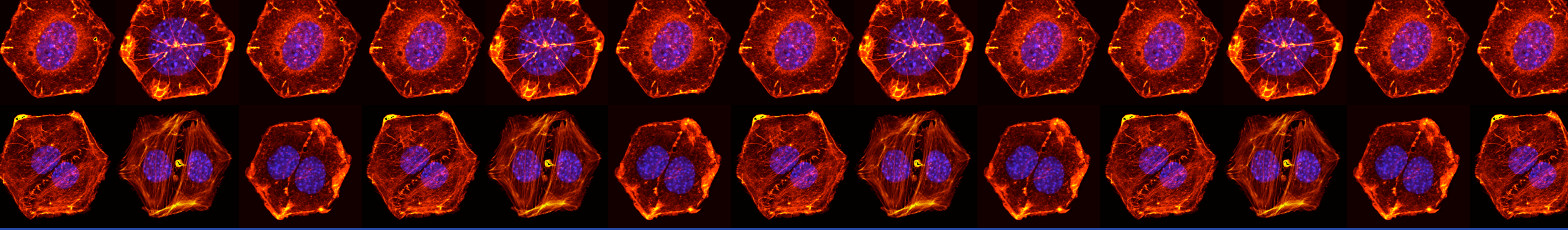
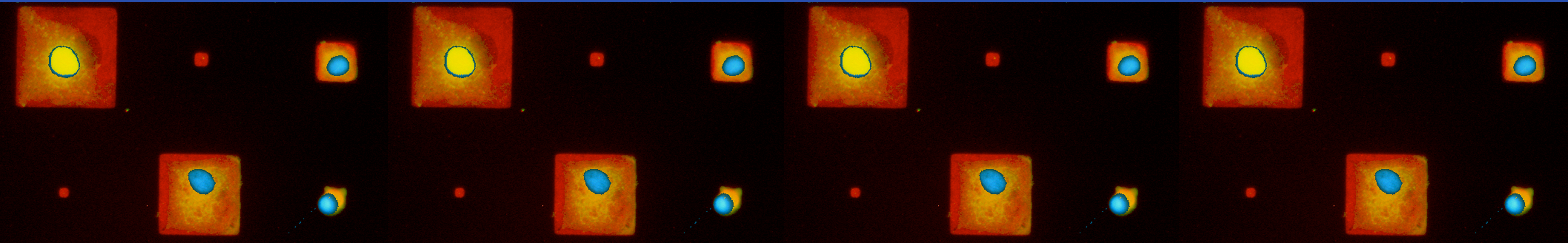


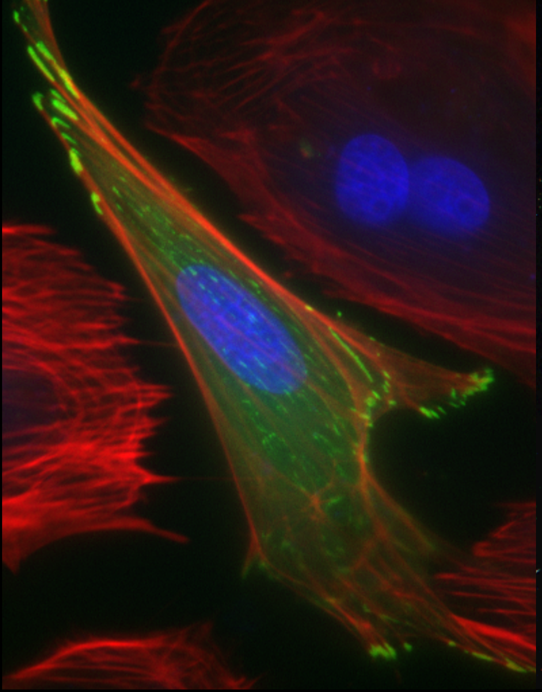
Mechanobiology and Diseases of Mechanotransduction

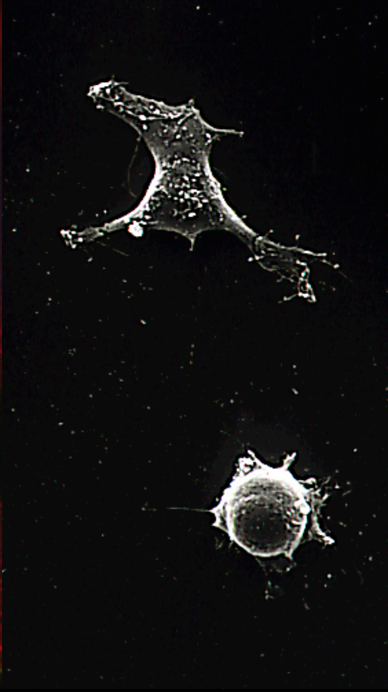
Don Ingber, MD,PhD

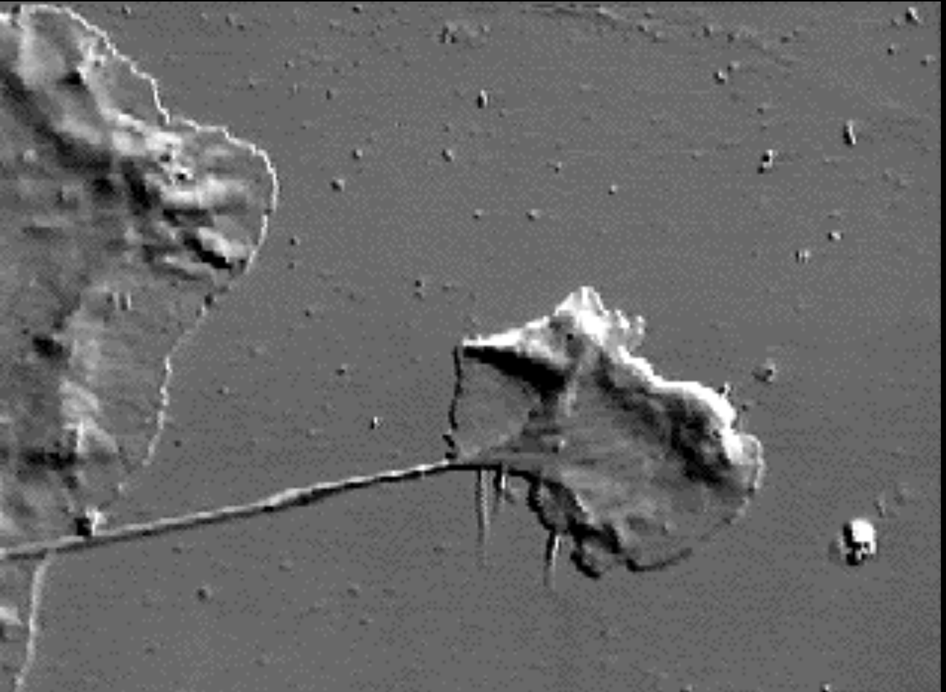
***Judah Folkman Professor of Vascular Biology*, Harvard Medical School & Children's Hospital**
Founding Director, Wyss Institute for Biologically Inspired Engineering at Harvard University
Professor of Bioengineering, Harvard School of Engineering & Applied Sciences

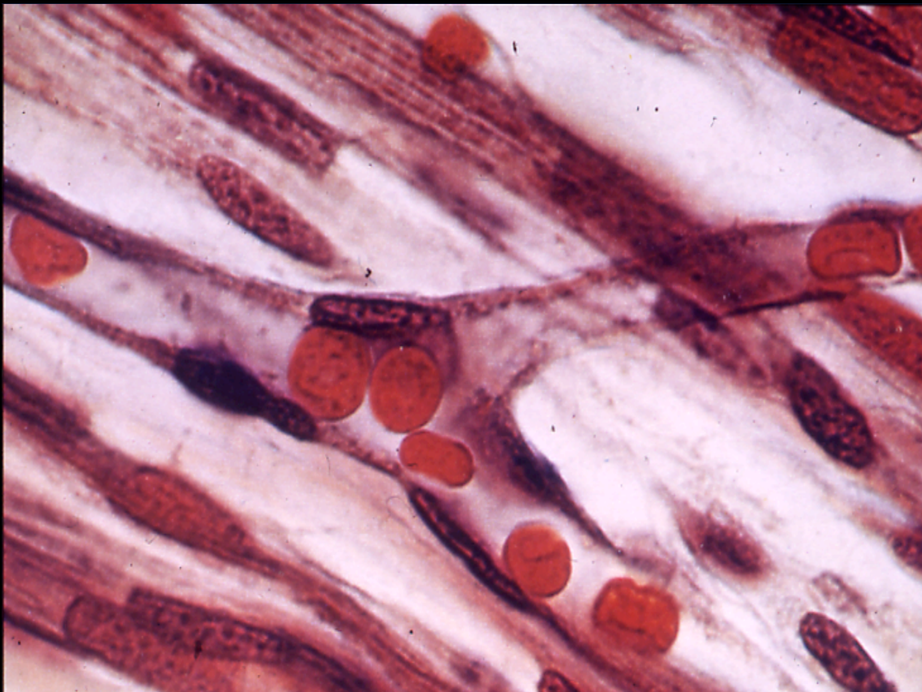


How are living cells and tissues constructed?







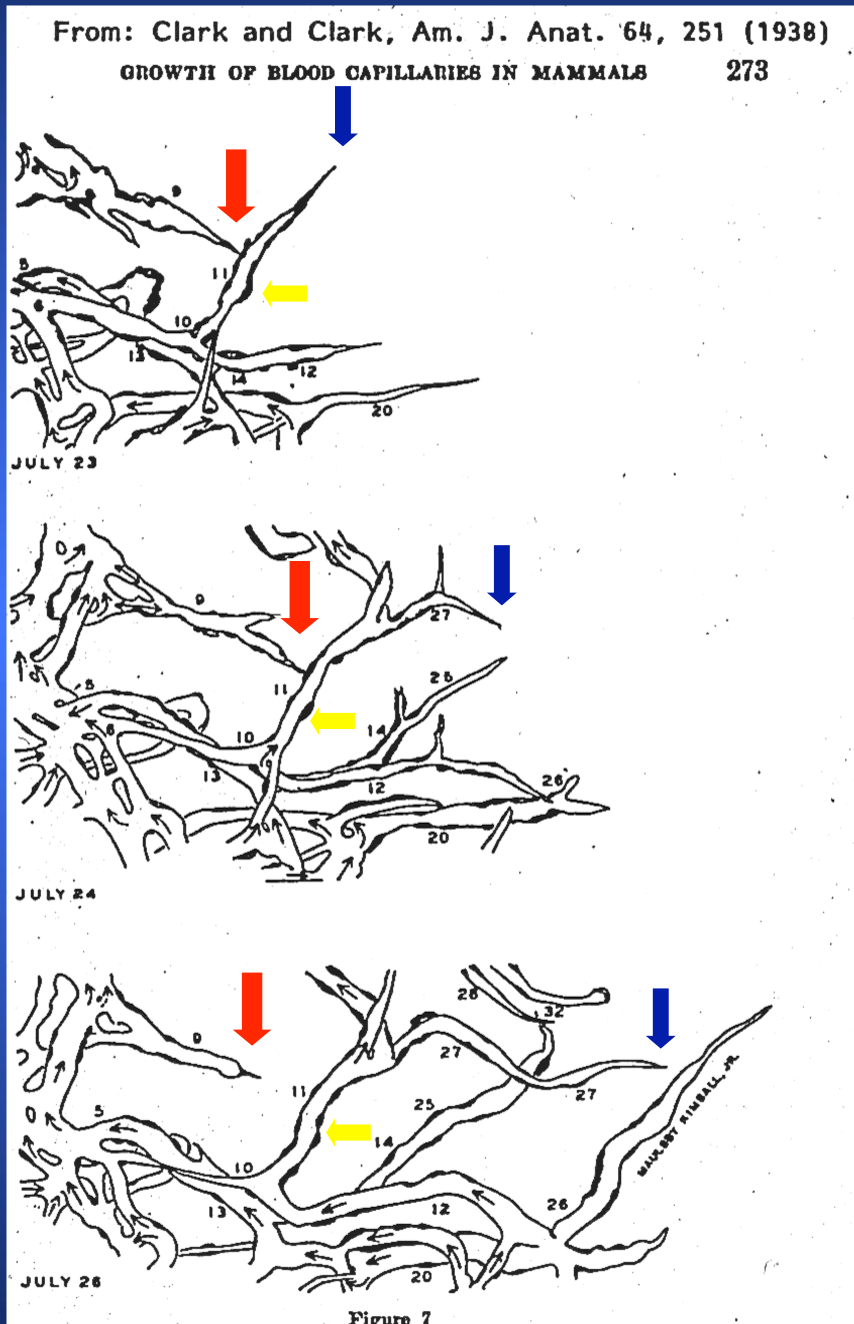


A Linear View of Tissue Development

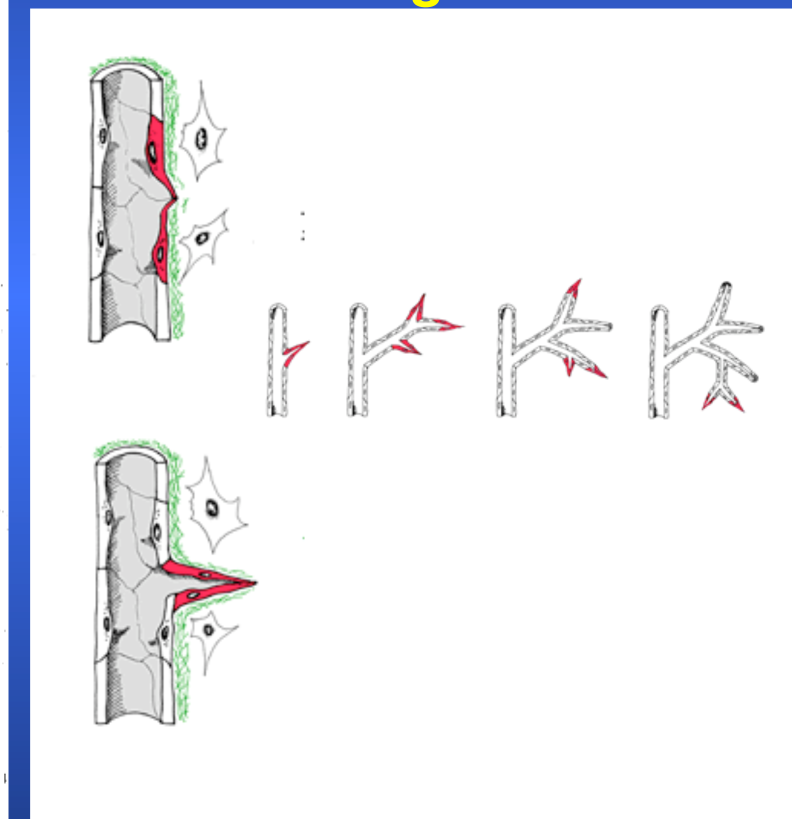
(Tumor Angiogenesis = blood capillary formation)

(NOVA WGBH Boston)

Local Control during Angiogenesis



Branching Patterns



Local Control during Angiogenesis

From: Clark and Clark, Am. J. Anat. 64, 251 (1938)

GROWTH OF BLOOD CAPILLARIES IN MAMMALS 273

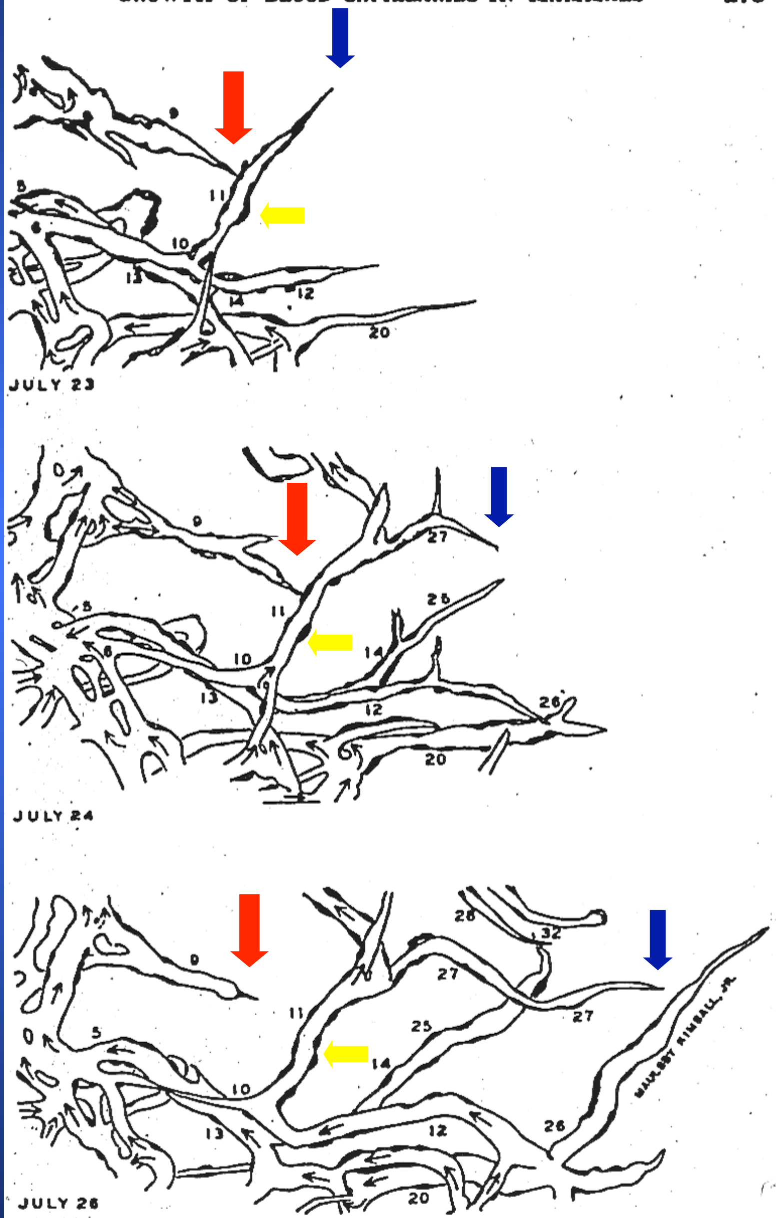
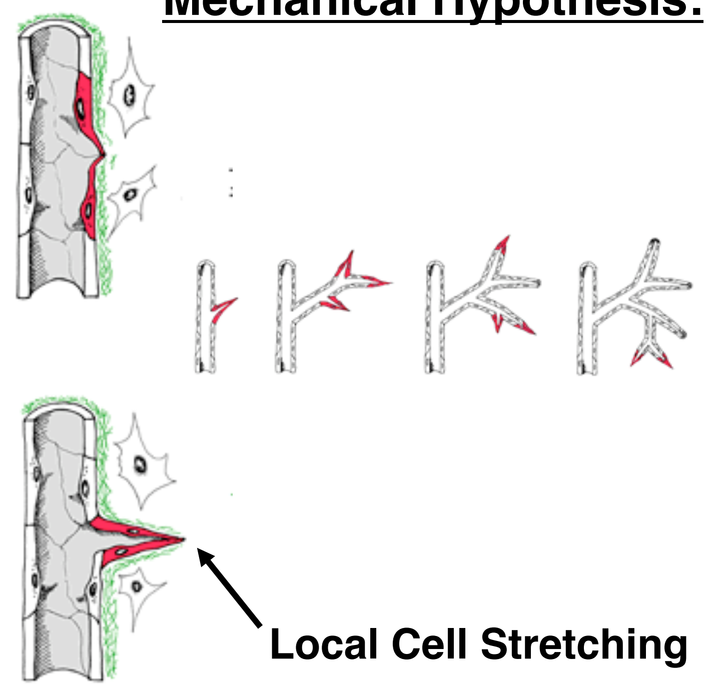
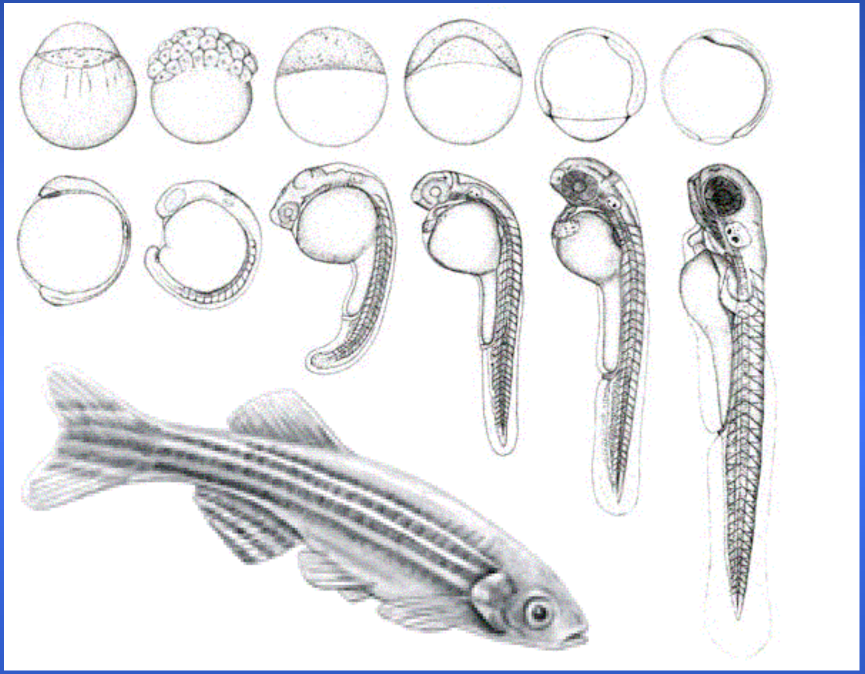


Figure 7

Mechanical Hypothesis:



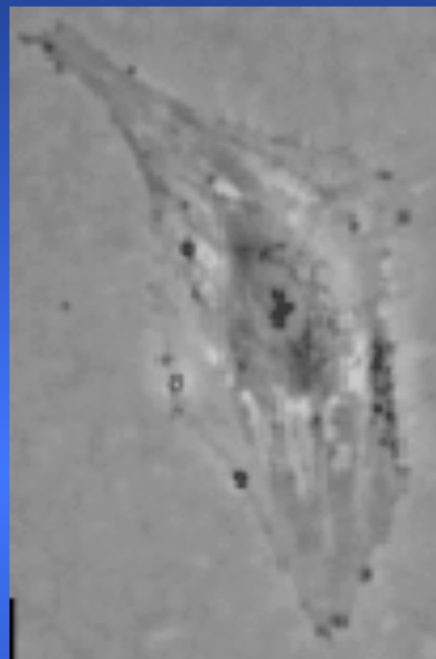
Mechanical Influences during Embryo Formation

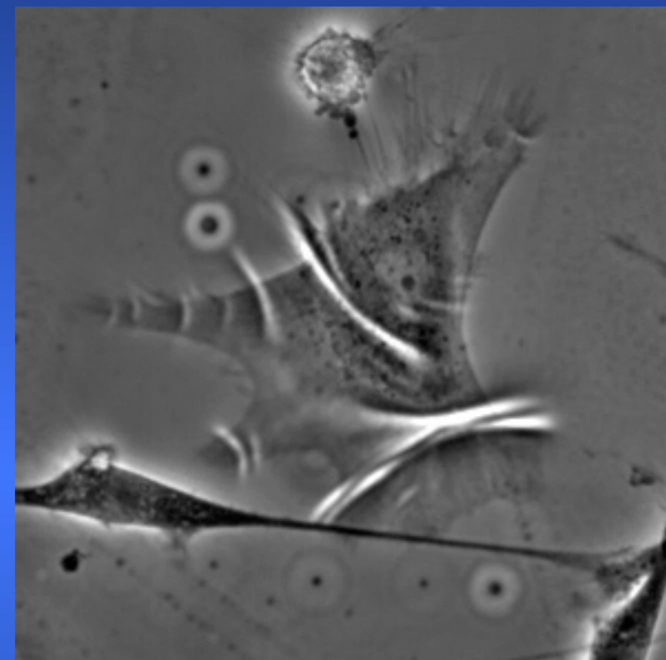


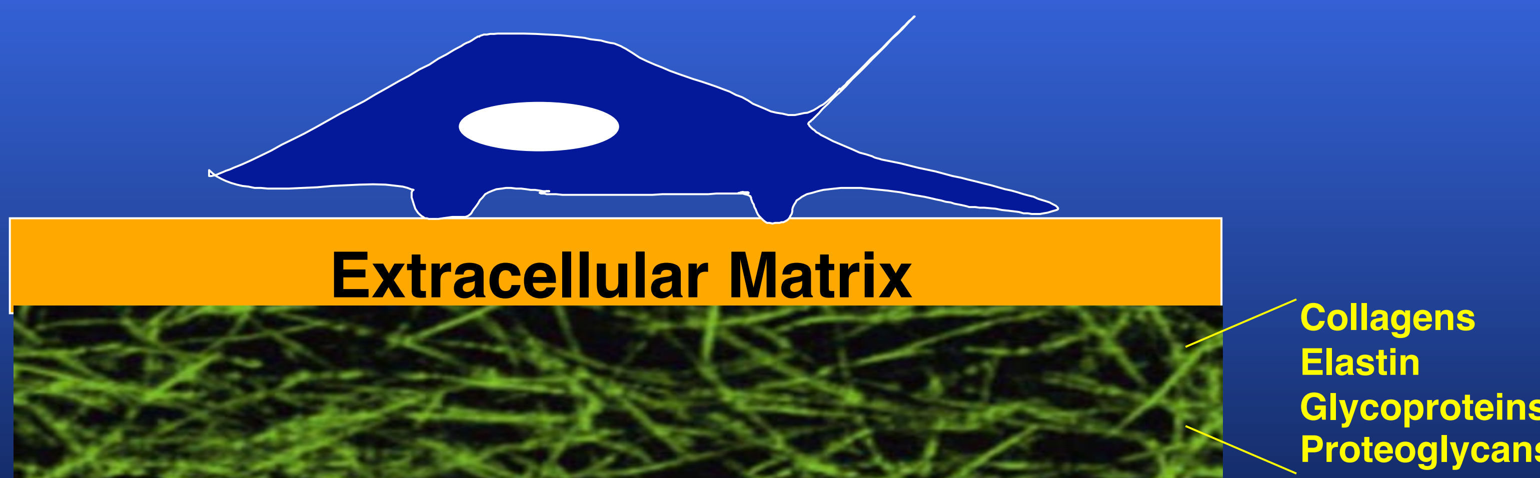
ZEBRA FISH Development

(from R. Karlstrom and D. Kane; http://zfin.org)

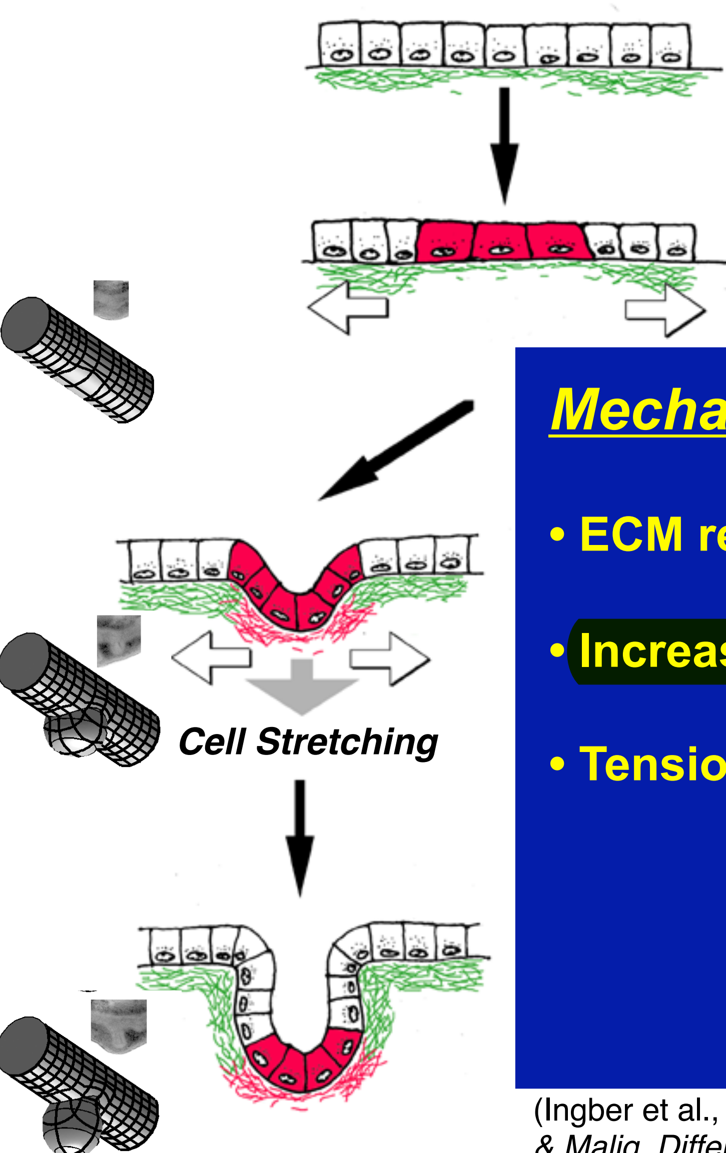
All Cells Exert Tension on their Matrix Adhesions

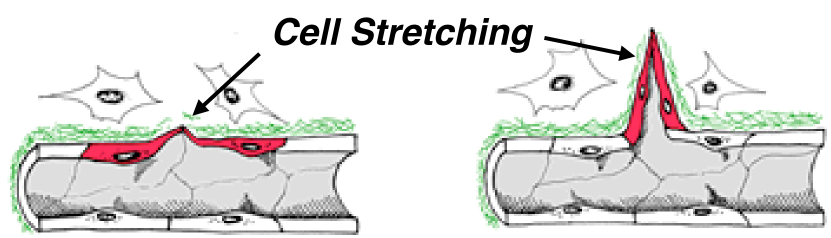






Micromechanical Control of Morphogenesis





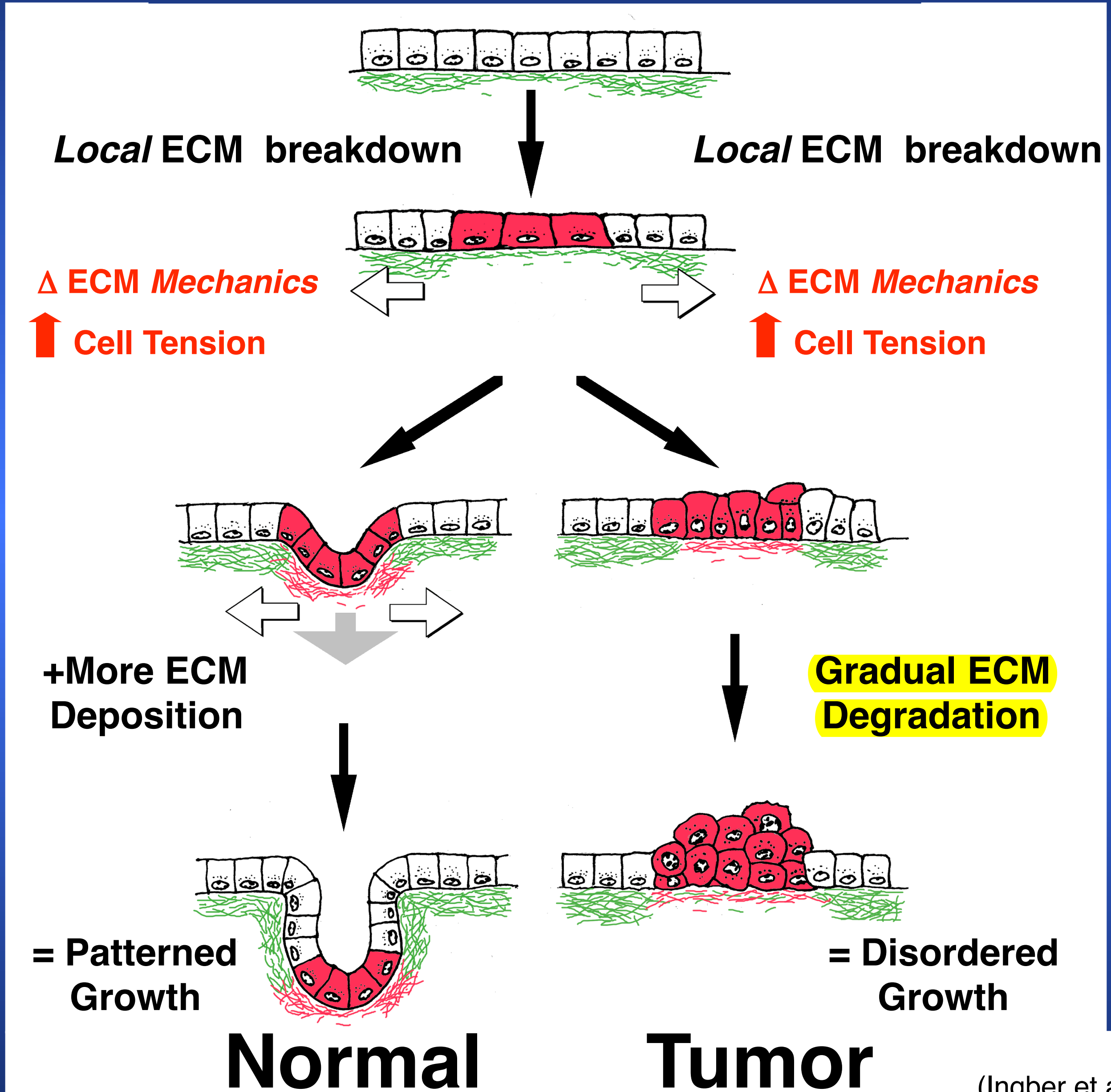
Mechanical Theory of Tissue Patterning:

- **ECM remodeling changes LOCAL MECHANICS**
- **Increasing ECM flexibility promotes cell stretching**
- **Tension on Adhesion Receptors & distortion of the cytoskeleton alters cellular biochemistry**

Localized Growth & Motility

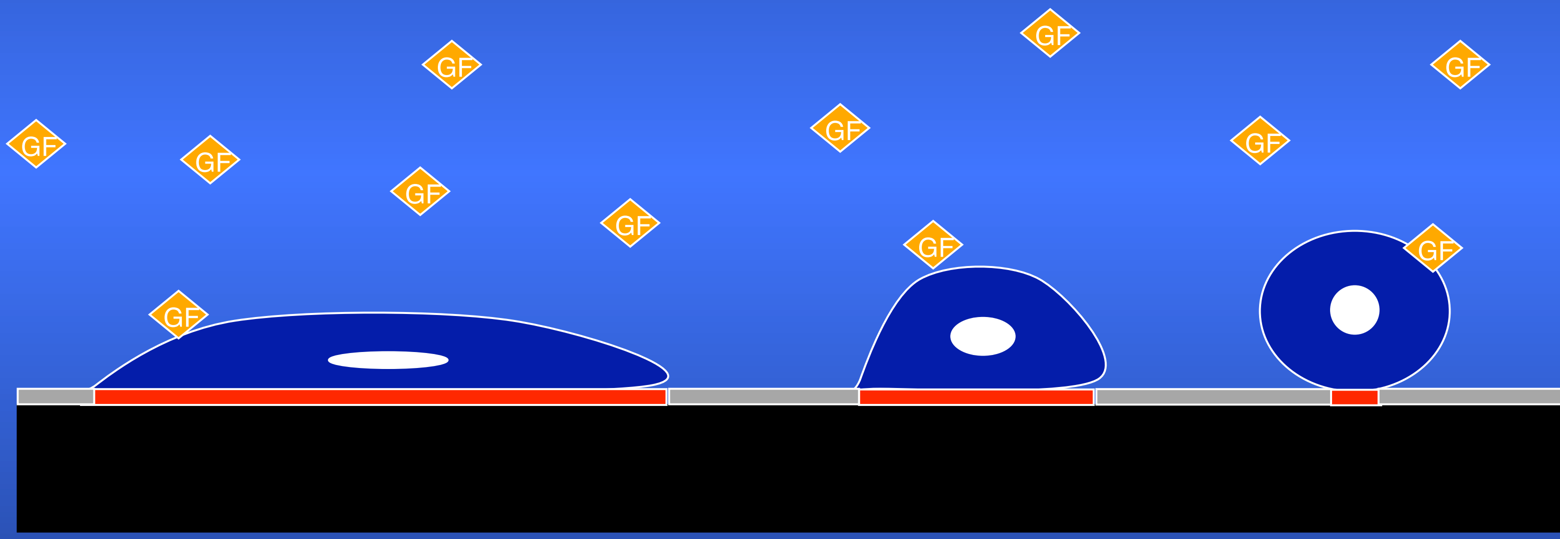
(Ingber et al., *PNAS* 78:3901-5, 1981; Ingber & Jamieson, In: *Gene Expression During Normal & Malig. Differ.* ,1985; Huang and Ingber, *Nature Cell Biol.* ,1999)

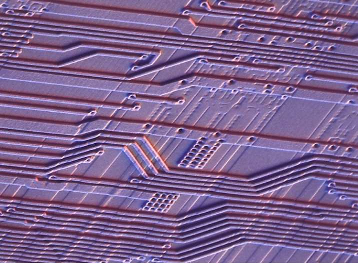
Implications for Cancer Formation



(Ingber et al., *PNAS*, 1981;
Huang & Ingber, *Nature Cell Biol.* 1999)

Does Cell Distortion Control Cell Function?



