Research on Tap:
Mechanobiology: How Force and Stretch Shape Life

April 2, 2019

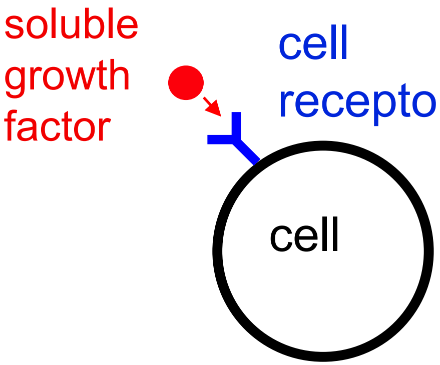
Boston University Office of the Vice President and Associate Provost for Research

Growth Factor Mechanobiology in Musculoskeletal Tissues

Michael B. Albro

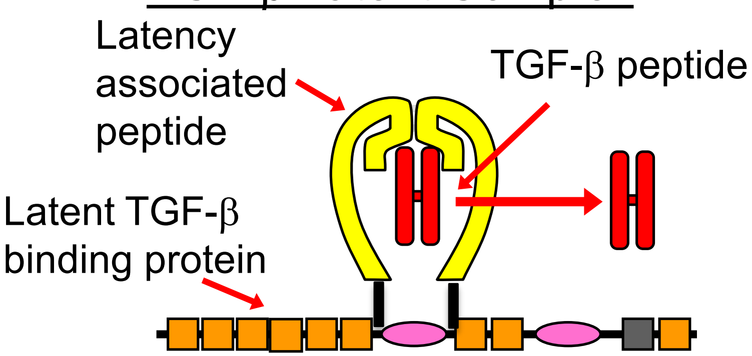
Assistant Professor
Mechanical Engineering
Materials Science & Engineering

- Anabolic growth factors
  - Highly potent signaling molecules
  - Regulation of growth, differentiation, ECM biosynthesis
  - Transforming growth factor beta (TGF-β), insulin-like growth factor (IGF), fibroblast growth factor (FGF)



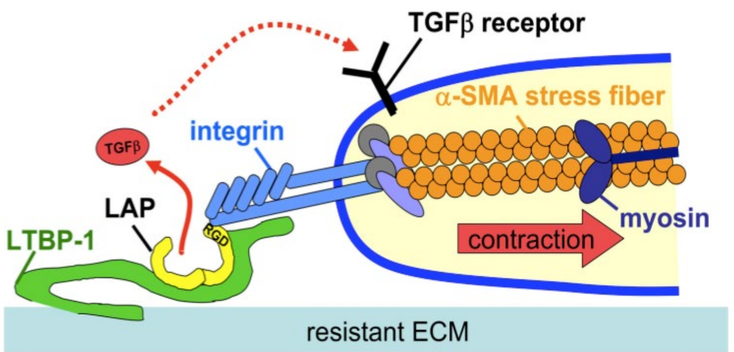
- What mechanisms regulate growth factor activity in the extracellular environment?

