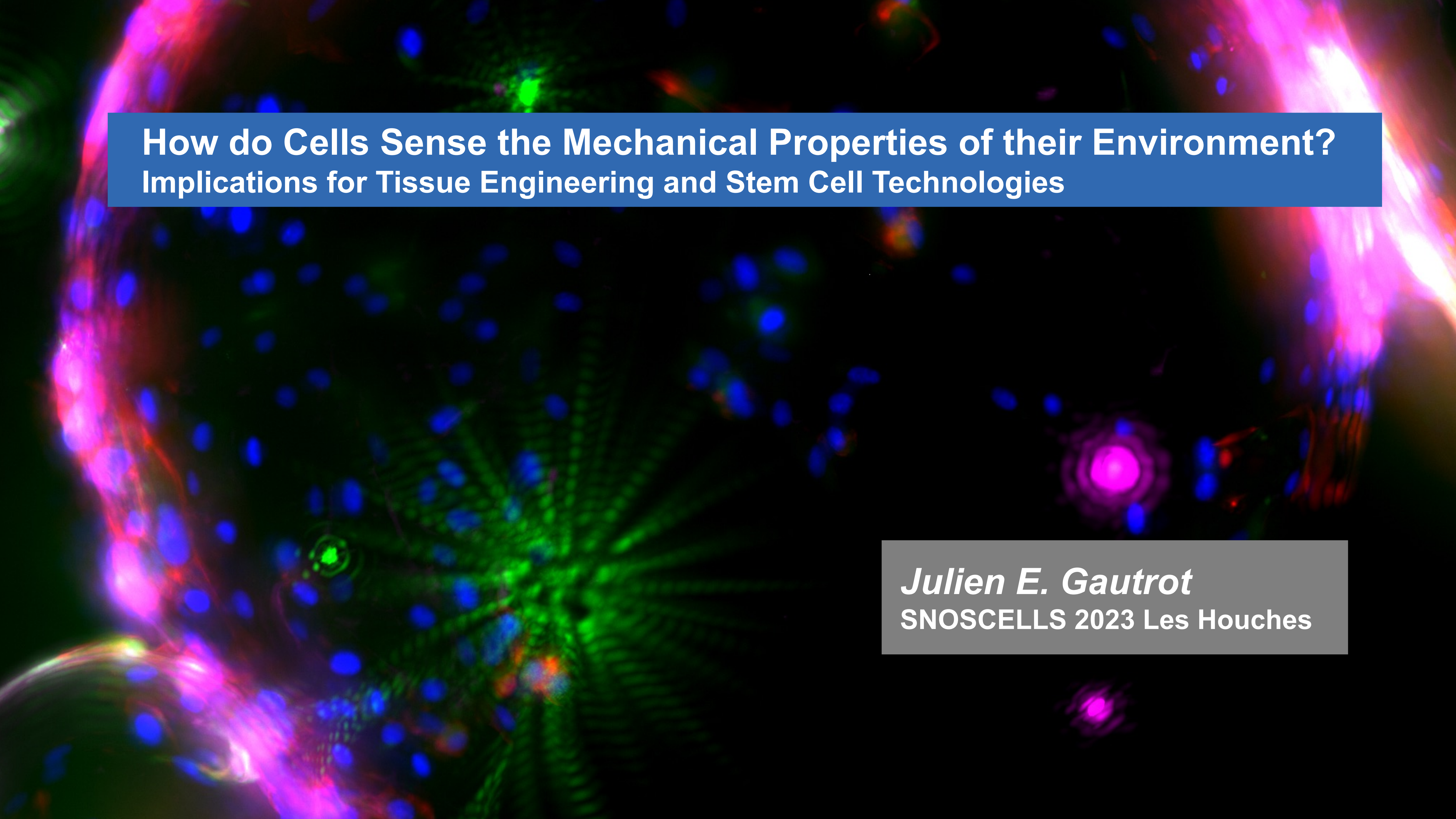
How do Cells Sense the Mechanical Properties of their Environment?

Implications for Tissue Engineering and Stem Cell Technologies

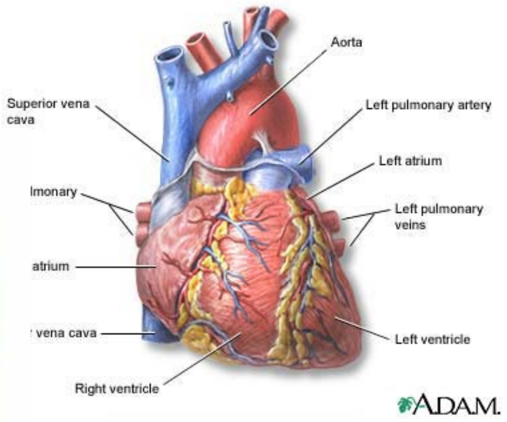


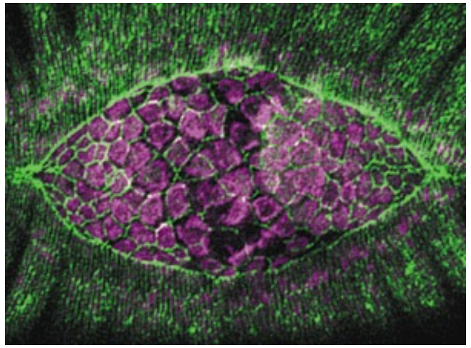
Julien E. Gautrot

SNOSCELLS 2023 Les Houches

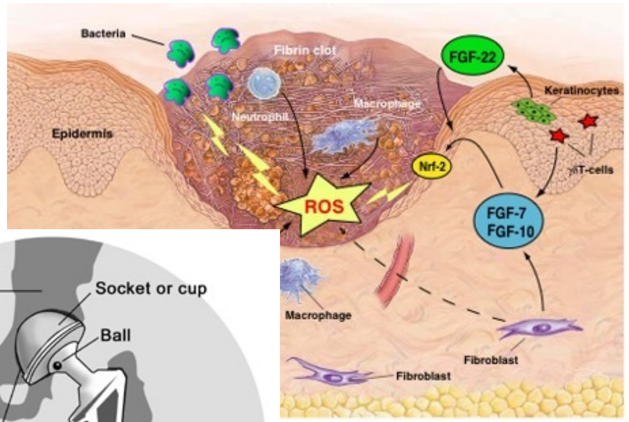
Physical Forces Matter in Biology

Muscles

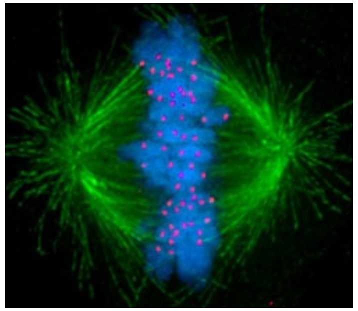




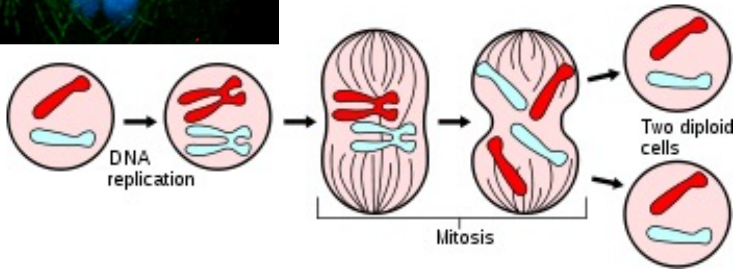
Development

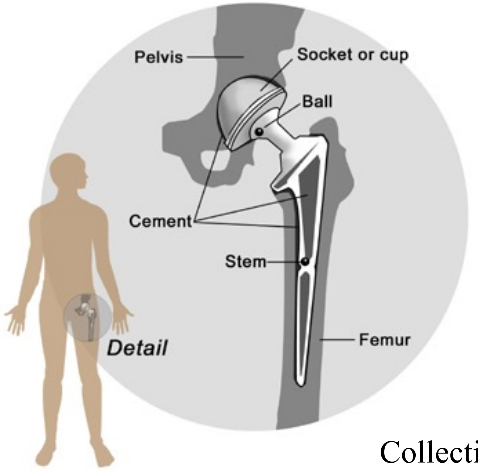


Physical parameters are important at all scales and functions.



Mitosis

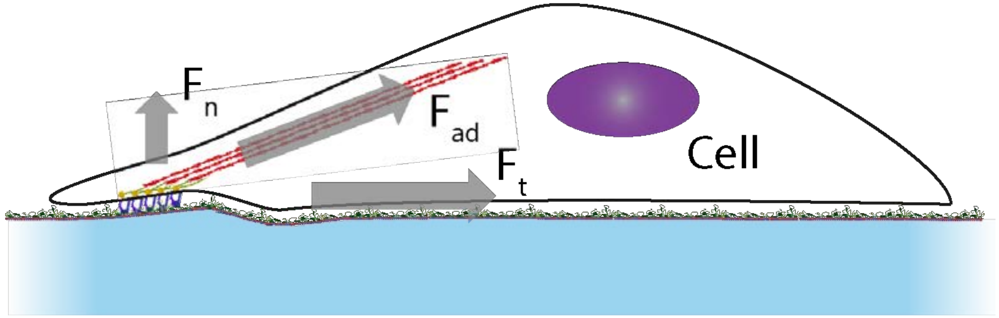




Biomedical Applications

Collection of images from the web

Cell Sensing of the Mechanical Properties of their Environment



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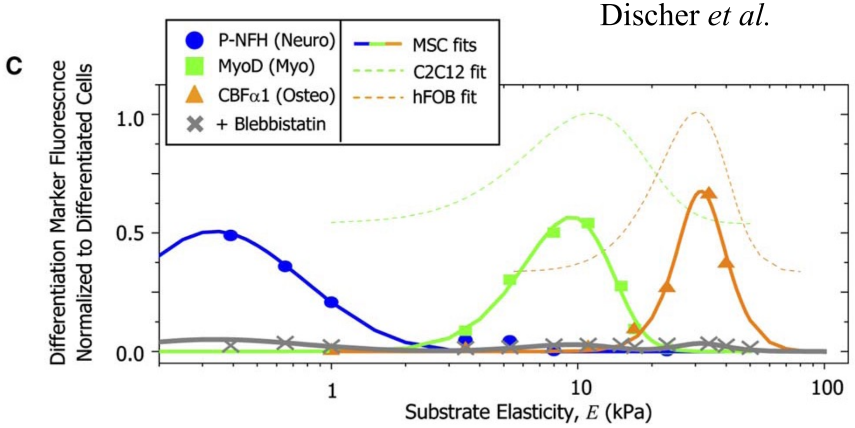
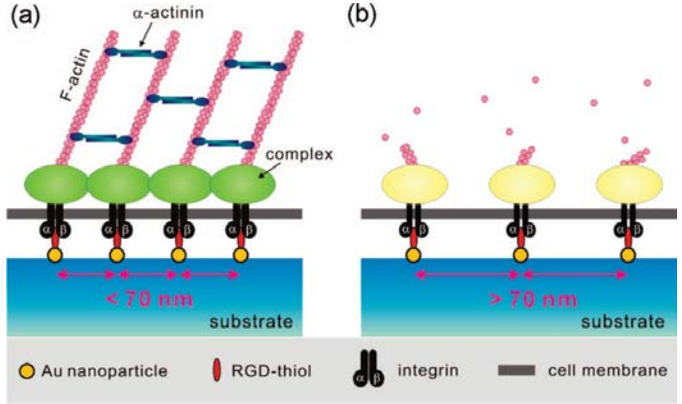
Cells Sense Multiple Physical Signals

Discher *et al.*



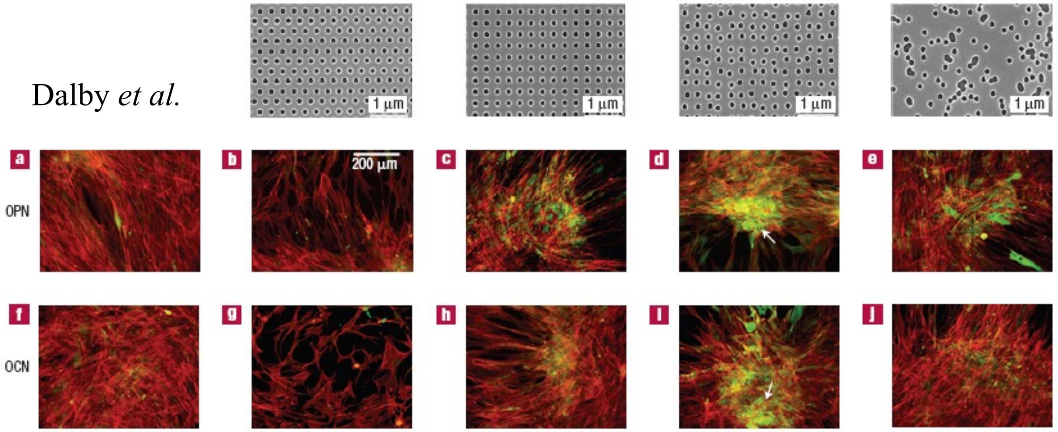
Mechanical Properties

Geometry



Spatz *et al.*

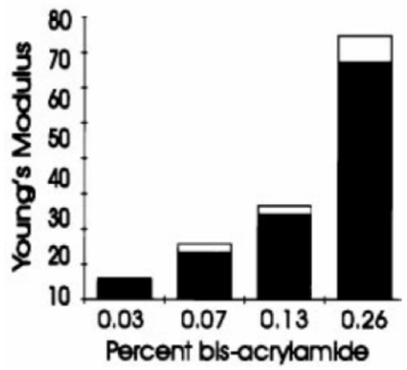
Dalby *et al.*



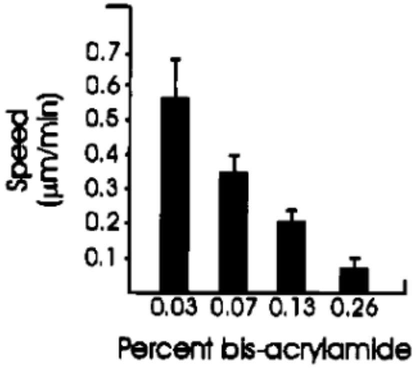
Topography (3D Geometry)

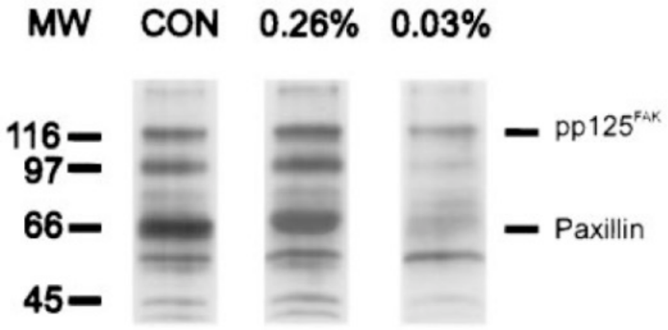
Matrix Stiffness Controls Cell Adhesion and Motility

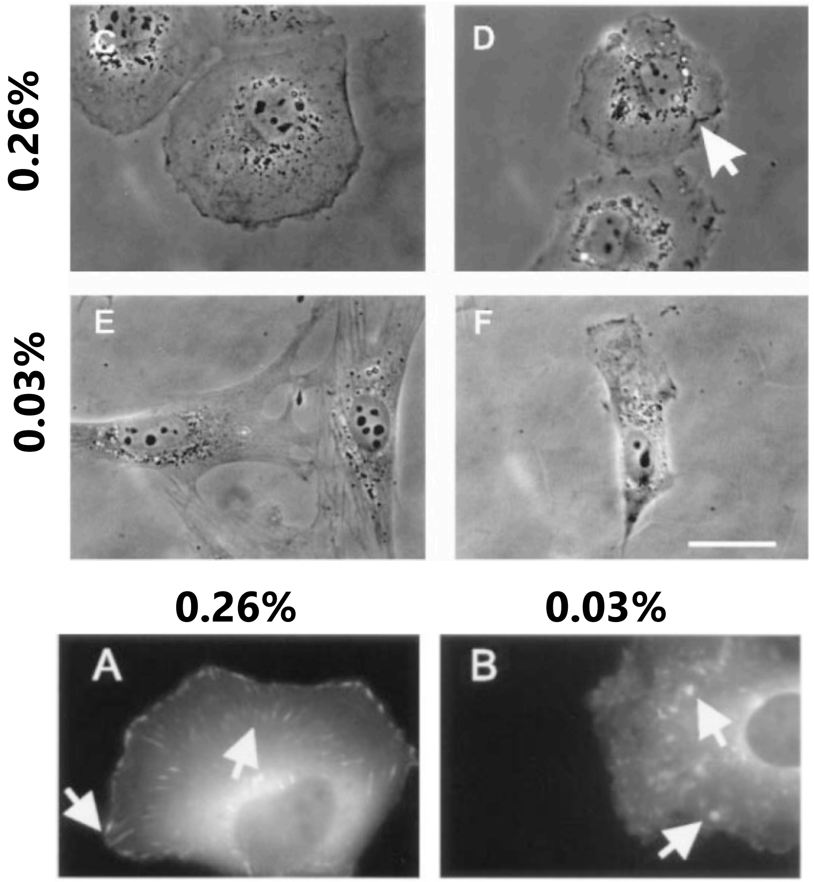
Gel Stiffness



Cell Motility



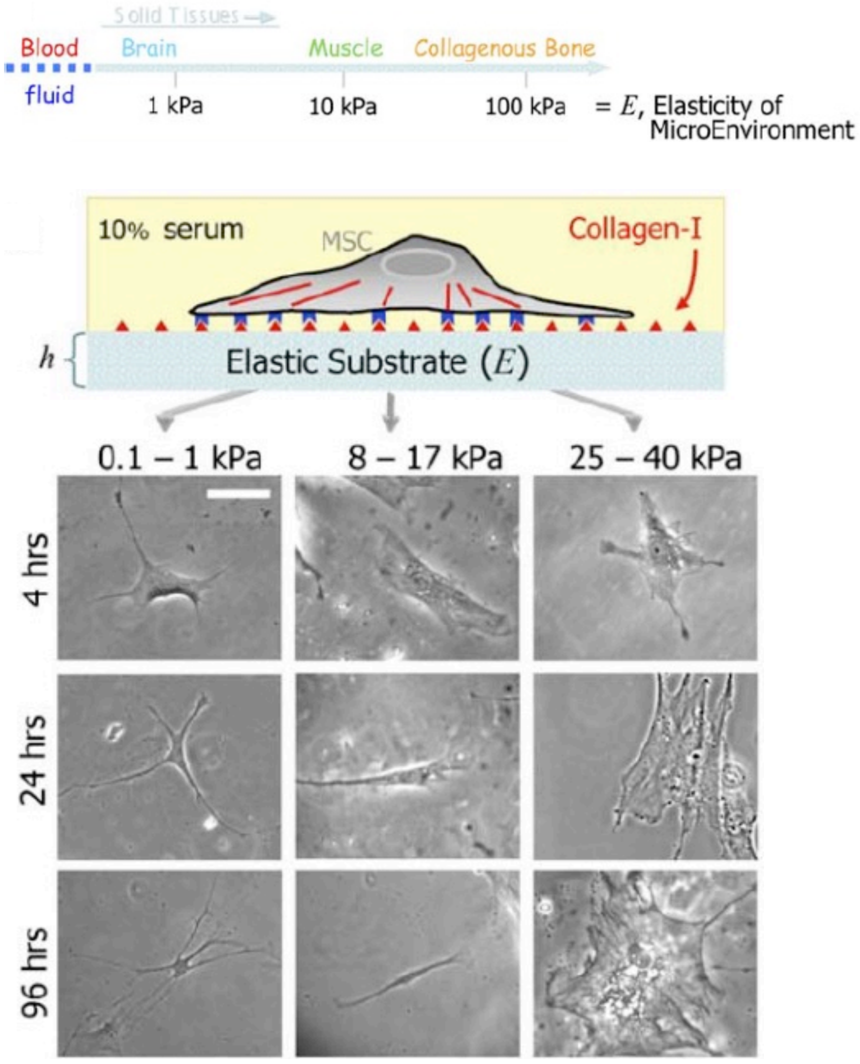




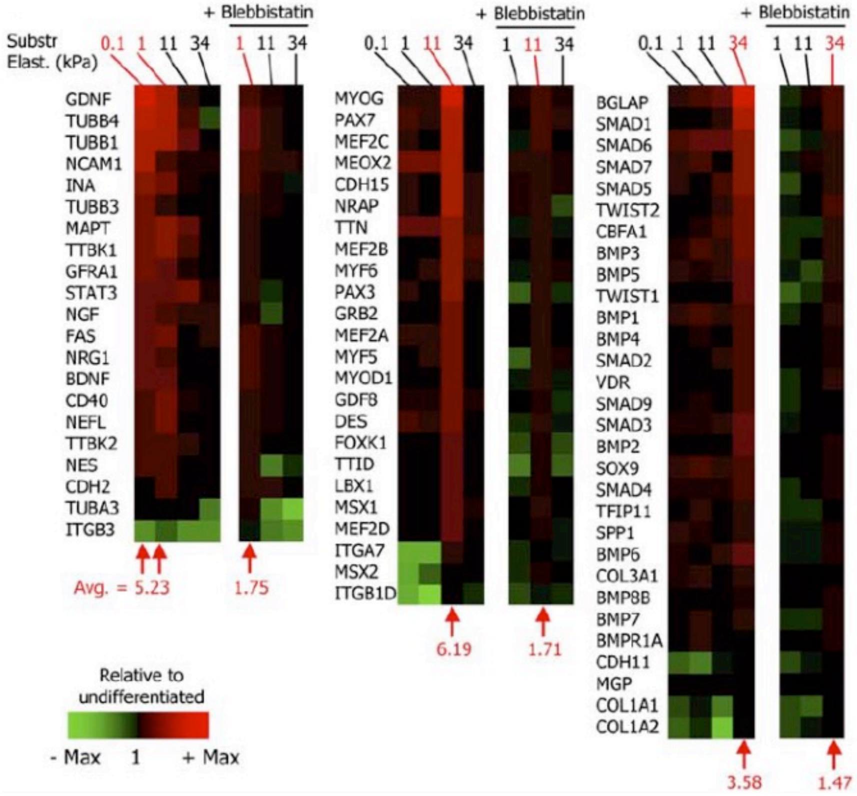
Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 13661–13665, December 1997

- The stiffness of hydrogels such as poly(acrylamide) gels regulates cell spreading.
- Focal Adhesion formation and protein phosphorylation are also affected.
- Cell motility is also regulated by matrix mechanics.

Matrix Mechanics Impacts Stem Cell Differentiation



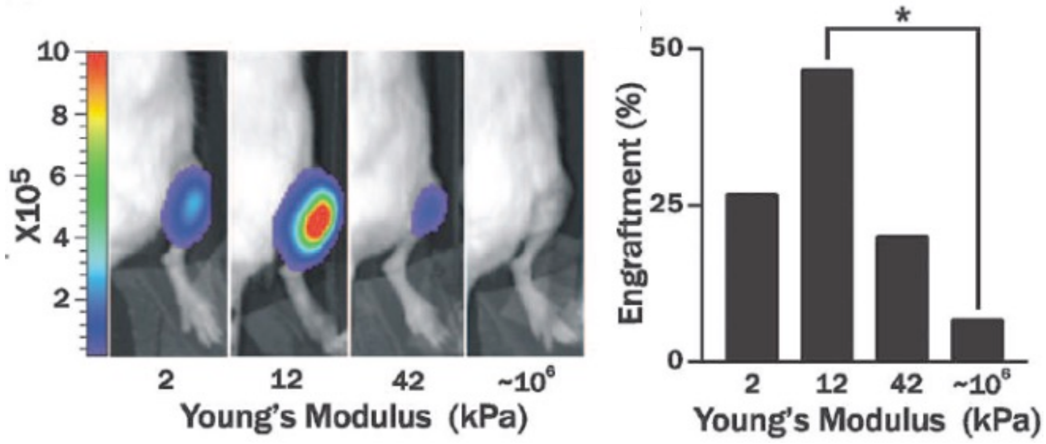
Cell *126*, 677–689, August 25, 2006



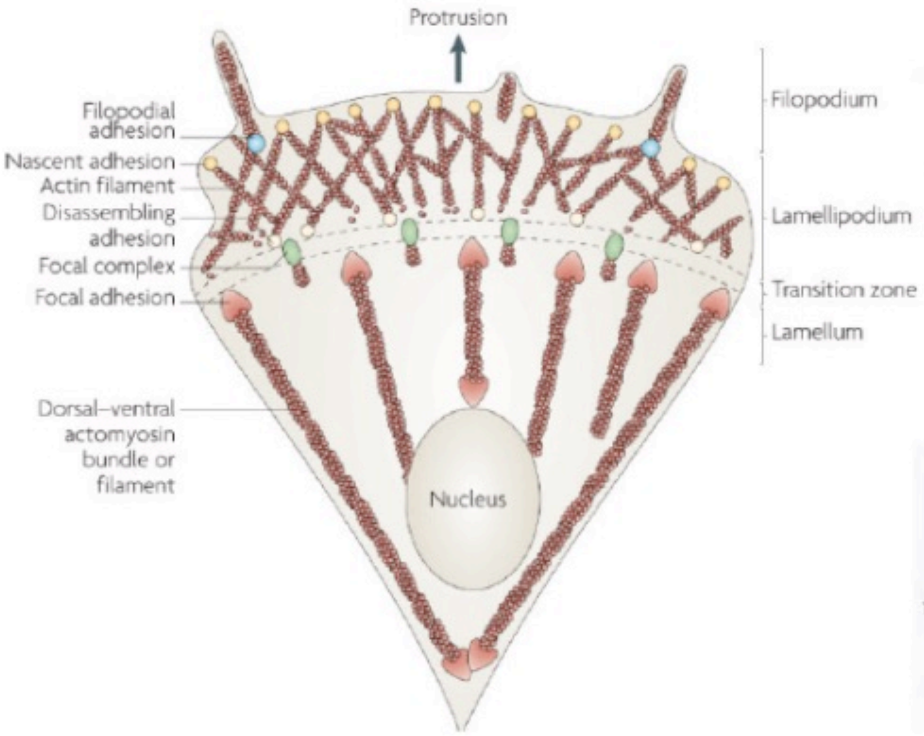
- Mesenchymal Stem Cells (MSCs) differentiation is directed by matrix mechanics.
- Expression of differentiation markers correlates with matrix mechanics.

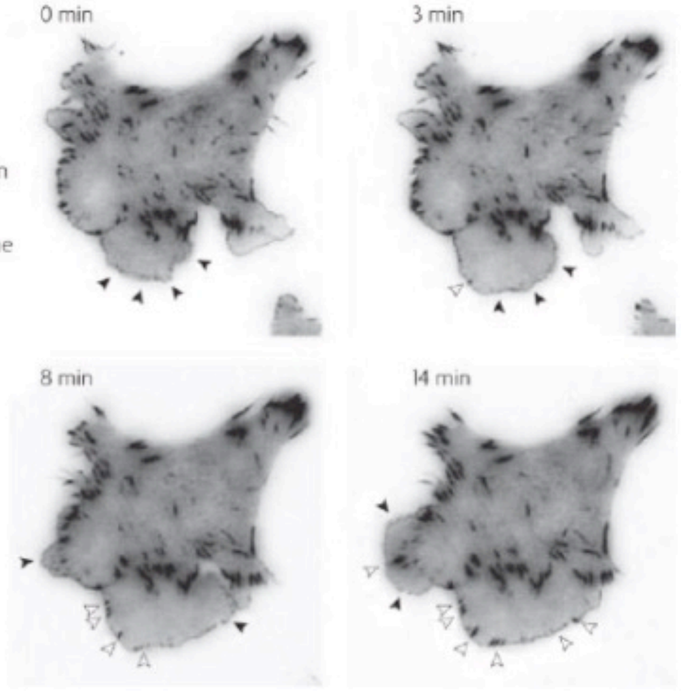
Stem Cell Self-Renewal is Regulated by Matrix Stiffness

- Muscle Stem Cell self-renewal is regulated by matrix stiffness.
- Results in improved engraftment in vivo.
- Should be important design parameter for tissue engineering.



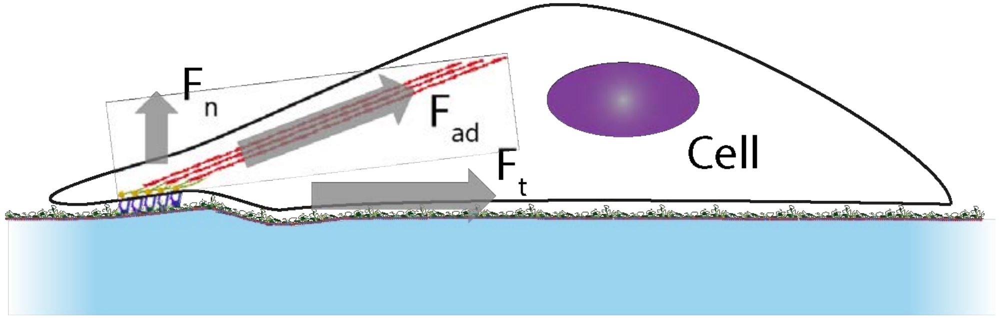
How to Organise a Complex Dynamic Contractile Cytoskeleton?





Nat Rev Mol Cell Biol. 2010 September ; 11(9): 633–643.