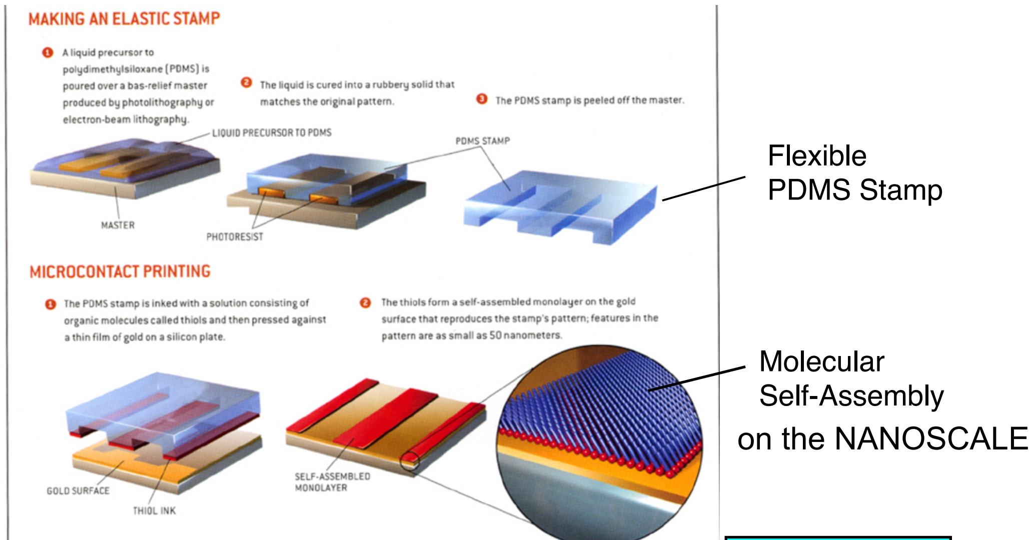


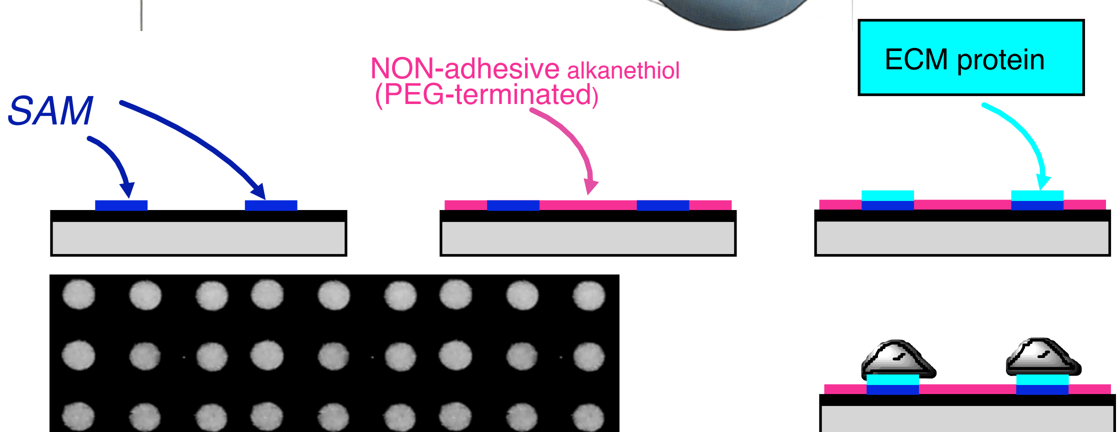
Nanotechnology-Based Microfabrication

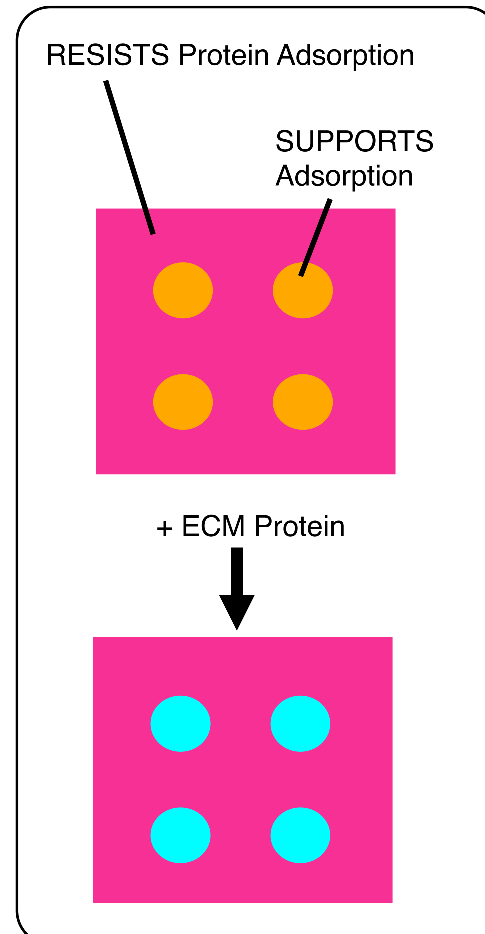
(Soft Lithography + Self Assembling Monolayers)

(with George Whitesides, Chemistry Dept. Harvard U.)

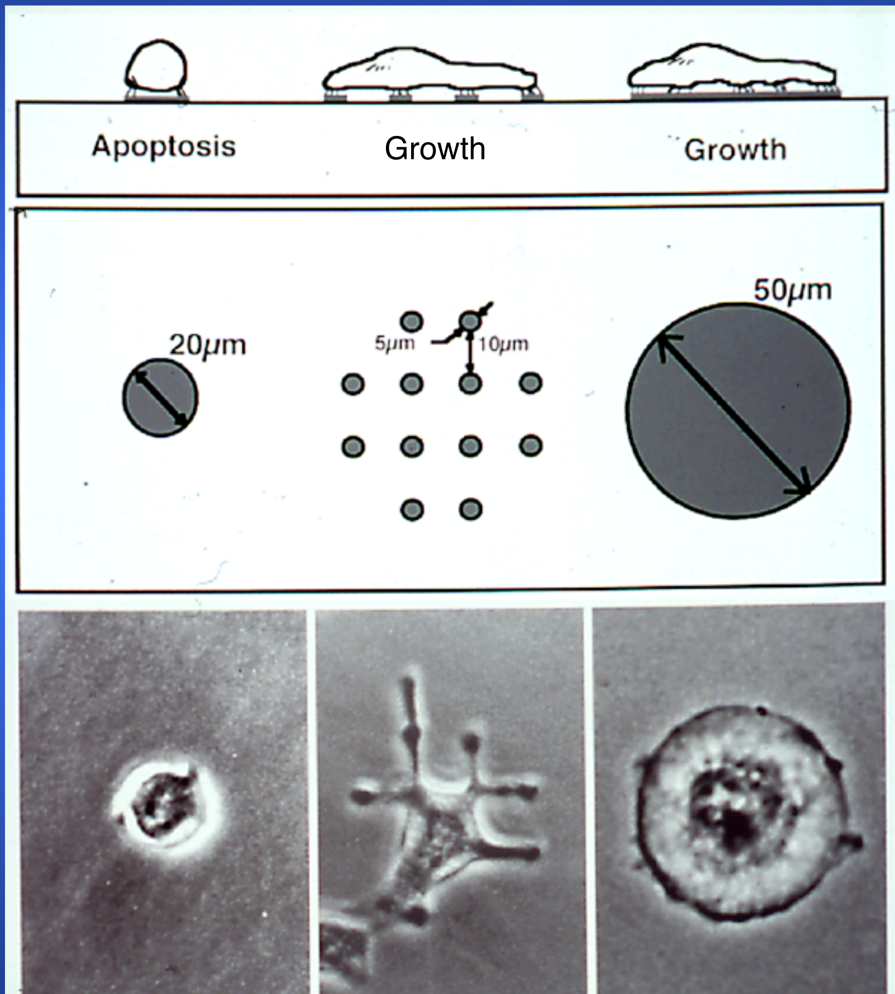
(Singhvi et al., *Science* 1994; Chen et al. *Science* 1997; Chen et al. *Methods Mol. Biol. 2000;* 139: 209-219)

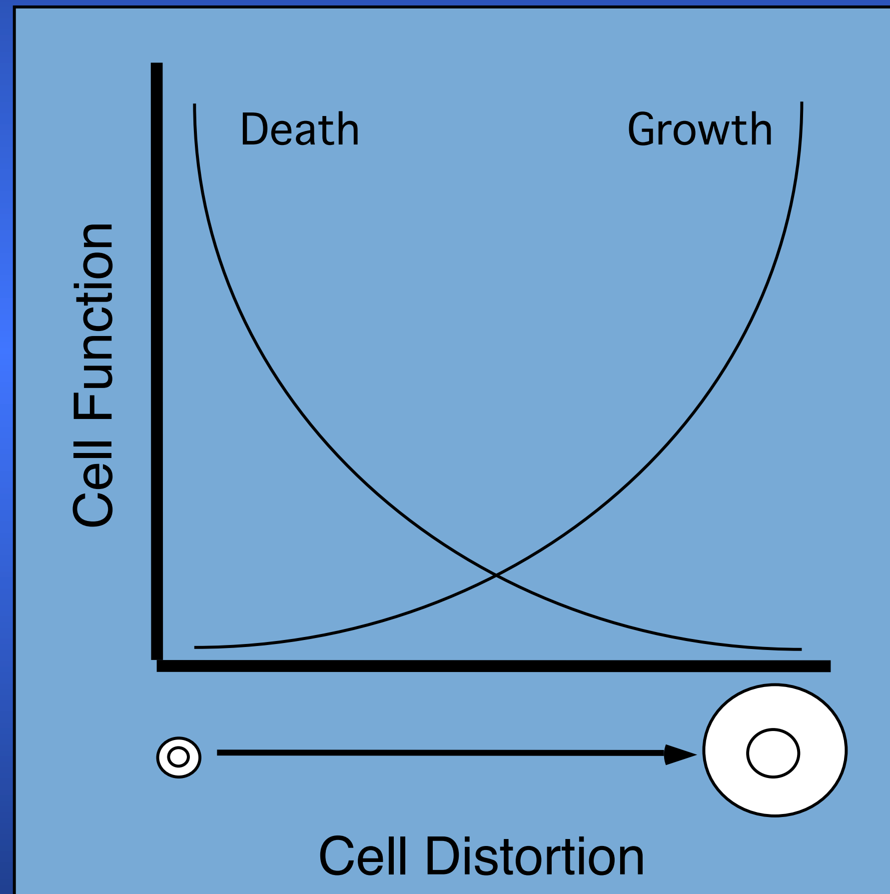






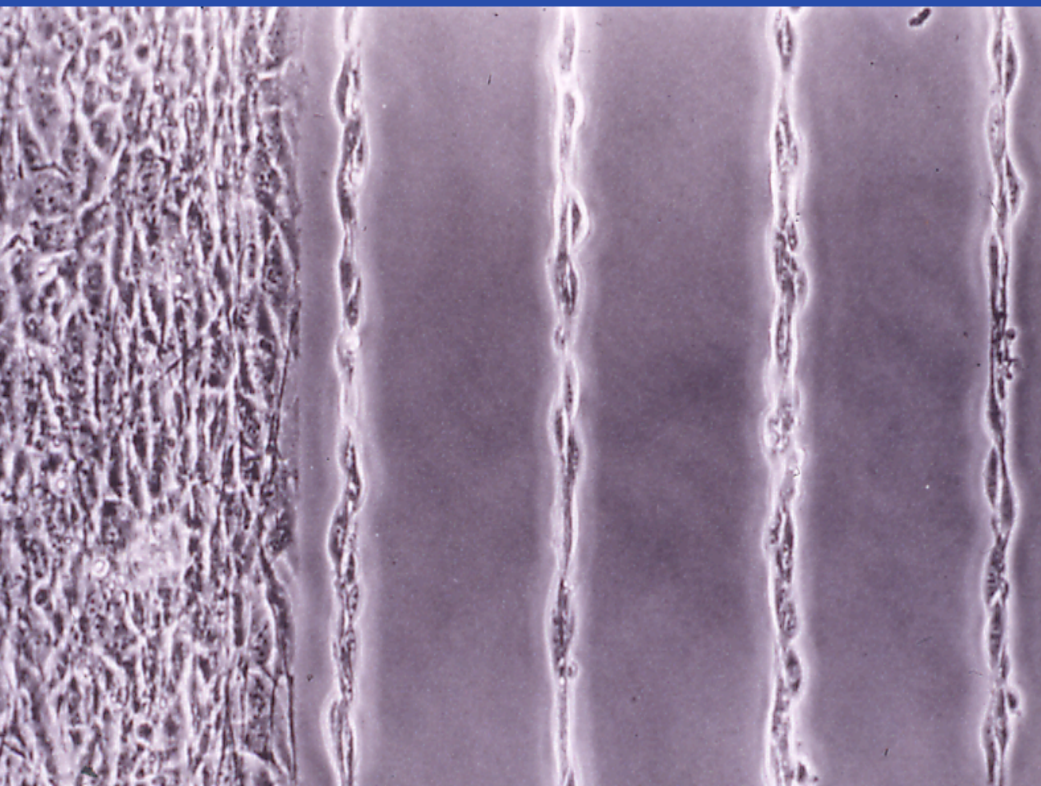
Stretching Cells Makes Them Grow And Rounded Cells Die

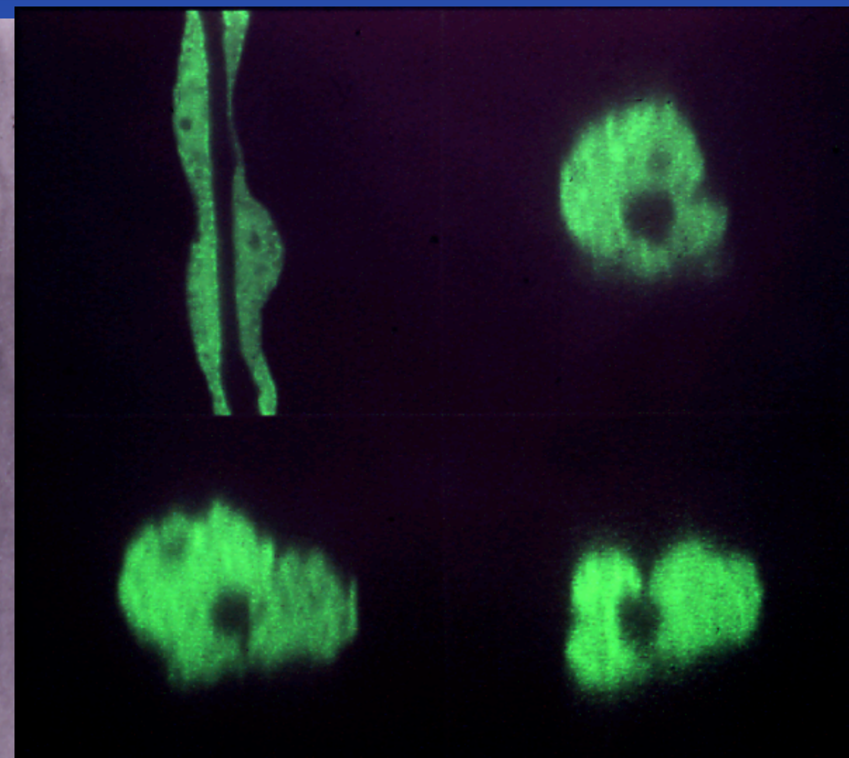




(Singhvi et al. *Science* 1994; Chen et al. *Science* 1997)

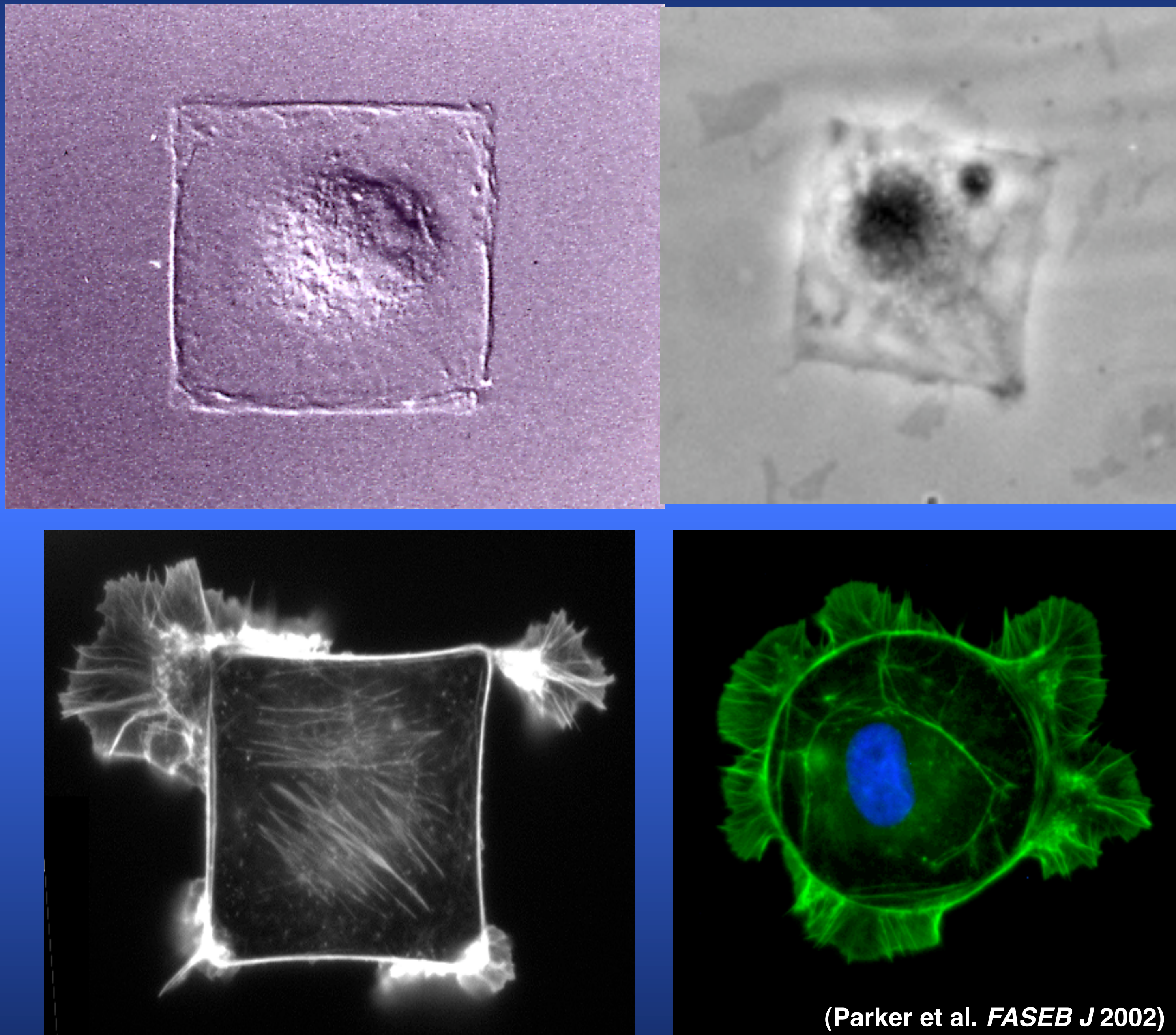
Capillary Blood Vessel Formation In A Dish





(Dike et al. *In Vitro Cell Dev Biol* 1999)

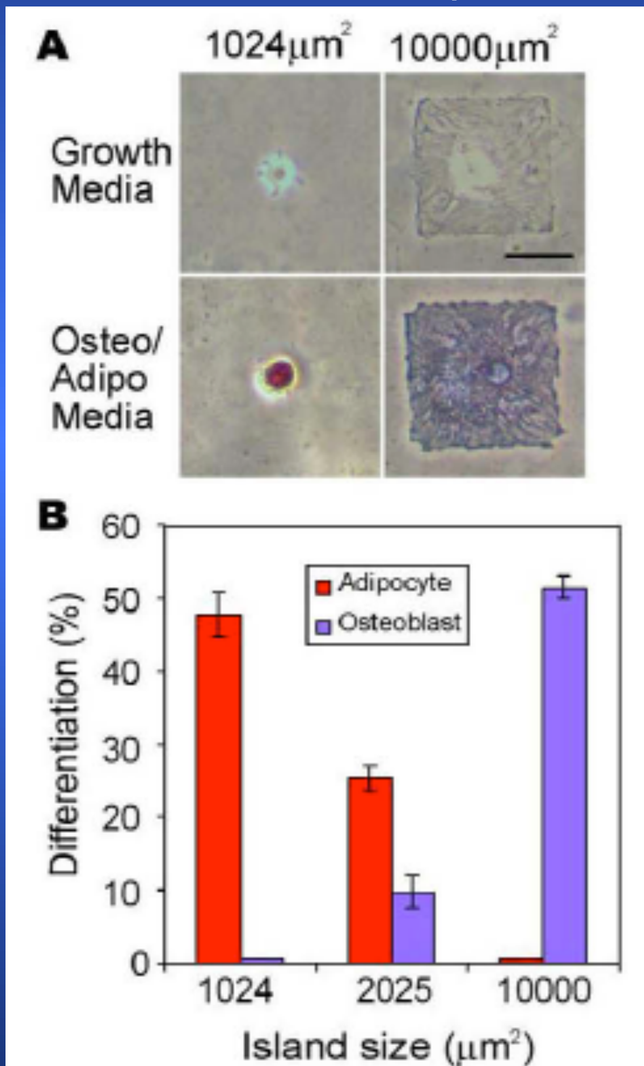
Stretch-Dependent Control of Directional Motility



(Parker et al. *FASEB J* 2002)

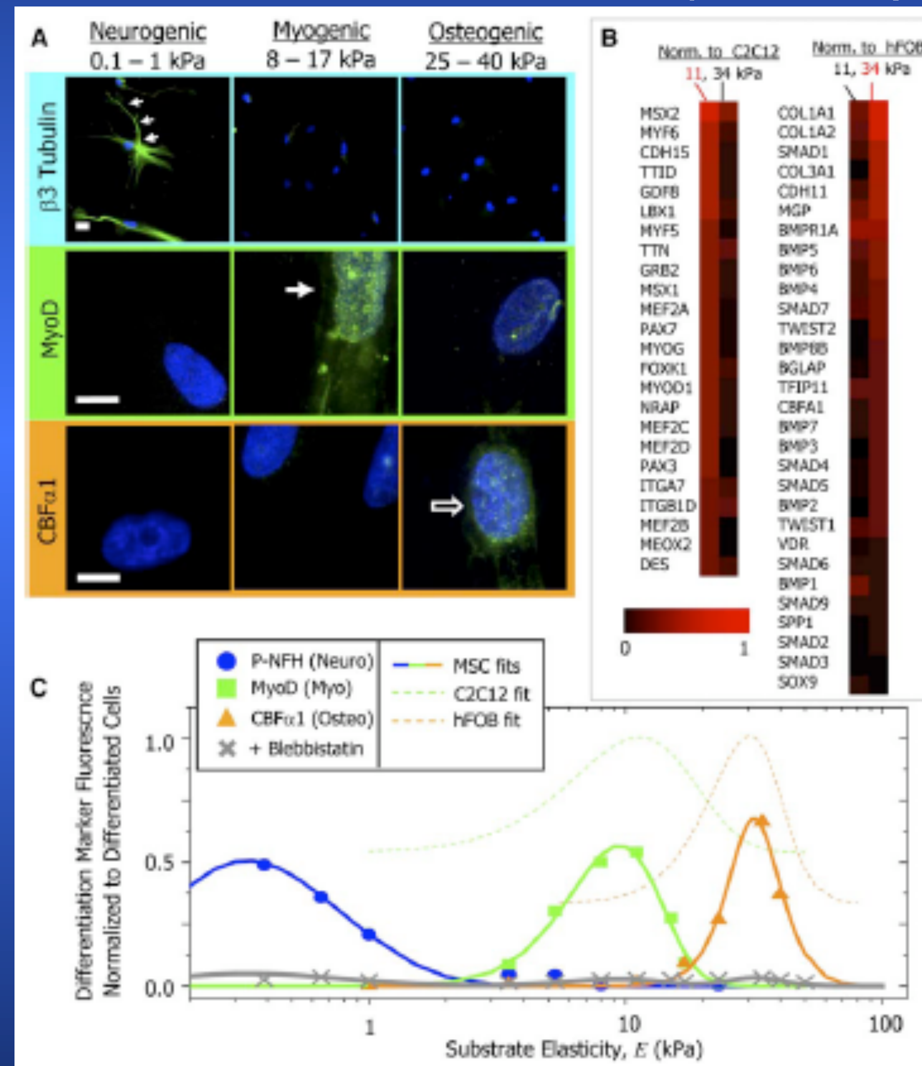
Cell Shape & ECM Mechanics Control Human Mesenchymal Stem Cell Lineage Switching

Work of Chris Chen (U. Penn)



(McBeath et al., *Dev. Cell.* 2004)

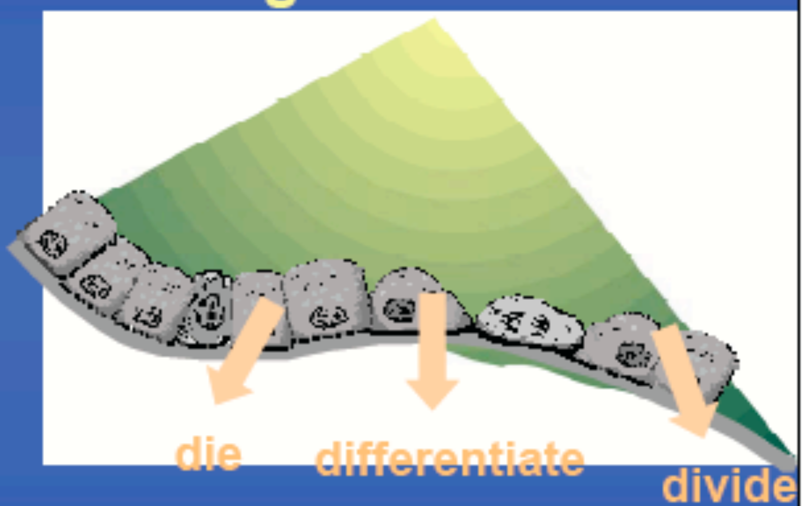
Work of Dennis Discher (U. Penn)

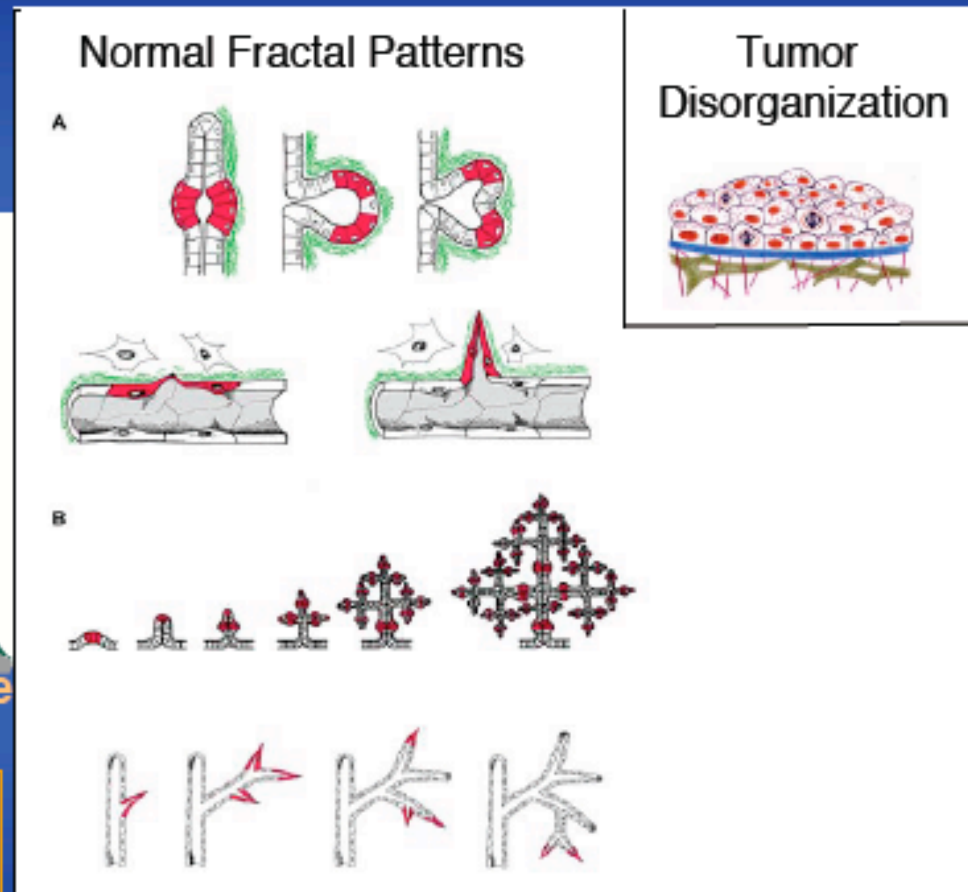


(Engler et al, *Cell* 2006)

Tissue Patterning Governed by Physical Interactions between Cells and ECM

Soluble growth factors

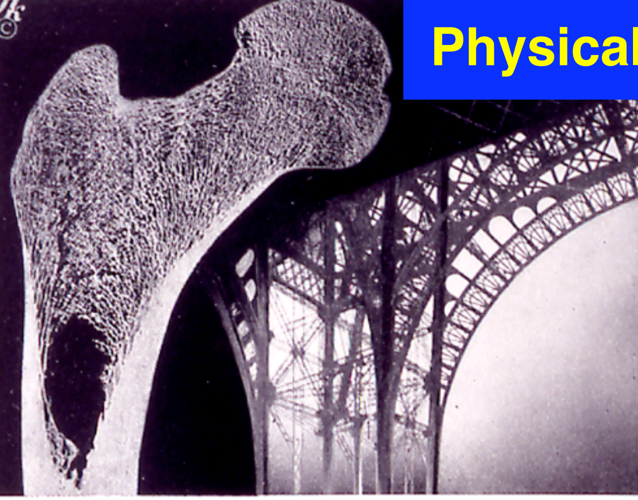


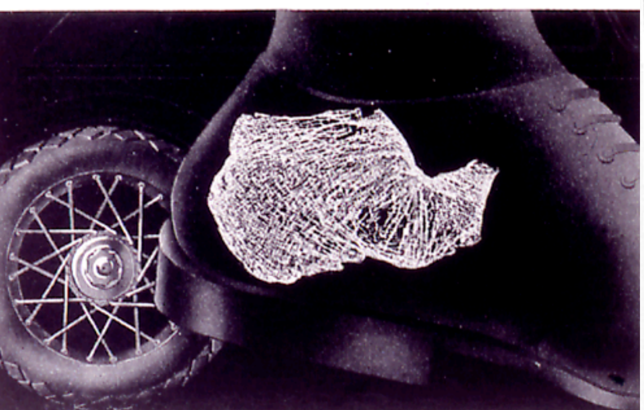


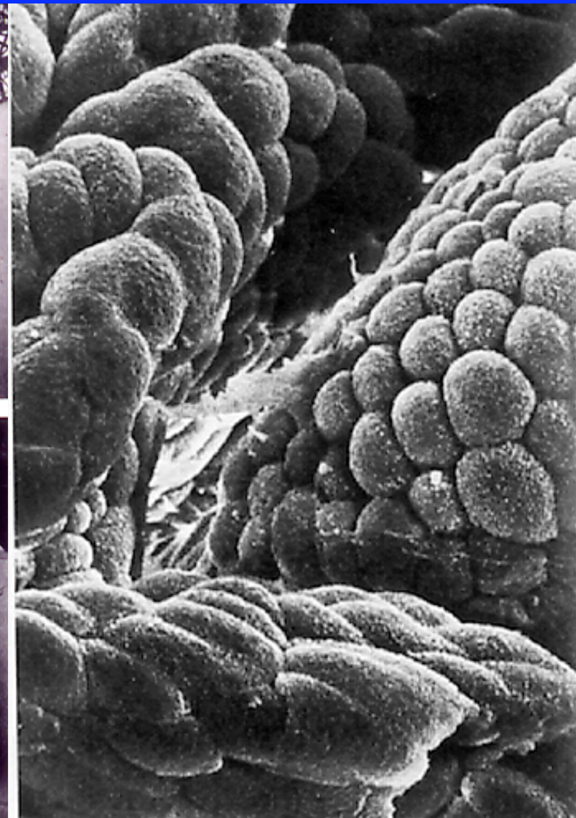
→ Spatial heterogeneity of cell fates drives morphogenesis

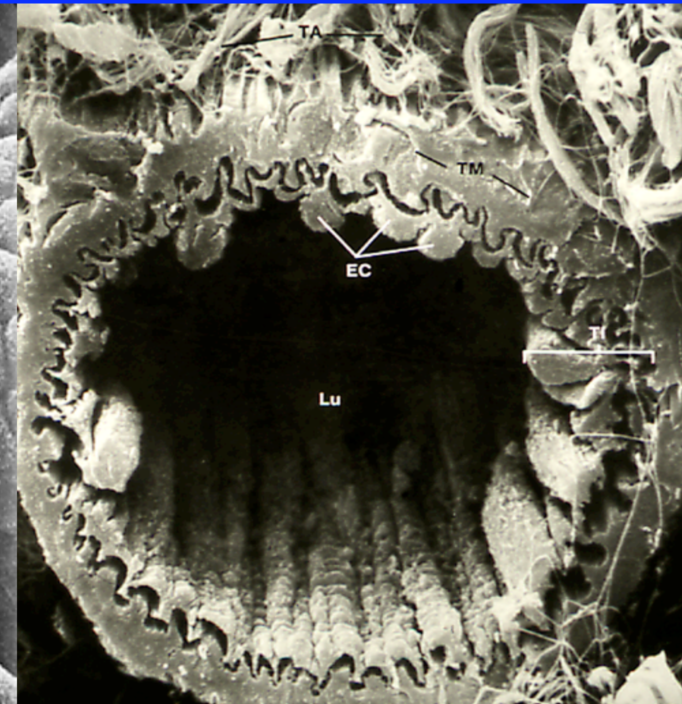
Cell fate switching depends on physicality of microenvironment

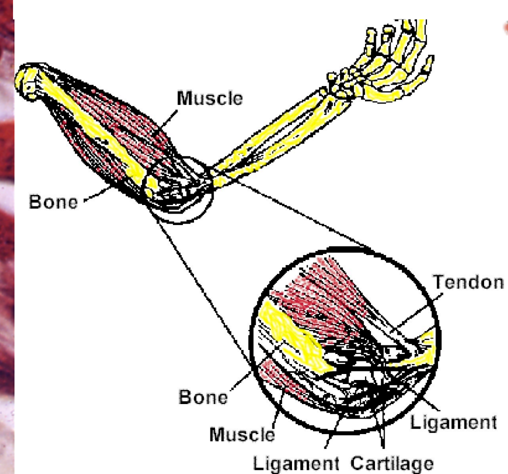
Physical Forces Influence Form & Function of all Tissues

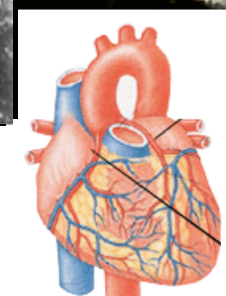


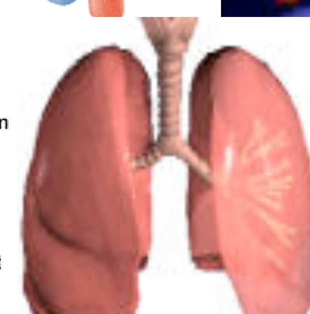




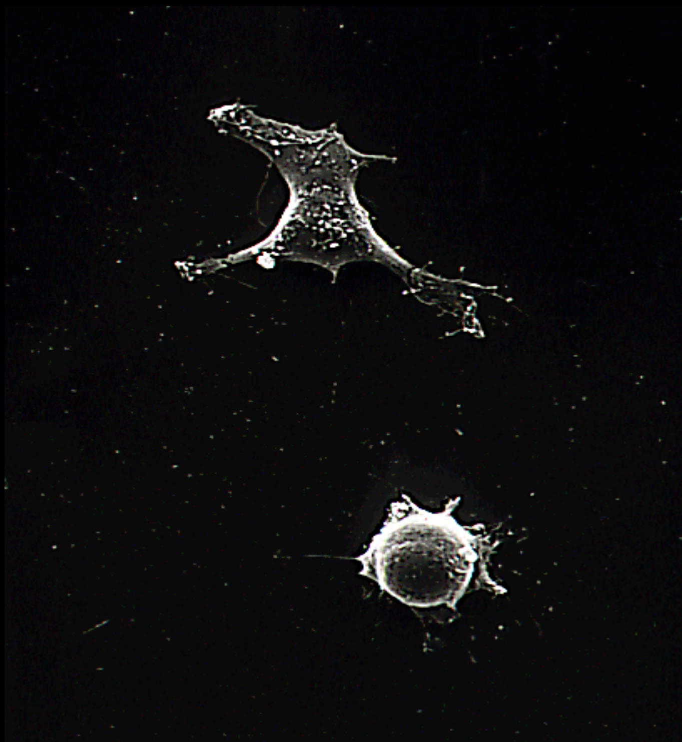








So how do cells sense and respond to *physical forces*?
(= 'Mechanotransduction')



Old View:

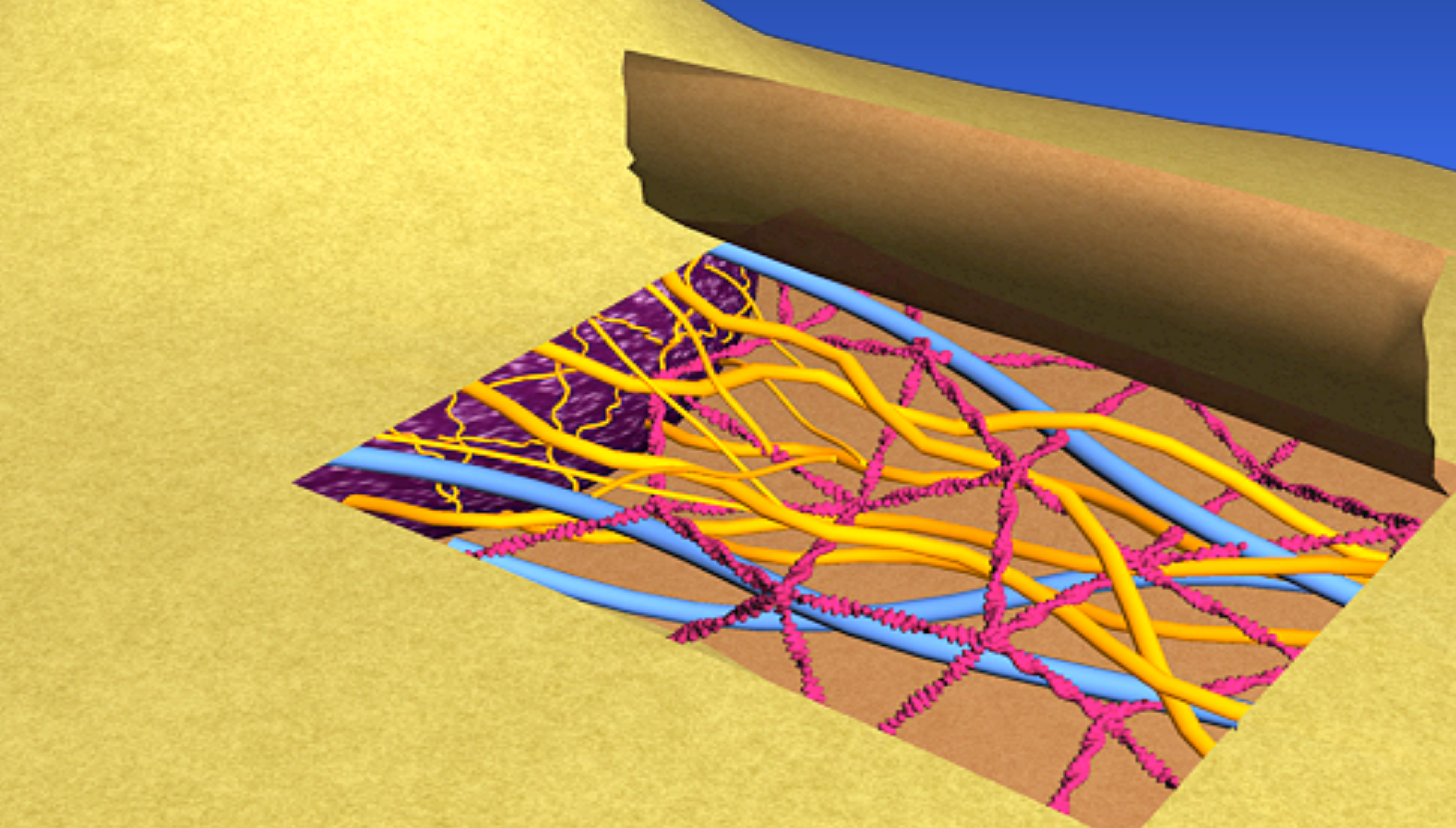
Cells are like Water Balloons

Hypothesis:

Cells are Built Like Tents

The CYTOSKELETON

(internal framework composed of molecular polymers)



The CYTOSKELETON

(Most Biologists Study its

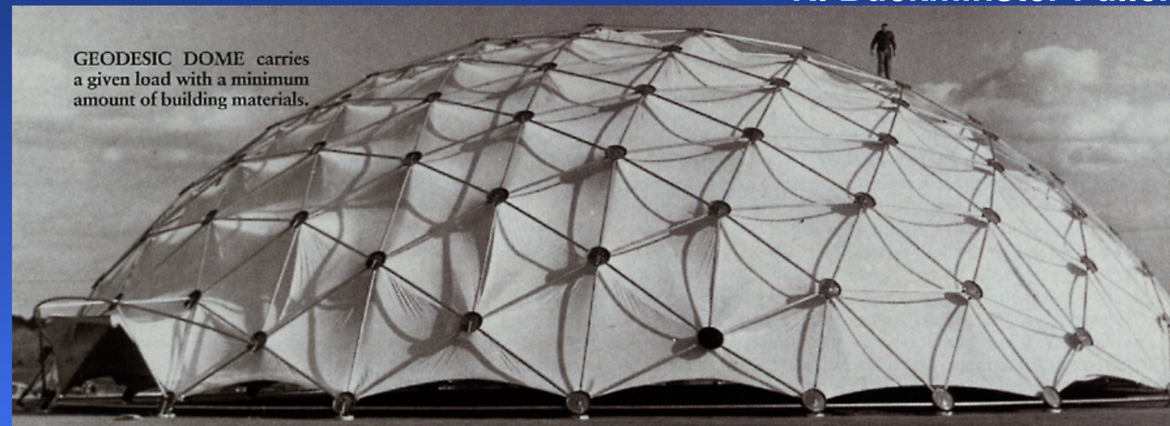
GEL PROPERTIES)

Tensegrity Architecture

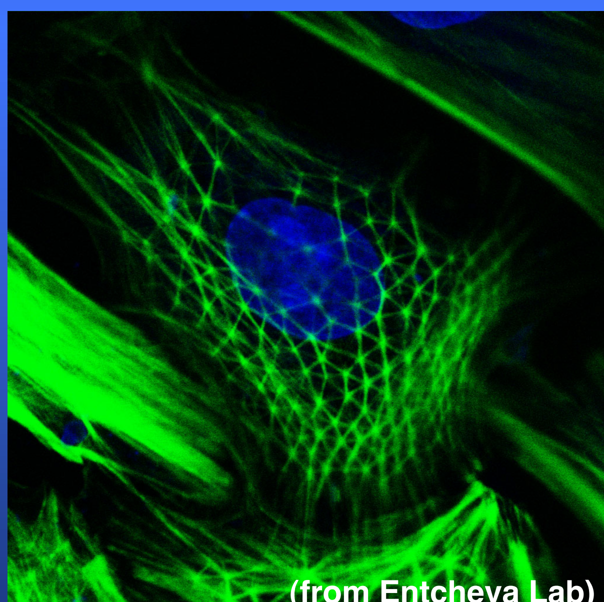
- Uses "*continuous tension*" (tensional integrity)

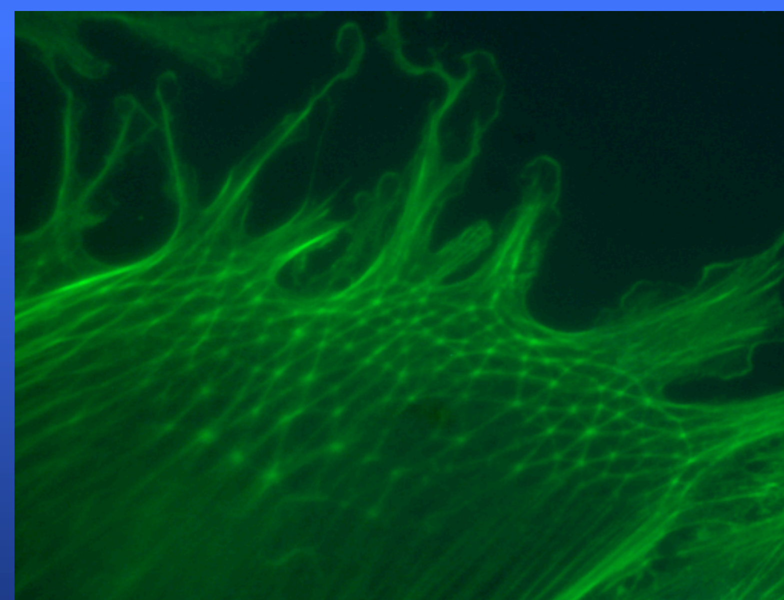

Kenneth Snelson

R. Buckminster Fuller



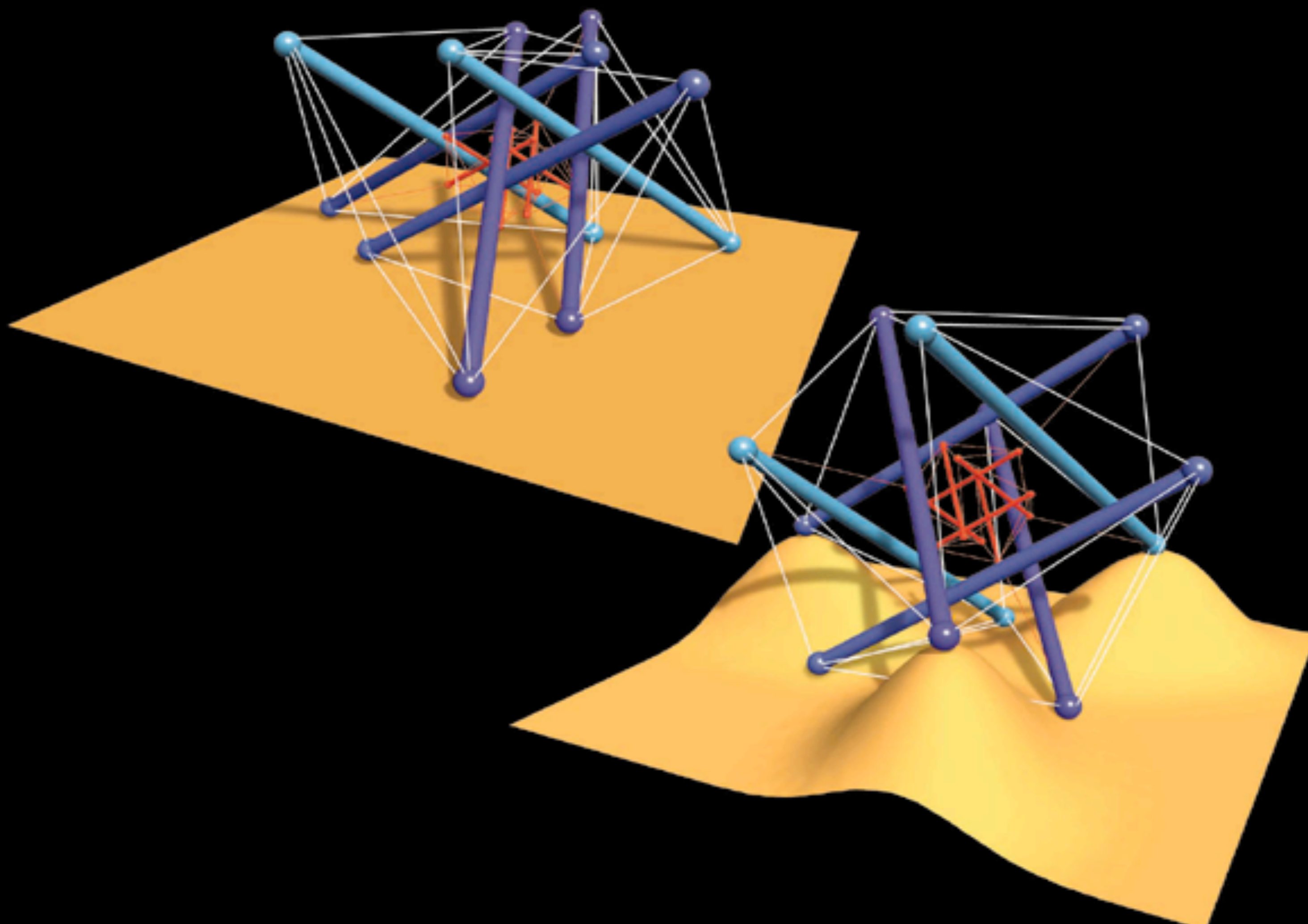
Geodesic Dome Building


(from Entcheva Lab)



Geodesic Domes in Cytoskeletons of Living Cells

Cellular Tensegrity Model

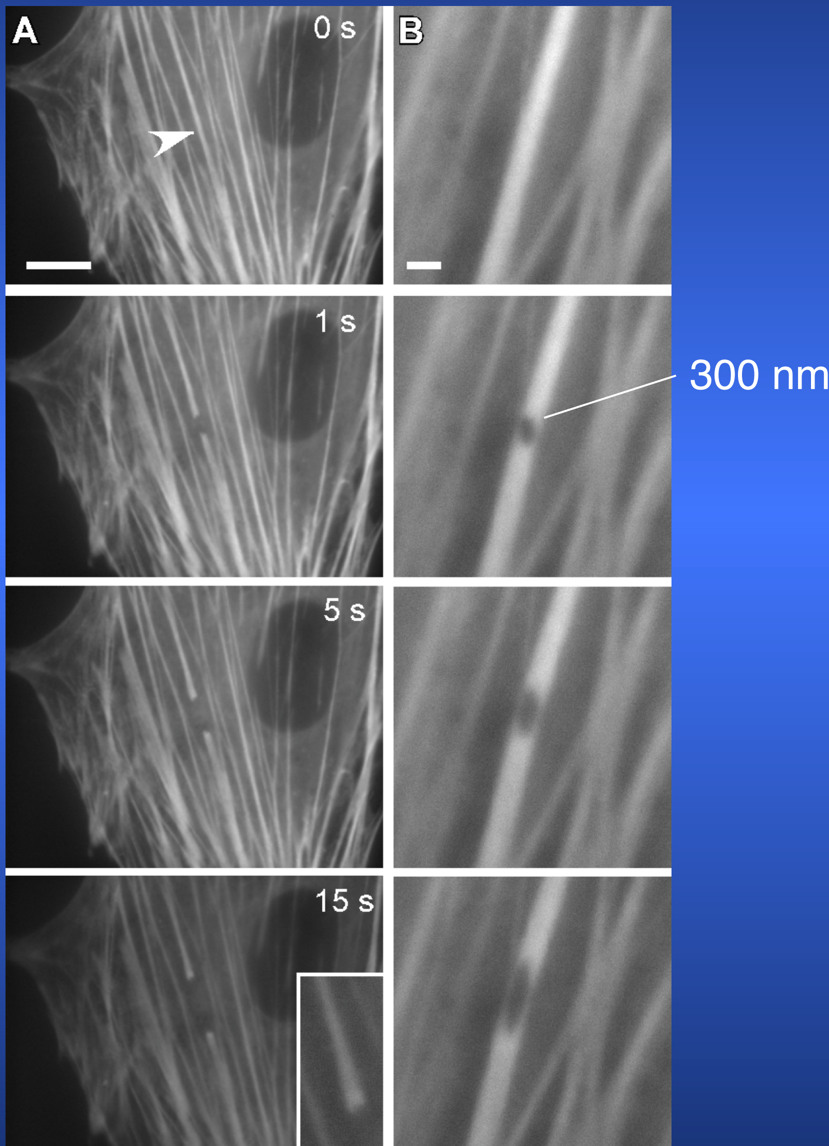


(Ingber et al., *PNAS* 78:3901-5, 1981; Ingber & Jamieson,1985;
Wang et al. *Science* 1993, *PNAS* 2001; Ingber *J. Cell Sci* 1993, 2003)

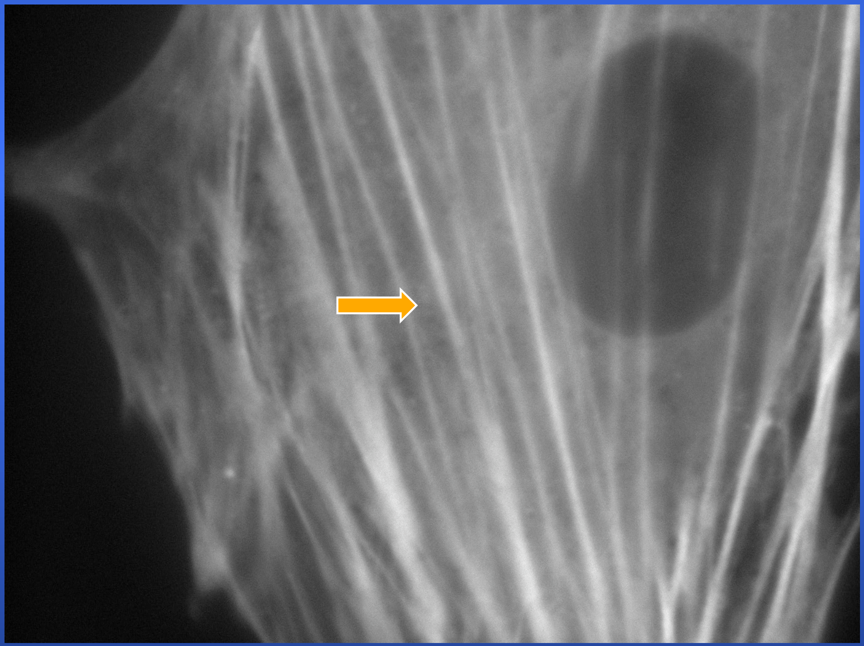
Living Stress Fibers are Tensed Molecular 'Cables'

(revealed using Femtosecond Laser Nano-Surgery)

(with Eric Mazur, Physics, Harvard)



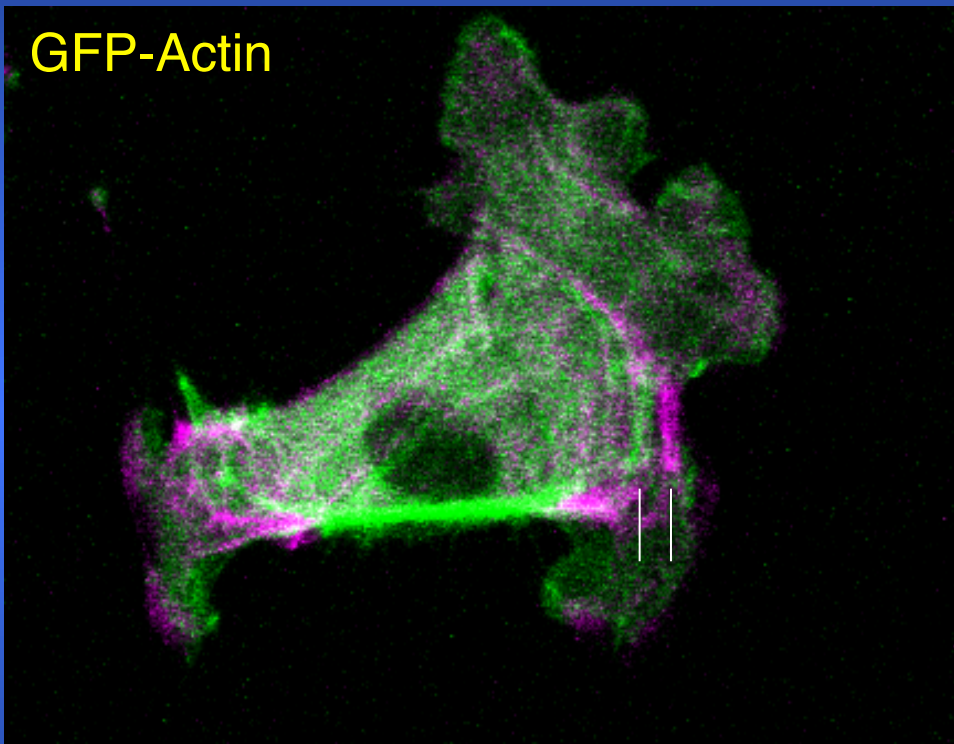
Retraction of a single actin stress fiber in a living cell

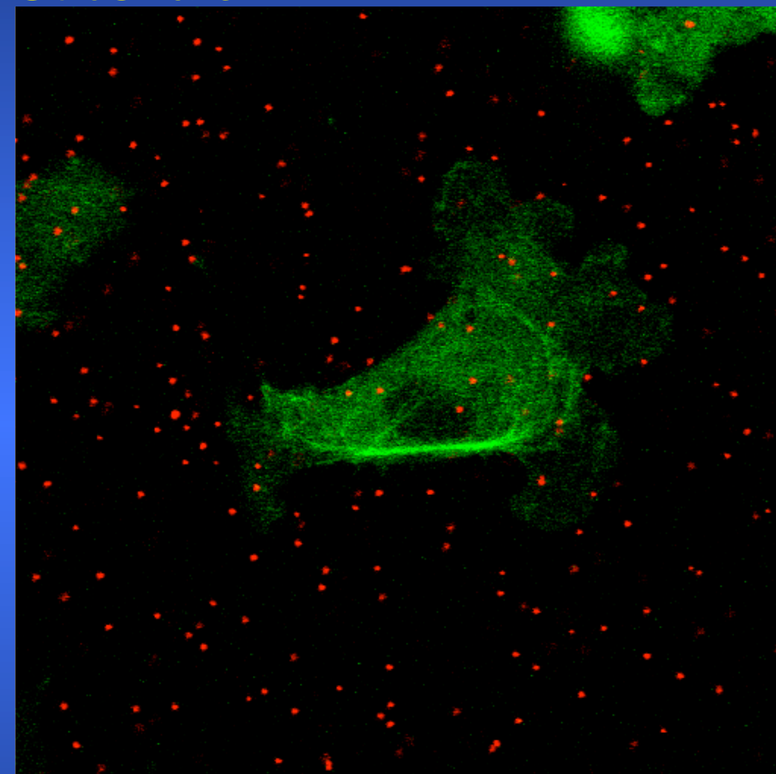


(Kumar et al., *Biophys J.* 2006)

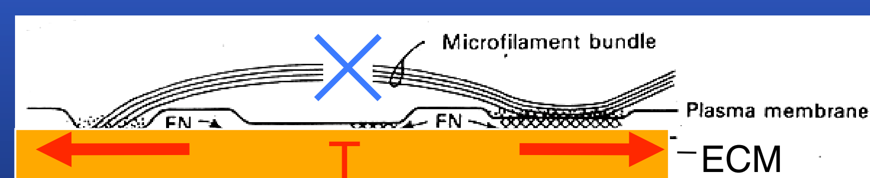
Mechanical Continuity & Prestress in the Cytoskeleton and ECM

Flexible ECM Substrate



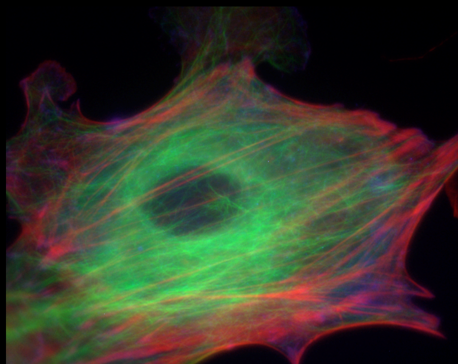


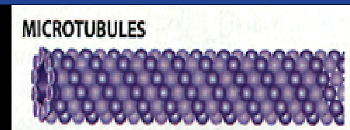
Before Cut: Green
After Cut: Magenta



(Kumar et al, Biophys J 2006)

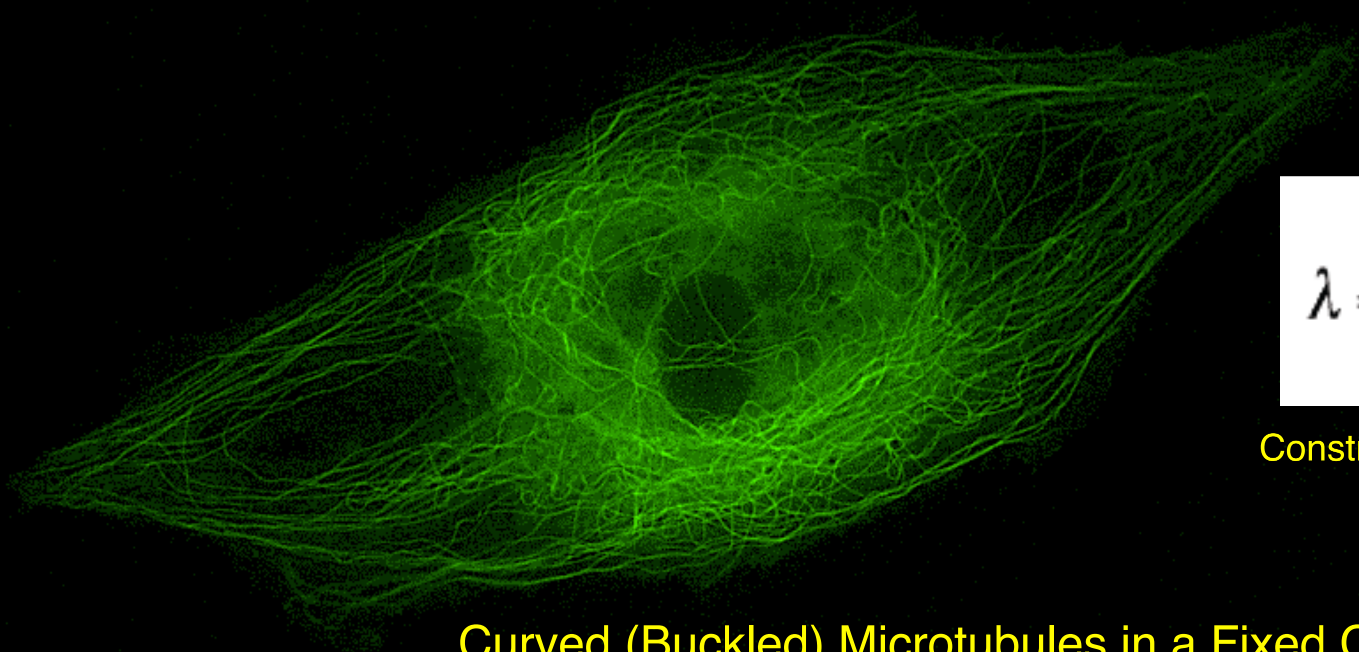
Microtubules are Semi- Flexible Struts that Bear Compression in Living Cells





Live Beating Heart Cell

(Brangwynne et al, *J Cell Biol 2006 with D. Weitz & K. Parker, Harvard U.* & F. Macintosh, Amsterdam)



$$\lambda = 2\pi \sqrt[4]{\frac{\kappa}{\alpha}}$$

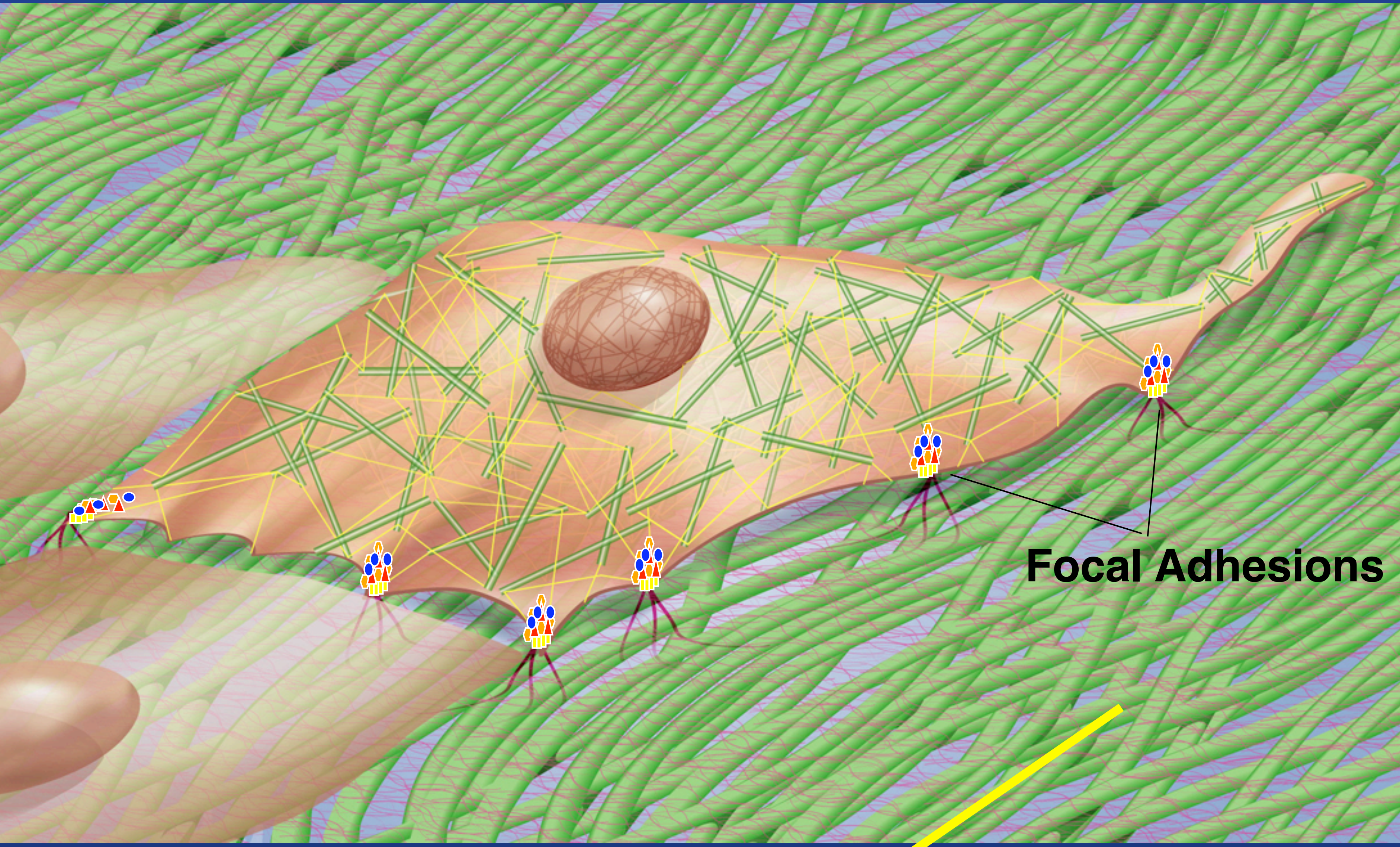
Constrained Buckling Theory

Curved (Buckled) Microtubules in a Fixed Cell

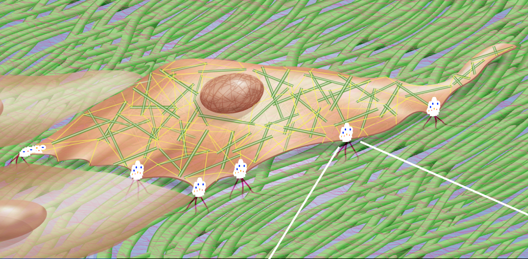
Cell Shape Stability Depends on Semi-flexible Microtubule struts balancing Tensed Actin Filaments

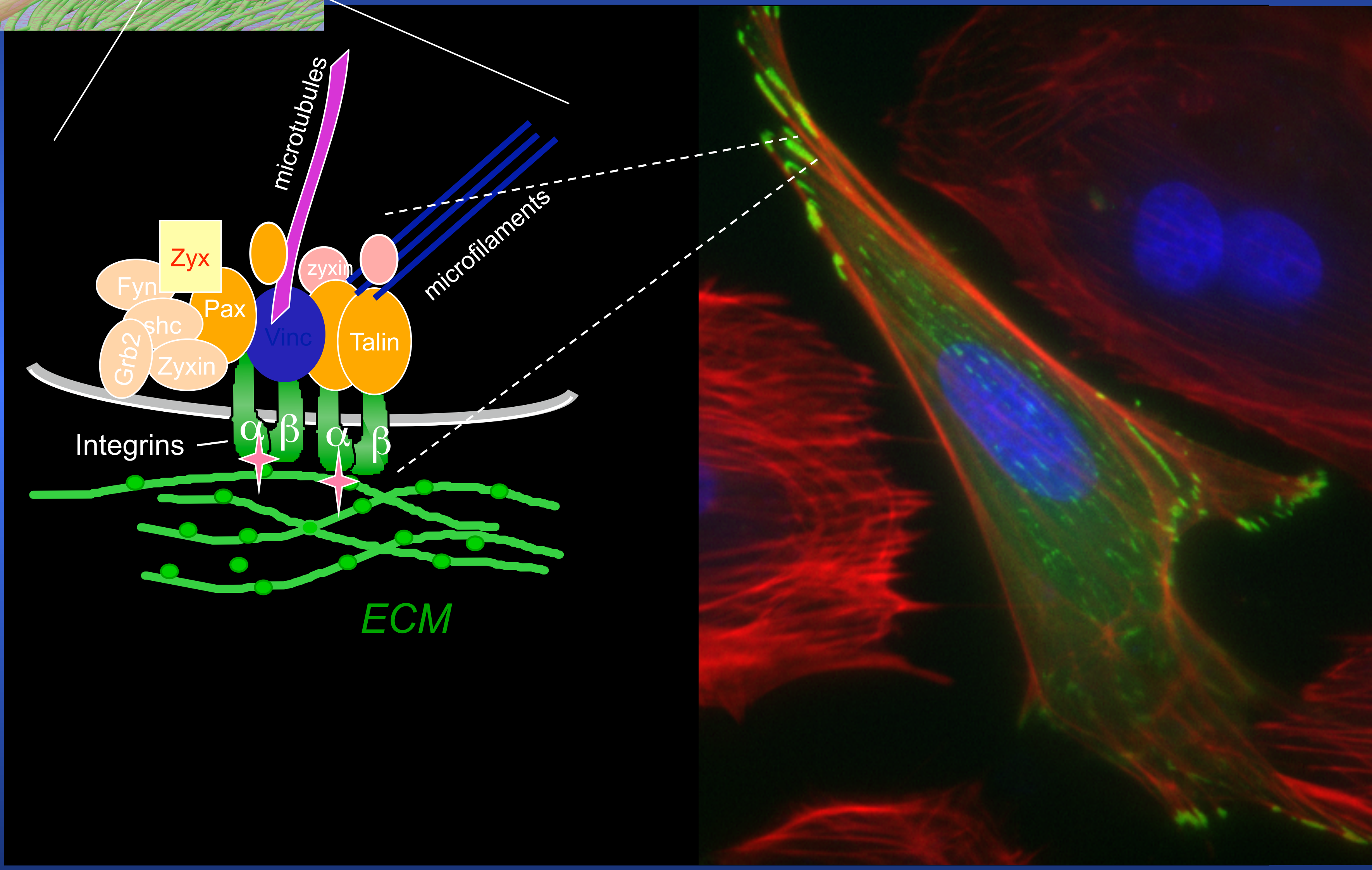
Spider Web Tensegrity

Cells Anchor to Substrates Through Multiple Small Tethers
(= "tent pegs")



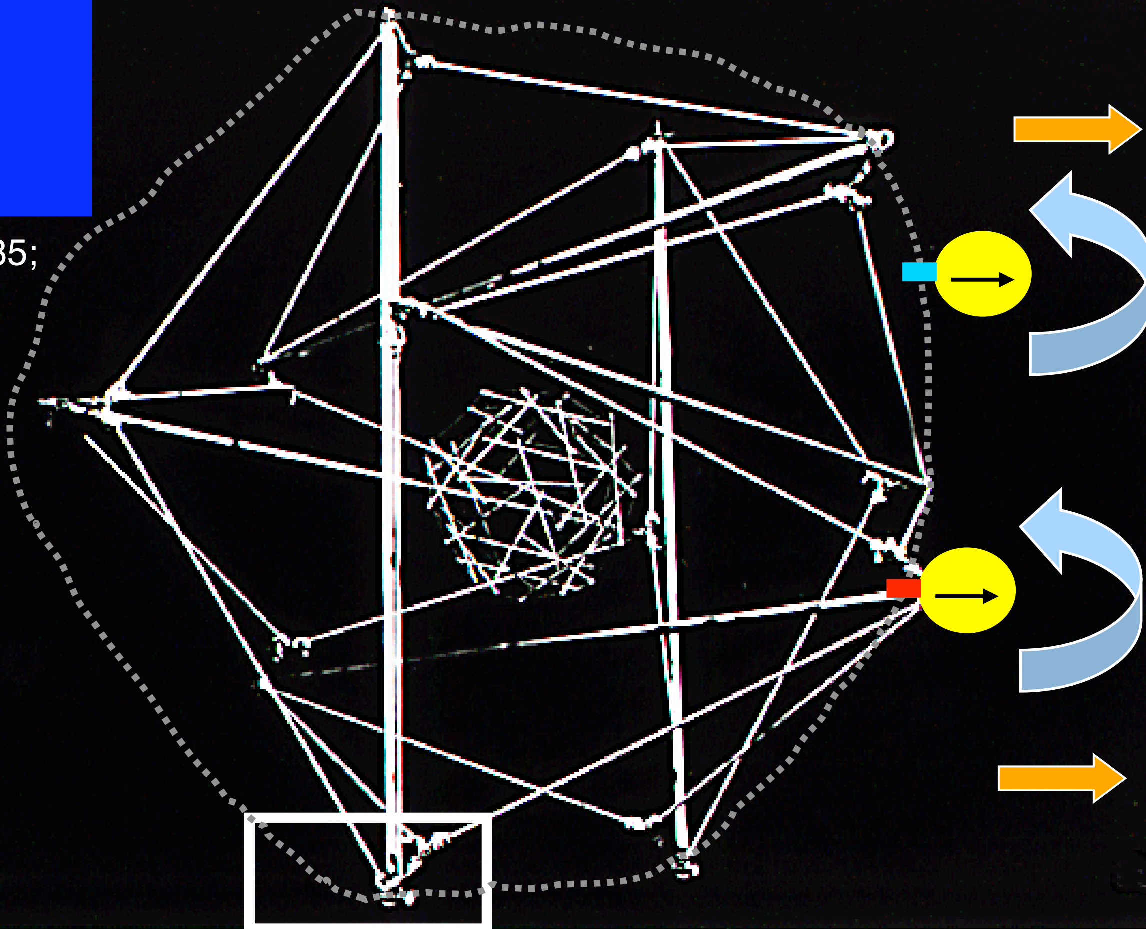
Cells Anchor through Integrin Receptors in Focal Adhesions (“tent pegs”)

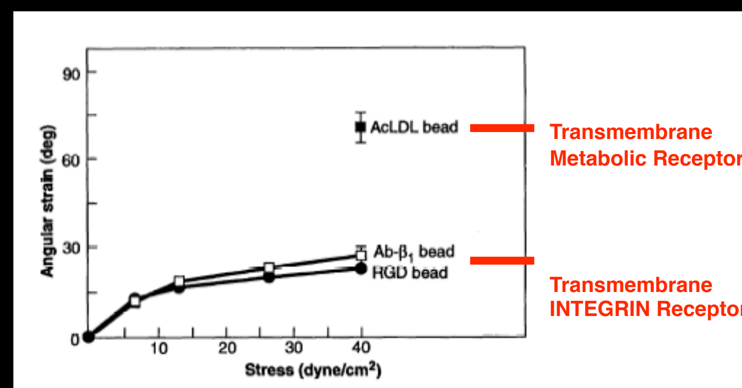




Tensegrity predicts Integrins act as Mechanoreceptors

(Ingber & Jamieson, *Gene Express. &…*, 1985; Ingber, *Curr. Opin Cell Biol.* 1991)

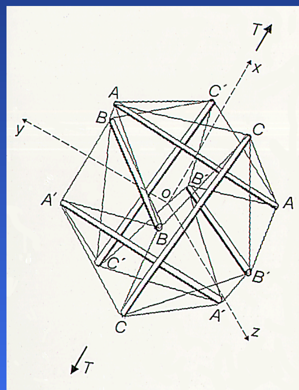


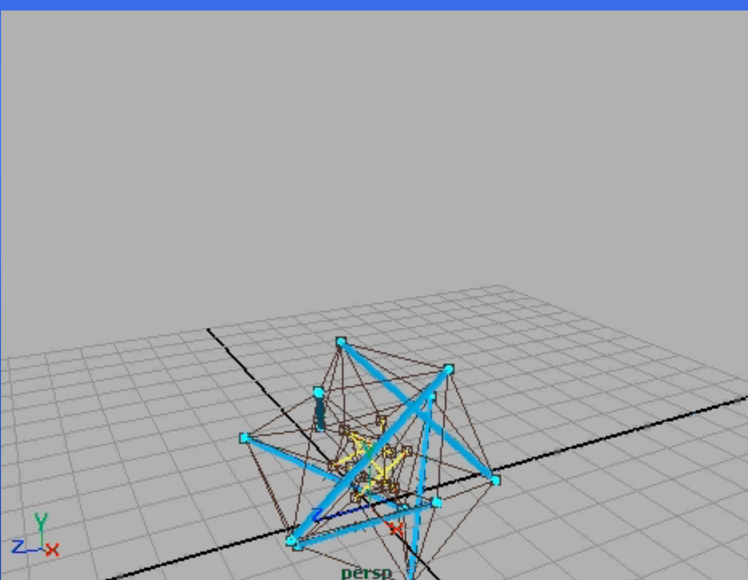


(Wang et al., *Science* 1993)

Mathematical Tensegrity Model of the Cell

(with D. Stamenovic, Boston U.)





