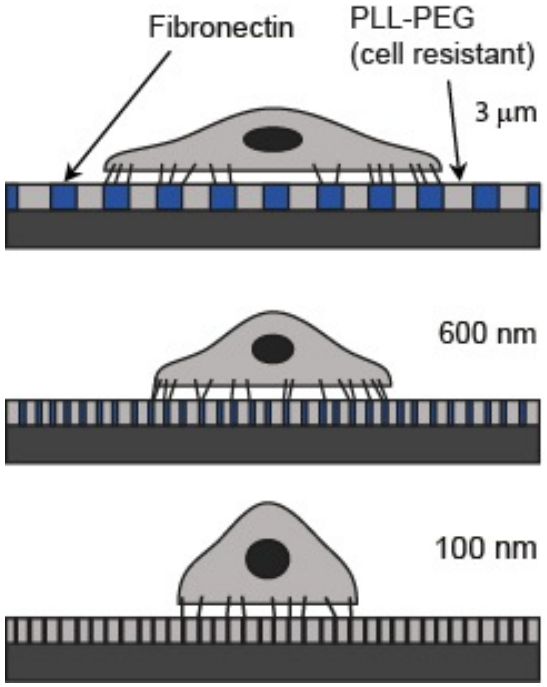


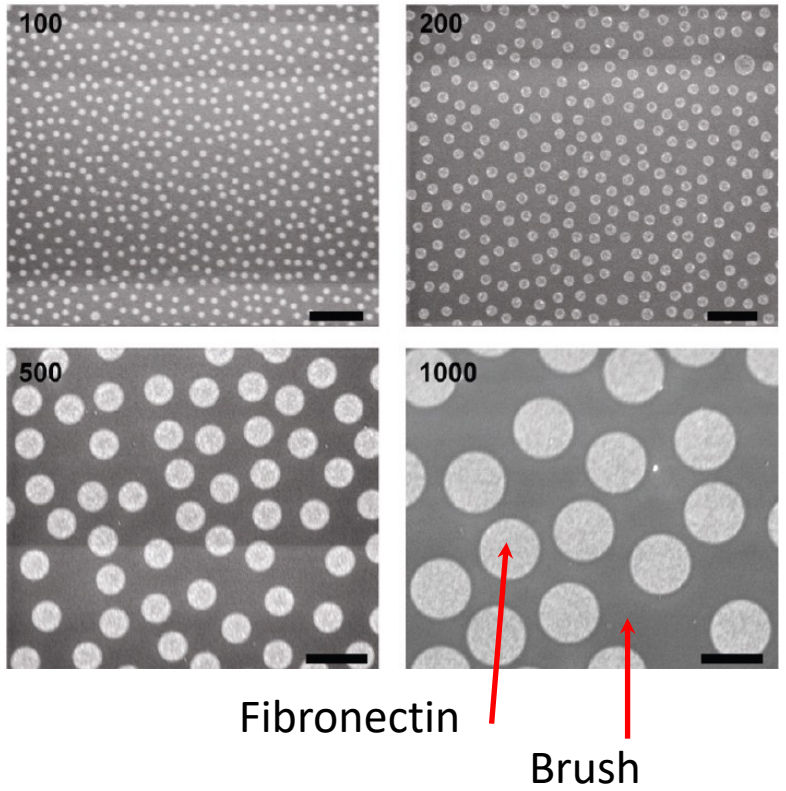
Kanchanawong, Shtengel et al. *Natures*, 2010, 580.

- Focal adhesions are micron-size molecular complexes with apparent nano-scale lateral homogeneity, but highly structured in the z-direction.
- How does nano-topology and topography impact the formation of focal adhesions?



1. Nano-Patterning Substrates for Controlling Cell Adhesion

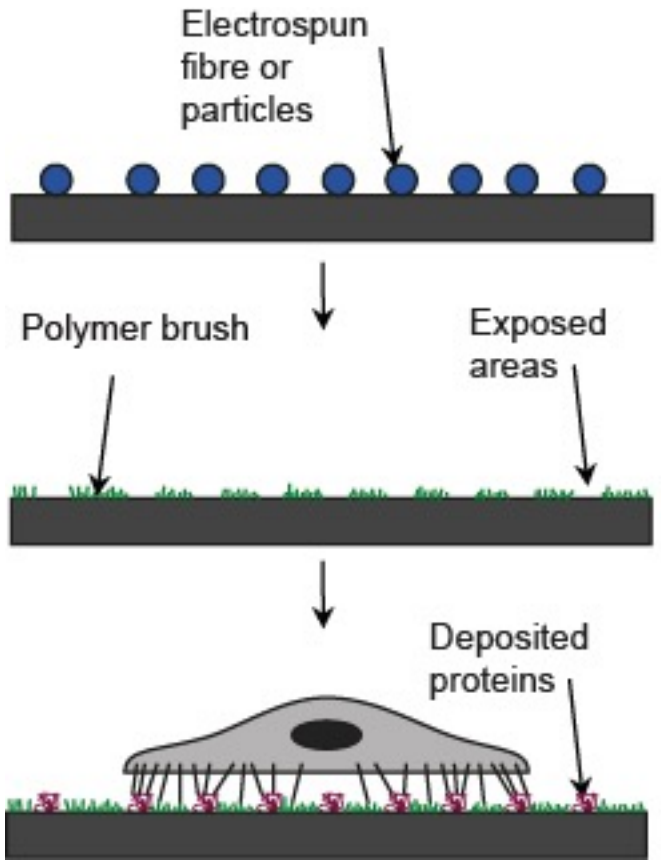


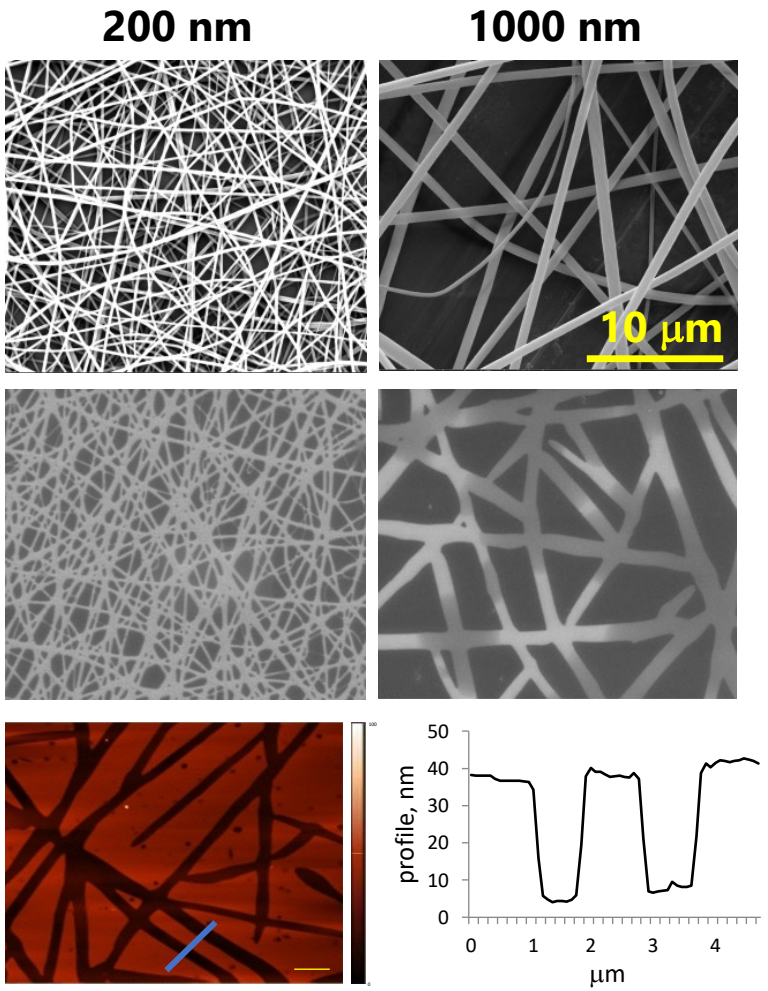


- Patterning of nano-sized gold patches using colloidal lithography.
- Background protection using polymer brushes with high protein resistance.
- Deposition of fibronectin or other ECM proteins on the patch, directly from solution.

Duncan Sutherland
Jenny Malmstrom
Nano Letters, 2010
Nano Letters, 2011

1. Electrospun Nanofibre Lithography to Generate Fibrillar Nanopatterns

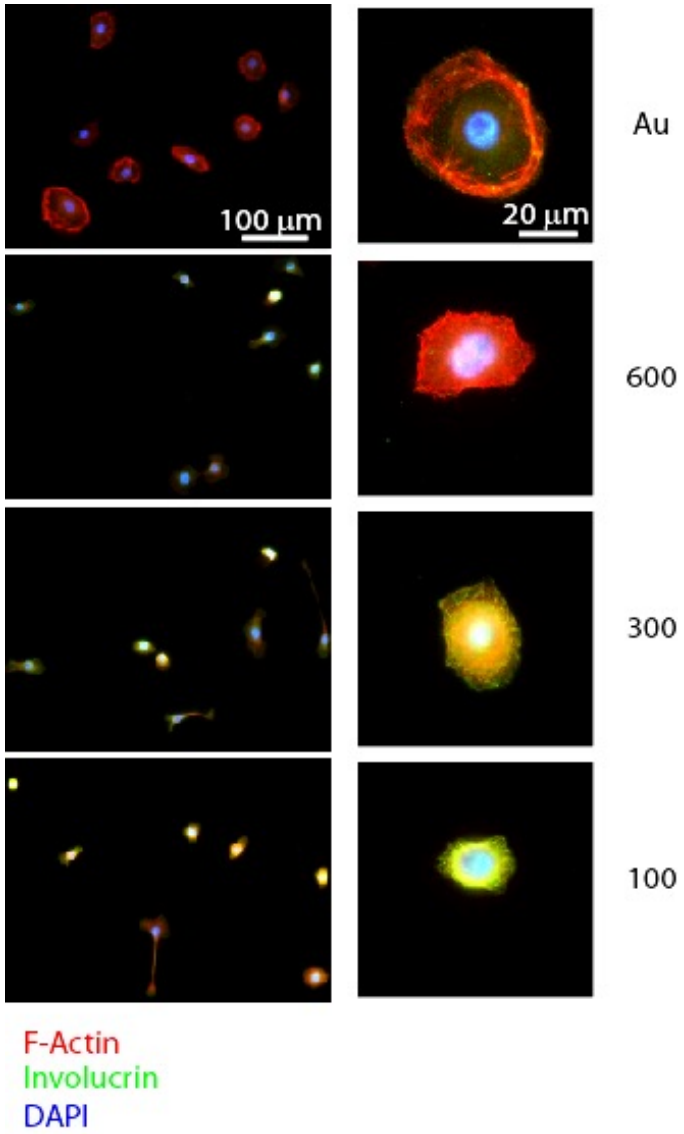


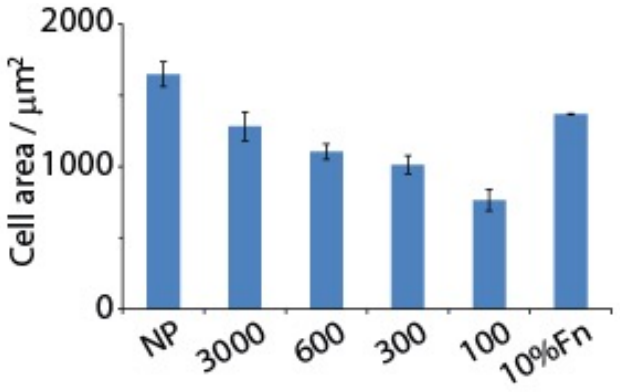


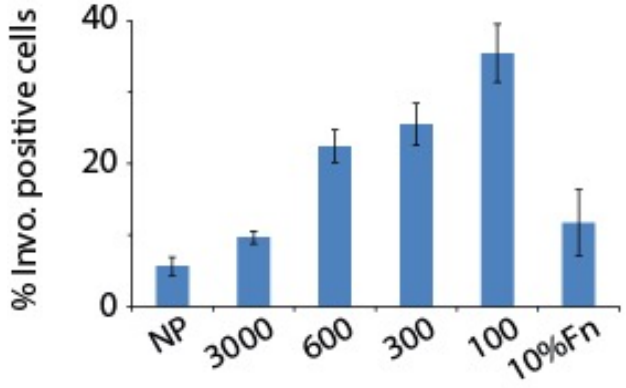
Di Cio et al. *Acta Biomaterialia* 2017

- Electro-spinning of PMMA fibres on initiator functionalised substrates followed by brush growth.
- Method suitable for controlling fibres size and patterning of large scale substrates.

1. Size of Fibronectin Nano-Patterns Correlates with Differentiation



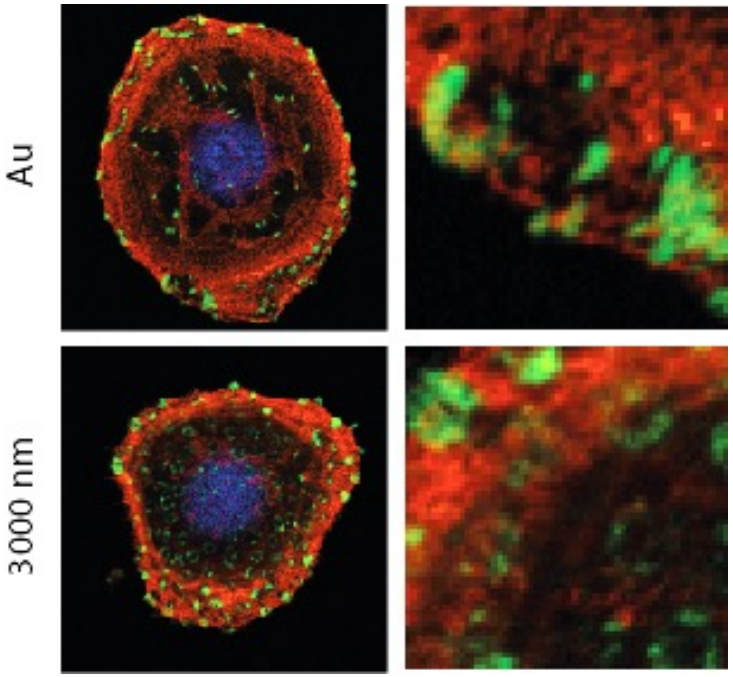




Gautrot et al. *Nano Letters* 2014

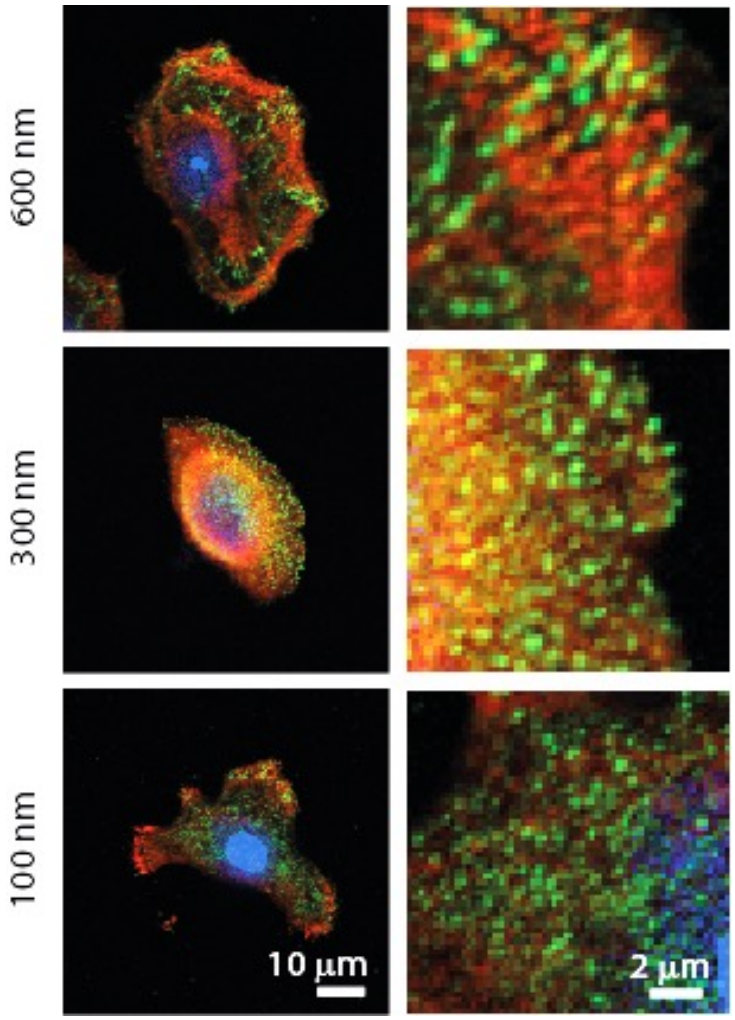
- Cell spreading is gradually impaired by the size of ECM patches.
- Nano-size confinement of focal adhesions restricts cell adhesion and triggers keratinocyte differentiation.

1. Controlled Size of Adhesions Formed



Gautrot et al. *Nano Lett.* 2014

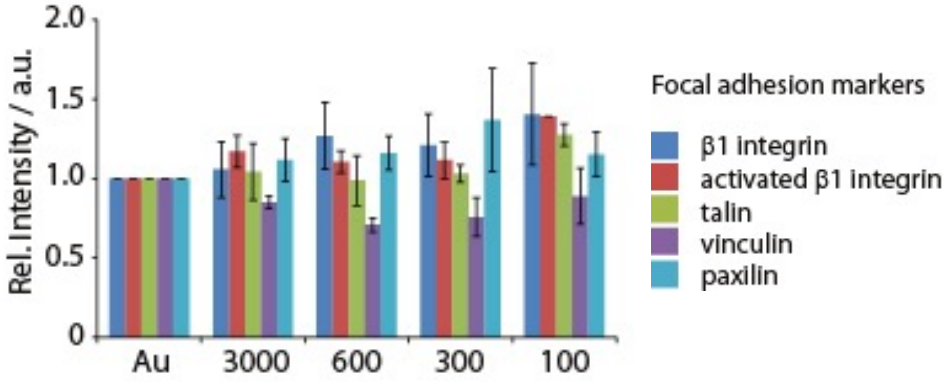
- The size of cell adhesions follows closely the size of fibronectin patches.
- The recruitment of vinculin does not seem to be affected by nanoconfinement.



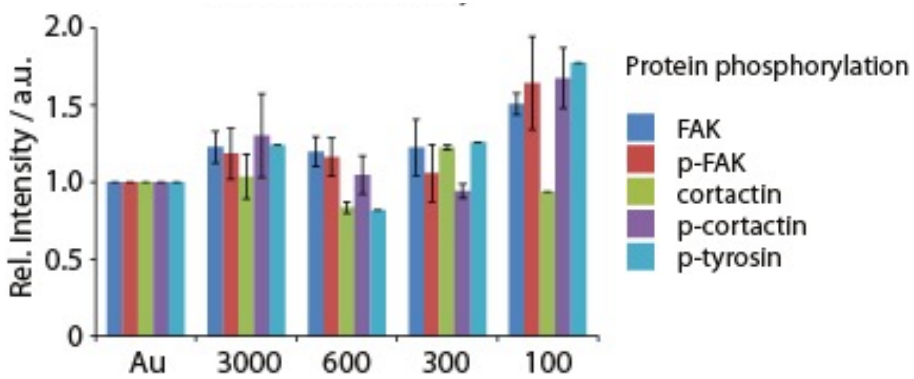
Vinculin Myosin IIa

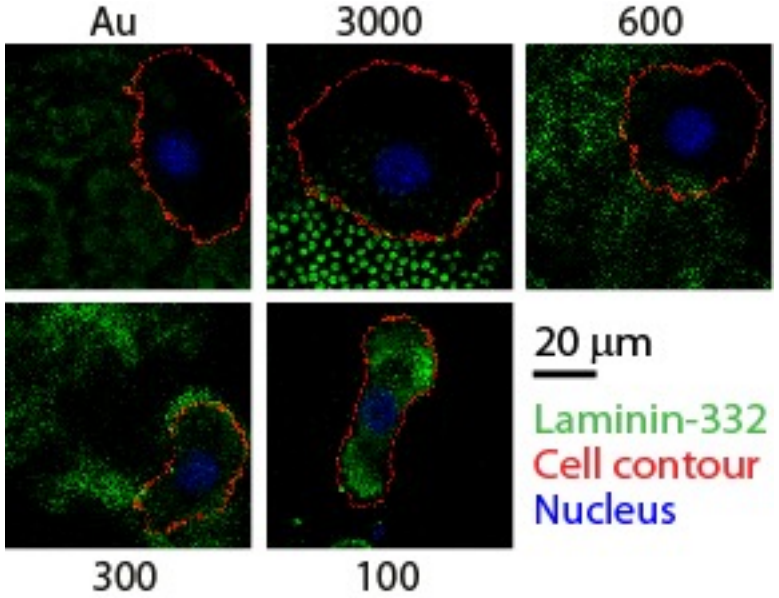
1. Biochemical Maturity of Adhesion Sites

Focal adhesion recruitment



Impact of nano-scale on protein phosphorylation



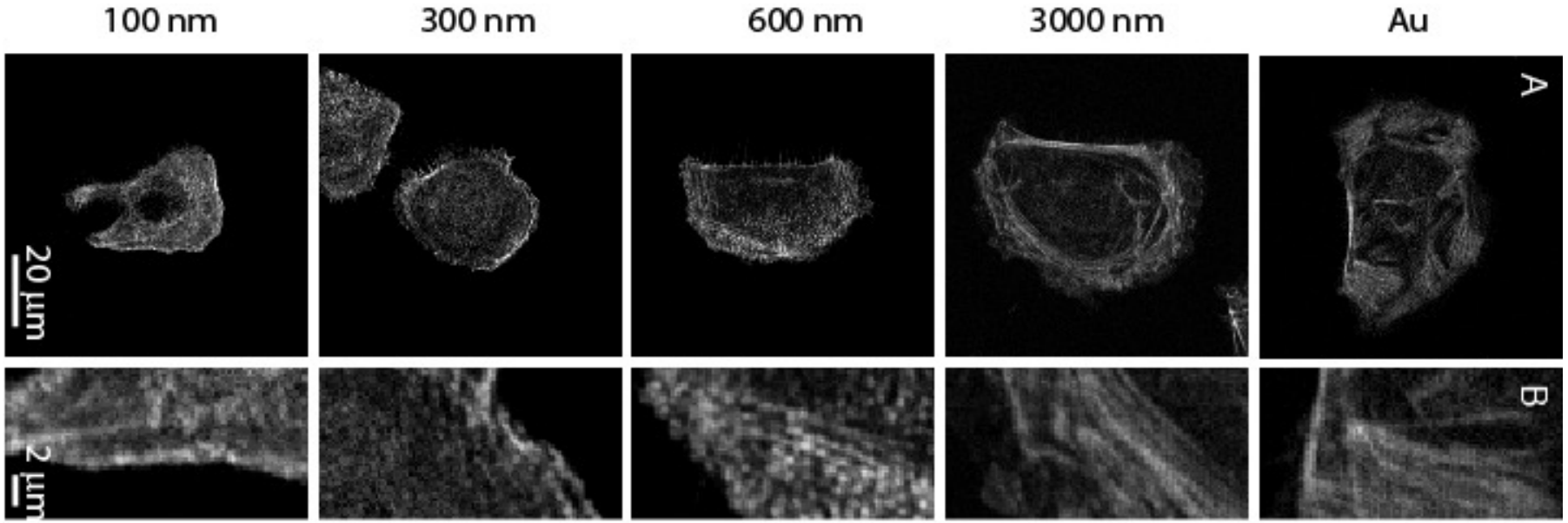


- Focal adhesions formed on nanopatterned ECM are relatively mature from a biochemical point of view.
- However cell spreading is clearly impacting by nanoconfinement of ECM.
- What is inhibiting cell spreading?

