Which properties of the extracellular matrix are important for cell behavior in 3-D?

Ben Fabry
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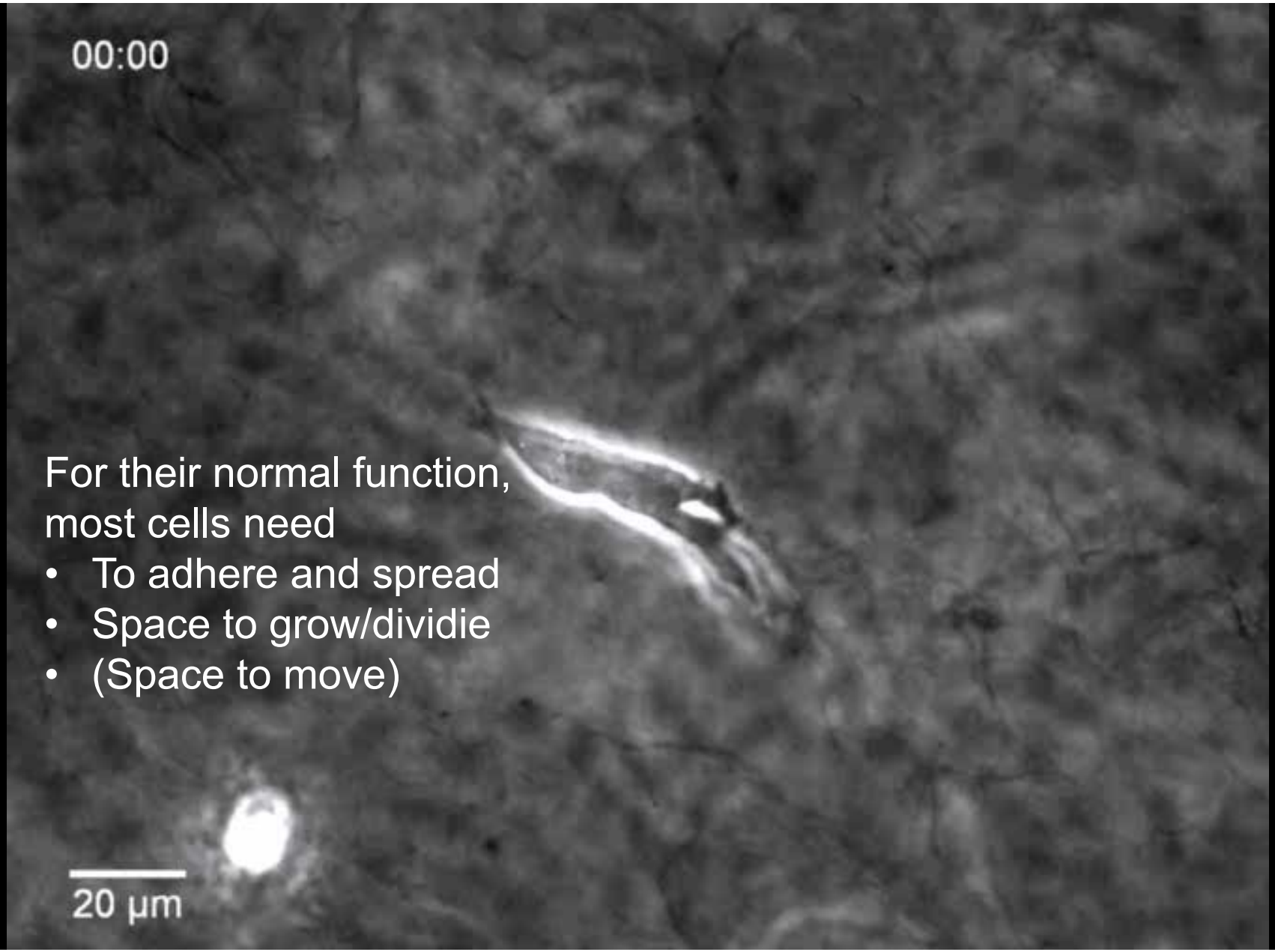
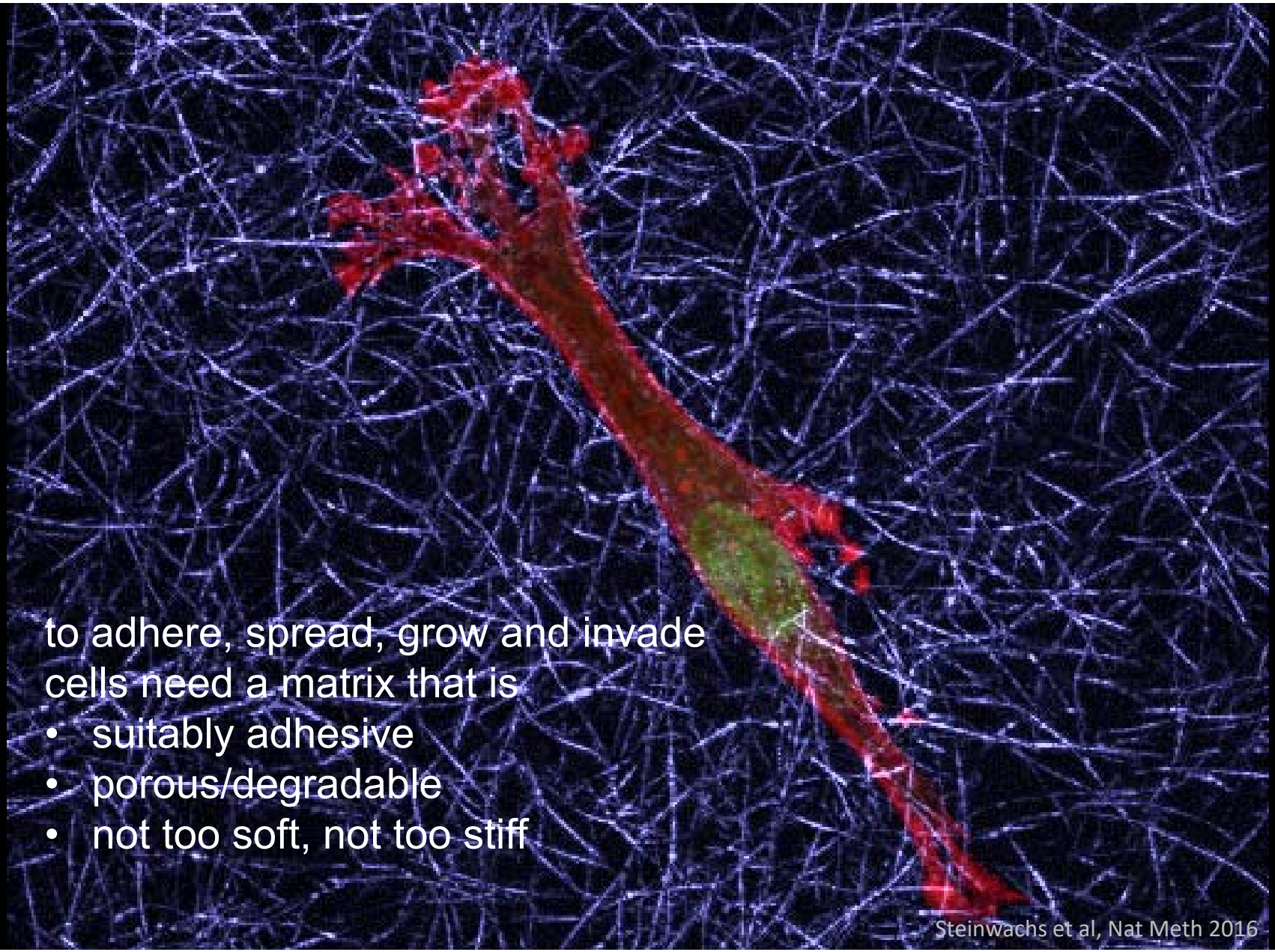
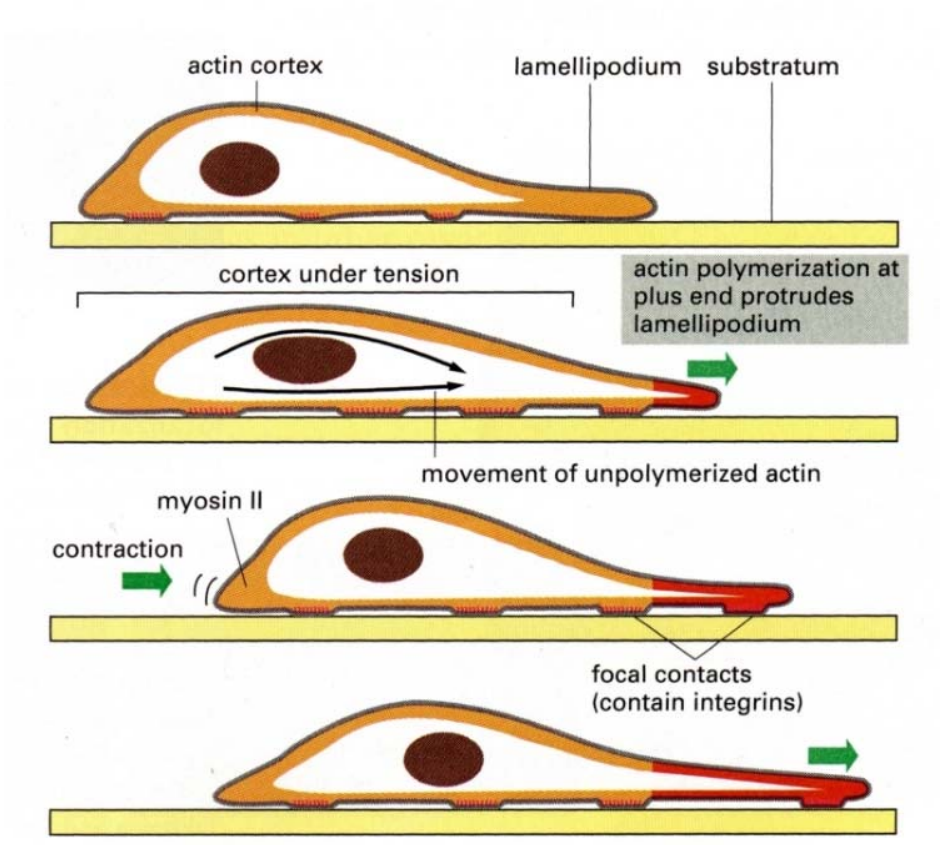
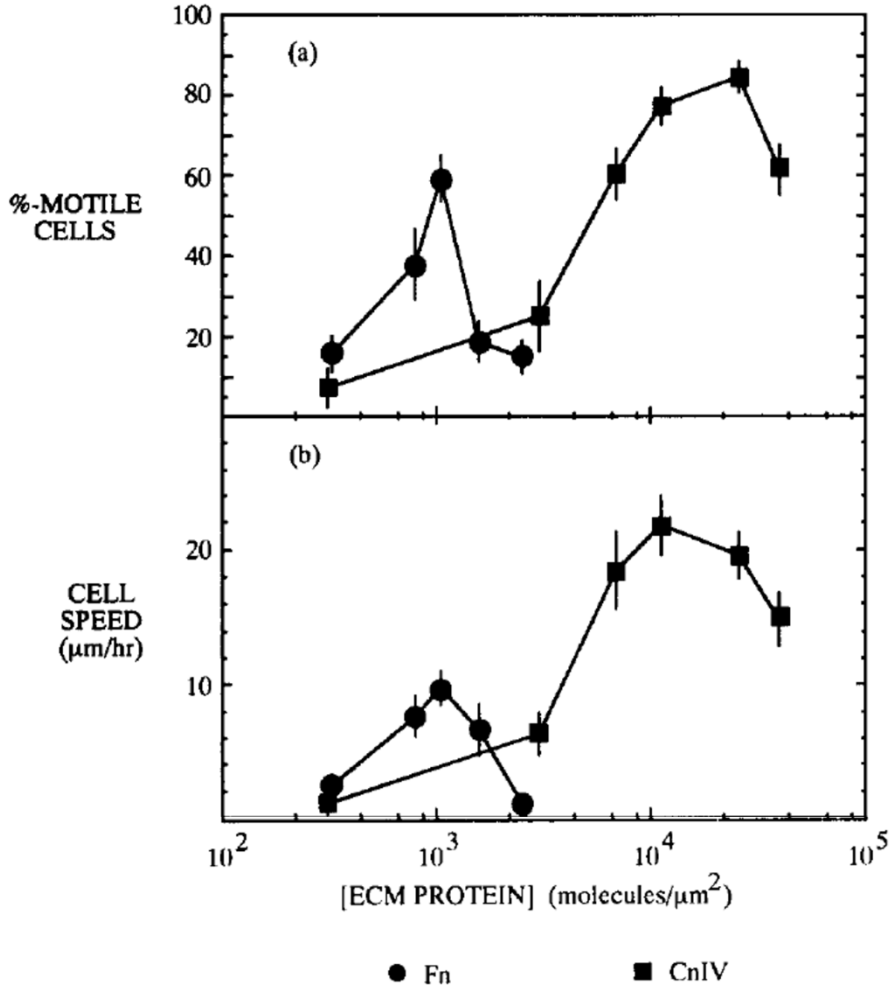