Cell Sensing of the Mechanical Properties of their Environment



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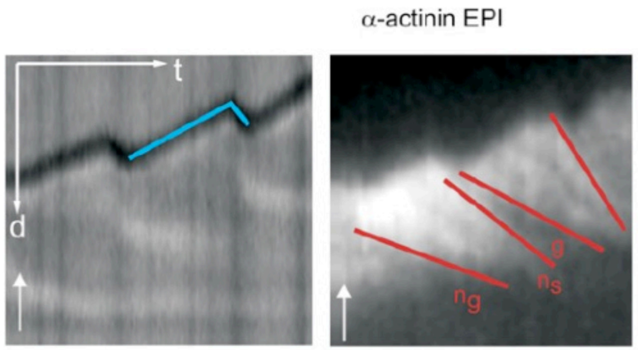
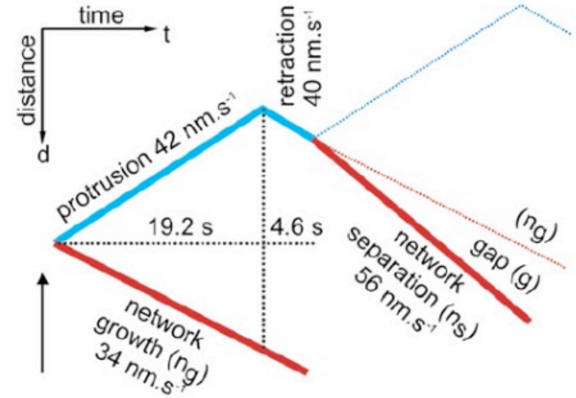
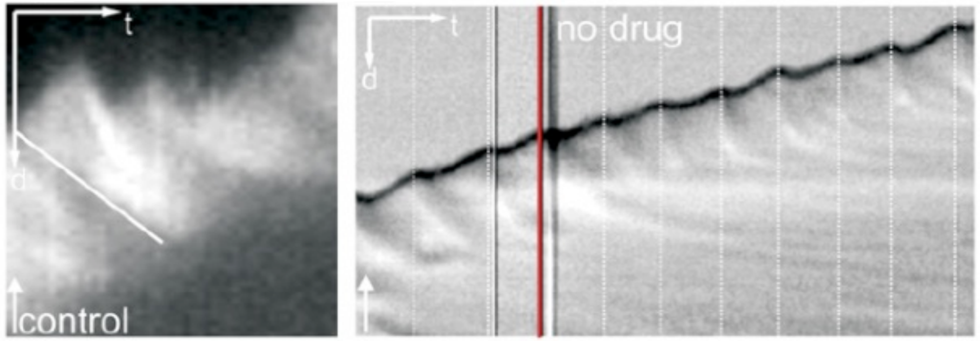
The Regulation of Cell Membrane Deformation at the Lamellum



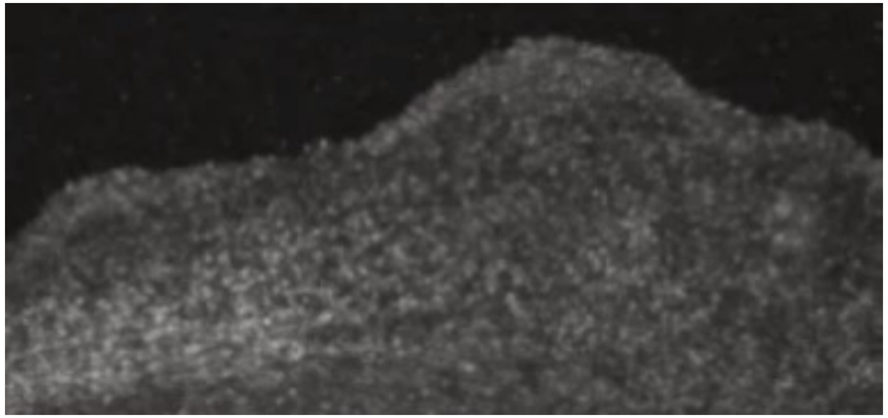


- Cell spreading and motility are sustained by cyclic progression of cell membrane (lamellipodium).
- Each cycle is associated with the persistence of adhesion molecules (α-actinin, paxilin).

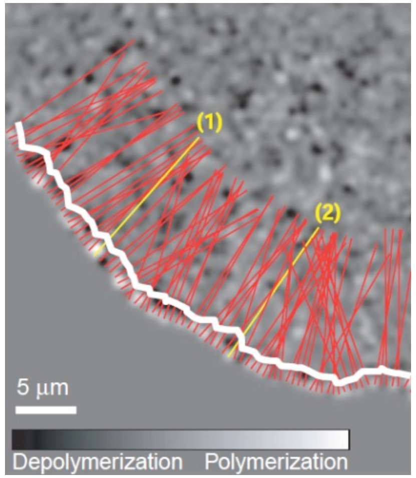


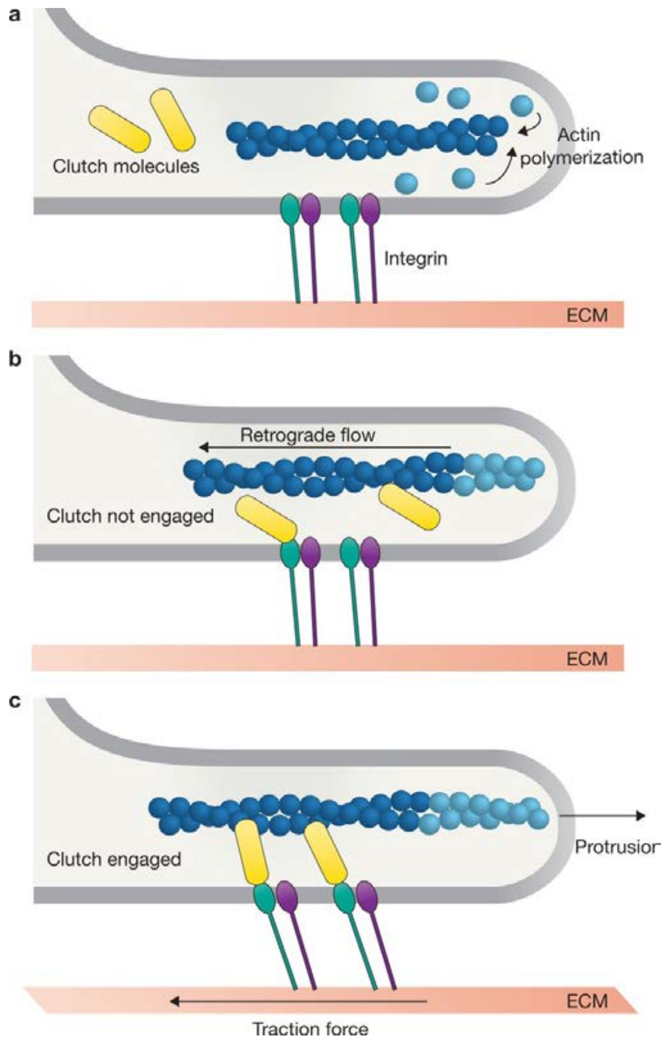
Cell *128*, 561–575, February 9, 2007

Actin Flow and the Molecular Clutch Model



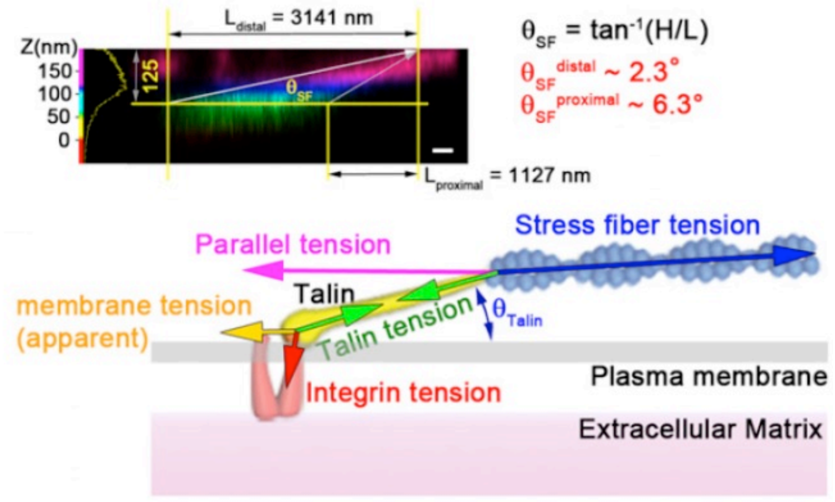
- Actin flow regulates membrane deformation and sustains forces associated with adhesion reinforcement.
- Actin flow dynamics defines the transition between the lamellipodium and lamella.
- A molecular clutch enables traction forces to be generated on the matrix.



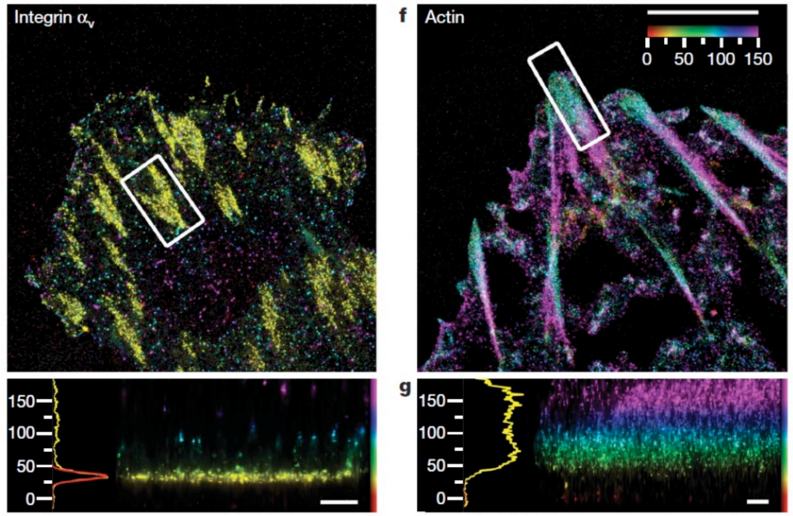


Nature Cell Biology 17(8). DOI 10.1038/ncb3191

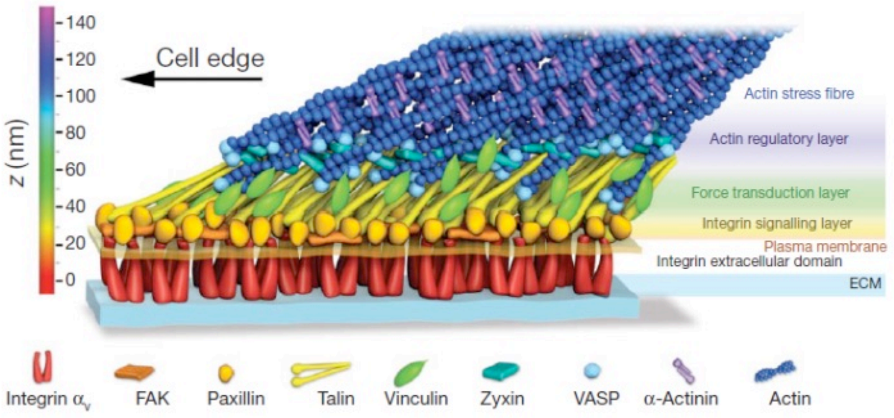
Focal Adhesion Formation



E4864–E4873 | PNAS | Published online August 17, 2015

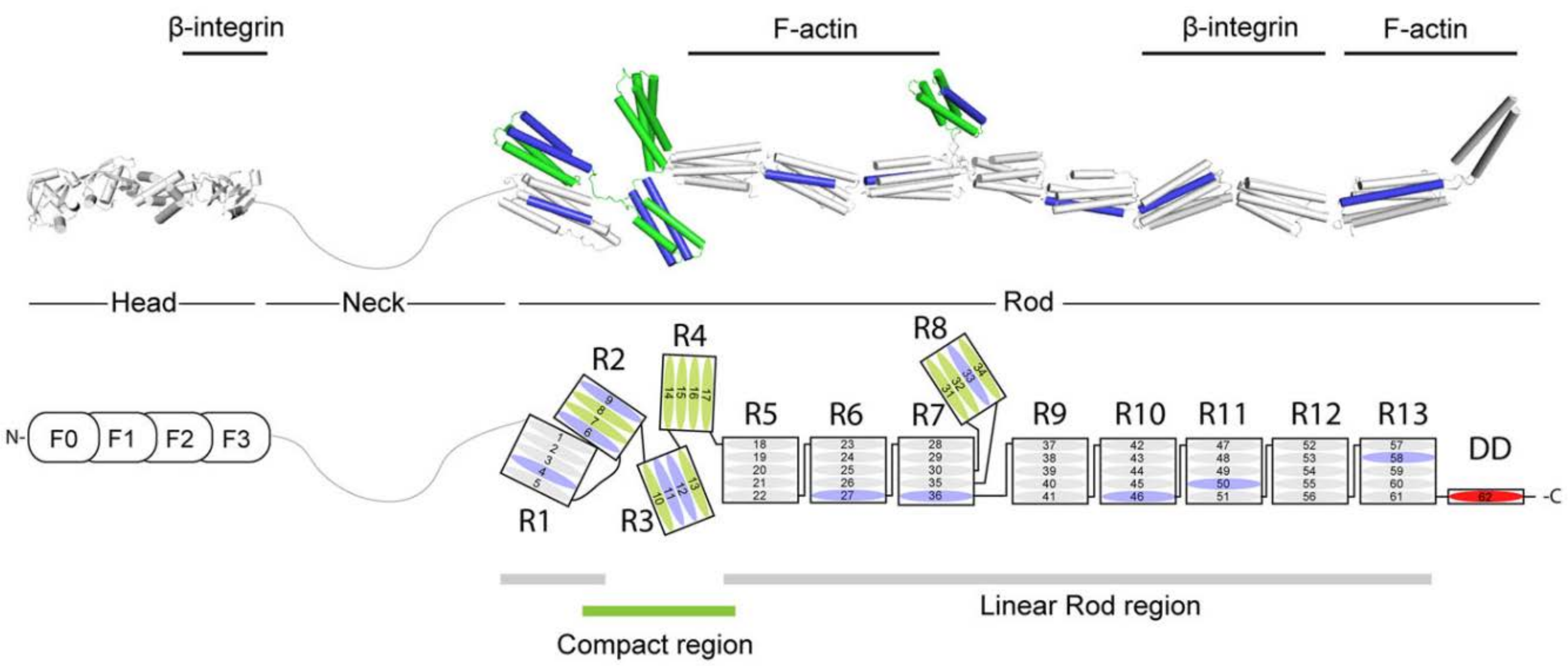


- Integrins bind talin, which can bind actin directly.
- Vinculin can bind talin when the talin rod is stretched. In turn vinculin binds more actin molecules.
- α-actinin crosslinks actin filaments to stabilise stress-fibres.



580 | NATURE | VOL 468 | 25 NOVEMBER 2010

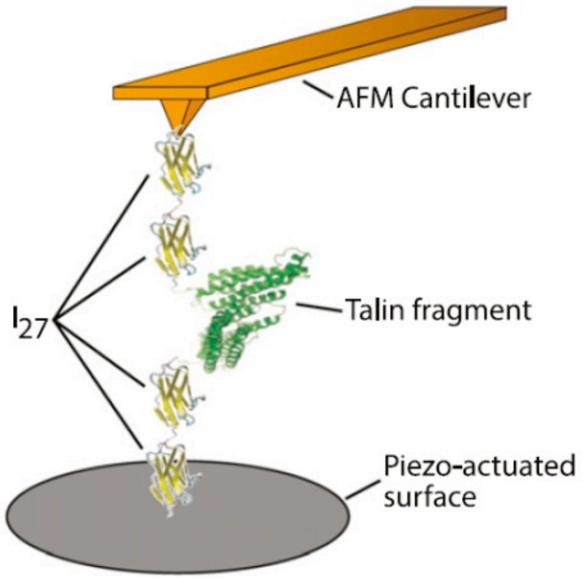
Talin is an Essential Mechano-Sensor of Cell Adhesions

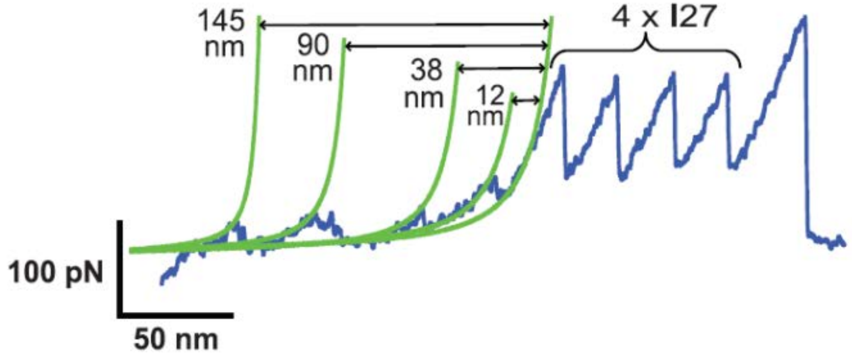


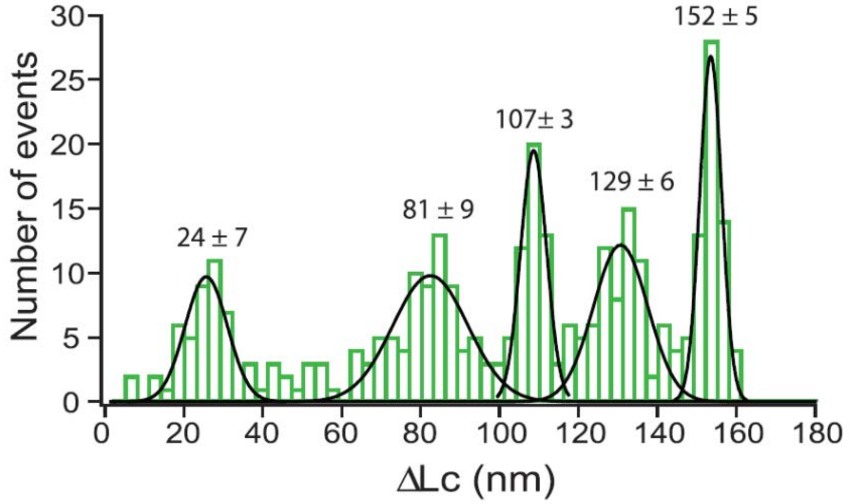
Cellular and Molecular Bioengineering, Vol. 8, No. 1, March 2015 (© *2014*) pp. 151–159

- Multi domain protein containing three main regions: head, neck and rod, with distinct functions.
- The talin rod is constituted of helix bundle repeats.
- The head binds integrins whereas the tail of the rod binds F-actin.
- There are up to 11 vinculin binding sites within the rod, some of which are cryptic (hidden).

Stretching Talin Molecules Unfolds Helix Bundles







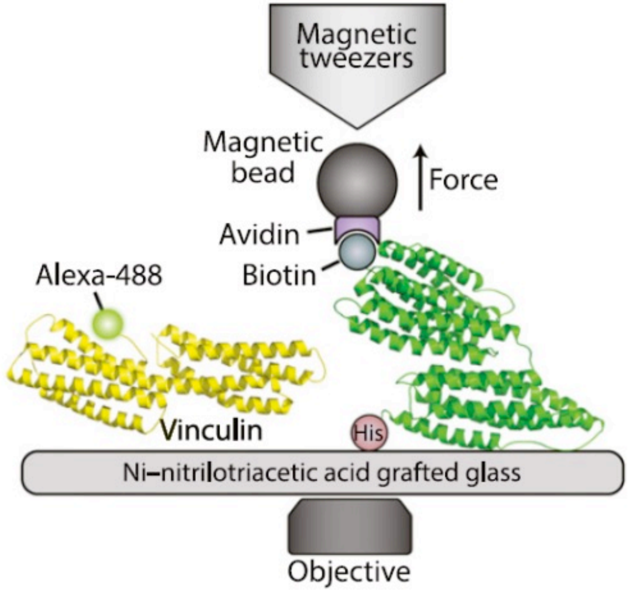
- Unfolding of helix bundles associated with forces in the range of 20-50 pN.
- Unfolded talin rod spans 145 nm.
- Talin unfolding exposes potentially hidden (cryptic domains).

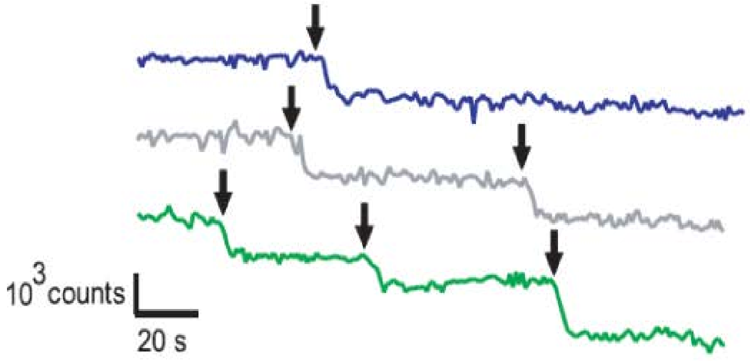
Del Rio et al. Faseb J. 2016

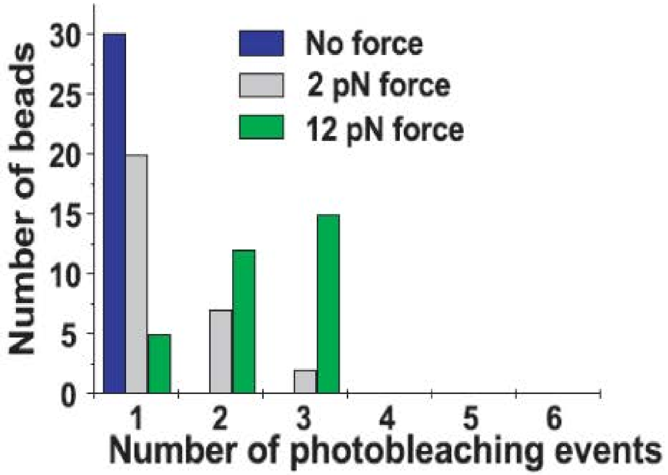
SCIENCE, 2009, Vol 323, p. 638-641

Talin Unfolding Exposes Cryptic Binding Sites for Vinculin

- Magnetic tweezers can be used to actuate magnetic beads.
- Used to stretch talin rod domain.
- Unfolding is associated with the binding of fluorescently tagged vinculin molecules that photobleach therefore enabling the counting of single molecules.

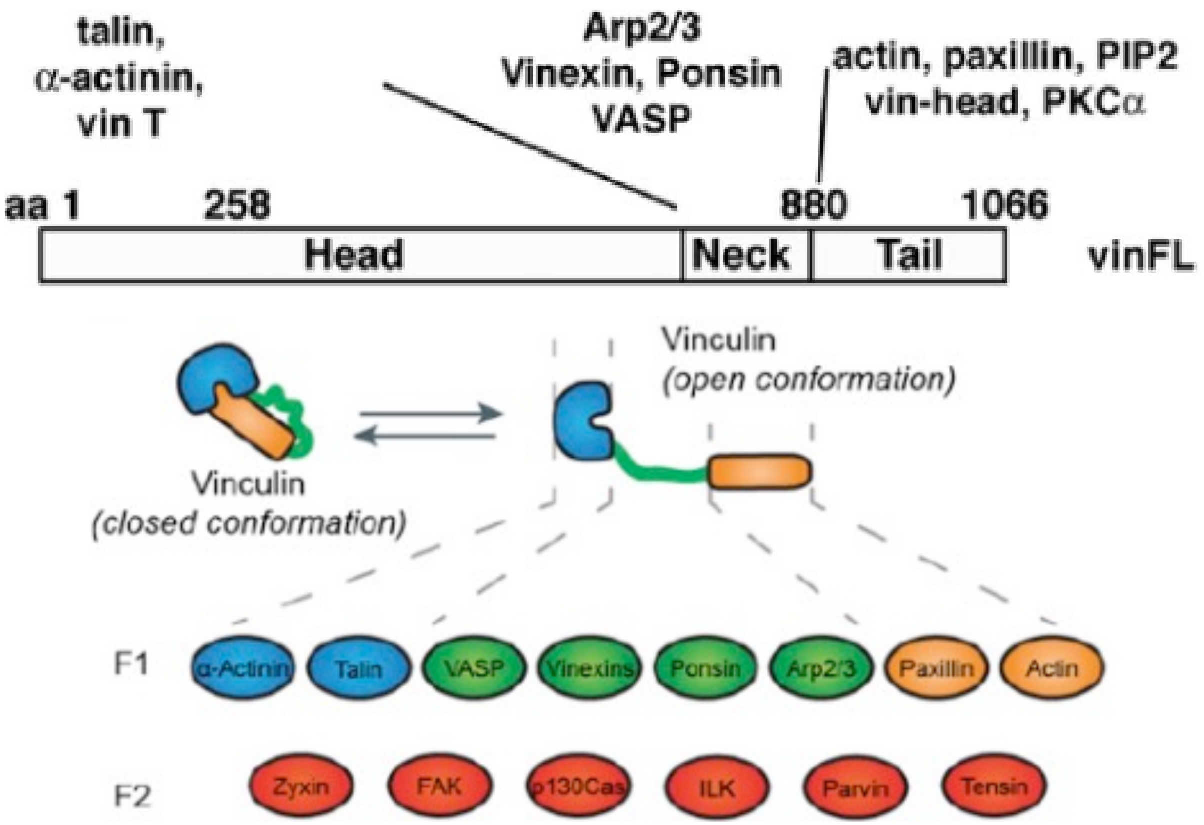






SCIENCE, 2009, Vol 323, p. 638-641

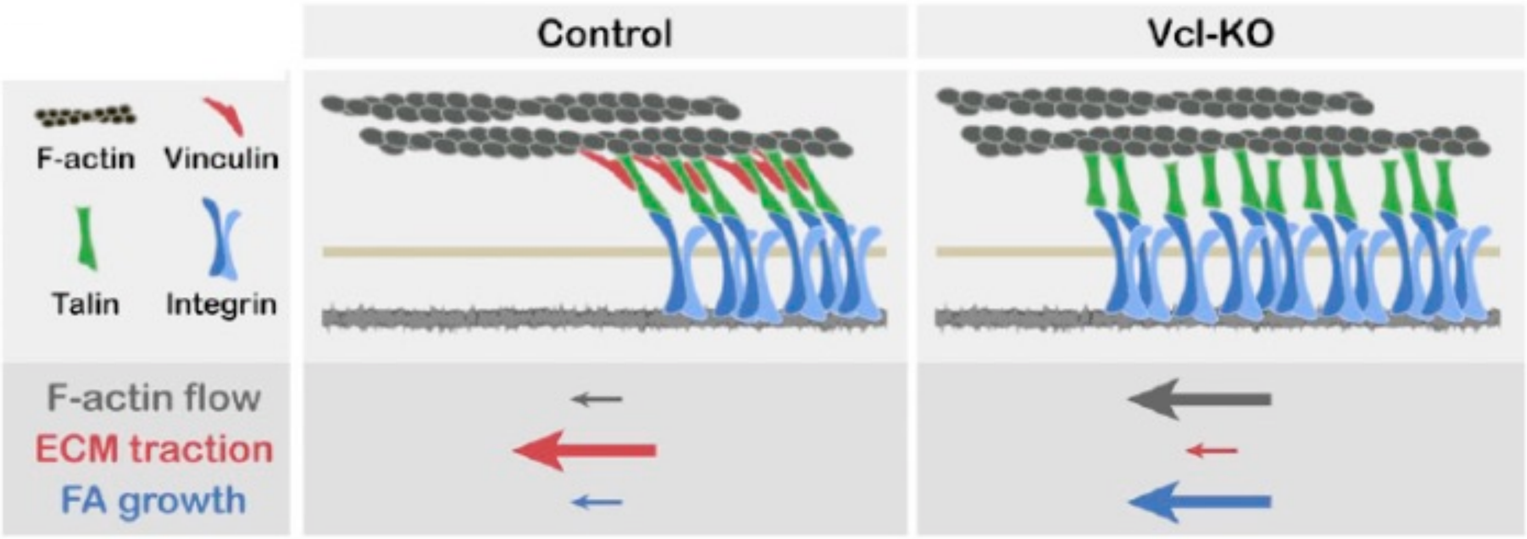
Vinculin Strengthens the Link Between Talin and F-Actin



Current Biology 23, 271–281, February 18, 2013

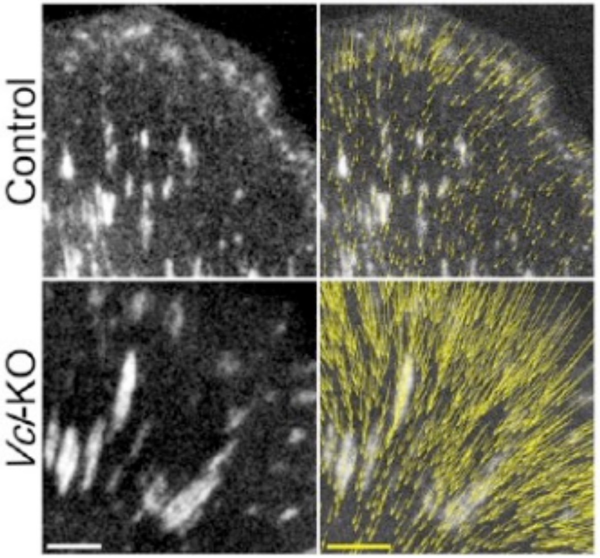
- Multi domain protein containing three main regions: head, neck and tail, with distinct functions.
- The head binds talin whereas the tail of the rod binds F-actin.
- Other binding sites for focal adhesion proteins.