<u>TGF-β Latent Complex</u>



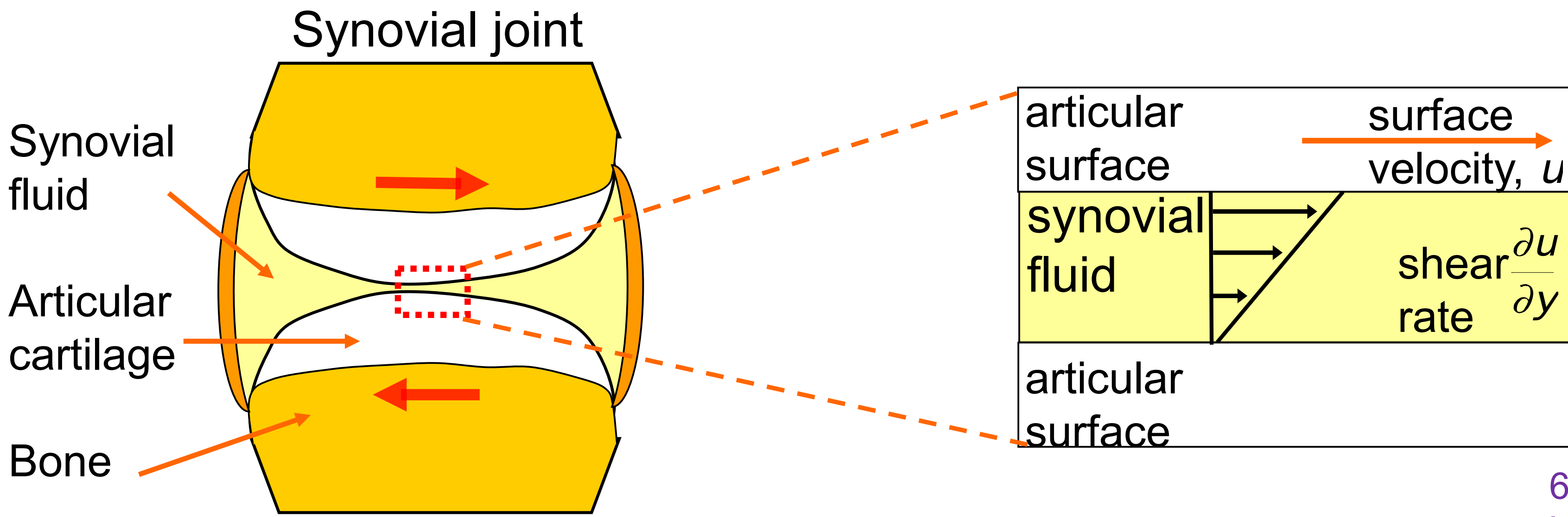
[Hyytiainen, 2004]