Laminin deposition

Gautrot et al. *Nano Lett.* 2014

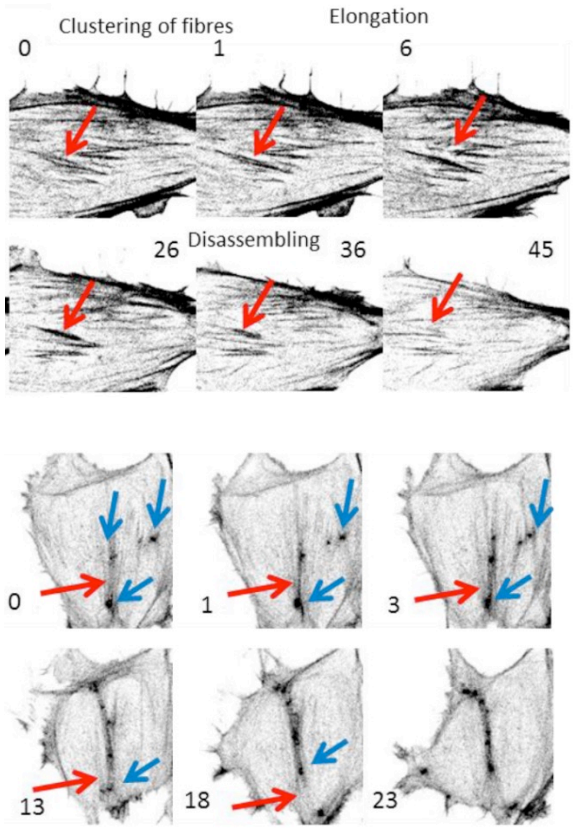
1. Impact on Cytoskeleton Assembly



- Clear decrease in F-actin cytoskeleton assembly as nano-pattern size is decreased.
- Could this be associated with a change in dynamics of adapter proteins or cytoskeleton assembly?

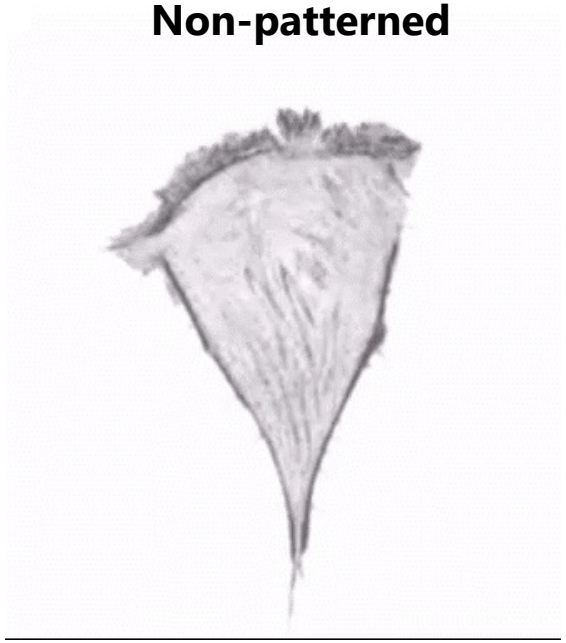
1. Changes in Actin Dynamics and Formation of Actin Foci

Non-patterned



1000 nm fibres

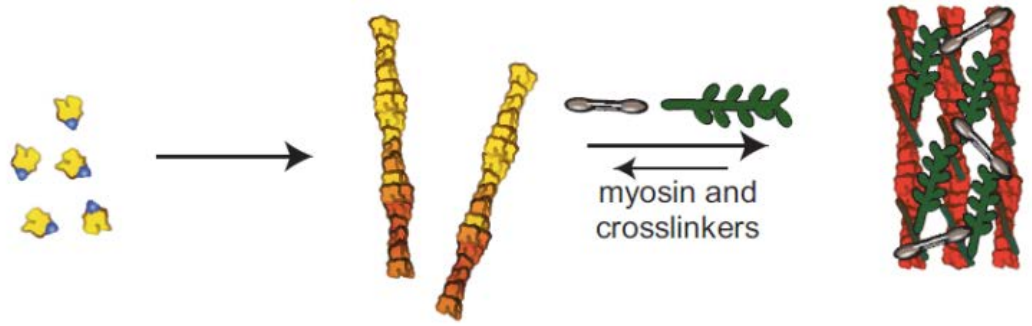
Non-patterned



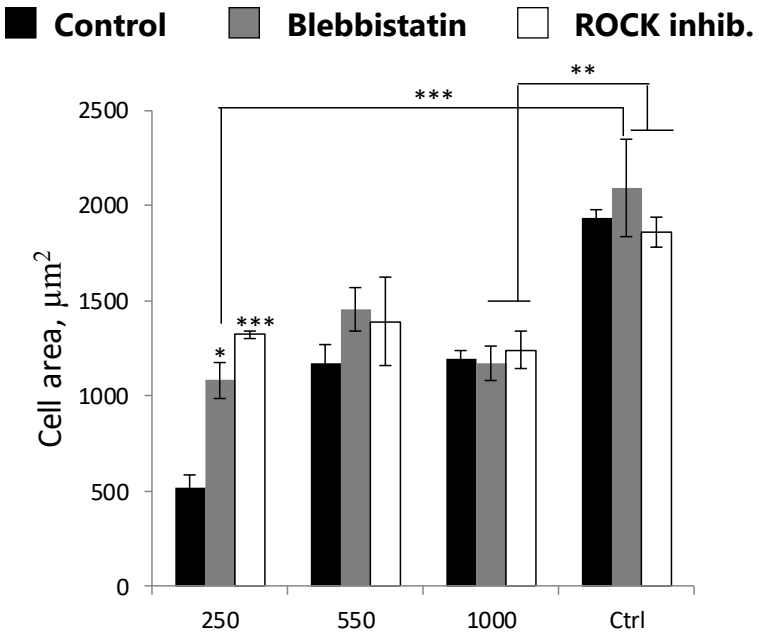
1000 nm fibres

- Actin dynamics is strongly affected by the nanotopography of the substrates.
- In β3 integrin expressing cells, the catastrophic collapse of the actin networks occurs, resulting in the formation of actin foci.

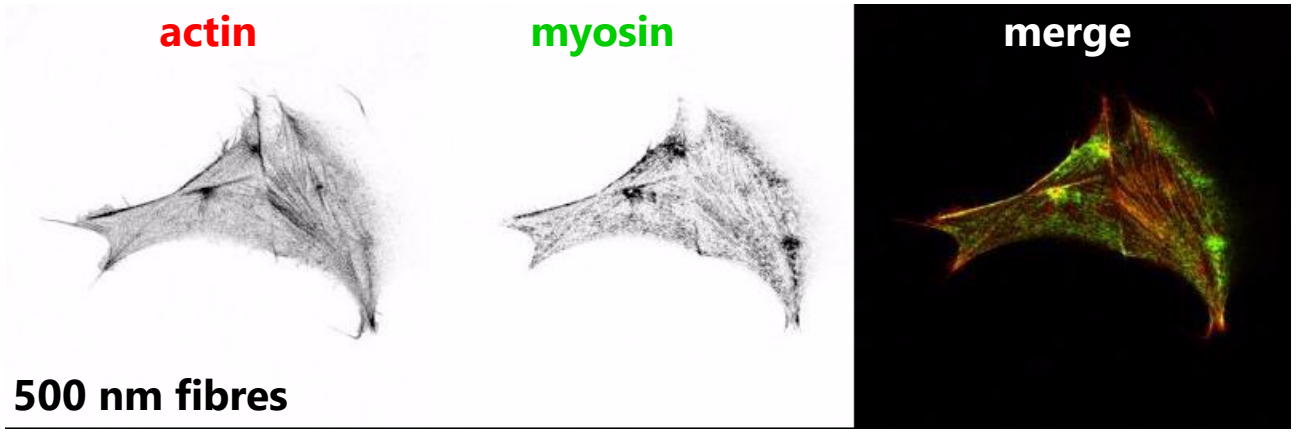
1. Actin Foci are surrounded by a Contractile Myosin Ring



Blanchoin et al. Physiol Rev 94: 235–263, 2014



- Cells treated with the myosin inhibitor blebbistatin or the ROCK inhibitor (disrupting actin polymerisation) become unaffected by the nanotopography.
- Myosin also seems to be recruited at actin foci and forms rings around the foci.



Queen Mary University of London

nature materials

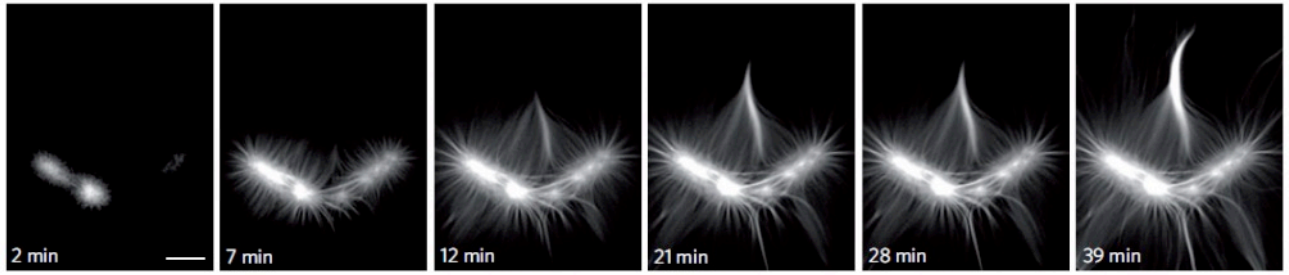
LETTERS

PUBLISHED ONLINE: 19 SEPTEMBER 2010 | DOI: 10.1038/NMAT2855

Nucleation geometry governs ordered actin networks structures

Anne-Cécile Reymann[1], Jean-Louis Martiel[1,2], Théo Cambier[1], Laurent Blanchoin[1], Rajaa Boujemaa-Paterski[1]* and Manuel Théry[1]*

NATURE MATERIALS | VOL 9 | OCTOBER 2010 | www.nature.com/naturematerials

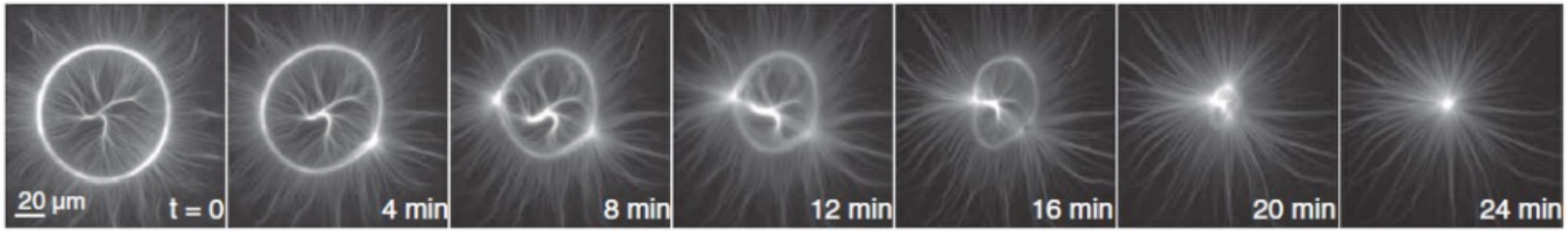


Science

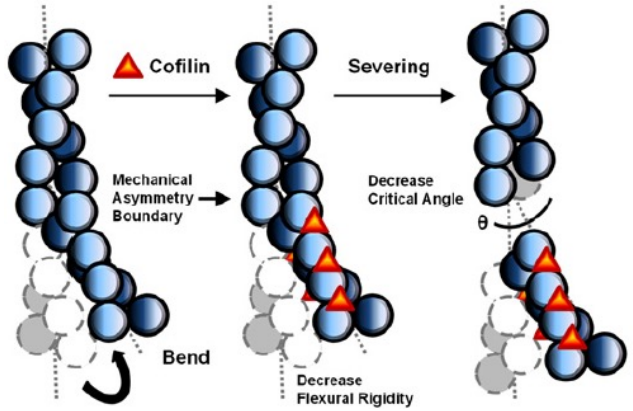
AAAS

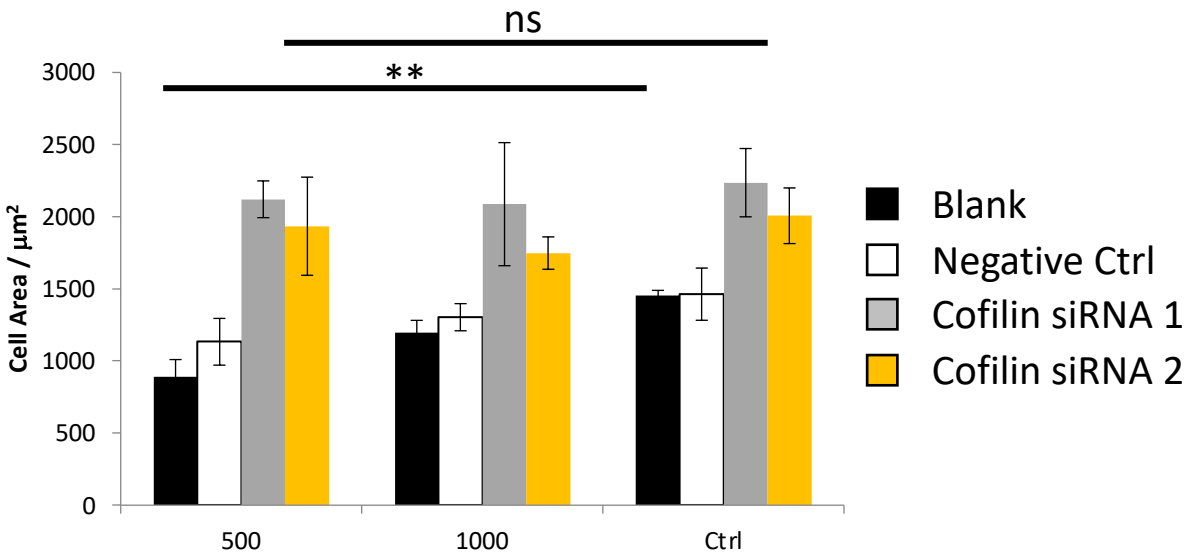
Actin Network Architecture Can Determine Myosin Motor Activity

Anne-Cécile Reymann *et al.*
Science **336**, 1310 (2012);
DOI: 10.1126/science.1221708

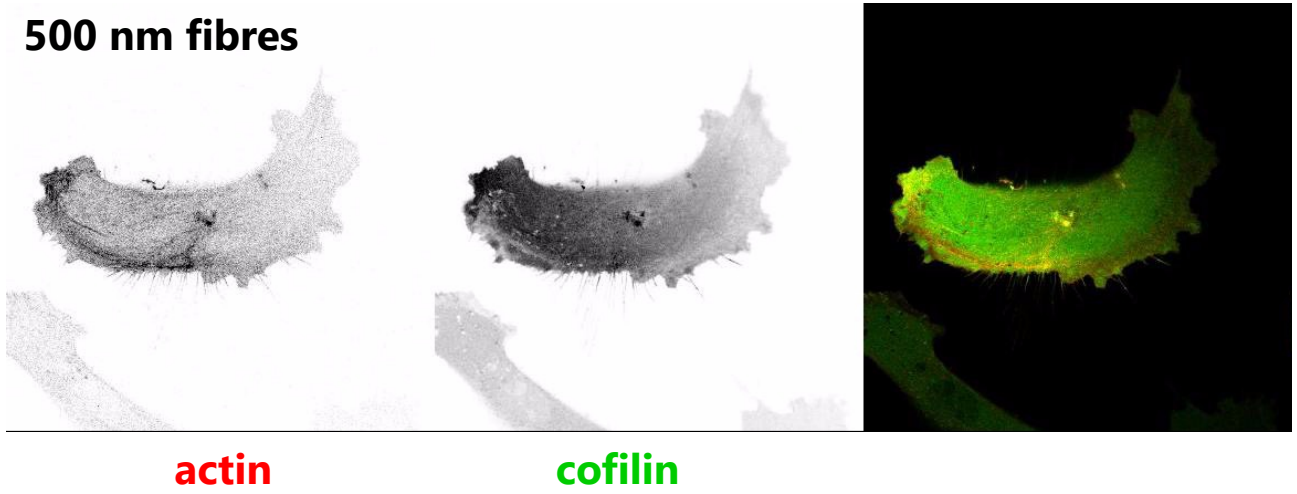


1. Cofilin Orchestrates the Actin Disassembly and Nanotopography Sensing





- Cofilin knock down also results in a lack of sensitivity to nanotopography and enhances overall cell spreading.
- Co-localisation live imaging studies confirmed that cofilin was recruited at actin foci.