Vinculin Activation Allows Talin-F-Actin Strengthening



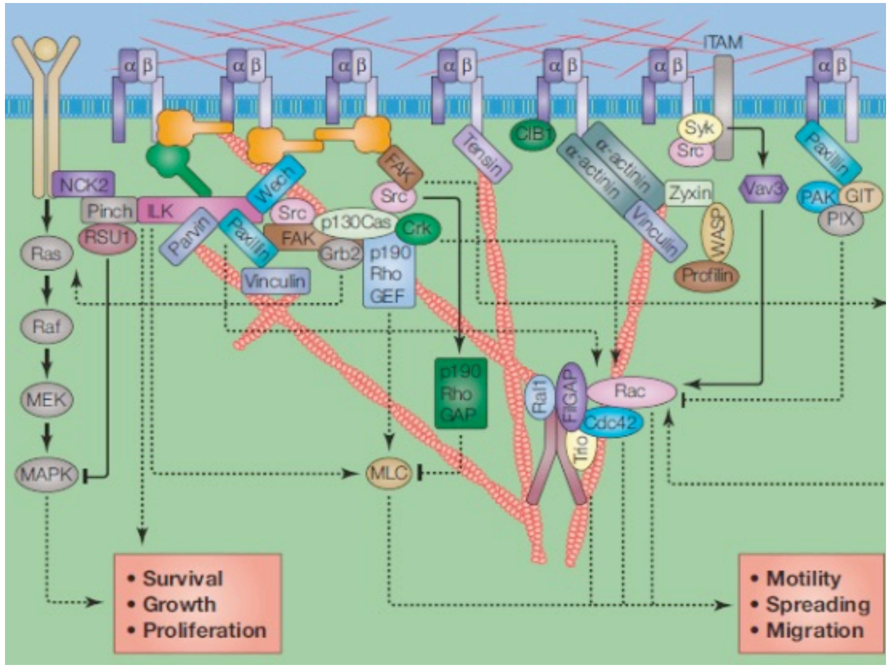
J. Cell Biol. Vol. 202 No. 1 163–177

Paxilin staining and Actin Flow Maps

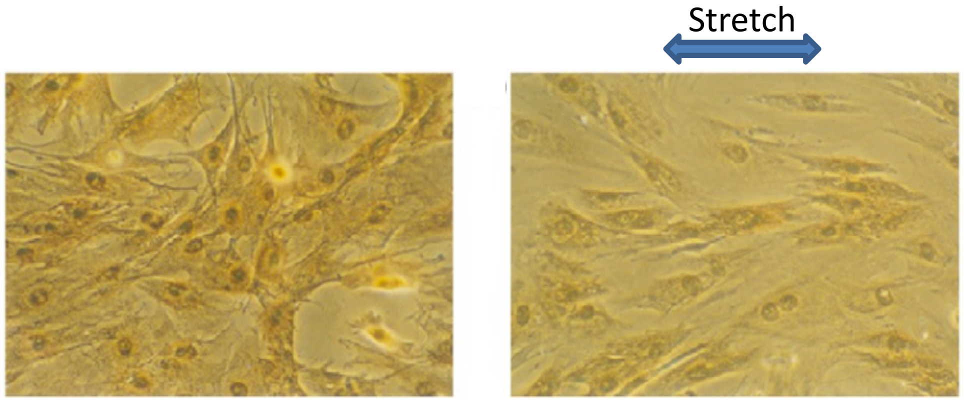


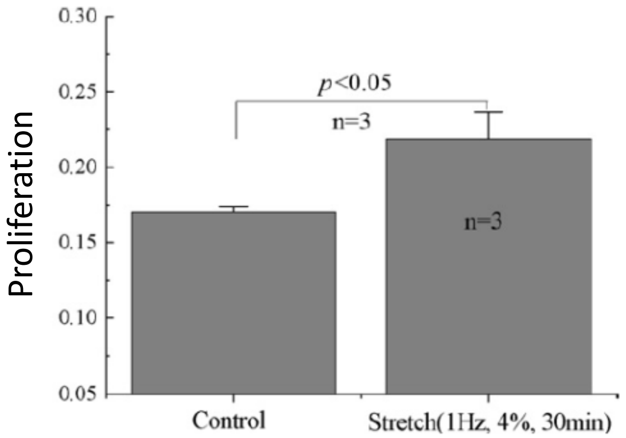
- Talin unfolding regulates vinculin recruitement.
- Vinculin recruitment is associated strengthening and force transmission.
- However focal adhesion maturation is not associated with mechanical strengthening.
- Basis for the revised molecular clutch mechanism.

Recruitment of Focal Adhesion Proteins and Signalling



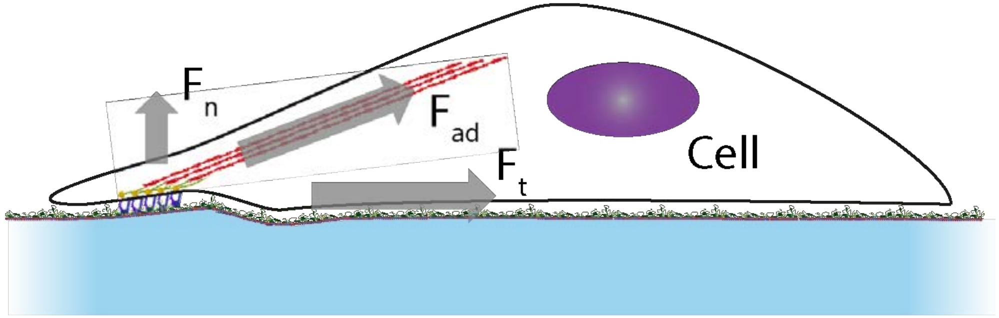
- Recruitment of many other proteins to focal adhesions.
- Enzymes such as kinases (including focal adhesion kinase or Src).
- Direct or indirect impact on growth factor receptors.
- Signalling cascade involving MEK and MAP kinases.
- Control of many cell functions.





Colloids and Surfaces B: Biointerfaces 58 (2007) 271–277

Cell Sensing of the Mechanical Properties of their Environment



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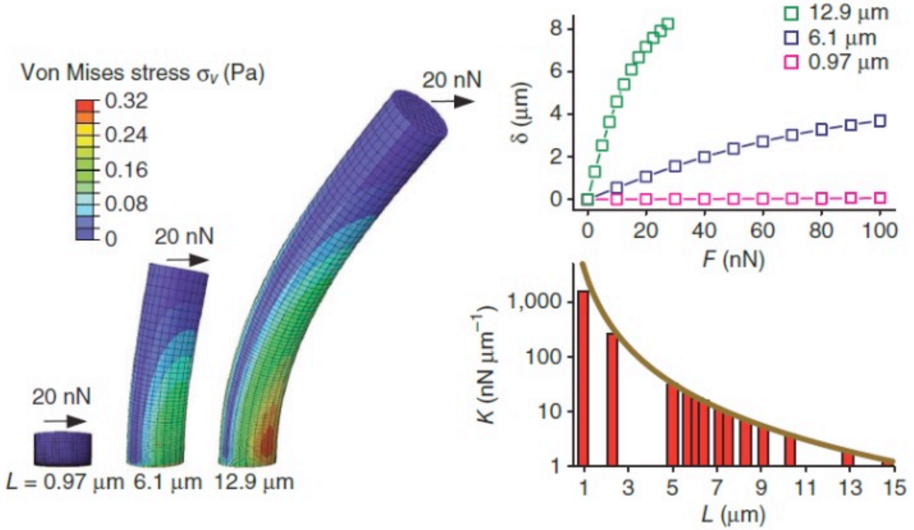
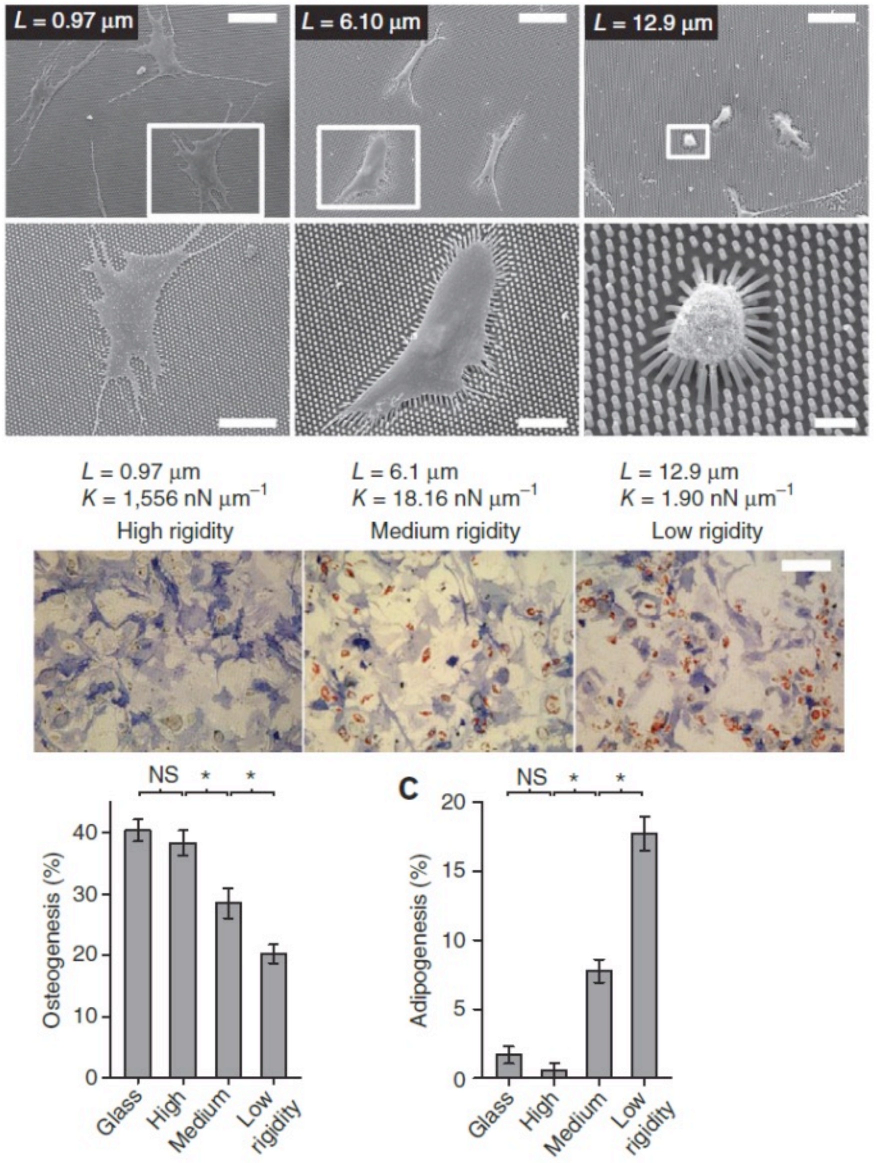
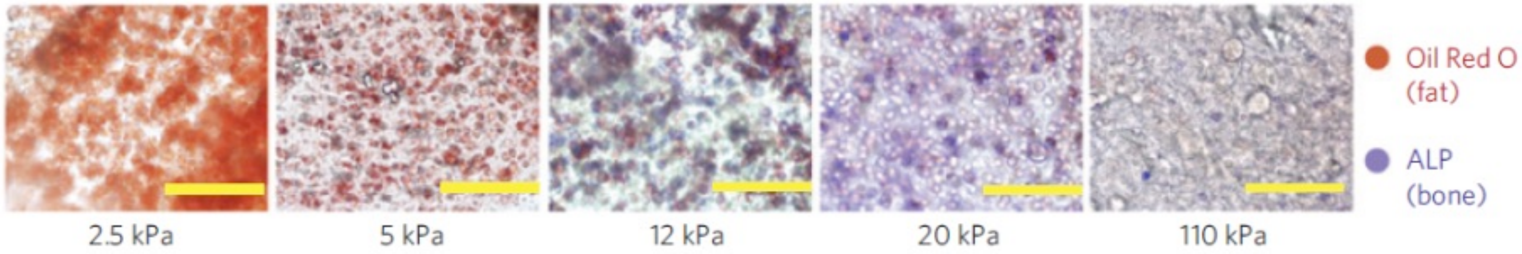
Stiffness Sensing or Deformation Sensing?



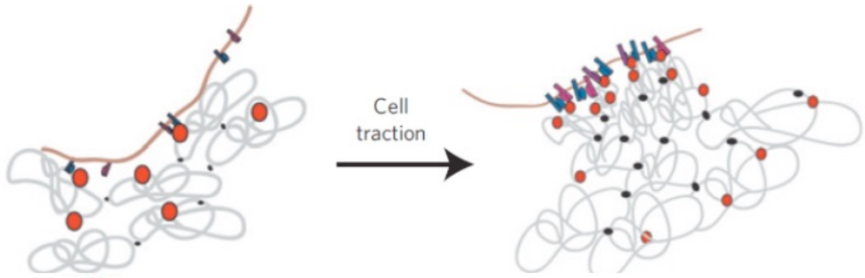


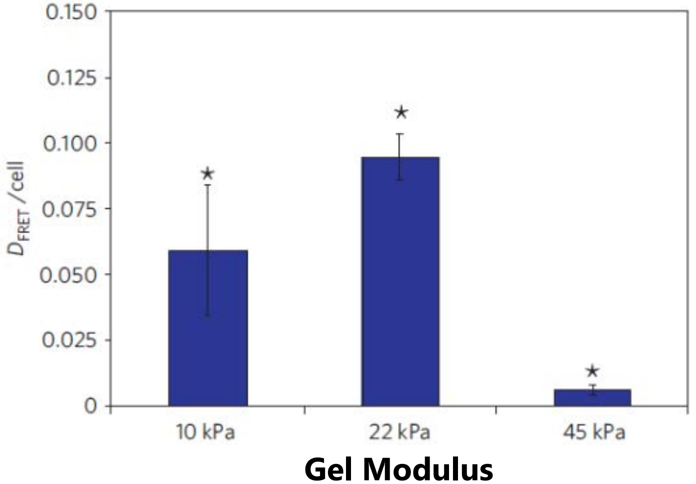
- PDMS microposts display controlled flexural moduli.
- Cells respond to such apparent change in stiffness, as on hydrogels.
- Results in changes in cell spreading and phenotype (MSC differentiation).
- Cells seem to respond to matrix deformation.

NATURE METHODS | VOL.7 NO.9 | SEPTEMBER 2010 | 733



Ligand Clustering

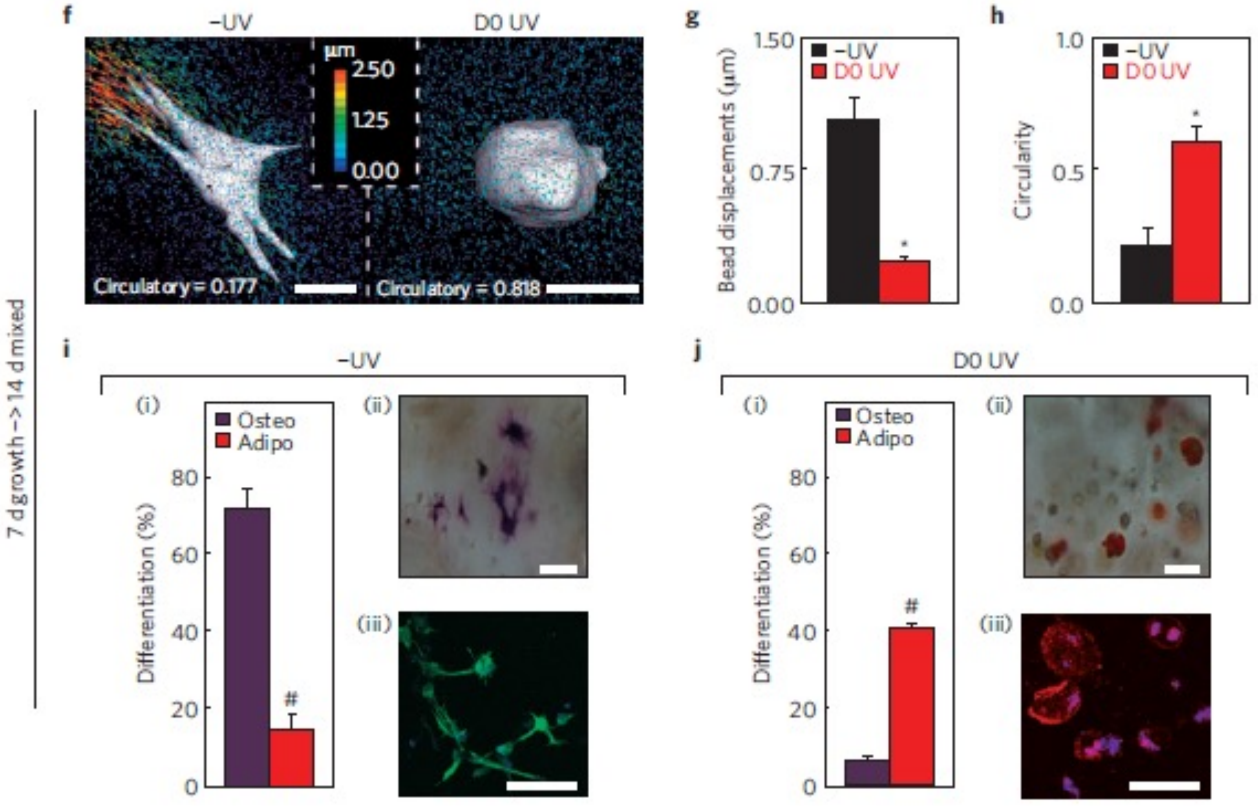




- MSCs cultured in non degradable, predominantly elastic alginate hydrogels.
- Cell traction results in matrix local deformations, despite the absence of cell spreading.
- Mechanical sensing results in altered MSC phenotype, as on 2D matrices.

NATURE MATERIALS | VOL 9 | JUNE 2010 518

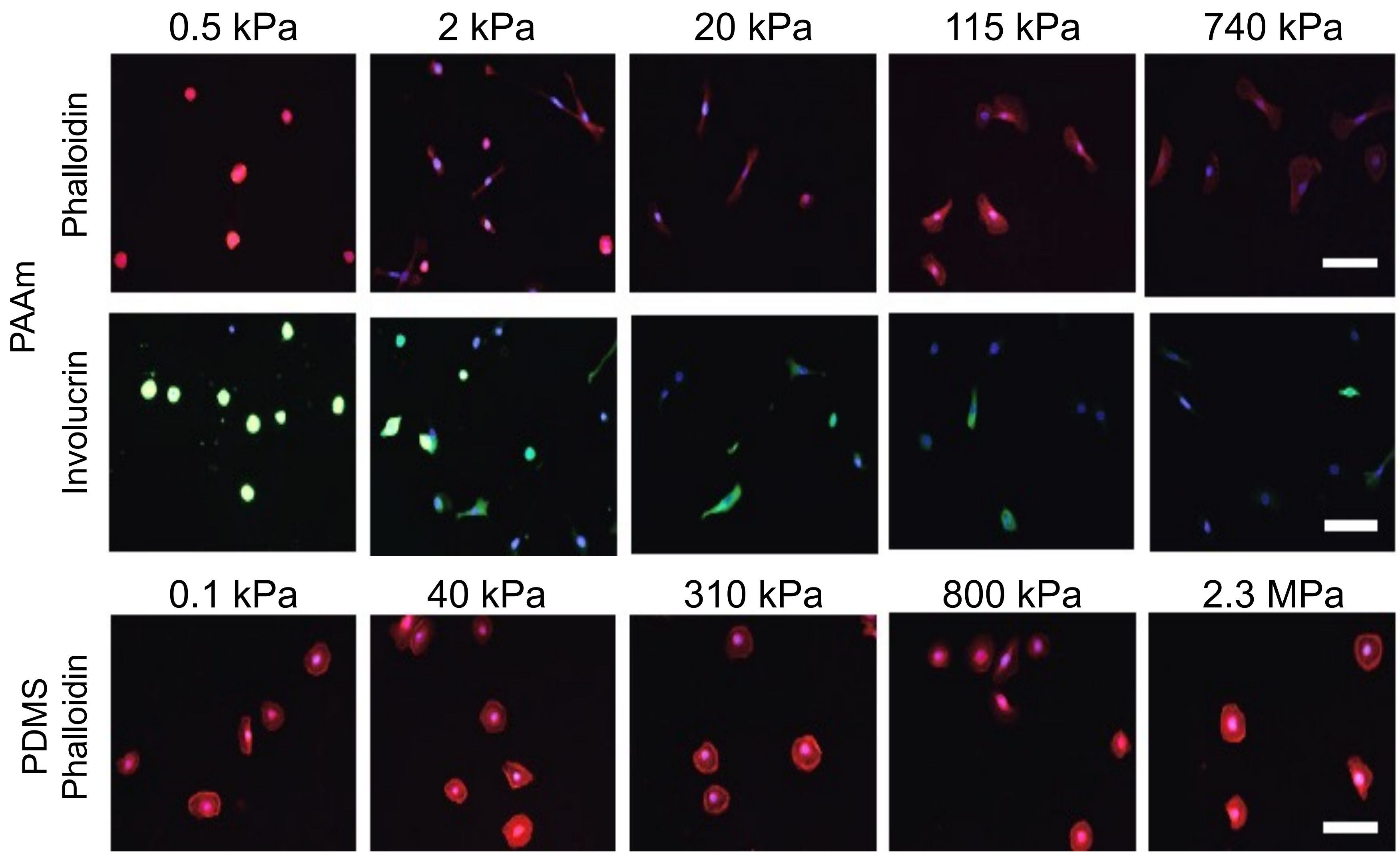
Cell Phenotype and Matrix Mechanics Are Not Always Correlated



Burdick et al. *Nature Mater.* 2013

- MSCs differentiate into osteoblasts in soft matrices allowing remodelling and spreading.
- Degradation-mediated cellular traction directs stem cell fate in covalently crosslinked three-dimensional hydrogels
- The exact opposite to what occurs in non-degradable matrices and 2D matrices.

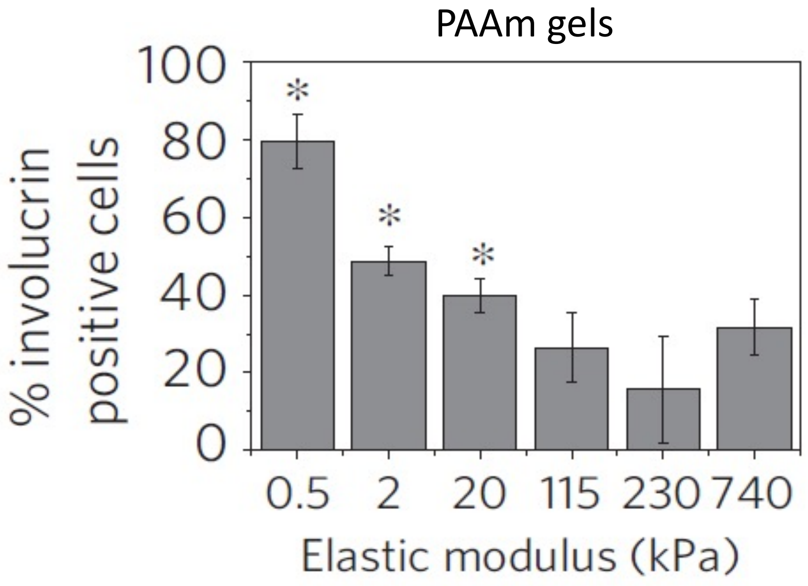
Do Cells Sense Bulk Mechanical Properties ?

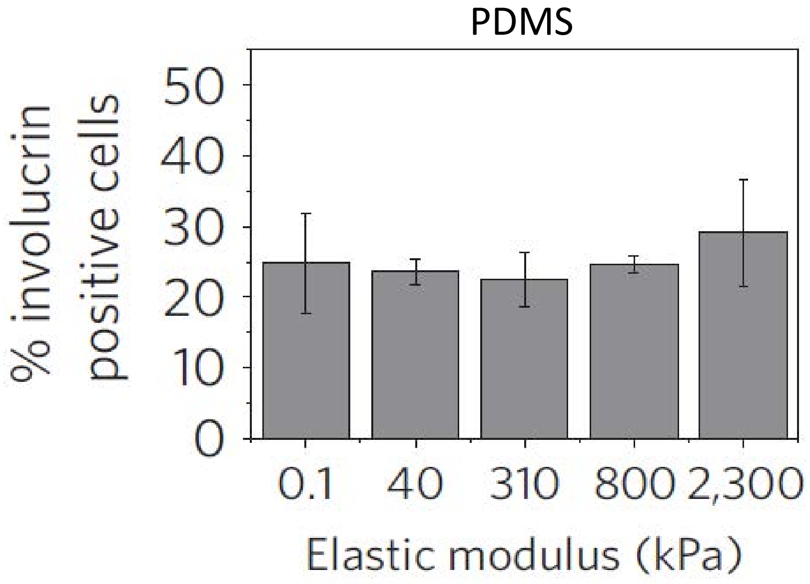


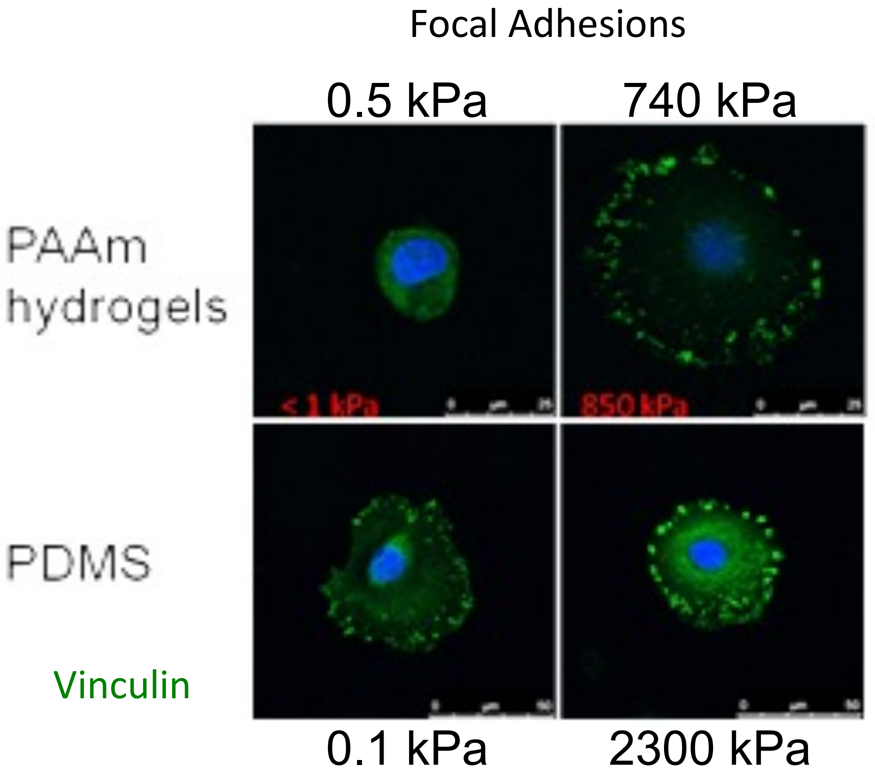
PDMS and Polyacrylamide experiments are apparently contradicting: do cells actually feel the bulk modulus?

Trappmann, Gautrot et al.
Nature Mater. 2012

Substrate Mechanics and Cell Adhesion/Spreading



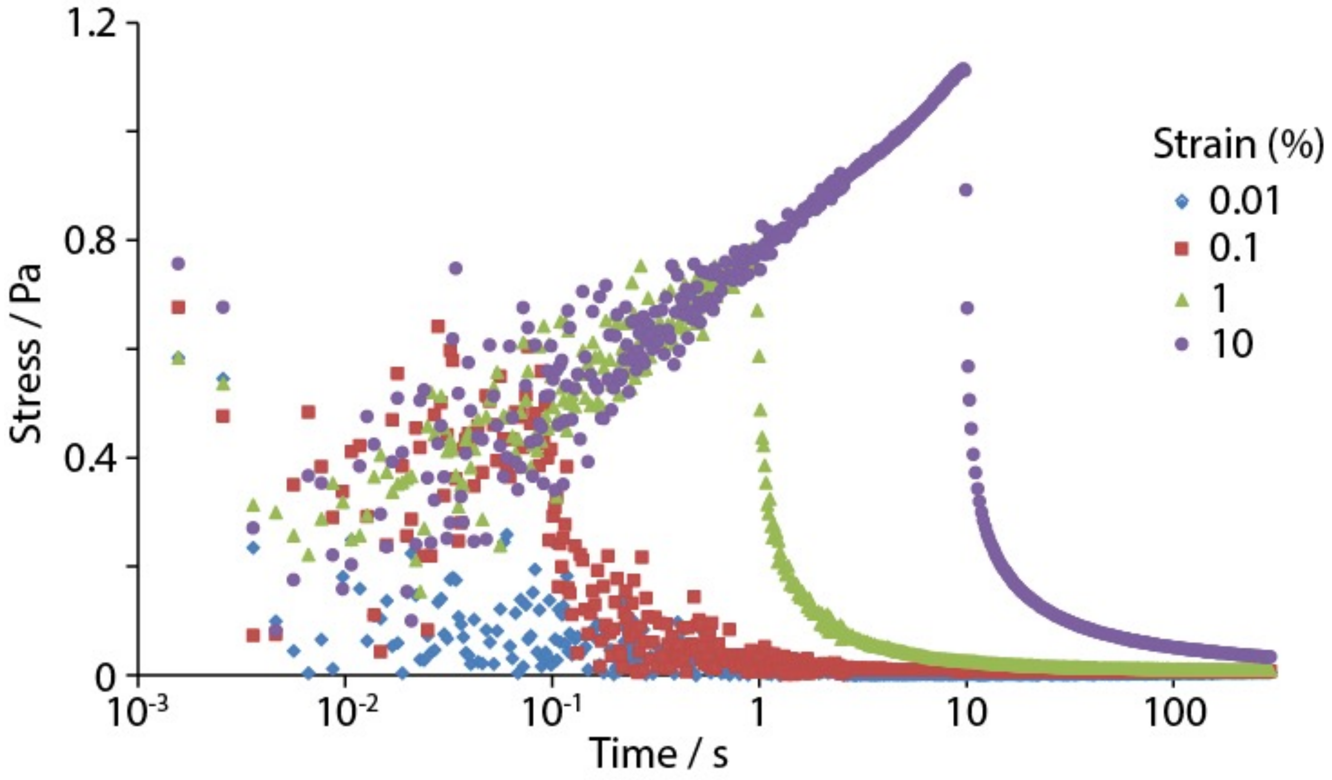




Focal adhesion formation is not sensitive to bulk mechanical properties!