<u>TGF-β Mechanobiology</u>

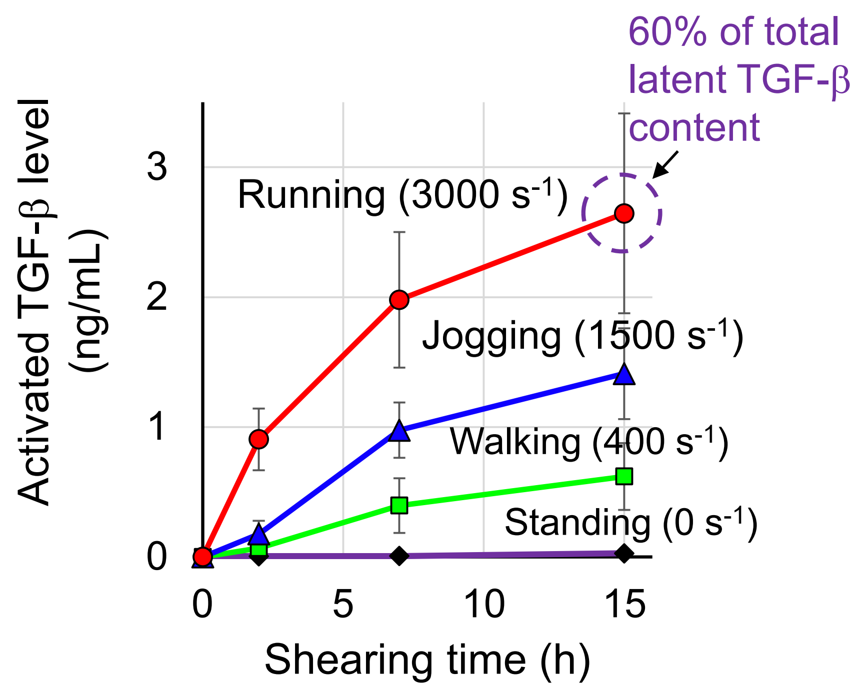


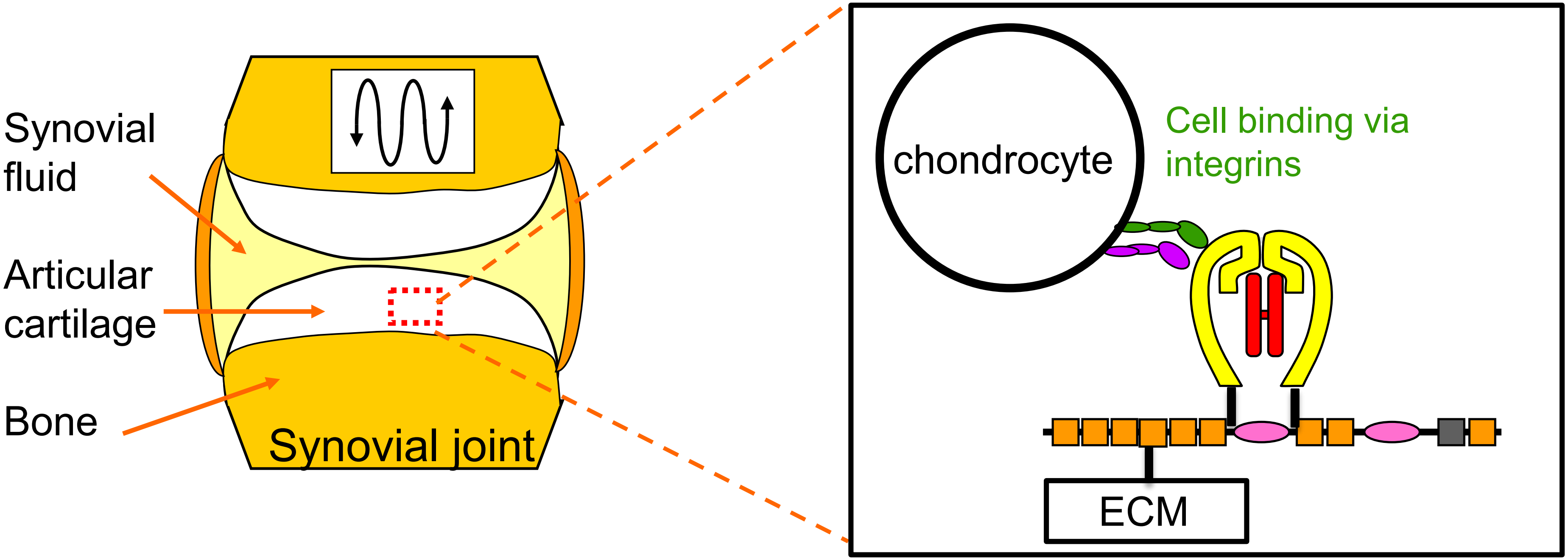
[Wipff, 2008]

- Activation is the major regulatory feature of TGF-β in native environment
- Mechanical forces can activate latent TGF-β



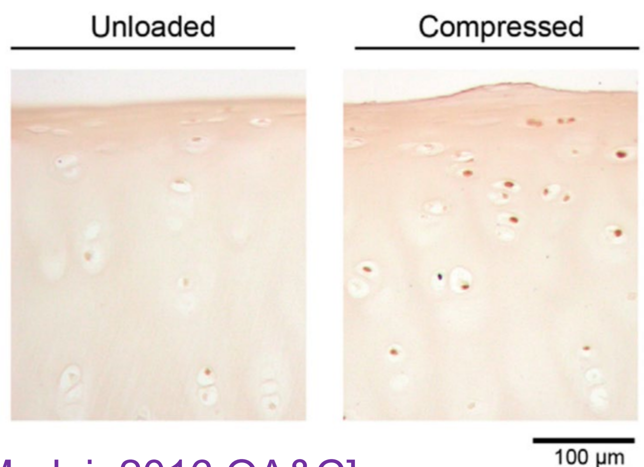
- Synovial joint tissues undergo deformations in response to joint motion
- Large amounts of latent TGF-β in synovial fluid
- Can physiologic shearing of synovial fluid activate its latent TGF-β content?