00:00
For their normal function,
most cells need
• To adhere and spread
• Space to grow/dividie
• (Space to move)
20 µm


to adhere, spread, grow and invade
cells need a matrix that is
• suitably adhesive
• porous/degradable
• not too soft, not too stiff
Steinwachs et al, Nat Meth 2016

Maximum motility at intermediate adhesiveness



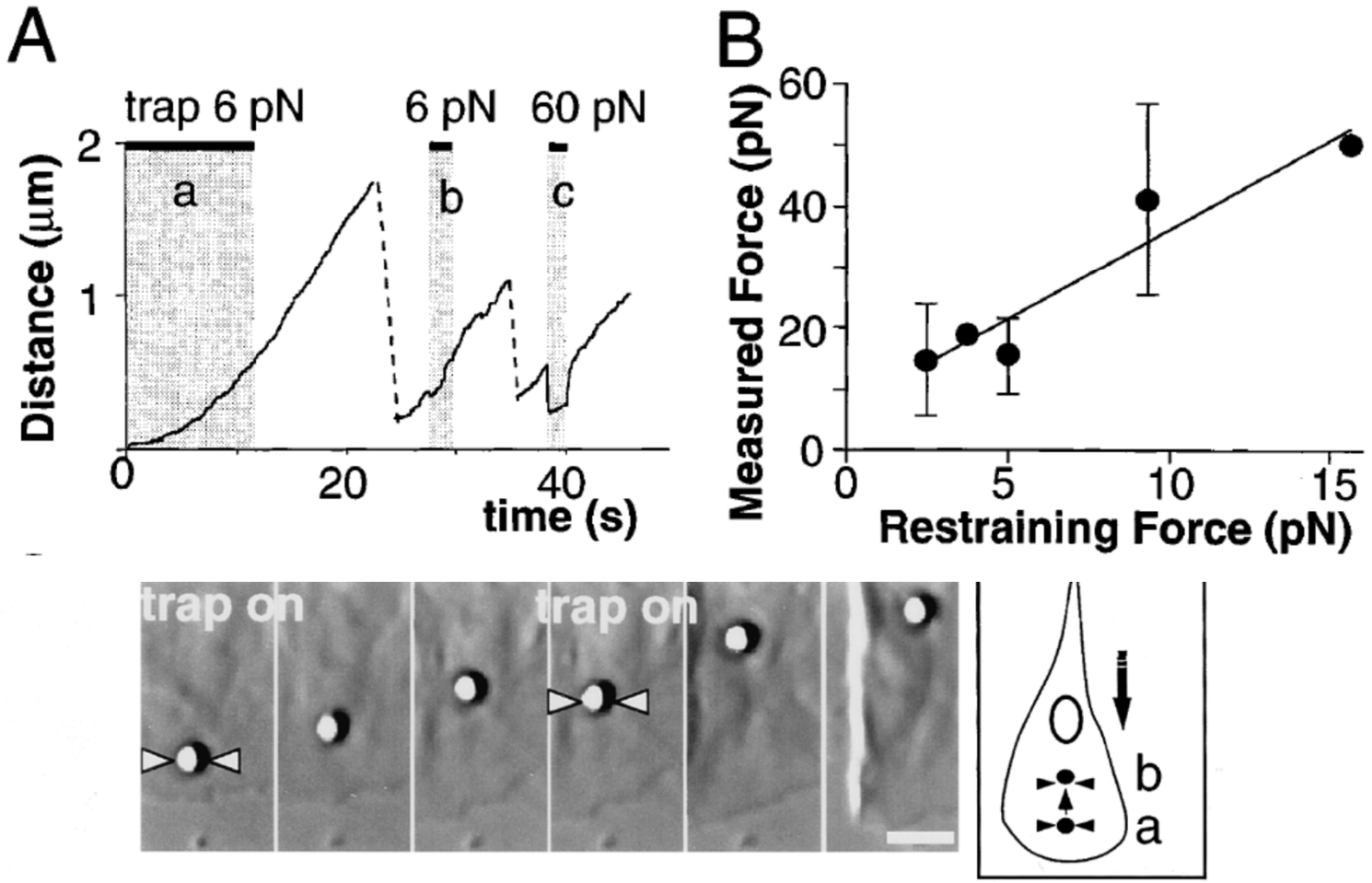
(Alberts B. *et al.*, Molecular Biology of the Cell)



Di Milla,..., Lauffenburger, JCB 1993

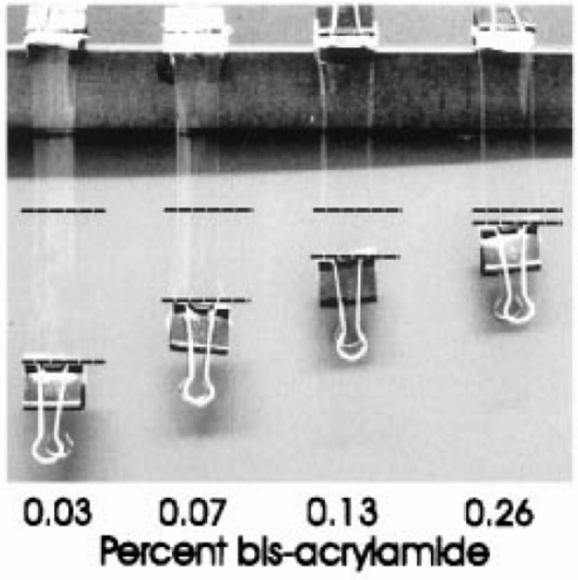
Integrin re-inforcement depends on applied force

Di Choquet,..., Sheetz, Cell 1997



Cell behavior depends on matrix stiffness

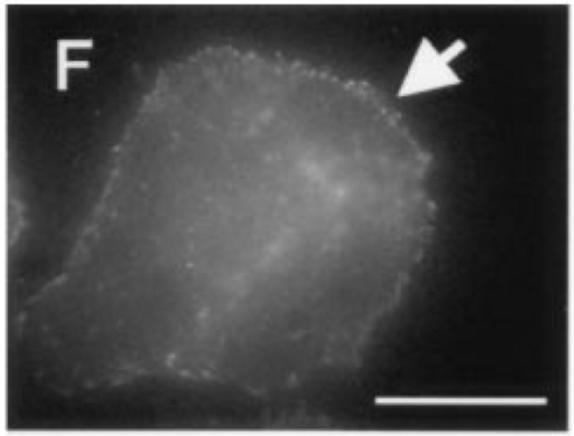
soft ……stiff

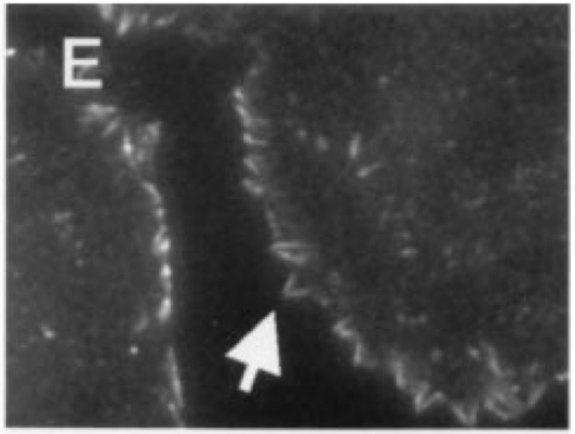


Pelham and Wang, PNAS 1997

Amplitude and speed of lamellipodium fluctuations decrease on stiffer substrates

Size, tyrosine phosphoryl. and stability of focal adhesions increase on stiffer substrates