(Stamenovic et al. J. Theor. Biol.1996; Coughlin & Stamenovic, J App Mech 1997,1998, J Theor Biol. 1999 & J Biomech. Engin. 2000; Wendling et al, J Theor Biol 1999; Wang & Stamenovic, Am J Physiol Cell Physiol. 2000; Volokh et al. J. Biomech. 2000; Stamenovic,J. Biomech.,2005.; Canadas et al., J Theor Biol 1992, J Biomech Engin. 2006; Shen & Wolynes, *Phys Rev E* 2005 [STATISTICAL PHYSICS MODEL….)

A Priori Predictions now Confirmed:

•*TENSILE PRESTRESS GOVERNS CELL MECHANICS*
(Wang & Ingber, Biophys. J. 1994; Lee et al., Am. J. Physiol. 1997)

•Linear relation between Stiffness and *Applied* Stress
(Wang et al., Science 1993; Wang and Ingber, Biophys. J. 1994))

•Linear relation between Stiffness and Prestress
(Wang et al., PNAS 2001; Wang & Stamenovic, Am. J. Physiol 2002)

•Quantitative Prediction of Cellular Elasticity
(Stamenovic and Coughlin, J. Biomech. Engineer. 2000)

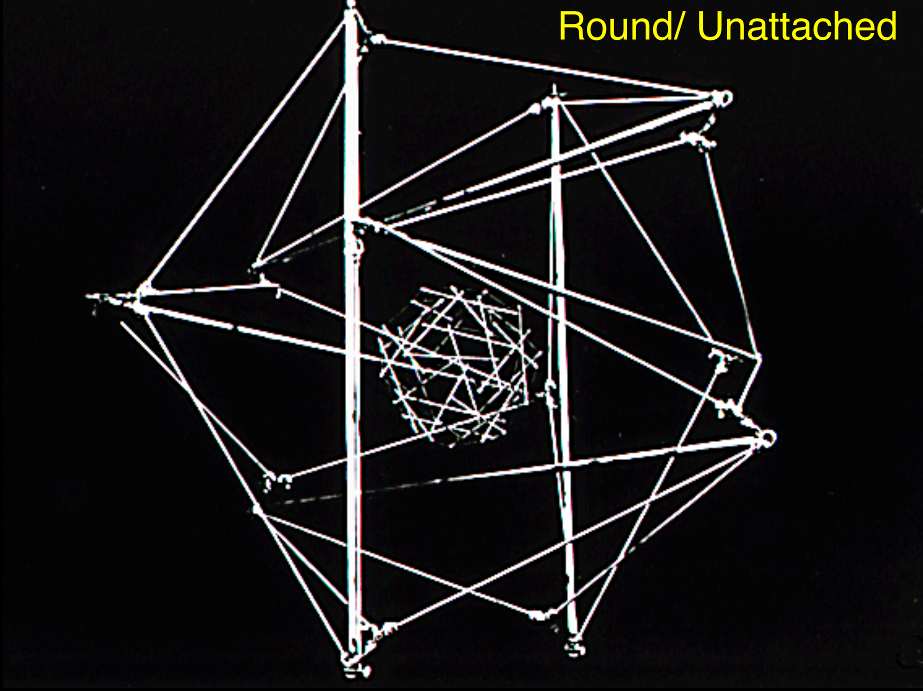
•Prediction of Dynamic Mechanical Behavior
(Sultan et al., Ann Biomed Engin. 2004)

•Mechanical Contribution of Intermediate Filaments to Cell Mechanics
(Wang and Stamenovic, Am J Physiol Cell Physiol, 2000)

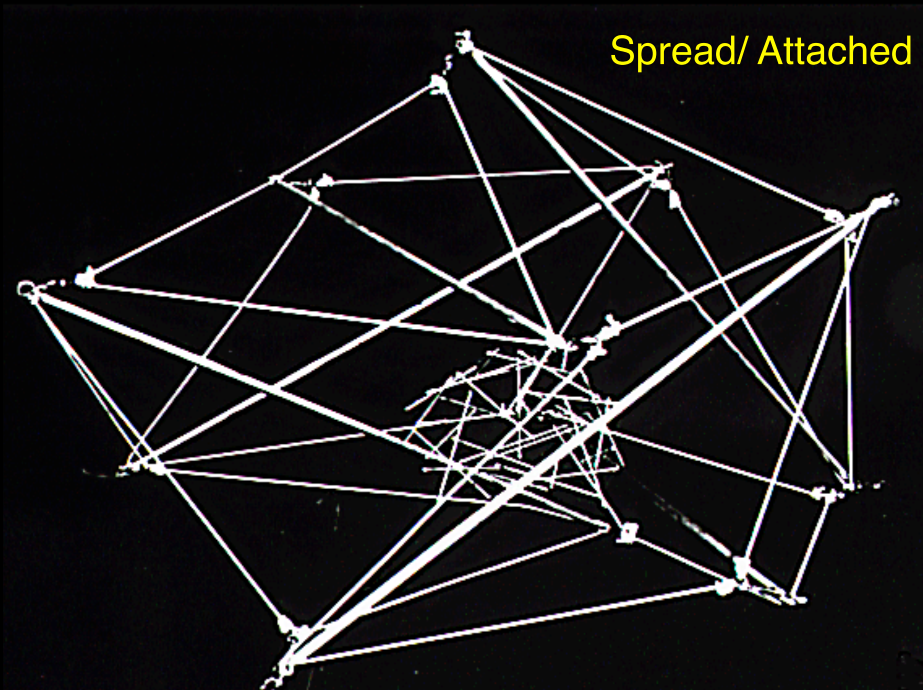
•Microtubules Bear Compression
(Keach et al., 1996; Wang et al., 2001; Hu et al., Bioscience, 2004; Brangwynne et al., J Cell Biol 2006)

•Hysteresivity independent of prestress
(Maksym et al.,Am. J. Phys. 2000;Wang et al., PNAS 2001)

'Hierarchical' Tensegrity Cell Model with a Nucleus



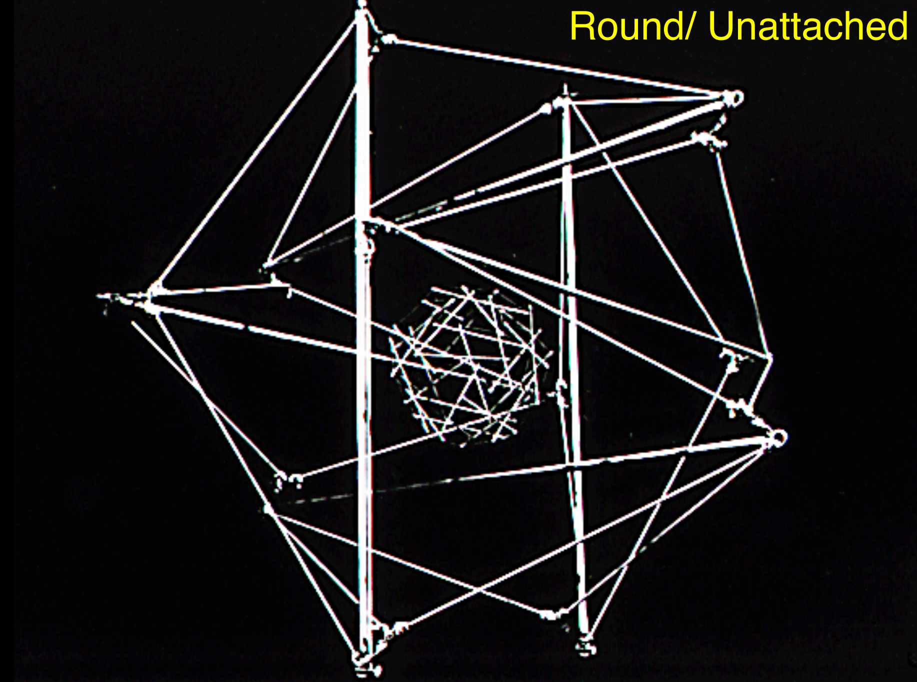
Tensile connections promote coordinated 'cell' and 'nuclear' spreading



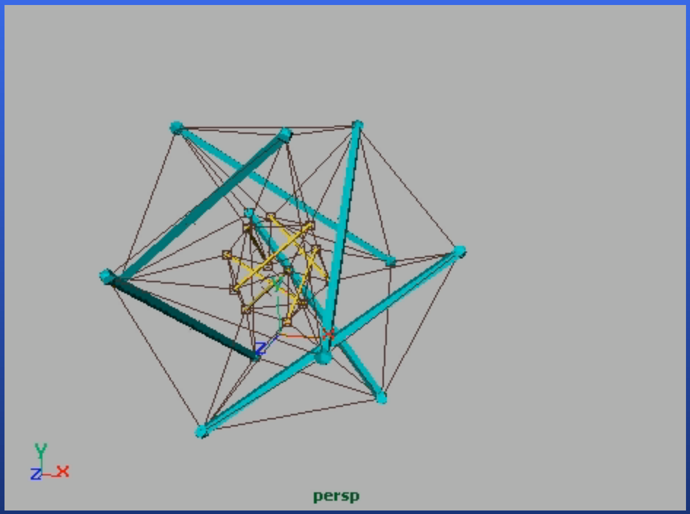
(Ingber et al., *PNAS* 1981; Ingber & Jamiesion, 1985; Ingber, *J Cell Sci* 1993; Ingber, *J Cell Sci* 2003)

Coordinated cell and nuclear spreading in a living cell

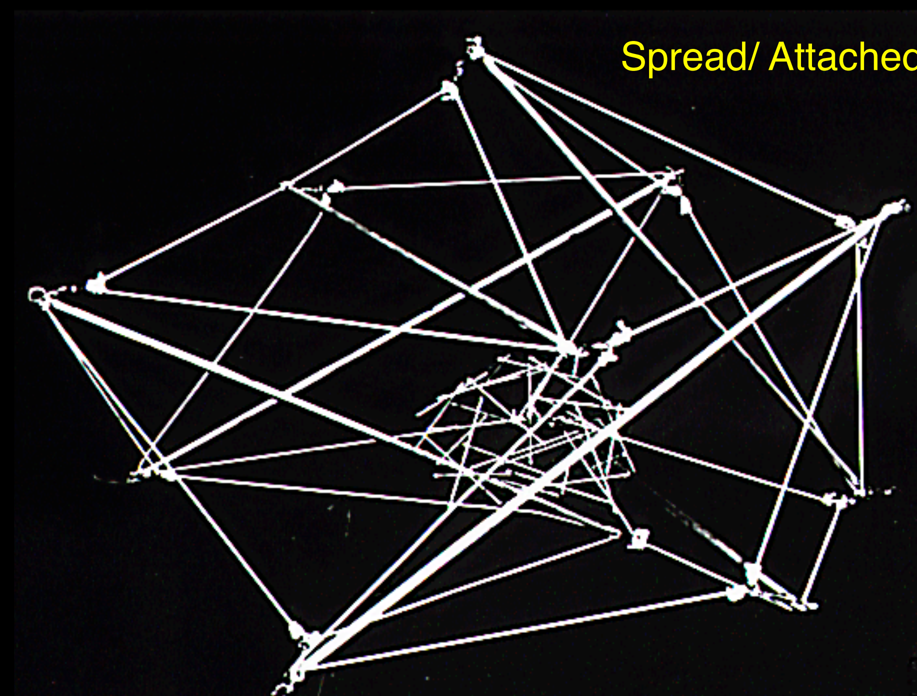
(Ingber, *PNAS* 1990)



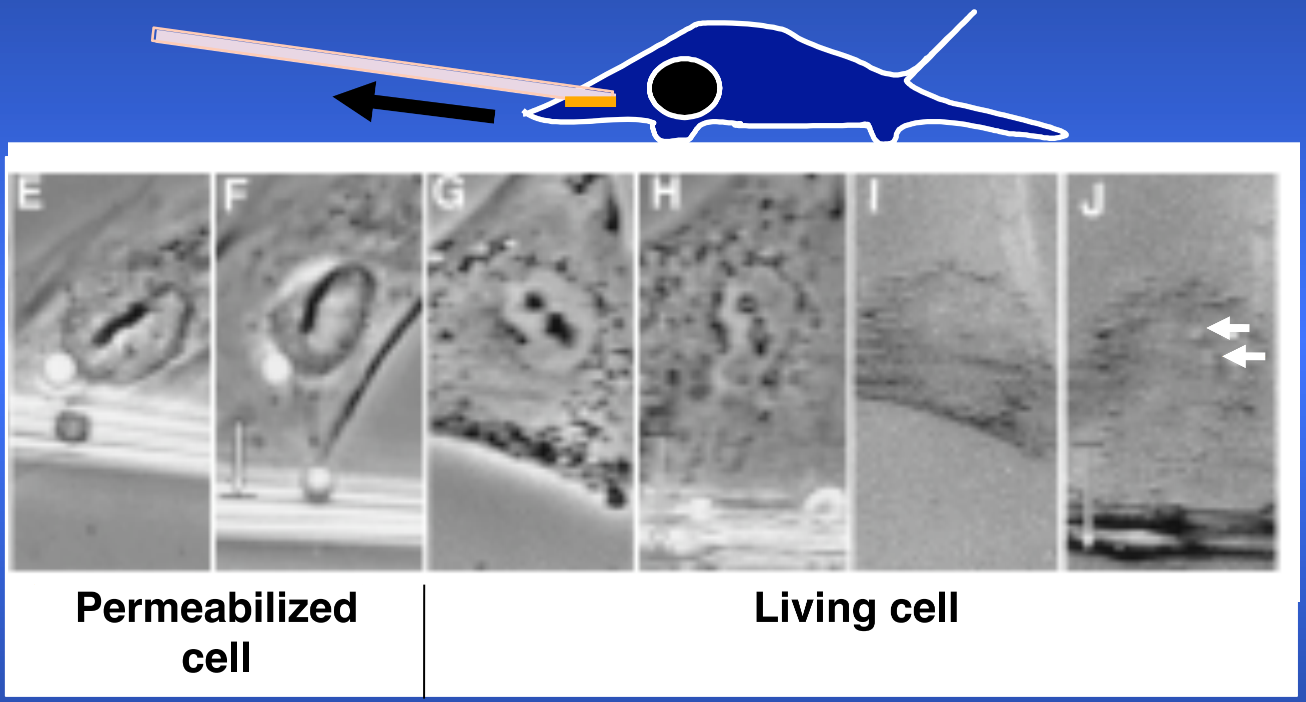
A simulated tensegrity cell



(Computer Simulation by Eddy Yuan, U. Toronto)



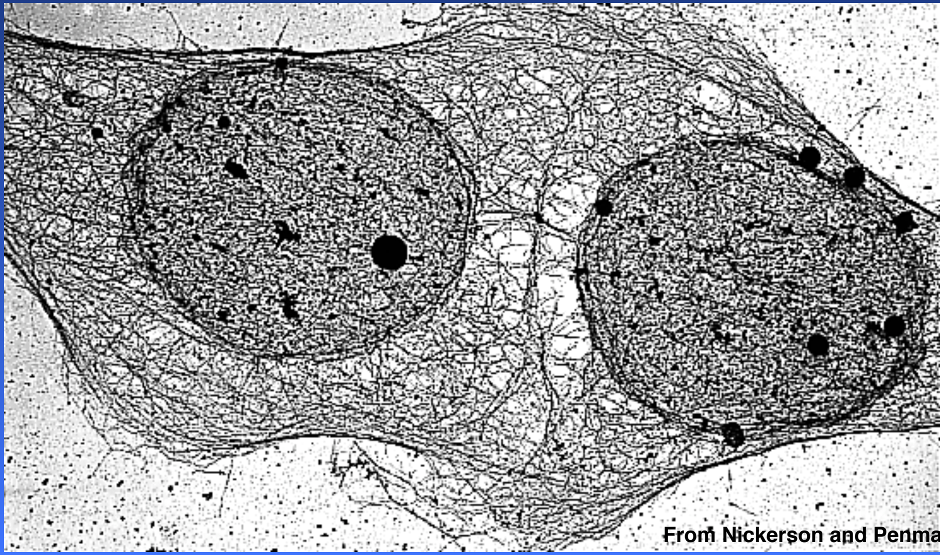
Long Distance Force Transfer in Living Cells from Integrins to Nucleoli



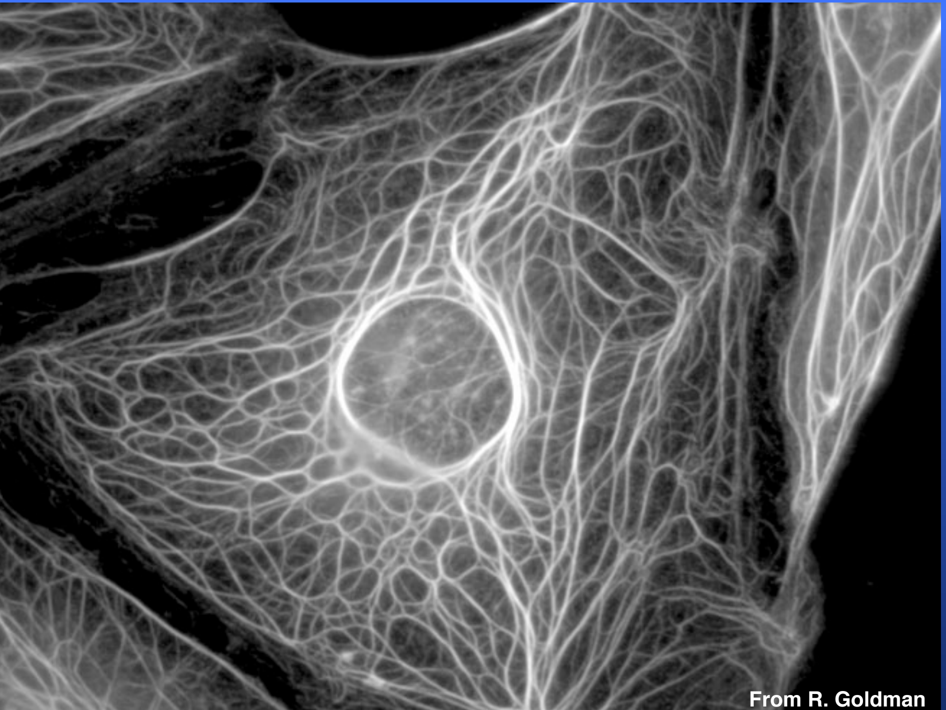
(Maniotis et al., *PNAS* 1997)

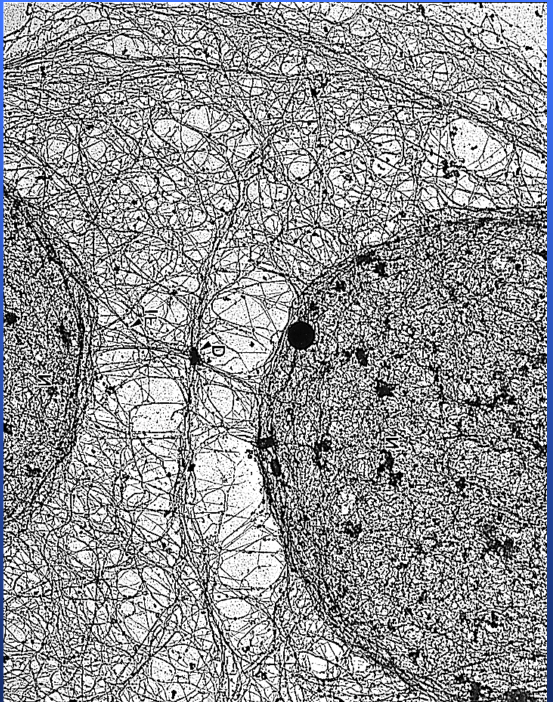
Intermediate Filaments are Suspensory Cables

(Maniotis et al. PNAS 1997; Eckes et al. JCS1998)

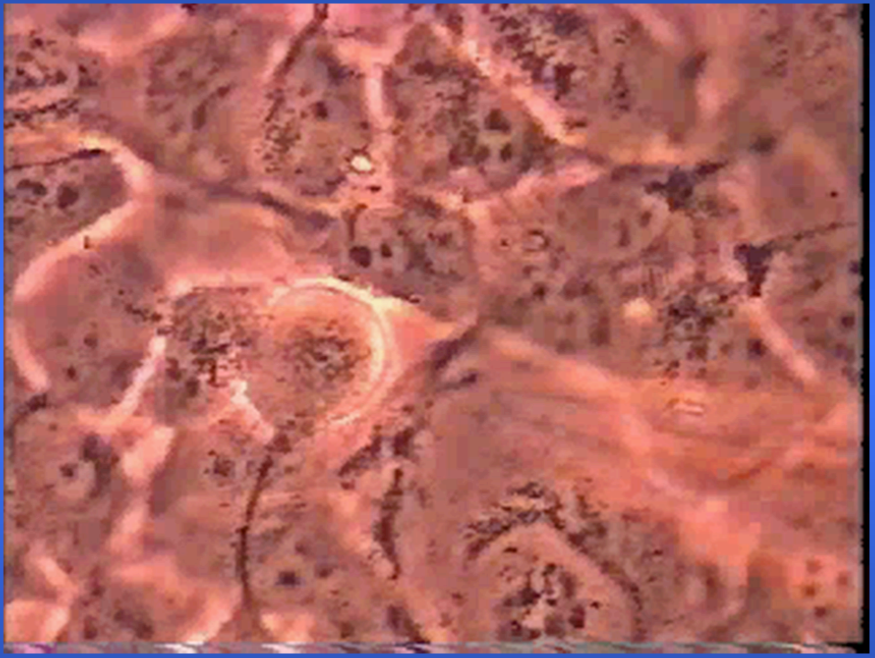


Link other filaments & membrane to the nucleus





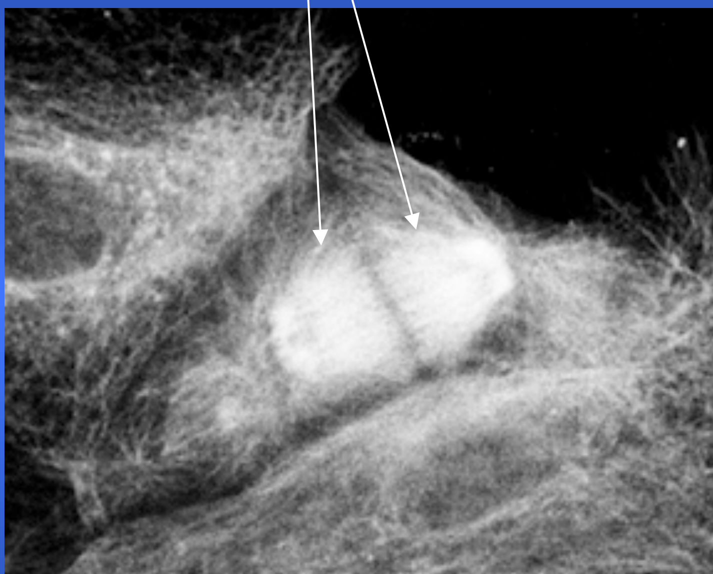
Mechanical Connectivity in the Human Genome

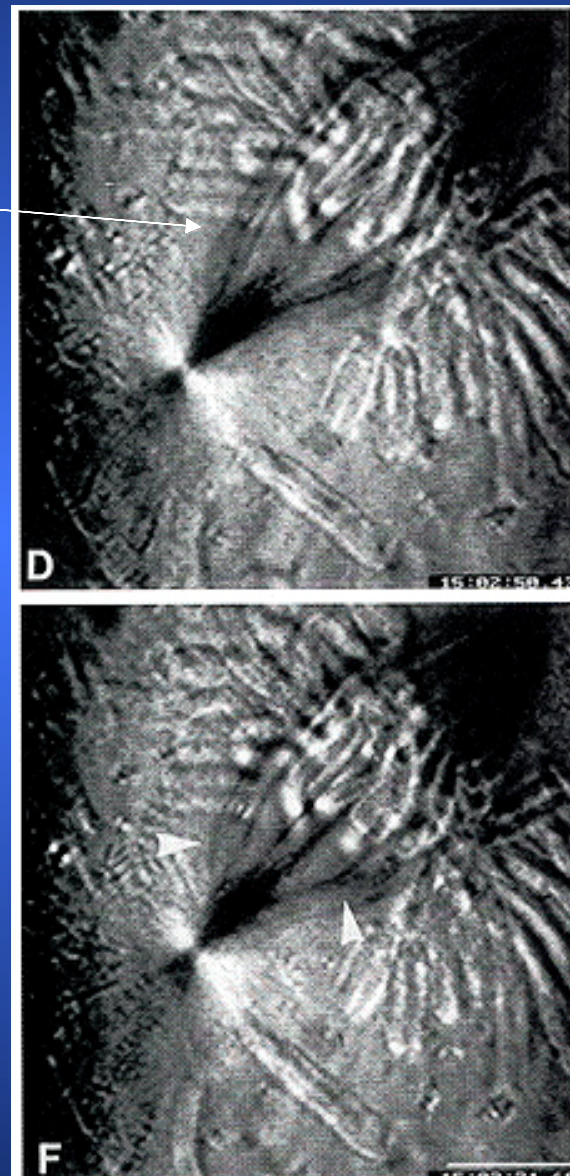


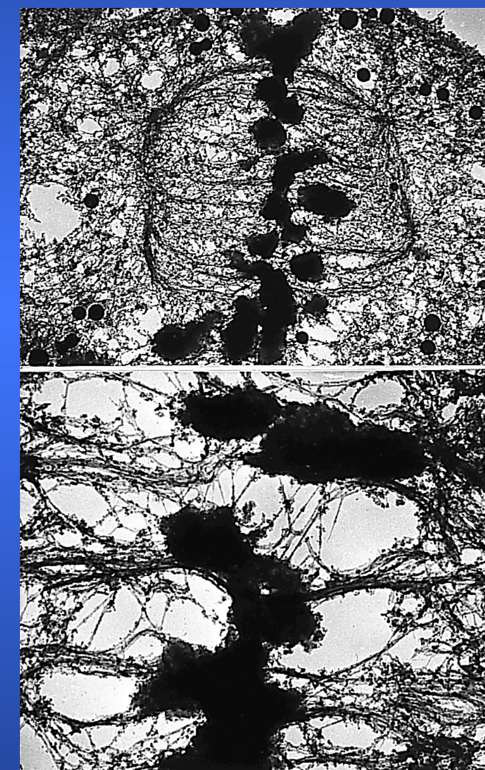
(Maniotis et al., *J. Cellul. Biochem.* 1997)
(Movie by A. Maniotis & J. Karavitis)

Mitotic Spindle as a Prestressed Tensegrity Structure

Spindle
Microtubules





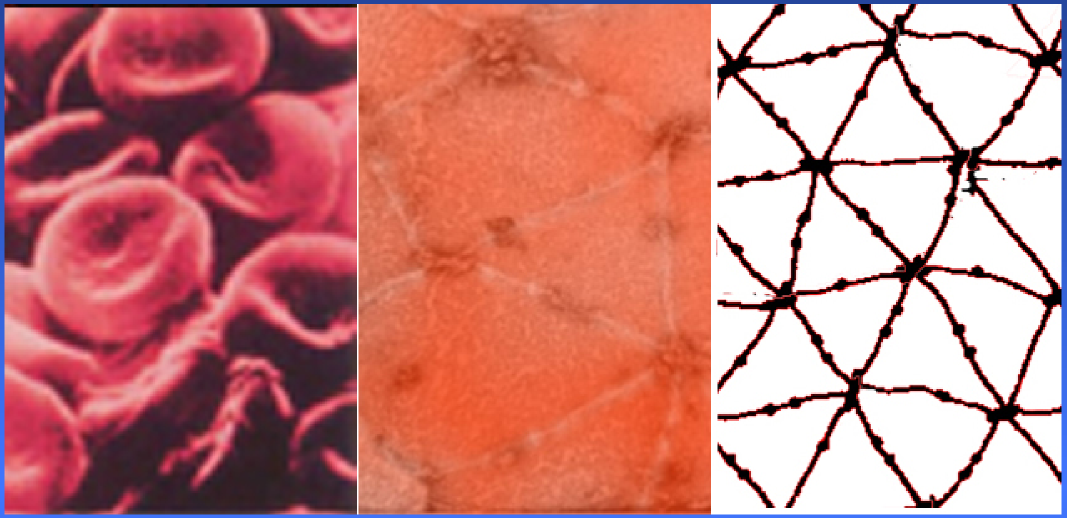


(Nickerson & Penman)

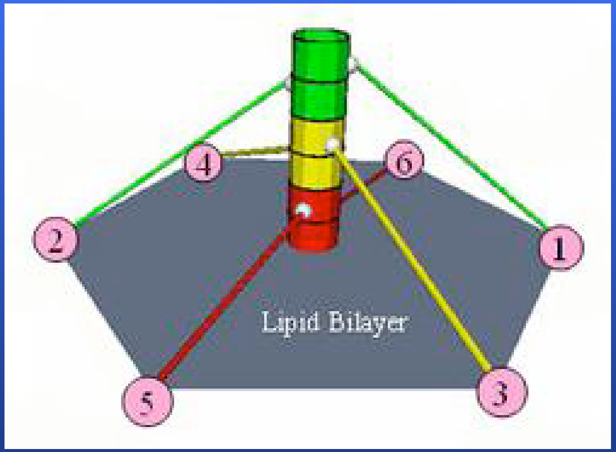
(Pickett-Heaps et al., *Cell Motil Cytosk* 1997)

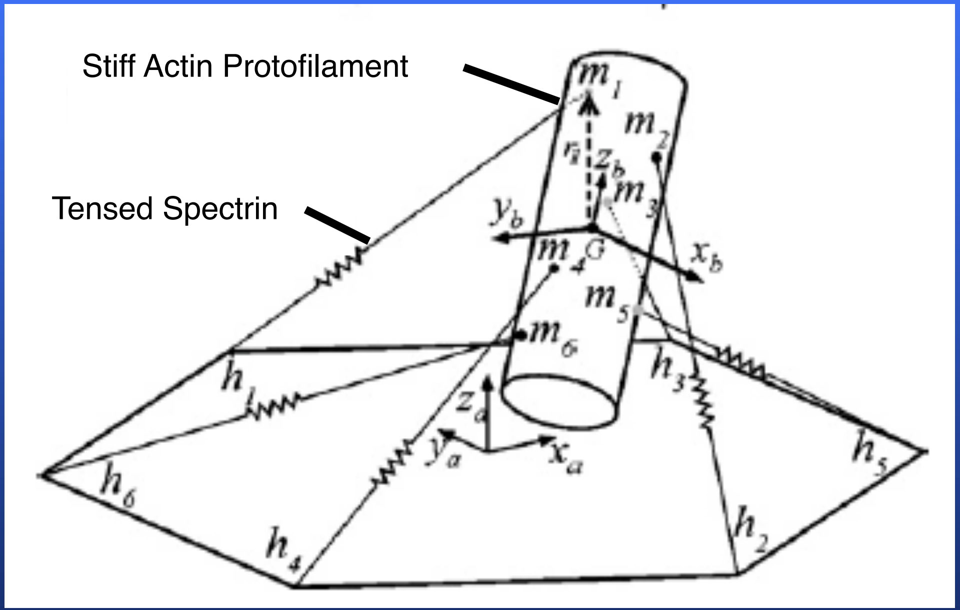
Cortical Membrane as a Prestressed Tensegrity

(Vera et al. *Annals Biomed. Engin.* 2005; Sung & Skelton, UCSD)



www.jacobsschool.ucsd.edu/news_events/releases/release.sfe?id=484

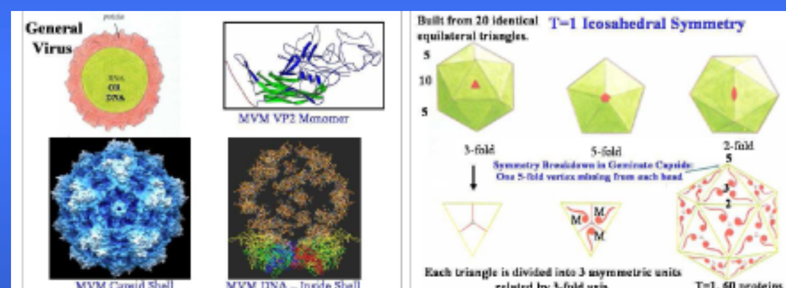




Viruses are Geodesic Tensegrities

(Klug and Caspar)

Local Compression
(buckling instabilities)
in a viral capsid
(David Nelson, Harvard U.)