Large amounts of latent TGF-β in ECM of synovial joint tissues (300ng/mL)

pSmad2 staining



Chondrocyte smad2/3 phosphorylation in response to physiologic dynamic compression

[Madej, 2016 OA&C]

TGF-β Mechanosignaling: Tip of the Iceberg

- What are the detailed mechanisms responsible for load-induced activation of latent TGF-β in native musculoskeletal tissues?
- What is the functional role of TGF-β mechanosignaling in maintaining musculoskeletal tissue health/homeostasis?
- How does TGF-β mechanosignaling break down with age and tissue degeneration?

Mechanobiology of Soft Tissue Repair and Skeletal Tissue egeneration

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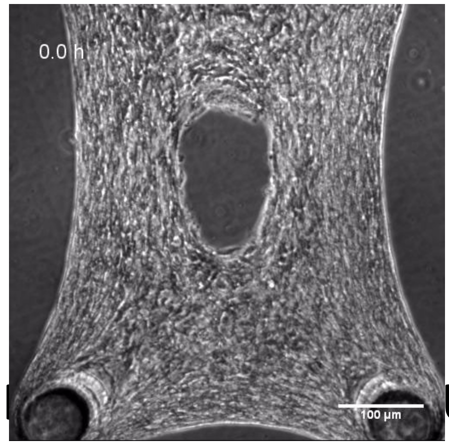
BOSTON UNIVERSITY

LaSER Laboratory for Skeletal Engineering and Regeneration

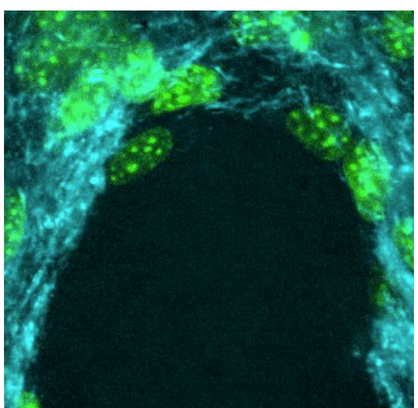
Thrust 1: Gap closure and wound healing of soft tissues



How do cells build a ue architectures?

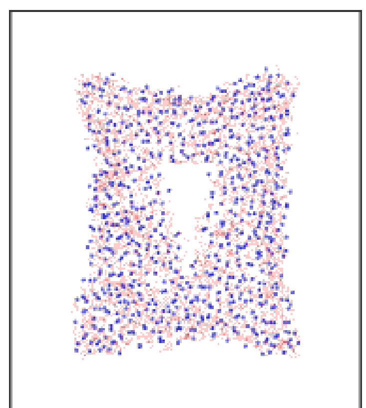
(Sakar, Eyckmans et al., Nat Comm, 2016)