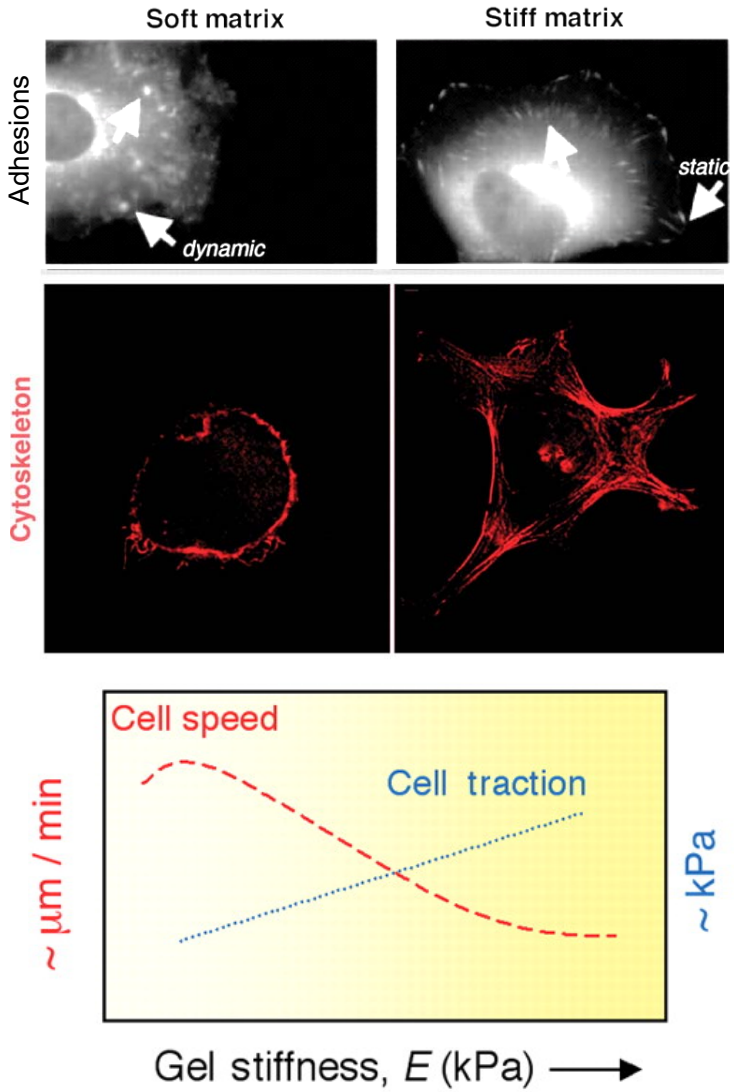




Cell behavior depends on matrix stiffness

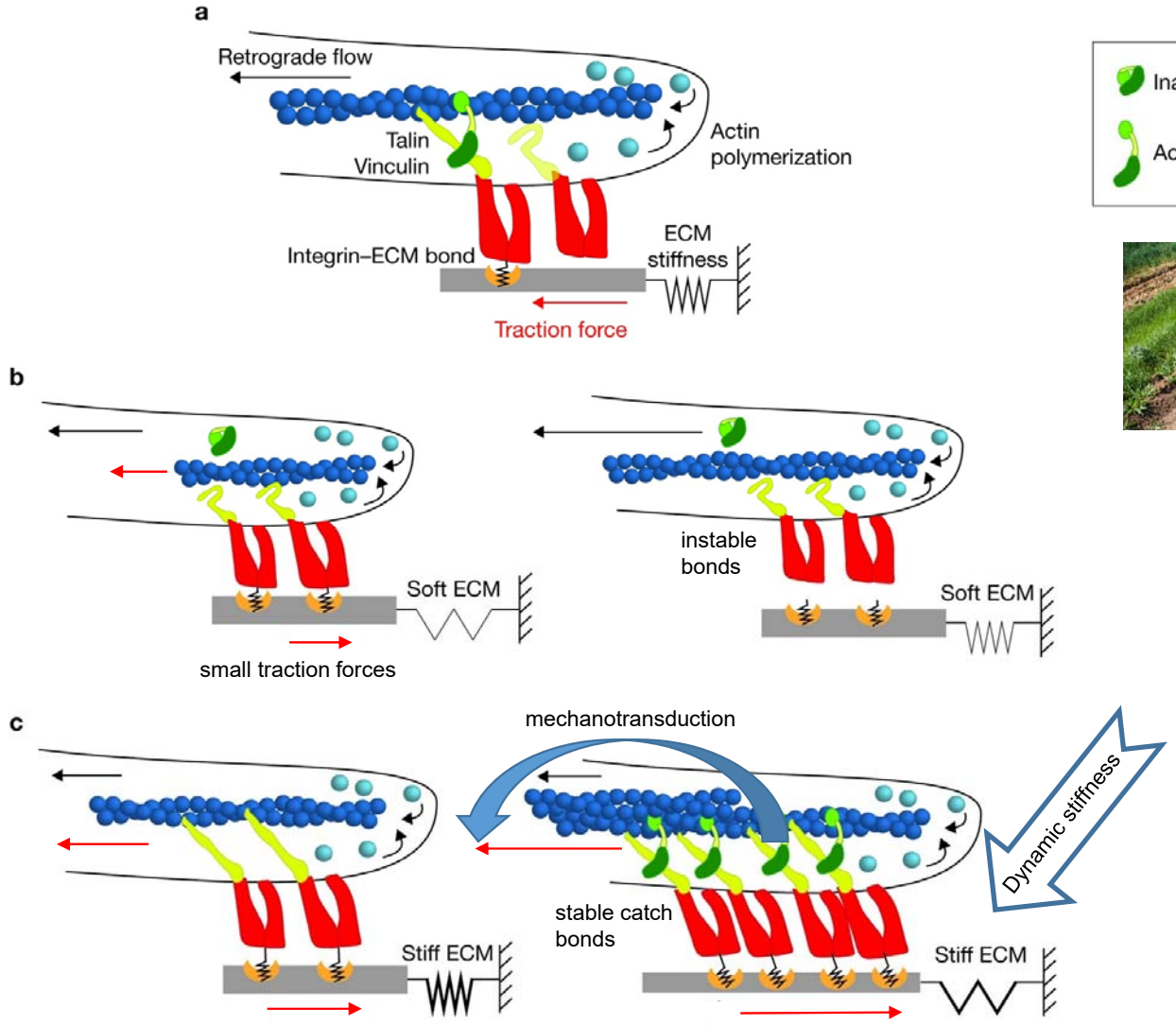
[Disher et al, Science, 2005]

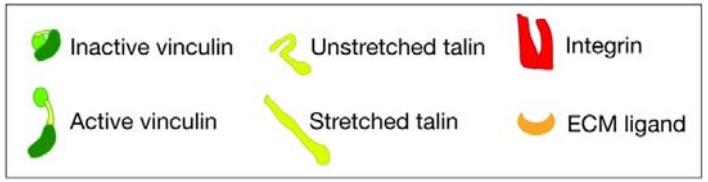
	soft matrix	stiff matrix
Adhesion	poor	good
Spreading	low	high
Contraction	weak	strong
Actin CSK	cortical	stress fibers
Migration	fast	slow



Clutch-hypothesis

Swaminathan & Waterman, Nat Cell Biol 2016





Mechano-transmission & mechanotransduction: outside in / inside out

external forces

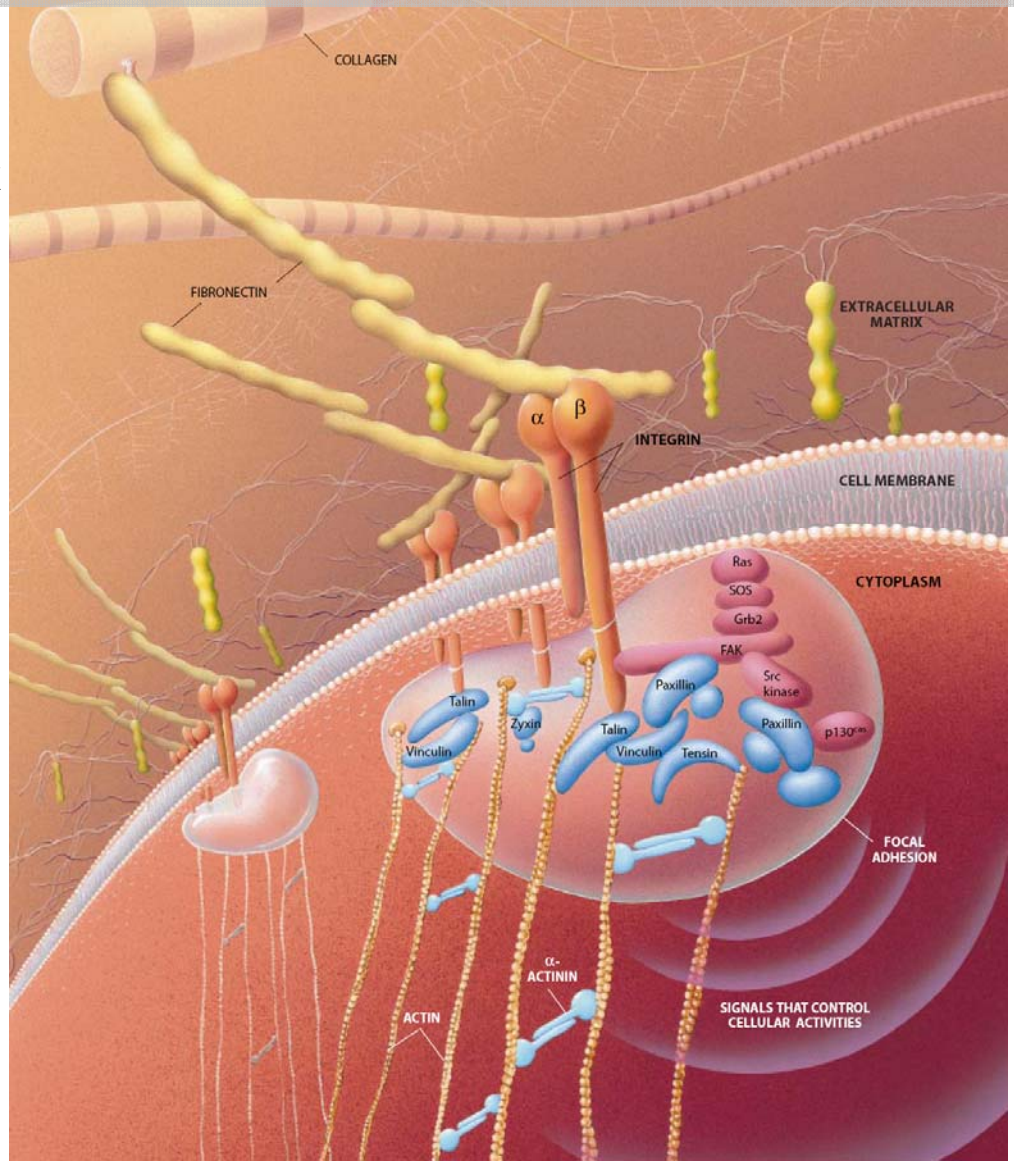
extracell. matrix (collagen, fibronectin)

adhesion receptors (integrins)

focal adhesion complex

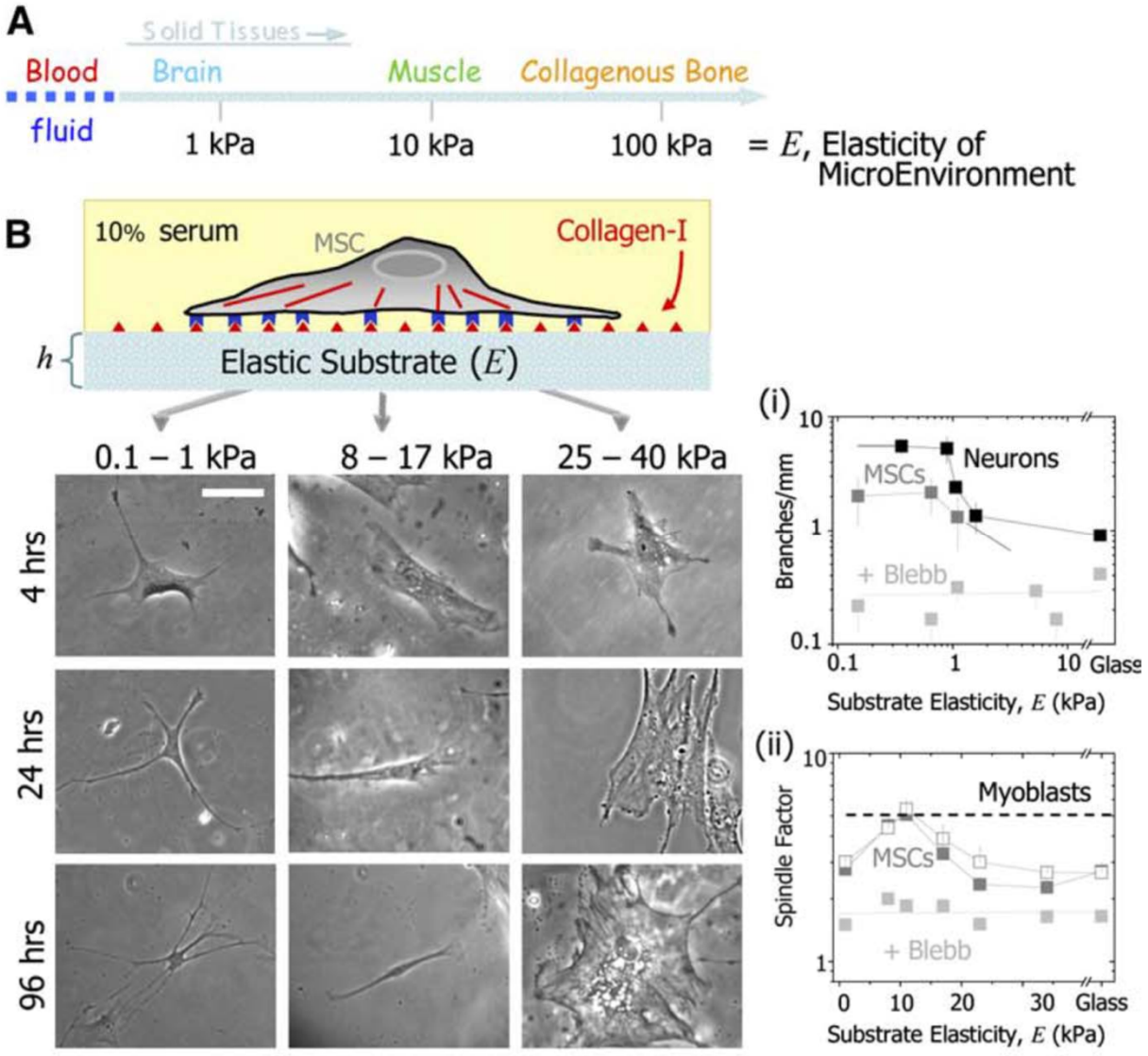
cytoskeleton

prestress (acto-myosin)