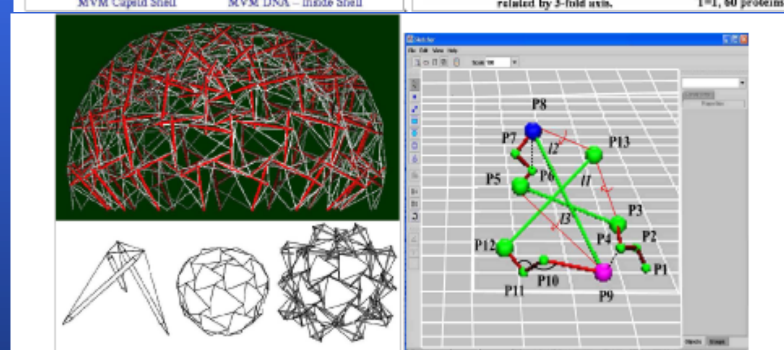
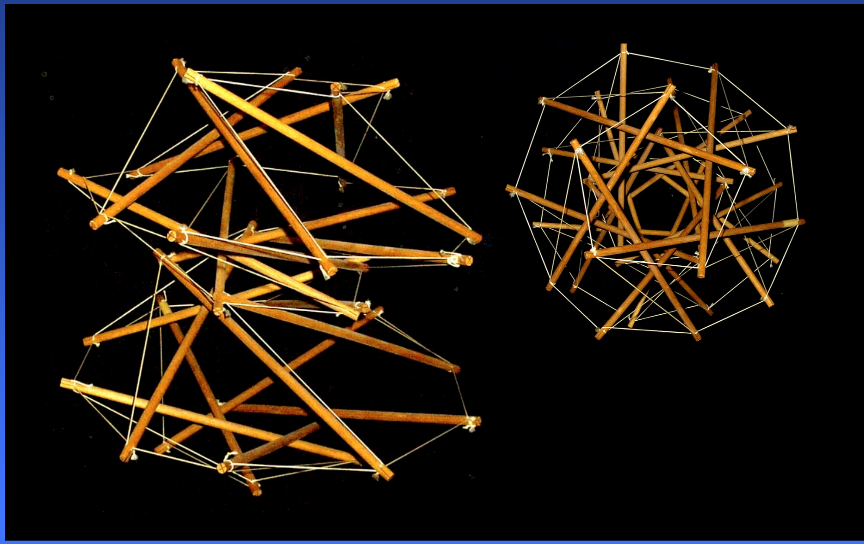


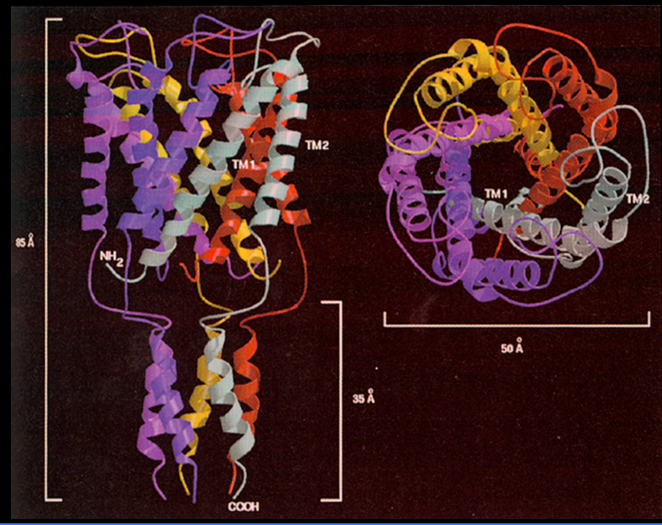
Figure 5: (Left) Tensegrity systems. (Right) Example monomer primitives and constraints. Balls (points) - atomic markers; Green line segments - variable length bonds; Arrows - torsion angles between green line segments (primary structure) Red - distances representing fixed length bonds (primary structure), Arcs – angles (primary structure), Dotted lines – distances (weak force) (using FRONTIER [107])

Tensegrity Modeling
(Sitharam and Agbandje-McKenna, *J Comput Biol*, 2006)

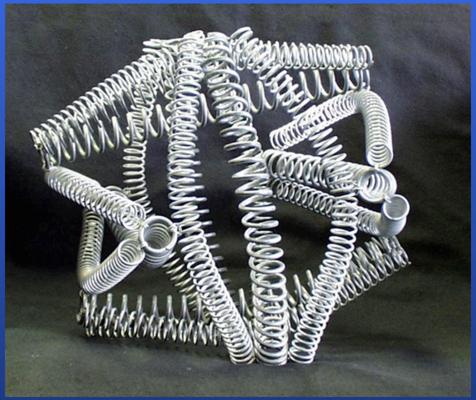
Molecules as Prestressed Tensegrity Structures



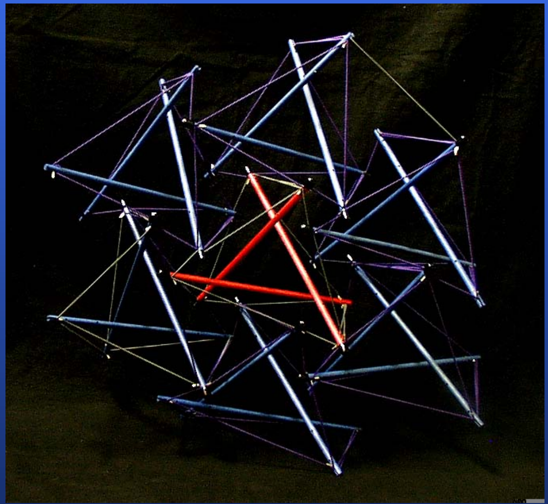
Tensegrity Stick-and-String Models



Stretch-Sensitive
Ion Channel

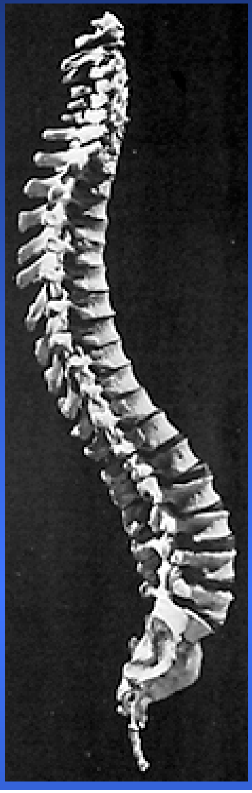


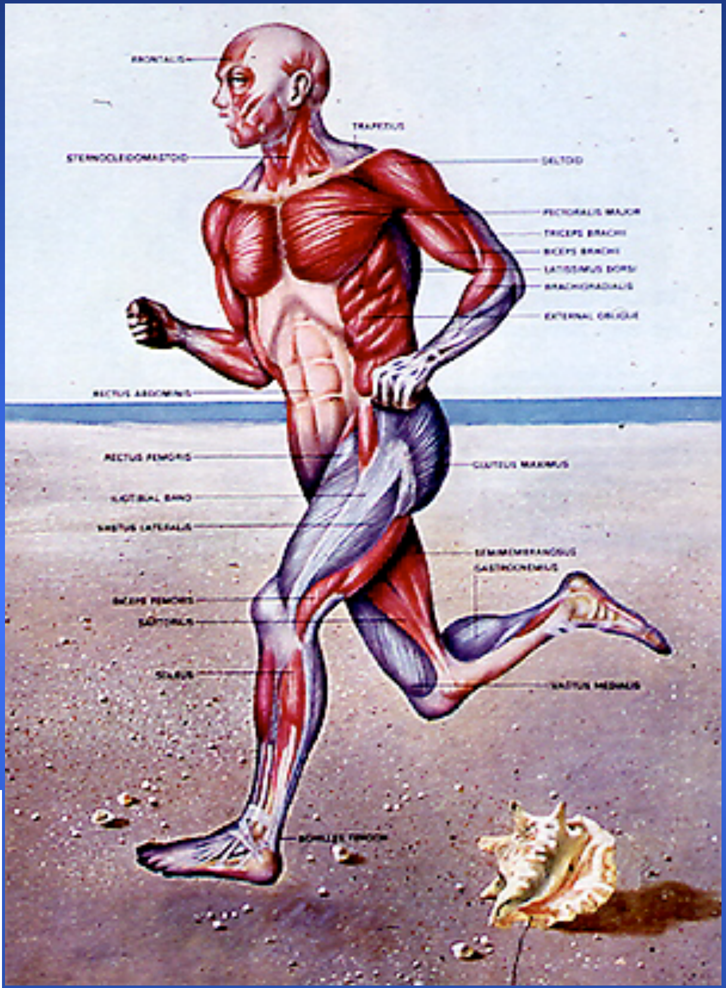
CLUSTERED
RECEPTORS?

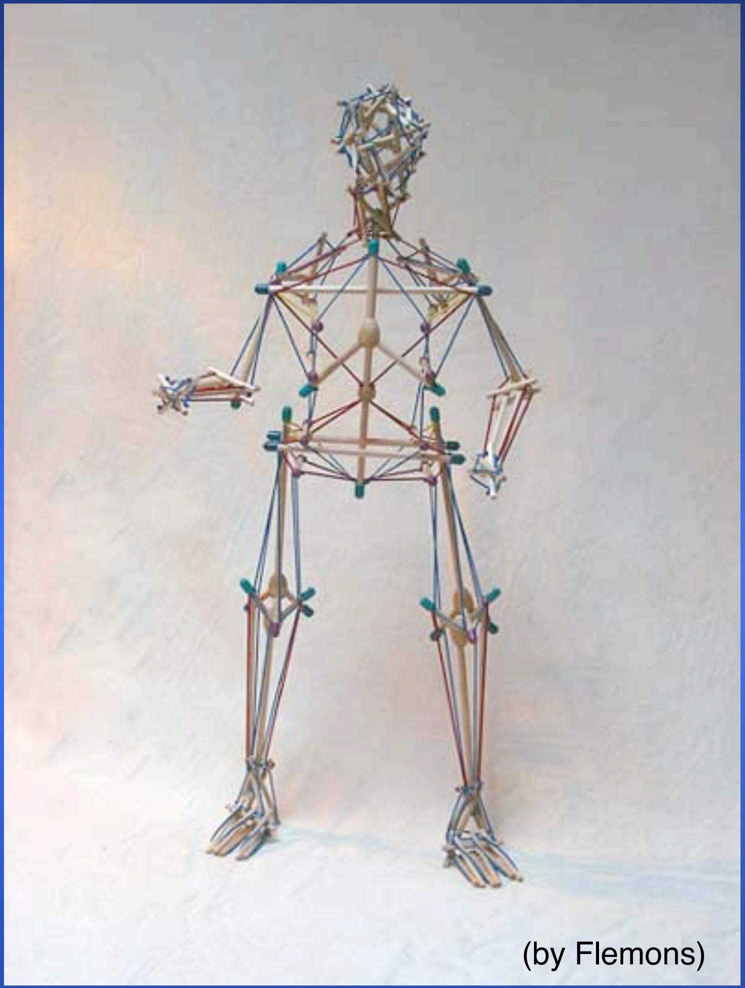


(Ingber, *Sci Am* 1998, *Bioessays* 2000, *J Cell Sci* 2003;
Zanotti and Guerra, *FEBS Let* 2003)

Tensegrity at the Organism Level







(by Flemons)

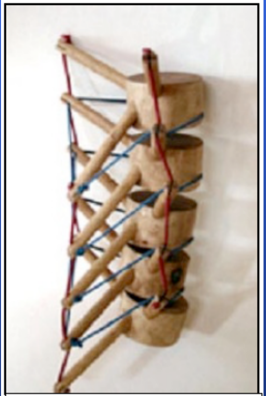
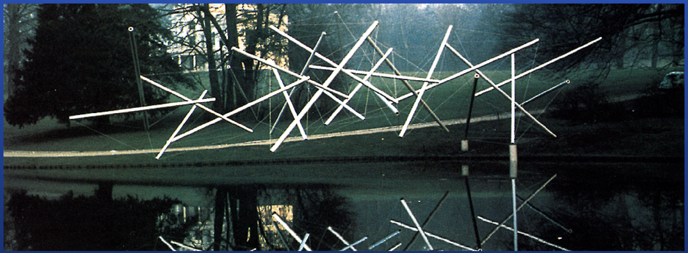


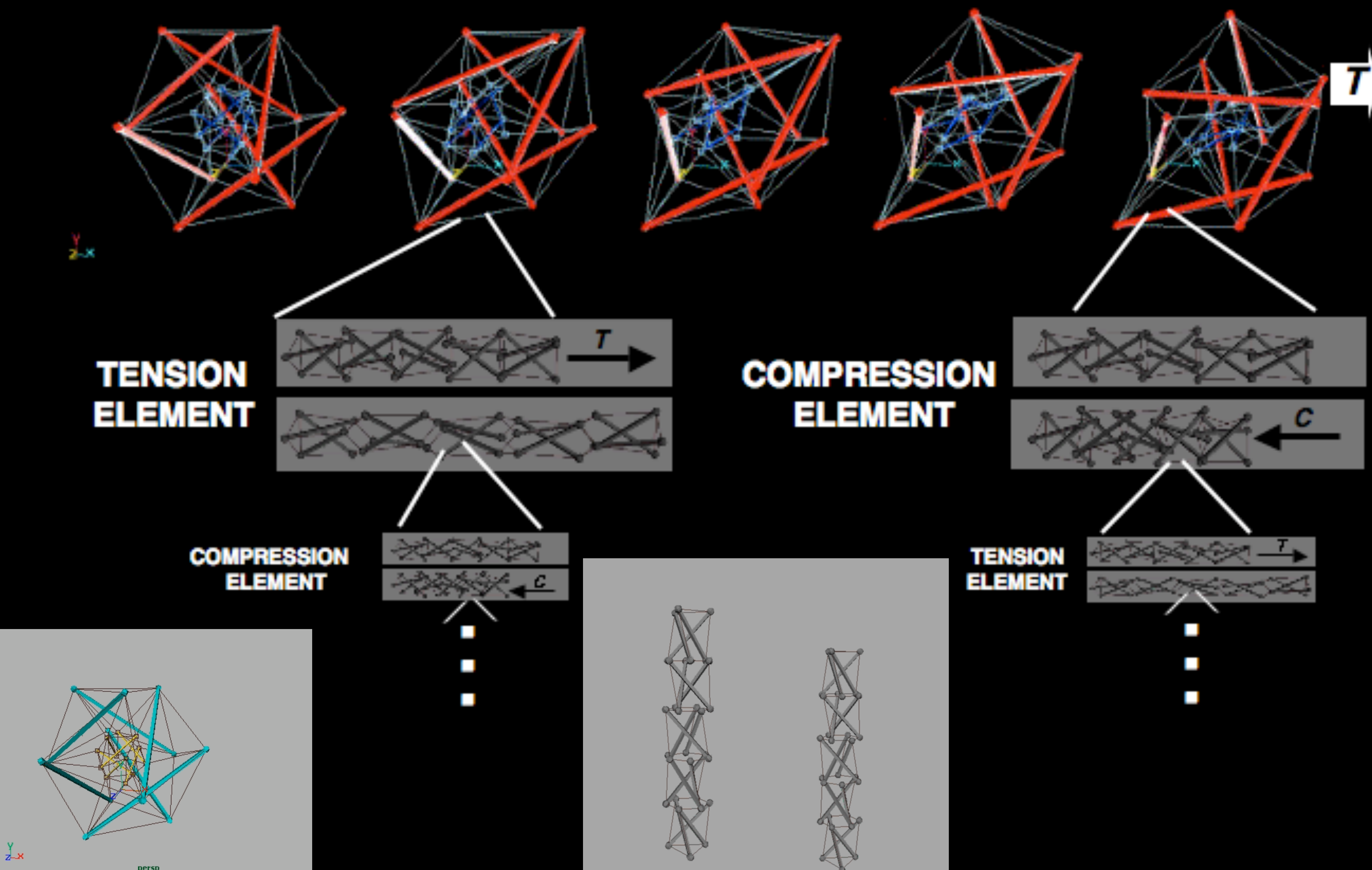
Fig. 3.16.
"Tensegrity Thoracic Vertebrae"
Illustration taken from Levin (2002)



(Ingber, Scientific American 1998)

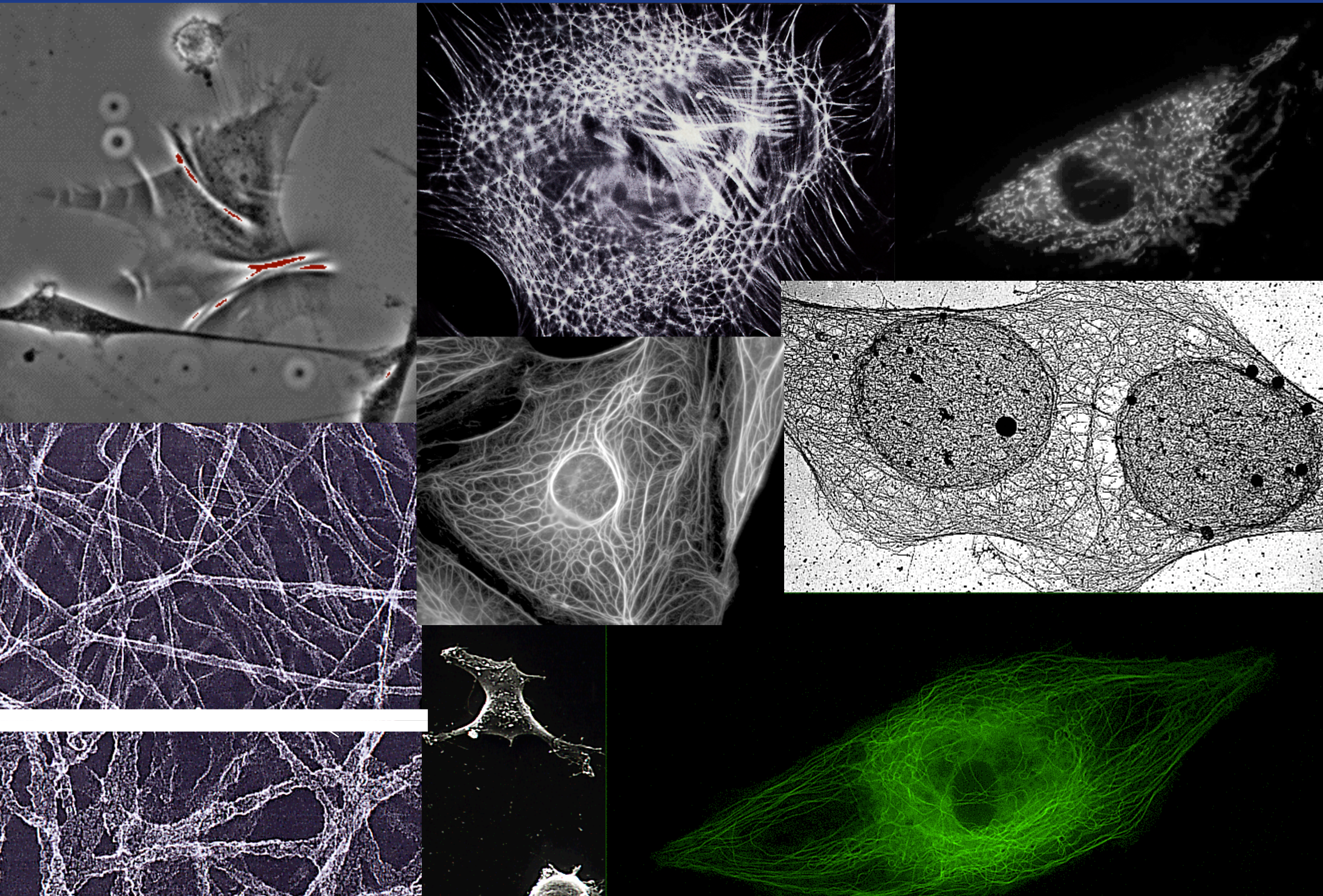
Tensegrity-Based Hierarchical Integration

(computer images by Eddy Xuan, U. Toronto)



(Ingber, *FASEB J* 2006)

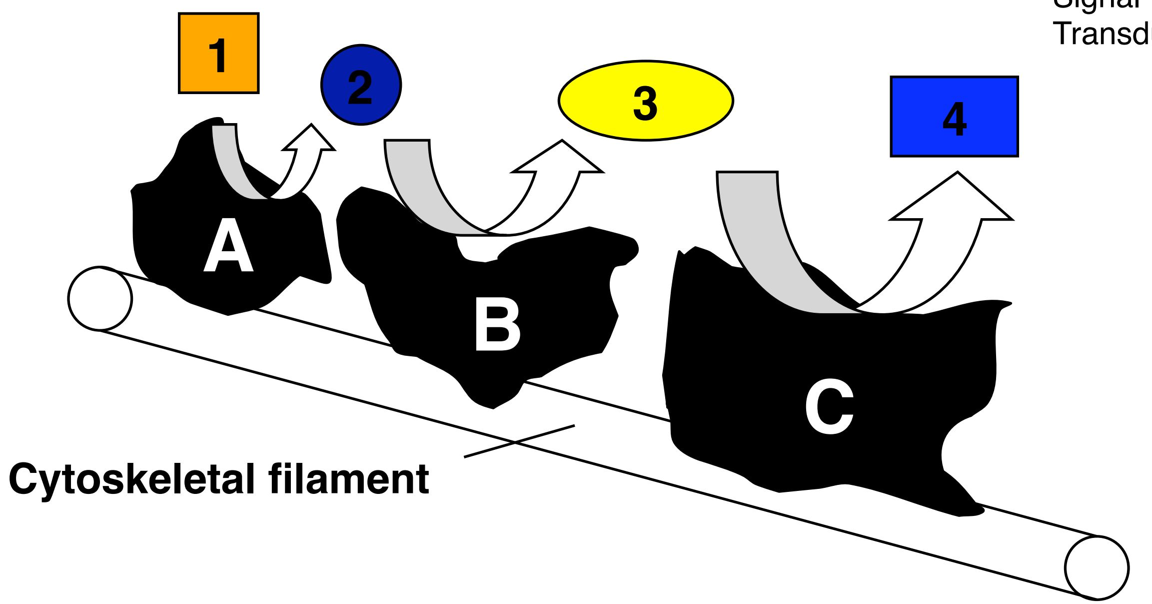
Cytoskeleton is More than a Mechanical Scaffold



Solid-State Biochemistry on Cytoskeletal Scaffolds
(Structure = Catalyst)

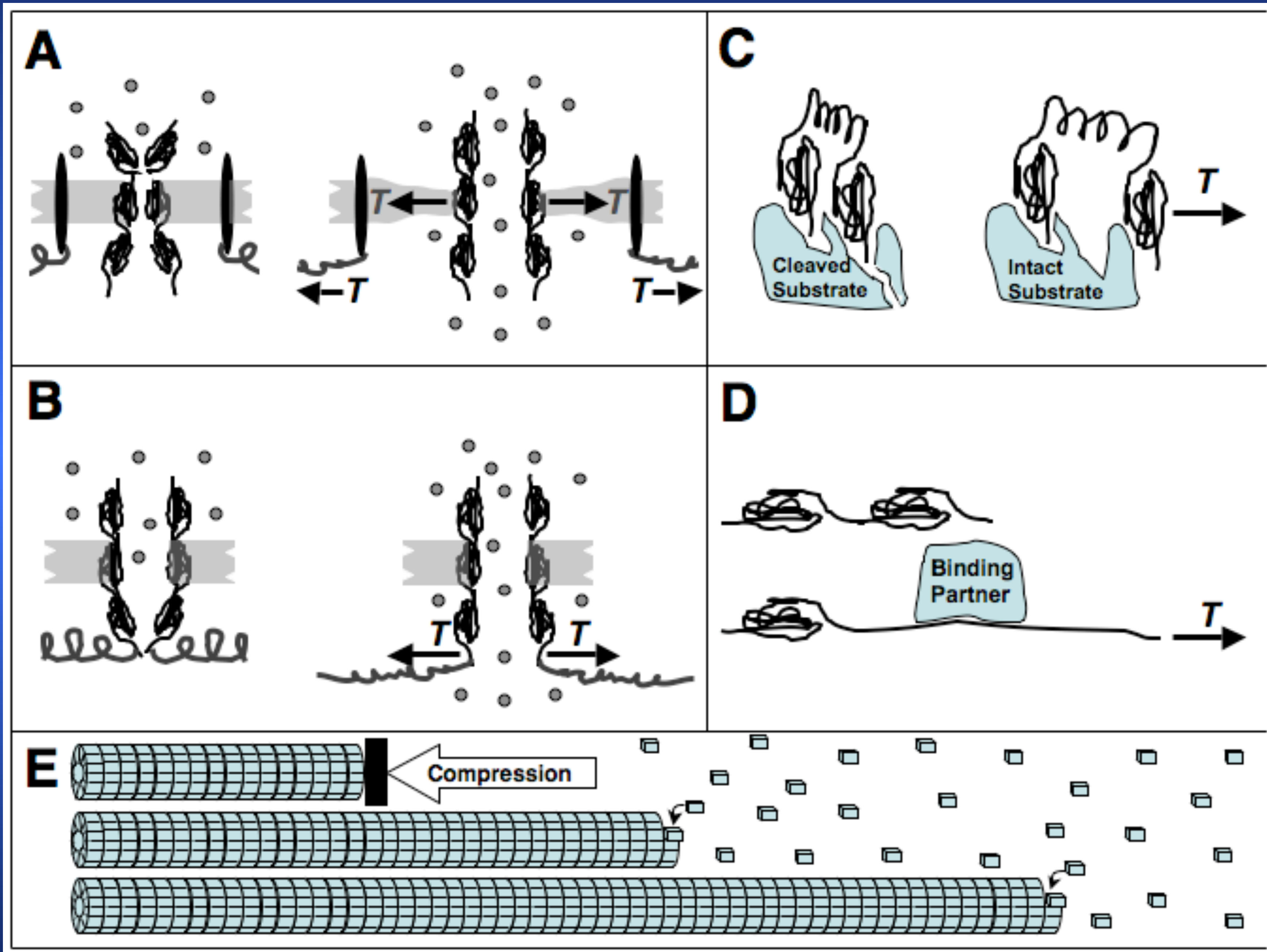
'Channeling' of Chemical Reactions:

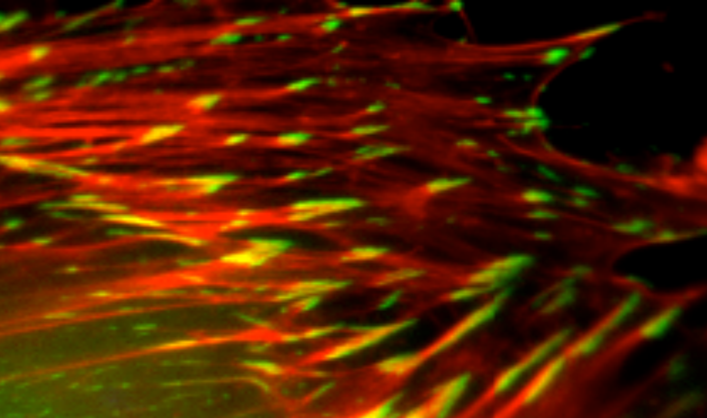
DNA replication
RNA Processing
Transcription
Translation
Glycolysis
Signal
Transduction



(Ingber, *Cell* 1993)

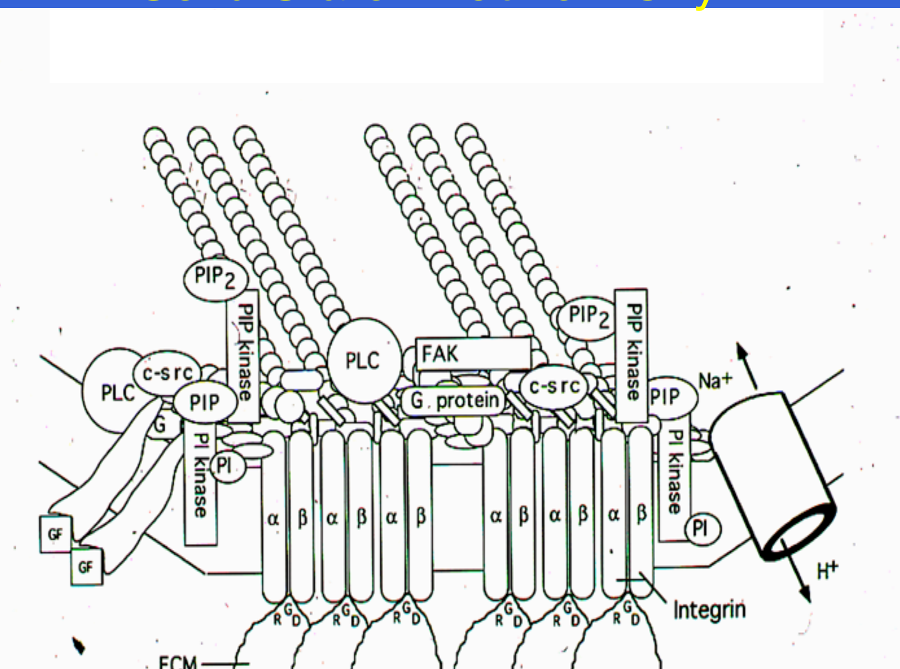
Mechano-Chemical Conversion at the Molecular Level





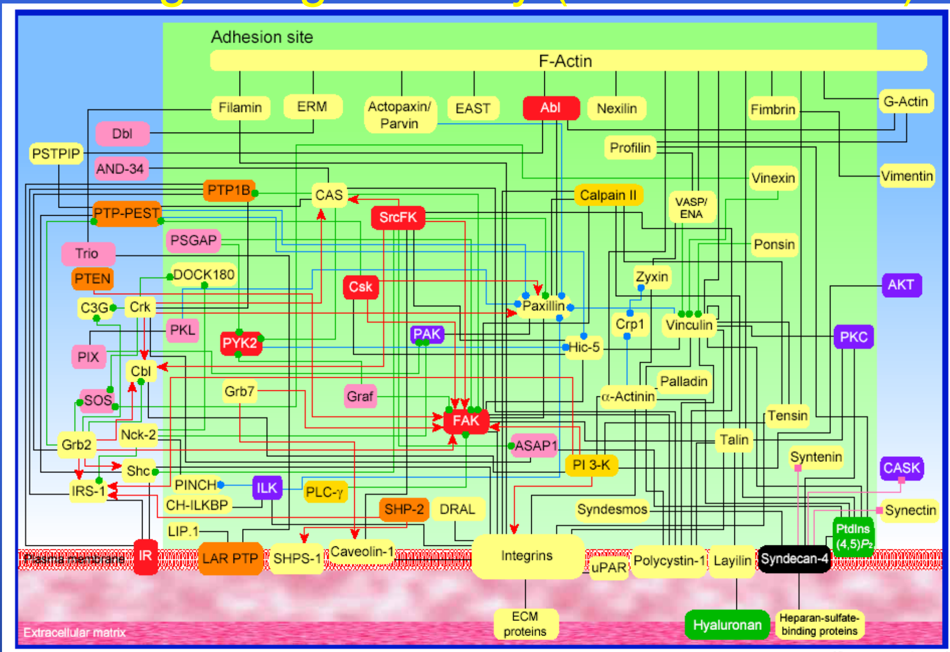
'Solid-State" Signal Integration in the Focal Adhesion (Integrins = TENT PEGS)

'Solid State' Biochemistry



(Ingber Curr Opin Cell Bio 1991; Miyamoto et al., *Science & JCB* 1995; Plopper et al., *Mol Biol Cell* 1995)

Signaling Circuitry (> 50 elements)

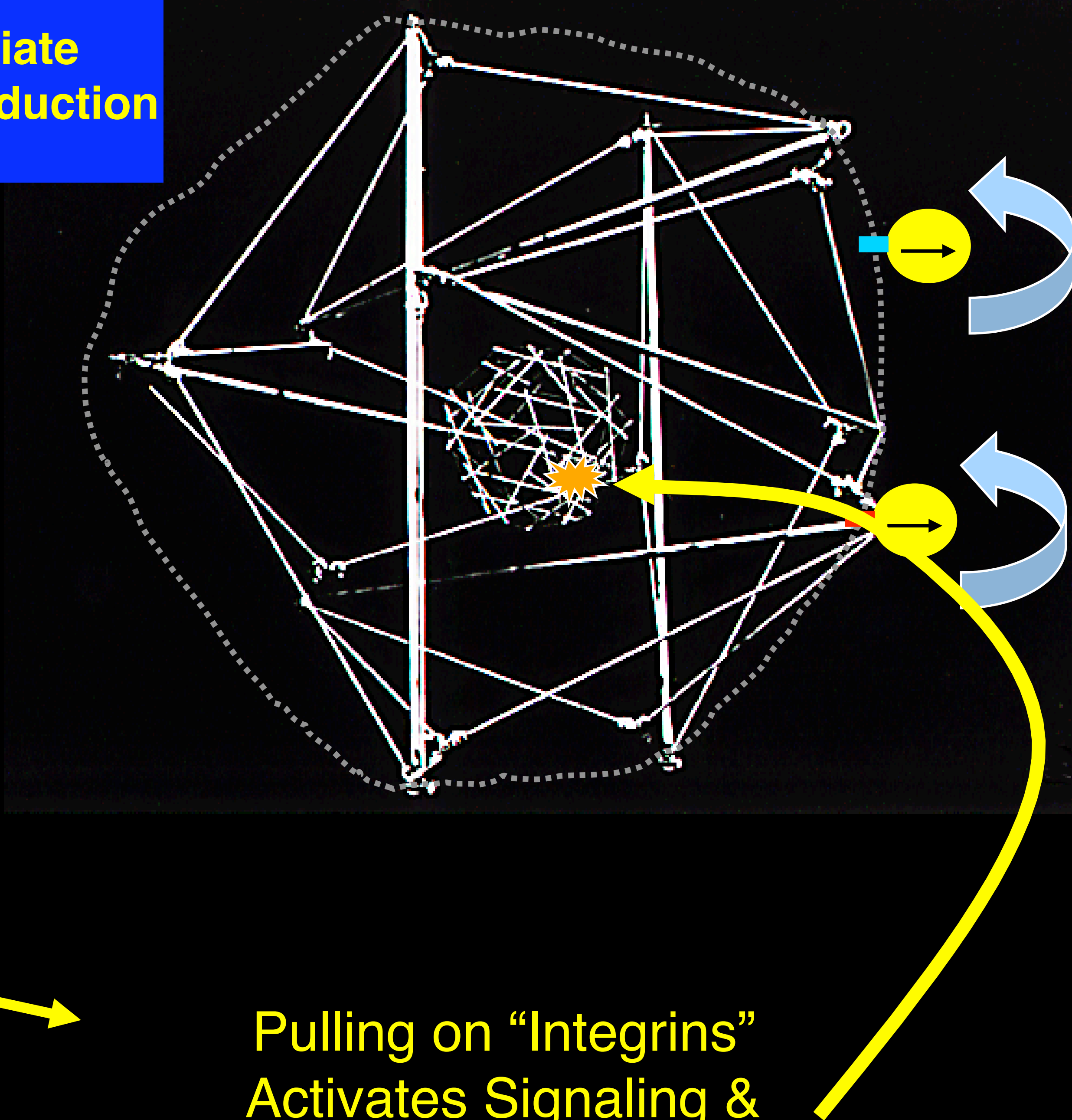


(See poster insert)

(Zamir and Geiger, *J Cell Sci.* 2001)

Signaling molecules are immobilized on the insoluble scaffolds in the focal adhesion

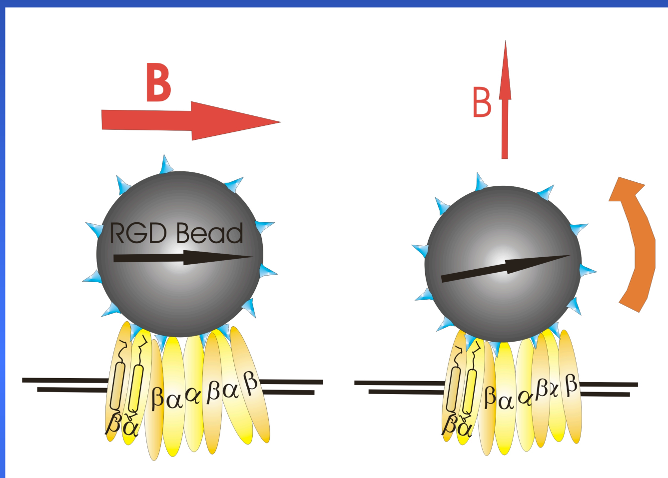
Surface Integrins Mediate Mechano-Chemical Transduction



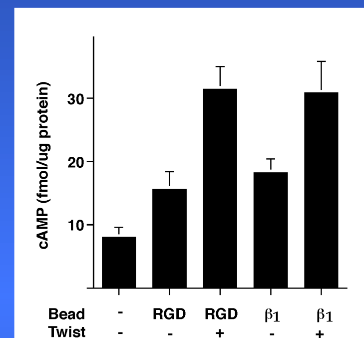
Pulling on “Integrins” Activates Signaling & Gene Transcription

Mechanical Control of Gene Transcription

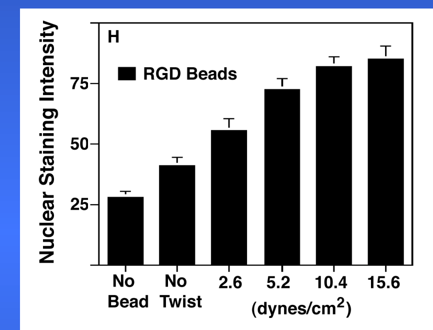
Activation of G_α proteins and cAMP Signaling by Mechanical Force Transmitted Across Integrin Receptors



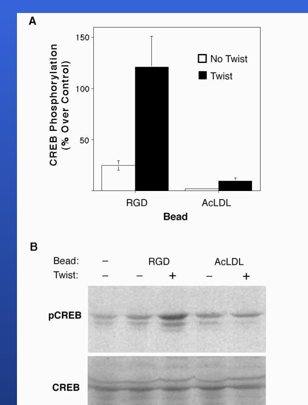
+ TWIST



cAMP Levels



PKA Translocation



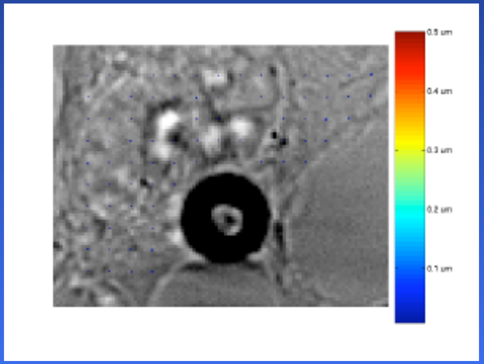
CREB Activation

Gene Transcription

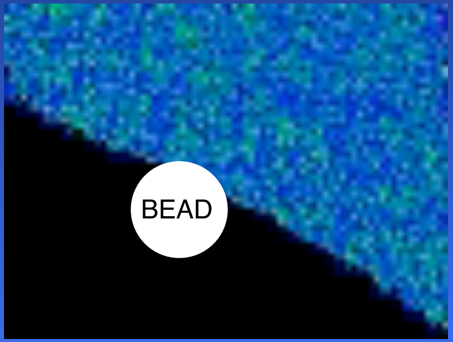
(Meyer et al., *Nature Cell Biol.* 2000; Alenghat et al., *J. Cell Biochem.* 2009)