1. Fibronectin recycling



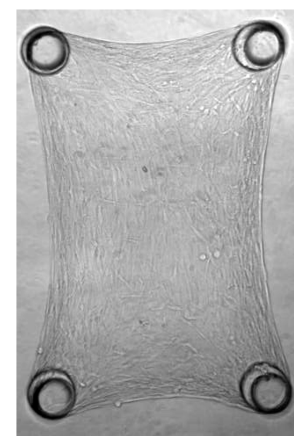
Shoshana Das

2. Modeling fibrous tissue closure



Feng Liu, PhD

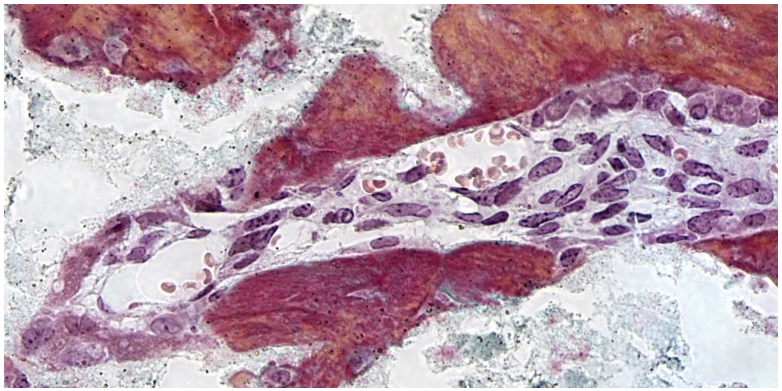
3. Laser ablation

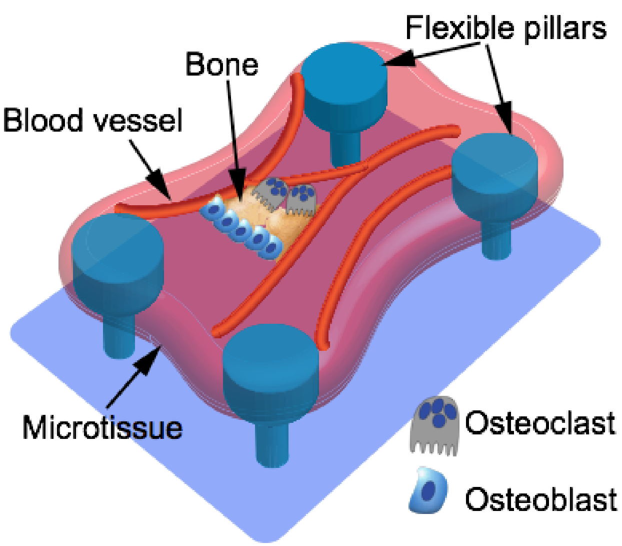


Megan Griebel

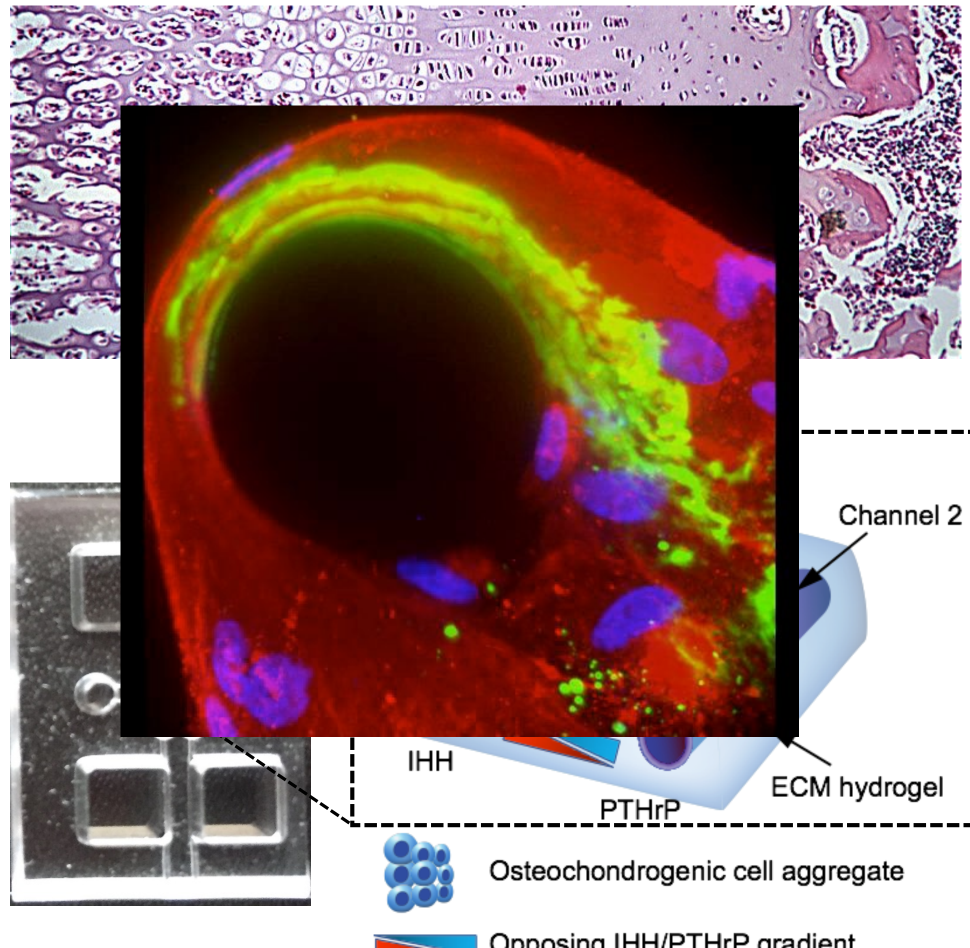
Thrust 2: Engineering skeletal tissue models on-chip.