1. The Actin Network Orchestrates Nanotopography Sensing

FAs

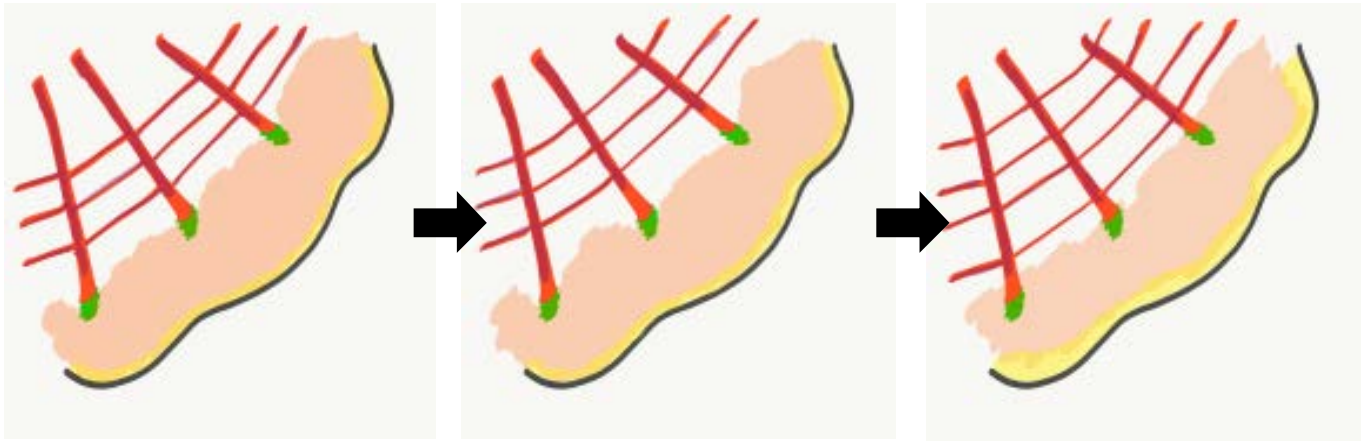
Actin gel

Stress fiber

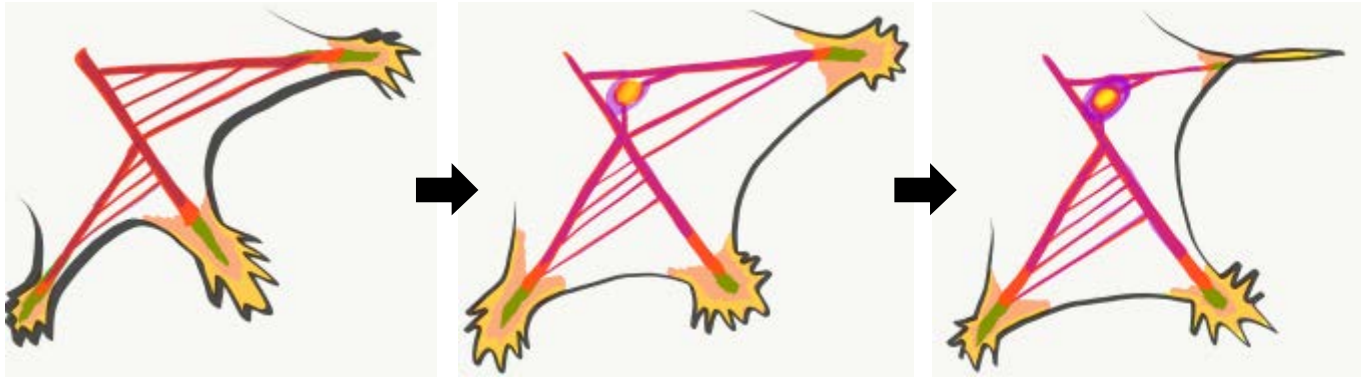
Myosin

Cofilin

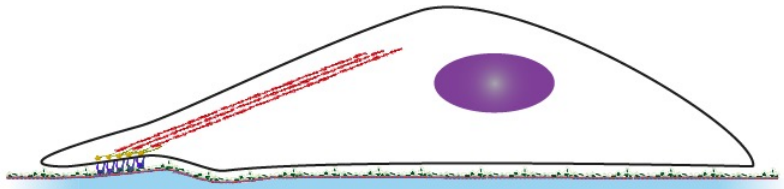
On Homogenous Substrates



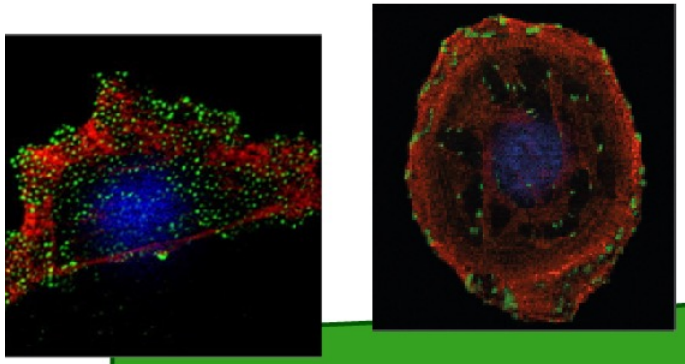
On Nanofibrous Substrates



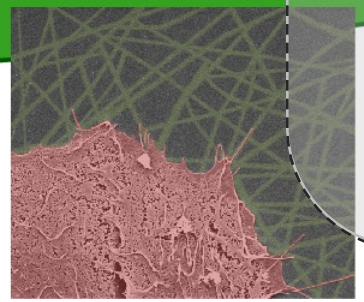
Engineering the Cell Microenvironment at Multiple Scales

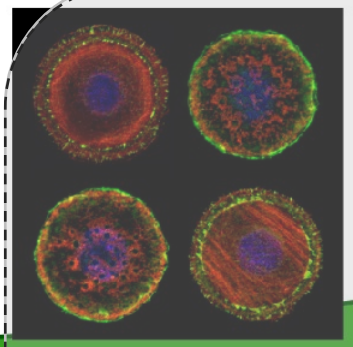


Kong et al. *ACS Nano* 2018
Kong et al. *Nano Letters* 2018
Trappmann, Gautrot et al. *Nat. Mater.* 2012
Costa et al. Acta Biomater. 2014
Gautrot et al. *Nano Letters* 2014

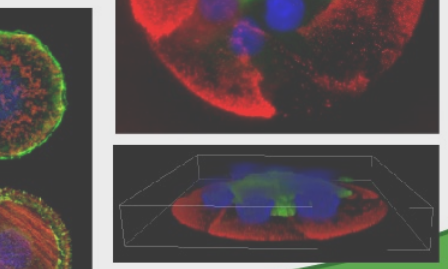


100 nm

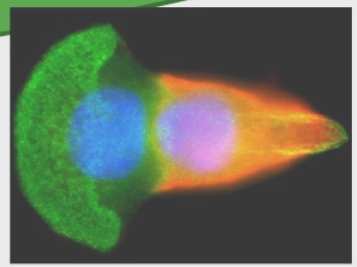


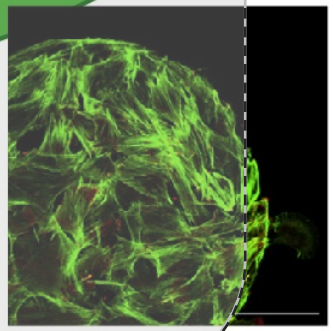


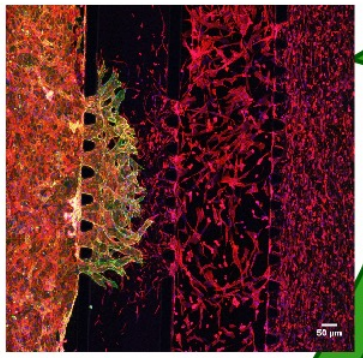
1 µm



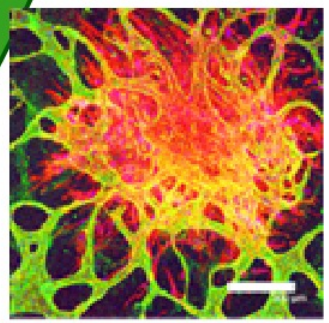
100 µm

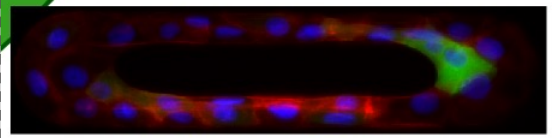






1 mm

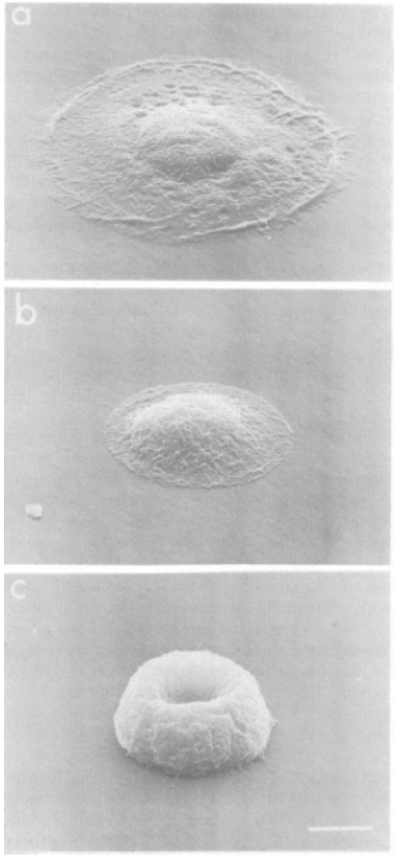


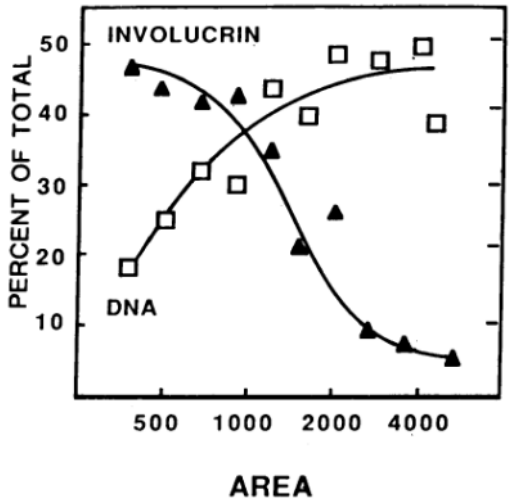


Colak et al. Biomacromolecules 2018
Di Cio et al. *Acta Biomat.* 2016
Di Cio et al. *Acta Biomat.* 2017
Tan et al. Integ. Biol. 2013
Connelly et al. *Nat. Cell Biol.* 2010
Gautrot et al. *Biomaterials* 2012

2. Cell Shape Regulates Cell Function

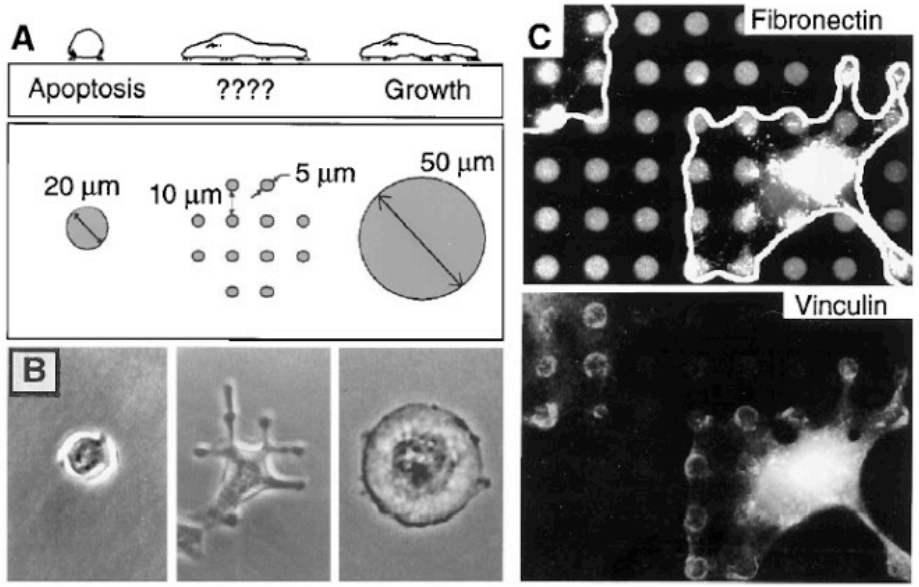
Differentiation





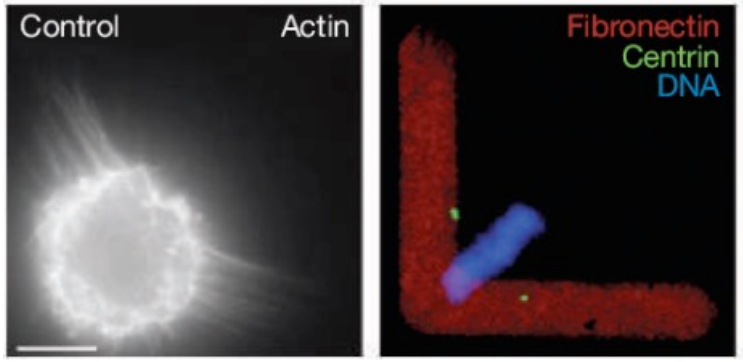
Watt et al. PNAS (1988), *85*, 5576.

Apoptosis



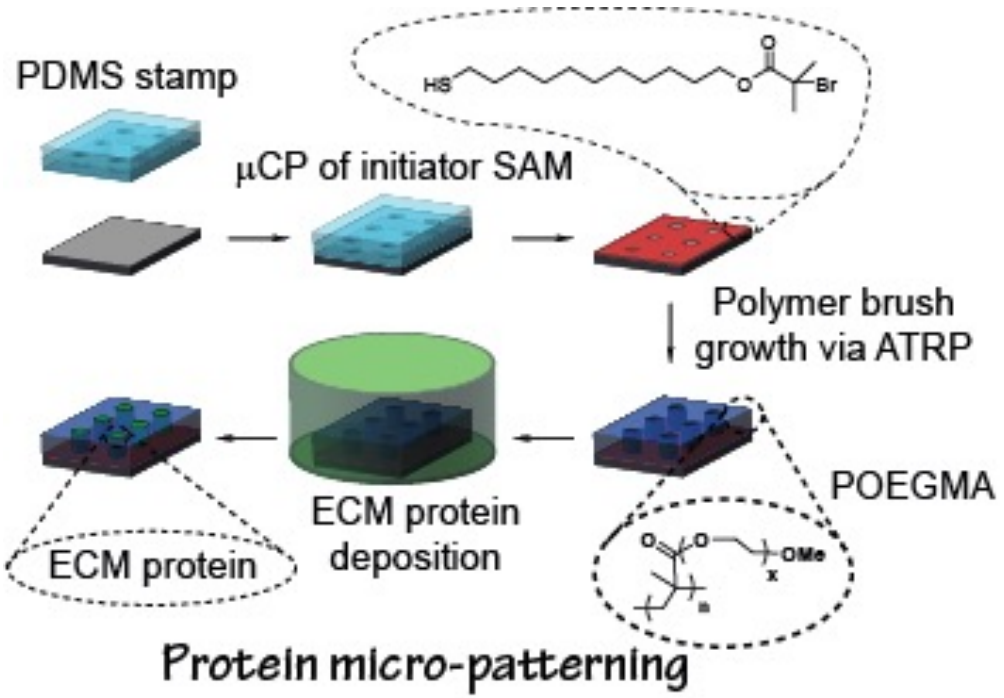
Chen et al. Science (1997), *276*, 1425

Division

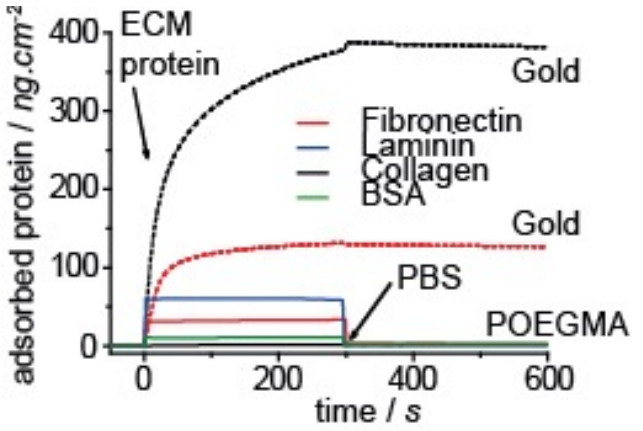


Thery et al. Nat. Cell Biol. (2005), *7*, 947

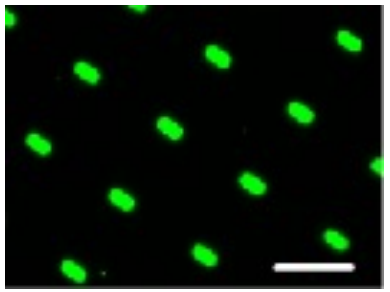
2. Protein Micro-Patterning using Polymer Brushes



Protein micro-patterning



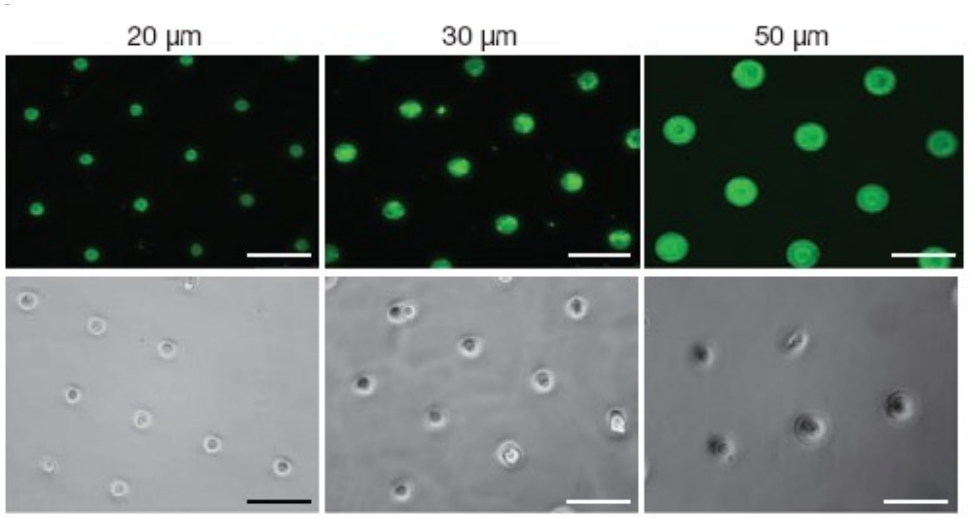
Protein resistance examined by SPR



Gautrot et al.
Biomaterials 2010

- Brushes can be patterned to restrict protein adsorption to defined areas.
- Use of ultra-low fouling protein resistant polymer brushes.
- Efficient and simple patterning of proteins with μm-resolution.

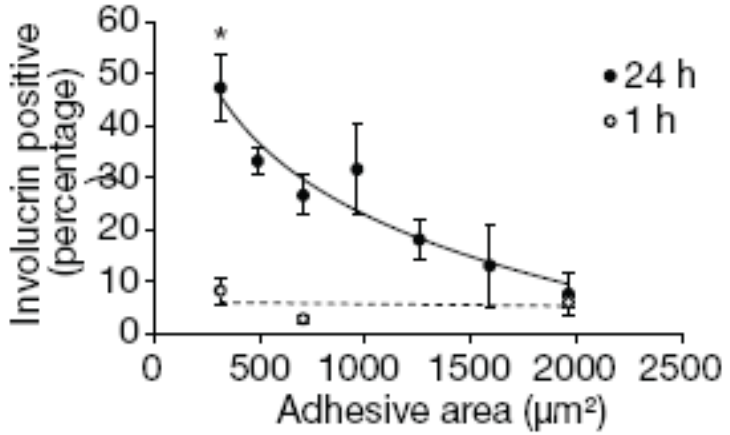
2. Shape Induced Differentiation Assay



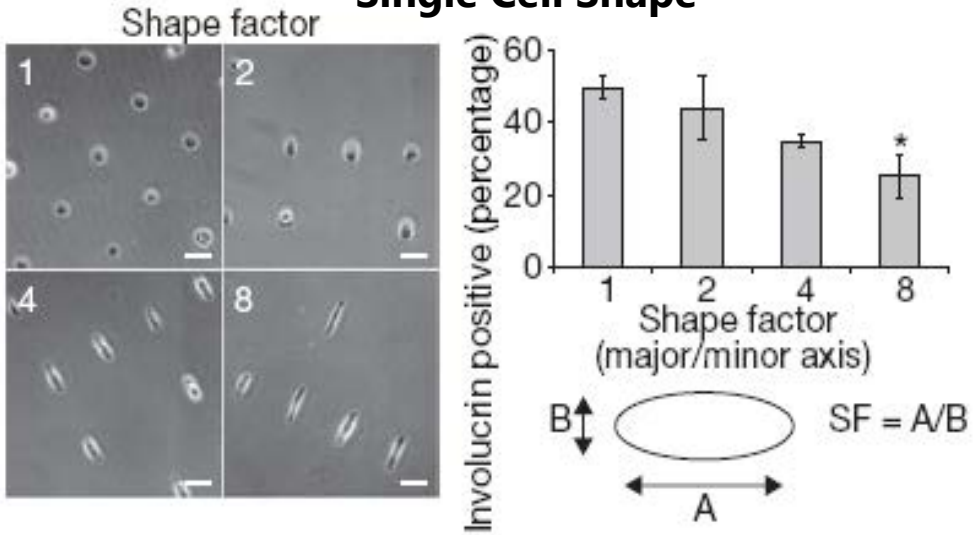
Connelly, Gautrot et al. *Nature Cell Biology* 2010

- ECM protein patterns (based on collagen or fibronectin) guide the formation of cell adhesions and control cell spreading.
- Cell adhesive islands area and shape directs cell spreading and shape.
- This in turn affects cell behaviour and differentiation.