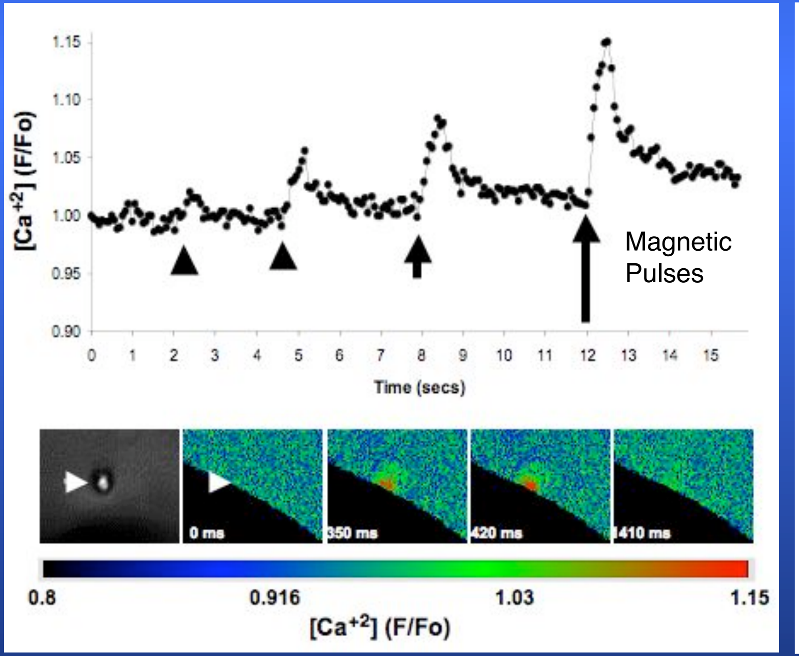
Pulling on Integrins Specifically Activates Ca^{+2} Influx
(Time scale < 10 milliseconds)

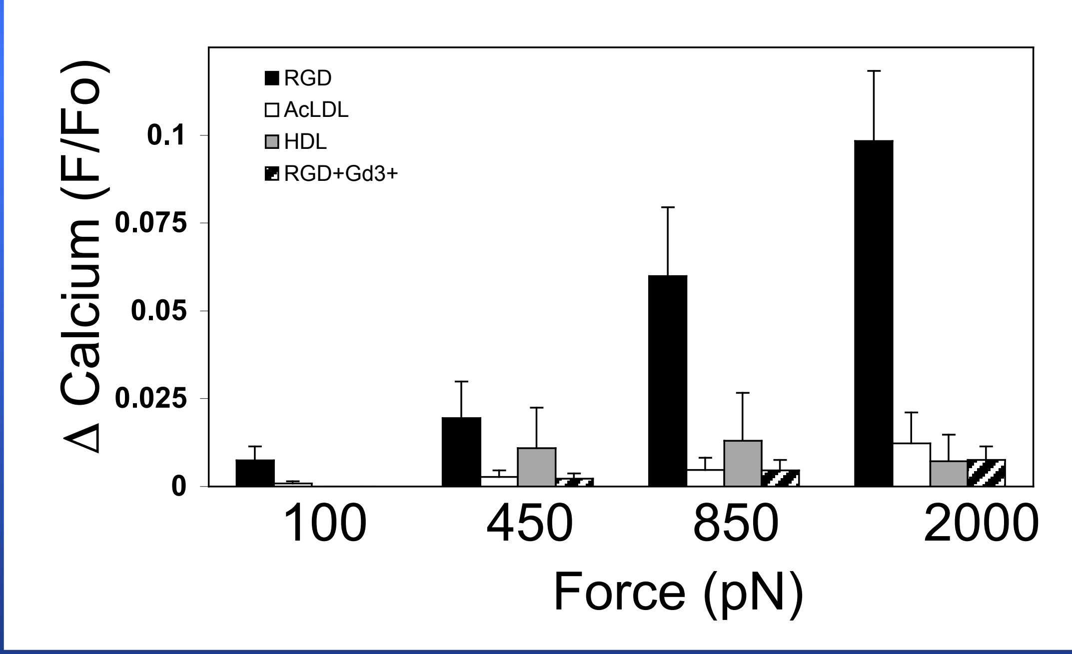
Cytoskeletal Strain



Calcium (FLUO4)





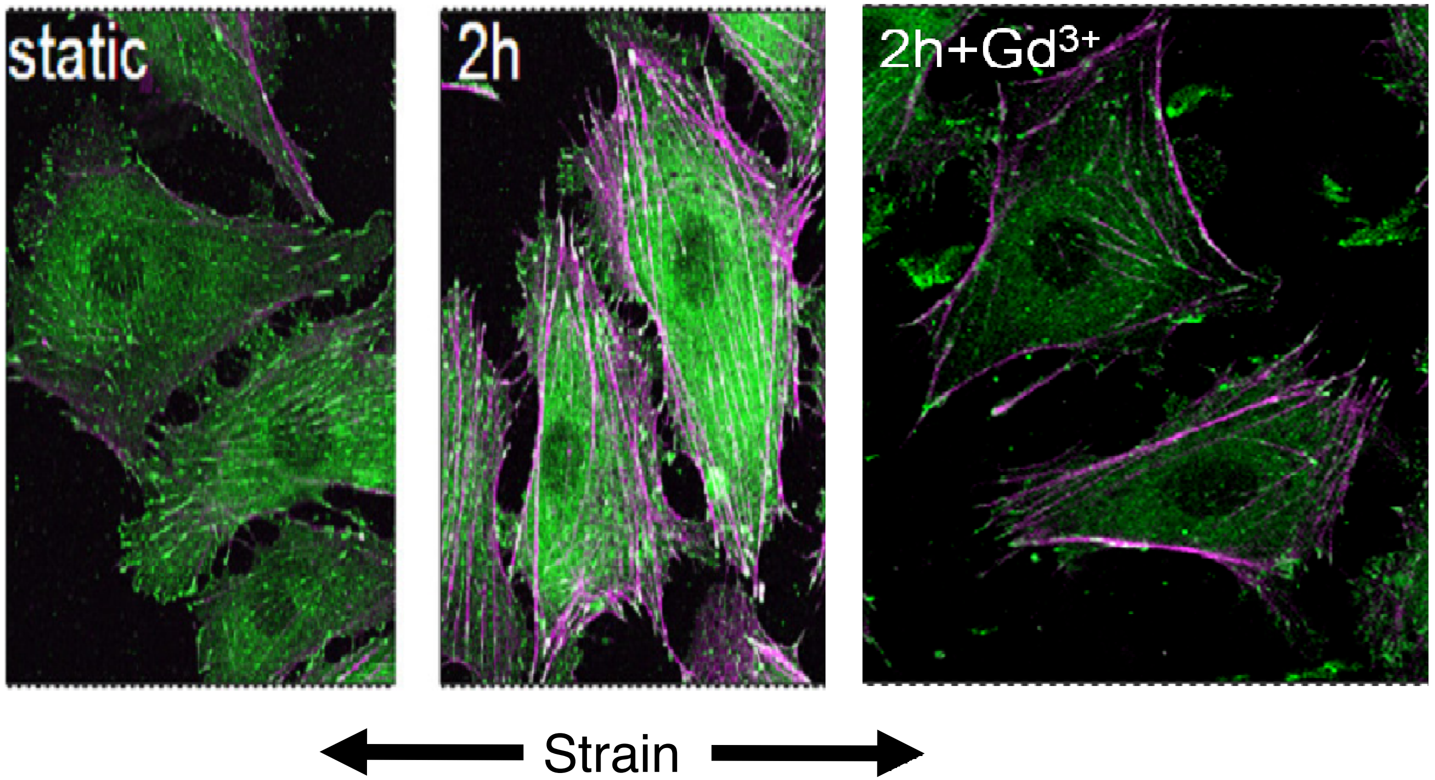


Force Dependence

Force & Integrin Dependence

(Matthews et al., in review)

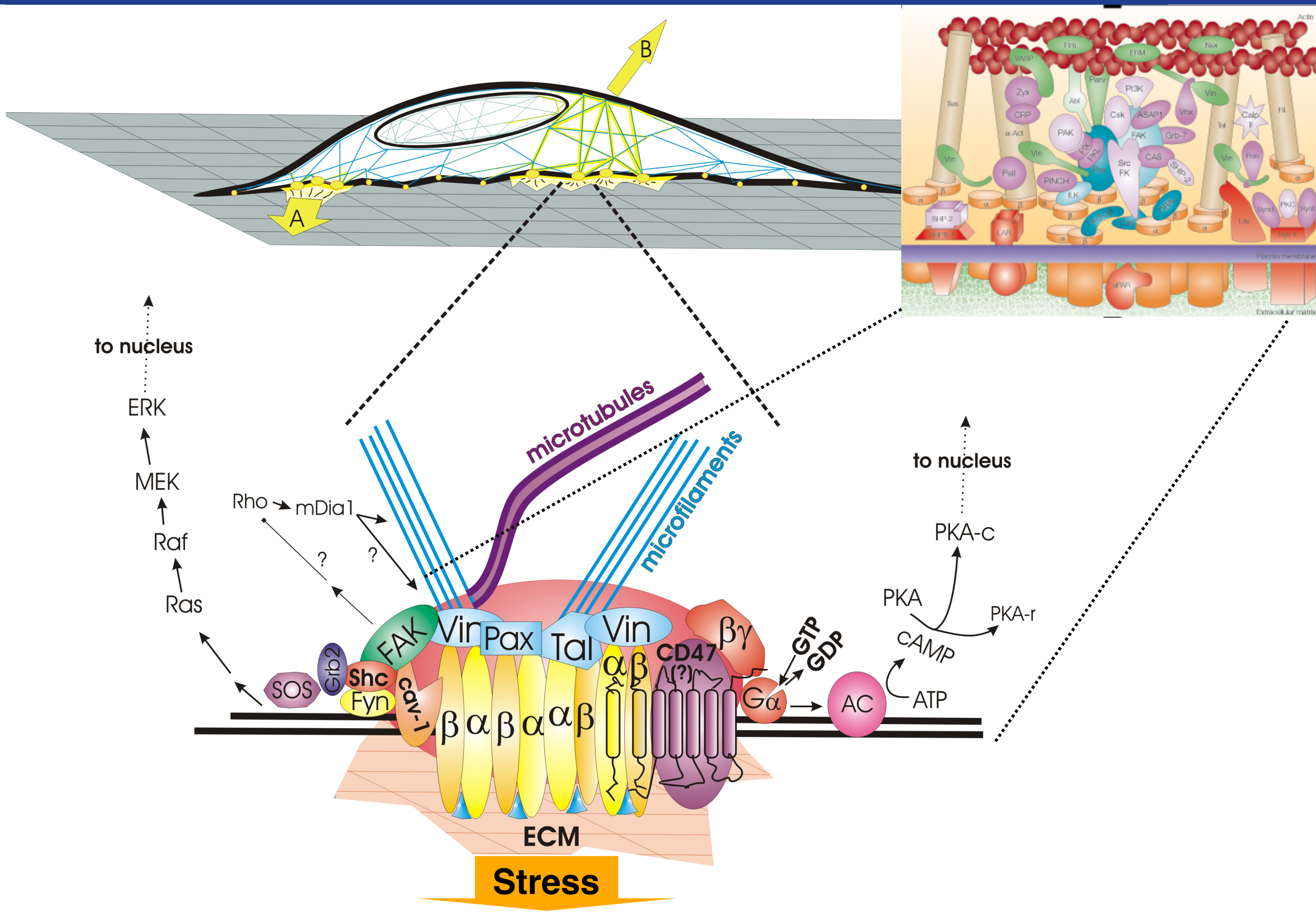
Strain-Induced Realignment of Endothelium is mediated by Mechanosensitive TRPV4 Channels and Rho



Force on Integrin → SA Channel → Rho → FA Remodeling

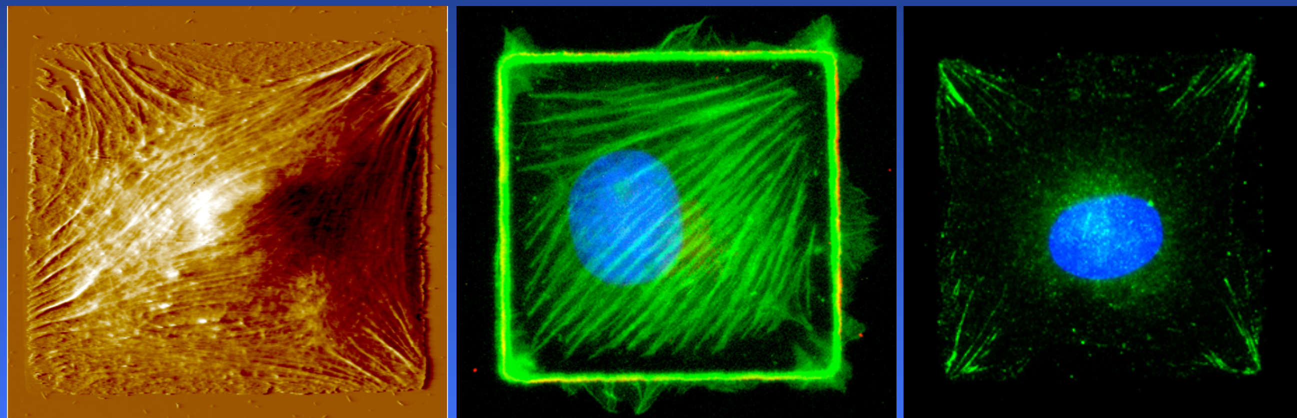
(Thodeti et al., *Circ. Res.* 2009)

Focal Adhesion is a Nanoscale Mechanochemical Machine



Revisiting How Cells Move

Cell Distortion Redirects Focal Adhesion Assembly

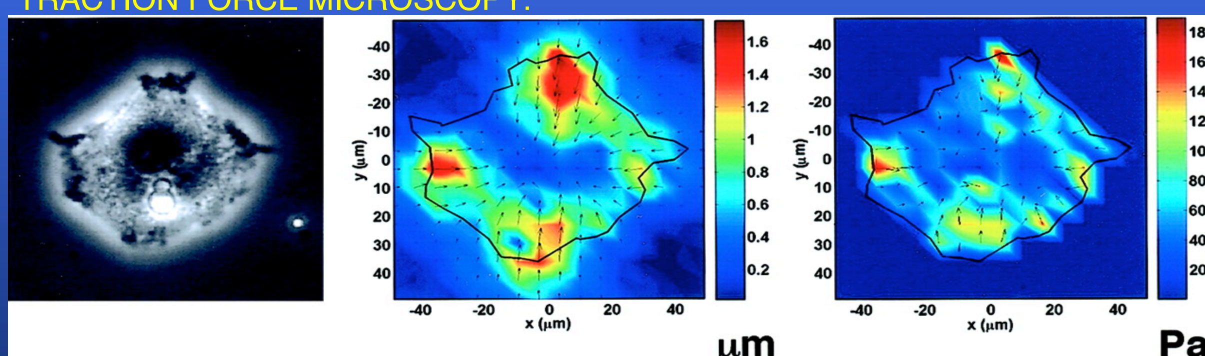


Actin Stress Fibers
(AFM) (F-Actin)

Focal Adhesions
(Vinculin)

Guided by Localized Tension Application in Cell Corners

TRACTION FORCE MICROSCOPY:



Cell Morphology Strain Map Stress Map

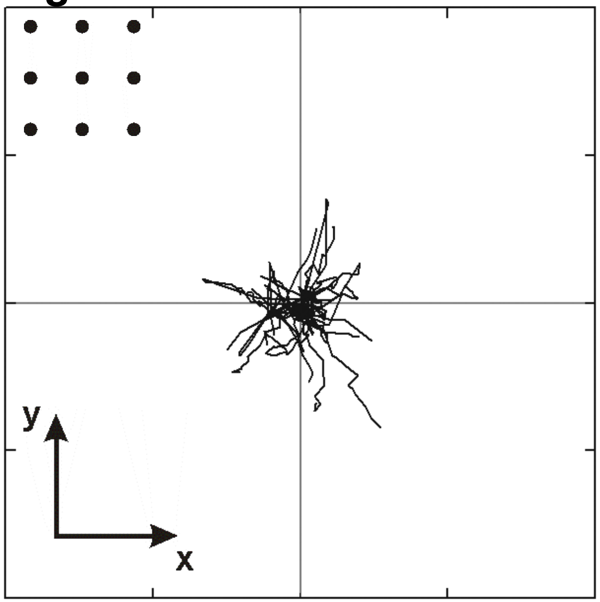
(Parker et al. *FASEB J* 2002; Wang et al., *Cell Cytosk. Motil.* 2002; Brock et al. Langmuir 2003)

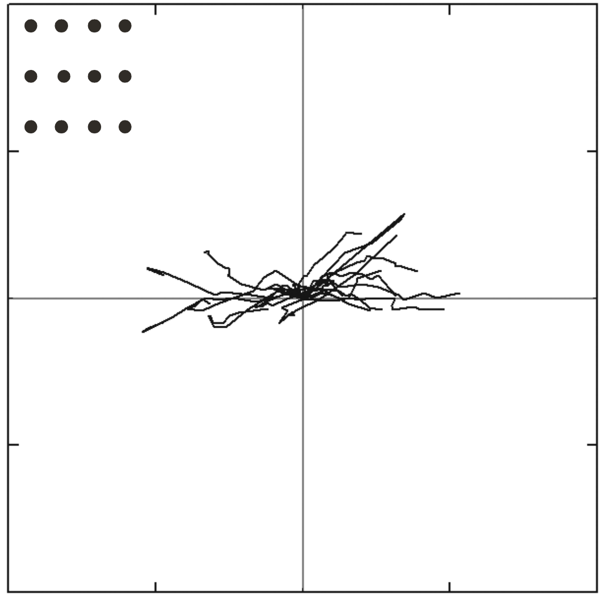
Physical ECM Pattern Governs Directional *Motility*

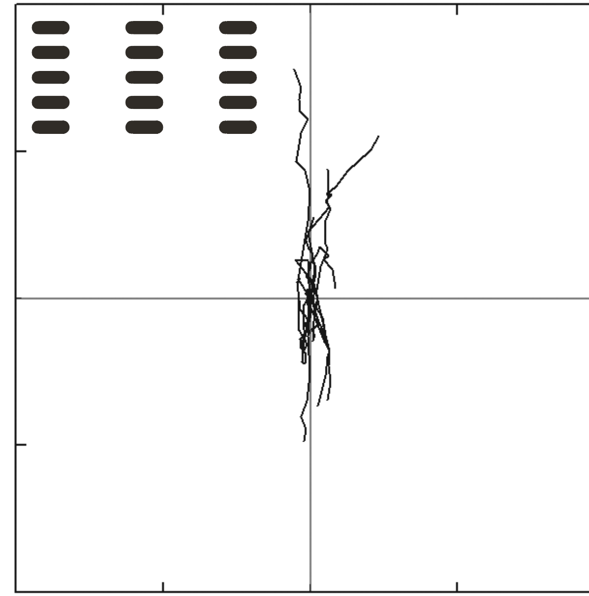
+ PDGF (NO CHEMICAL GRADIENT!)

(Xia et al., *FASEB J* 2008)

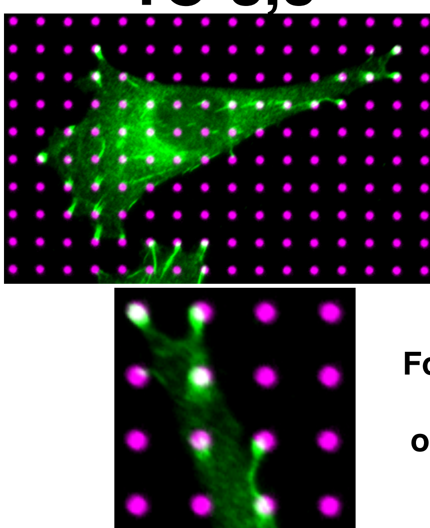
Migration Paths:



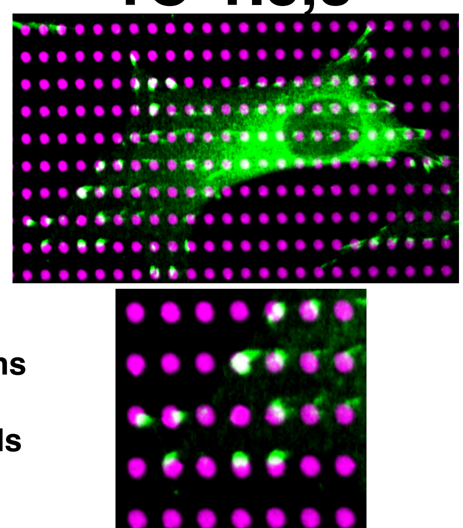




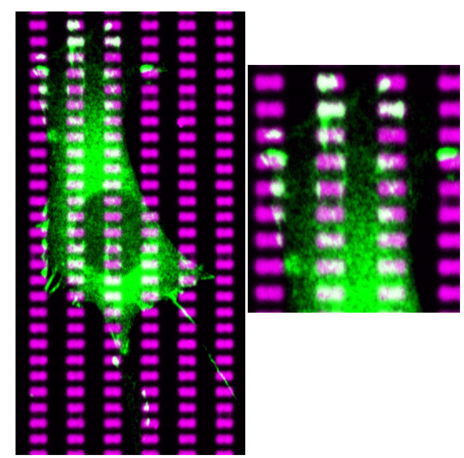
1C-3,3



1C-1.5,3



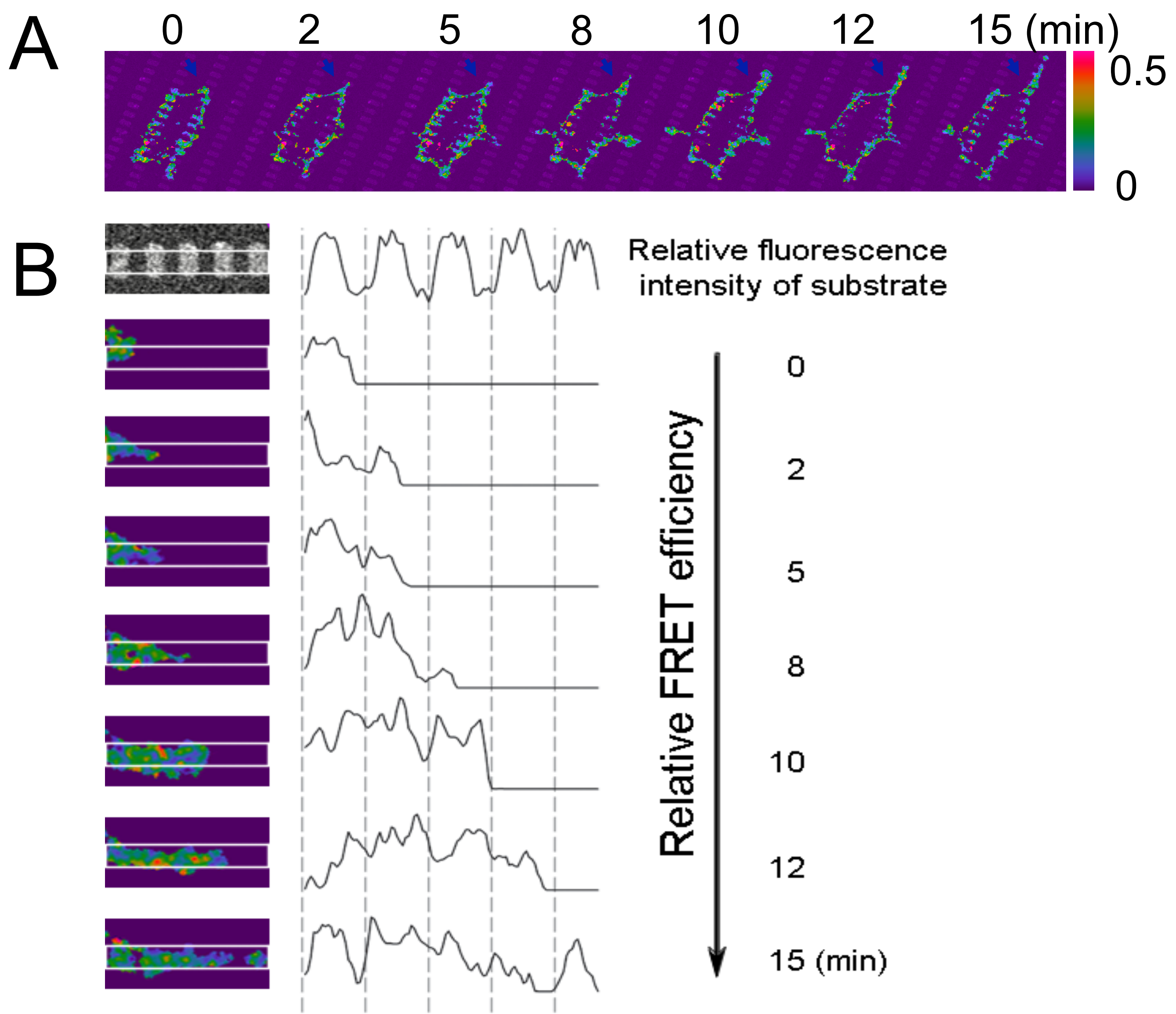
3L-4.5,1



Focal adhesions only form on ECM islands

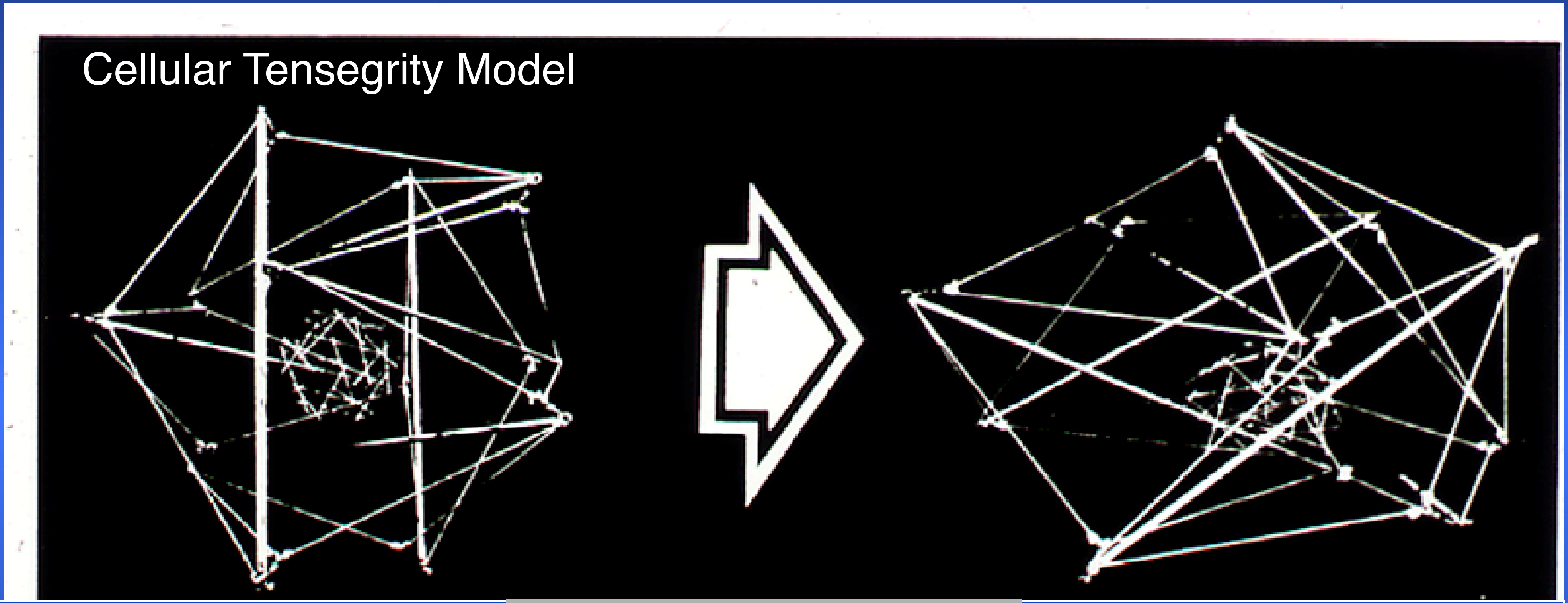
Real-Time Visualization of Rac Activation *in* Focal Adhesions

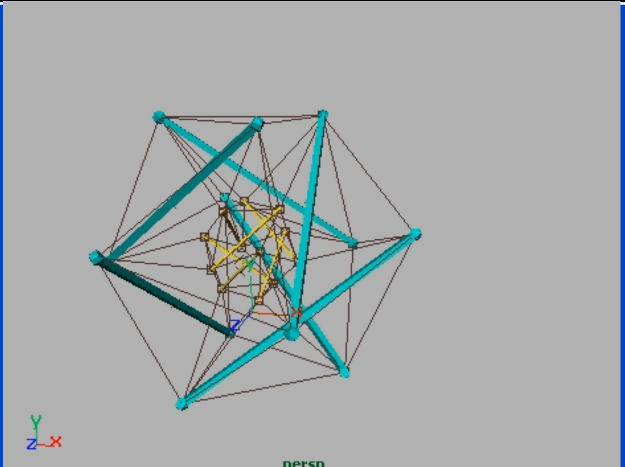
(using Rac-FRET)



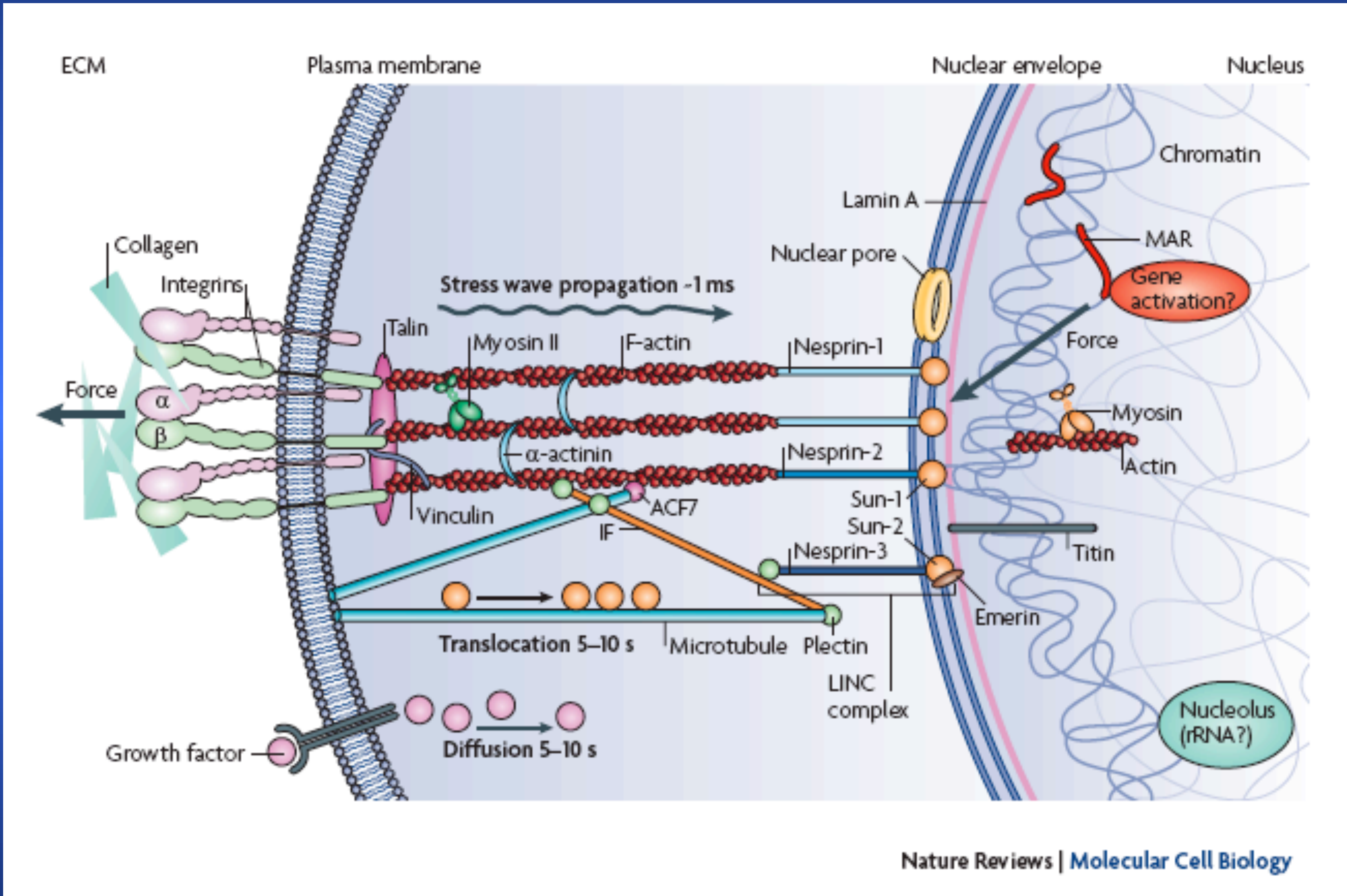
Long Distance Force Transfer Through the Cytoskeleton

(“Action at a Distance”)





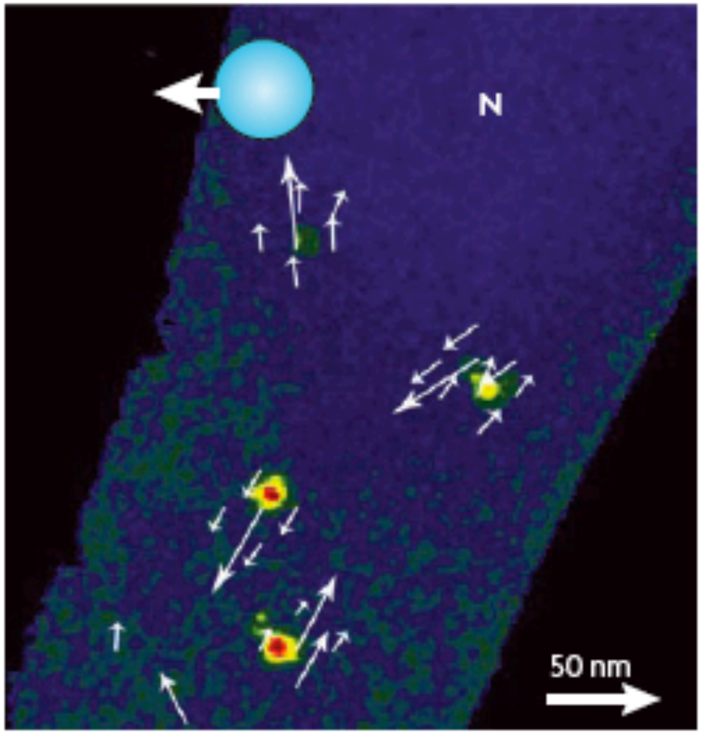
Molecular Hard-Wiring Between Integrins and Nuclei



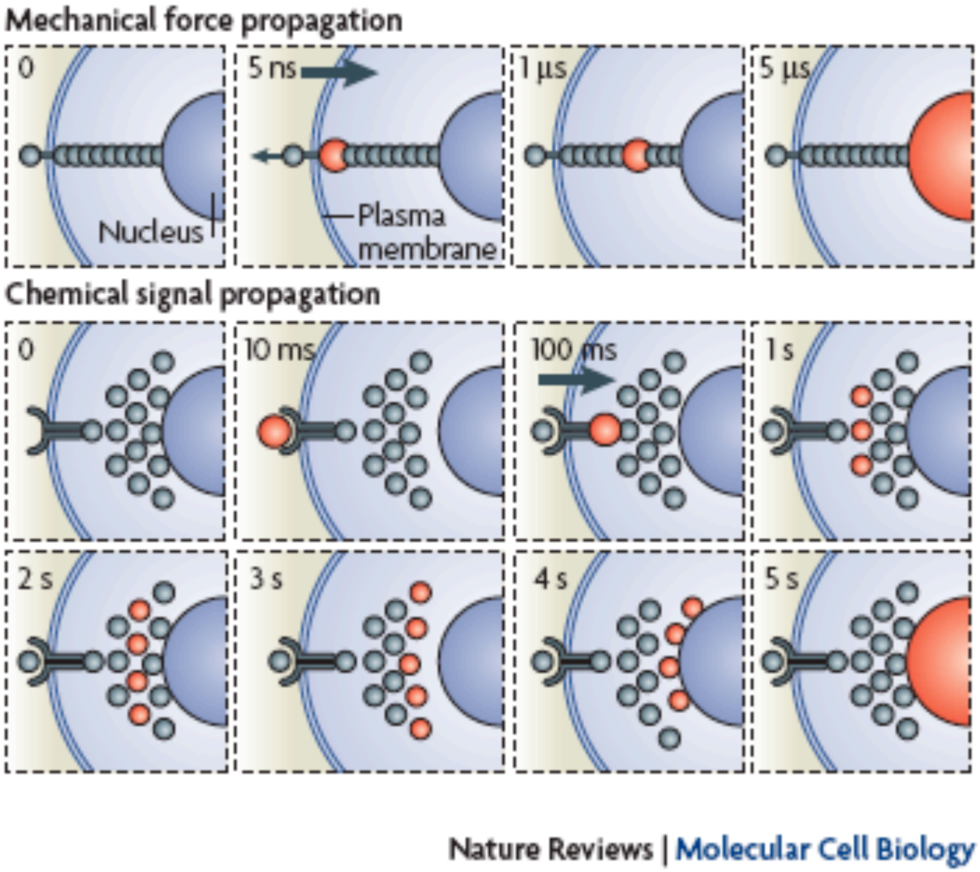
(Wang et al., *Nat. Rev. Mol. Cell Biol.* 2009)

Mechanical Signaling is More Rapid than Chemical Signaling
[work of Ning Wang (UIUC)]