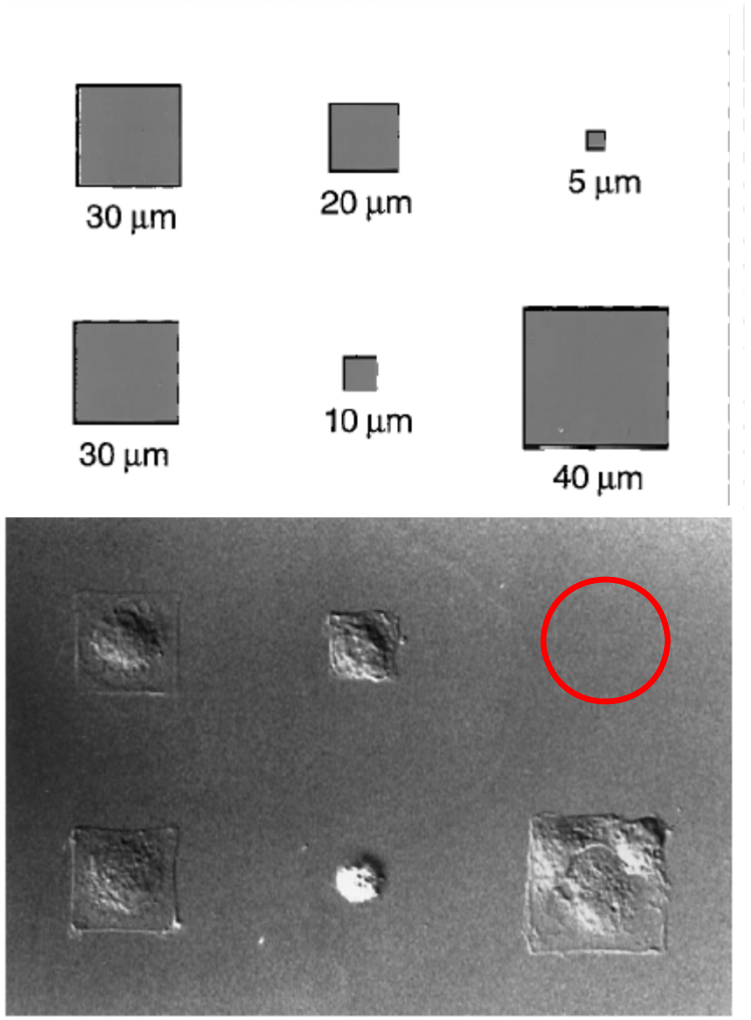
Horwitz AF (1997)
Integrins and Health

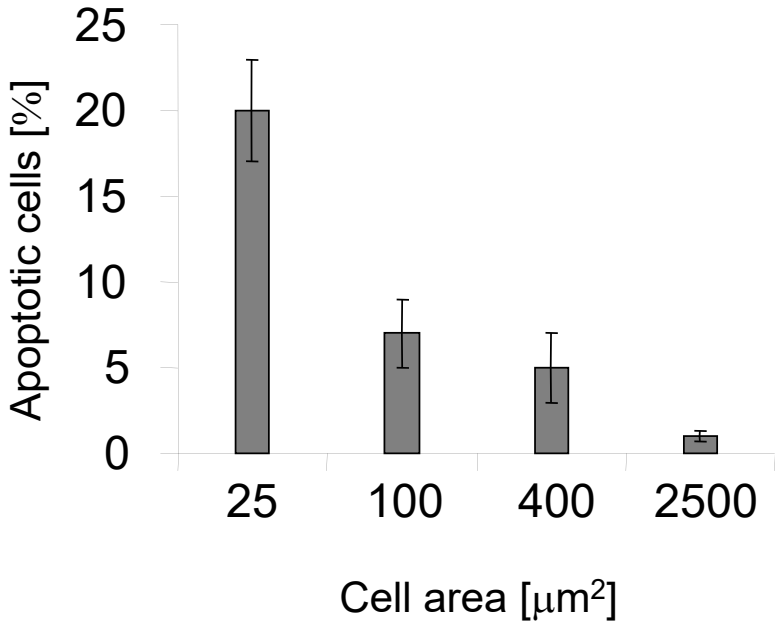
Matrix Elasticity Directs Stem Cell Lineage Specification