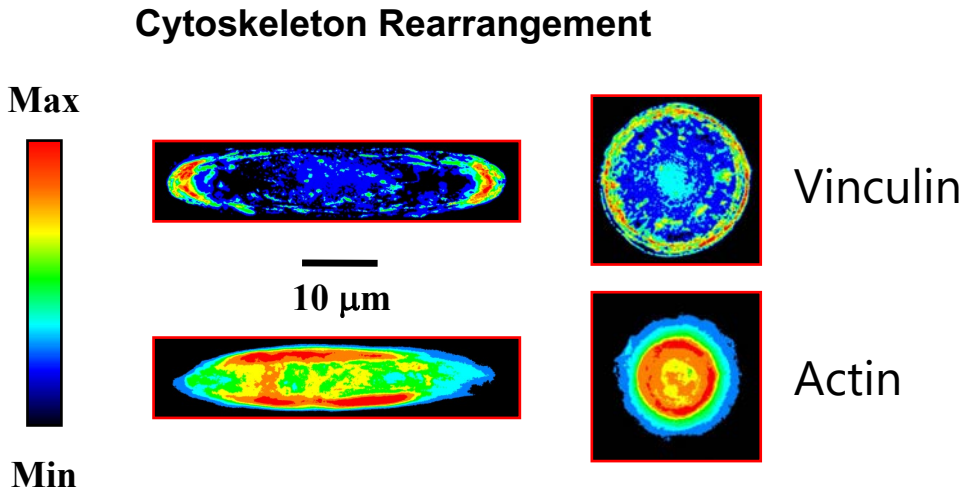
Single Cell Spreading Area

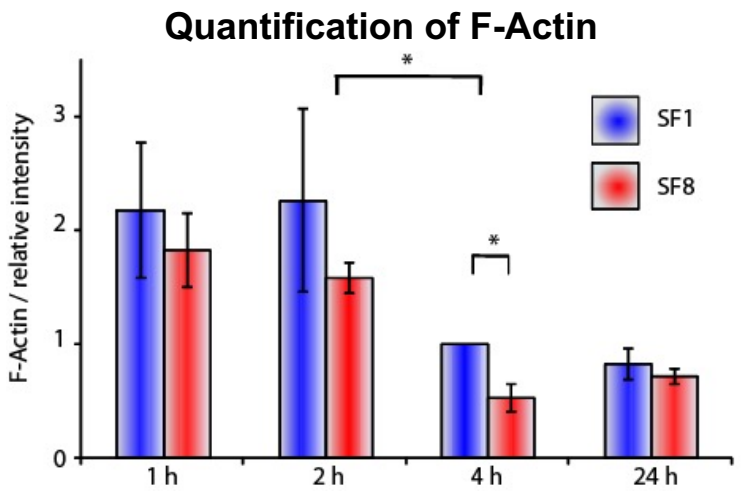


Single Cell Shape

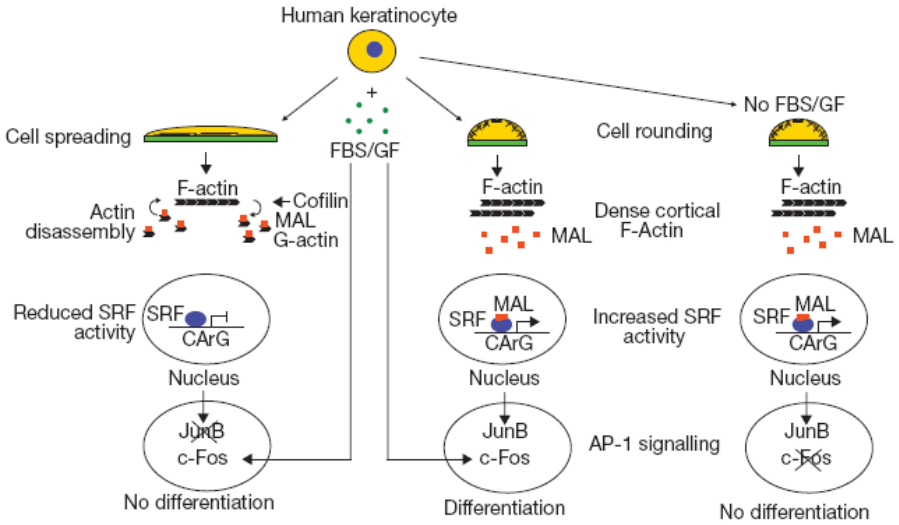


2. Cytoskeletal Reorganisation Directly Regulates Differentiation Through MAL/SRF





- Changes in cell shape are associated with a complete rearrangement of the actin cytoskeleton.
- Counter-intuitively, the pool of F-actin is enhanced on small rounded islands/cells.
- This leads to the release of the co-factor MAL, which can translocate to the nucleus and regulate SRF and downstream genes controlling differentiation in keratinocytes.

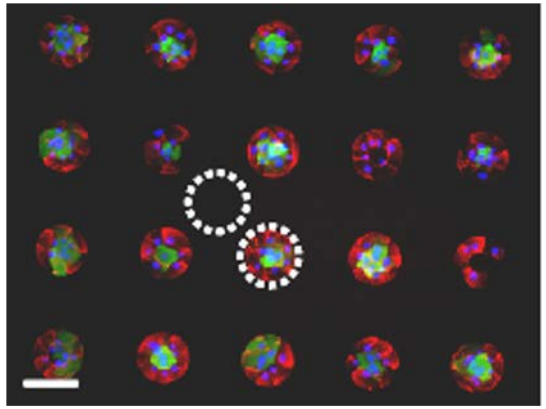


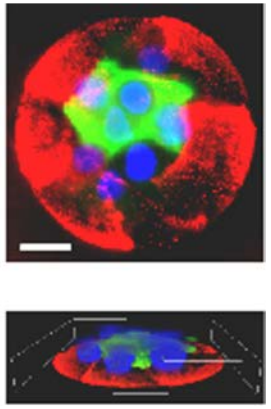
Connelly, Gautrot et al. *Nature Cell Biology* 2010

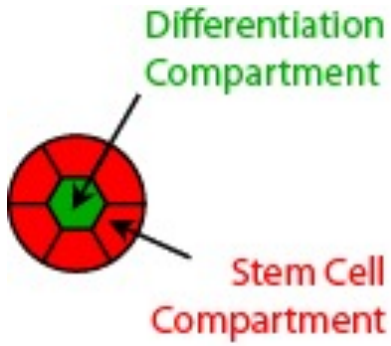
Queen Mary University of London

2. Engineering of Compartmented Micro-Epidermis

Compartmented cell cluster arrays

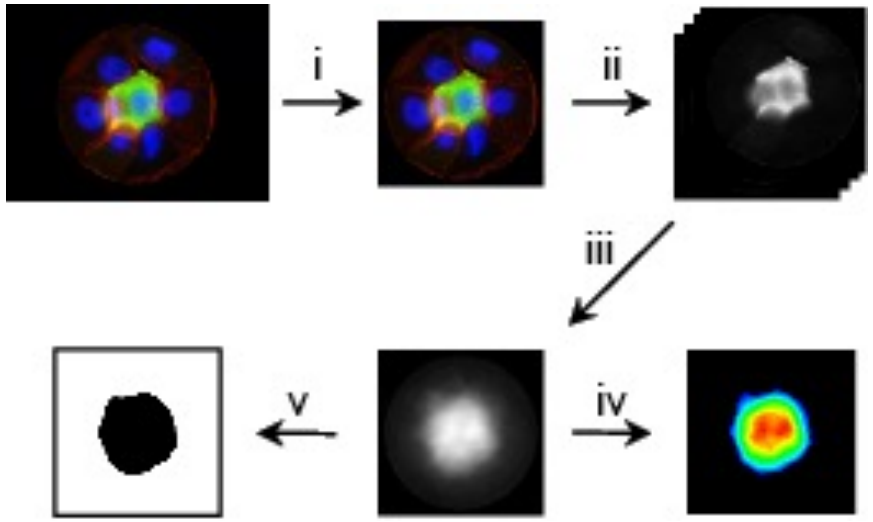






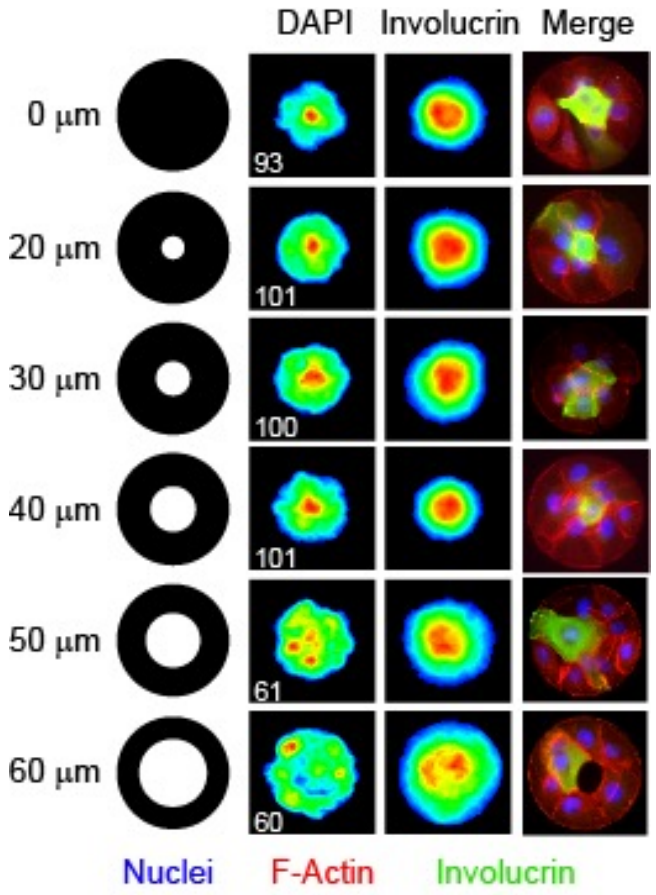
Gautrot et al. *Biomaterials* 2012.

Generation of heatmaps/quantification

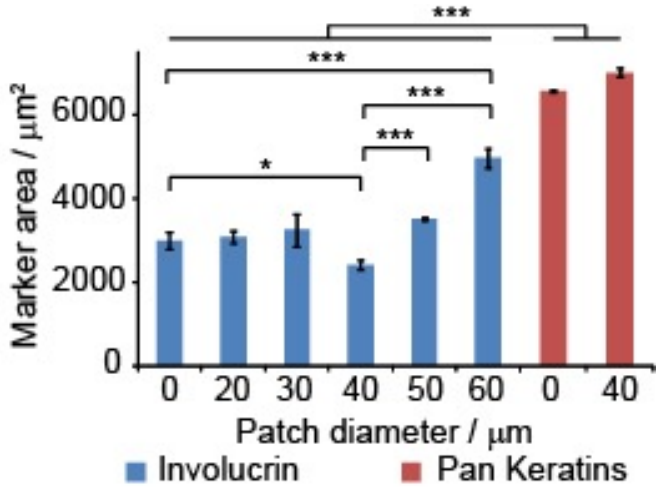


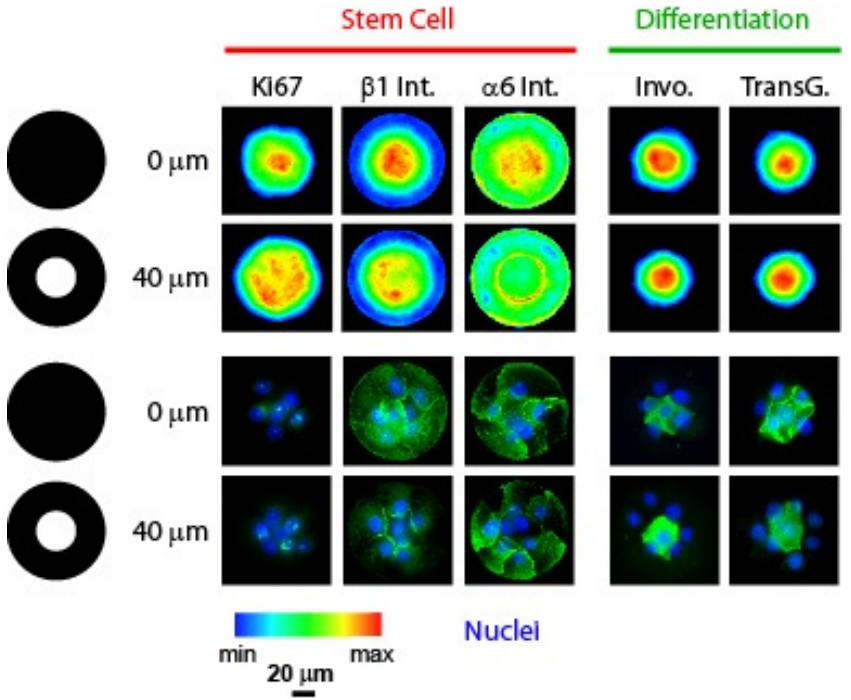
- Larger cell adhesive ECM protein patterns (100 μm) allow the formation of micro-array of cell clusters containing in average 5-10 cell.
- Images allow the quantification of the expression level of specific proteins or markers.
- In addition, images allow the generation of heatmaps conveying information regarding the localisation of cell populations within the cluster.

2. Island Microscale Geometry and Cell Segregation



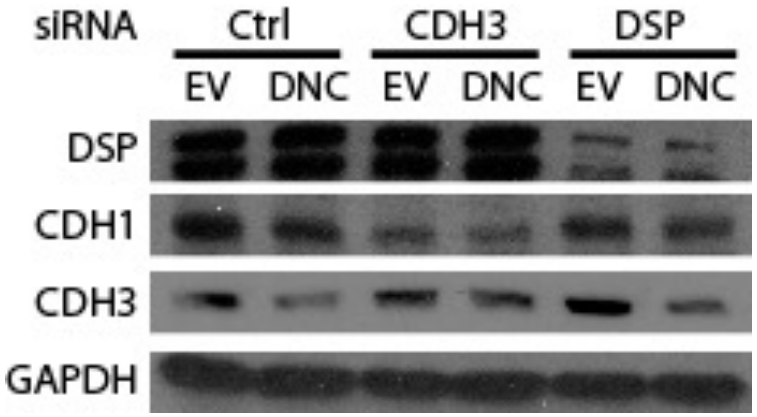
Localisation of differentiating cells



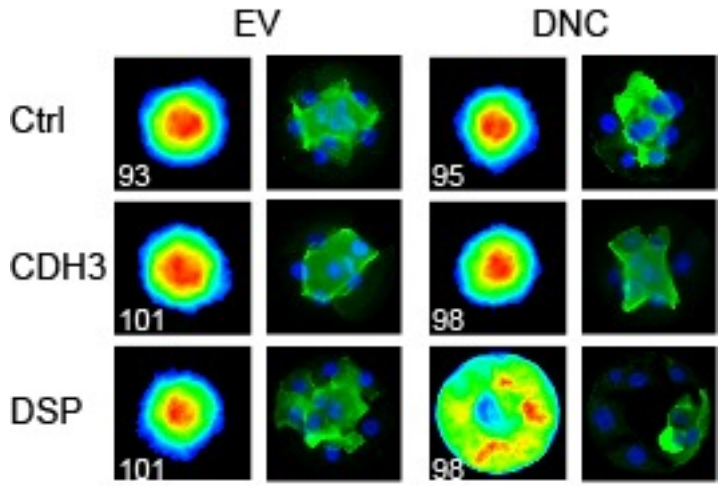


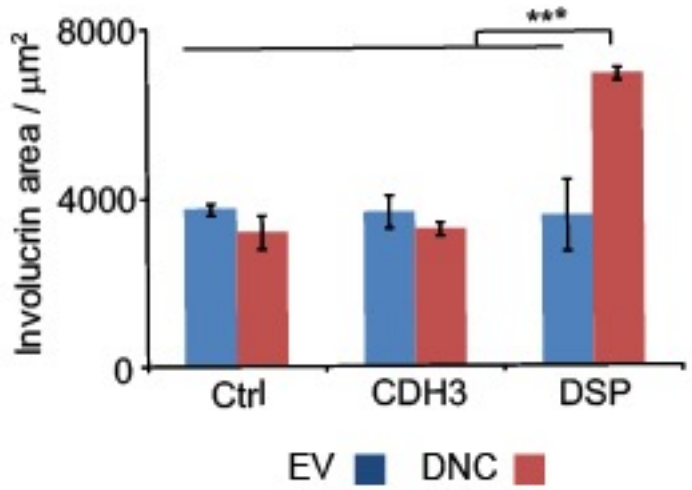
- The microscale geometry of adhesive islands impacts the localisation of differentiated cells and their confinement to the centre of cell clusters.
- Similarly, stem cell localisation is impacted by the geometry of the adhesive landscape.
- Rings of ECM with 40 mm non-adhesive inner islands enable the optimisation of the partitioning of stem cells and differentiated cells to defined compartments.

2. Probing the Role of Cell-Cell Adhesion in Micro-Tissue Formation

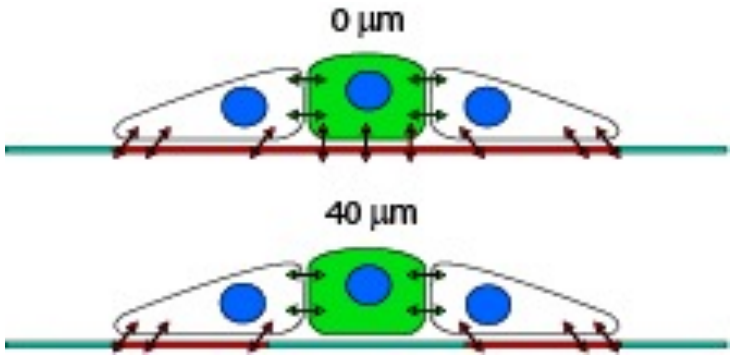


Gautrot et al. *Biomaterials* 2012.

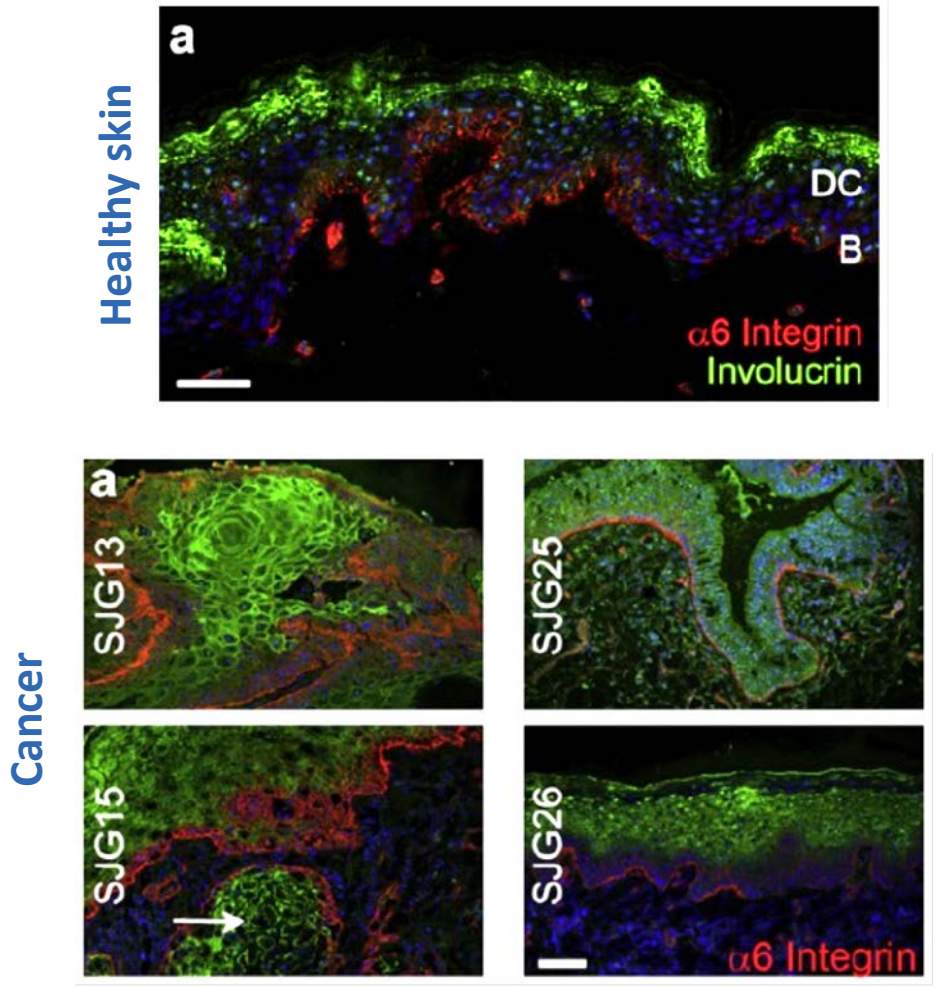




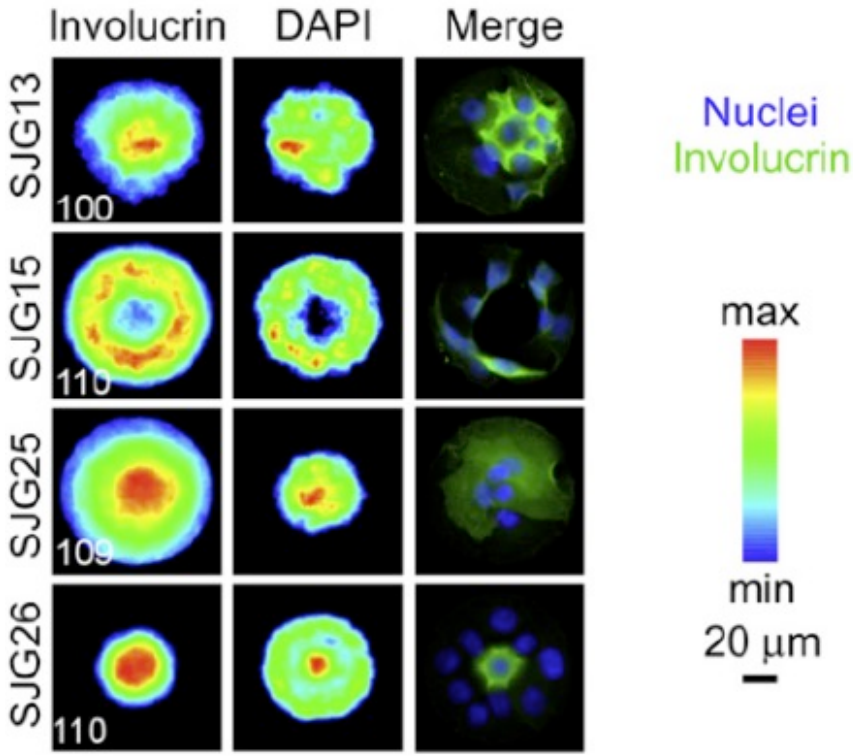
- Combination of knock down and dominant negative mutants allowed to identify the cohesion redundancy between adherens and desmosomal junctions.
- This constitutes a proof of concept that cell-based assays can enable the probing of molecules and genes involved in differentiation and the maintaining of compartment architectures.



