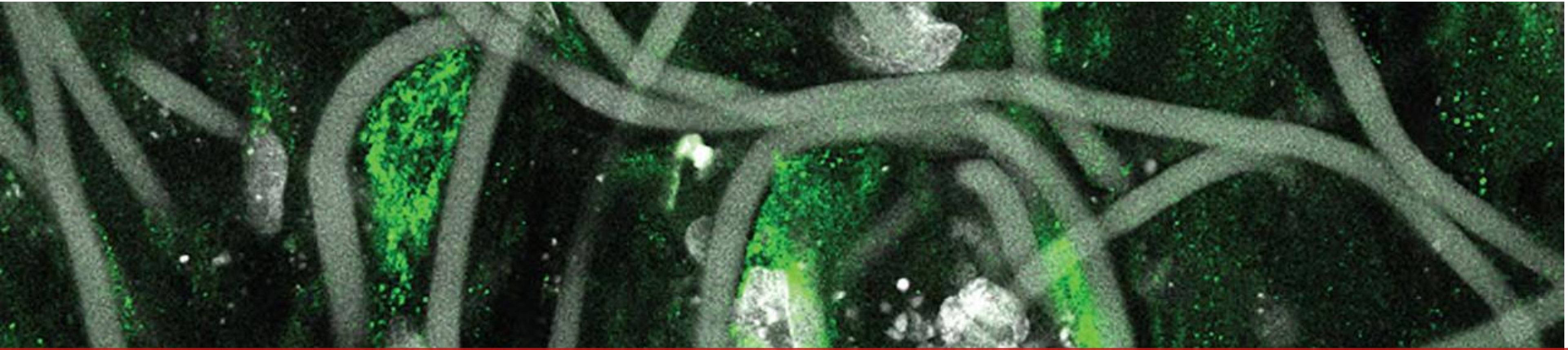


Mechanobiological control of cell phenotype and tissue development

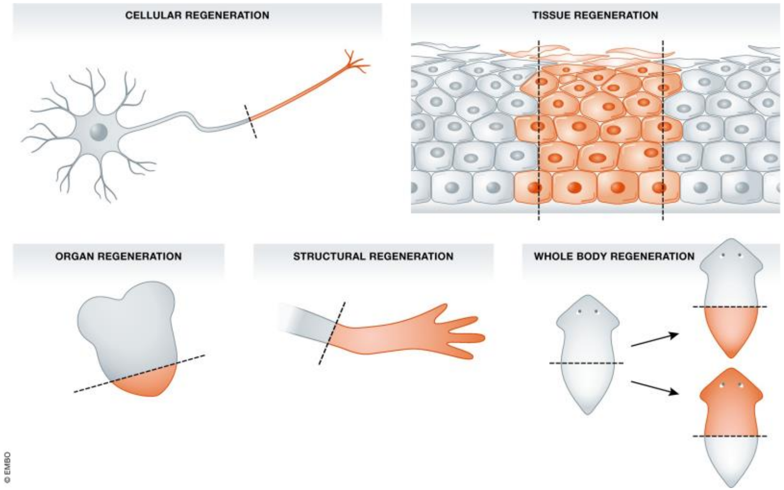
Nicholas A. Kurniawan

TUM talk, 4 July 2023

Regenerative medicine

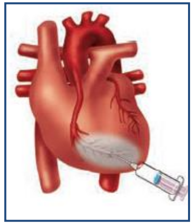
- Huge potentials:
  - Treatment of symptoms → Cure disease
  - Regenerate damaged tissue
  - Replace entire organs
  - Restore function

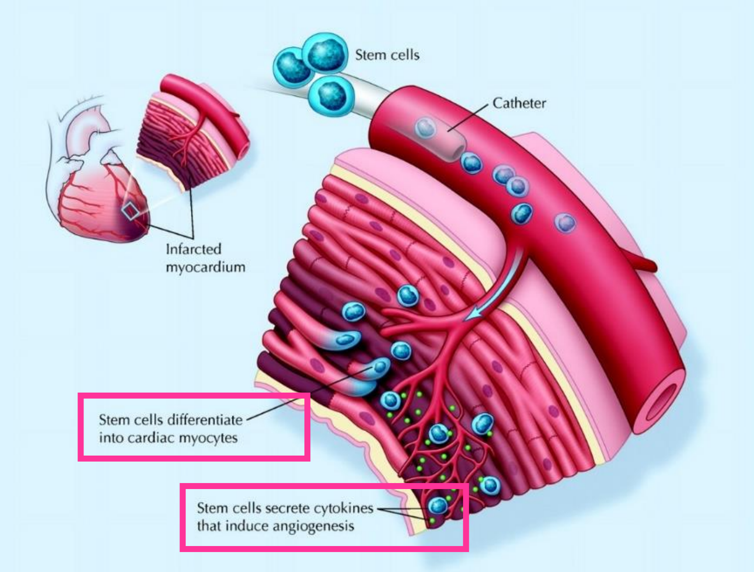
- Harnesses body's own healing abilities