Bone remodeling unit on-chip





Growth plate on-chip



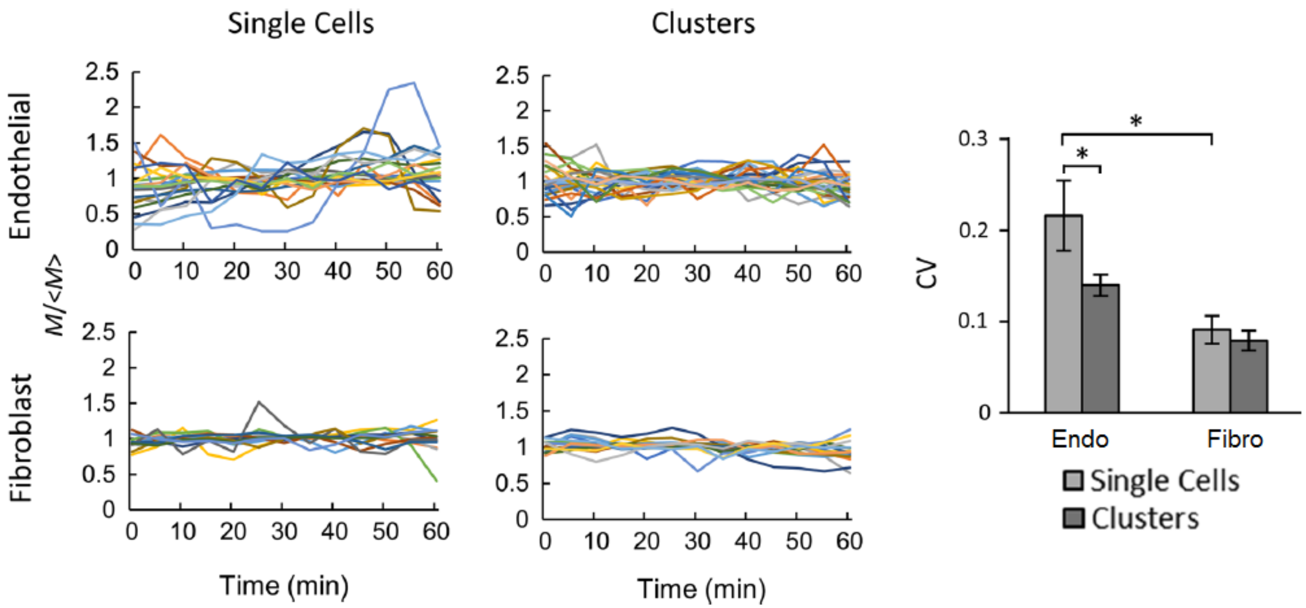
Tensional Homeostasis of Adherent Cells

Dimitrije Stamenović

Professor
Department of Biomedical Engineering, College of Engineering

Definition: Tensional homeostasis is the ability of cells to maintain a consistent level of cytoskeletal tension with low temporal fluctuations.

Observations: Tensional homeostasis is cell-type dependent: in certain cell types (e.g., endothelial cells), it can be achieved only in multicellular clusters; in other cell types (e.g., fibroblasts), no clustering is required.



Promoting homeostasis:
- Increasing number of FAs
- Stable FAs
- Small temporal fluctuations of FA forces
- Homogeneous FA forces
- Uncorrelated FA forces

Detrimental to homeostasis:
- Unstable FAs
- Large temporal fluctuations of FA forces
- Heterogeneous FA forces
- Correlated FA forces

Question: How do cells achieve tensional homeostasis *in vivo* in the presence of the detrimental factors?