Mechanical Activation of Src

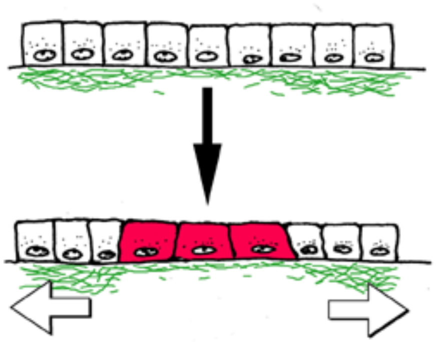


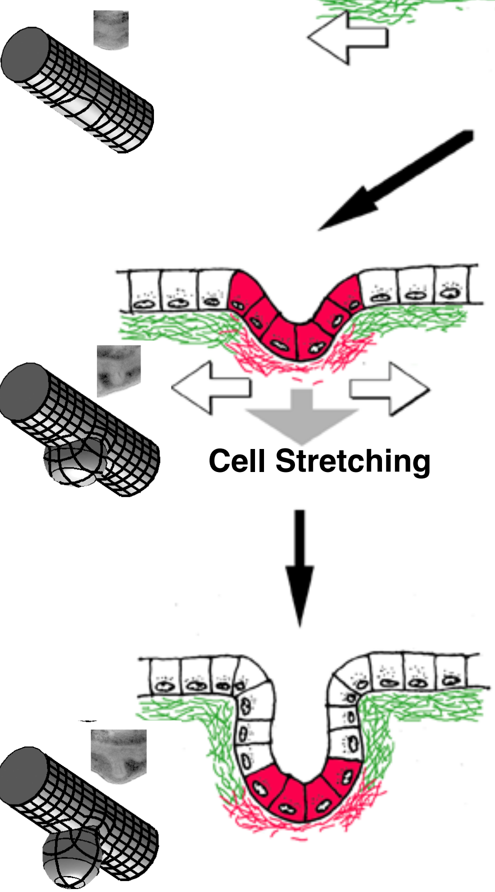
(Na et al., *PNAS* 2008)

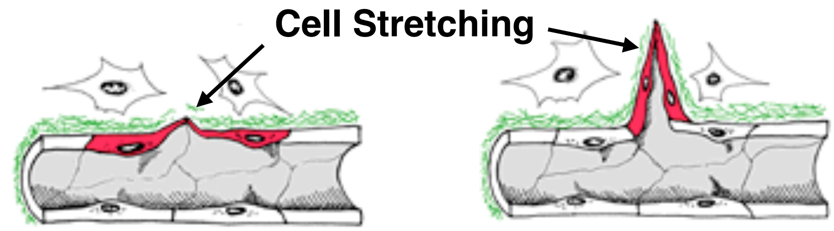


(Wang et al., *Nat. Rev. Mol. Cell Biol.* 2009)

Micromechanical Control of Morphogenesis







Underlying Hypothesis:

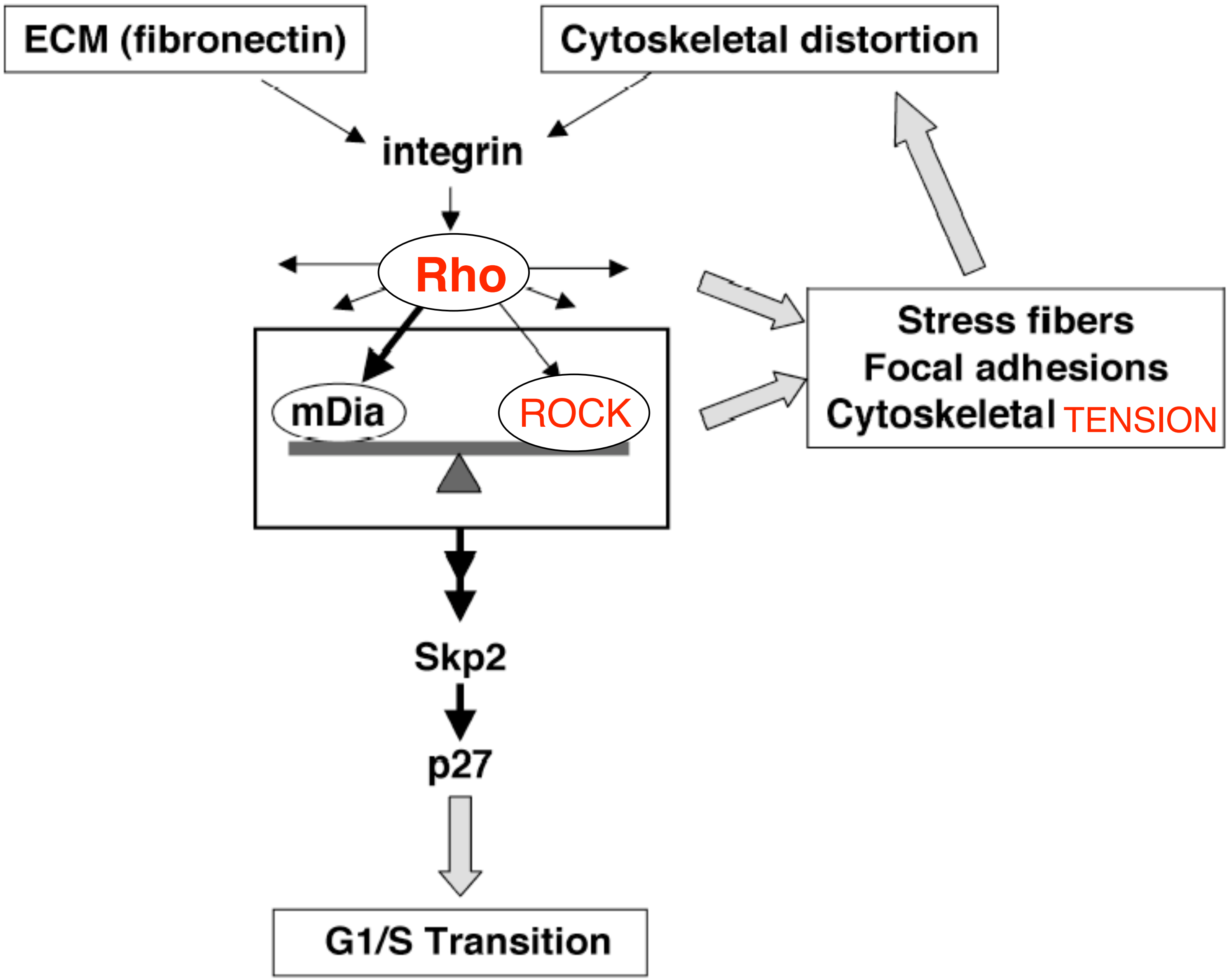
- **ECM remodeling changes LOCAL MECHANICS**
- **Increasing ECM flexibility promotes cell stretching**
- **Tension on Adhesion Receptors & distortion of the cytoskeleton alters cellular biochemistry**

↓

Localized Growth & Motility

(Ingber et al., *PNAS* 78:3901-5, 1981; Ingber & Jamieson, In: *Gene Expression During Normal & Malig. Differ.* ,1985; Huang and Ingber, *Nature Cell Biol.* ,1999)

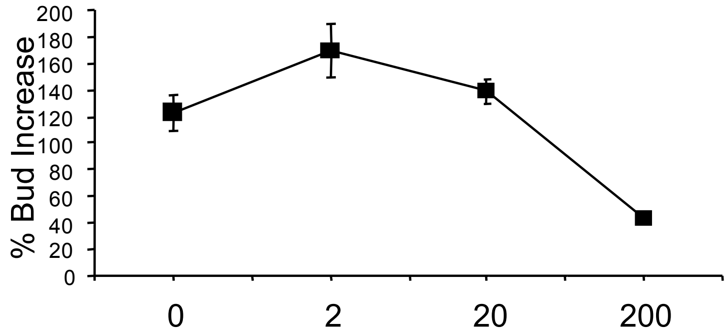
Rho Mediates Cell Shape-Dependent Growth Control



(Huang et al., *Mol. Biol. Cell*, 1998; Huang & Ingber, *Exp Cell Res.* 2002; Numaguchi et al., Angiogenesis 2003; Mammoto et al., *J. Biol. Chem. 2004 & J. Cell Sci. 2007*)

Whole Organ Development Requires a Fine Balance of Forces

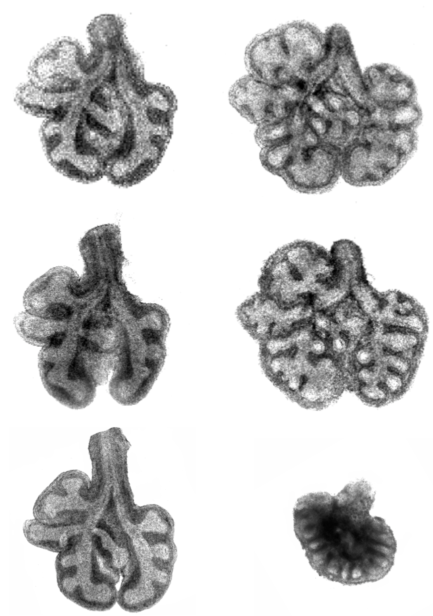
Lung Bud Inducing Activity



Control

Rho ↑ CNF-1 (2-20 ng/ml) ↑ Tension

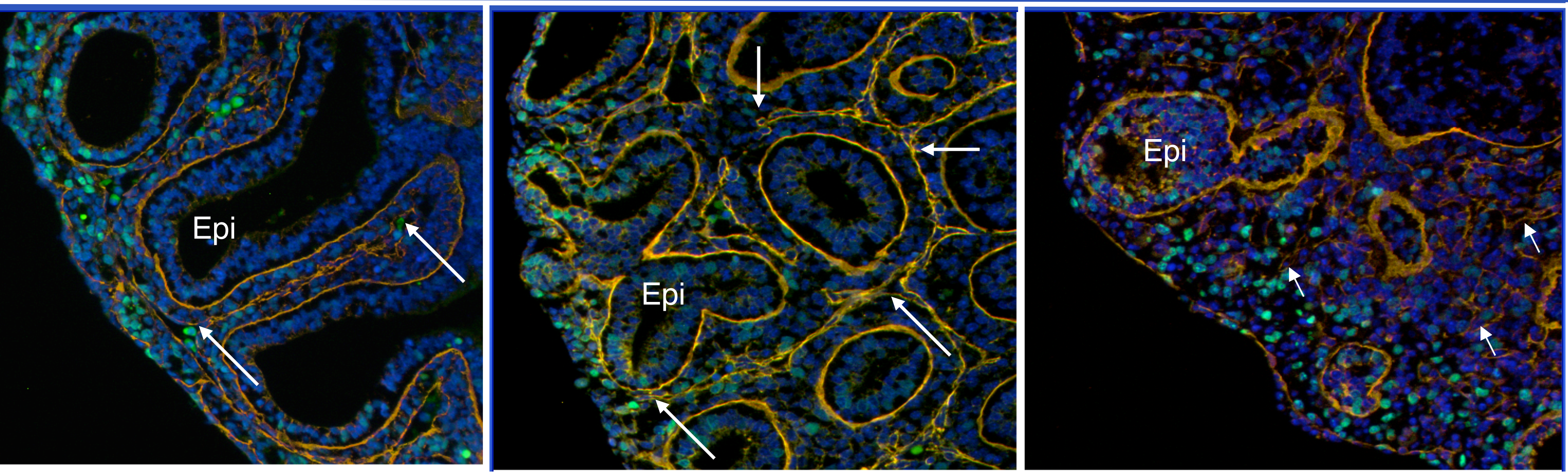
Rho ⬆ CNF-1 (200 ng/ml) ⬆ Tension



Time (hrs): 0 48

(Moore et al, *Dev. Dynamics* 2005)

Epitheliogenesis & Angiogenesis in Embryonic Lung can be Controlled by Altering Cytoskeletal Tension



Control

CNF-1 (20 ng/ml)

↑ TENSION

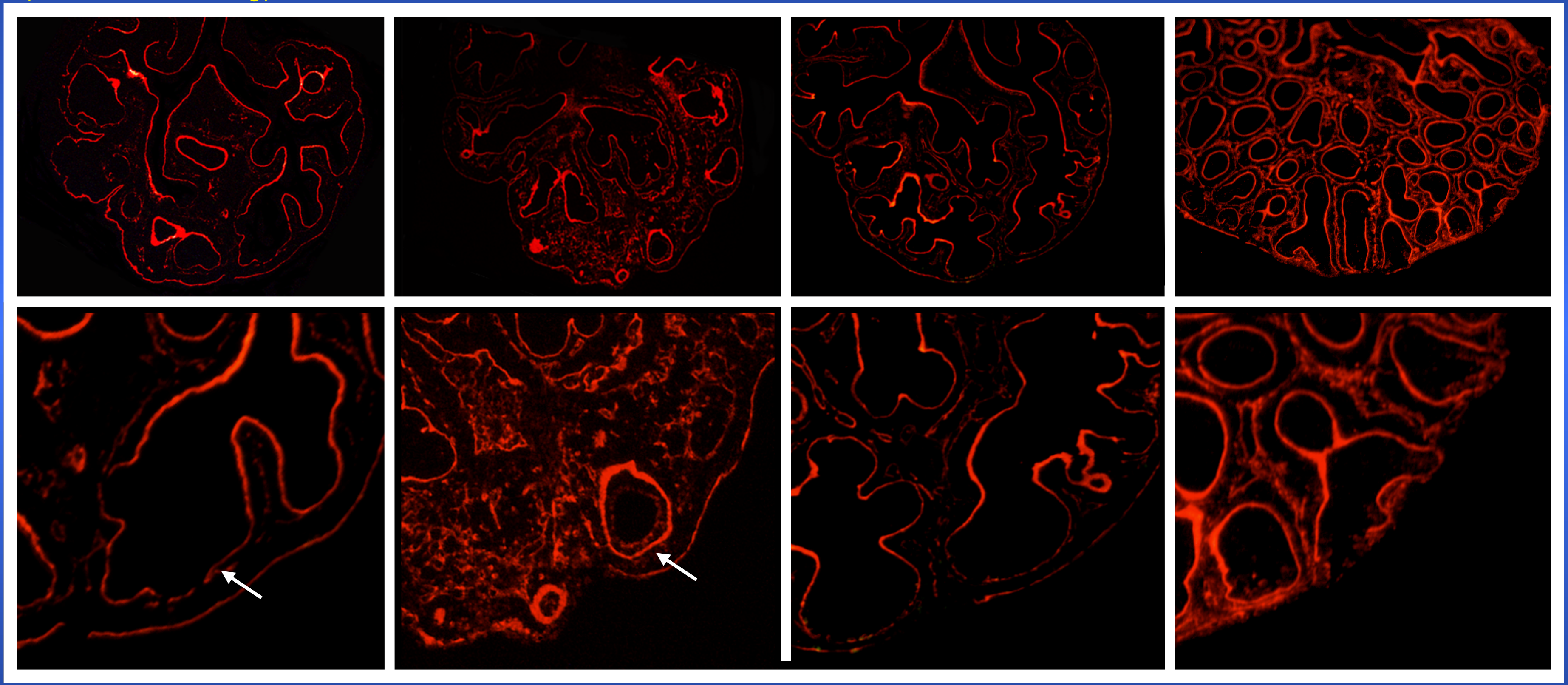
Y27632 (40 uM)

↓ TENSION

(Moore et al, *Dev. Dynamics* 2005)

Dissipation of CSK Tension Prevents ECM Thinning And Inhibits Morphogenesis

(Laminin Staining)



Control Y27632 Rescue CNF-1

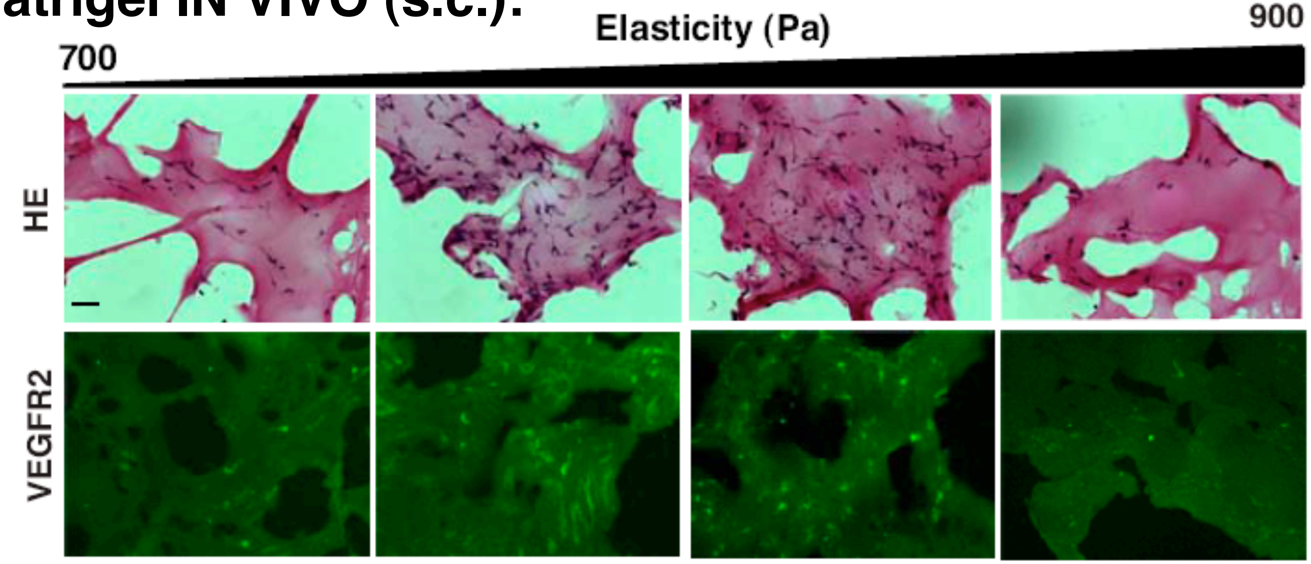
(Moore et al, *Dev. Dynamics* 2005)

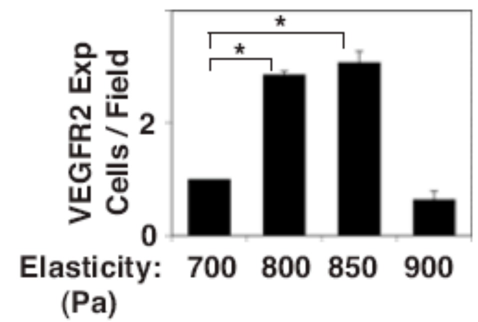
Matrix Mechanics Controls Angiogenesis In Vivo

(*Modulation of VEGFR2 Expression via Mechanical Control of Gene Transcription Factors*)

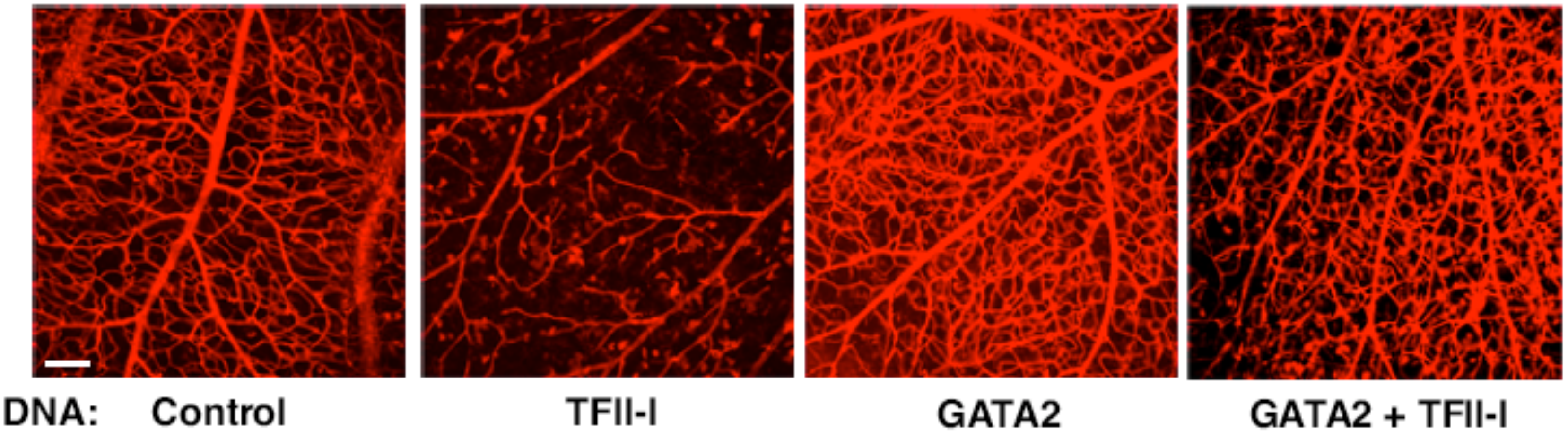
(Mammoto et al., *Nature* 2009)

Matrigel IN VIVO (s.c.):

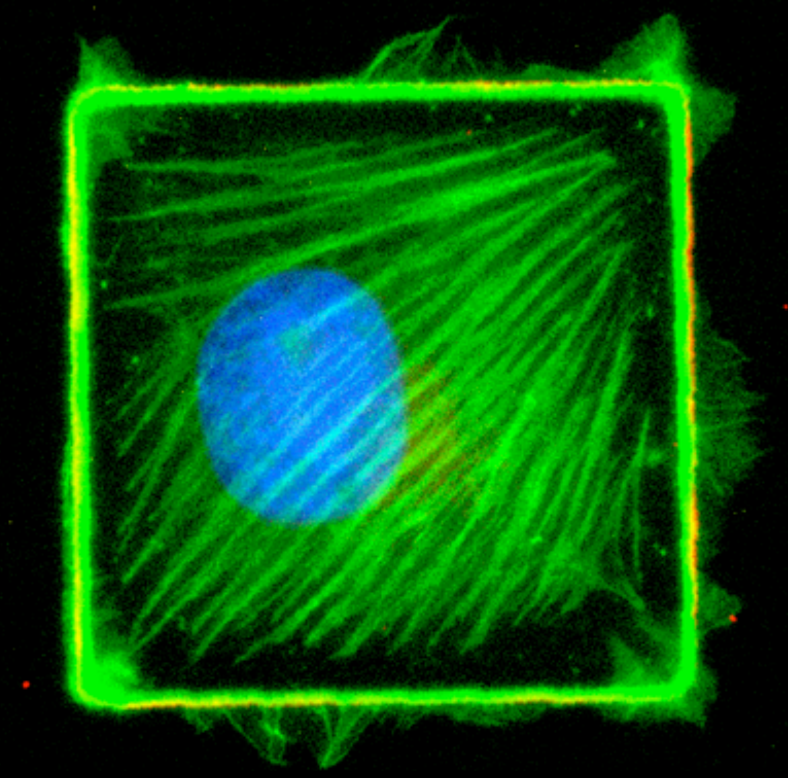


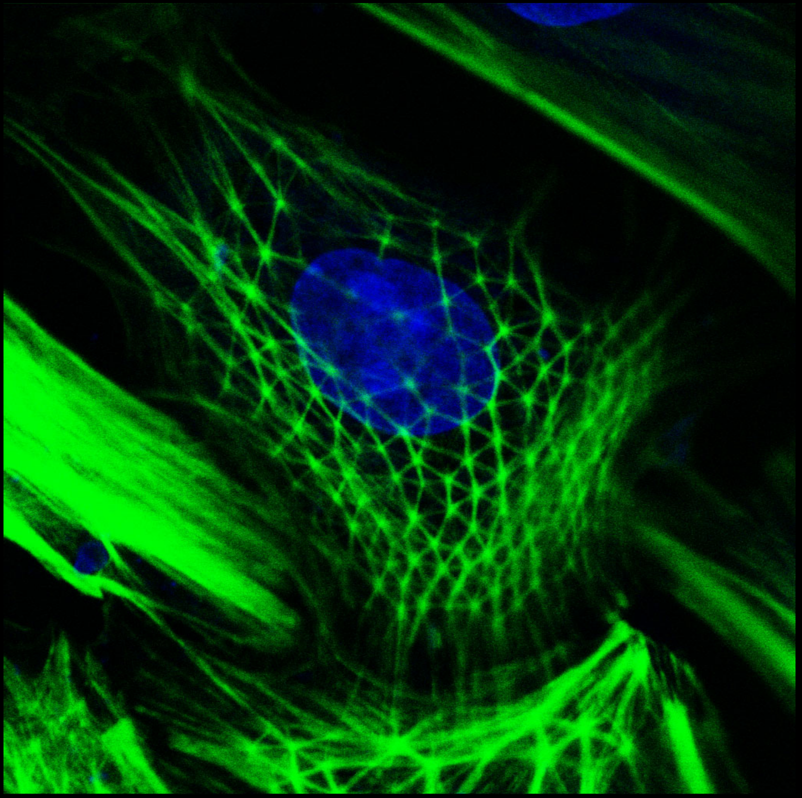


Mouse Retina IN VIVO:



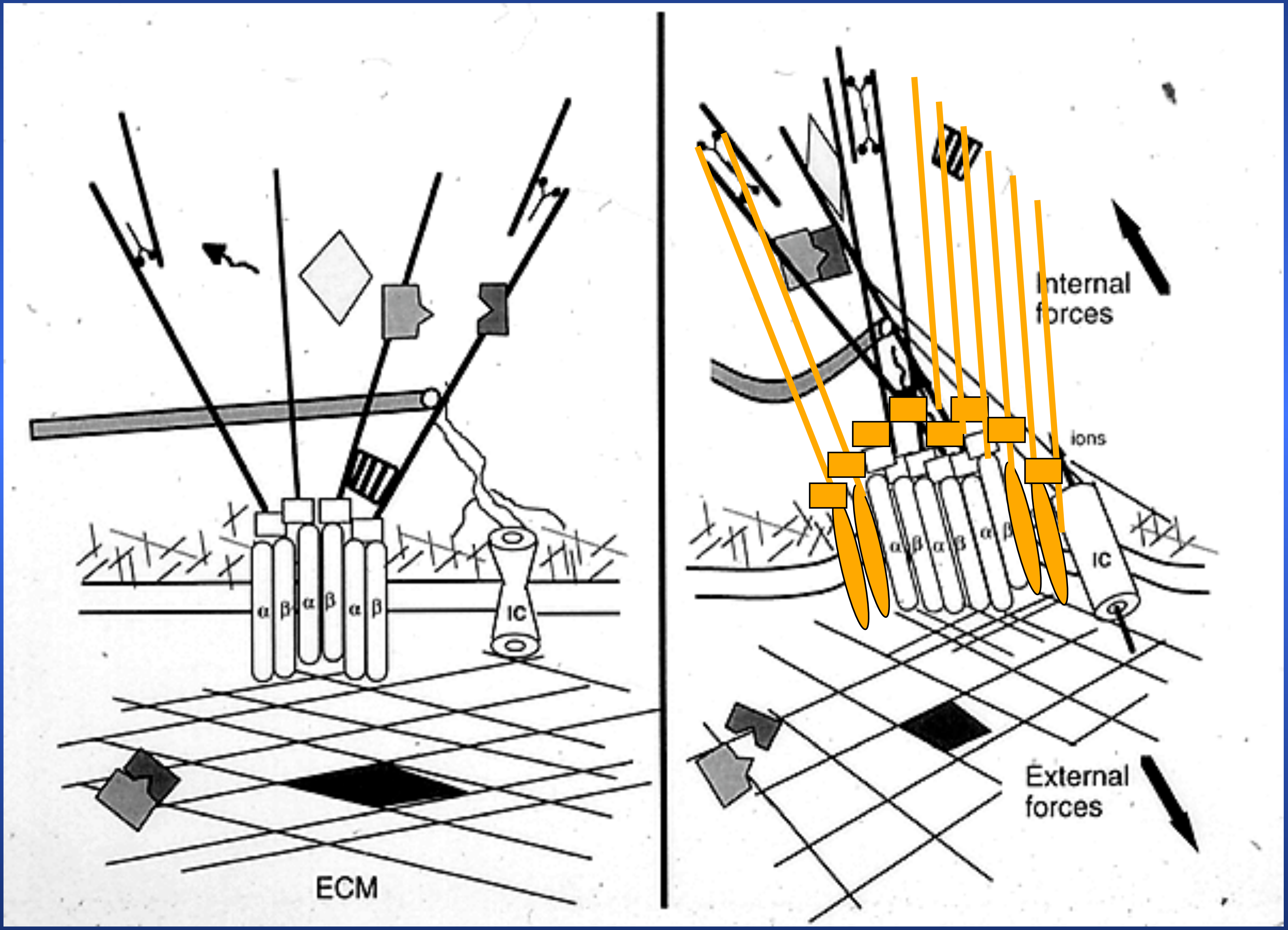
Mechanical Forces Exerted on the ECM & Cytoskeleton Are Key Regulators of Tissue Growth & Development



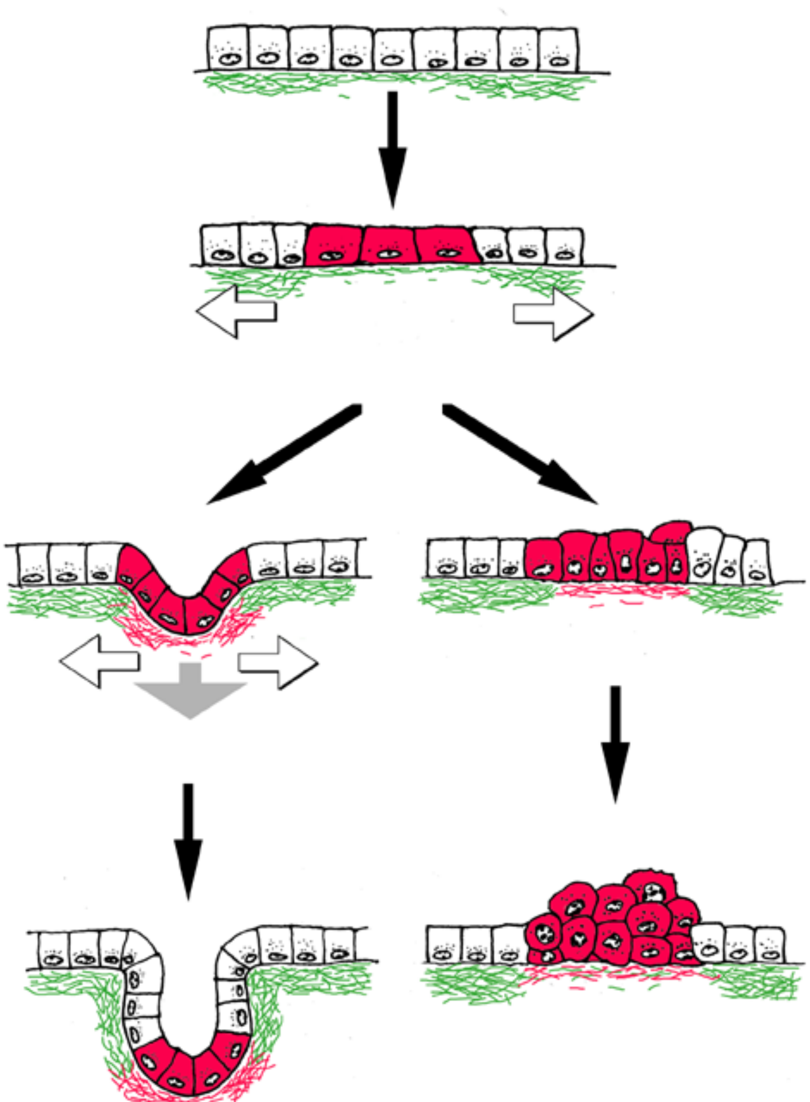


(From Encheva lab)

Cellular Control Lies in the Balance of Forces

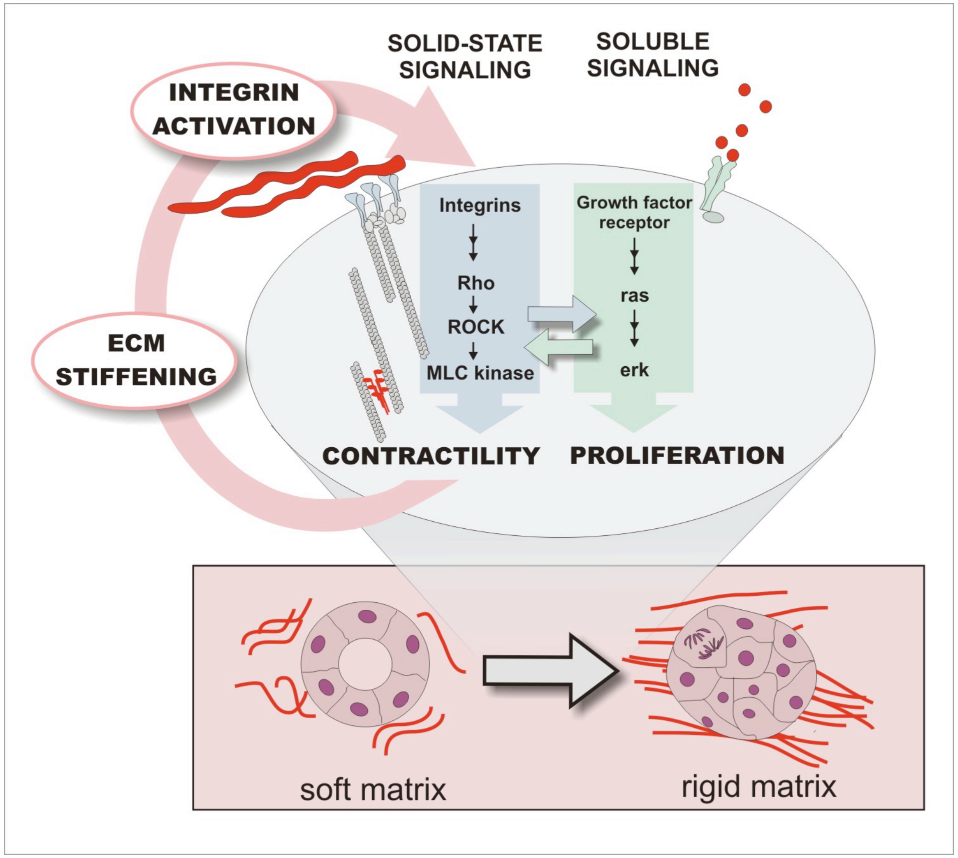


ECM Structure & Cell Tension also Contribute to Tumor Formation



Transgenic Stromelysin Mice Form Tumors
(work of Zena Werb & Mina Bissell)

Mechanical Feedback Loop
(work from Val Weaver Lab)



Ingber et al., *PNAS* 1981; Ingber & Jamieson, In: *Gene Expression During Normal & Malig. Differ.* ,1985; Huang and Ingber, *Nature Cell Biol.* ,1999; Sternlicht et al., *Cell* 1999; Paczek et al., *Cancer Cell* 2004; Huang & Ingber *Cancer Cell* 2005.