Trappmann, Gautrot et al. *Nature Mater.* 2012

Stress Relaxation in Soft PDMS

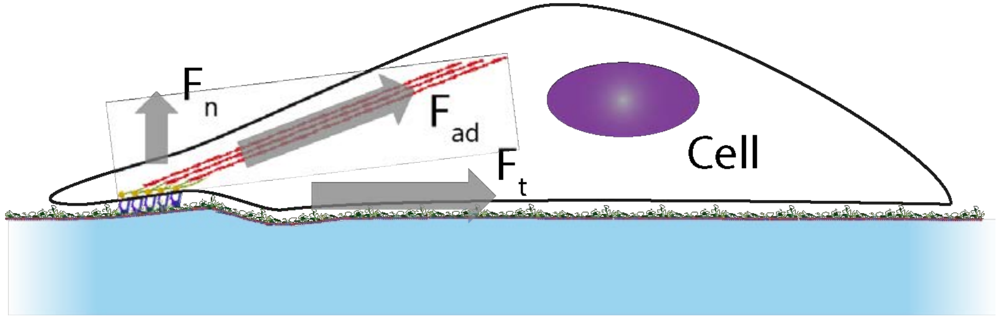


Kong et al. *Faraday Discussions*, 2017, 204, 367-381.

- No residual stress after long relaxation times.
- Ultra soft PDMS (Sylgard 100:1) behaves more like a liquid than a solid.

Queen Mary University of London

Cell Sensing of the Mechanical Properties of their Environment



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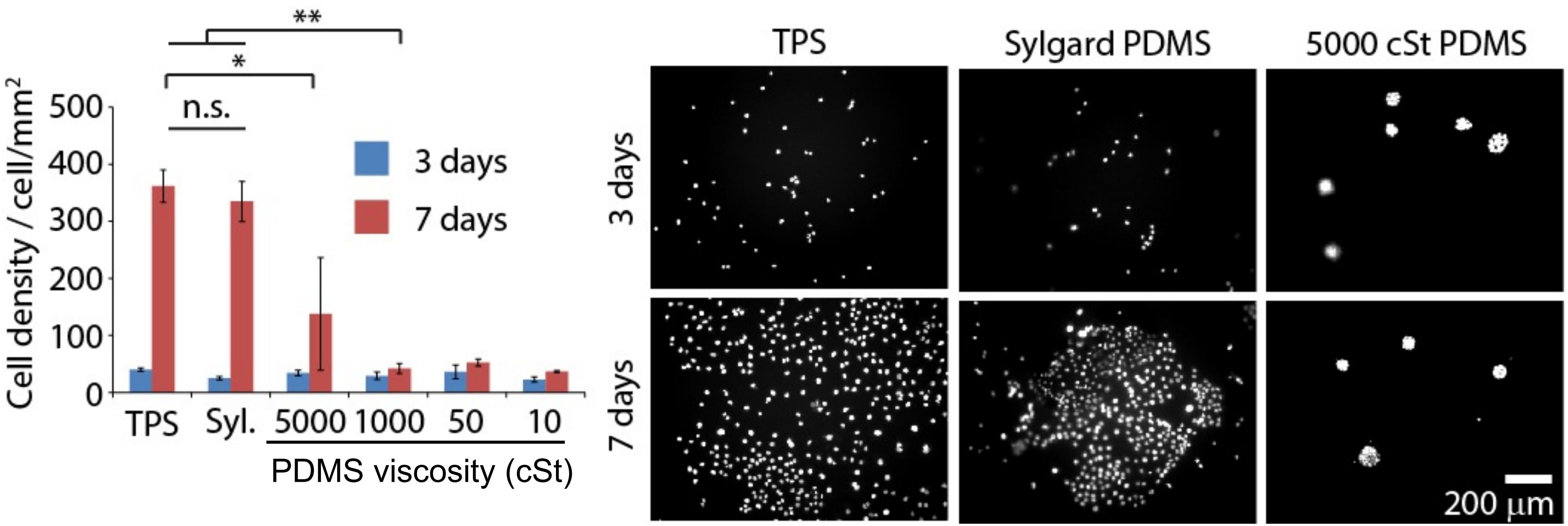
Cell Can be Cultured on Liquid Silicones



Kong et al. *Faraday Discussions*, 2017, 204, 367-381.

- HaCaT culture on liquid silicone (Sylgard).
- Not on defined PDMS oils with a wide range of viscosities.

Suggest a role for additives or surfactants in this process.

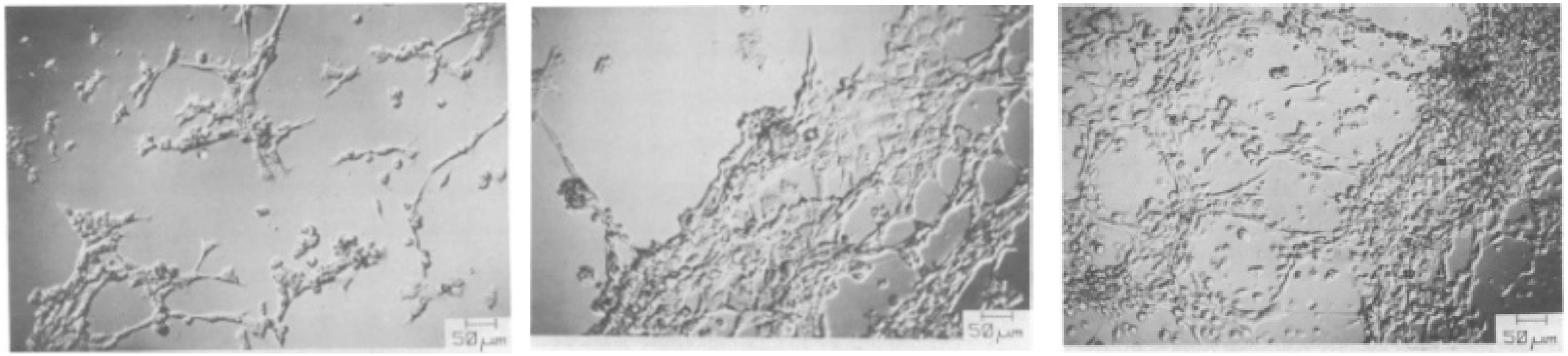
Queen Mary
University of London

Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 219–222, January 1983
Cell Biology

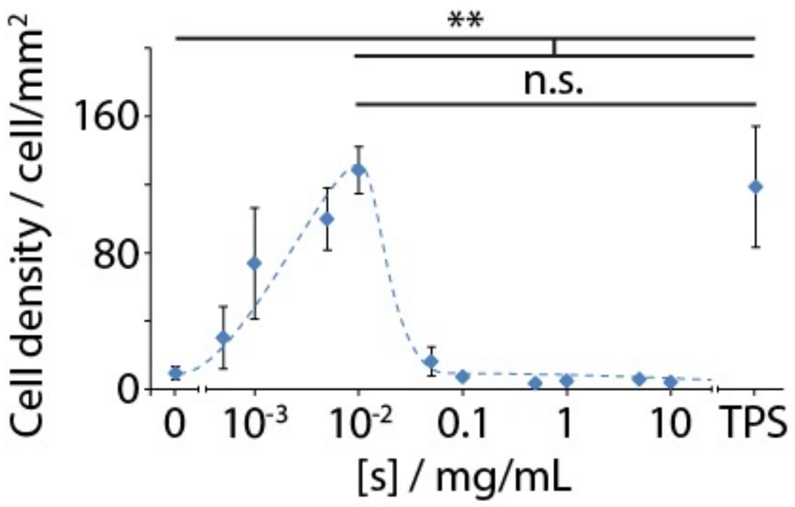
Behavior of cells at fluid interfaces

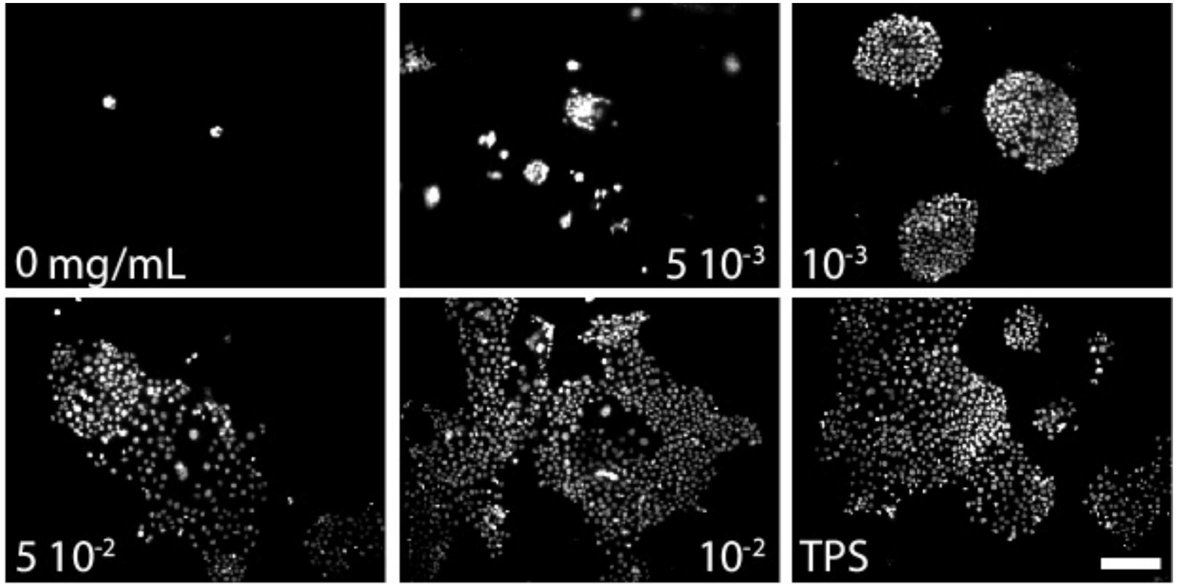
(protein adsorption at interfaces/fluorocarbon fluid substrates/cellular growth patterns)

IVAR GIAEVER AND CHARLES R. KEESE*

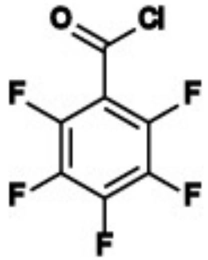


Cell Culture on Liquid Substrates is Controlled by the Presence of Surfactants





Kong et al. *Nano Letters*, 2018, 18 (3), 1946-1951.



- HaCaT culture at the surface of non viscous fluorinated oil (0.77 cSt).
- Behaviour depends on the concentration of surfactant.

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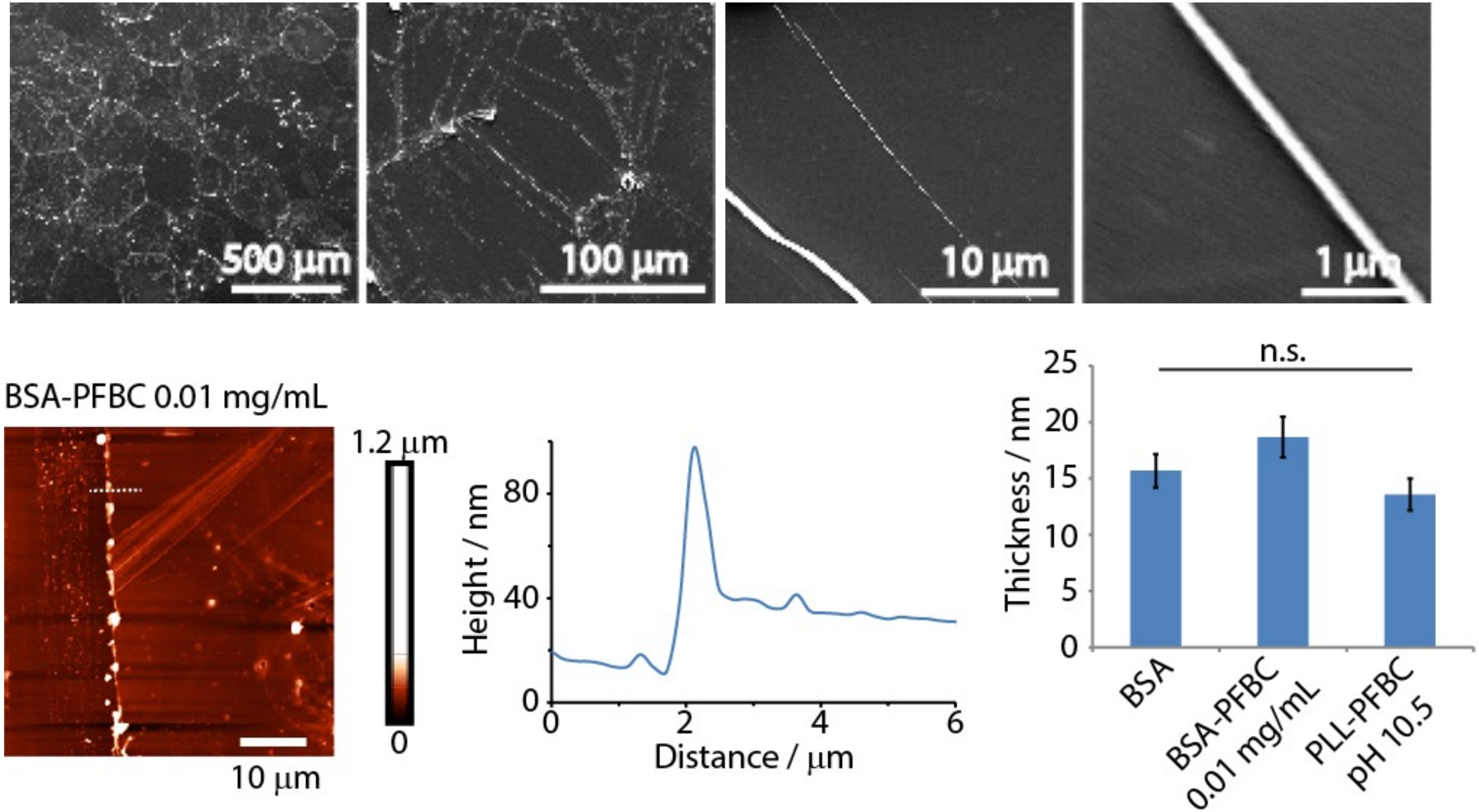
A Nanoscale Quasi 2D Interfacial Layer

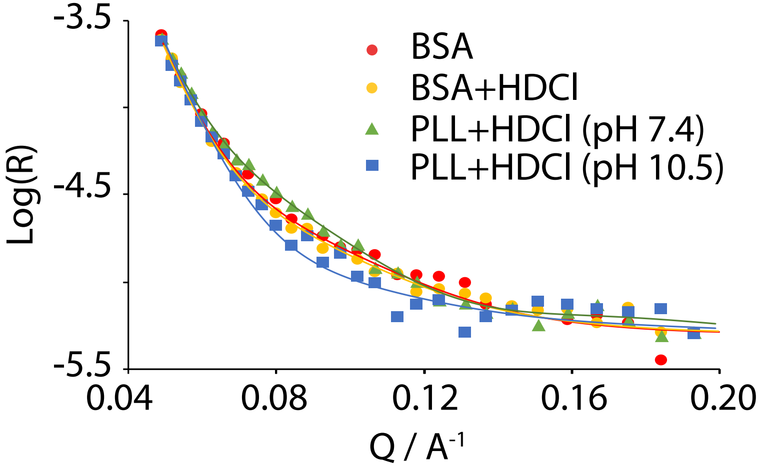


Kong et al. *Nano Letters*, 2018, 18 (3), 1946-1951.

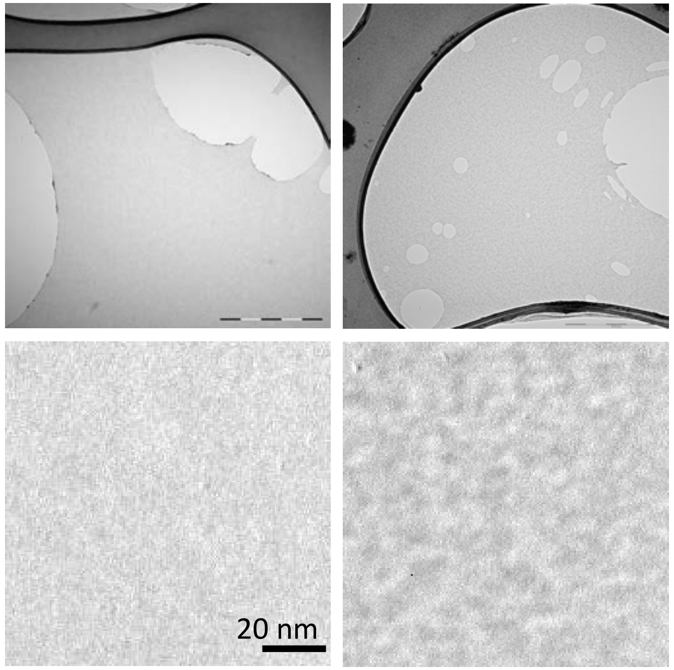
The Nanoscale Architecture of Protein Nanosheets

Ali Zarbakhsh

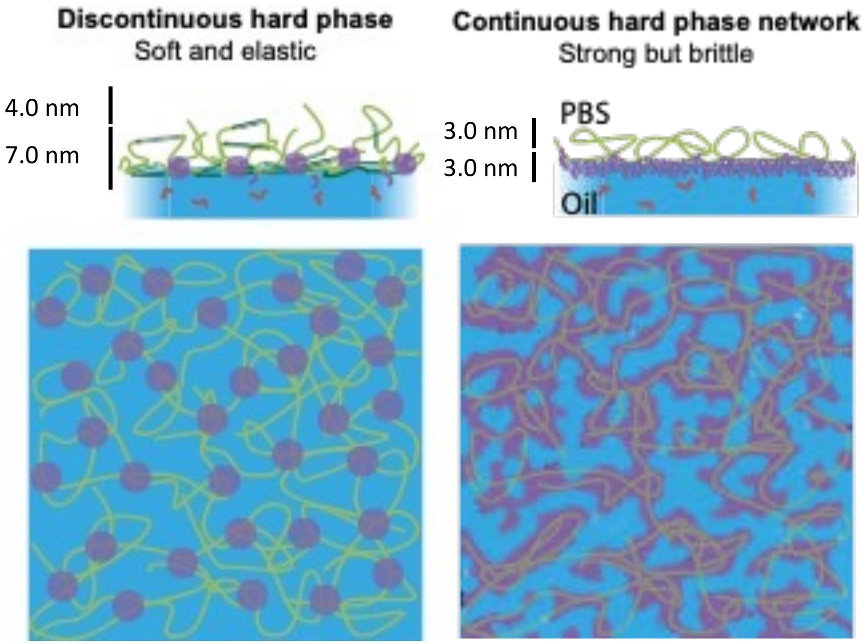
Neutron Reflectometry



TEM



Proposed Model



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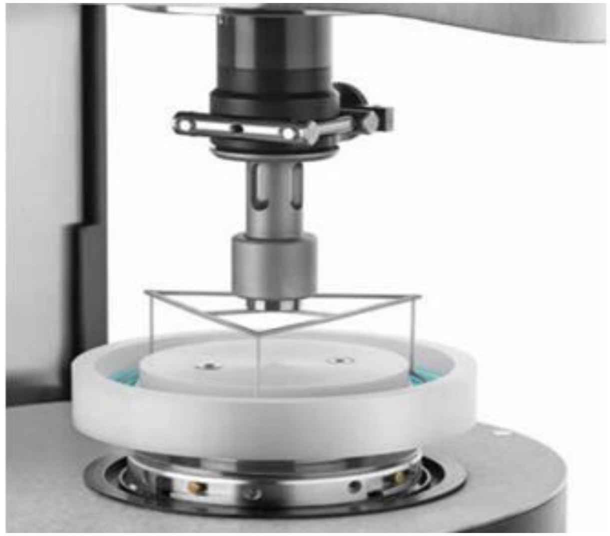
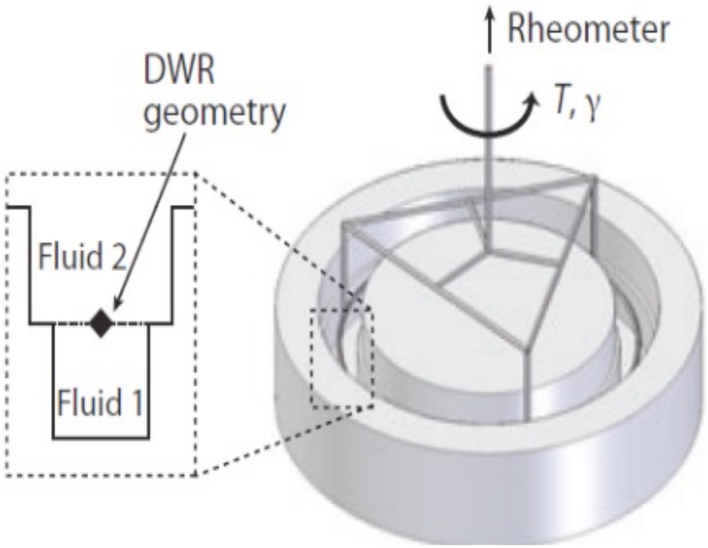
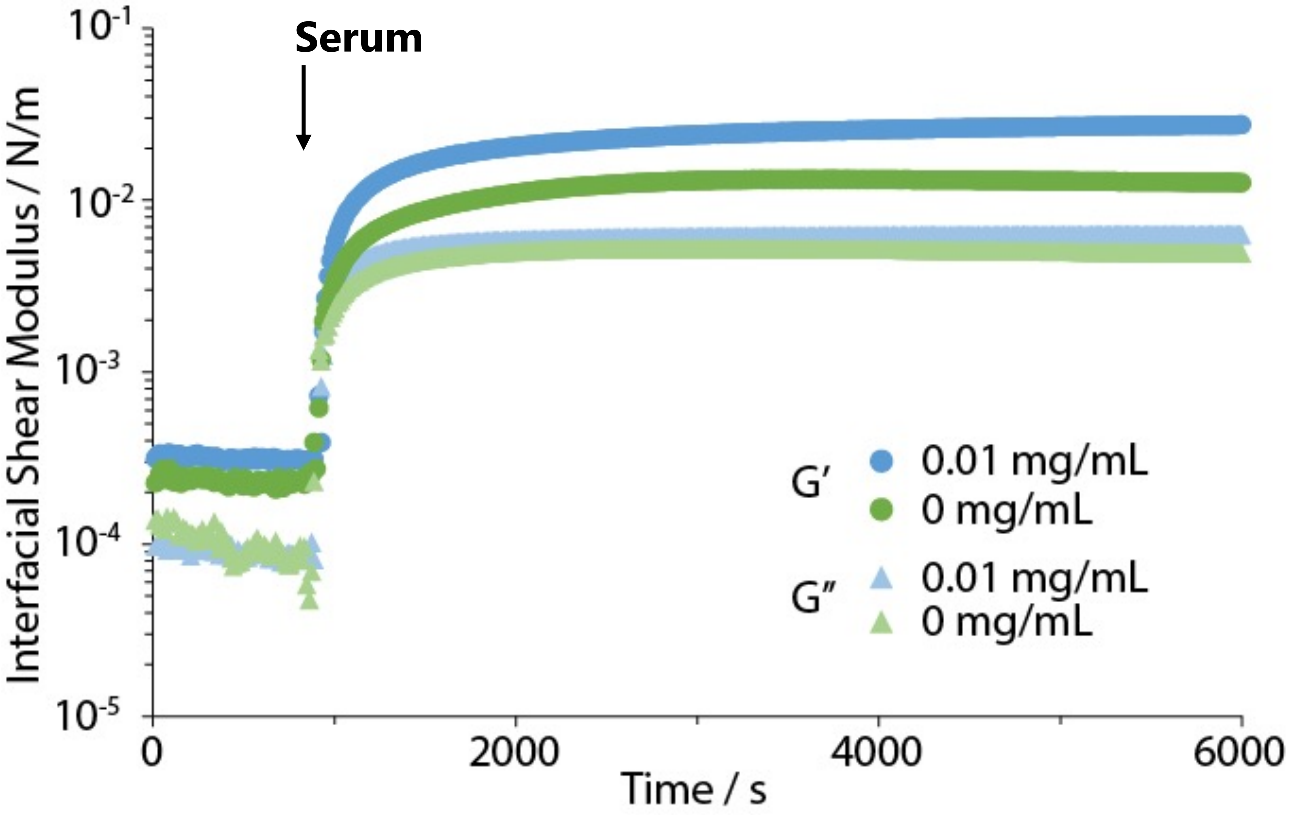


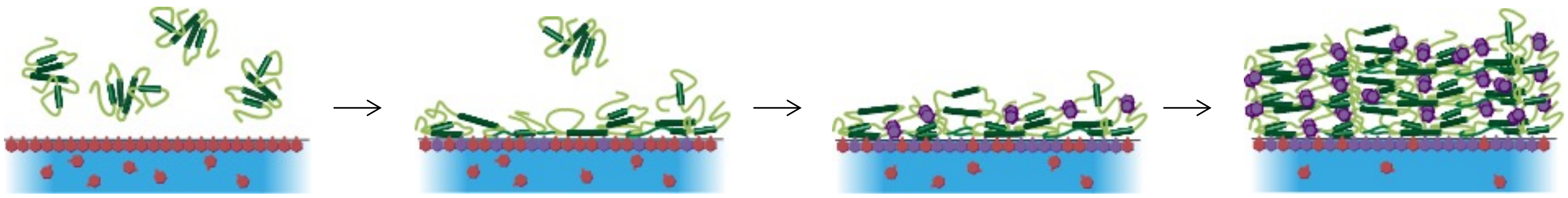


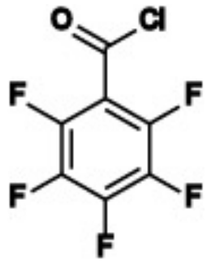
Interfacial Rheology

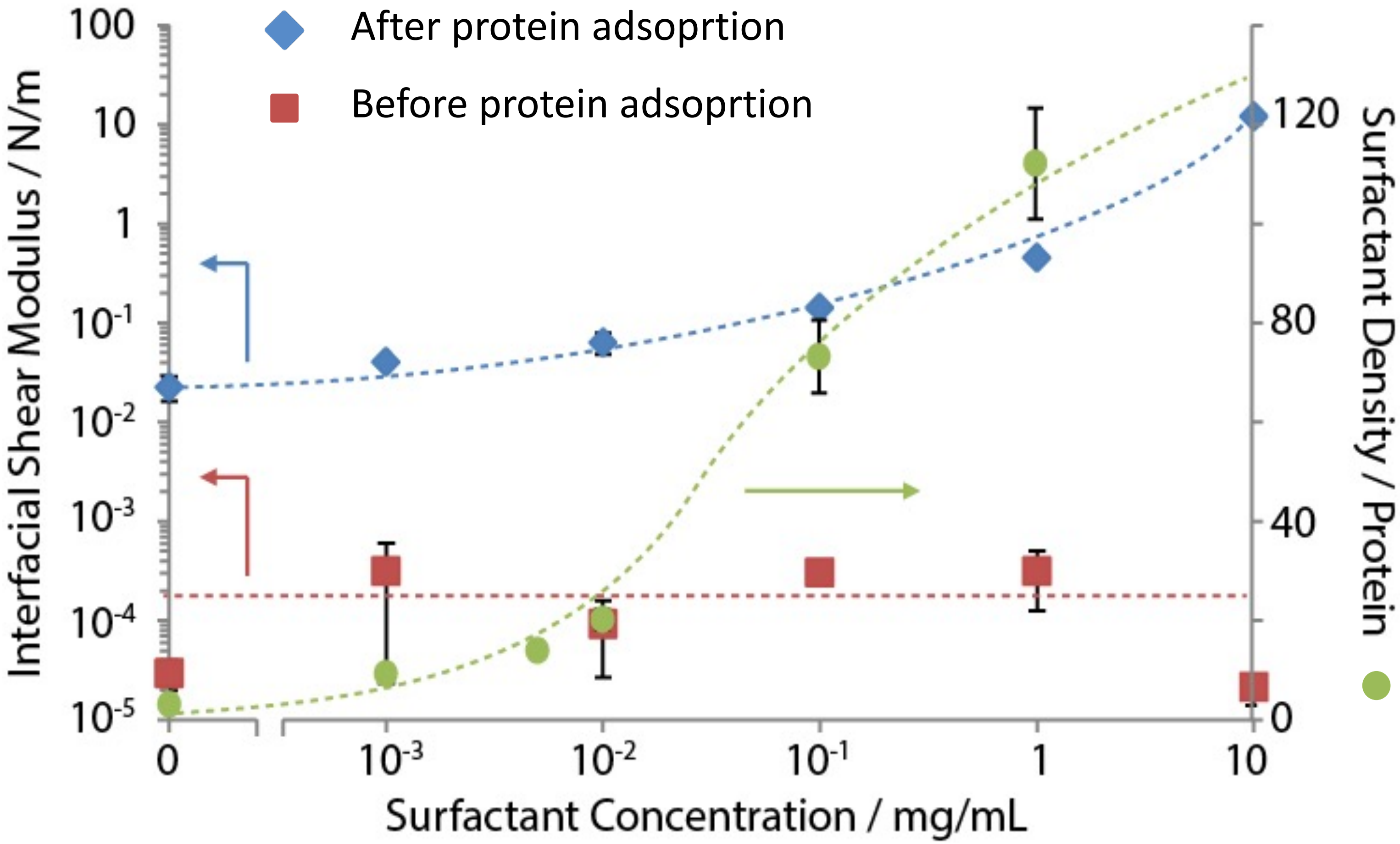


Kong et al. *Faraday Discussions*, 2017, 204, 367-381.