Slack *EMBO Rep* 2017

Case: cell replacement therapy



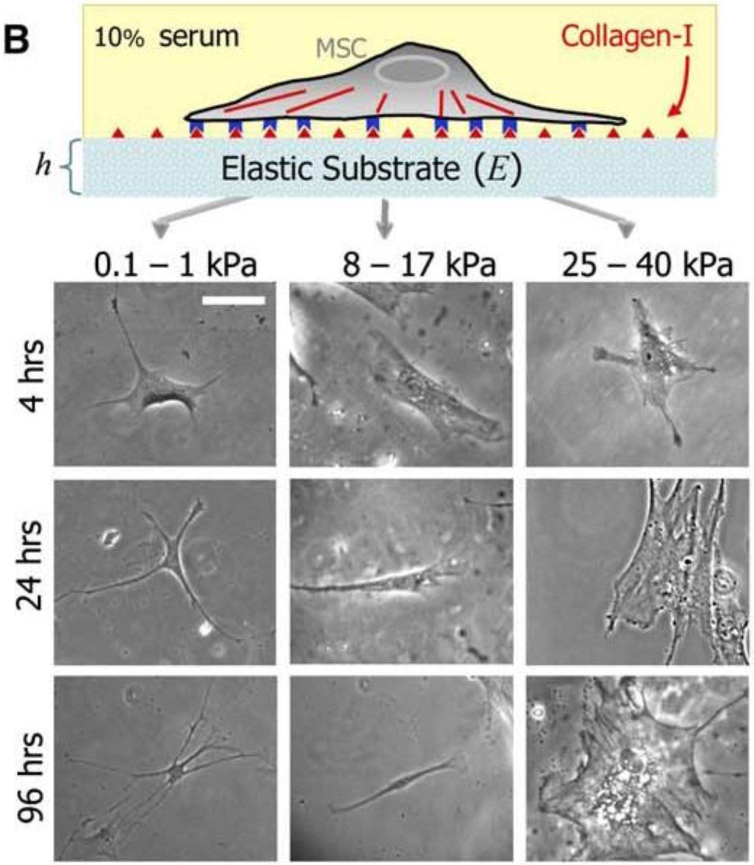


Kang+ *CMAJ* 2004

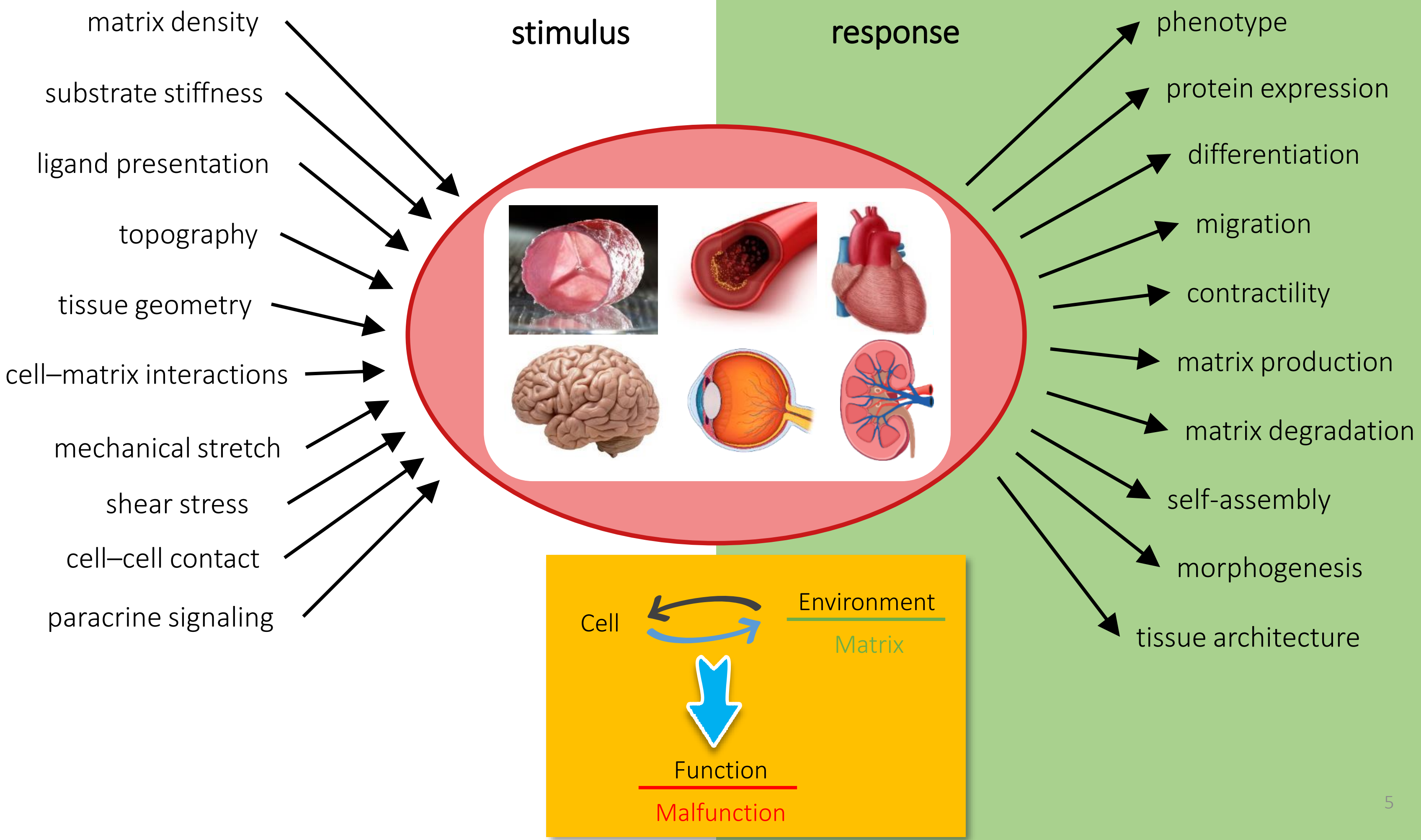
Limited outcomes:
- 4–6 % increase in cardiac function
- Very low cell retention
- Cell death due to hostile environment
- No differentiation into heart muscle cells
- Cells don’t ‘home’ to the infarcted area

What do the cells sense in their ‘new’ environment?
And how do they respond?

Stem cell differentiation is influenced by substrate stiffness



Engler+ *Cell* 2006

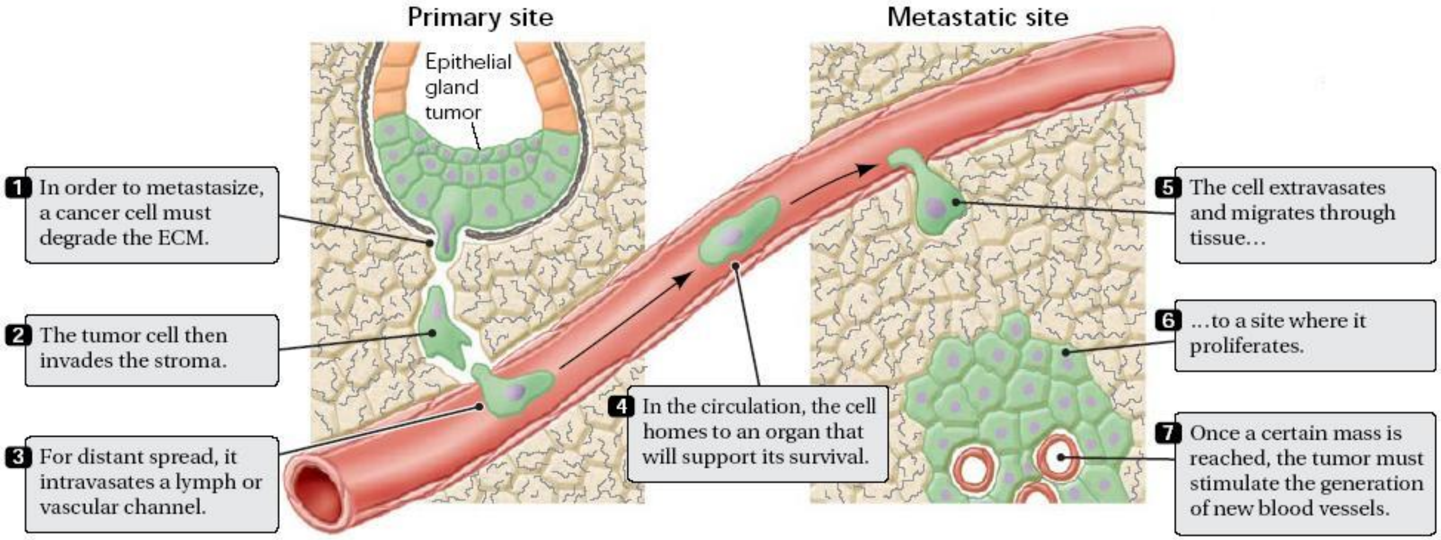

stimulus
response
matrix density
substrate stiffness
ligand presentation
topography
tissue geometry
cell–matrix interactions
mechanical stretch
shear stress
cell–cell contact
paracrine signaling
phenotype
protein expression
differentiation
migration
contractility
matrix production
matrix degradation
self-assembly
morphogenesis
tissue architecture
Cell
Environment
Matrix
Function
Malfunction

Mechanobiological adaptability

- Cell migration
- Dynamic reciprocity → decoupling multifactorial problem
- Curvature, geometry, and dimensionality

Cancer metastasis

- Responsible for >90% deaths related to solid tumors



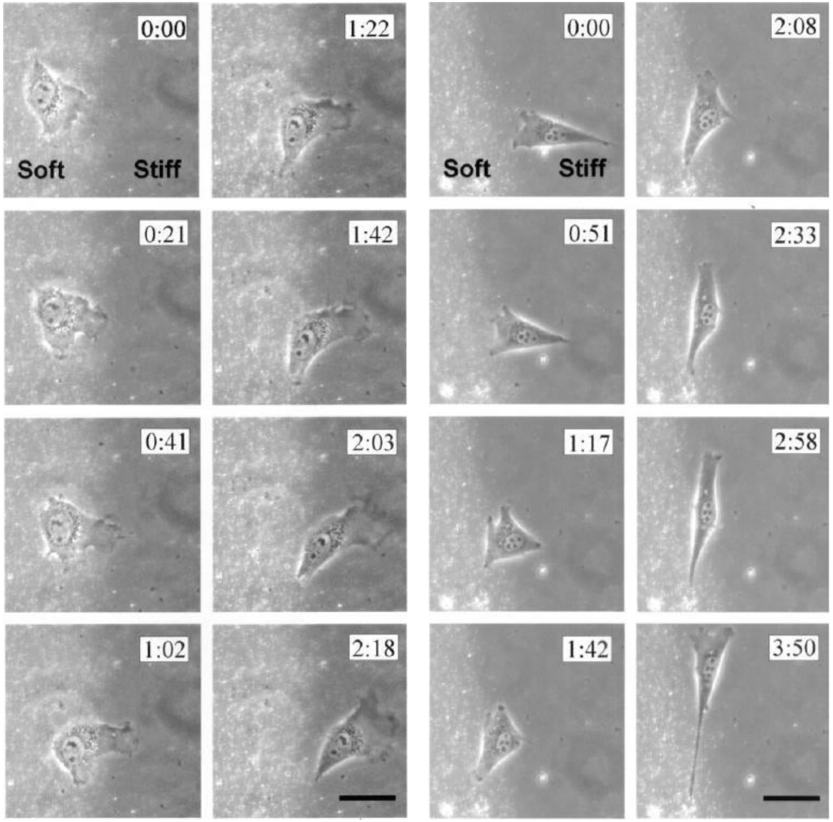
Cells in extracellular matrix (ECM)