DISEASES OF MECHANOTRANSDUCTION

Many unrelated diseases in all fields of medicine & surgery share the common feature that their etiology or clinical presentation result from abnormal mechanotransduction, due to:

- **changes in cell mechanics**
- **changes in ECM structure**
- **altered mechanosensation**
- **deregulated mechano-chemical conversion**

(Ingber, *Annals of Medicine*, 2003)

DISEASES OF MECHANOTRANSDUCTION

Cardiology/Cardiac Surgery
- Angina (vasospasm)
- Atherosclerosis
- Atrial fibrillation
- Heart failure
- Hypertension
- Intimal hyperplasia
- Valve Disease

Dermatology
- Scleroderma

Gastroenterology
- Achalasia
- Irritable bowel syndrome
- Volvulus

Nephrology
- Diabetic nephropathy
- Glomerulosclerosis

Neurology/Neurosurgery
- Cerebral edema
- Facial Tics
- Hydrocephalus
- Migraine
- Stroke
- Stuttering

Oncology
- Cancer
- Metastasis

Opthalmology
- Glaucoma

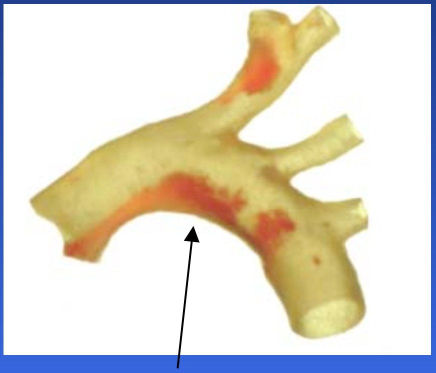
Orthopedics
- Ankylosing spondylitis
- Carpal tunnel syndrome
- Chronic back pain
- Dupytren's contracture
- Osteoporosis
- Osteoarthritis
- Rheumatoid arthritis

Pediatrics
- Pulmonary hypoplasia
- Collagenopathies
- Deafness
- Mucopolysaccharidoses
- Musculodystrophies
- Osteochondroplasias
- Pulmonary hypertension of newborn
- **Polycystic kidney disease**

Pulmonary Medicine
- ARDS
- Asthma
- Emphysema
- Pulmonary fibrosis
- Pulmonary hypertension
- Ventilator Injury

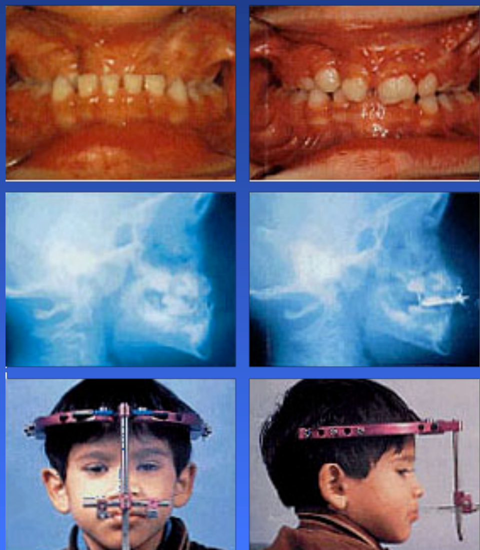
Reproductive Medicine
- Pre-eclampsia
- Sexual dysfunction (male & female)

Urology
- Urinary frequency / incontinence



Atherosclerotic plaque in areas of disturbed flow

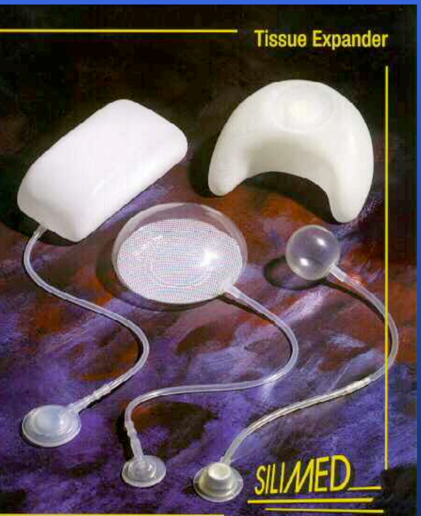
MECHANICAL THERAPIES



Distraction osteogenesis

Acupuncture
Anti-arrhythmic drugs
Anti-spasmodic drugs
Bone fracture healing
Botox
Cardiac perfusion
Distraction osteogenesis
Inotropic drugs
Lung ventilation
Massage therapy
Muscle relaxants
Orthodontics
Physical therapy
Rho-kinase inhibitor (fasudil)
Stents
Surfactant
Tissue engineering (manufacturing process)
Tissue expansion (e.g., breast)
Vasodilators
Ventilator therapy
Wound closure (e.g., vacuum-assisted)

External fixator



Lung ventilator

Bioinspired Technology Fallout:

‘Organs-on-Chips’

Microfluidic Systems

(Artificial Microvascular Networks)

Reynolds number

$$\mathrm{Re} = \frac{\text{Inertial forces}}{\text{Viscous forces}} = \frac{\rho U L}{\mu} < 1$$

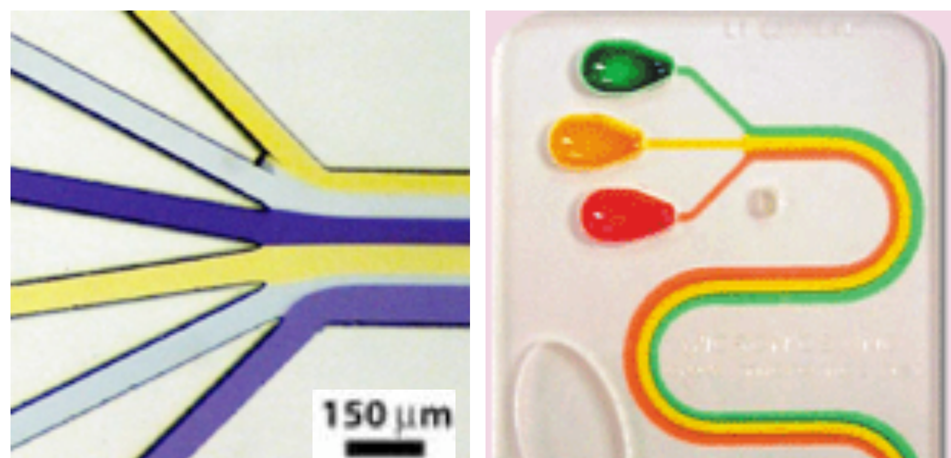
ρ = density of fluid

μ = viscosity of fluid

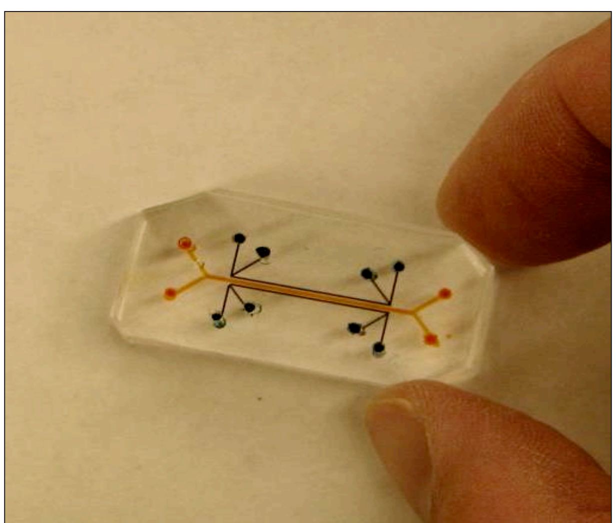
U = velocity

L = characteristic length

Turbulent flow (high Re)

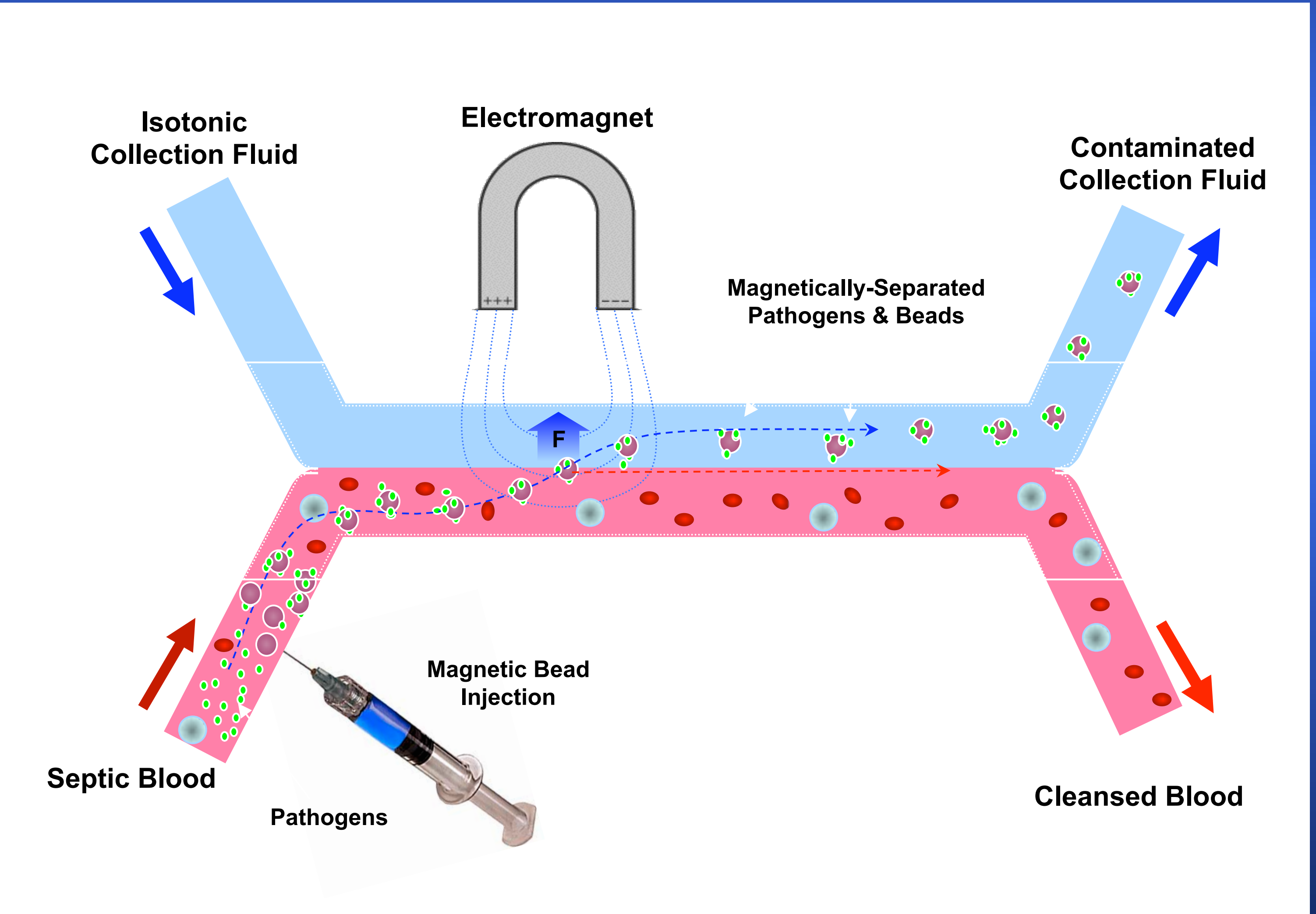


Laminar flow **with orderly fluid motion (low Re)**



NANOMAGNETIC-MICROFLUIDIC CELL SEPARATION DEVICE

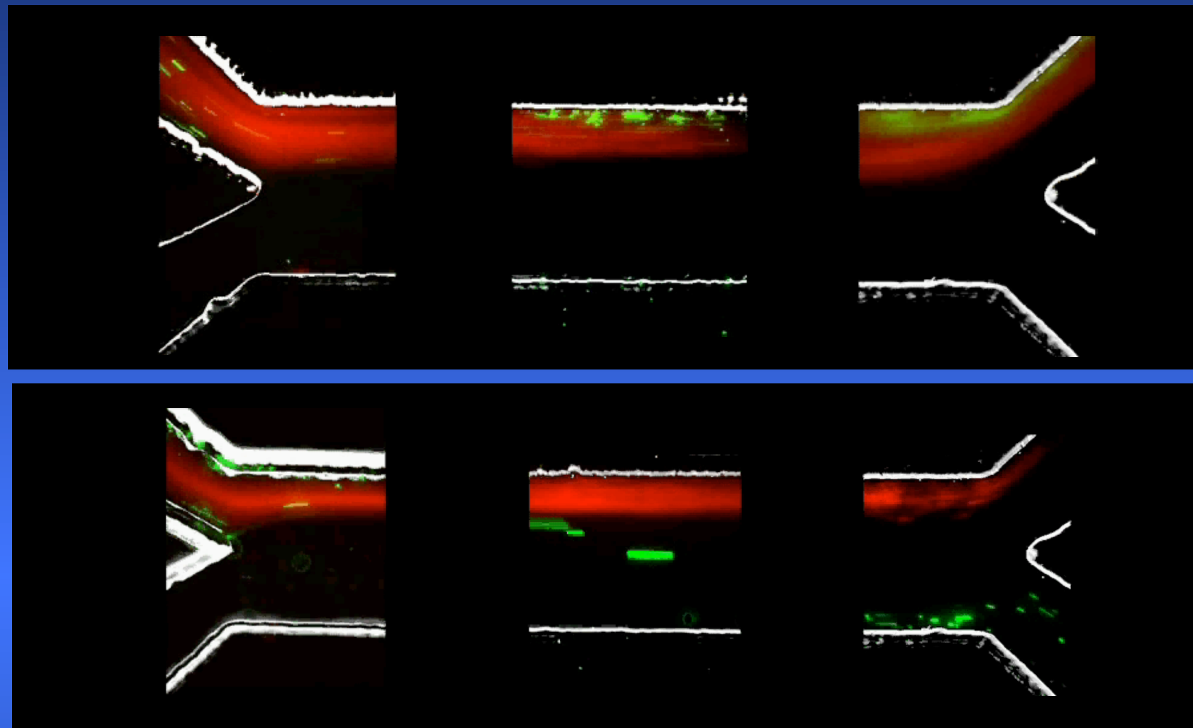
An extracorporeal microdevice
that functions like an "artificial spleen"
for Sepsis Therapy



Magnetic Separation of Particles from Flowing Blood

- Magnet

+ Magnet

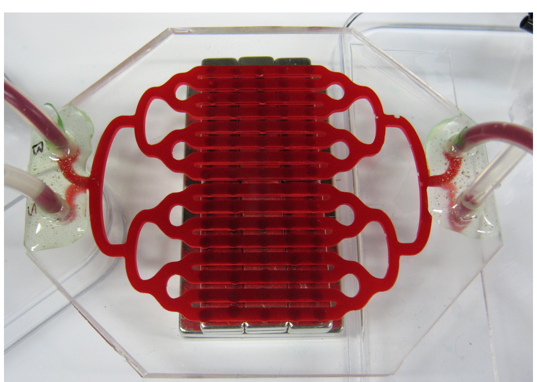


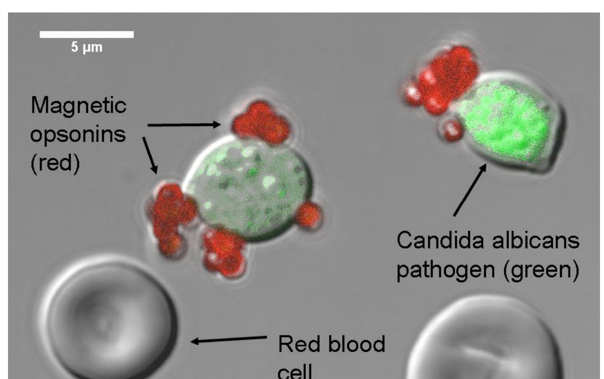
(Xia et al, *Biomed. Microdev.*, 2006; Yung et al., *Lab on a Chip* 2009)

[Work of Chong Yung & Ryan Cooper w/ Mark Puder]

C. *Albicans* Fungi in Whole Human Blood

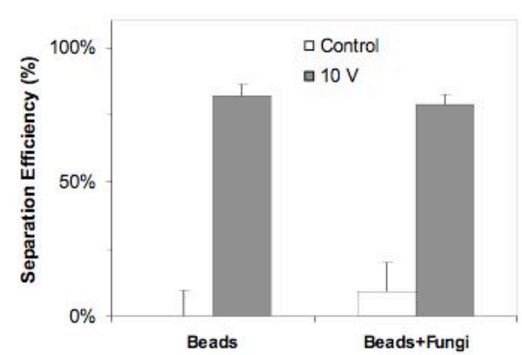
(with funding from CIMIT & Wyss Institute)



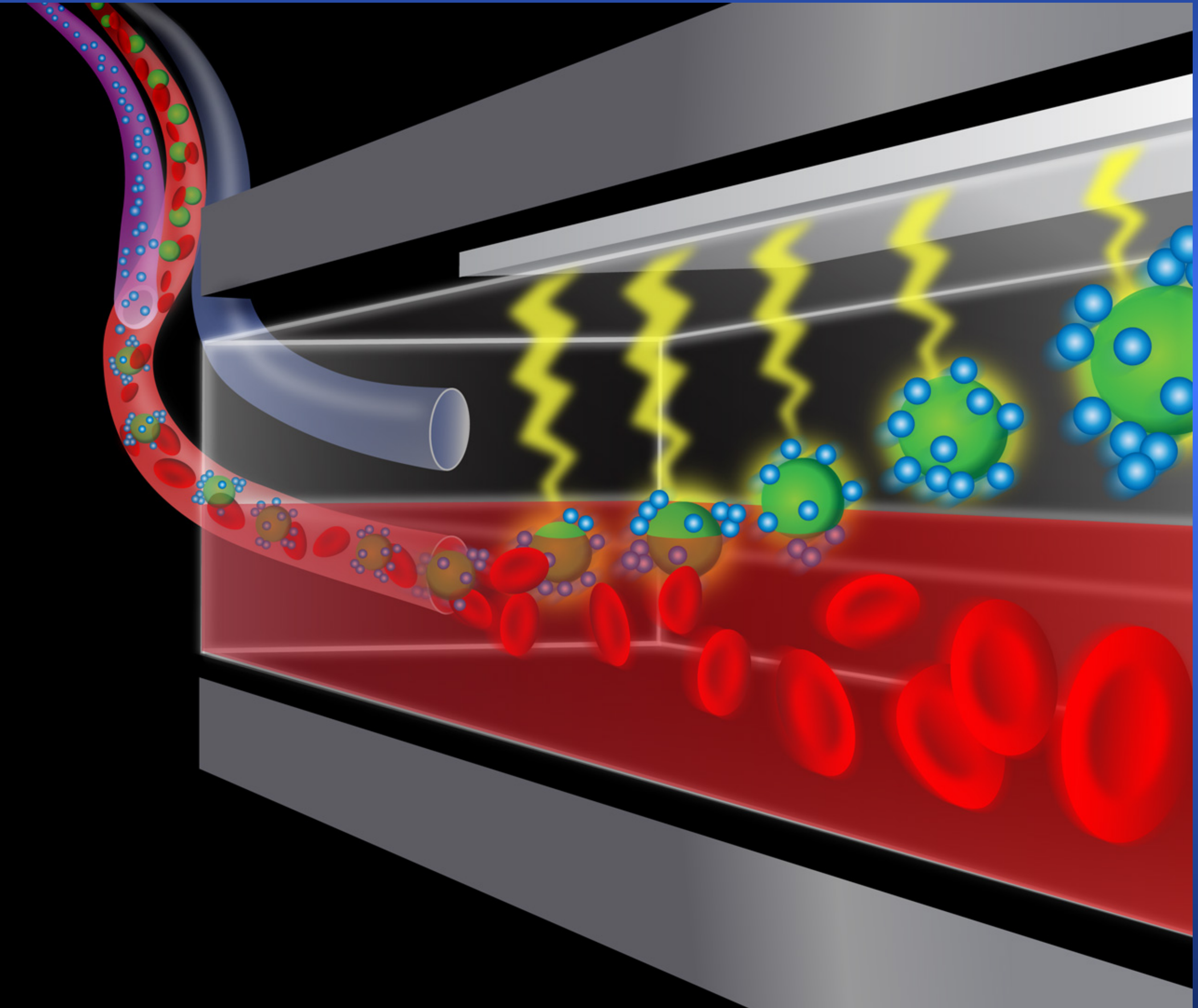


Human Whole Blood

(4-channel device, 20 mL/hr)



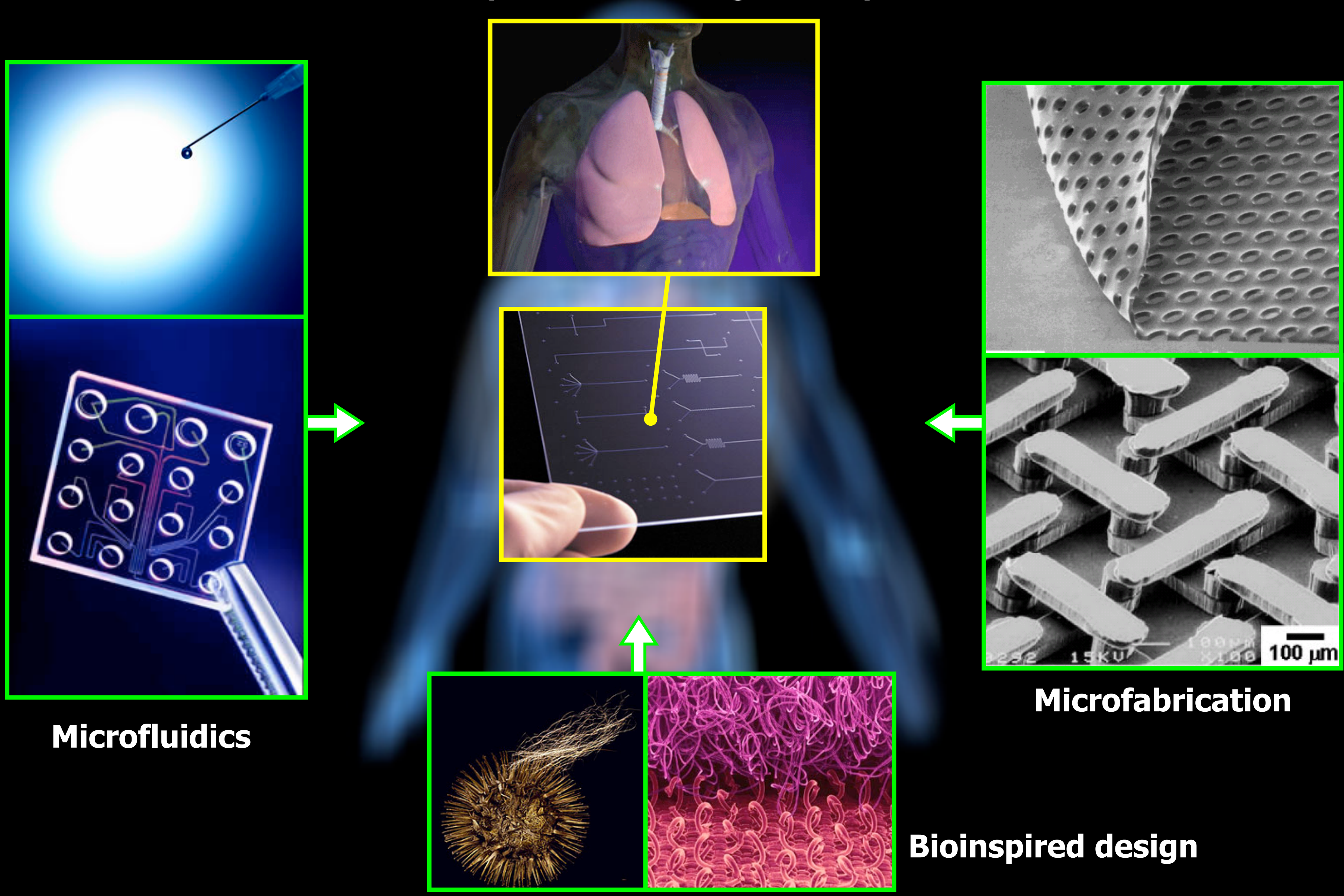
New Blood Separation Platform With Unlimited Capacity



- *Pathogens*
- *Cancer Cells*
- *Stem Cells*
- *Inflammatory Cytokines*
- *Fetal Cells (in maternal circulation)*
- *…*

Human Breathing Lung-on-a-Chip

(Work of Dan Dongeun Huh)

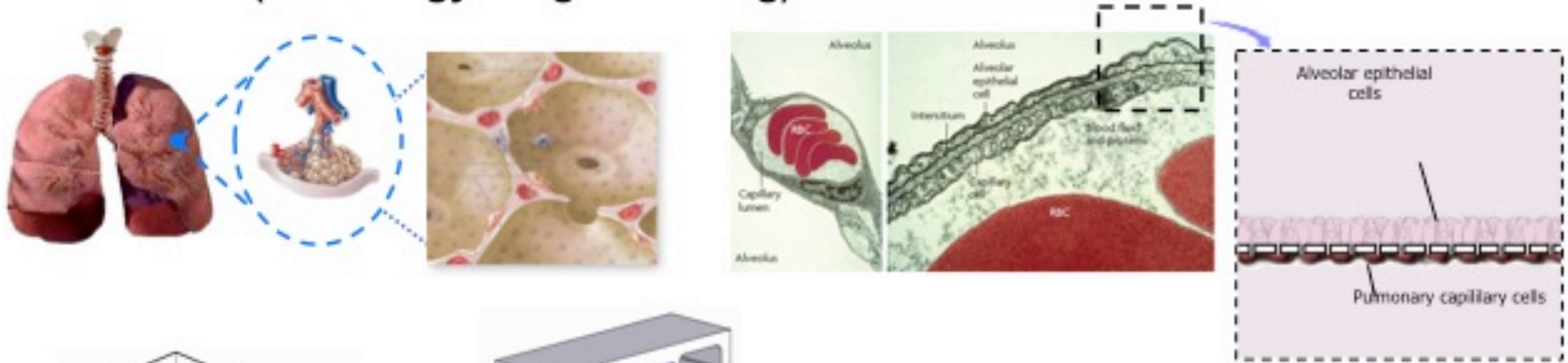


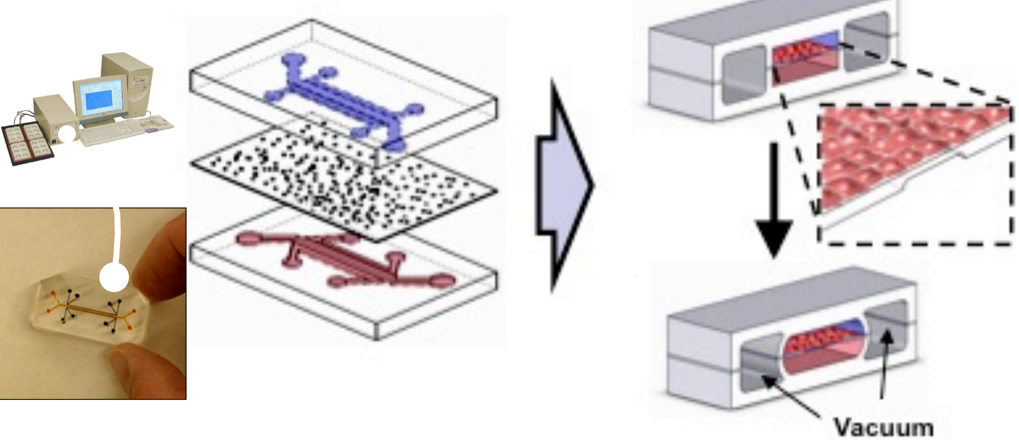
WYSS INSTITUTE

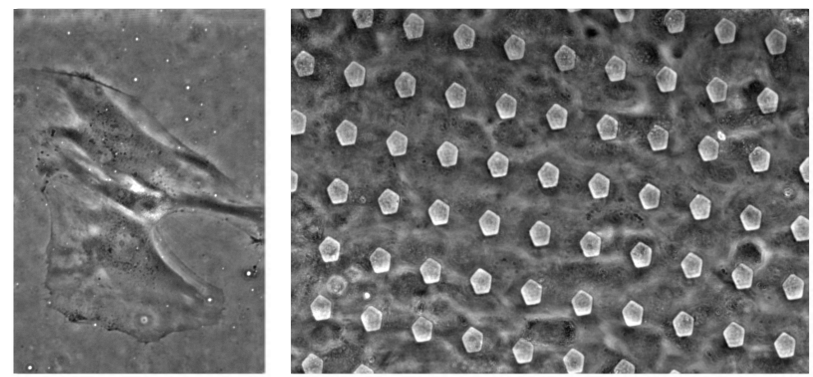
BIOMIMETIC MICROTECHNOLOGIES: Lung on a Chip

(Toxicology/Drug Screening)

(Huh et al., *Science* – in press)

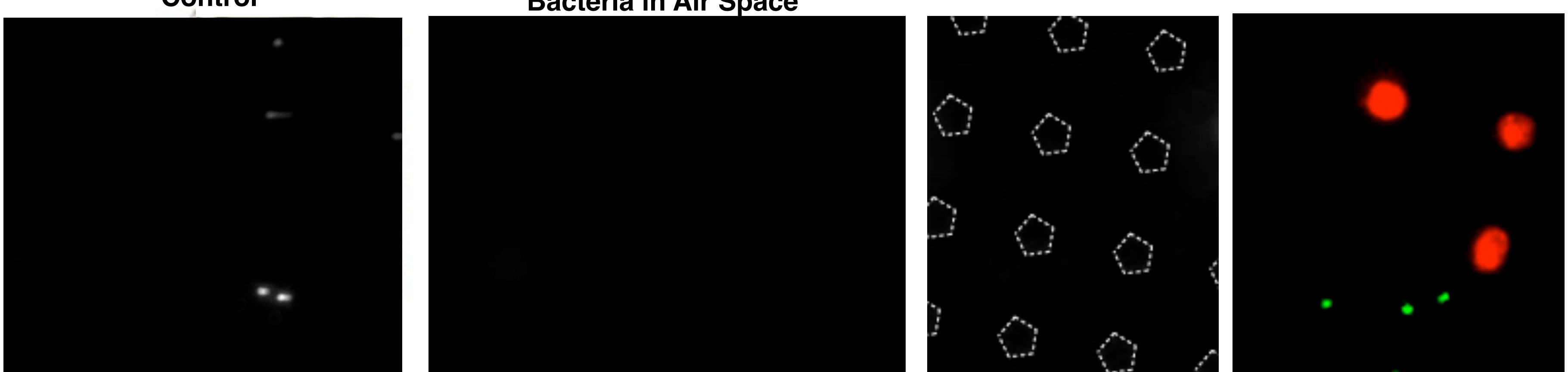




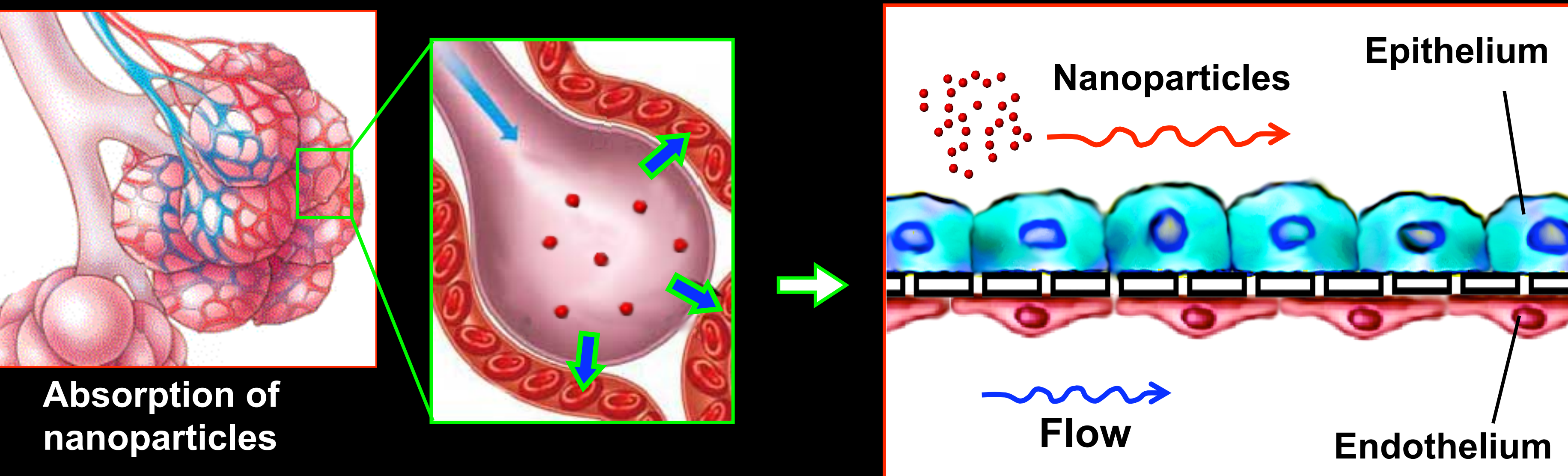


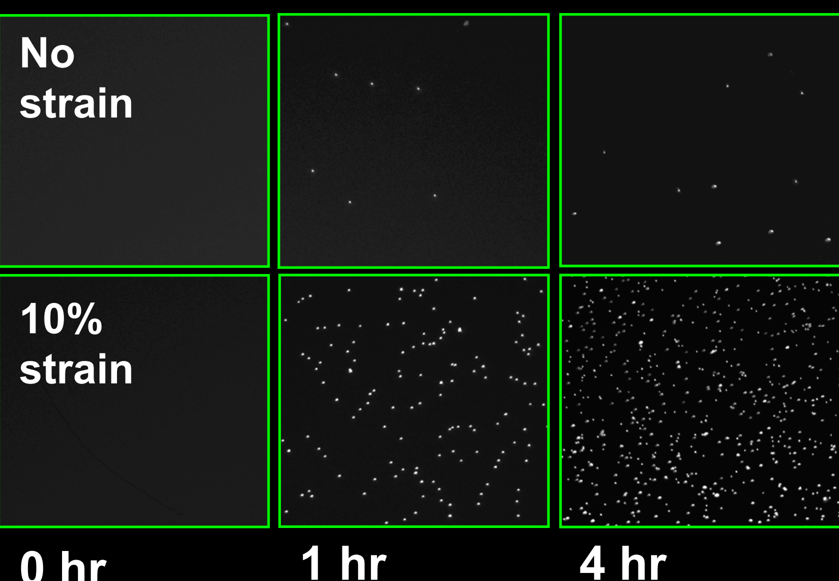
Control

Bacteria in Air Space

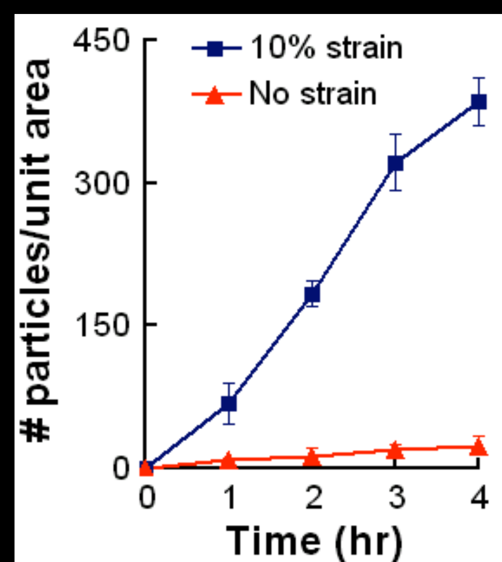


Influence of Breathing on Nanoparticle Absorption

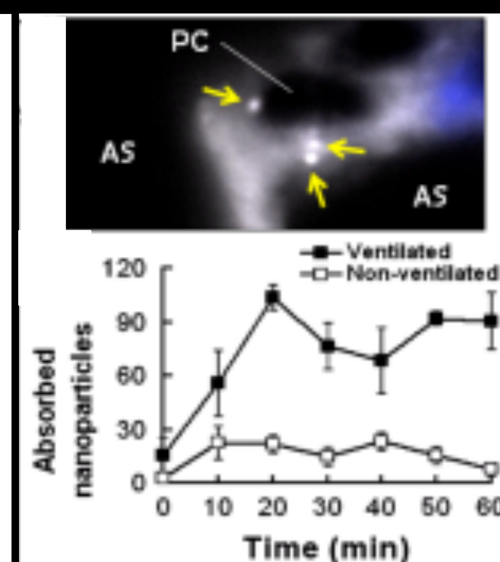




Lung-on-a-Chip

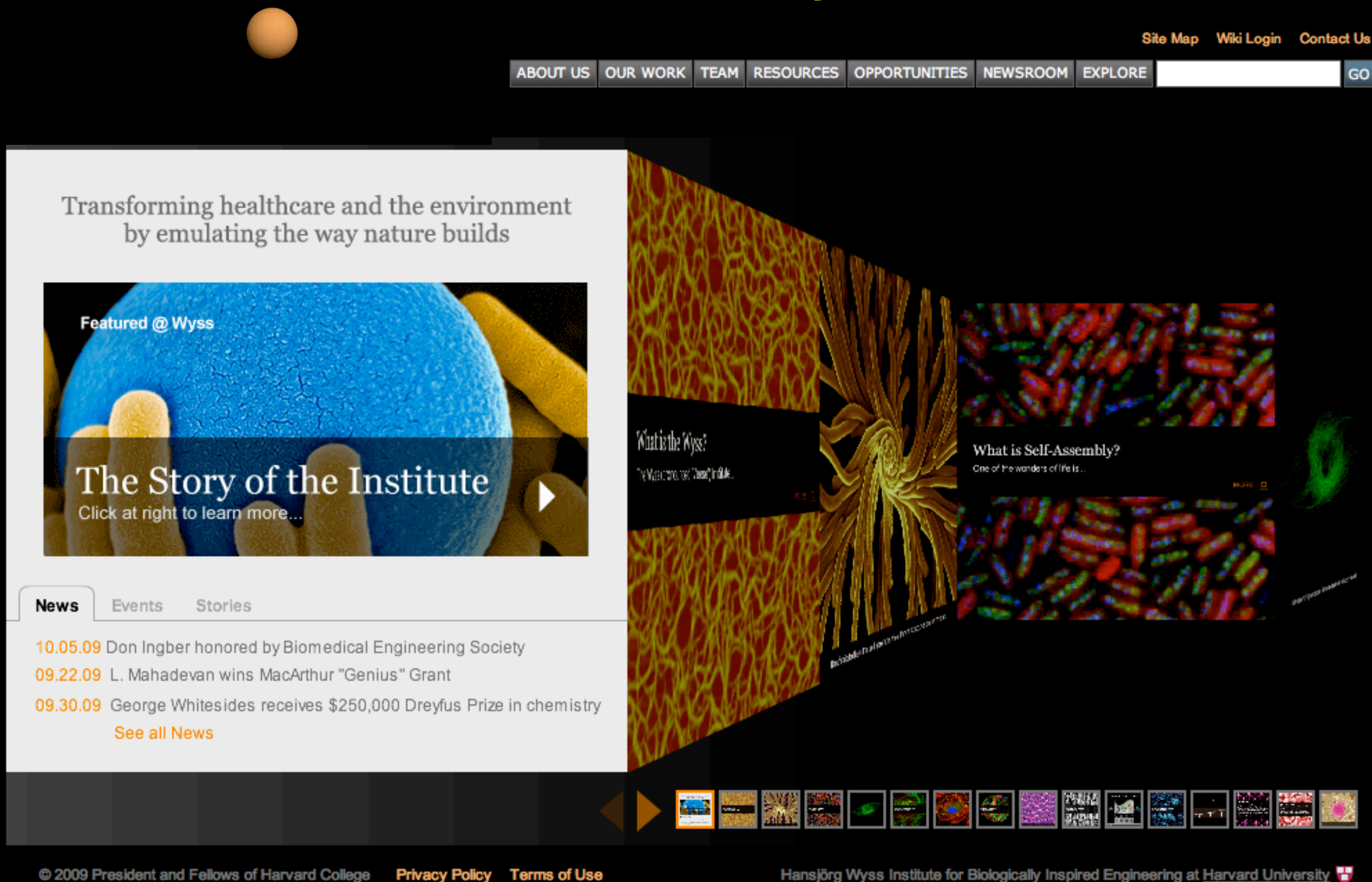


Whole Mouse Lung



(Huh et al., *Science* – in press)

www.wyss.harvard.edu



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