Proteins Assembly at Oil-Water Interfaces

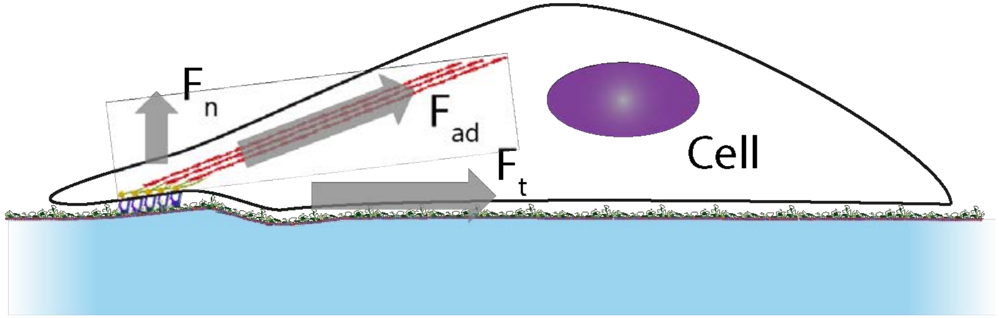






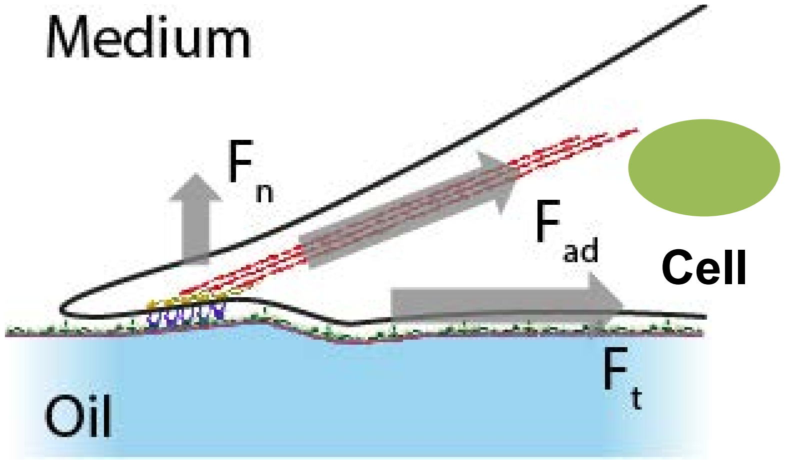
Kong et al. *Nano Letters*, 2018, 18 (3), 1946-1951.

Cell Sensing of the Mechanical Properties of their Environment



1. Cells respond to the mechanics of their substrates
2. Molecular mechanisms of mechanosensing
3. Complex response to mechanical properties
4. Cells can adhere and grow on liquids !?
5. Cells sense the nanoscale mechanics of their environment
6. Liquid substrates and emulsions for stem cell technologies

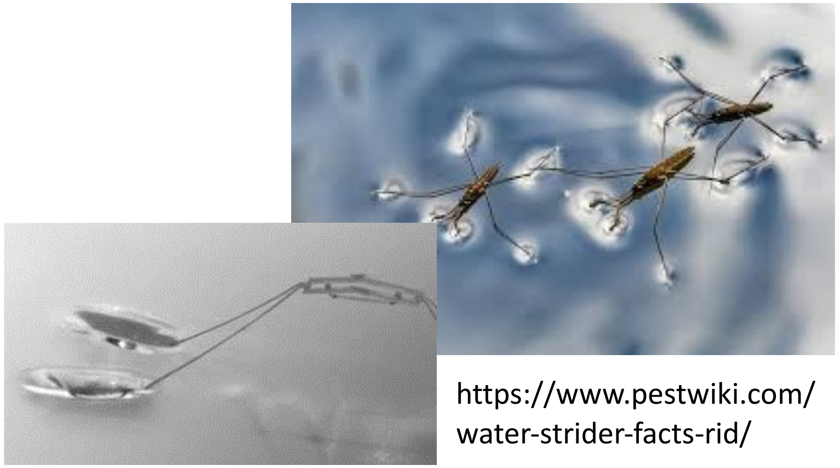
What is the Adhesion to Liquids Physical Mechanism?



Gecko – the Molecular Adhesion and Friction Driven

http://www.sciencemag.org

Water striders – Surface Tension Driven



https://www.pestwiki.com/water-strider-facts-rid/

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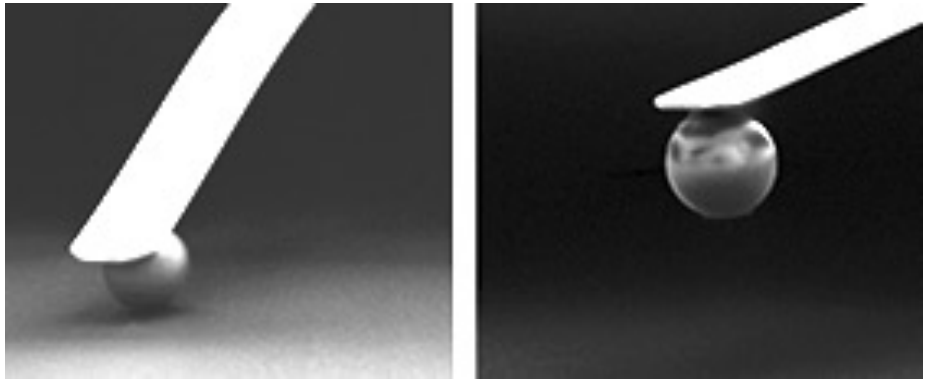
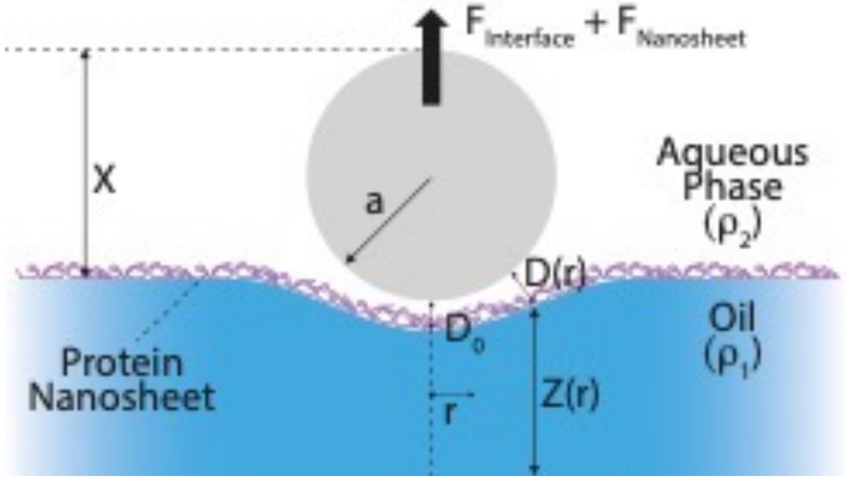
Model of AFM Indentation at Liquid Interfaces

Colloidal Probe Force Microscopy





Megone et al. *JCIS*, 2021, 594, 650-657.

Augmented Young – Laplace Model (YLM)

$$D'' + \frac{1}{t}D' - \left(2 - \frac{a\Pi(D)}{\gamma}\right)D_0 = 0$$

Superposition of YLM with model of deformation of supported membrane

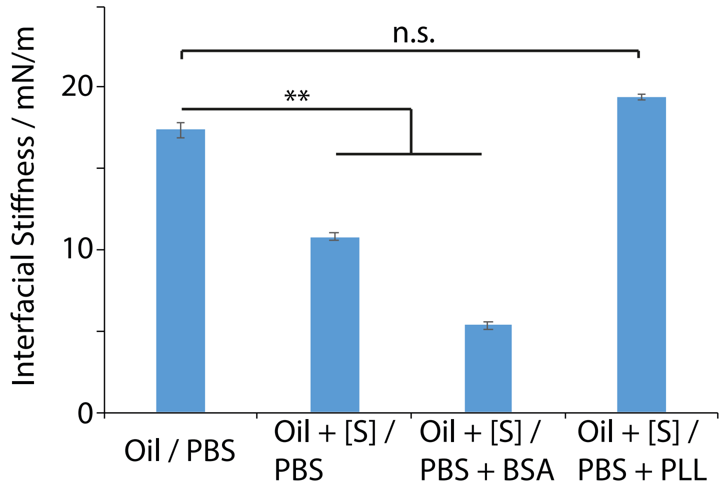
$$F_{probe} = F_{interface} + F_{nanosheet}$$

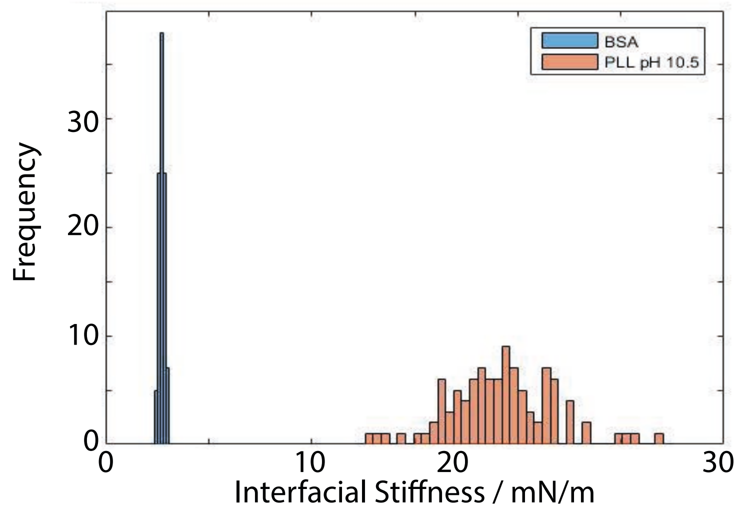
$$v = \frac{(1+v)F_{nanosheet}{a_{drop}}^2}{E}\left[\sin\varphi \ln(1+\cos\varphi) - \frac{\sin\varphi}{1+\cos\varphi}\right]$$

- YLM only taking into account electrostatic and van der Waals components of the disjoining pressure Π.
- Supported membrane model in shear deformation.

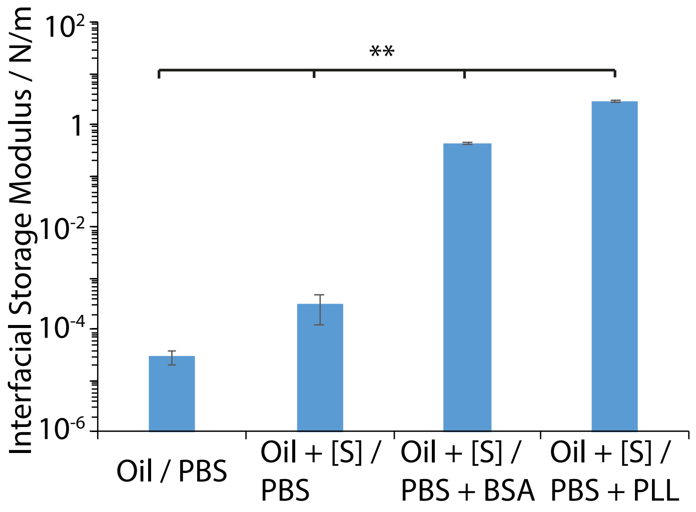
Orders of Magnitude Switch in Mechanical Anisotropy

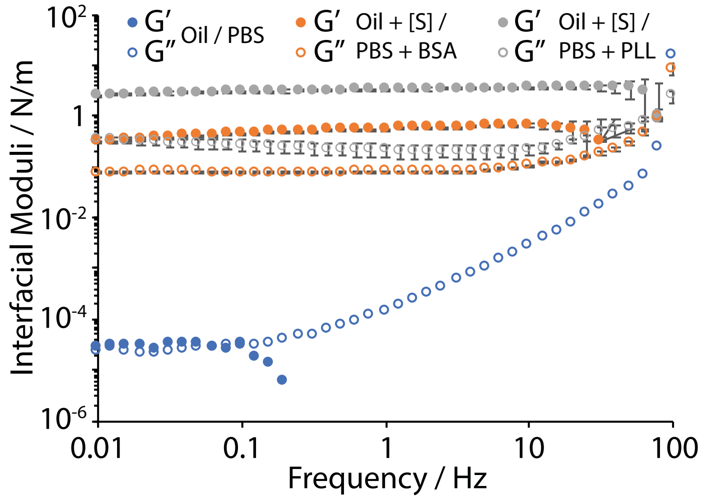
AFM Indentation





Interfacial Rheology





Mechanical anisotropy switches by 5 orders of magnitude (from 10^{-3} before nanosheet adsorption to 10^{2} after self-assembly).

Megone et al. *JCIS*, 2021, 594, 650-657.

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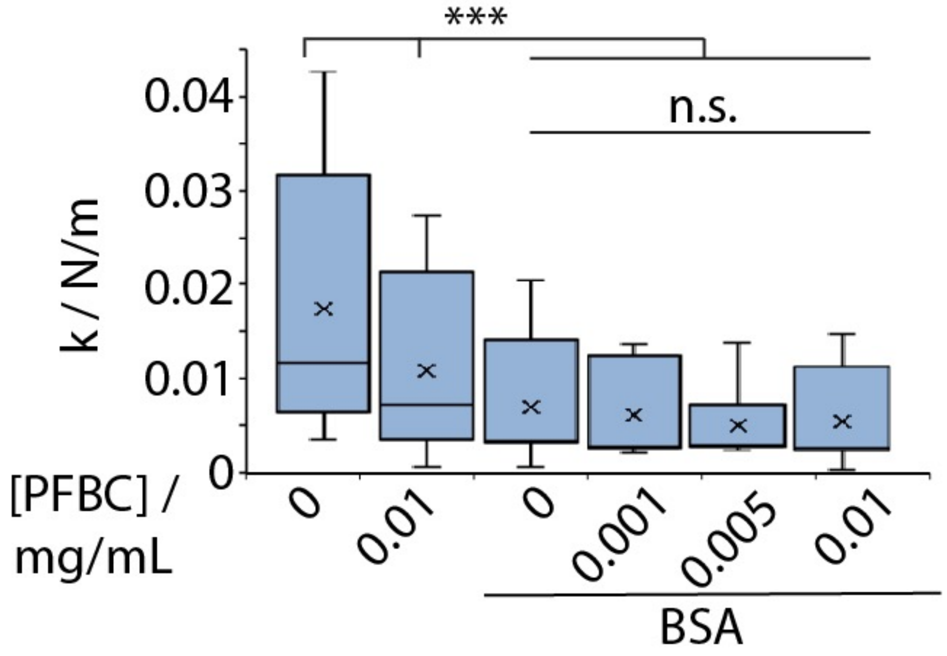
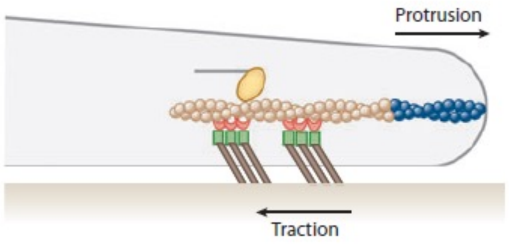
Overall Contribution of Interfacial Shear Mechanics to Cell Adhesion

Impact of Pro-Surfactant on Indentation Mechanics

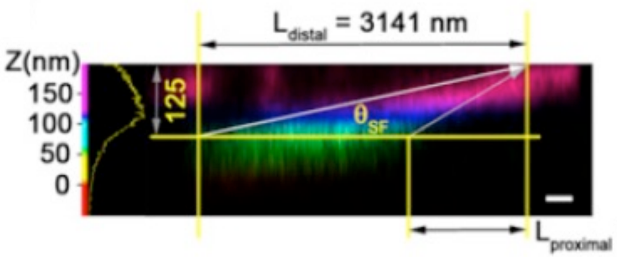


Kong et al. *Nano Letters*, 2018, 18 (3), 1946-1951.



Cell Adhesion Mainly Contributes to Shear Deformation

Annu. Rev. Cell Dev. Biol. 2010. 26:315–33



$\theta_{SF} = \tan^{-1}(H/L)$

$\theta_{SF}^{distal} \sim 2.3°$

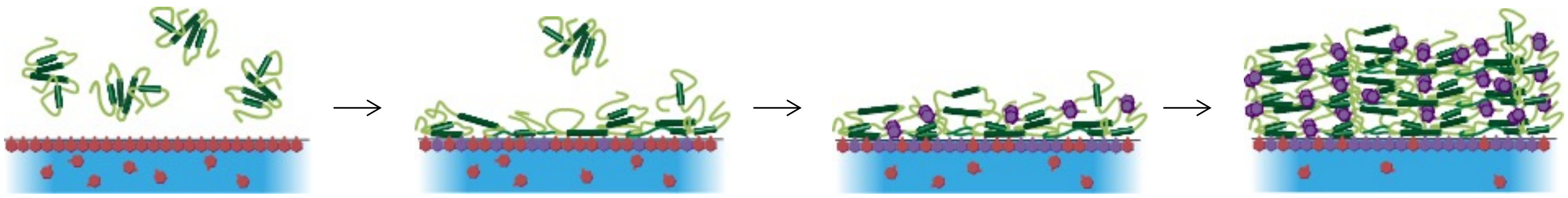
$\theta_{SF}^{proximal} \sim 6.3°$

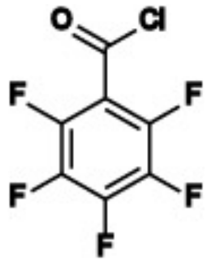
E4864–E4873 | PNAS | Published online August 17, 2015

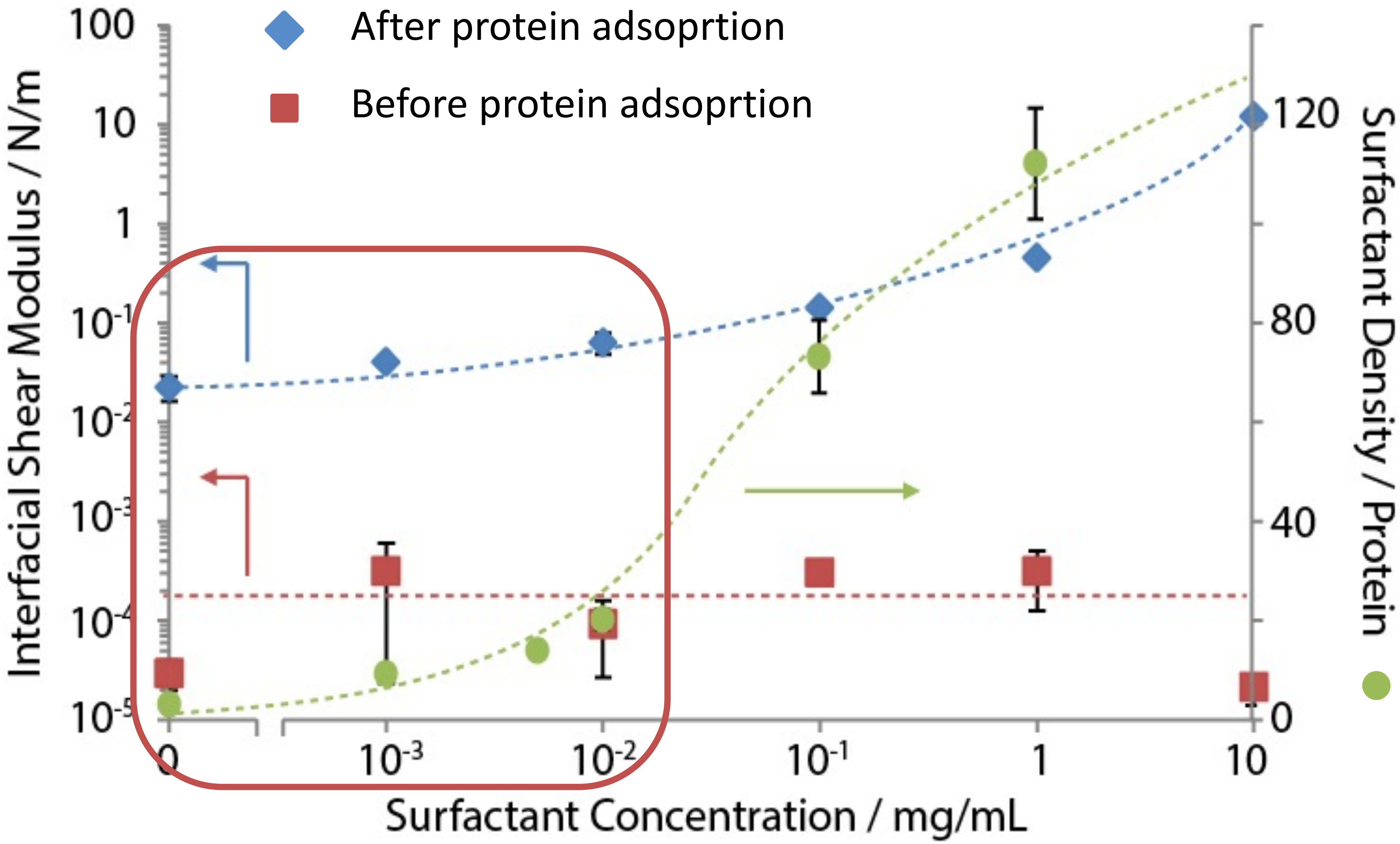
- Little impact of pro-surfactants on indentation stiffness of protein nanosheets.
- Interfacial stiffness mainly determined by surface tension.

Interfacial shear properties dominate cell adhesion.

Proteins Assembly at Oil-Water Interfaces

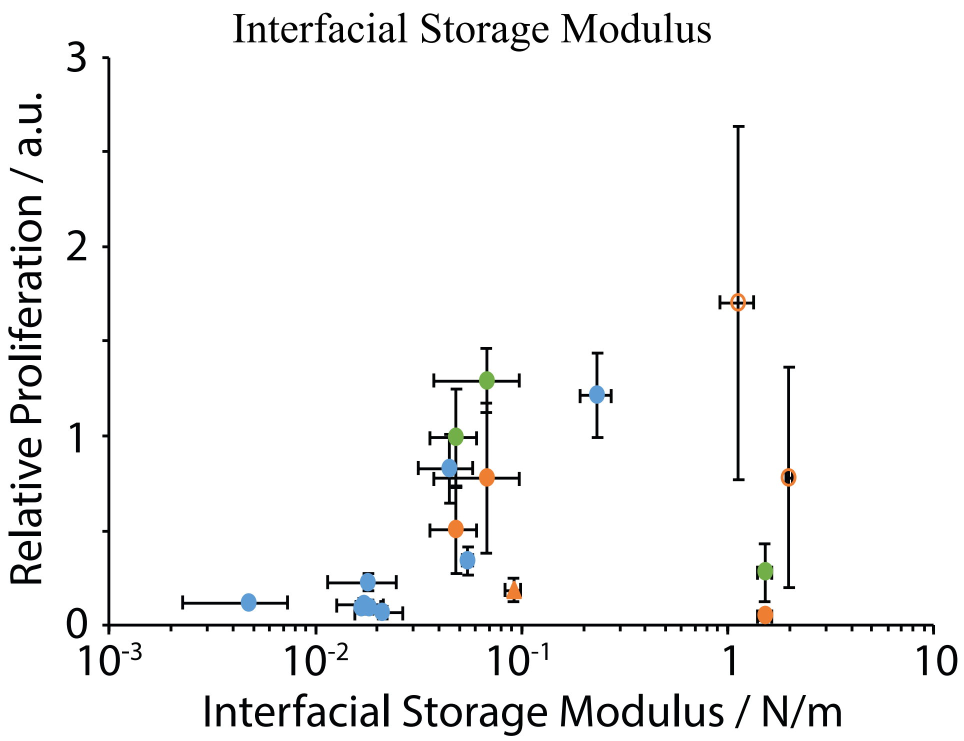


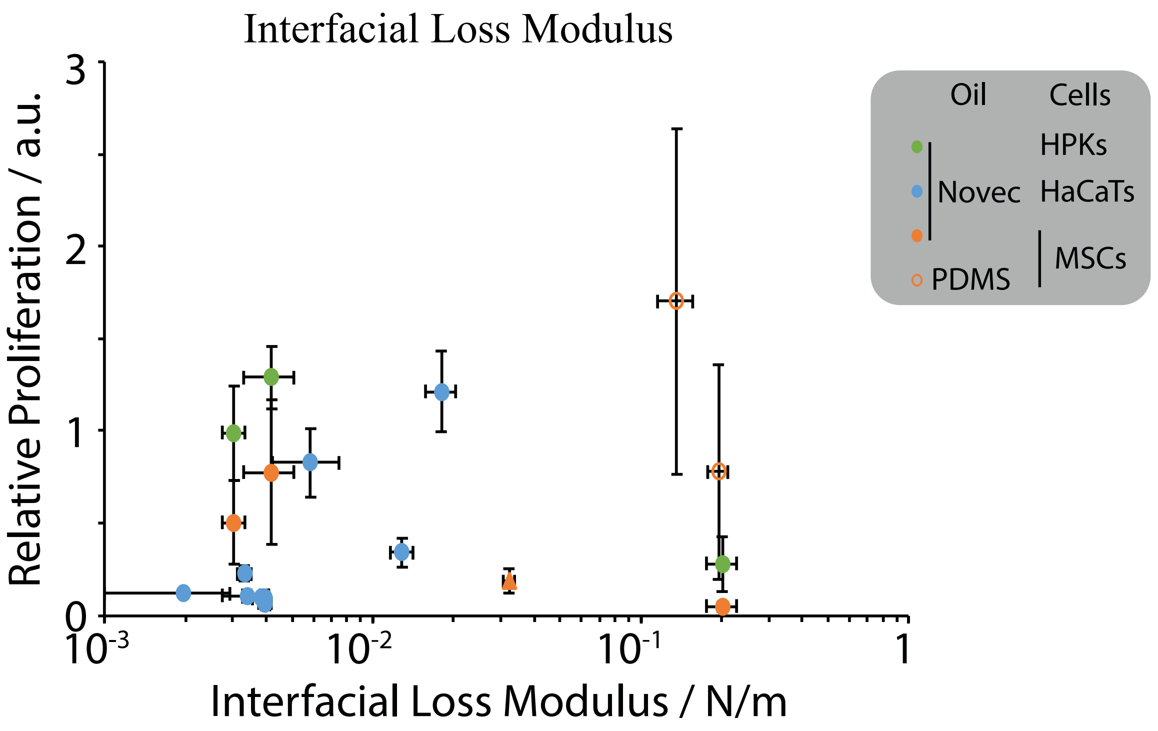




Kong et al. *Nano Letters*, 2018, 18 (3), 1946-1951.

Correlation Between Cell Expansion and Interfacial Mechanics?





- Interfacial shear moduli poorly correlate with cell expansion at the surface of liquids.
- What nanoscale mechanical properties do cells sense?

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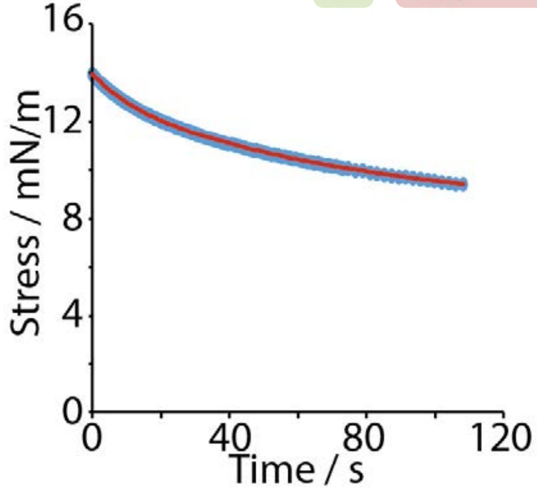
Impact of Surfactant on Interfacial Stress Relaxation

Interfacial Stress Relaxation

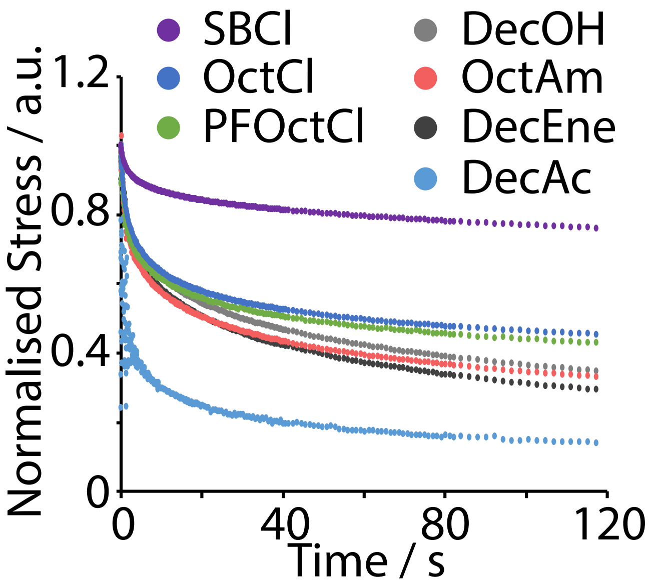
$$\sigma = \sigma_e + \sigma_1\left(1 - e^{-t/\tau_1}\right) + \sigma_2\left(1 - e^{-t/\tau_2}\right)$$



$\sigma_1 + \sigma_2$ viscous relaxation

σ_e, elastic stress

Impact of Different Surfactants on Interfacial Viscoelasticity



- Fit stress relaxation profiles with a double exponential.
- Surfactant concentration strongly impact elasticity level.