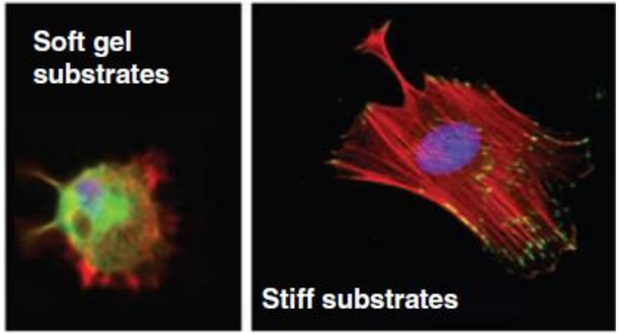
HL-60 cell

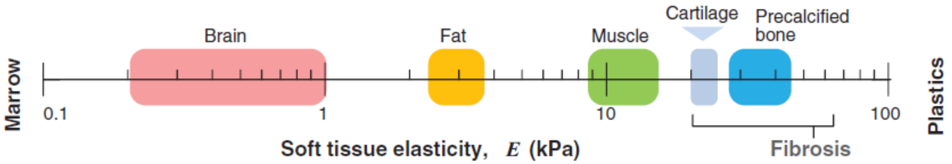
mCherry - utrophin   FITC - collagen

Chen+ *Science* 2014

Mechanical properties matter



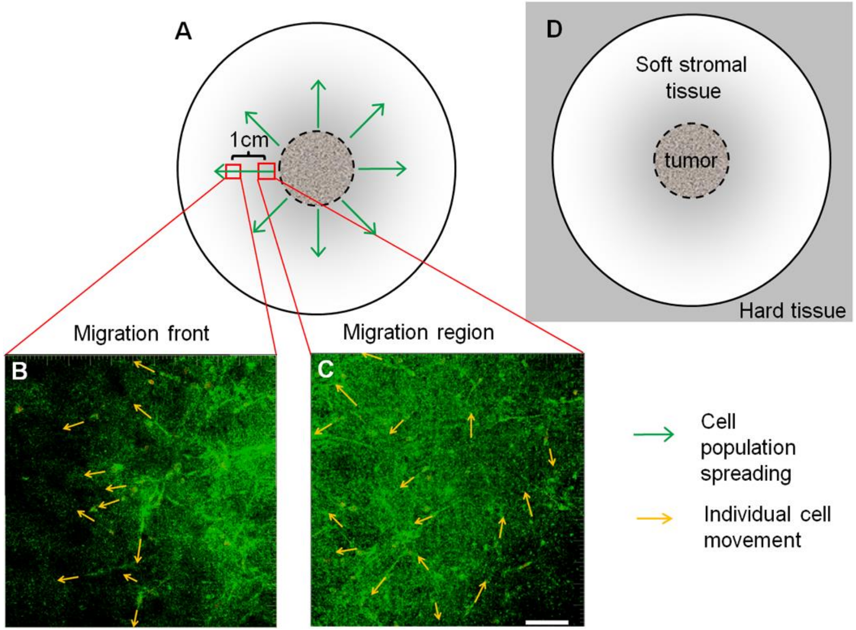




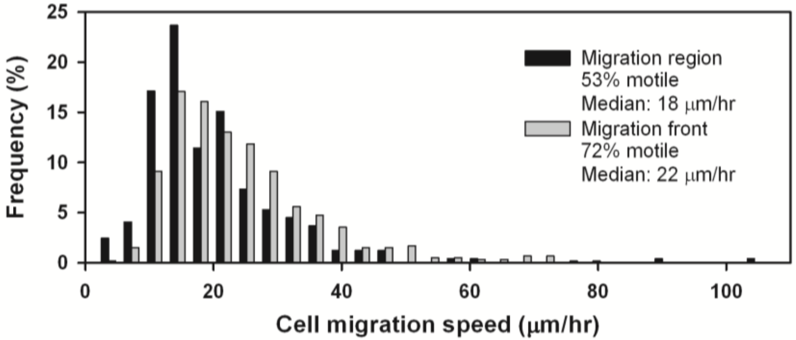
Discher+ *Science* 2009

Lo+ *Biophys J* 2000

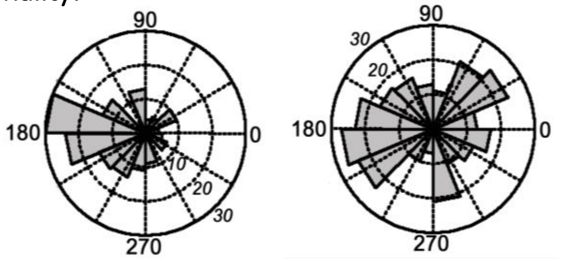
Modeling cancer invasion



Speed:



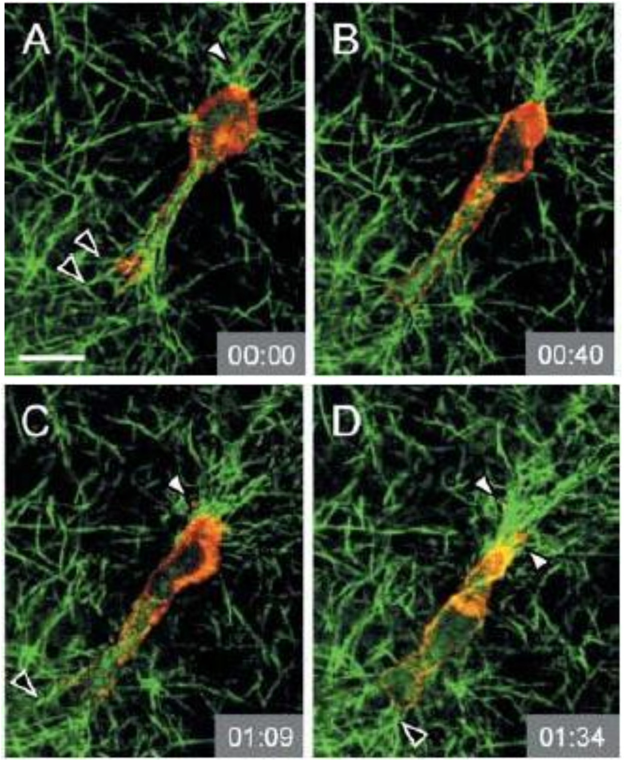
Directionality:



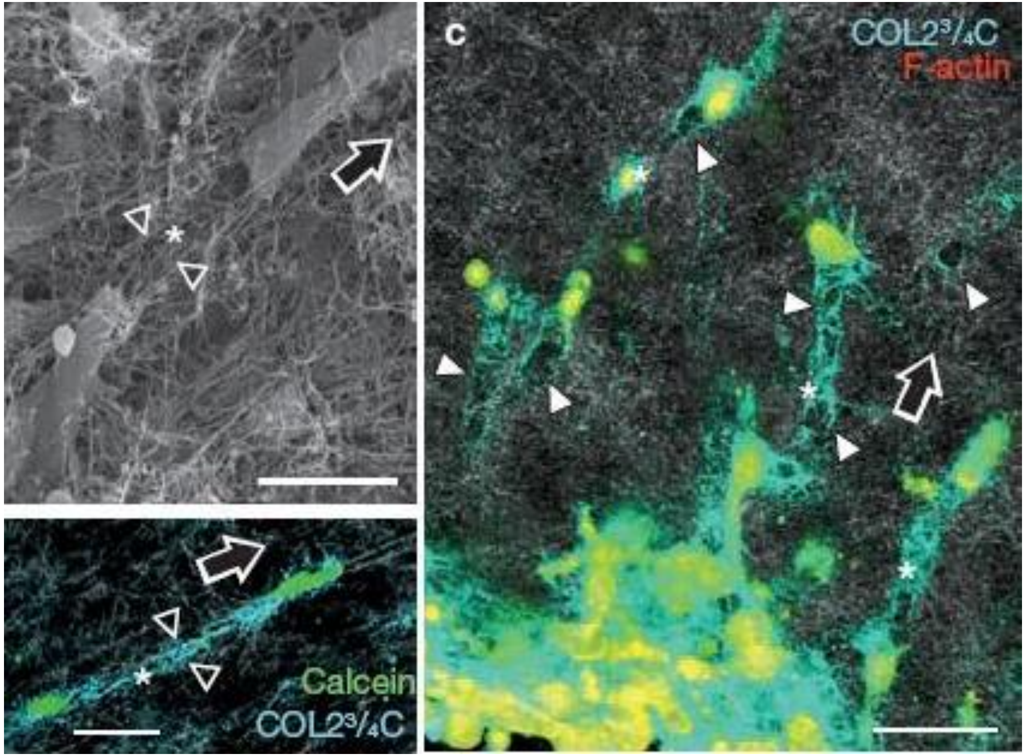
Migration front   Migration region

Sun+ *Cell Mol Bioeng* 2014, Kurniawan+ *JoVE* 2015

Cells can remodel ECM

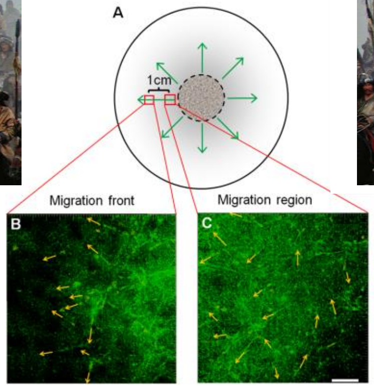


Friedl *Histochem Cell Biol* 2004

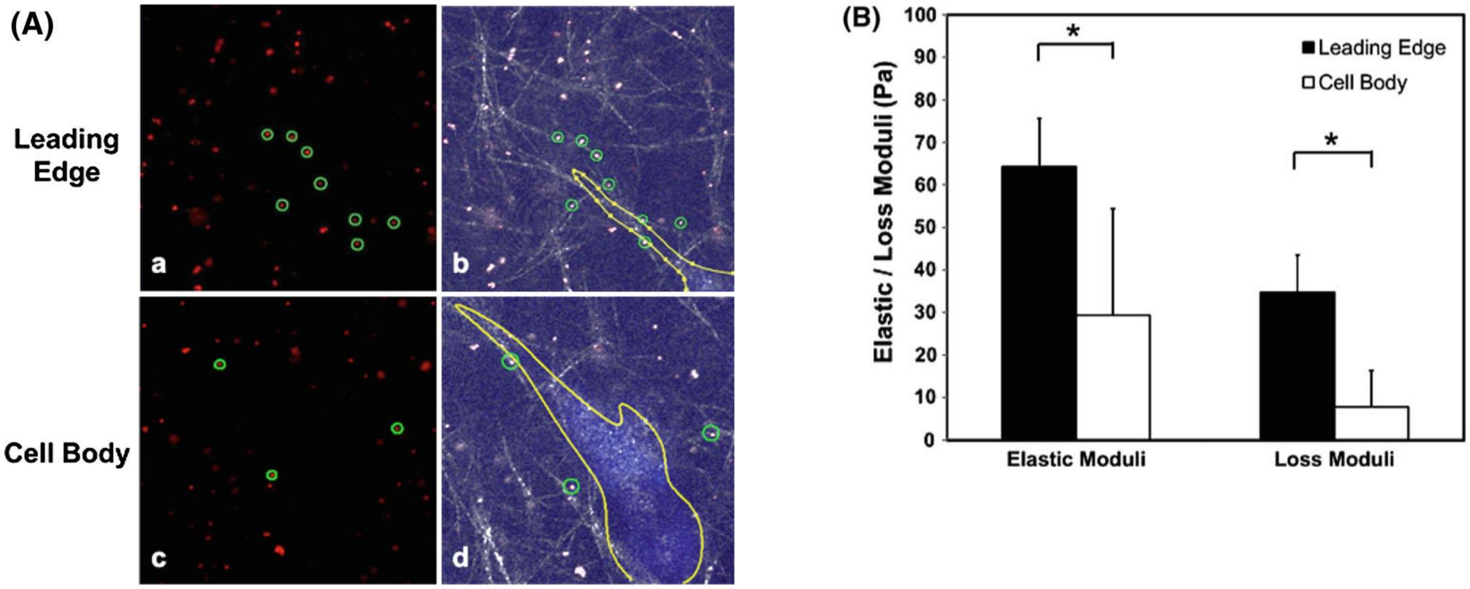


Wolf+ *Nat Cell Biol* 2007

ECM remodeling explains history dependence

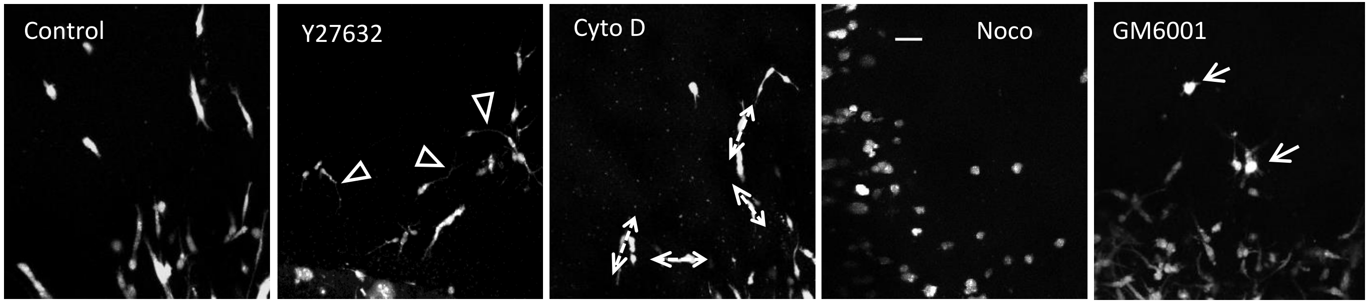


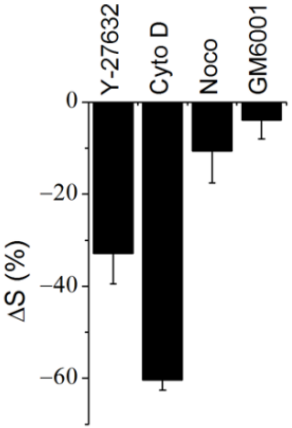
Cells alter local ECM mechanical properties

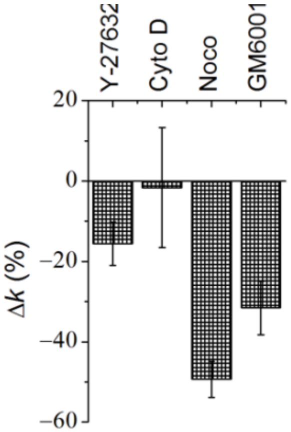


Wong+ *Biomech Model Mechanobiol 2014*

Messing with the wheels



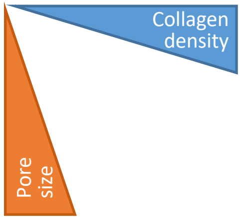


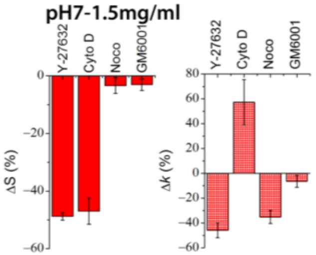


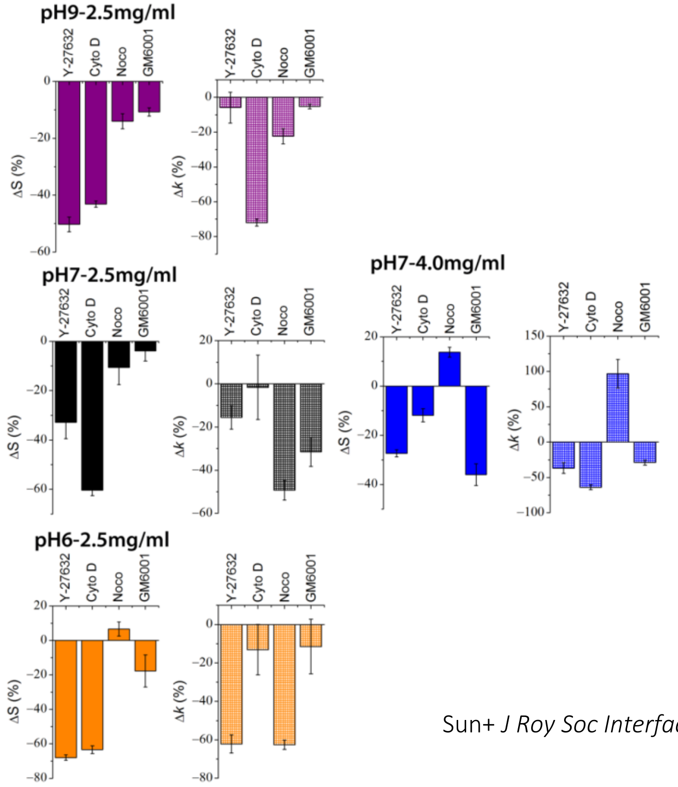
ΔS: changes to migrational speed
Δk: changes to migrational persistence

Cytochalasin D: F-actin polymerization
Y-27632: ROCK inhibitor
Nocodazole: microtubule stability
GM6001: MMP inhibitor

Interplay between intracellular and extracellular cues





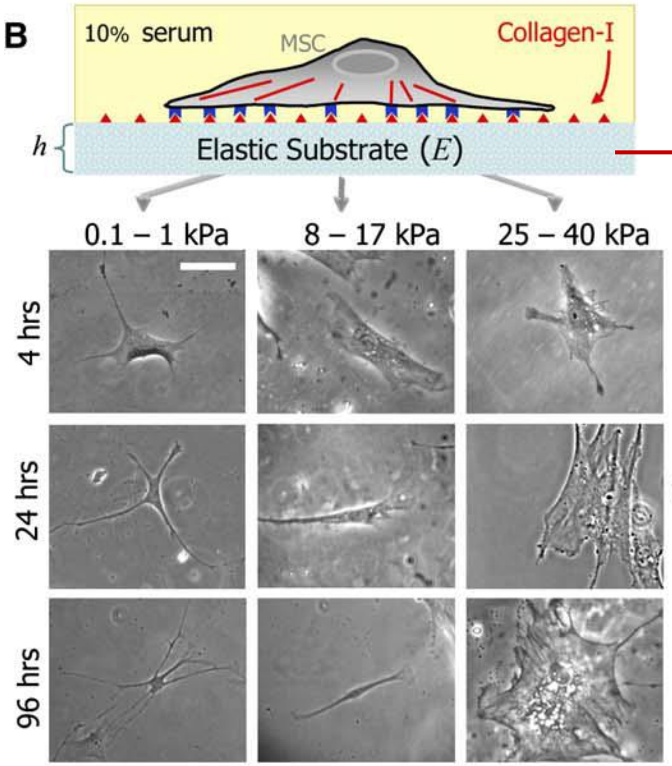


ΔS: changes to migrational speed
Δk: changes to migrational persistence

Cytochalasin D: F-actin polymerization
Y-27632: ROCK inhibitor
Nocodazole: microtubule stability
GM6001: MMP inhibitor

Sun+ *J Roy Soc Interface* 2014

Substrate stiffness determines stem cell differentiation



Synthetic materials

What about fibrous ECM?