Engler…. Discher, Cell 2006

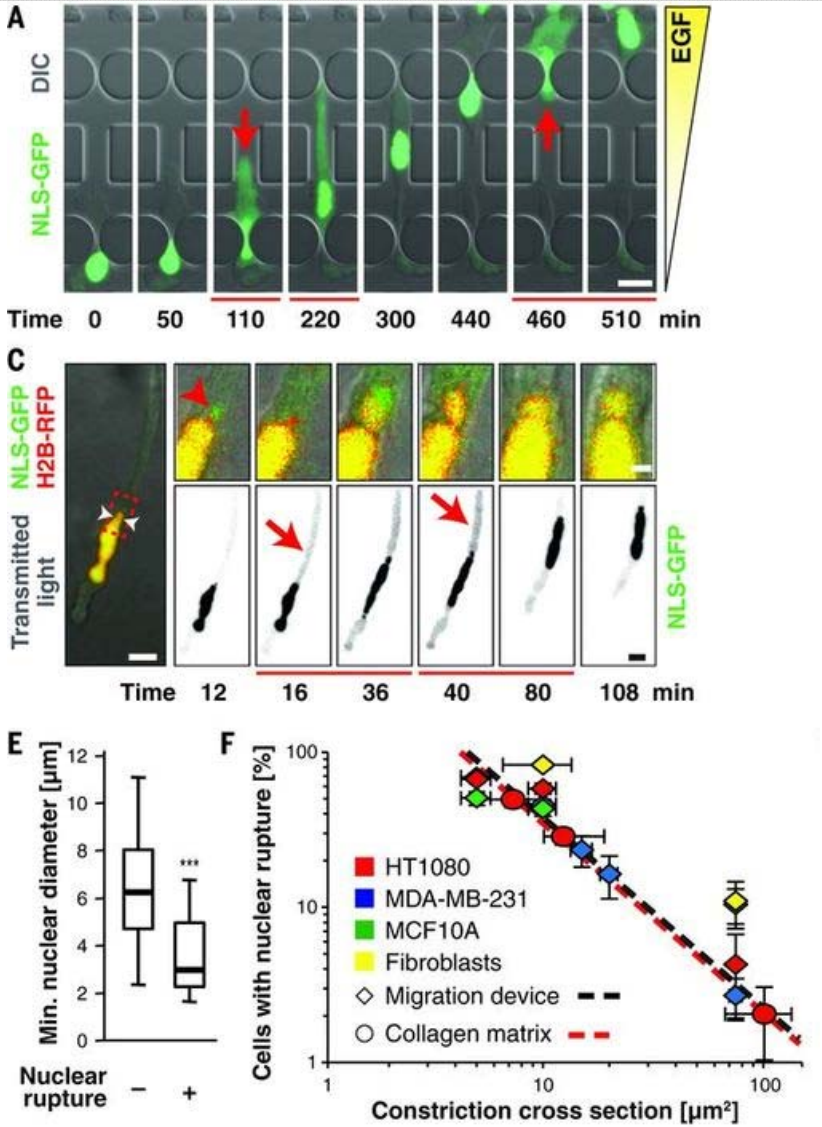
Geometry matters: cells need to spread





Chen … Ingber *J. Science* 1997; **276**:1426

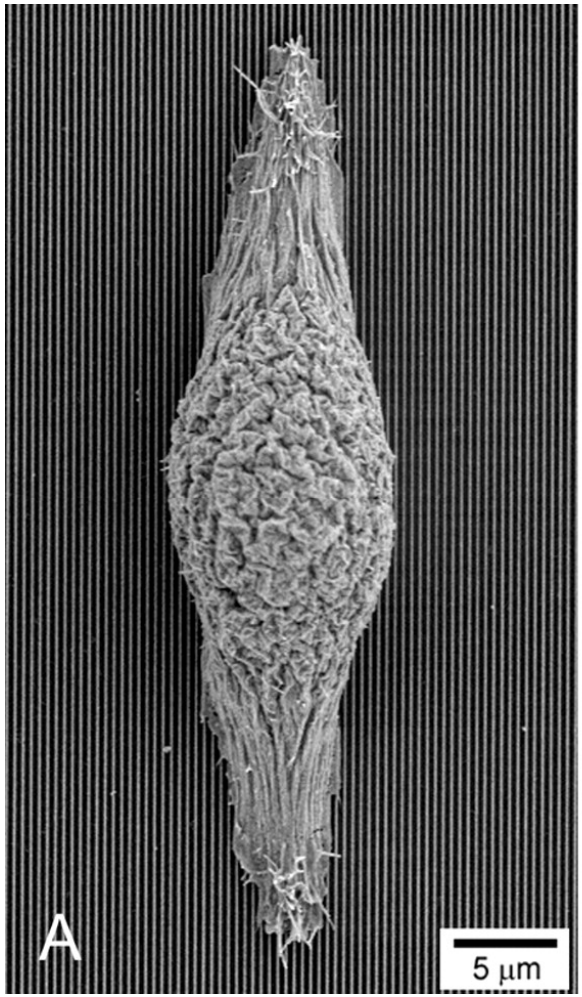
Nuclear rupture under confinement

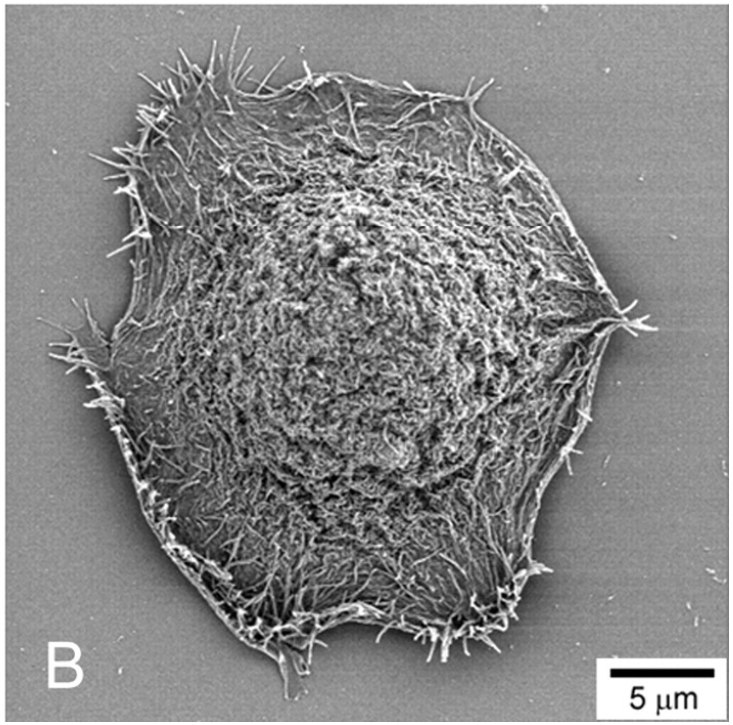


Denais,…., Lammerding Science 2016

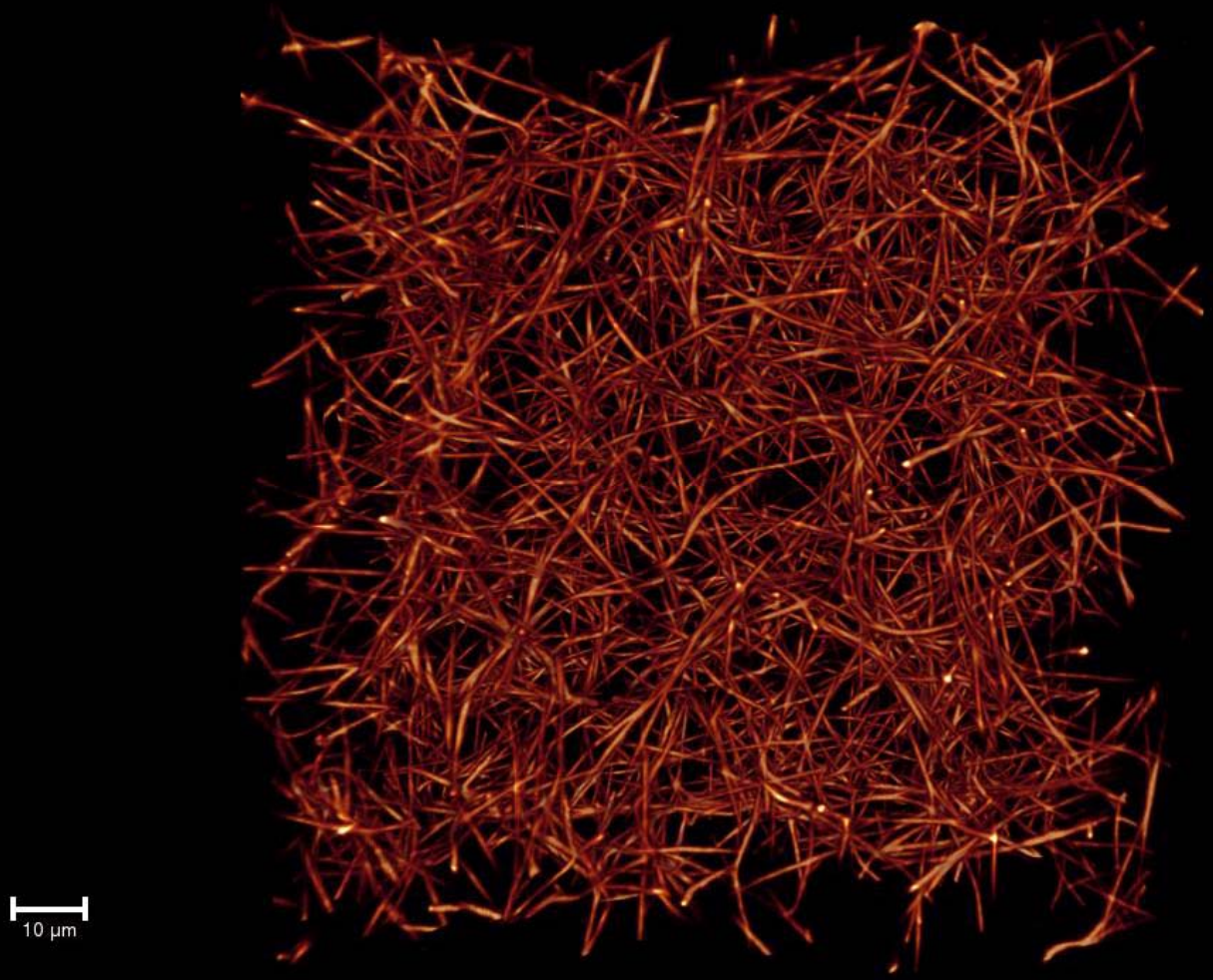
Contact guidance

Teixeira et al, *J Cell Science* 2003



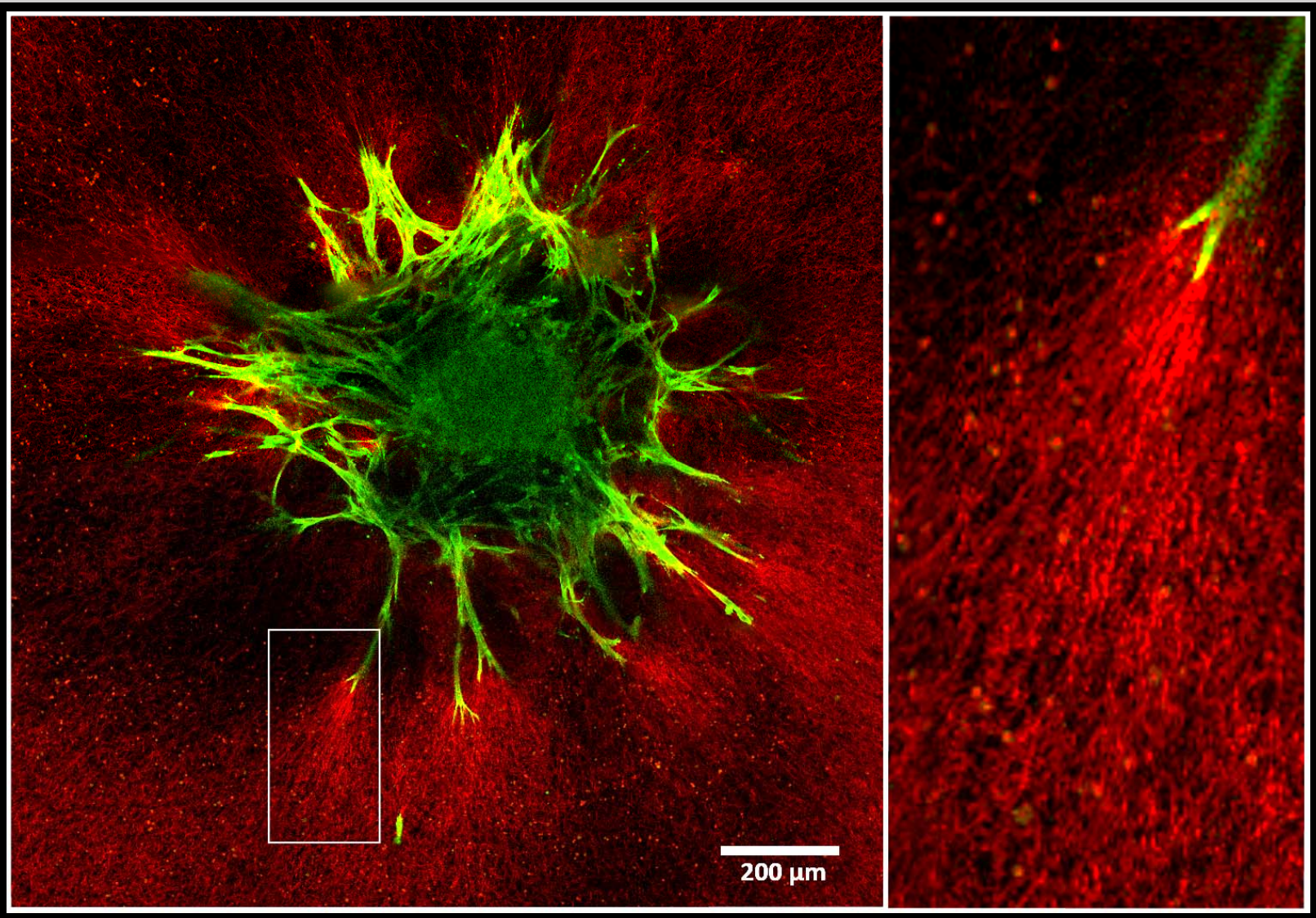


3-D collagen matrix



Steinwachs et al, *Nat Meth* 2016

Mechanical cell-matrix interactions – collagen alignment

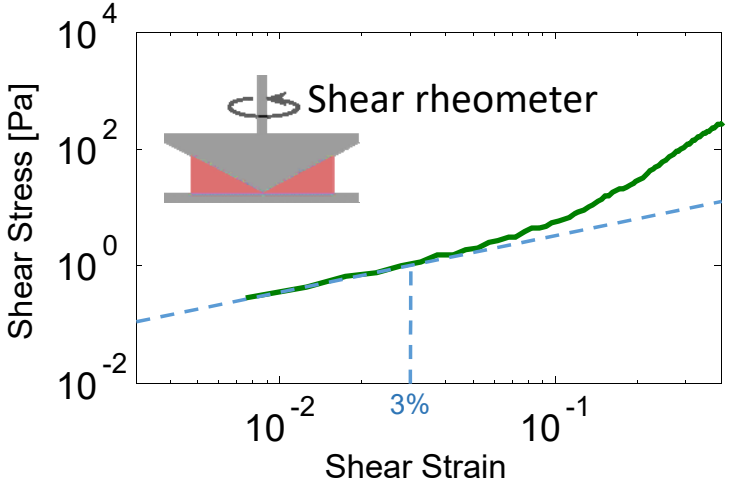


Grummel N, unpublished

Mechanical properties of 3-D collagen matrices

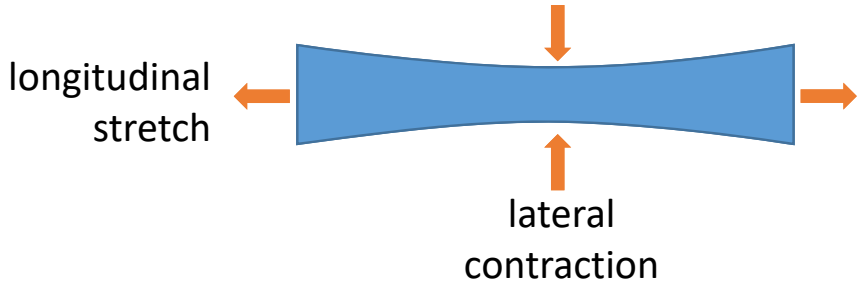
1. Strain stiffening

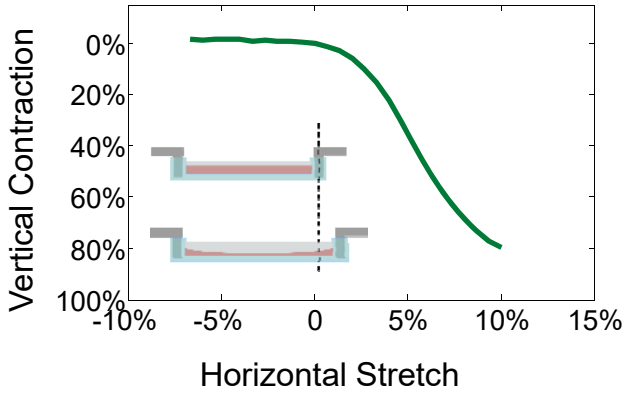