2. Probing Abnormal Behaviour in Disease

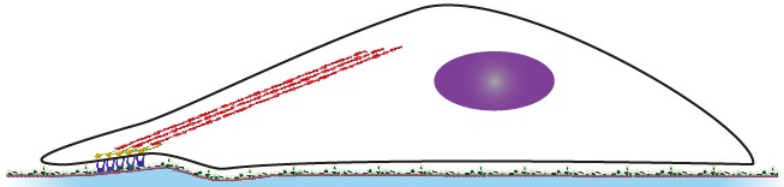


Gautrot et al. *Biomaterials* 2012.

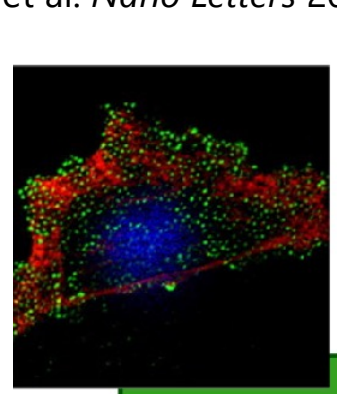


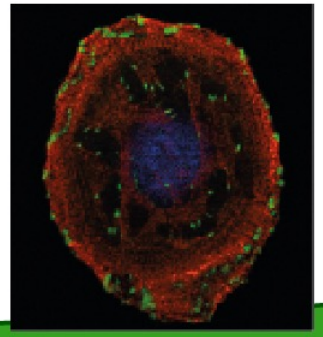
- Cell-cell and cell-matrix adhesions are typically perturbed in cancer.
- Micropatterns capture this abnormal organisation.
- Potentially, such cell-based assays could enable the screening of molecules or therapeutics restoring normal partitioning.

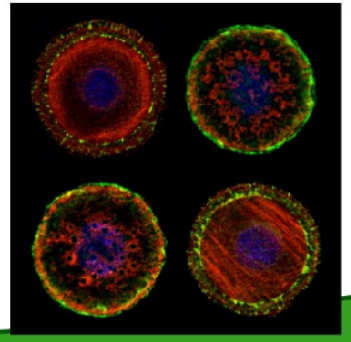
Engineering the Cell Microenvironment at Multiple Scales

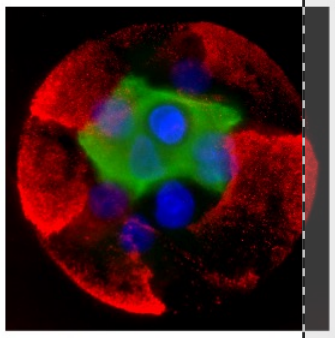


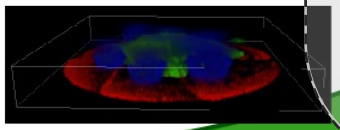
Kong et al. *ACS Nano* 2018
Kong et al. *Nano Letters* 2018
Trappmann, Gautrot et al. *Nat. Mater.* 2012
Costa et al. Acta Biomater. 2014
Gautrot et al. *Nano Letters* 2014

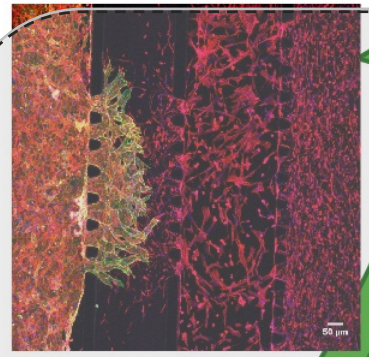


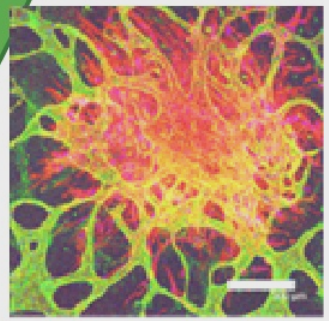


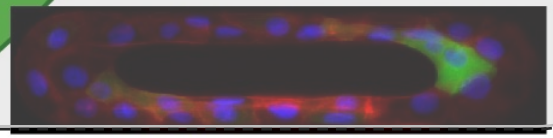








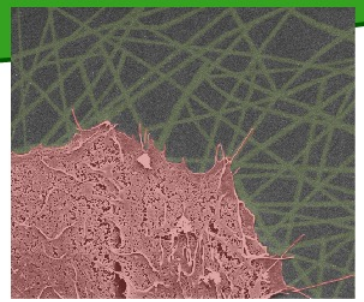




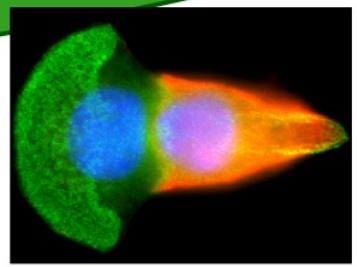
1 mm

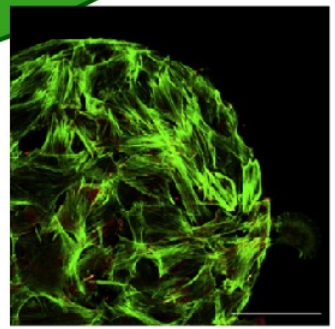
100 µm

100 nm



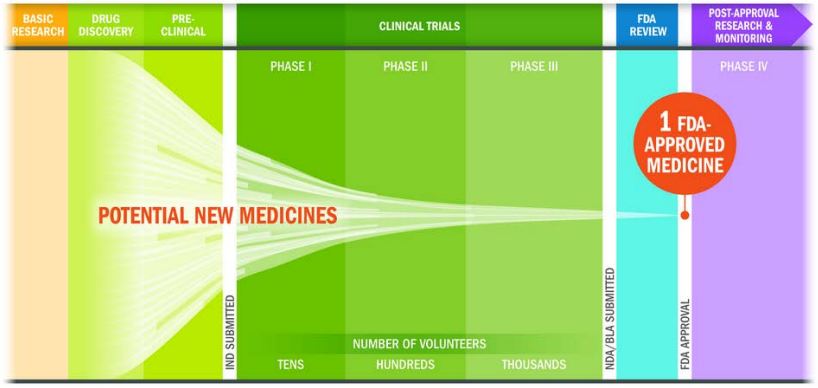
1 µm





Colak et al. Biomacromolecules 2018
Di Cio et al. *Acta Biomat.* 2016
Di Cio et al. *Acta Biomat.* 2017
Tan et al. Integ. Biol. 2013
Connelly et al. *Nat. Cell Biol.* 2010
Gautrot et al. *Biomaterials* 2012

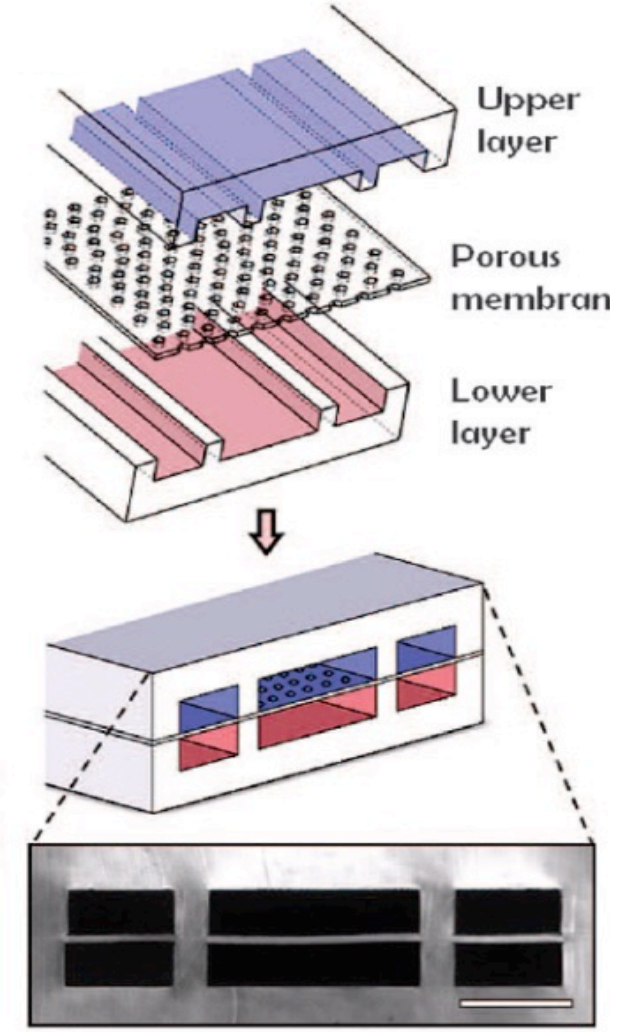
3. Better Testing in Vitro, in a Human Context

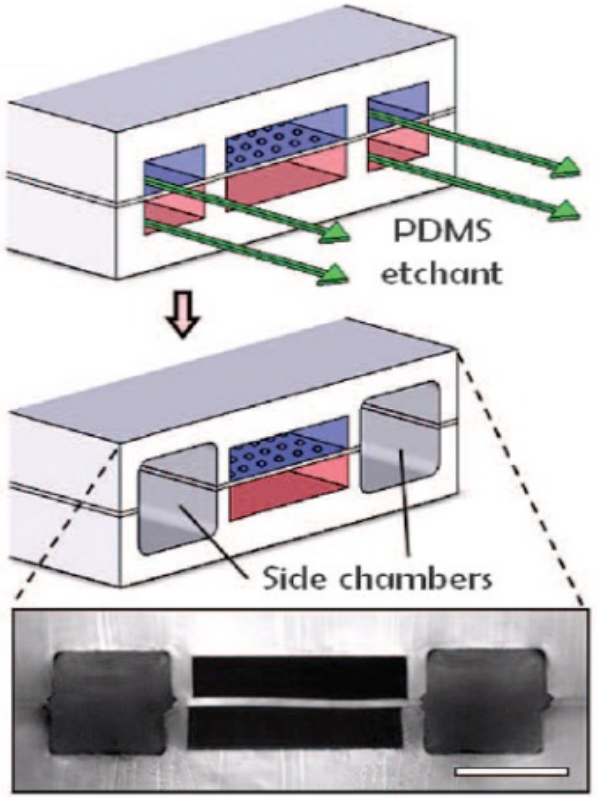


- The development of new drugs, biomaterials and biomedical devices require multiple levels of testing for efficacy and safety.
- We need better assays to predict safety and efficacy, directly in a human and potentially patient specific context.
- How can we predict the success of biomaterials for tissue engineering without animal testing?

3. Microfabrication of Chips for Biophysical Stimulation – Towards Organ-on-Chips

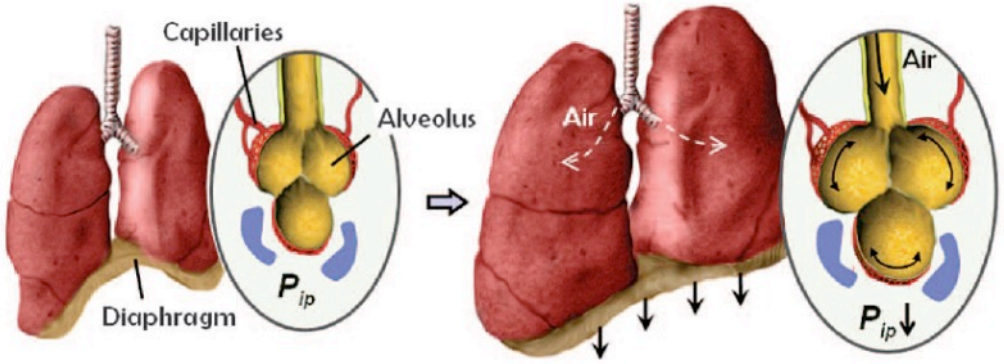
- Simple methods to mechanically stimulate tissues generated.
- In the lung-on-a-chip model, a stretchable membrane is stretched by two vacuum side chambers.
- Combination of conventional microfluidic fabrication and solvent etching.

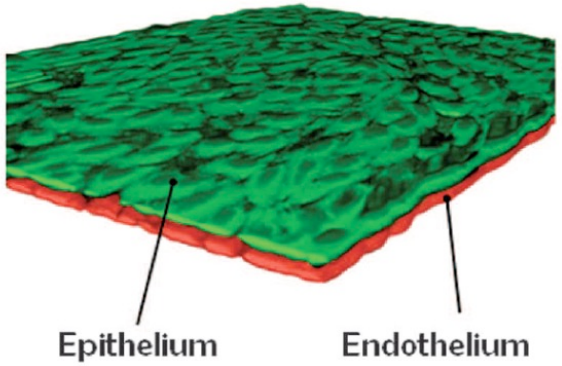


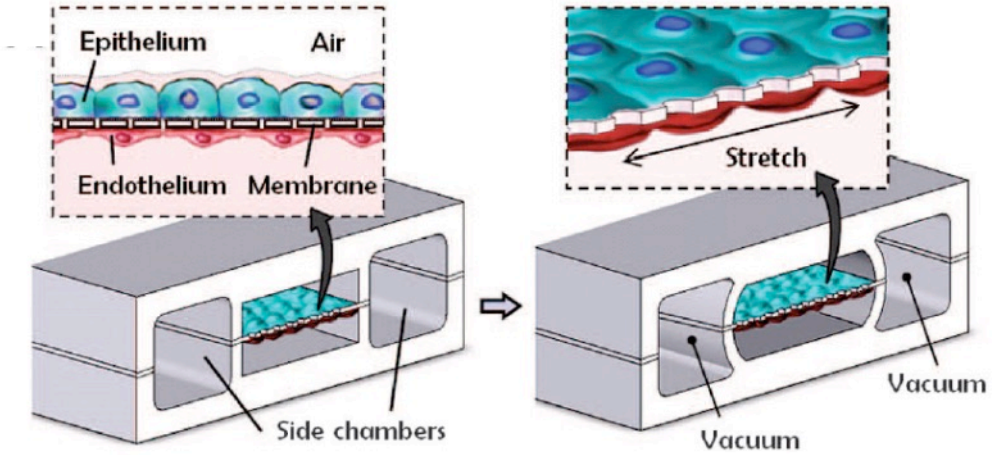


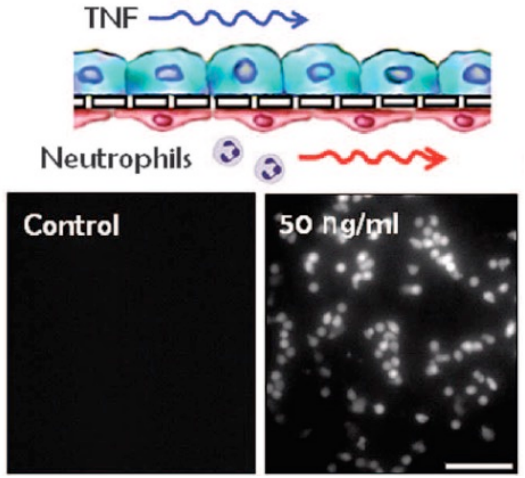
Science **328**, 1662 (2010)

3. Recreating Higher Level Organ Structure and Function





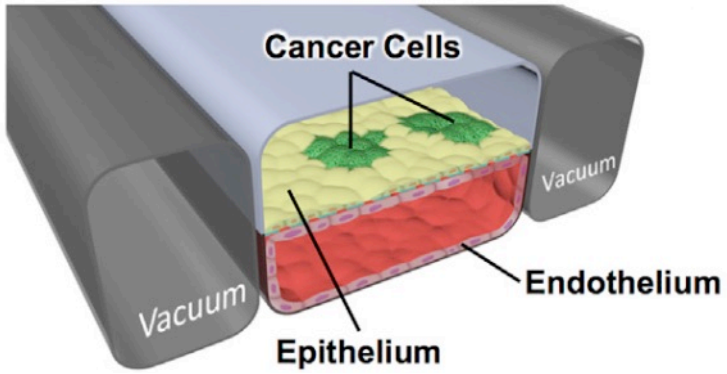


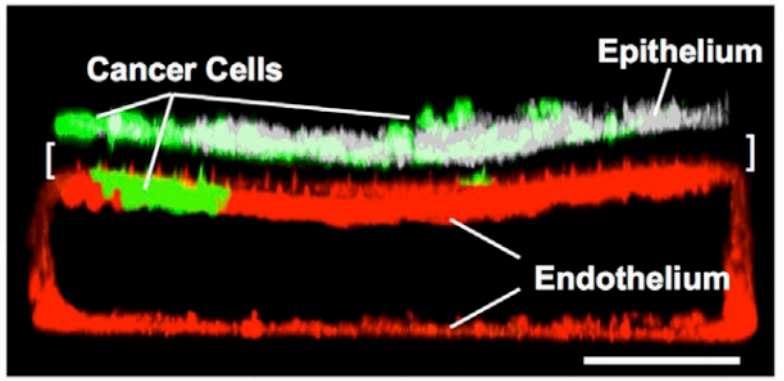


Ingber et al. *Science* **328**, 1662 (2010)

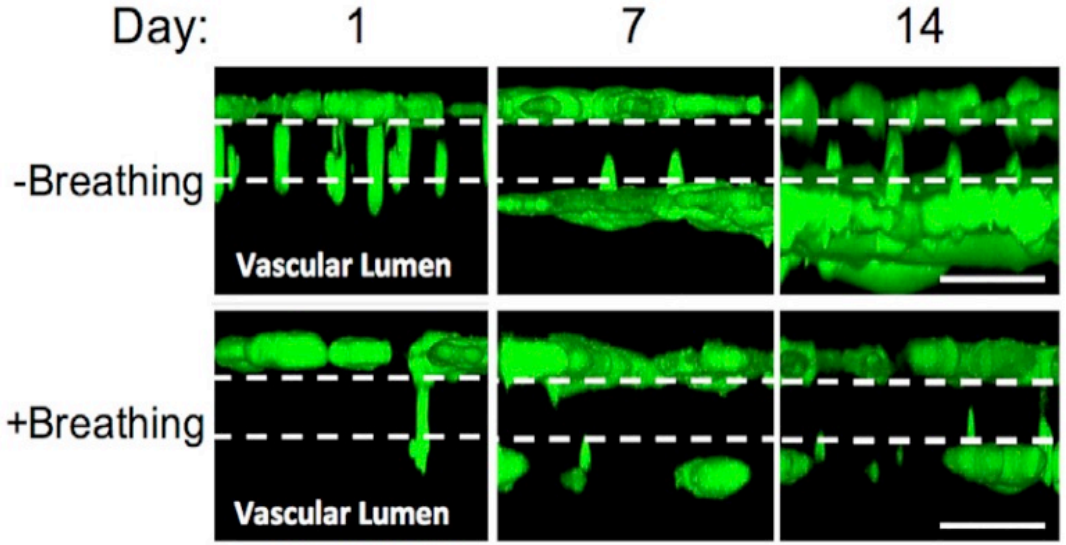
- Recreates structure and captures biophysics.
- Probes observed nanotoxicological response to nanoparticles (immune response), in particular in biophysical context (mimicking breathing).