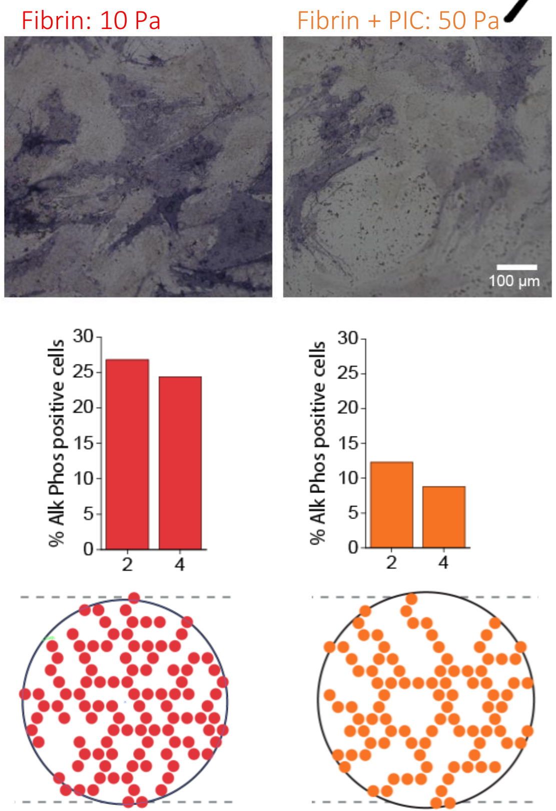
Engler+ *Cell* 2006

Do cells sense and respond to “global” (network) or “local” (fiber) stiffness?

Influence of *local* ECM mechanical properties

hMSCs

Alkaline
phosphate
(osteogenic)



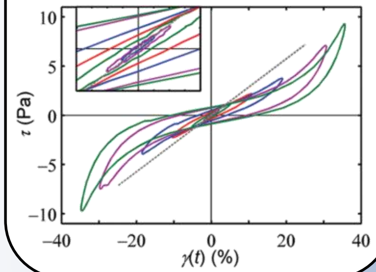
Stiffer in bulk, but less
differentiation to
osteoblasts..

.. because of lower
local fiber stiffness

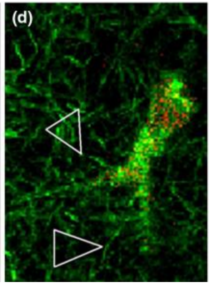
Bruekers+ *Cell Adh Migr* 2016

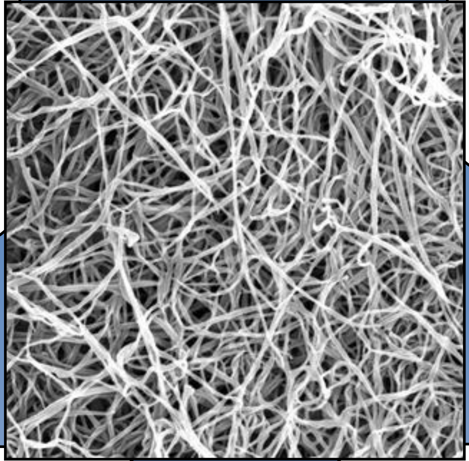
Peculiarities of fibrous ECM mechanobiology

Nonlinear viscoelasticity
Kurniawan+ *Biomacromolecules* 2012

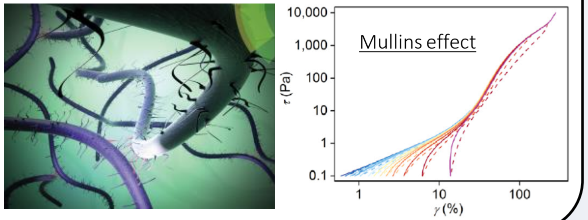


Cell-remodelable
Sun+ *Cell Mol Bioeng* 2014

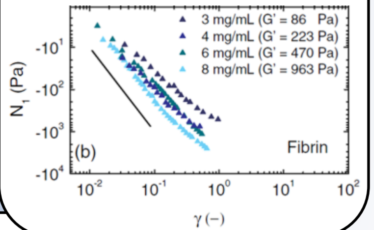




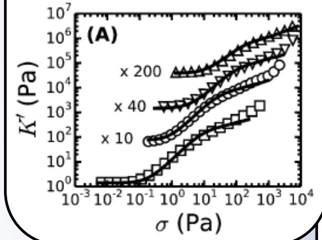
Self-reinforcing plasticity
Kurniawan+ *Biophys J* 2016, Vos+ *Soft Matter* 2017



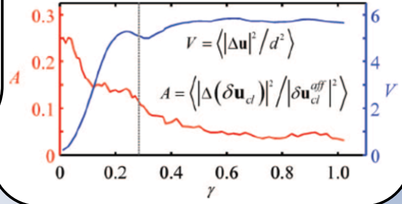
Negative Poynting effect
de Cagny+ *PRL* 2016



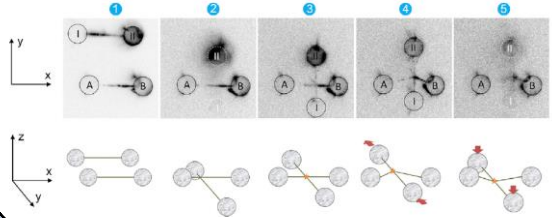
Multiscale strain-stiffening
Kurniawan+ *JTH* 2014,
Piechocka+ *Soft Matter* 2016



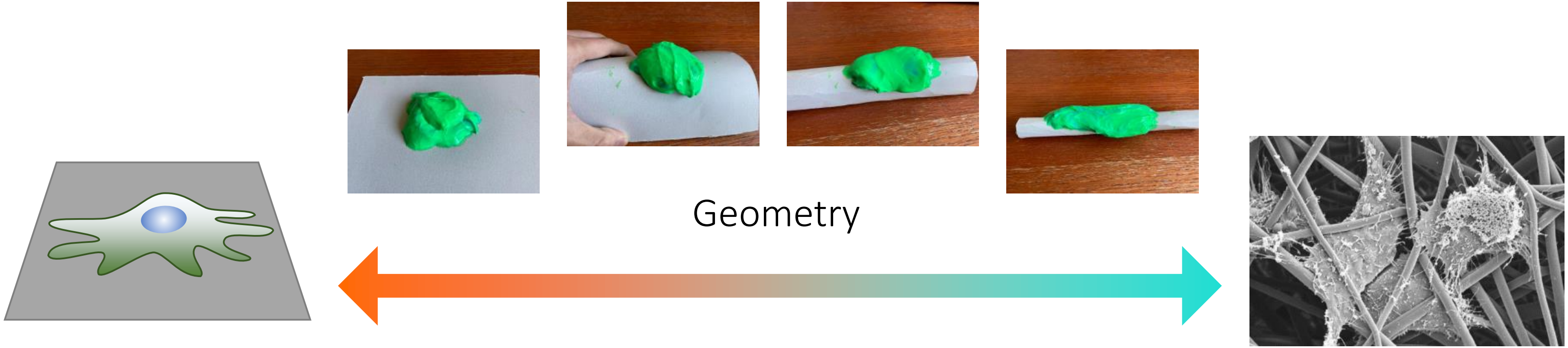
Role of entanglement and crosslinking
Kurniawan+ *JCP* 2012