Stiffness rises after 3% of shear



2. Abnormal Poisson-ratio

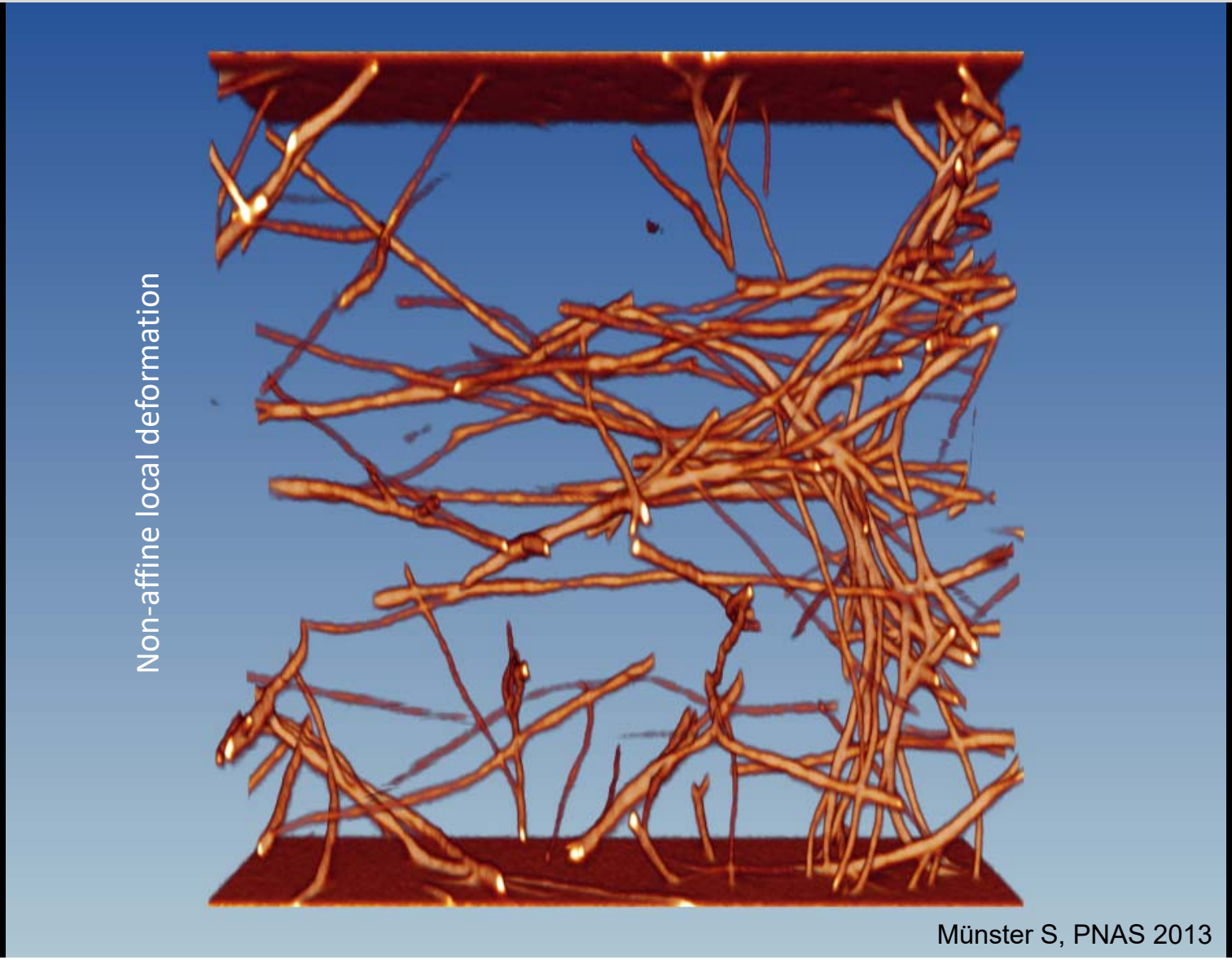
Strong contraction under uniaxial stretch (ν≈8)





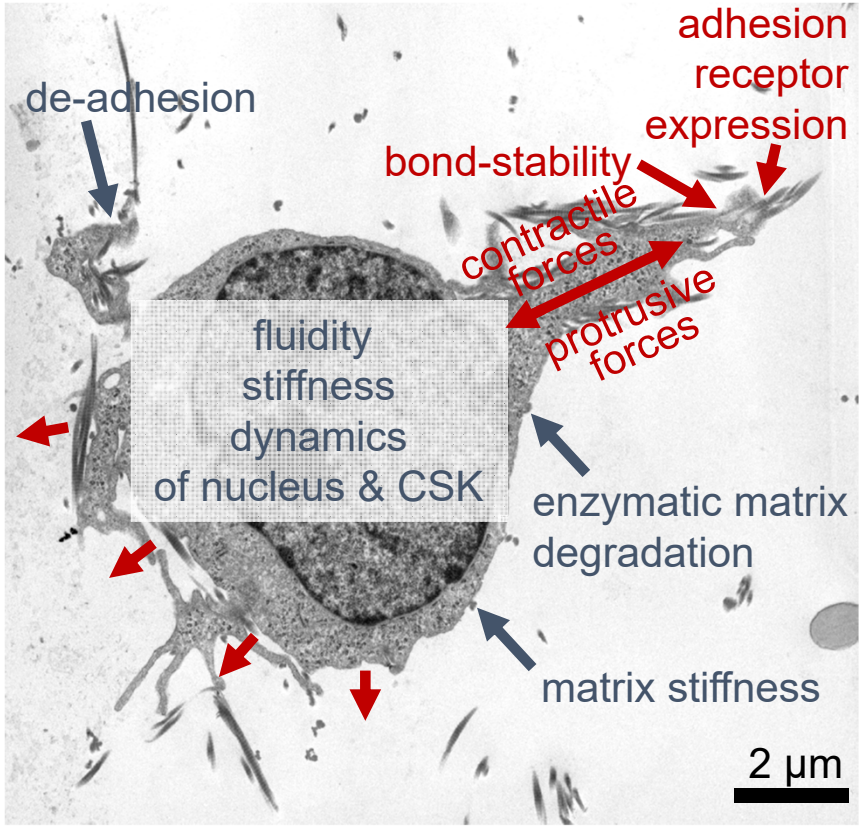
Steinwachs, Nat Meth 2016

Collagen fibers allign under mechanical stress



Münster S, PNAS 2013

Cell spreading and invasion is governed by a force balance

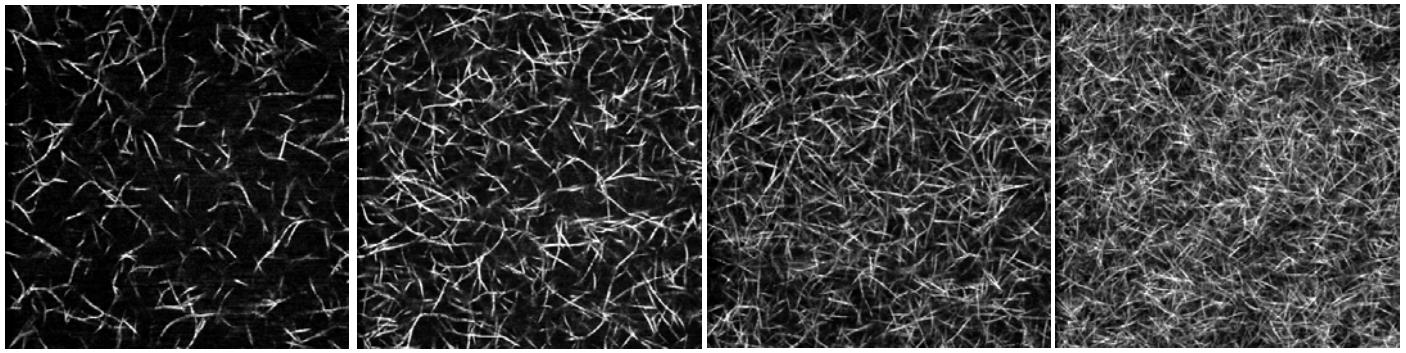


- protrusive forces
- traction forces — adhesion contraction
- cell resistive forces
- matrix resistive forces

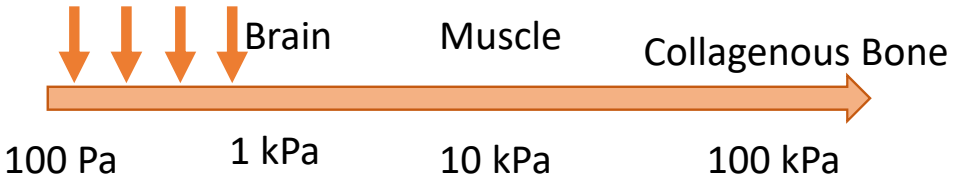
feedback

Eur J Cell Biol **87**:669, 2008

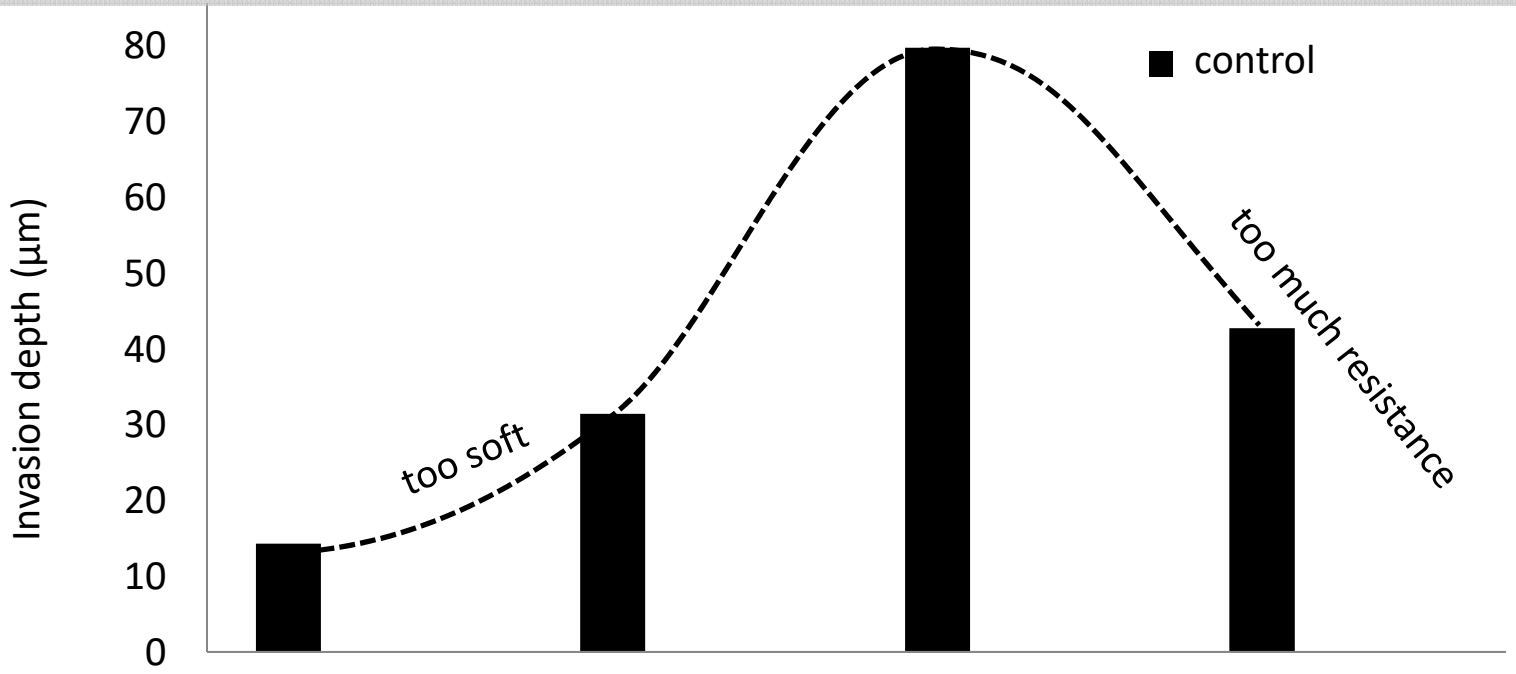
Cell invasion in collagen



Concentration (mg/ml)	0.3	0.6	1.2	2.4
Pore size (µm)	8.1	5.6	3.8	3
E-modulus (Pa)	100	250	650	1000
E-modulus x-linking (Pa)	380	580	1400	1800