3. Study of Cancer in Biophysical Conditions





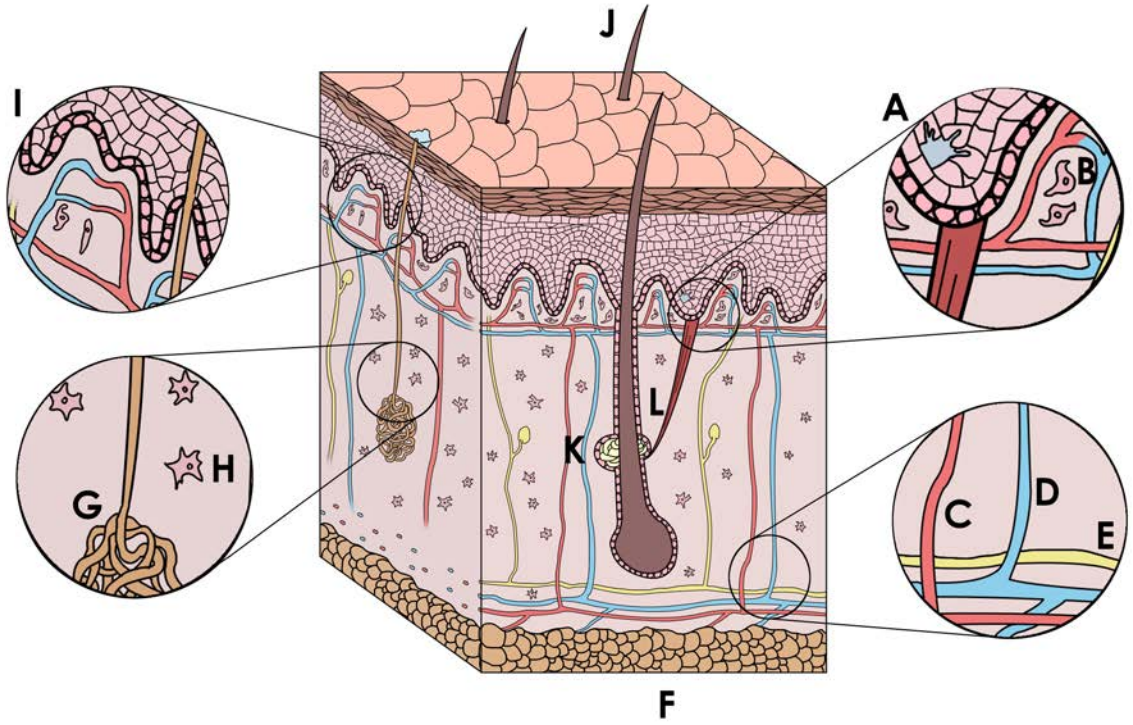
- Cancer cell biology is also affected by biophysical cues.
- In vitro models also need to capture this context.
- Ingber and Chen used the lung-on-a-chip system to study cancer development.
- Cancer invasion is reduced by breathing-mediated stretching.



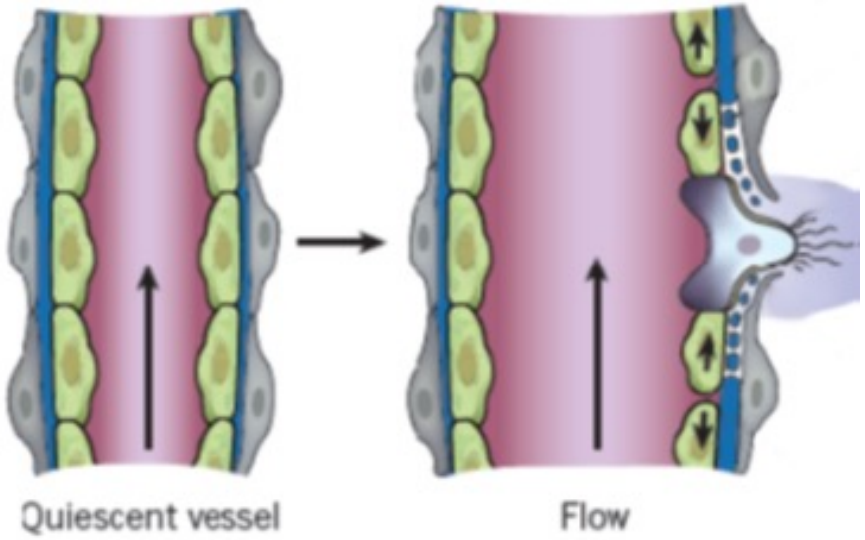
Cell Reports *21*, 508–516, October 10, 2017

3. Tissue Vascularisation and Angiogenesis

Vascularised Tissues



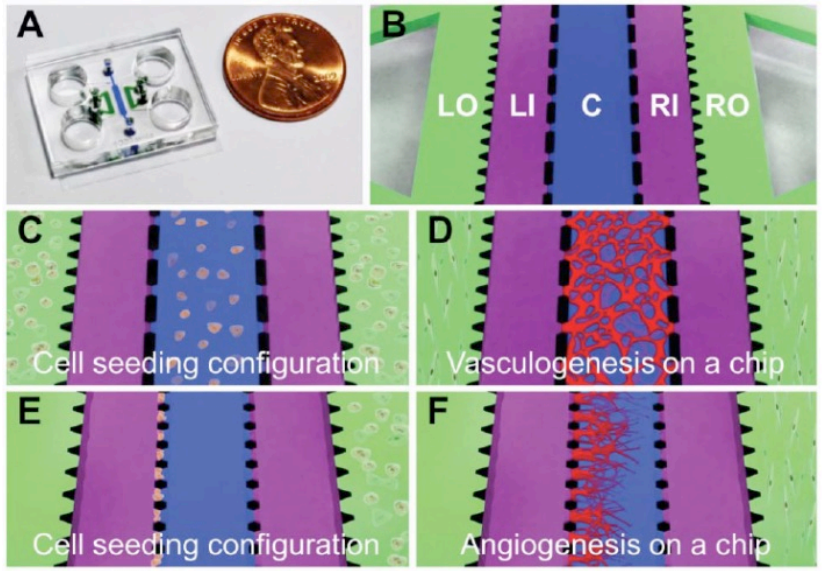
Angiogenesis Process



Carmeliet et al. Nature (2011), 473, 298.

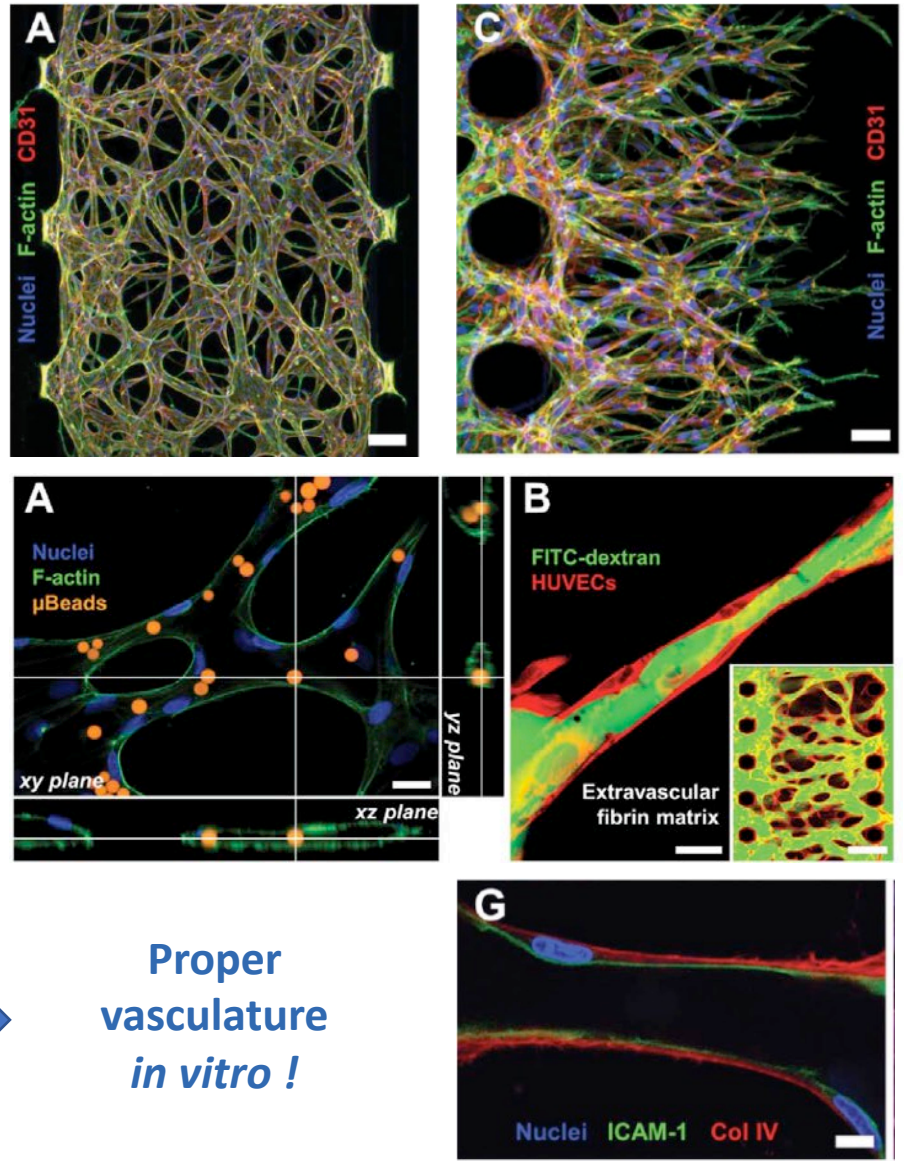
- The tissue-vascular interface is typically associated with microvascularised networks rather than two monolayers of cells juxtaposed.
- Processes such as angiogenesis regulate tissue development and repair and are altered in diseases such as cancer.
- Advanced organ-on-chip models should capture such structures.

3. Vascularisation On Microfluidic Chips



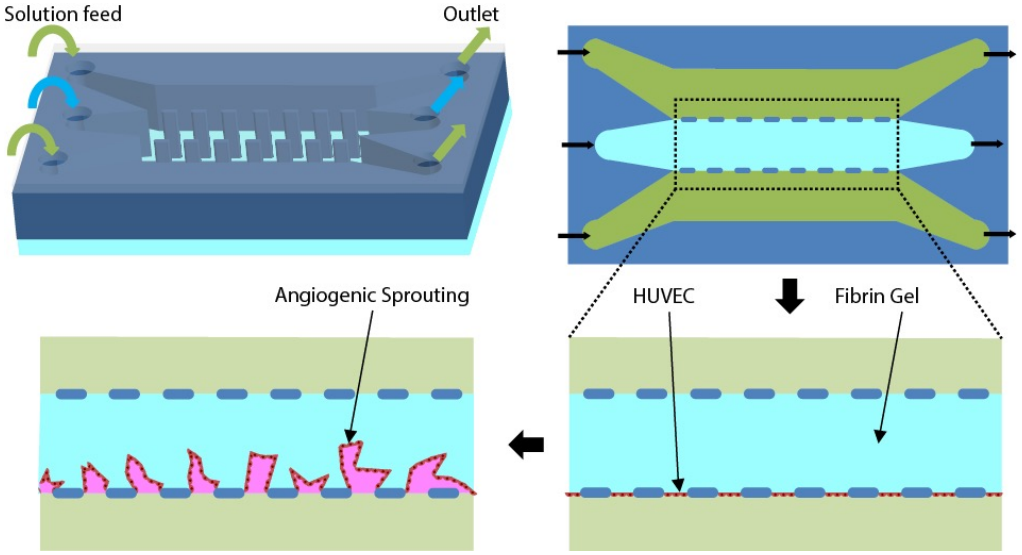
Lab Chip, 2013, **13**, 1489–1500

- Vacularisation and angiogenesis.
- The networks formed are laminated and display the correct polarity (ICAM-1 and Col IV expression).
- Perfusable and displaying good barrier functions.



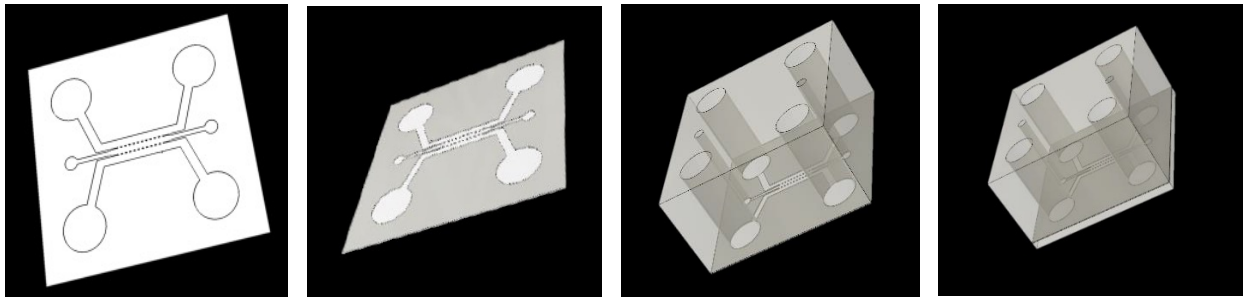
Proper vasculature *in vitro !*

3. Model of Angiogenesis and Vasculogenesis on Chip

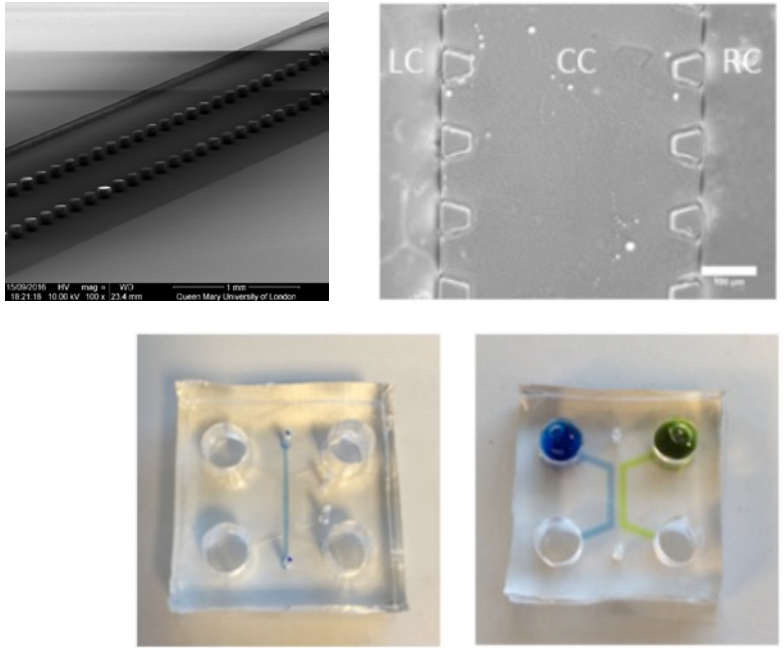


Dibble et al. *BioRxiv* 2022. doi.org/10.1101/2022.05.03.490457

Microchip Fabrication

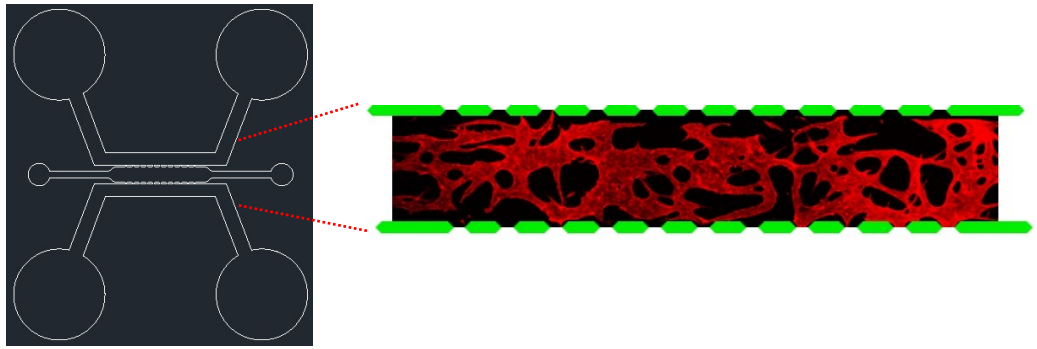


Mask | Photolithography | PDMS casting | PDMS-glass bonding



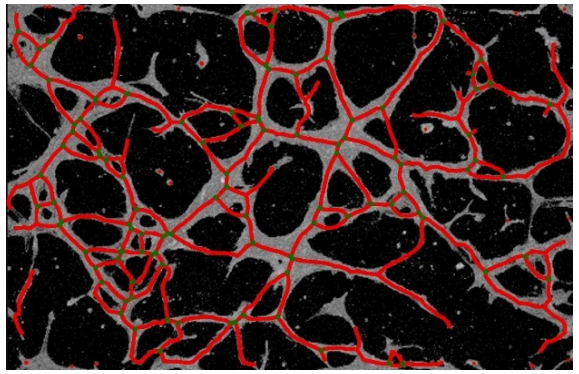
- A three channel microfluidic chip was adopted, based on the work of Kamm and co-workers.
- Endothelial cells are introduced in a central channel, together with a fibrin gel formulation (for vasculogenesis), or on the side of the gel, through one of the side channels (for angiogenesis).
- Microfabrication through photolithography and silicone elastomer replication was used to generate the chips.

3. Vasculogenesis-on-a-Chip

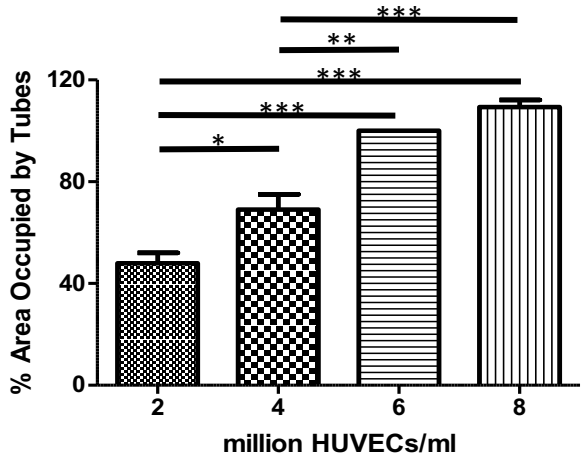


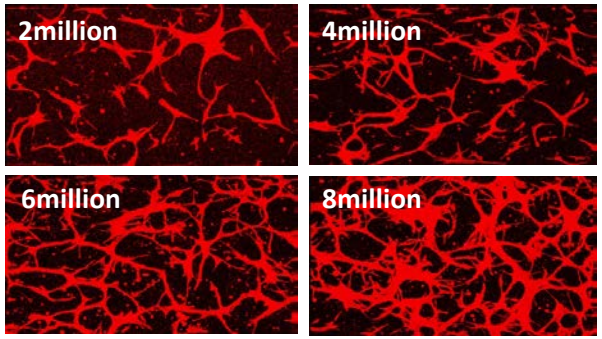
Dibble et al. *BioRxiv* 2022. doi.org/10.1101/2022.05.03.490457

Network Analysis



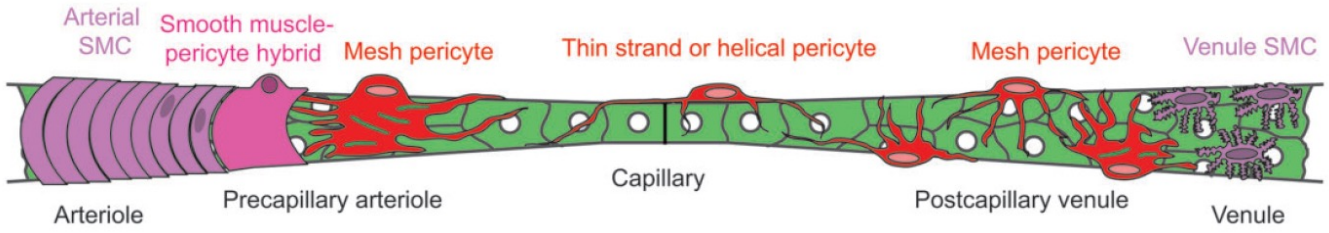
Impact of Cell Density





- Endothelial cells seeded in central channel form a vascular networks within 4 days of seeding.
- Networks can be characterised using quantitative protocols avoiding user bias.
- The initial cell density plays an important role in the quality of the networks formed.

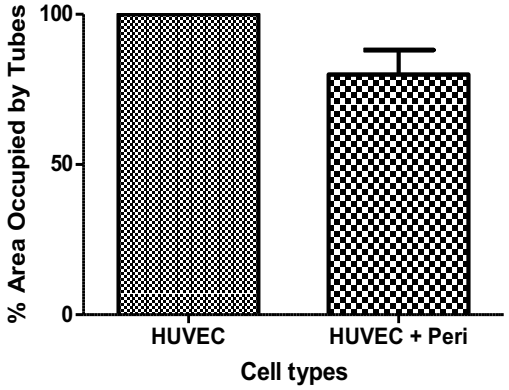
3. Pericyte Co-culture

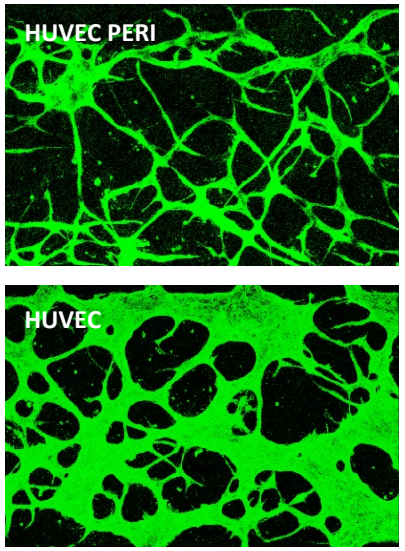


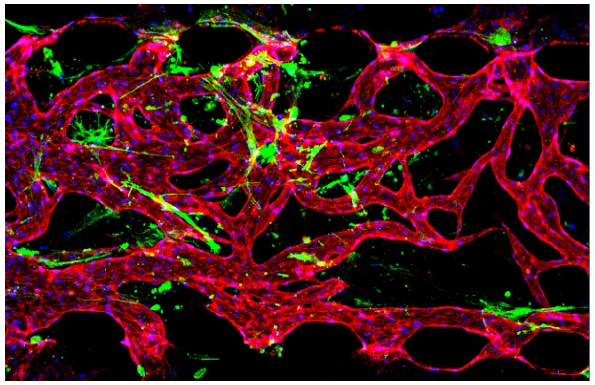
Attwell et al. Journal of Cerebral Blood Flow & Metabolism (2016).