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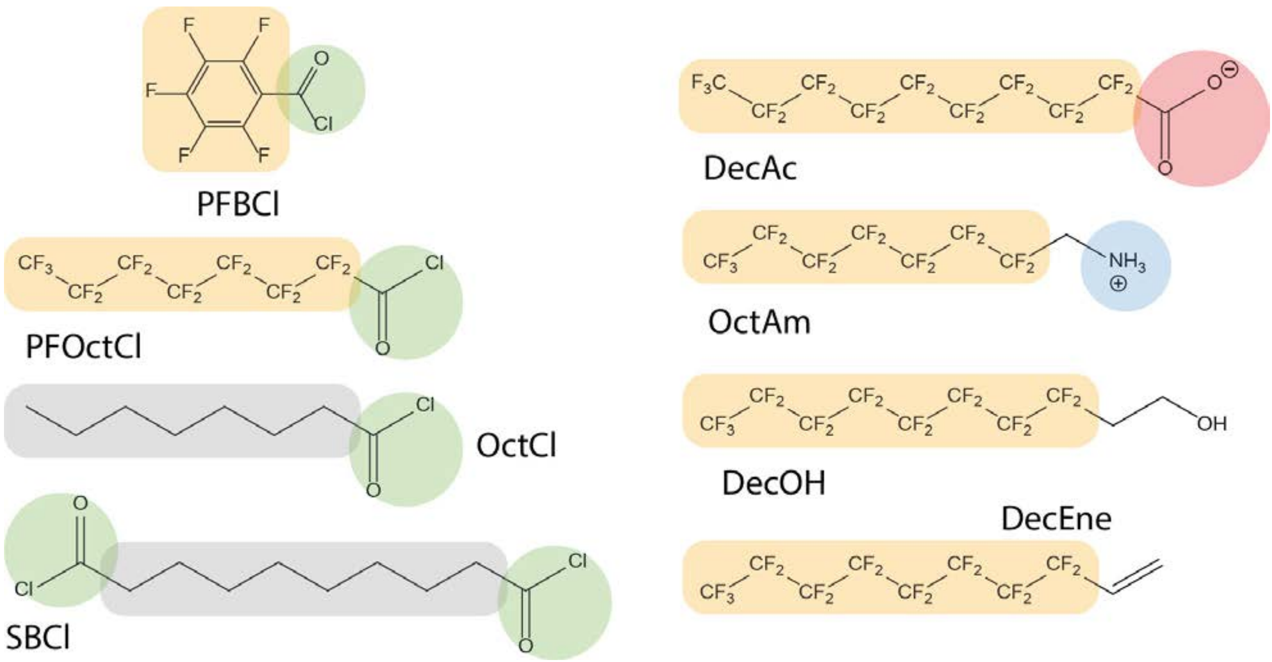
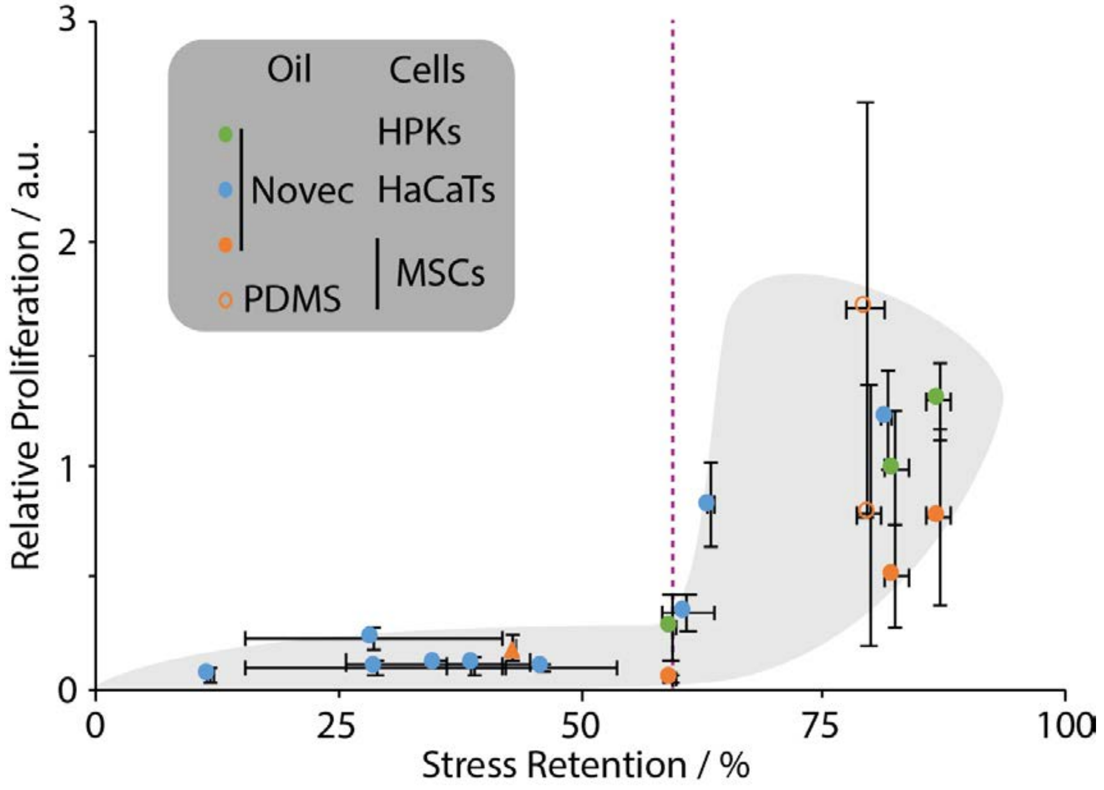
Interfacial Viscoelasticity Dictates Cell Proliferation on Liquids





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- Degree of elasticity predicts cell expansion on liquids.
- Reactive surfactants are essential to drive elasticity up.

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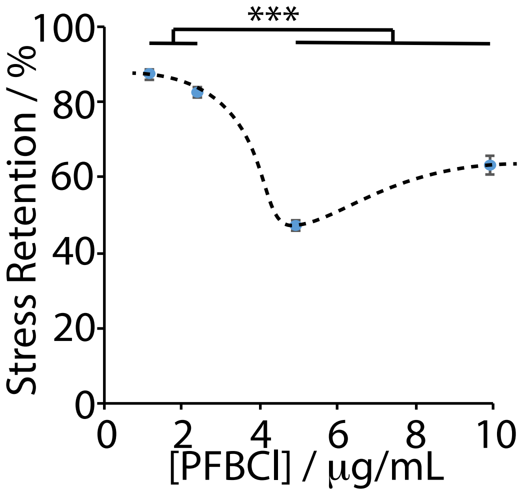
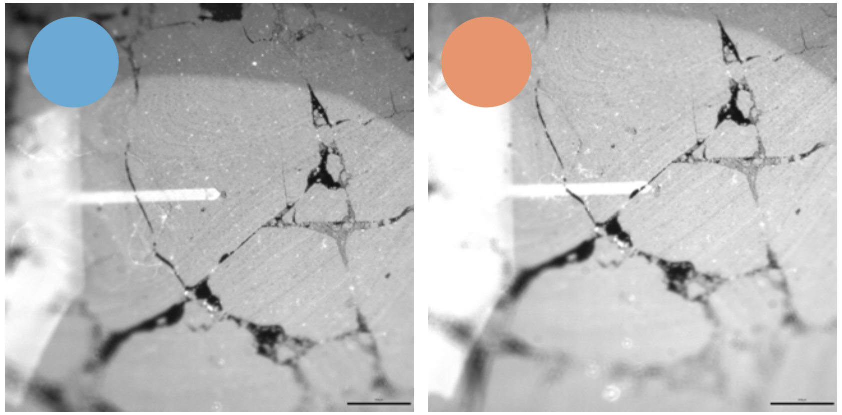
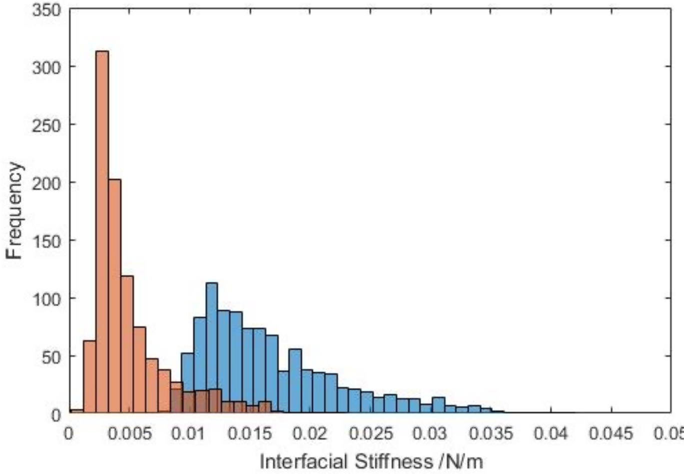
What is the Origin of Interfacial Viscoelasticity in Protein Nanosheets?

Impact of [PFBC] on PLL nanosheet viscoelasticity



AFM Characterisation of Microdomains





Megone et al. *JCIS*, 2021, 594:650-657.

Fluid interface → Jammed → Fractured

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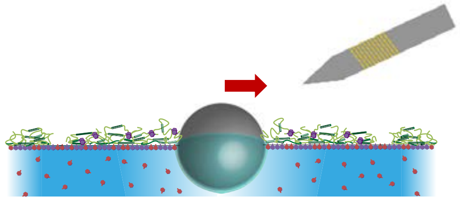
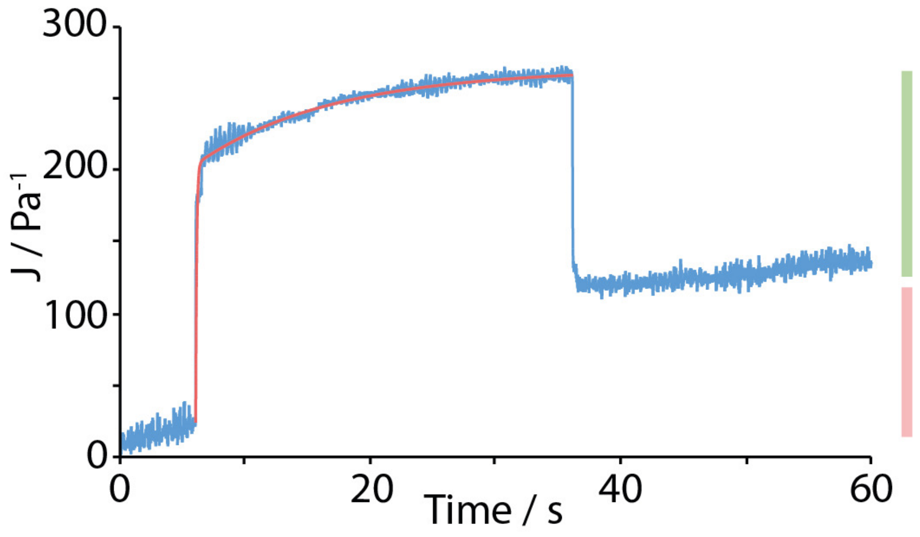
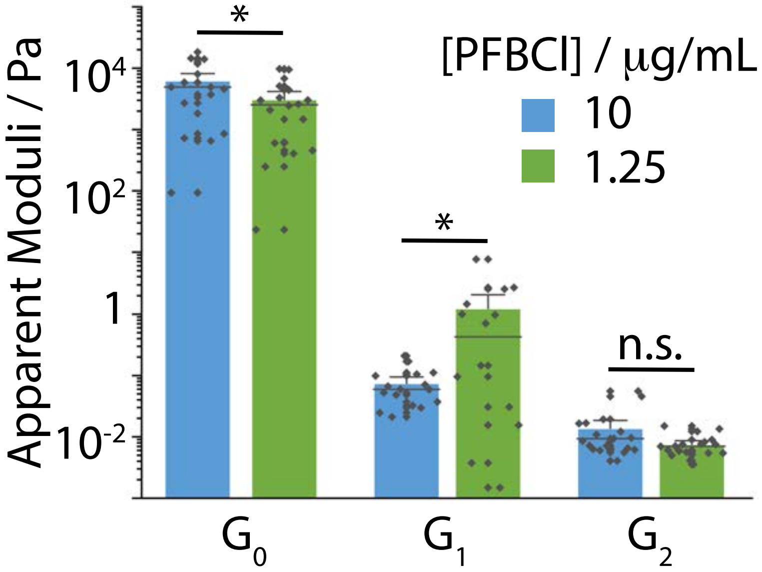
Microscale Viscoelasticity of Interfaces Reinforced with PLL Nanosheets

Armando Del Rio
Carlos Matellan

Creep assay with magnetic tweezer







6 Element Burguer' Model

$$J = \frac{1}{G_0} + \frac{1}{G_1}\left(1 - e^{-t/\tau_1}\right) + \frac{1}{G_2}\left(1 - e^{-t/\tau_2}\right) + \frac{t}{\eta}$$

- Reversed viscoelastic profile at the microscale.
- High heterogeneity in agreement with AFM indentation data and fluorescence microscopy.

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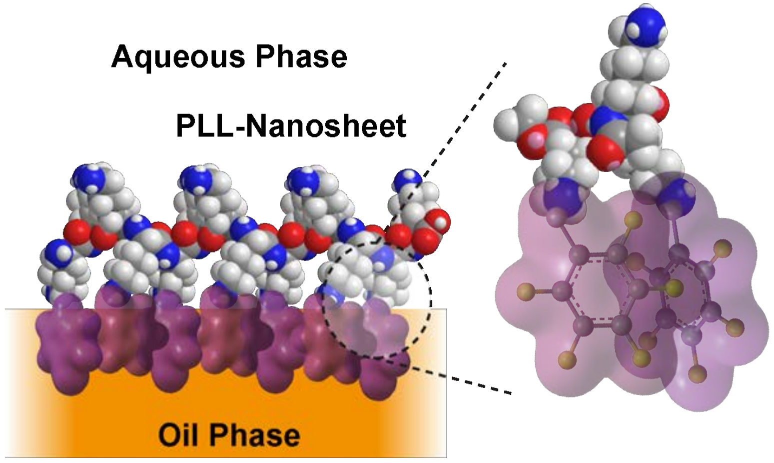
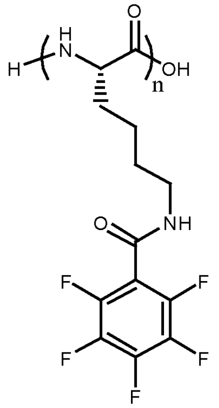
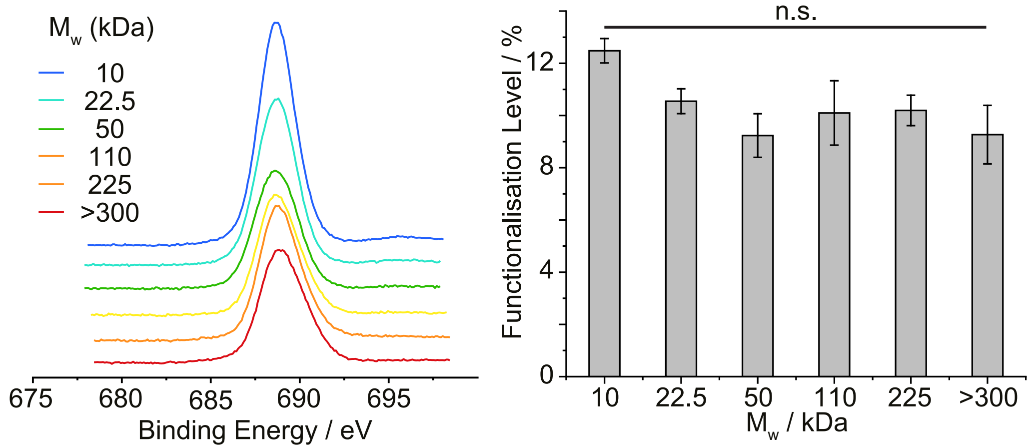
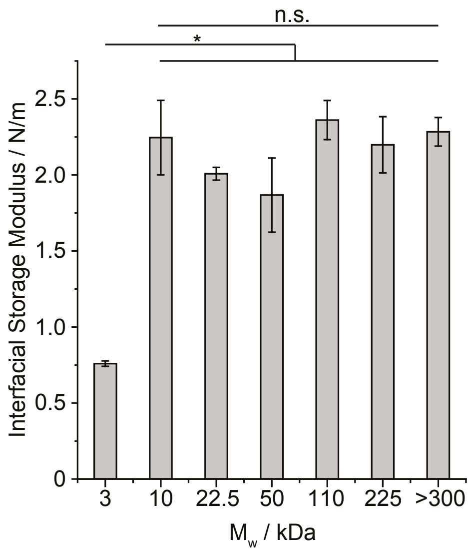
Impact of Molecular Weight on Interfacial Moduli





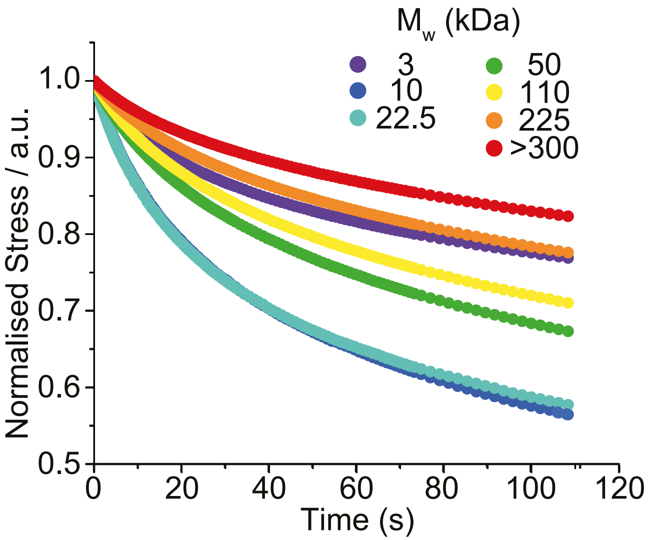


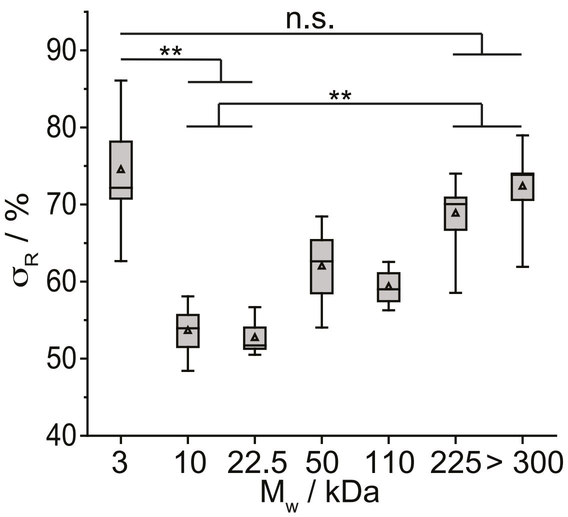


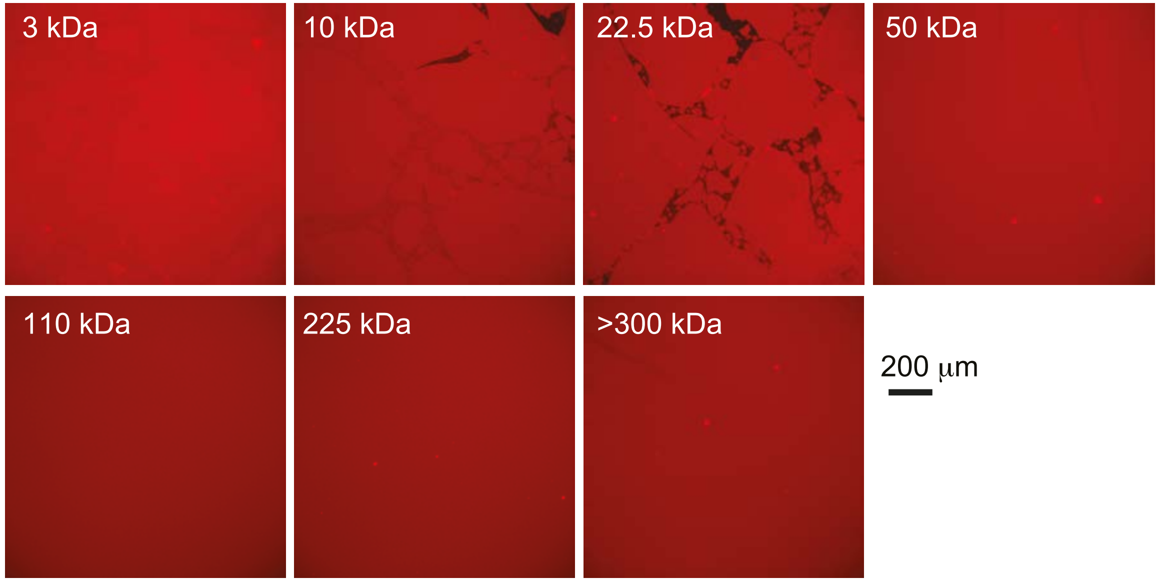
- PLL molecular weight does not significant impact on fluorination levels.
- Apart from the lowest molecular weight, no impact of M_w on interfacial stiffness.

Peng et al. *BioRxiv* doi.org/10.1101/2022.03.31.485540

Impact of Molecular Weight on Fracture and Interfacial Viscoelasticity







- Viscoelasticity is reduced on low Mw PLL nanosheets.
- This correlates with fracture mechanics and the formation of domains.

Peng et al. *BioRxiv* doi.org/10.1101/2022.03.31.485540

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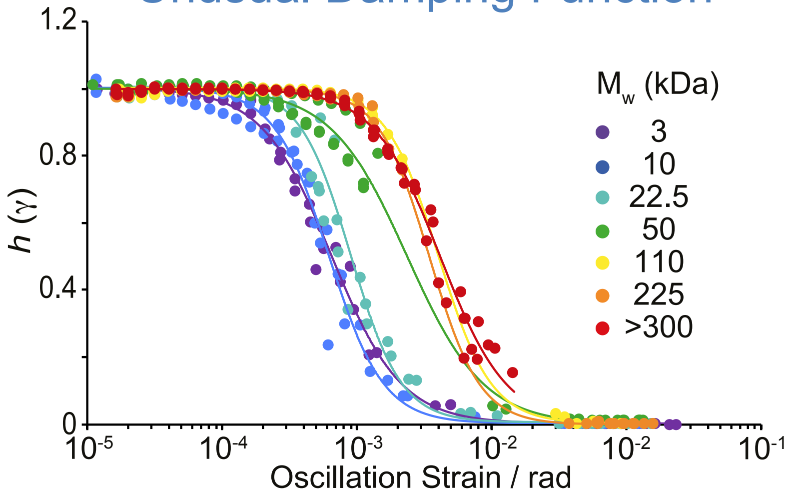
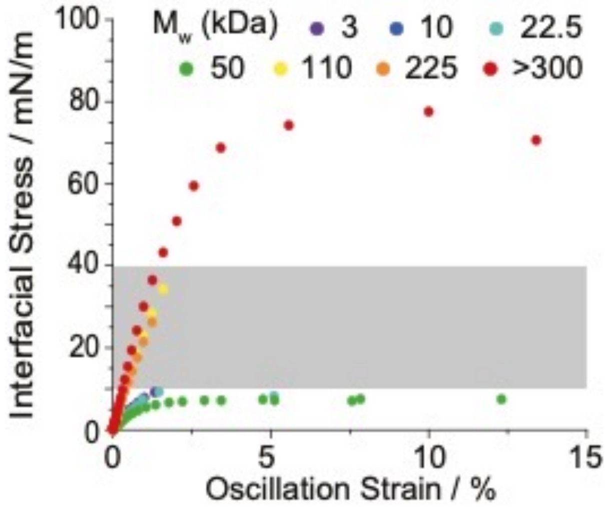
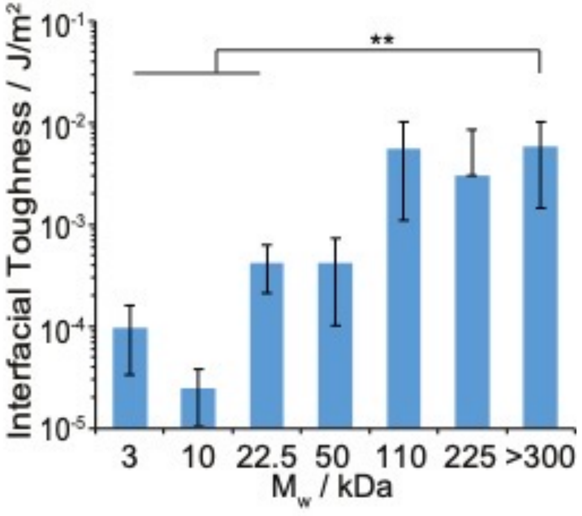
Impact of Molecular Weight on Interfacial Toughness

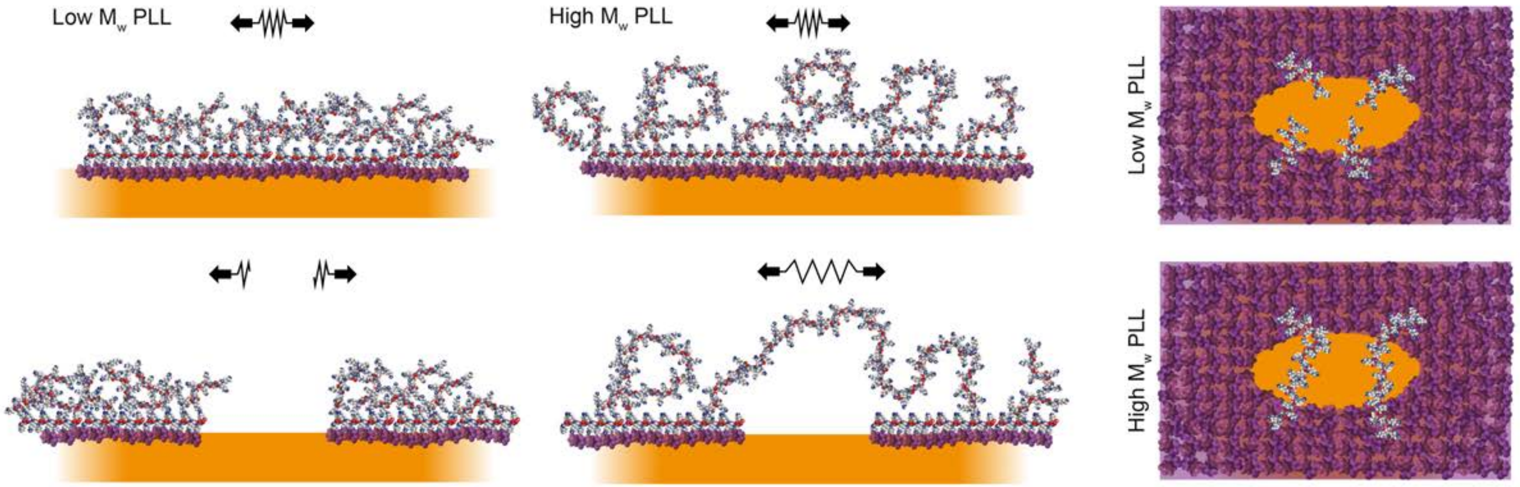
Unusual Damping Function





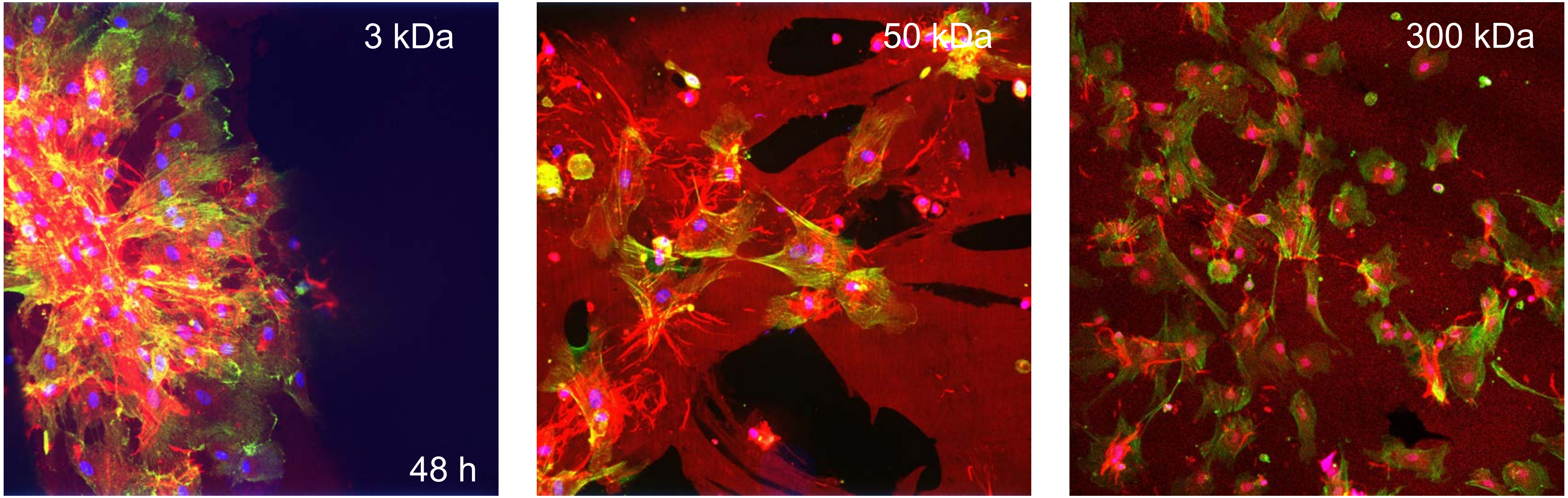


- Shift in damping function with higher M_w.
- Toughness increases with M_w.
- Soft domains dissipate energy.