Multiscale adaptability
Kurniawan+ *Biophys J* 2016

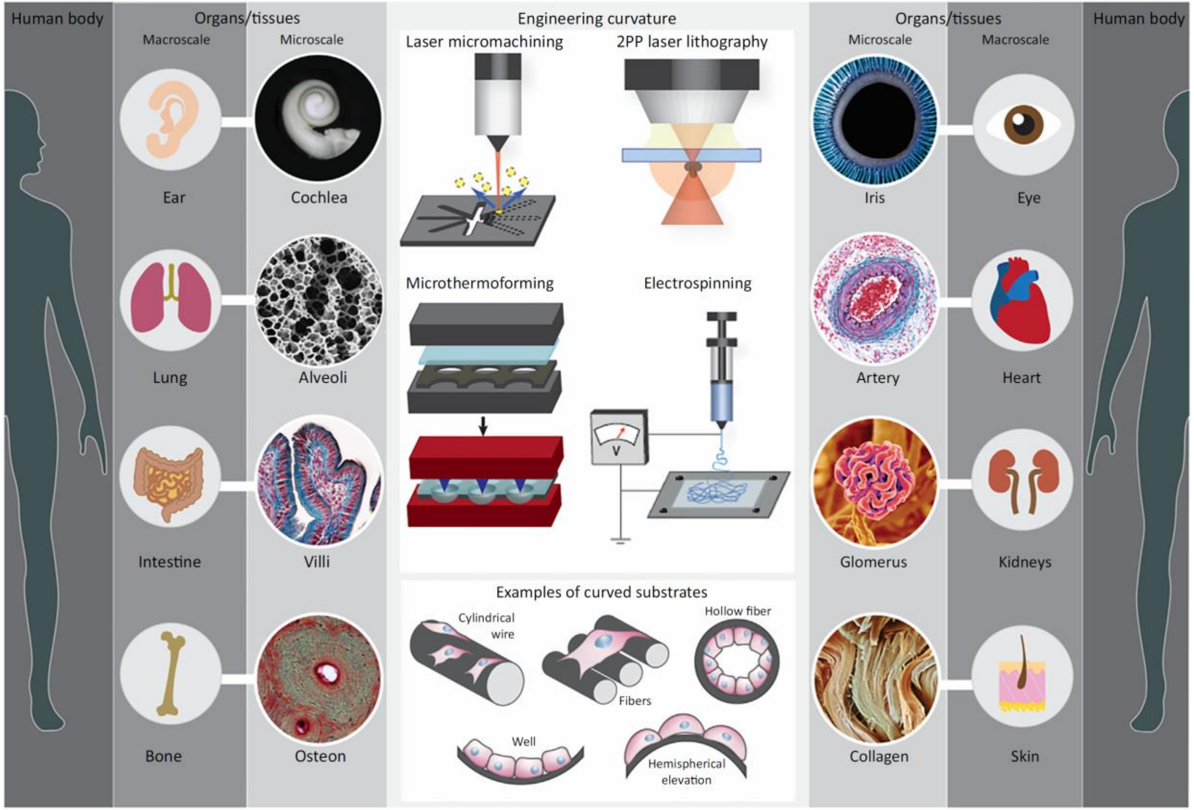


Cells and fibers



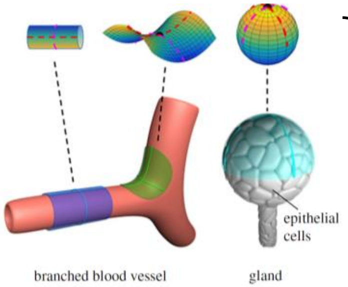
with help from Aubrey Kurniawan ☺

Ubiquity of non-planar geometry in biology

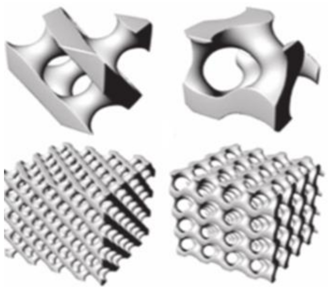


Baptista+ *Trends Biotechnol* 2019
Callens+ *Biomaterials* 2019
Werner+ *Materials* 2020
Schamberger+ *Adv Mater* 2023

Key challenge: understanding how cells recognize tissue and scaffold geometry

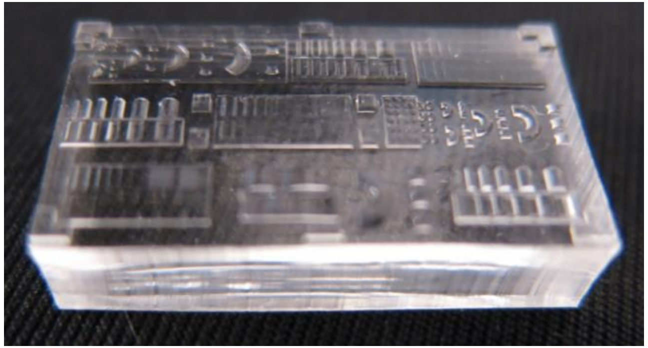


Assoian+ *Open Biol* 2019

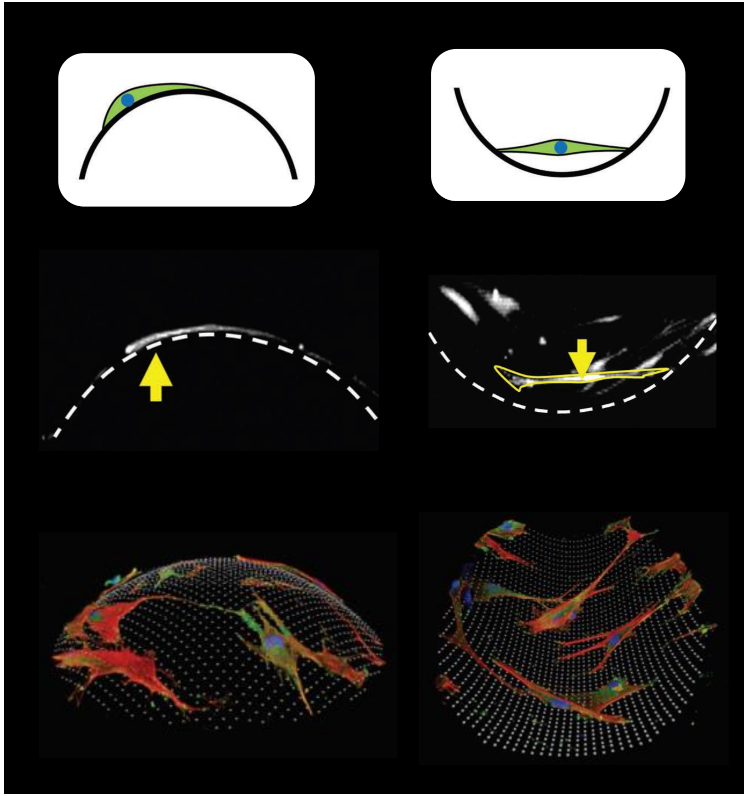


Blanquer+ *Biofabrication* 2017

2.5D "Curvo-Chip"

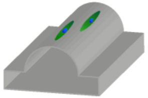


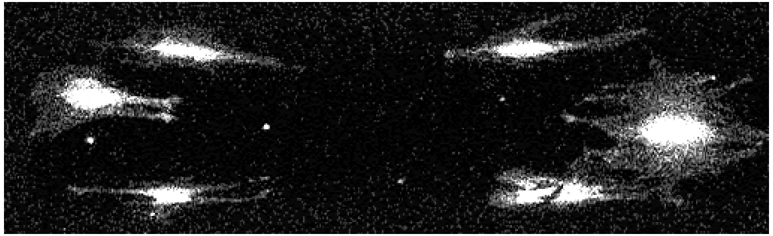
Maike Werner, Carlijn Bouten
Ansgar Petersen

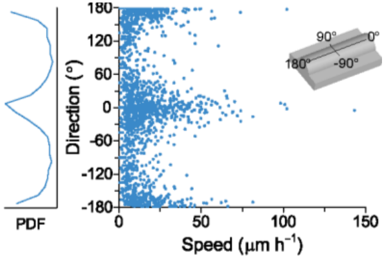


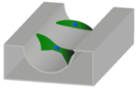
Cells dynamically sense geometrical cues

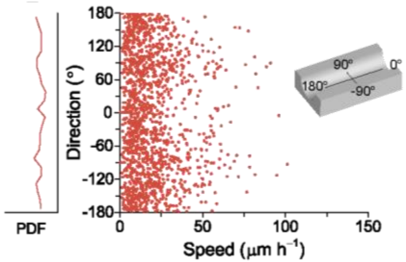
Distinct migration phenotypes on convex and concave structures