- Pericytes play an important role in supporting endothelial cells to stabilise the microvasculature.
- Introducing them in co-cultures in chips induces the stabilisation of networks (prevents hyperplasia) and allows the maintenance of stable cultures for > 4 weeks.

Impact on Microvasculature Structure

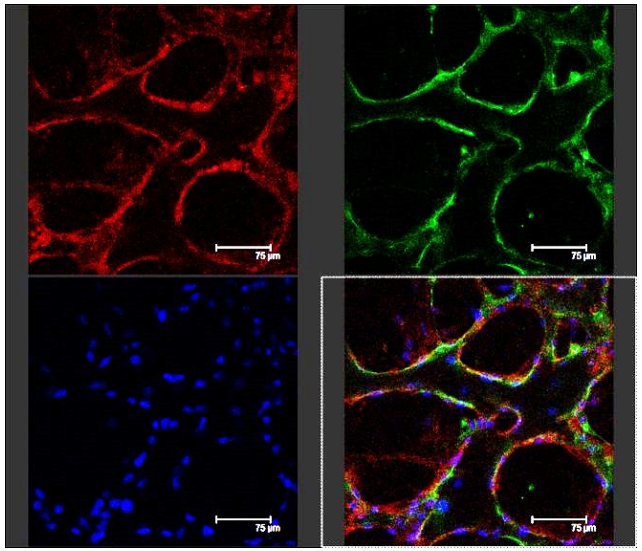






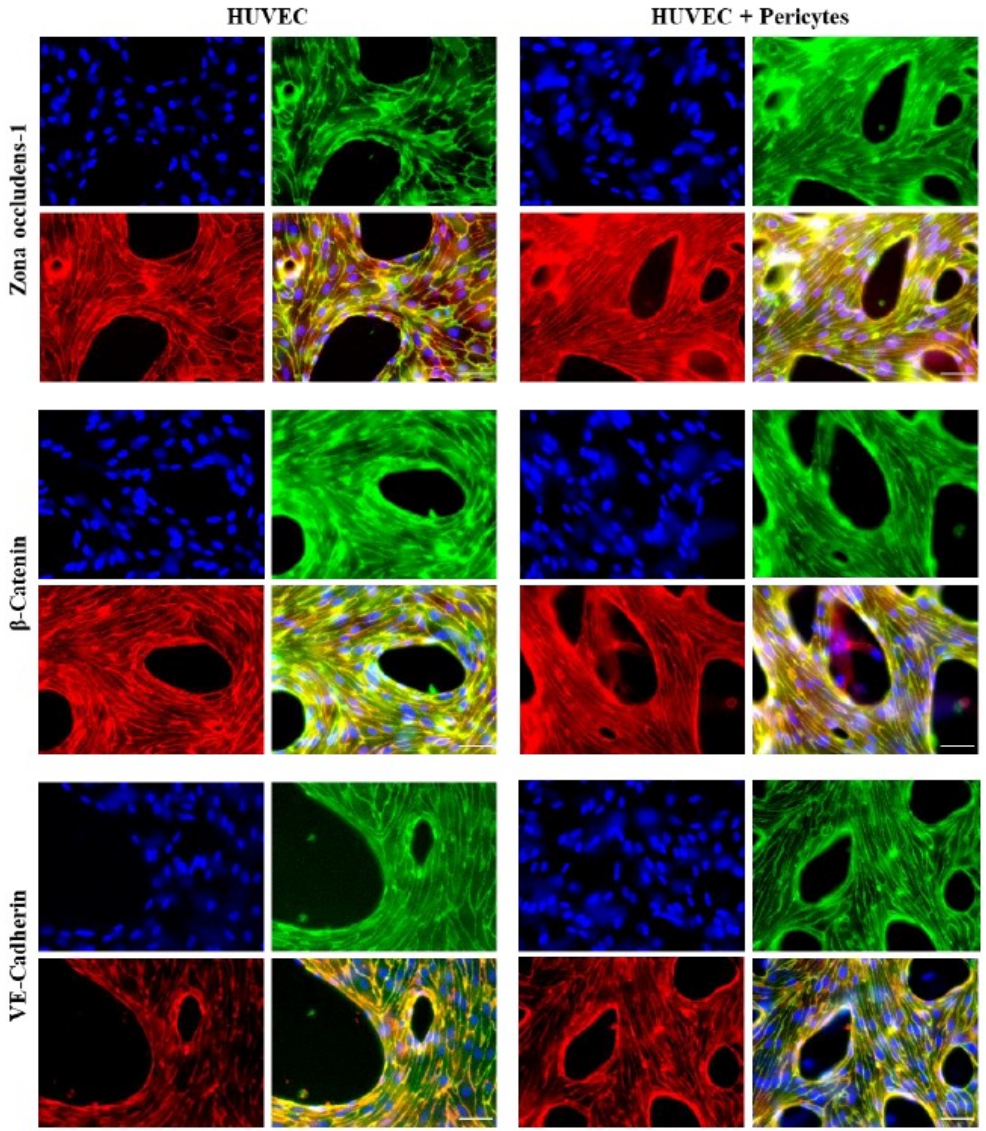
CD31, SMA, DAPI

Lumenated Structures

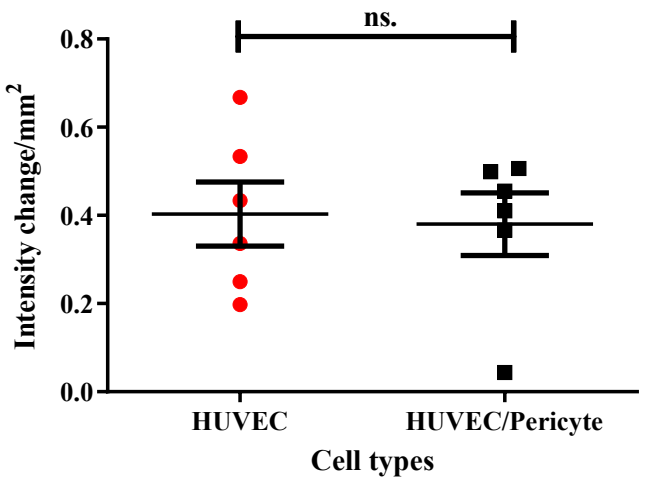


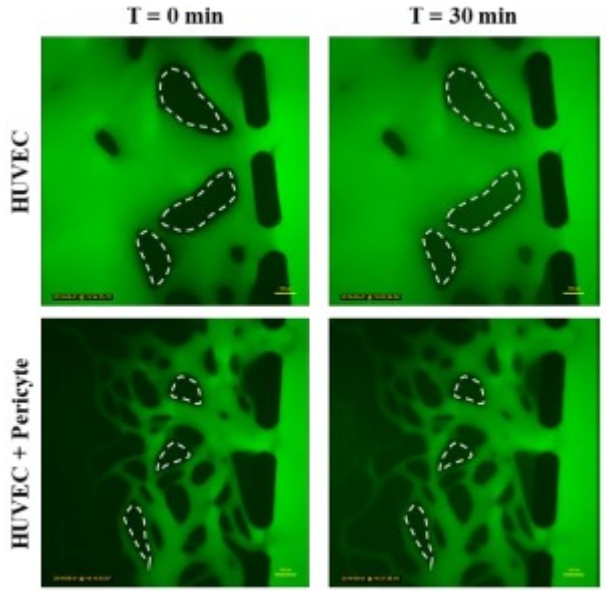
Dibble et al. *BioRxiv* 2022. doi.org/10.1101/2022.05.03.490457

3. Pericyte Co-culture Modestly Impacts the Maturity of the Endothelium



- Pericyte co-culture has little impact on the maturity of endothelial cell-cell junctions.
- No significant improvement of barrier function either was observed, in contrast to some of the literature.





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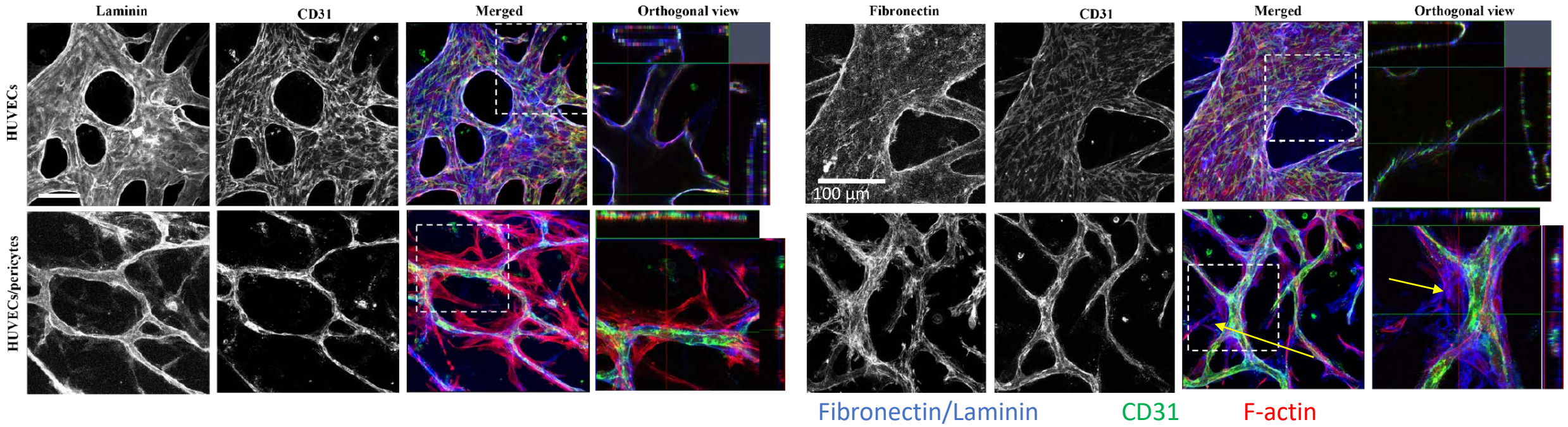
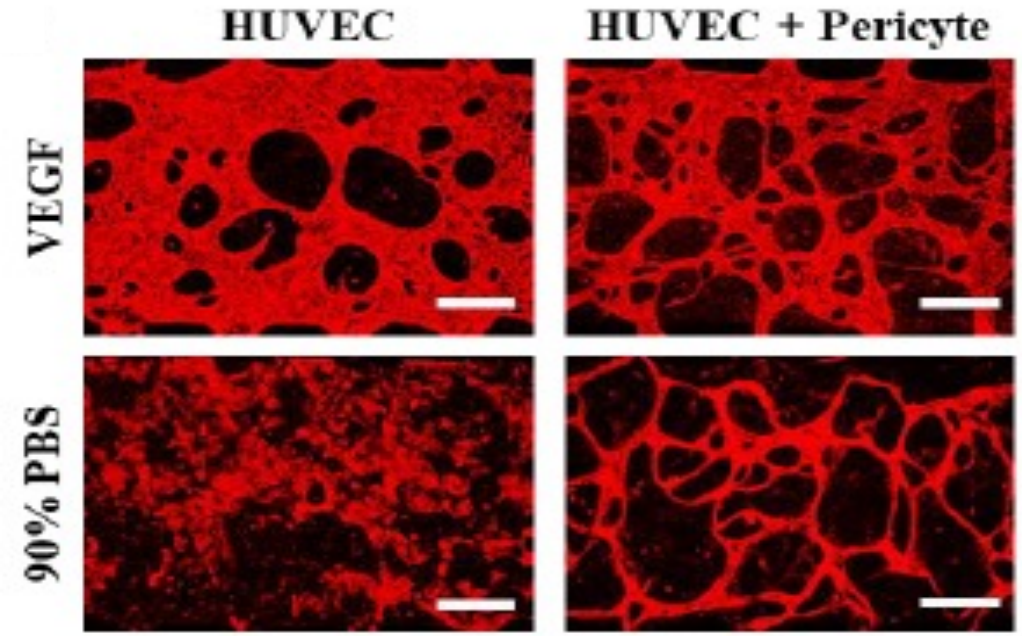
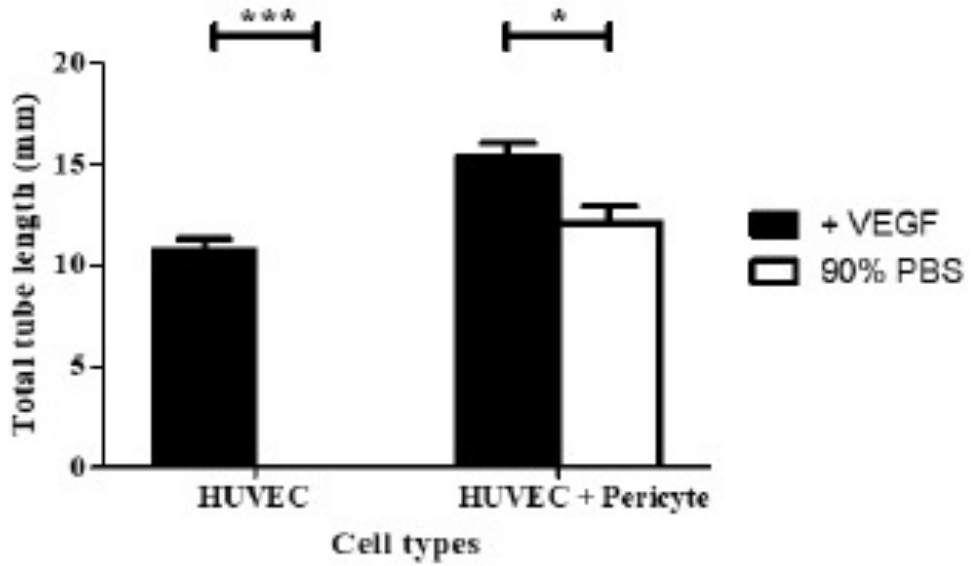
3. Pericytes Remodel the Peri-Vascular Matrix



- Pericytes wrap around endothelial cell networks (staining for CD31).
- Collagen IV, fibronectin and laminin are all deposited at the basal membrane of endothelial microvascular networks, whether in mono or co-cultures.
- Co-cultures also display clear signs of fibronectin perivascular deposition (likely by pericytes).
- Does this impact on the stability of vascular networks?

3. Pericytes Improve the Stability of Vascular Networks

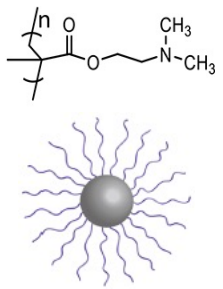


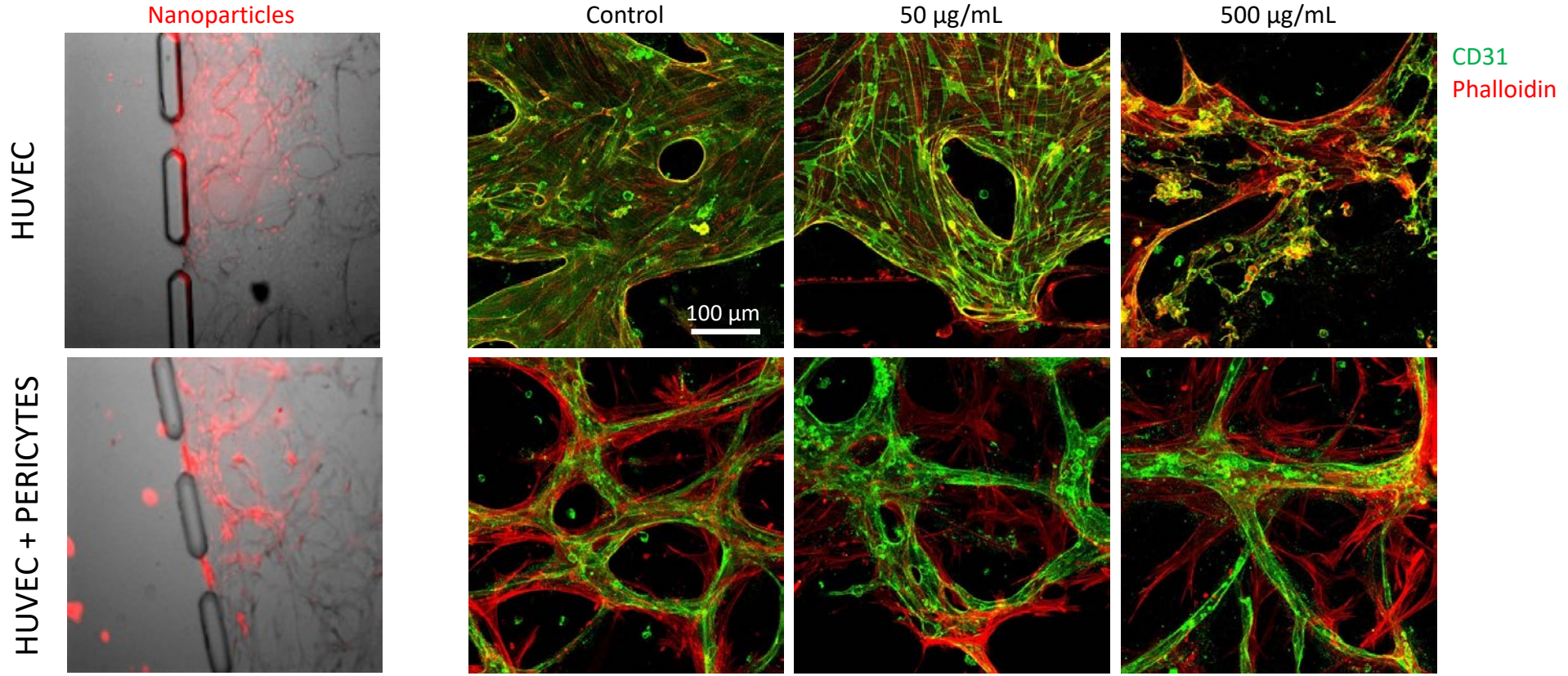


- When cultured in medium with low serum (90% PBS; 1 % serum), microvascular networks in mono-cultures rapidly regress and dissociate.
- In co-cultures, although networks do look thinner, they maintain their architecture for at least 3 days.
- Although this is very aggressive starvation regimen, this suggests that co-culture would help preserving microvascular networks in co-culture with other cells, when requiring different types of media.

3. Pericytes Improve the Stability of Vascular Networks in Response to Nanotoxicity

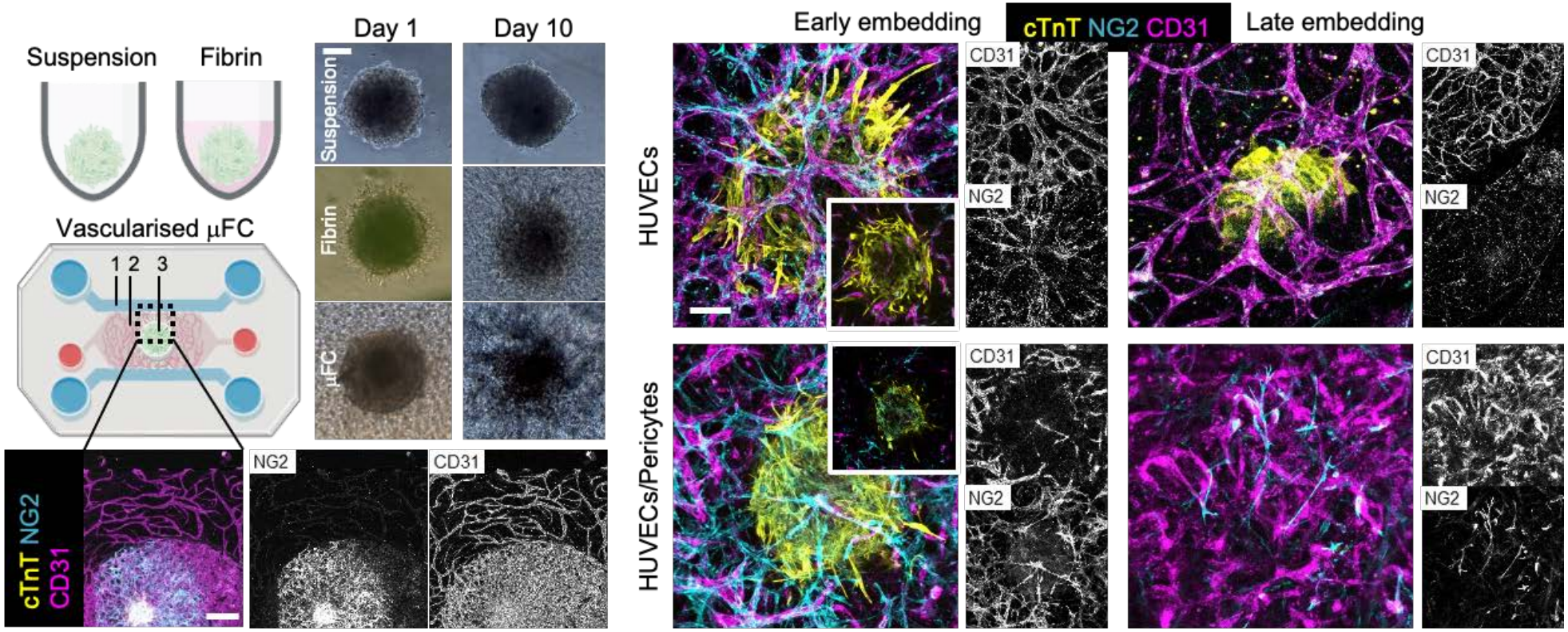
PDMAEMA brush





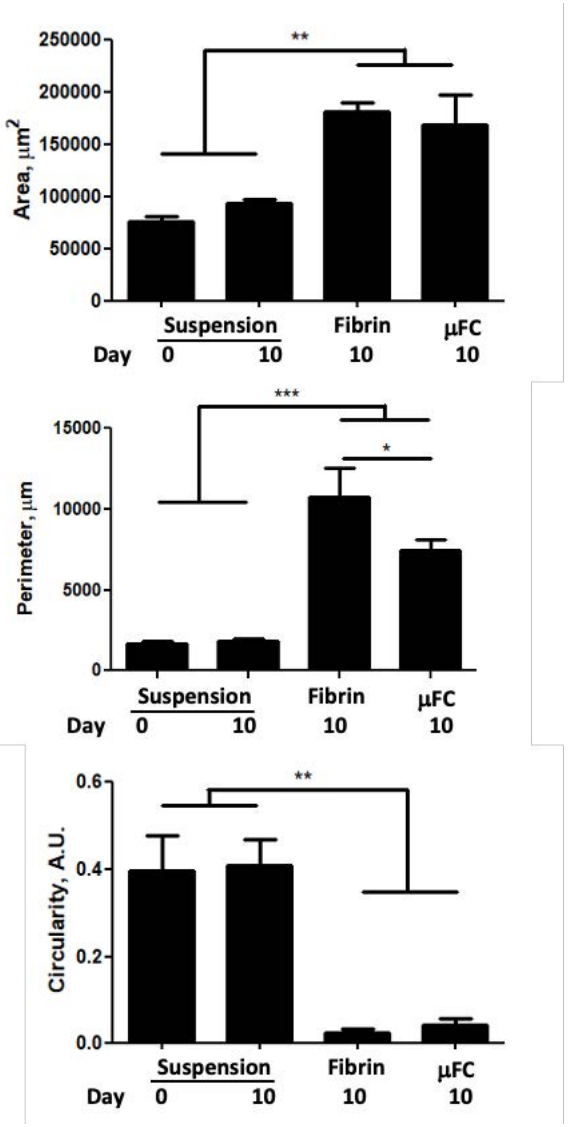
- Cationic nanoparticles induce pronounced cytotoxicity on microvascular networks in mono-culture.
- In co-culture, this phenomenon is reduced significantly.
- This could be a useful model of cytotoxicity to mimic systemic delivery.