Peng et al. *BioRxiv* doi.org/10.1101/2022.03.31.485540

MSCs Fracture Weak Protein Nanosheets

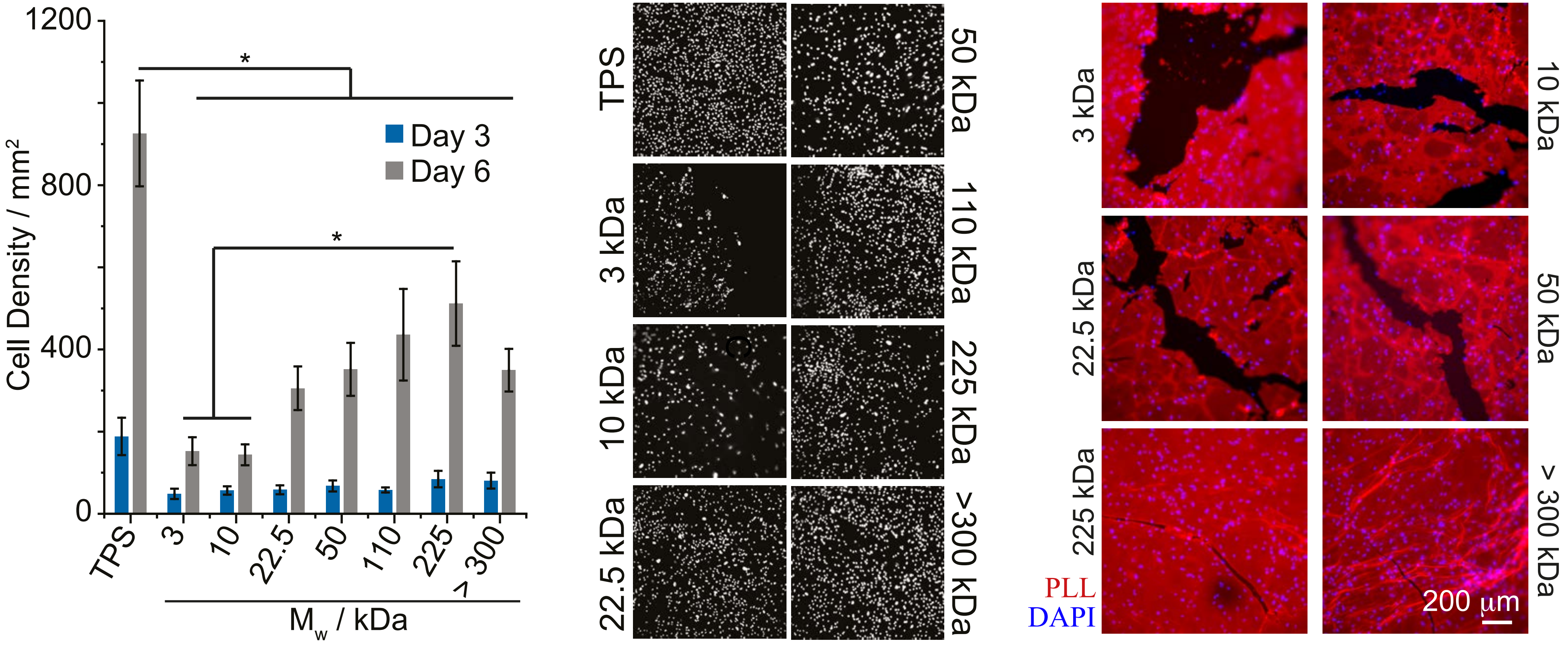


DAPI Actin PLL

- MSCs wrinkle nanosheets and fracture them.
- Nanosheet toughness prevents fracture and gap formation.

Peng et al. *BioRxiv* doi.org/10.1101/2022.03.31.485540

Nanosheet Toughness Impacts MSC Proliferation



Peng et al. *BioRxiv* doi.org/10.1101/2022.03.31.485540

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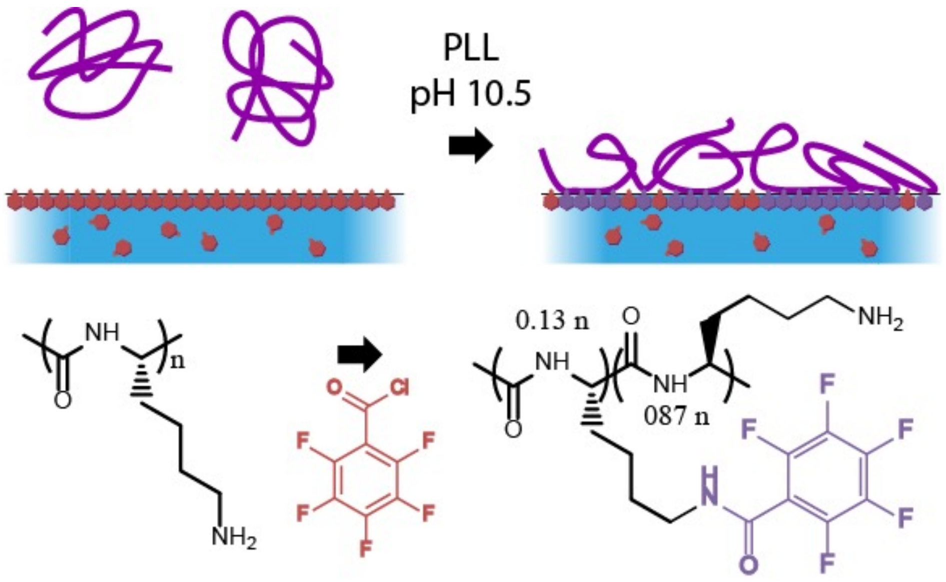
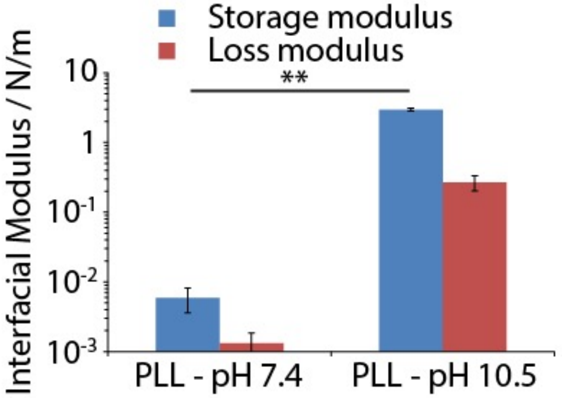
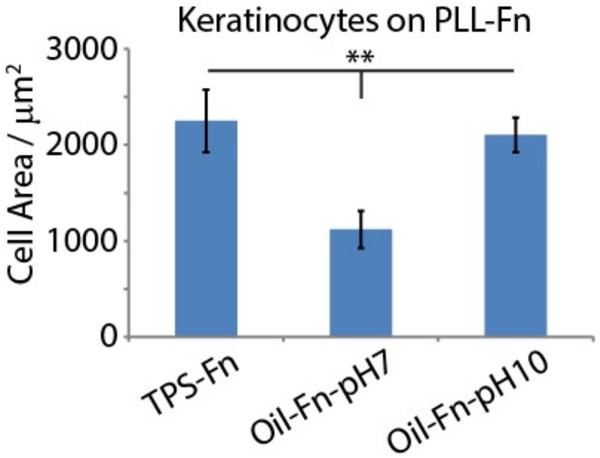
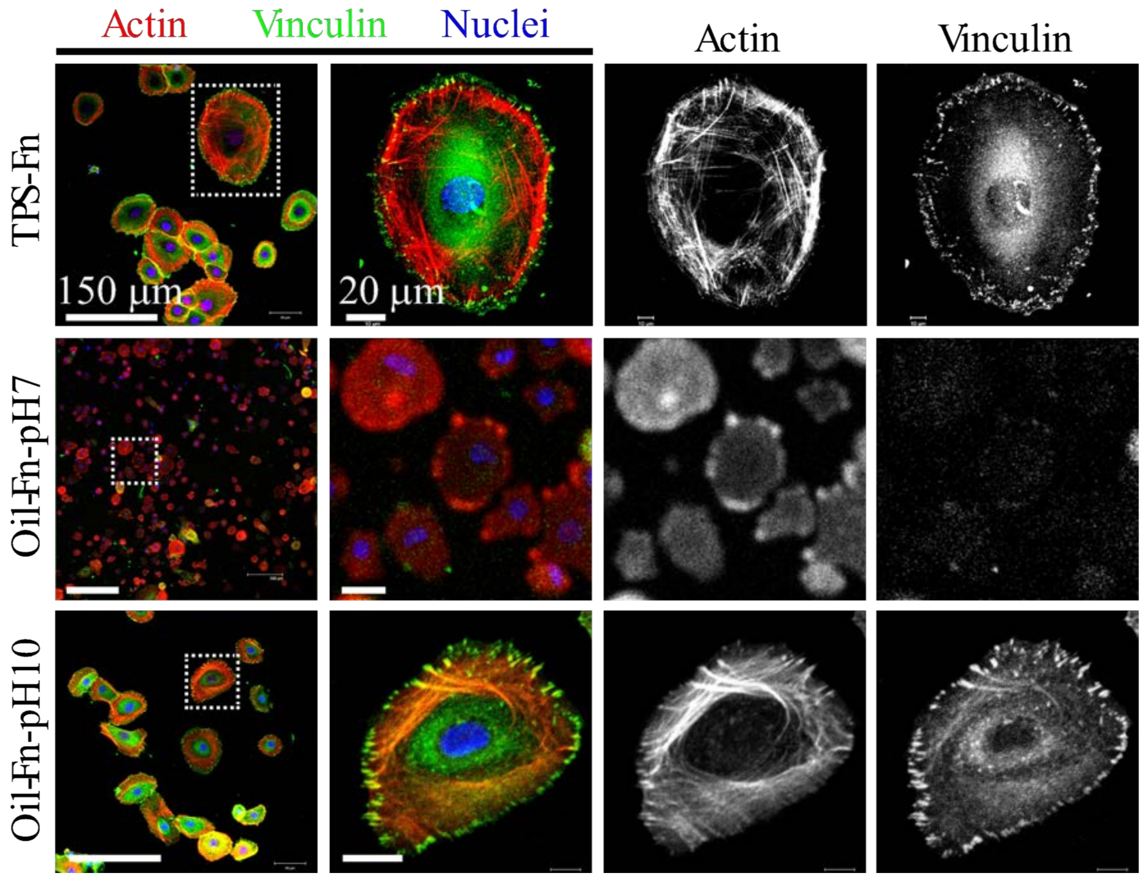
Keratinocyte Spreading on Nanosheet Reinforced Oils is Mediated by Focal Adhesions



- Primary keratinocyte spreading at liquid-water interfaces depends on stiffness.
- Controlled by focal adhesion formation and stress fibre generation.

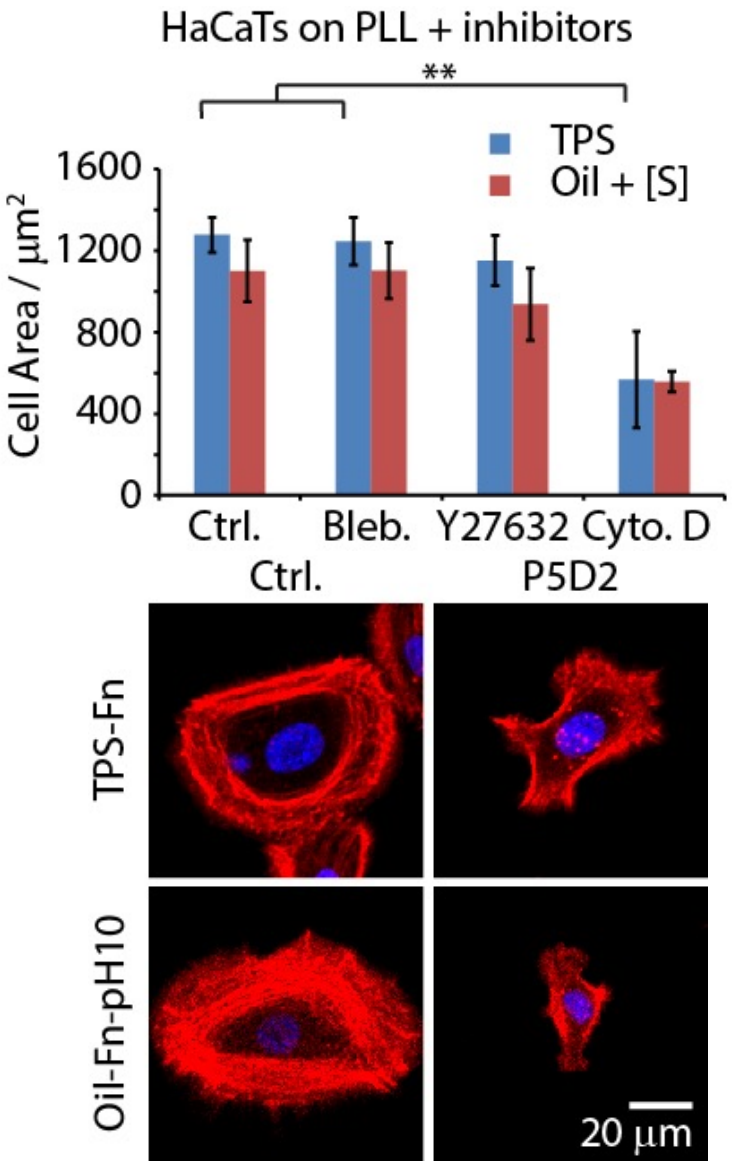




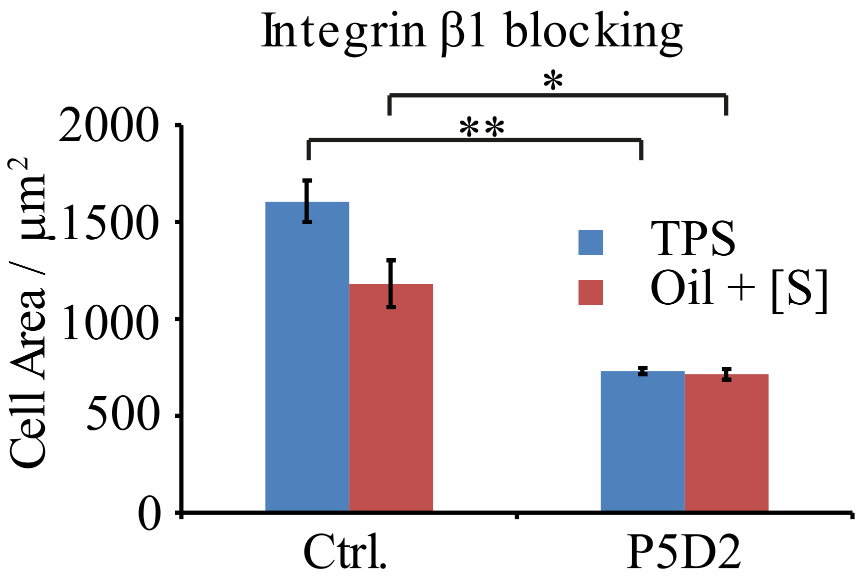


Dexu Kong, *ACS Nano*, 2018, 12 (9), 9206-9213.

Lamellipodia and Filopodia Formation on Oils



- Disruption of cytoskeleton assembly induces similar changes in cell spreading and shape on liquids.
- Blocking of integrin ligation results in comparable changes in cell spreading and actin assembly.



Dexu Kong, *ACS Nano*, 2018, 12 (9), 9206-9213.

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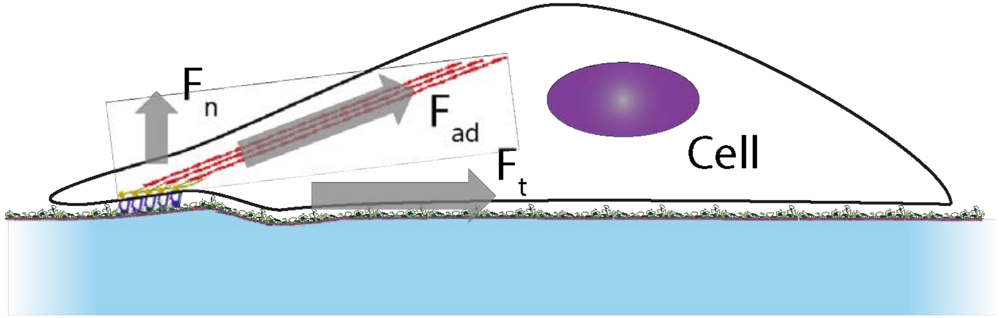
Cell Sensing of the Mechanical Properties of their Environment



1. Cells respond to the mechanics of their substrates
2. Molecular mechanisms of mechanosensing
3. Complex response to mechanical properties
4. Cells can adhere and grow on liquids !?
5. Cells sense the nanoscale mechanics of their environment
6. Liquid substrates and emulsions for stem cell technologies

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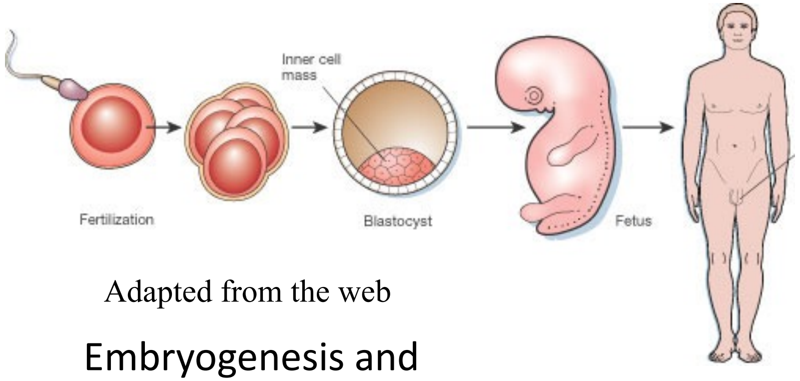
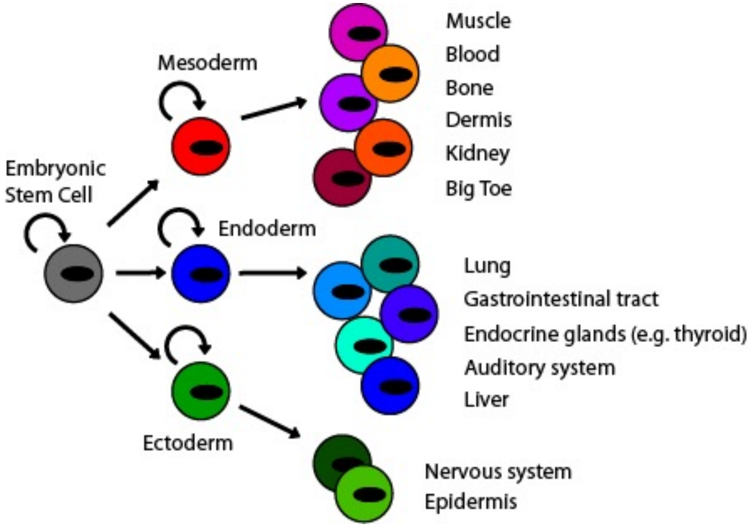
Rapid Growth in Stem Cell Technologies



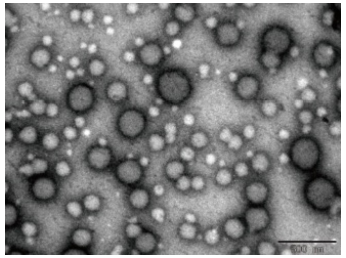
Adapted from the web

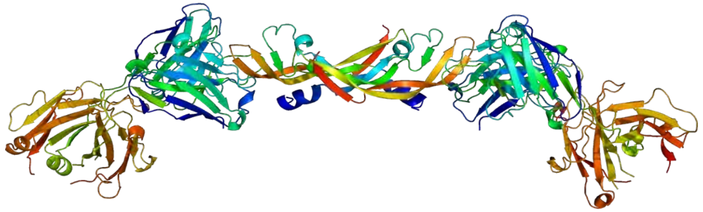
Embryogenesis and Development



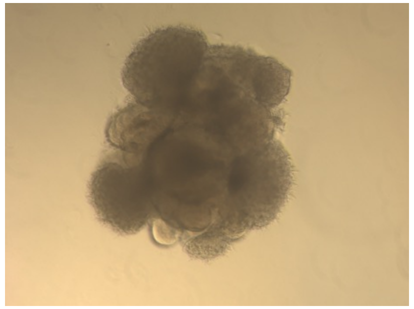
Tissue Engineering

Biotherapeutics Production

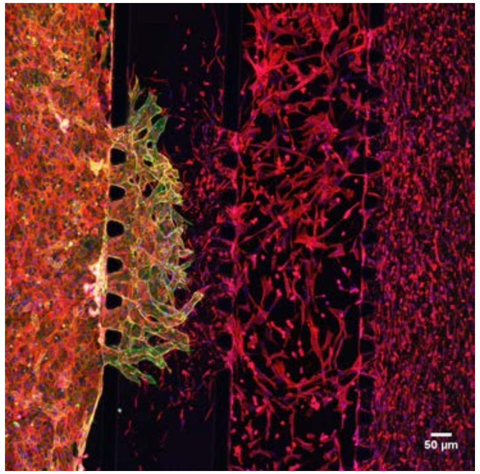




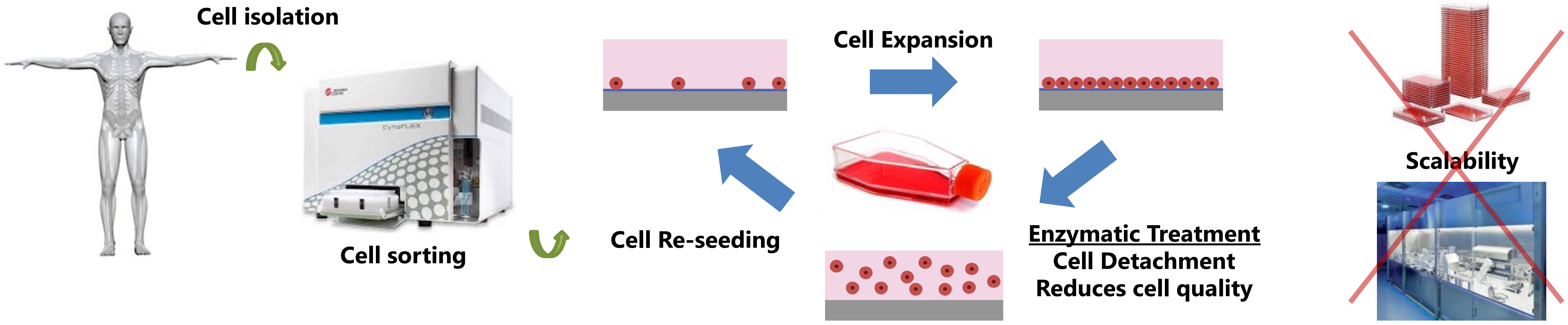
Organoids



Organ-on-Chips

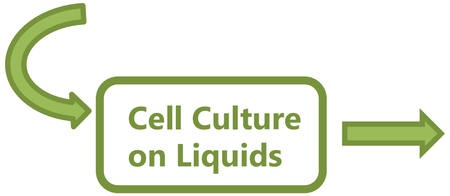


Cell Culture on Solid Substrate: A Hurdle for Cell Manufacturing and Biotechnologies

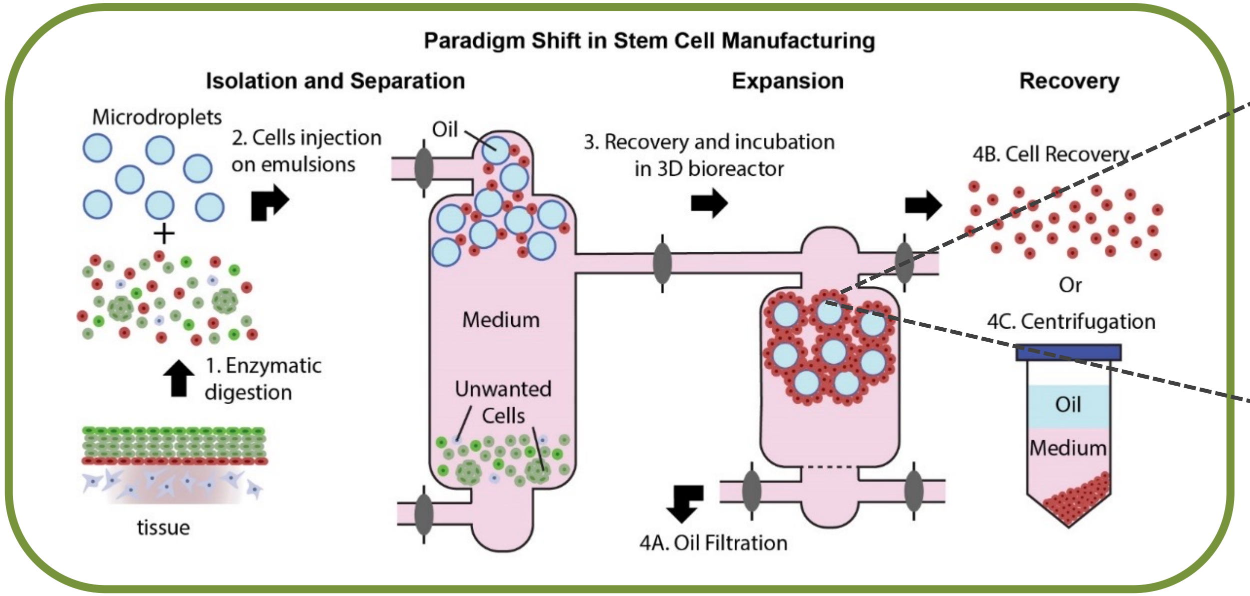


- Cell manufacturing remains difficult to automate, difficult to scale up.
- Reliance on expensive solid microparticles, difficult to separate from cell products and process.
- Systems remain highly reliant on plastics and microplastics.

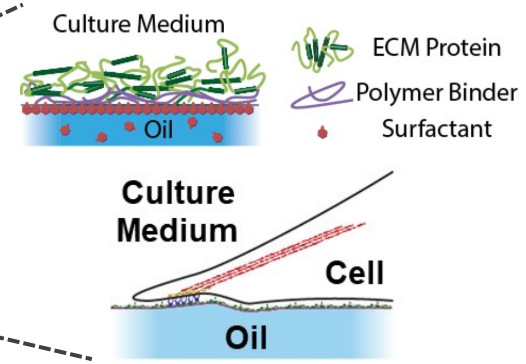
A Paradigm Shift in Stem Cell Manufacturing



Increased throughput ✓
Increased quality ✓
Reduced cost ✓

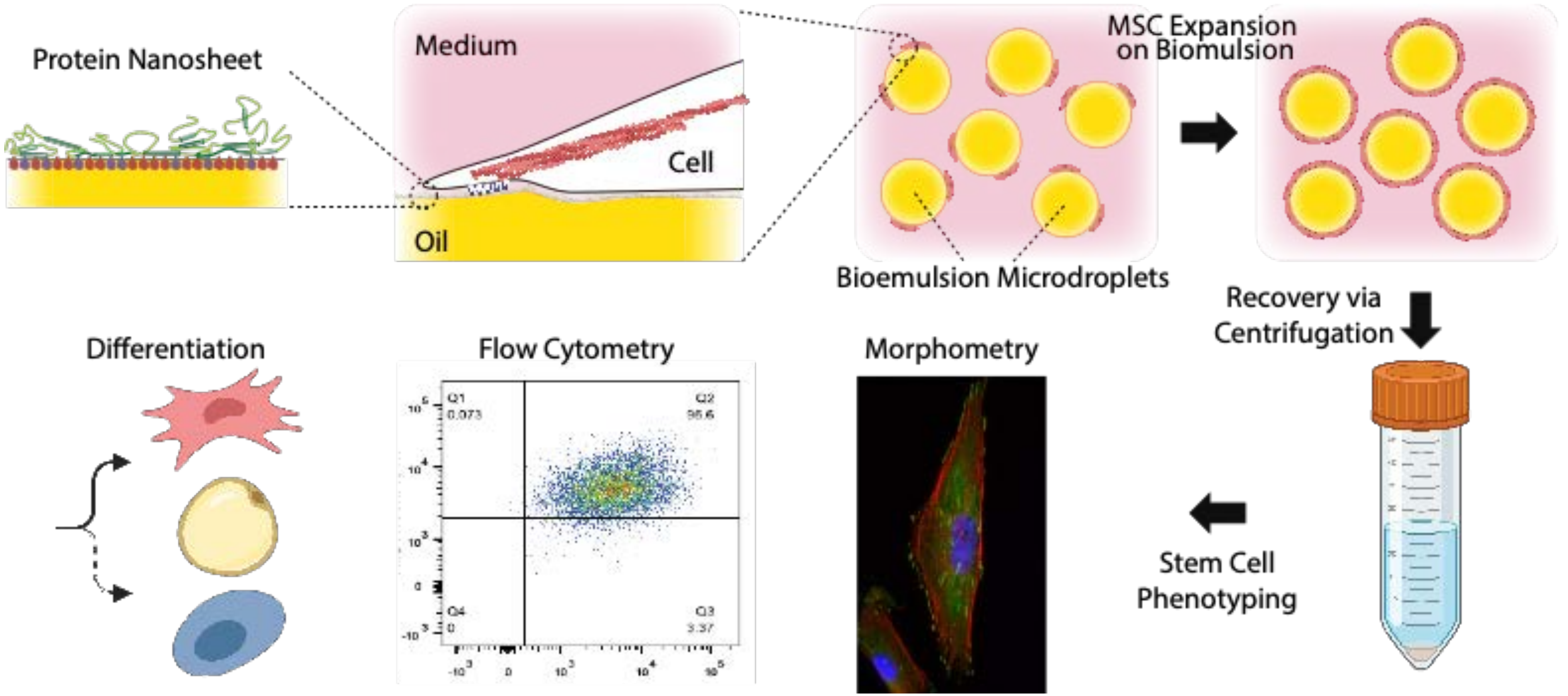


Cell Culture on Liquids



- Liquid-liquid systems such as emulsions simple to automate and process.
- Very competitive costs (>10 fold more affordable).
- Replacement of microplastics with oils validated for medical/consumer applications.