Invasion depth in collagen



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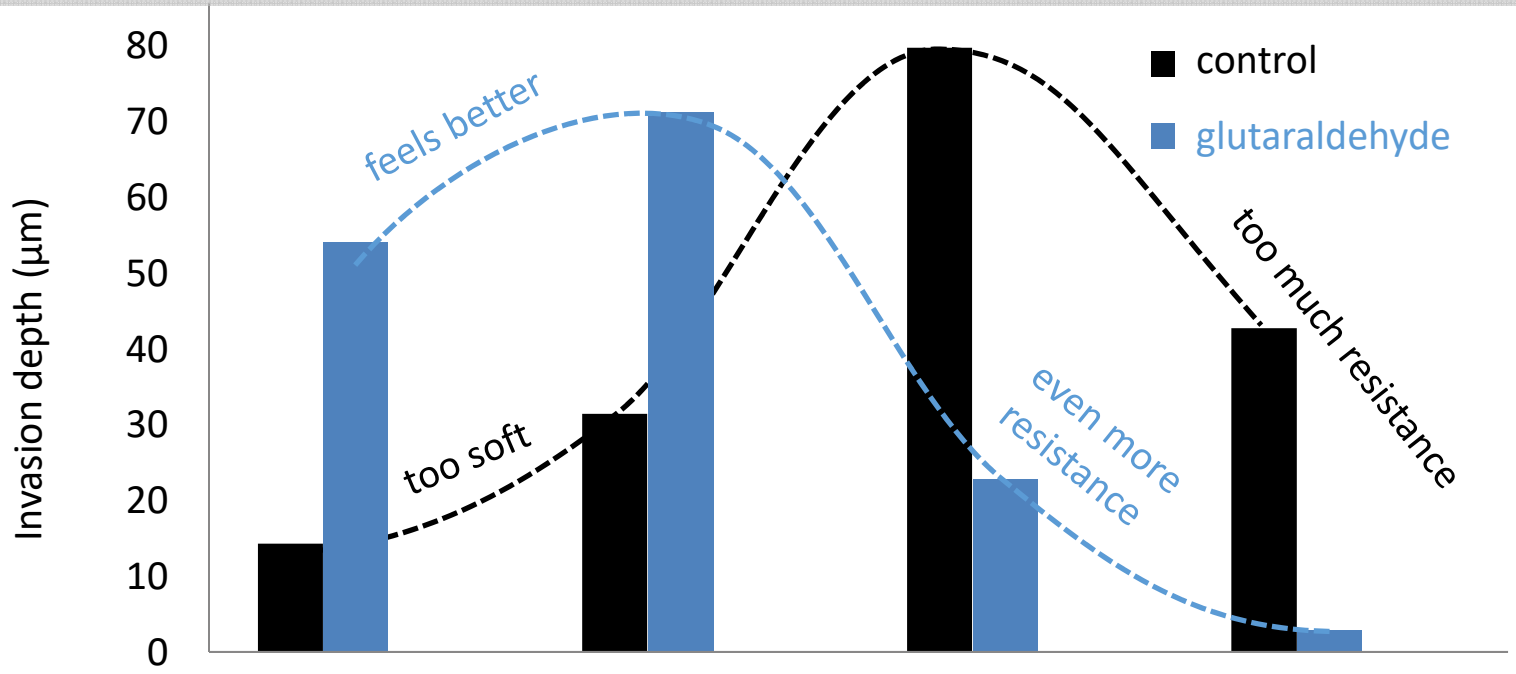
Lange Acta Biomat 2014

Invasion depth in collagen



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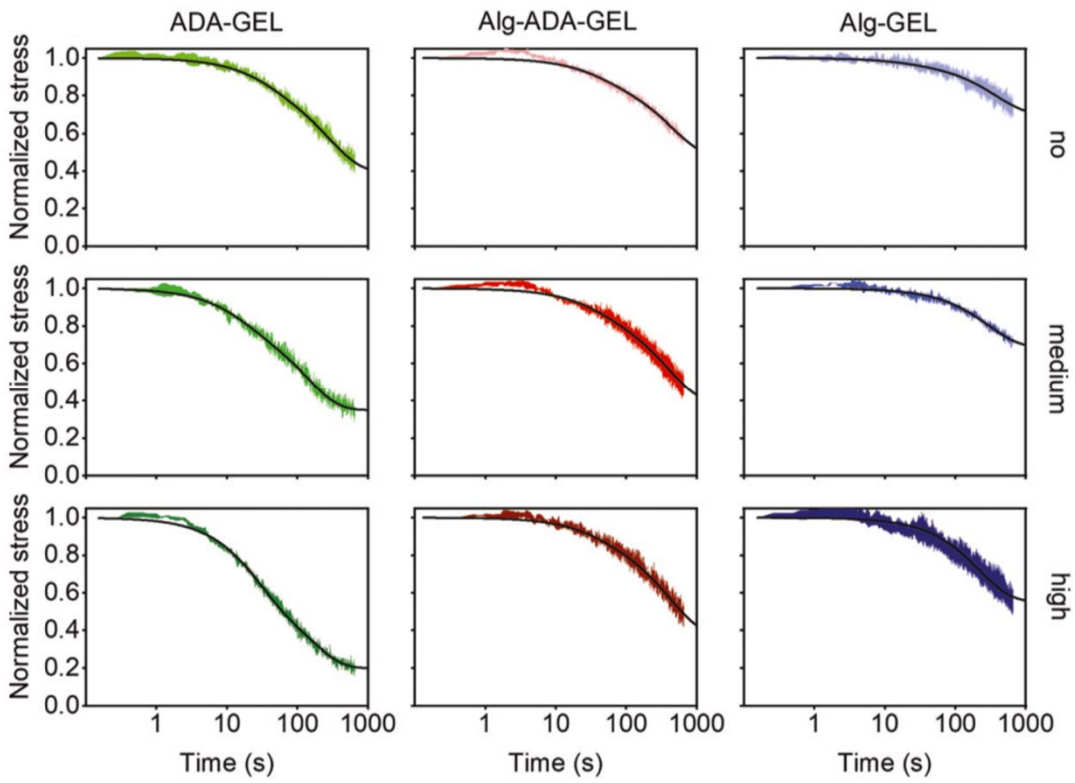
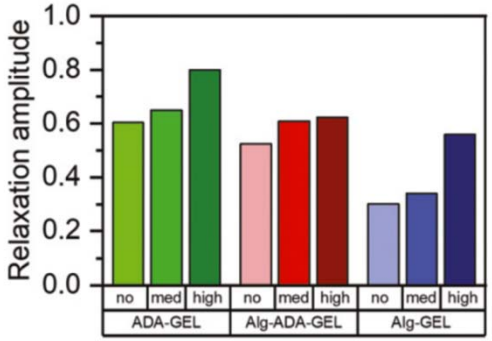
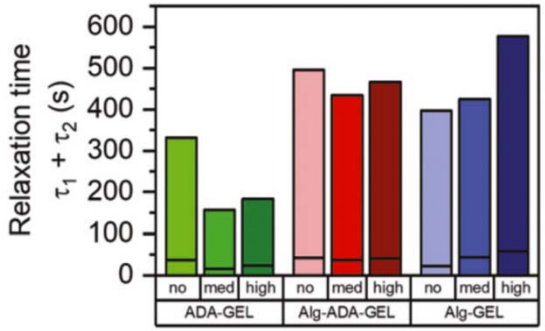
Stress relaxation amplitude of hydrogels determines migration, proliferation, and morphology of cells in 3-D culture†

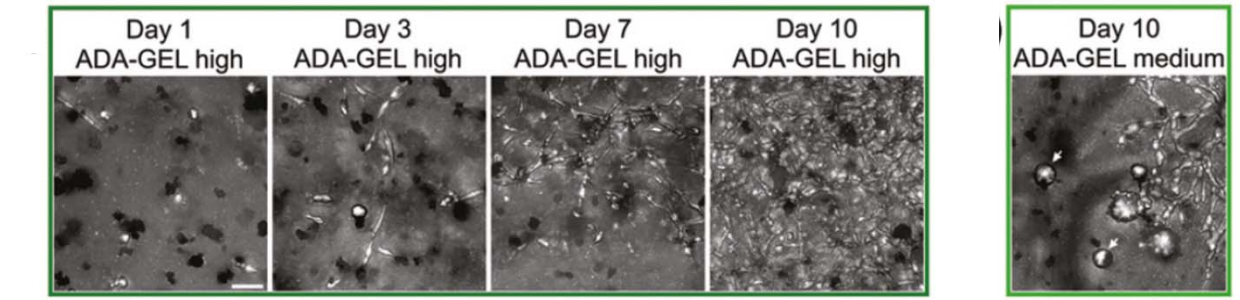
Jonas Hazur, [a] Nadine Endrizzi,[b] Dirk W. Schubert,[c] Aldo R. Boccaccini [a] and Ben Fabry*[b]



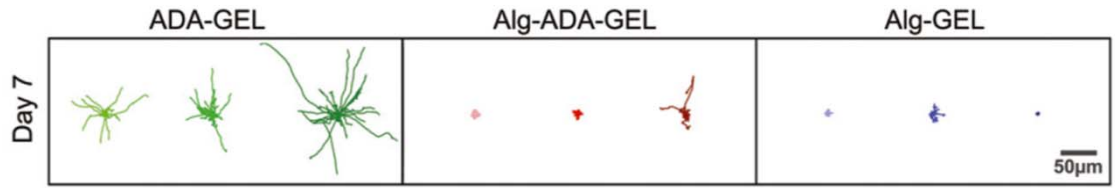




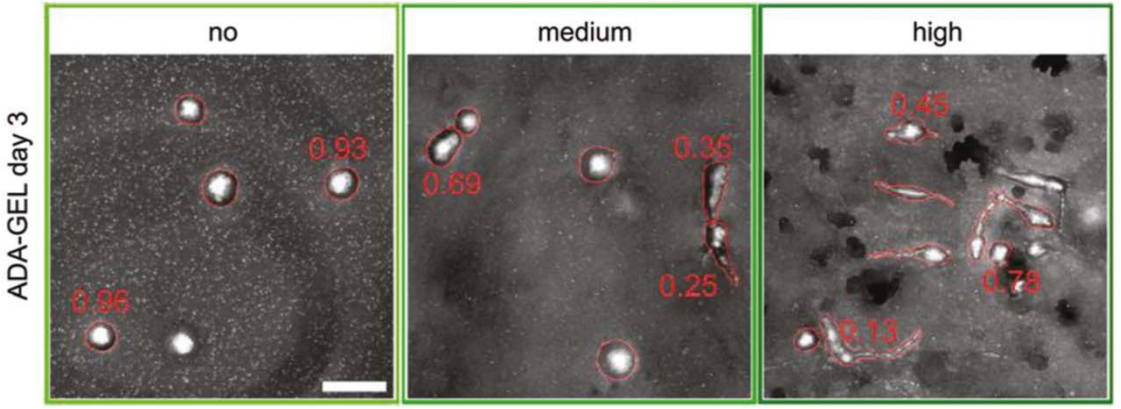
Stress relaxation amplitude (plasticity) of the ECM determines cell proliferation, migration, morphology