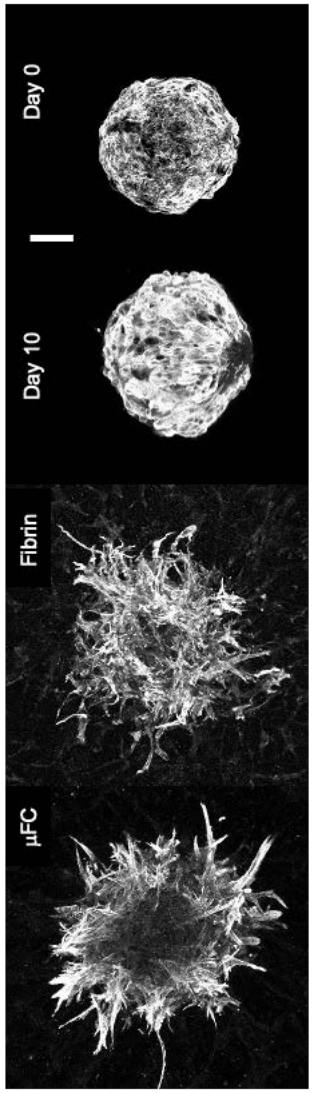
3. Towards Reliable Models of Microvascularised Tissues – Cardiac Vascularisation

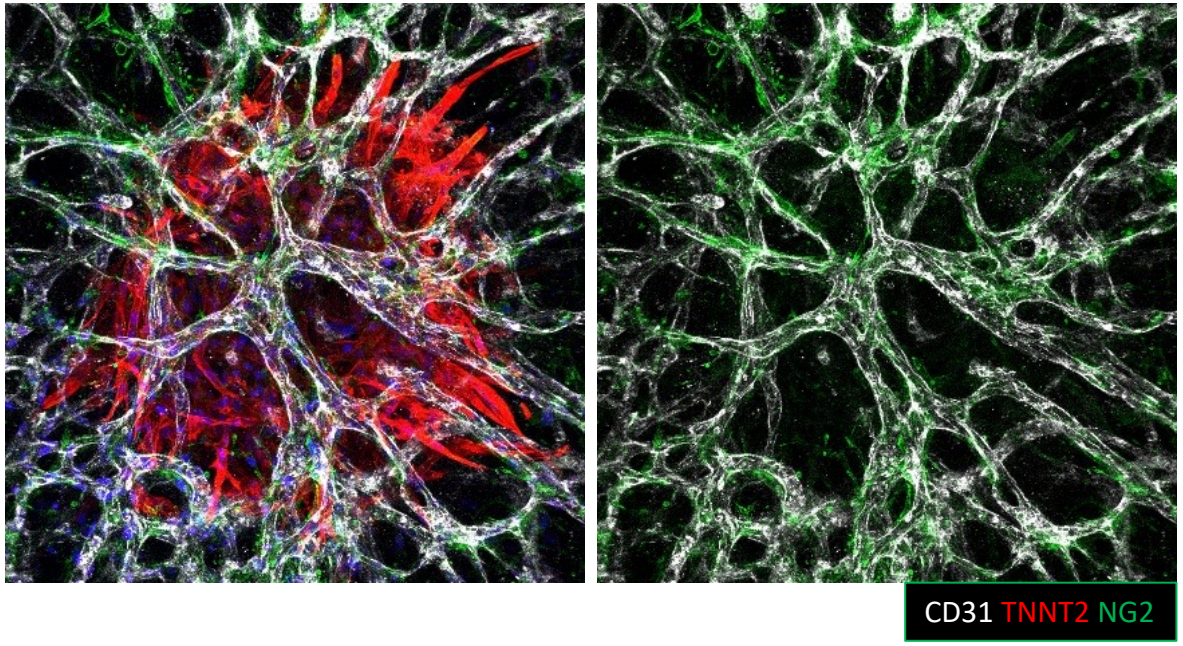


- To introduce tissues in the microfluidic chip models, a central well is engineered into the cell channel.
- Spheroids and other tissue/organoid structures can be introduced through this central well, directly above or together with endothelial cells.
- Cardiac spheroids were introduced using different protocols and found to integrate well if implanted together with endothelial cells.

3. Successful Implantation and Integration of Cardiac Spheroids Within Microvascular Networks







- Spheroids implanted retained cohesion, but clearly integrated within the matrix and endothelial network.
- Implantation was best achieved without pericytes, as fibroblasts expressing pericyte markers (NG2) were introduced together with the cardiac spheroid.
- TNNT2⁺ cells can clearly see to integrate within the surrounding matrix and network.

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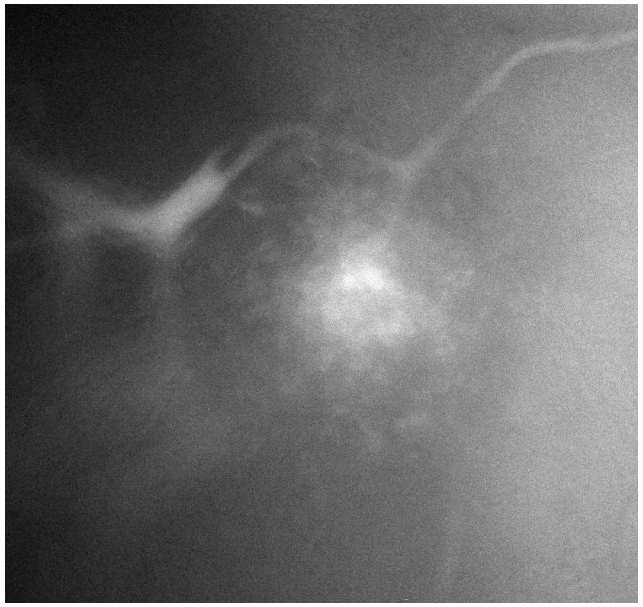
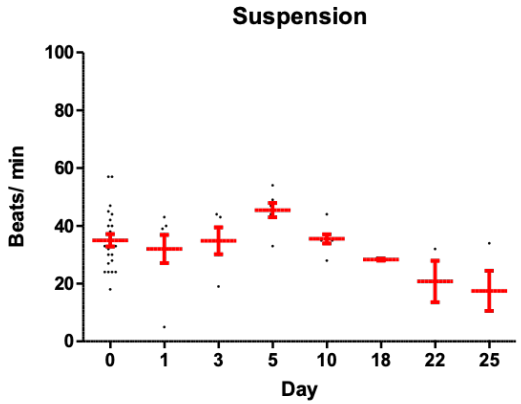
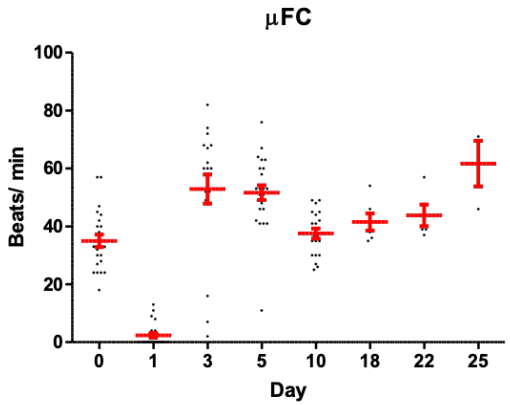
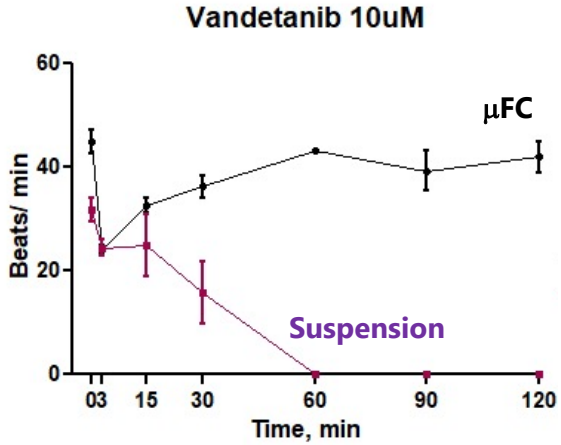
3. Functional Properties of Microvascularised Cardiac Spheroids

Mini Beating Hearts!





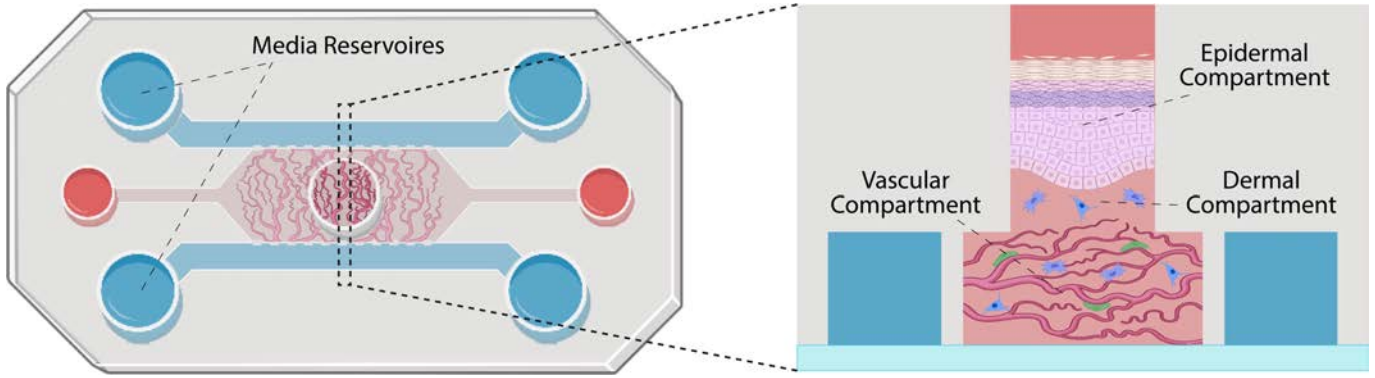




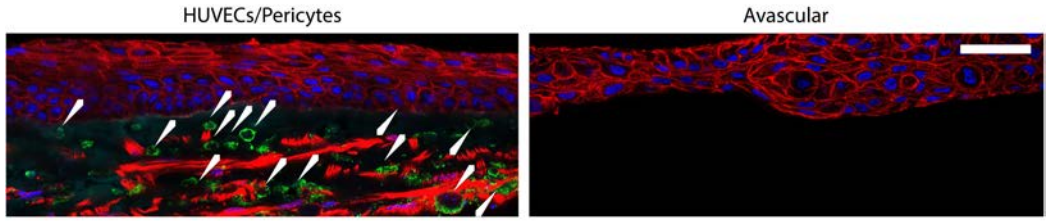
Di Cio, S et al. Soon on *BioRxiv* (2023)

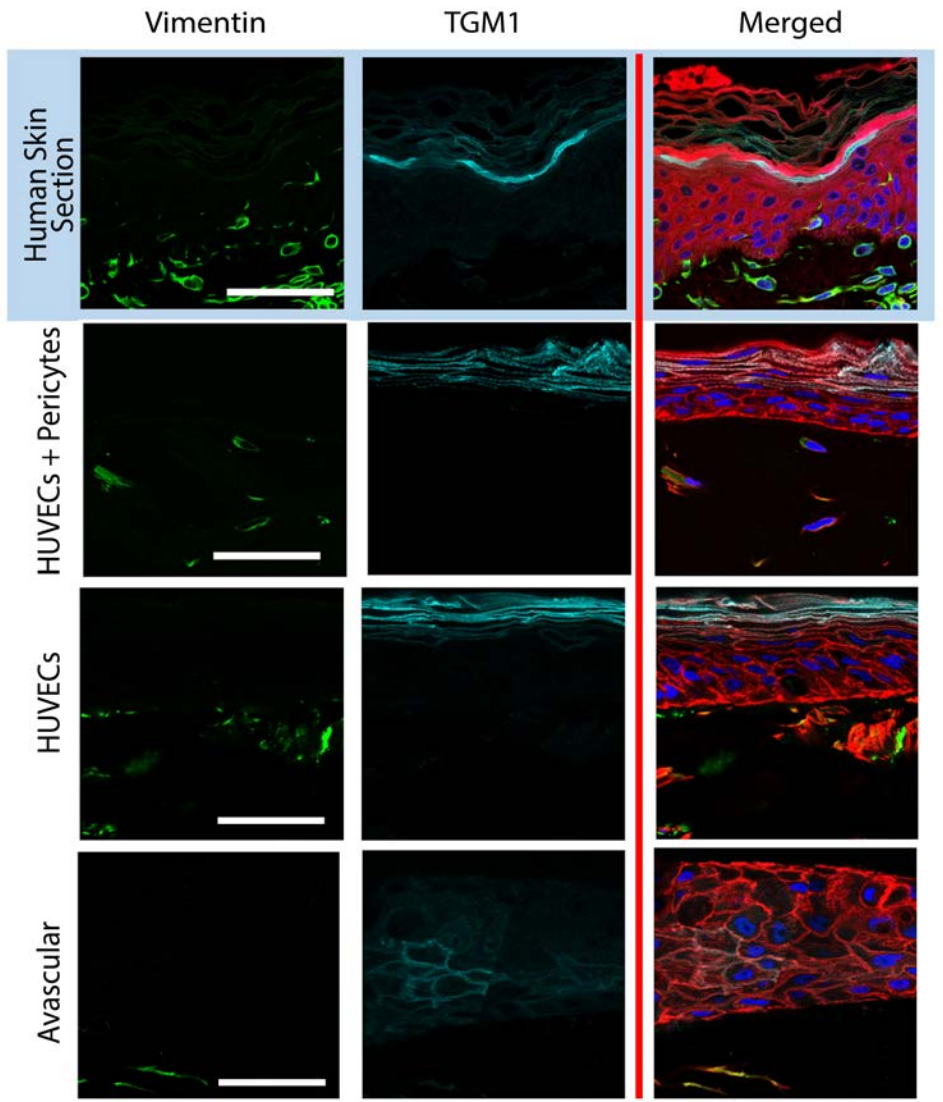
- Implanted cardiac spheroids remain functional, beating for at least three weeks, whilst spheroids maintained in suspension gradually start displaying a loss of contractile function.
- Mechanical function and actuation of the spheroid seems to impact the perfusion of the surrounding network, with apparent flow within capillaries.
- Treatment with the tyrosine kinase inhibitor Vandetanib (used in the treatment of advanced stages of medullary thyroid cancer) had a reduced impact on cardiac function compared to direct exposure in suspension, implying that microfluidic models could better recapitulate systemic delivery scenarios.

3. Microvascularised Skin-on-a-Chip



- Form a microvasculature first in the bottom compartment of the central channel.
- Then further embed a dermal compartment in the central well (fibroblasts in a collagen/matrigel gel).
- Seed keratinocytes on the surface.
- Barrier formation, with mature epidermal construct (involucrin, transglutaminase 1).

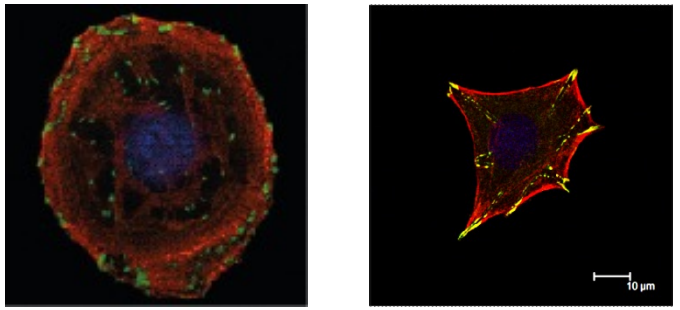


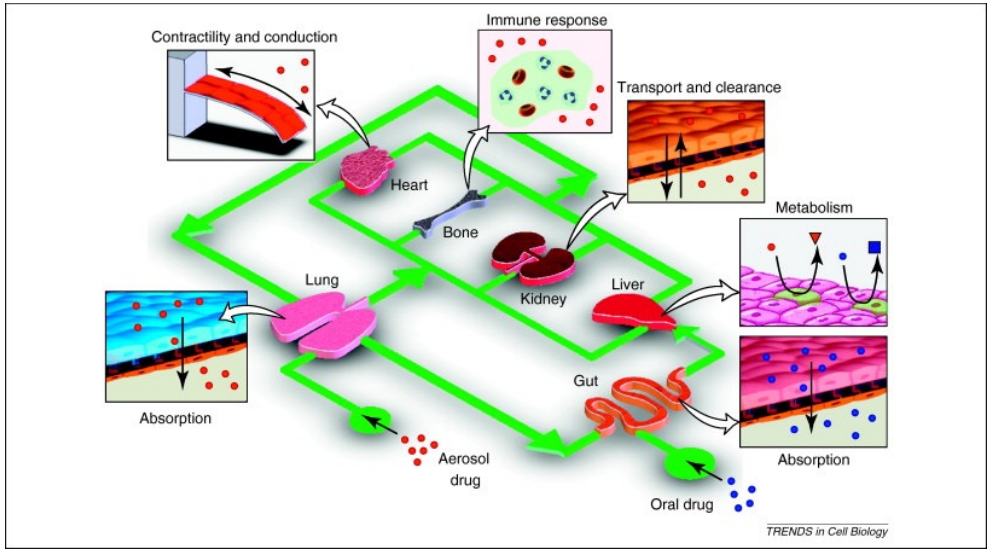


Jones, C et al. *Front. Bioeng. Biotechnol* (2022) 10, 915702

Conclusions

- Engineering the nano- to micro-scale geometry of adhesions impacts on cell adhesion formation and directs cell spreading, shape and regulates phenotypes.
- To some extent, matrix engineering allows the templating of multi-cellular assemblies and can direct partitioning and compartmentalisation.
- Microfluidic chips and 3D printing platforms can allow the formation of micro-tissues that allow recreating higher levels of tissue structure and function.
- Such advanced in vitro models are poised to revolutionise the field of in vitro testing.





Thank You

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William Megone
Matt Dibble
Piaopiao Luo
Ed Cozens
Yaqi You
Linke Wu
Christian Jones
Lihui Peng
Fauzia Quadir
Minerva Bosch
Alexandra Chrysanthou
Nam Nguyen
Chiara da San Martino

Collaborators

John Connelly (QMUL)
Fran Balkwill (QMUL)
Wen Wang (QMUL)
Adrian Biddle (QMUL)
Madeline Lancaster (LMB, Cambridge)
Pavel Novak (QMUL)
Madeleine Ramstedt (Umea Universtiy)
Armando del Rio (Imperial College)
Ali Zarbakhsh (QMUL)
Ken Suzuki (QMUL)
Helena Azevedo (QMUL)

Duncan Sutherland (Aarhus)
Jenny Malmstrom (Aarhus)
Christoph Ballestrem (Manchester)
Thomas Iskratsch (QMUL)
Mariah Sundh (Aarhus)
Fiona Watt (KCL)
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