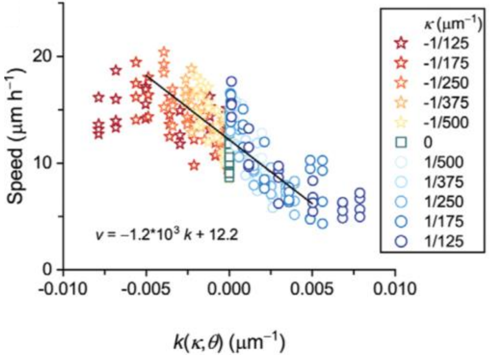






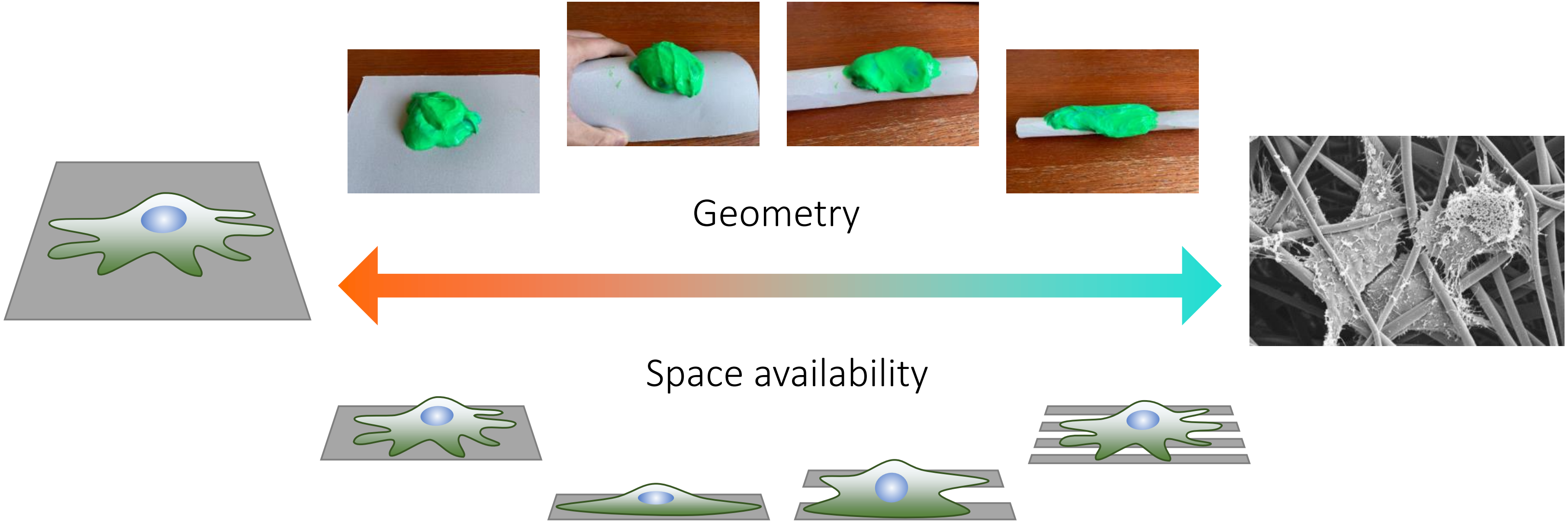


Universal relation between migration phenotype and perceived curvature

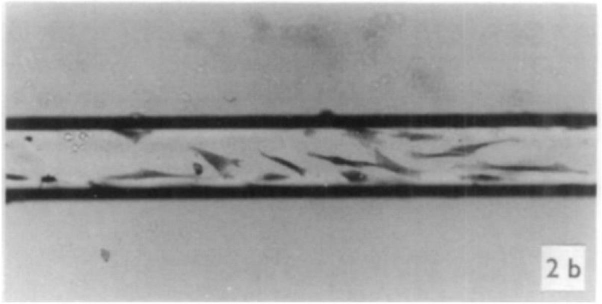


v Gaal+ *Adv Mater Interface* 2021, Werner+ *Materials* 2020, Werner+ *Adv Biosyst* 2019, Werner+ *Interface* 2018

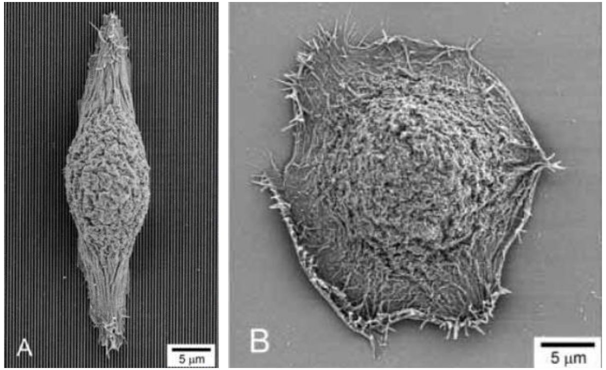
Cells and fibers



Contact guidance – well known but poorly understood



Dunn & Heath, *Exp Cell Res* 1976

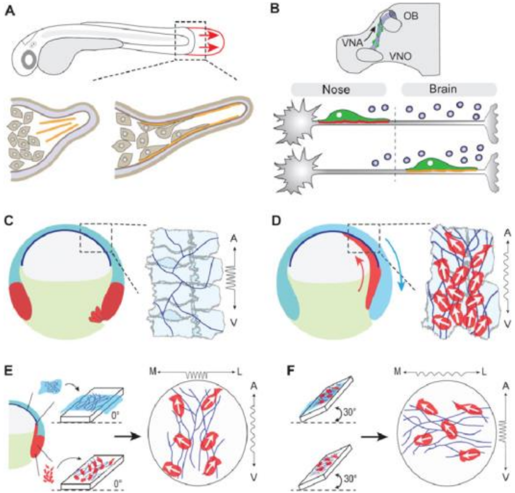


Anisotropic

Isotropic

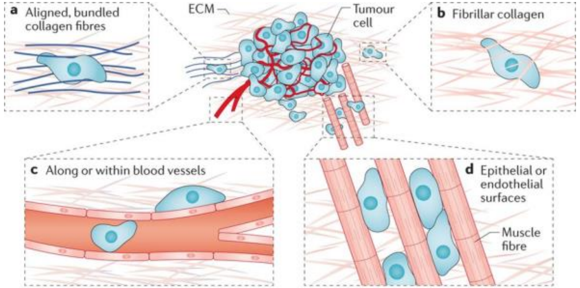
Teixeira+ *J Cell Sci* 2003

Development & Morphogenesis

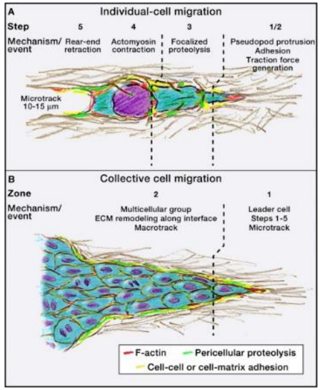


Reig+ *Development* 2014

Cancer invasion



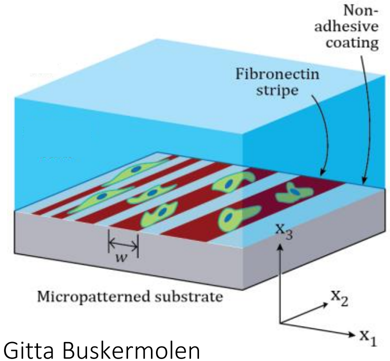
Paul+ *Nat Rev Cancer* 2016



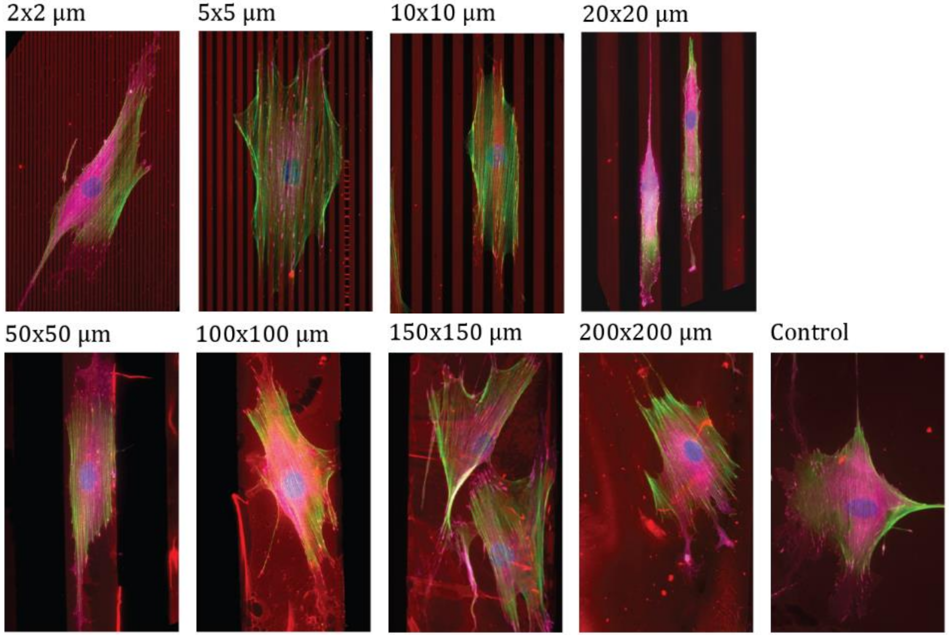
Friedl & Alexander, *Cell* 2011

What drives contact-mediated cell alignment?