proliferation



migration



spreading / aspect ratio

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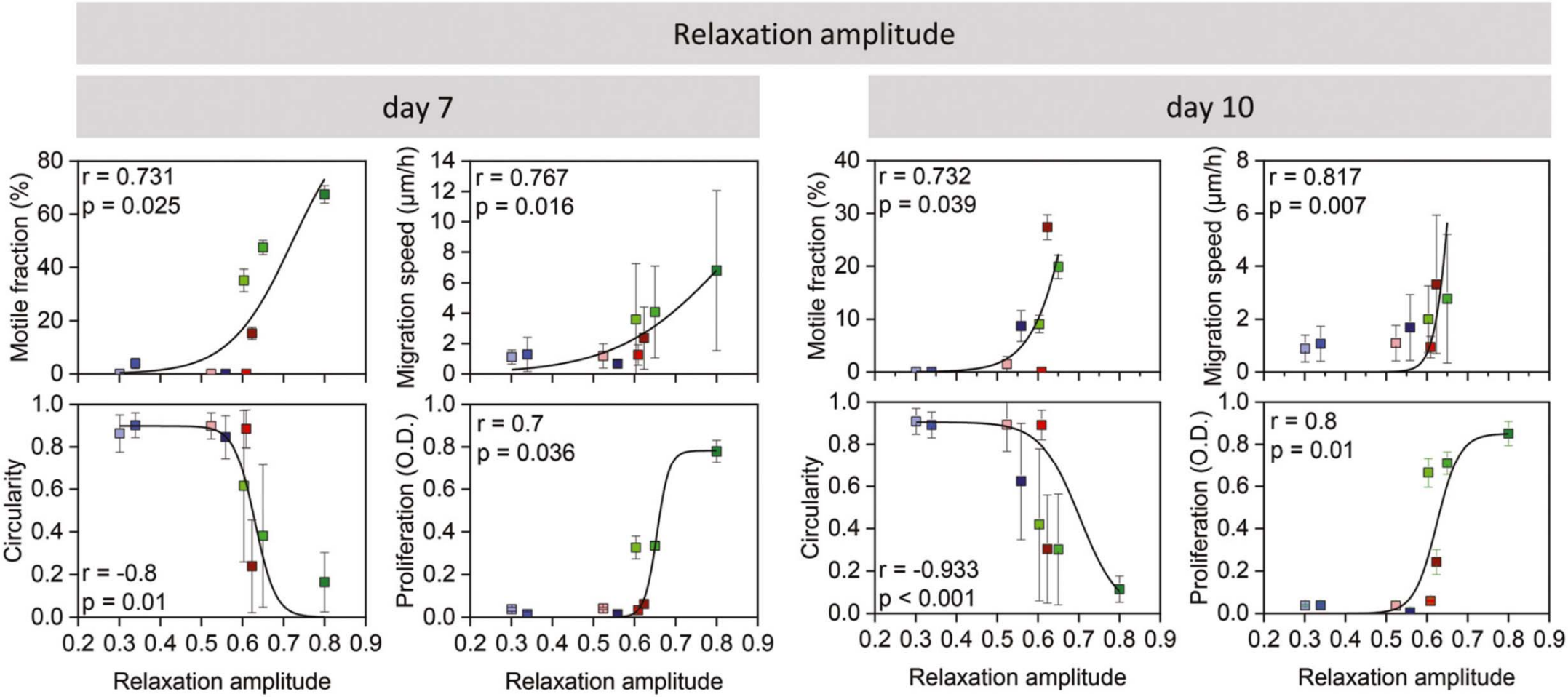

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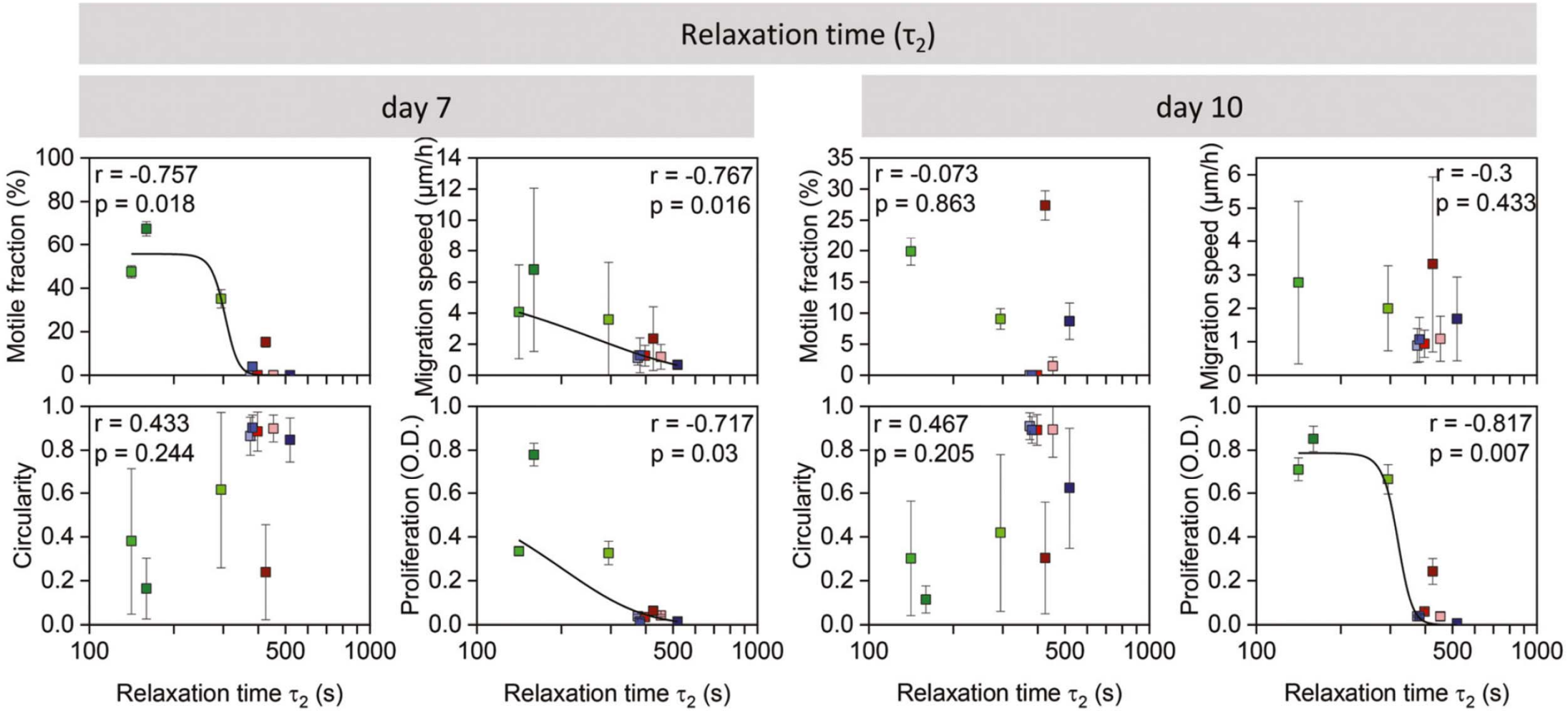
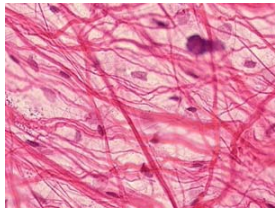


Specifications sheet for (extracellular) matrix biomaterials is very long

Mechanical properties
- Stiffness (Young‘s modulus)
- Poisson ratio, poroelasticity
- non-linearity (strain or stress stiffening)
- viscoelasticity (frequency response, creep)
- yield strain / yield stress
- plasticity and structural remodeling
- anisotropy, heterogeneity

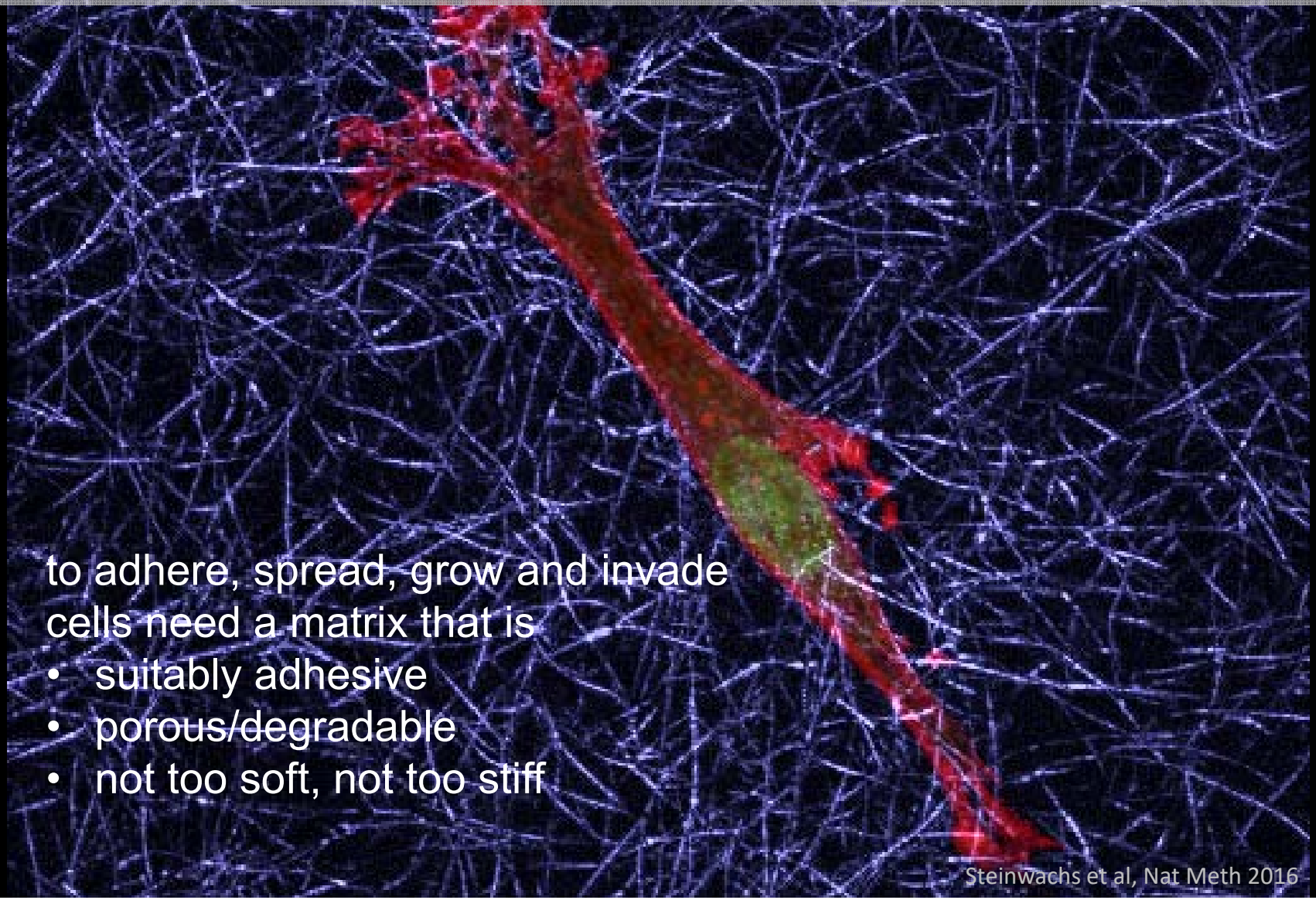


Structural properties
- solid fraction, porosity
- pore size distribution
- fiber diameter, anisotropy
- fiber connectivity

Chemical properties
- adhesive functionalization
- proteolytic degradation
- water binding capacity, surface charge
- inter- and intrafiber crosslinking

Summary



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