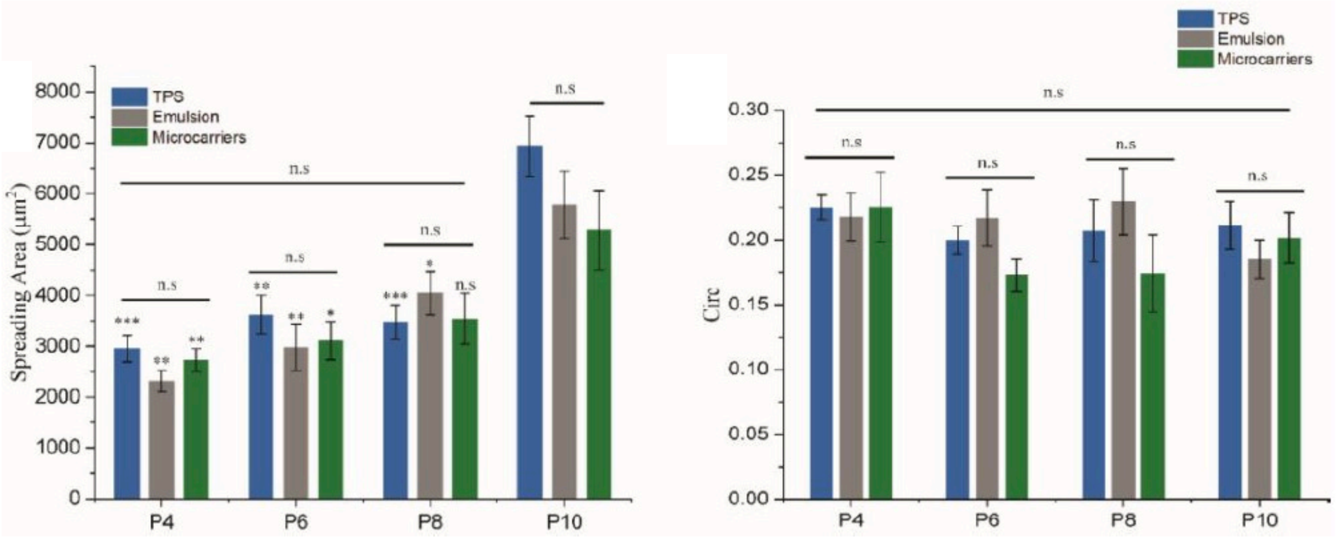
Impact of Long-Term Culture on Liquids on MSC Phenotype

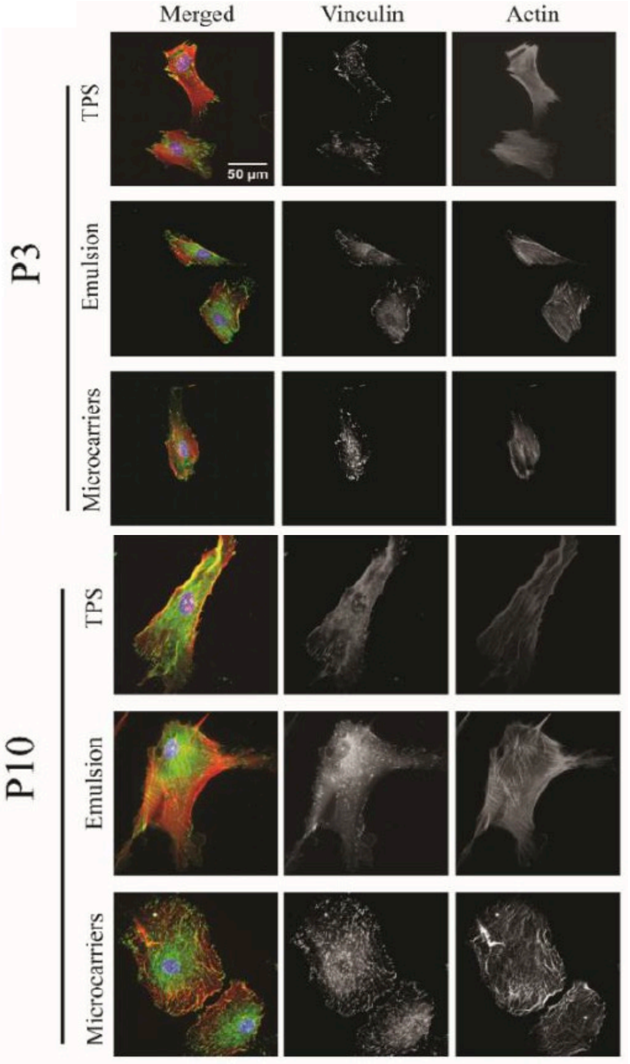


Peng et al. *Mat. Today Bio, 2021,* 12, 100159.

Morphological Analsysis

- Morphology of MSCs typically correlates with their phenotype.
- Cell morphologies comparable after culture on plastic (TPS), emulsions or solid microcarriers (Synthemax).
- Impact of passage time on morphology far more significant.





Nuclei
Actin
Vinculin

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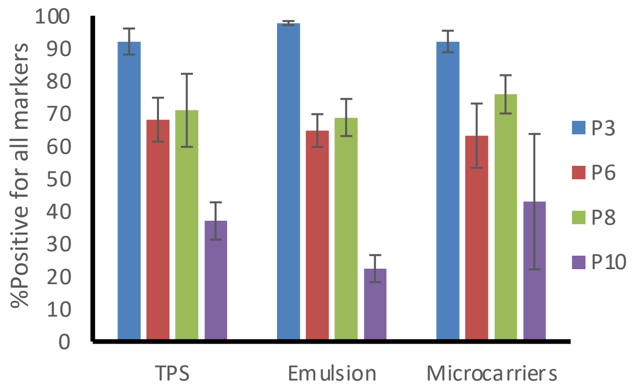
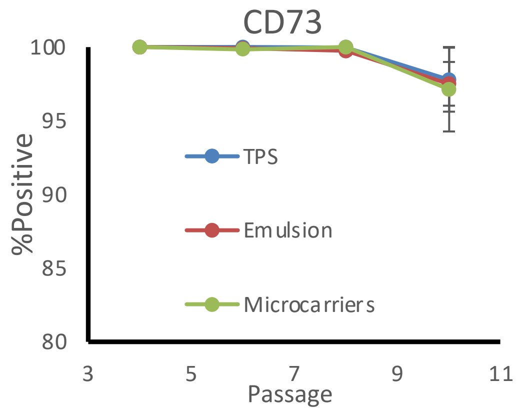
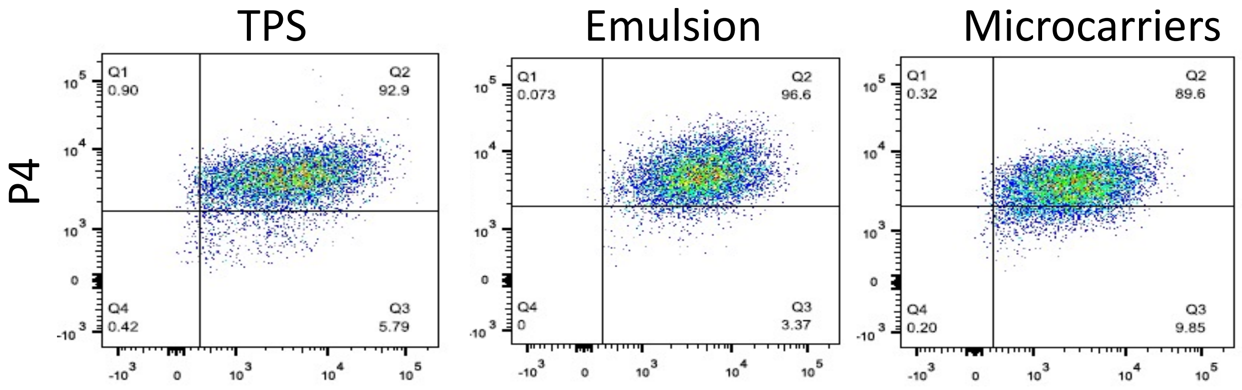
Long Term Retention of Stem Cell Phenotype

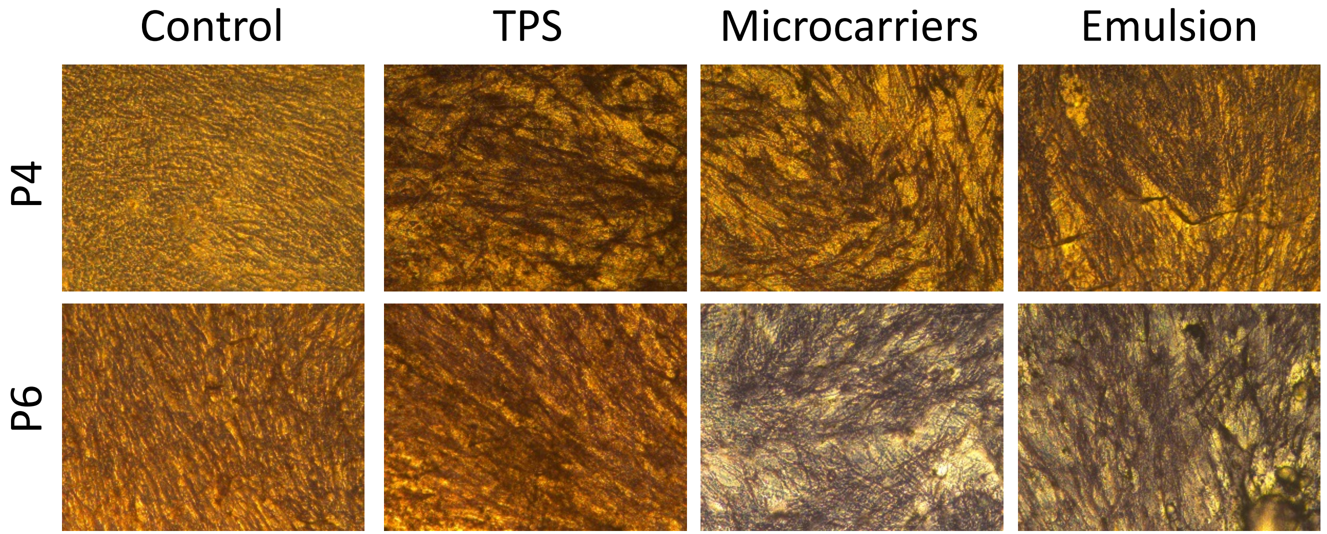
Flow Cytometry







Differentiation

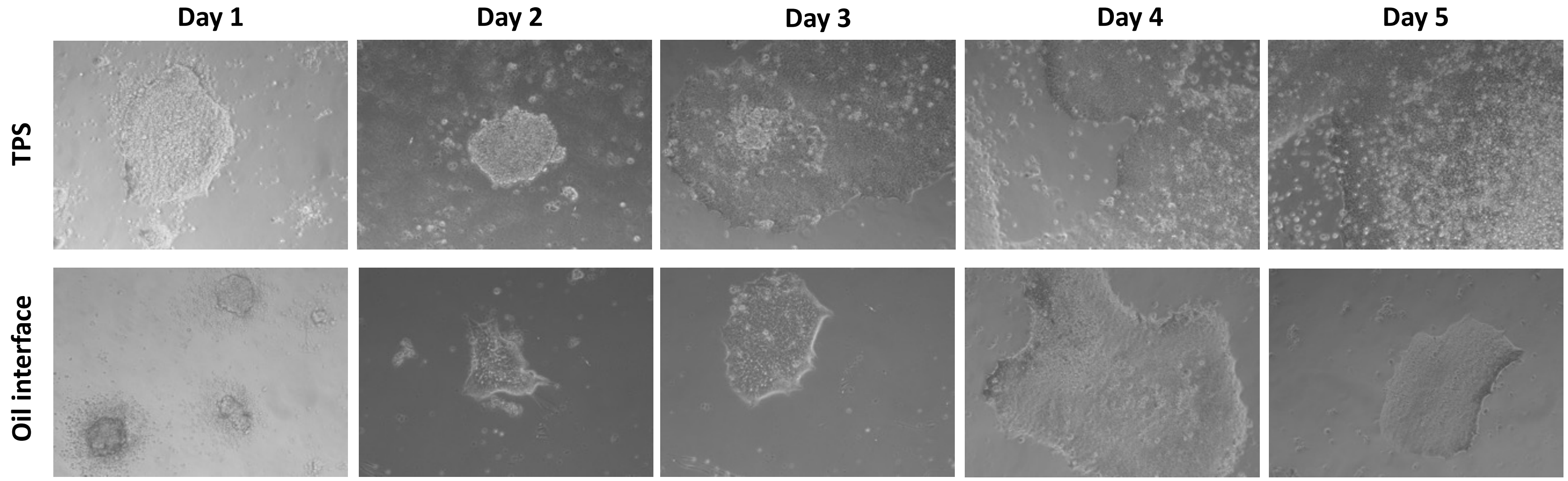


Peng et al. *Mat. Today Bio, 2021,* 12, 100159.

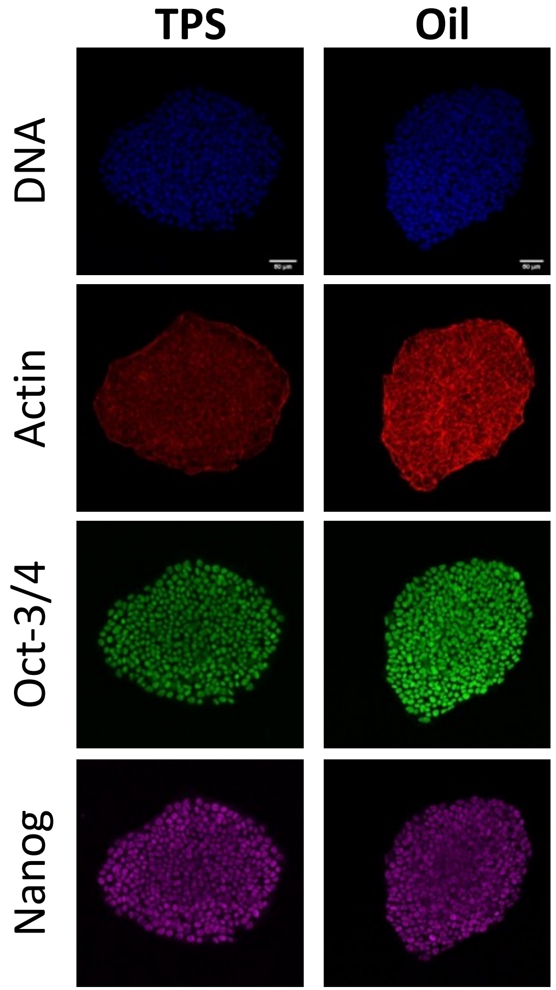
- Retention of key surface markers of MSC phenotype up to P8.
- Absence of negative markers.
- MSCs retain ability to differentiate into osteogenic lineages following long term expansion on Novec oil microdroplets stabilised with PLL nanosheets.
- Comparable results with Alizarin red stainings and with adipo/chondrogenic differentiation.

Culture of Broader Range of Stem Cells at Liquid Interface

Culture of iPSC Colonies

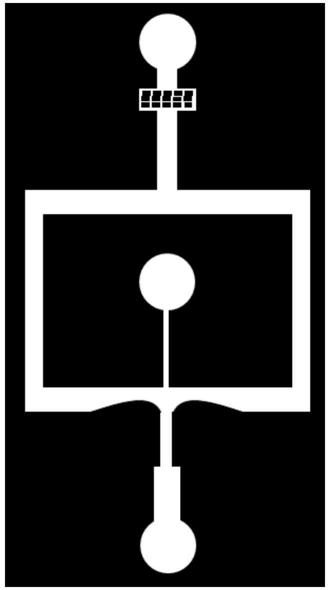


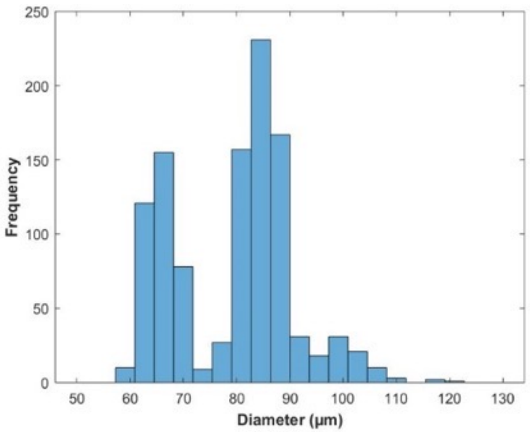
Stem Cell Markers



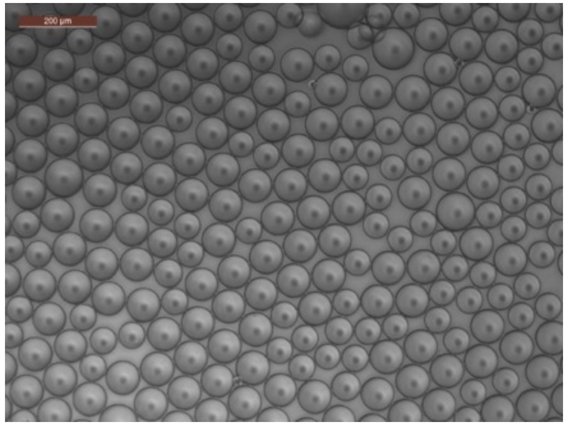
- Growth at liquid-liquid interfaces results in the formation of large colonies.
- Fewer single cells growing independently.
- Retention of stem cell markers Oct3/4 and Nanog.

iPSC Culture on Microdroplets



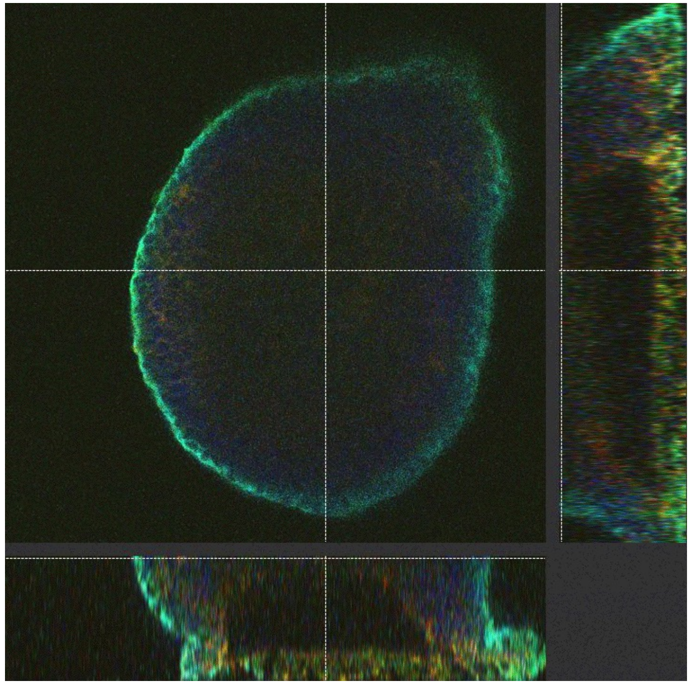


Microdroplet Fabrication



iPSC Culture

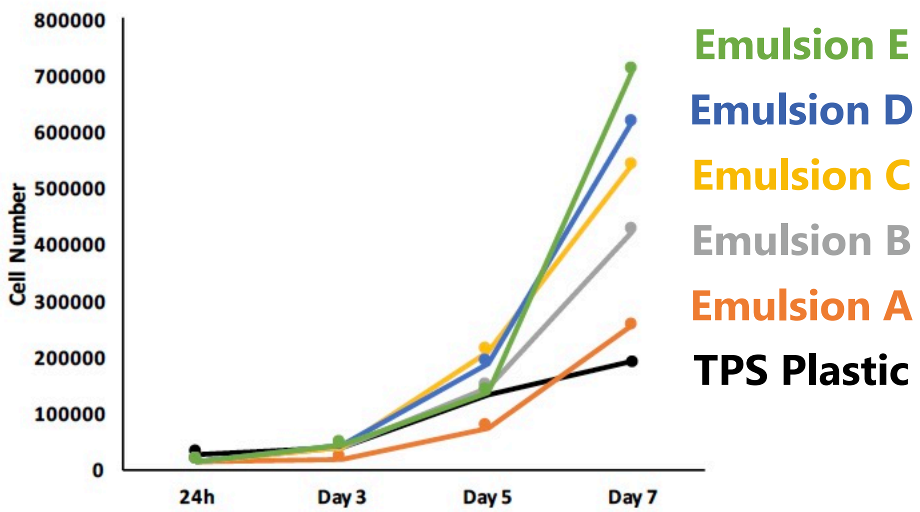
DAPI Phalloidin Vinculin Paxillin

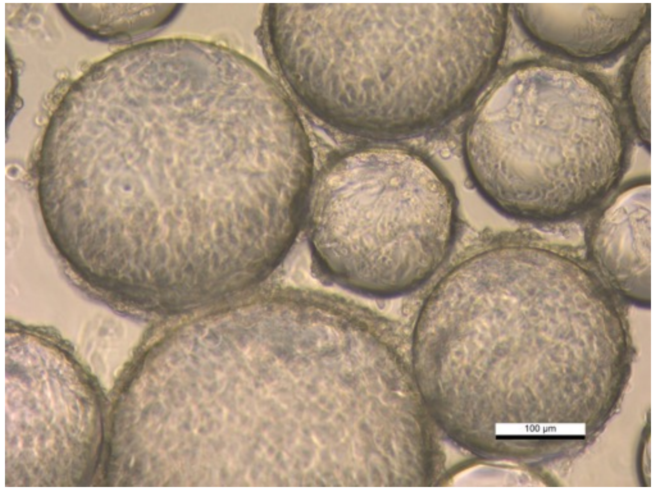


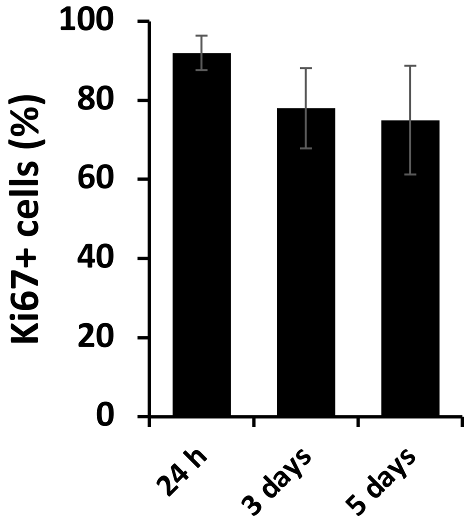
- Generation of microdroplets in a microfluidic system.
- Assembly of iPSCs at the surface of droplets and formation of large colonies.

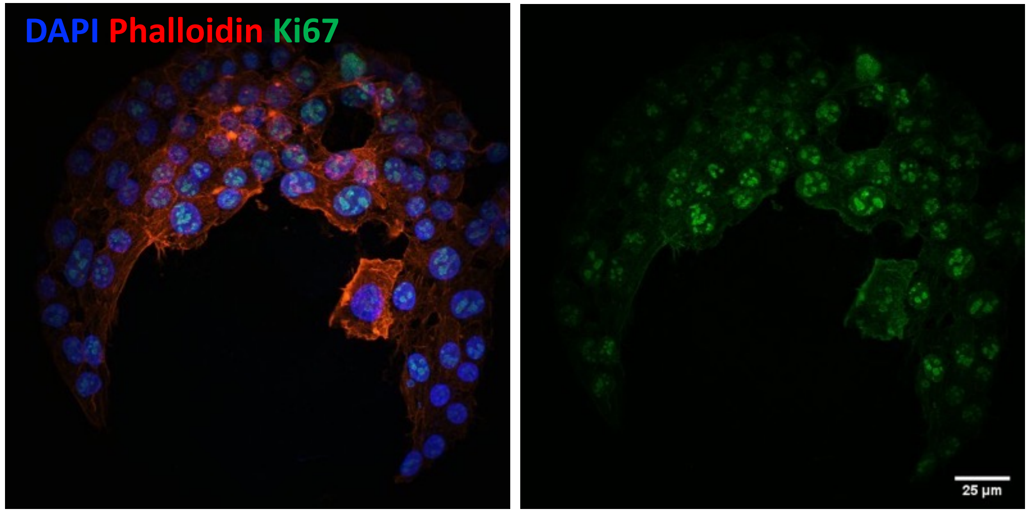
Bioemulsions for the Production of Biotherapeutics by Adherent Cells

Growth of HEK293 Cells









- HEK293 cells, commonly used for biotherapeutics manufacturing (recombinant proteins, exosomes, vaccines) particularly well in bioemulsions.
- Reduction in cost of carriers for 3D scale up compared to solid microcarriers by 20-50 fold.

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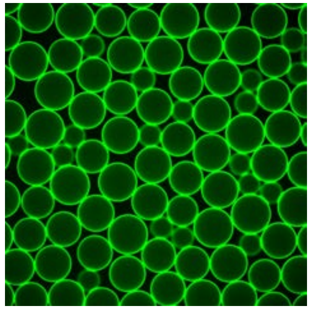
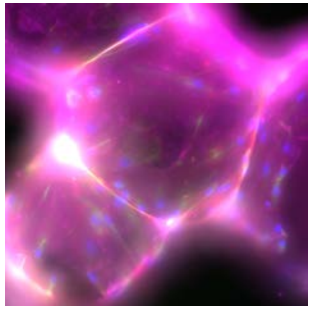
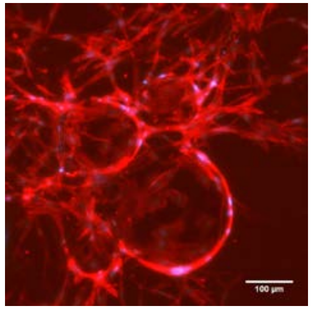
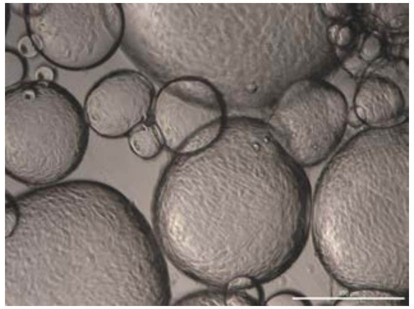
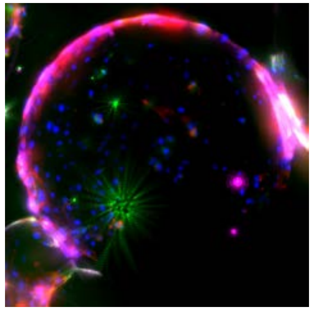
Conclusions

- Cell adhesions are important mechanosensing hubs that impact on downstream transcription factors and regulate a broad range of phenotypes.
- However cell response to the mechanics of their environment is complex and does not only correlate with bulk mechanics.
- Cells respond to biomaterials by directly probing their nanoscale mechanical properties.
- Adhesion to materials displaying “no” bulk mechanical properties but a stiff interface is mediated by integrins and acto-myosin contractility.
- Opens new opportunities for technology development in tissue engineering and regenerative medicine.

Thank You

John Connelly (QMUL)
Fran Balkwill (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)

Duncan Sutherland (Aarhus)
Jenny Malmstrom (Aarhus)
Christoph Ballestrem (Manchester)
Thomas Iskratsch (QMUL)
Mariah Sundh (Aarhus)
Fiona Watt (KCL)
Wilhelm Huck (Nijmegen)
Arnoud Sonnenberg (NKI)
Thereza Soares (Recife)

Burcu Colak
Stefania di Cio
Pei Tang
Dexu Kong
Khai Nguyen
Alex Moothedathu
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Fengqin Qu
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