Experiment: protein patterning



Gitta Buskermolen



Statistical mechanics model

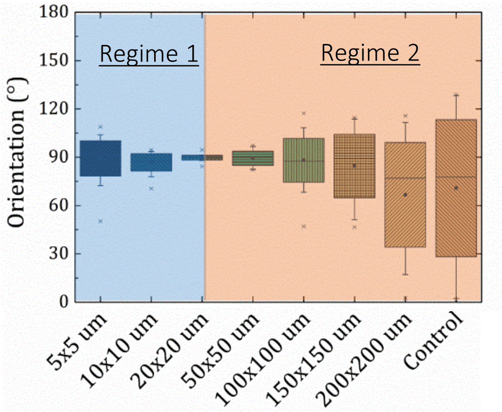
$$G^{(j)} = \int_{V_{cell}} f dV,$$

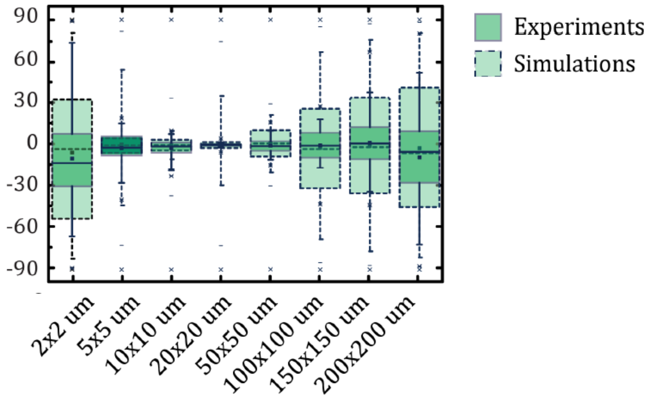
$$f = f_{cyto} + \Phi_{elas} + f_{adh}$$

$$f_{adh} = \begin{cases} \frac{(F(\boldsymbol{x}))^2}{2k_a}, & \text{if } \boldsymbol{x} \text{ is adhesive,} \\ \\ \frac{(F(\boldsymbol{x}))^2}{2k_n}, & \text{if } \boldsymbol{x} \text{ is non-adhesive,} \end{cases}$$

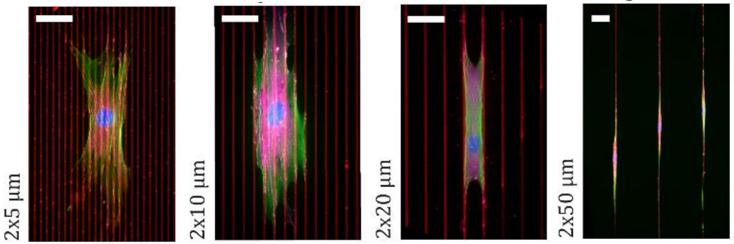
with Vikram Deshpande, Siamak Shishvan, Tommaso Ristori

Length-scale-dependent contact guidance mechanism

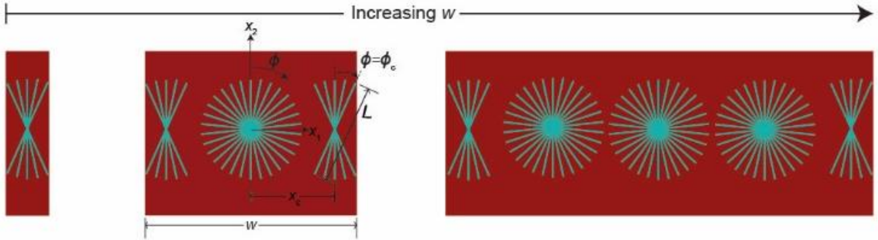




Gaps induce alignment at small length scales



Entropy drives alignment at large length scales



Buskermolen+ *Cell Rep Phys* Sci 2020, Buskermolen+ *Biophys J* 2019

Lesson learnt: Function follows form

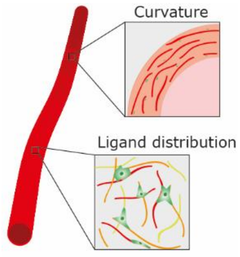
- Physical geometry of substrate induces distinct adhesion morphologies, cell morphologies, and contractility states
  - in a length-scale-dependent manner
  - in a dimension-dependent manner

- Possibilities for mechanobiology-motivated tool to direct cell response?

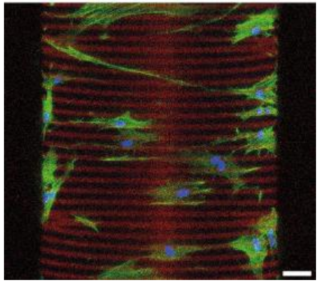
Underway..

Single cells

Combinations of cues

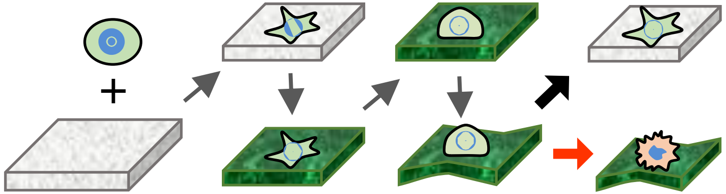


curvature + contact guidance + stiffness



Mirko D'Urso,
Dylan Mostert

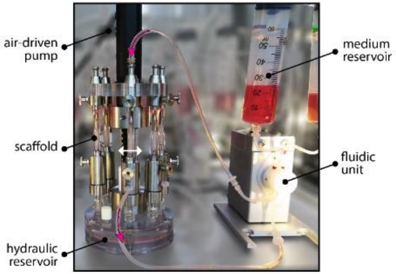
Dynamic manipulation & adaptation



Fundamental insight into cellular physico-sensing

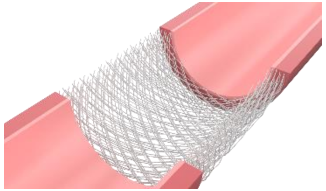
Maaike Bril

Multicellular constructs and tissues



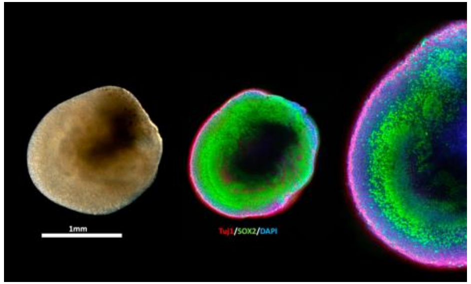
Multi-cue bioreactors

Mattia Manenti,
Dylan Mostert



curvature + contact guidance + shear + strain

Sarah Pragnere



Guided formation of tissues and organoids

Aref Saberi, Simone de Jong,
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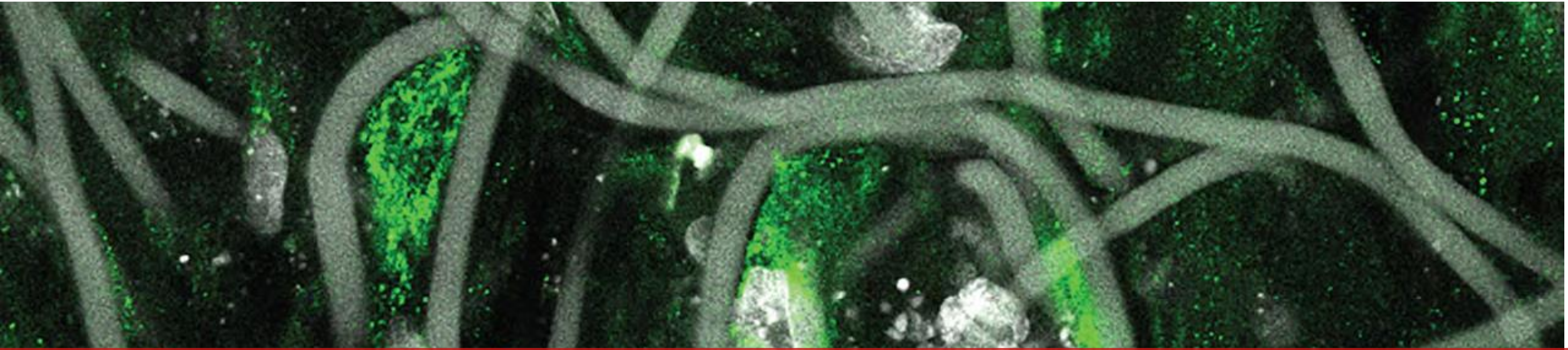

Mechanobiological control of cell phenotype and tissue development

Nicholas A. Kurniawan

TUM talk, 4 July 2023