On Force and Form: Mechanobiology of the Extracellular Matrix

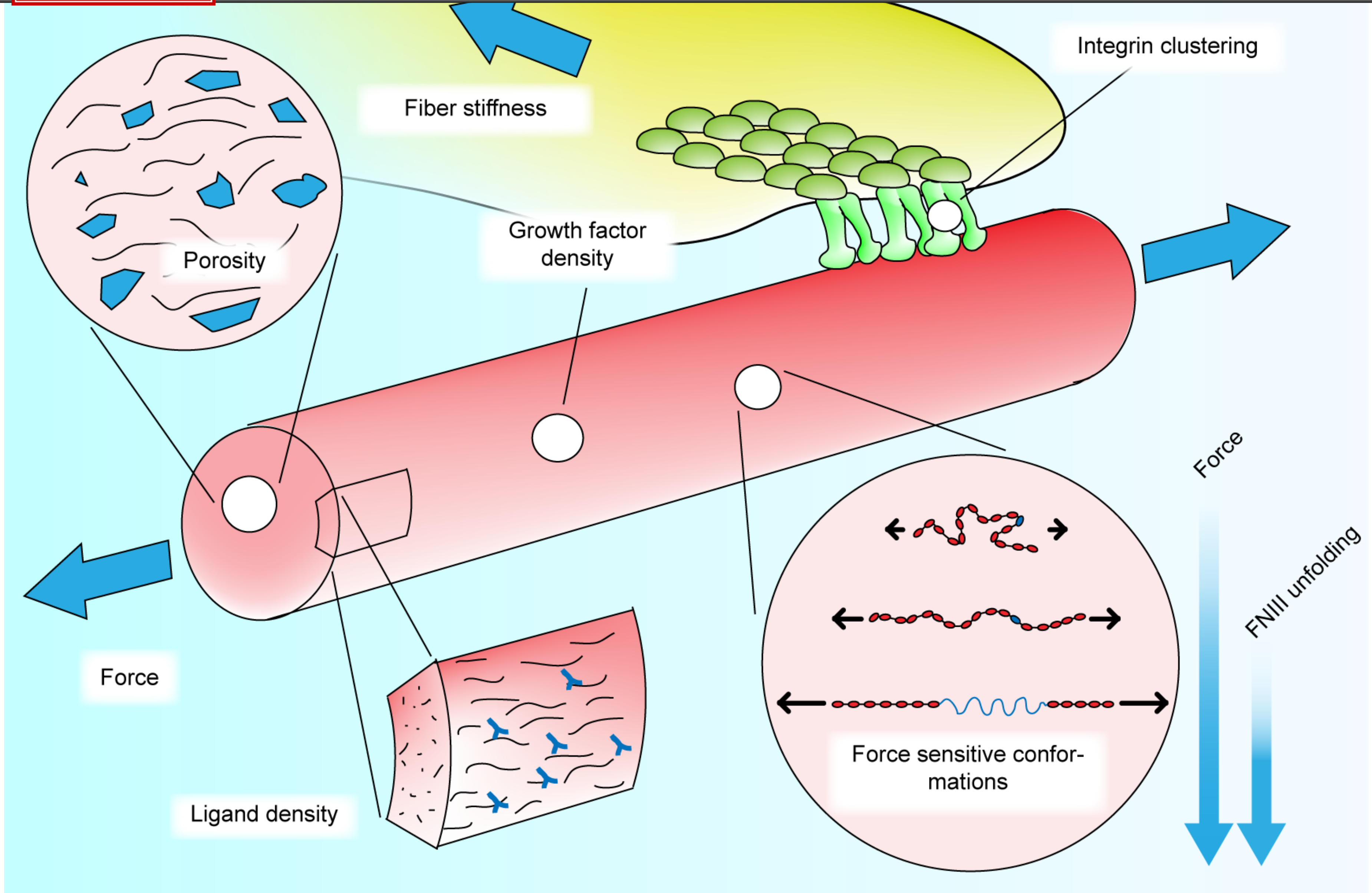
Michael L. Smith

Associate Professor
Department of Biomedical Engineering

On force and form: mechanobiology of the extracellular matrix

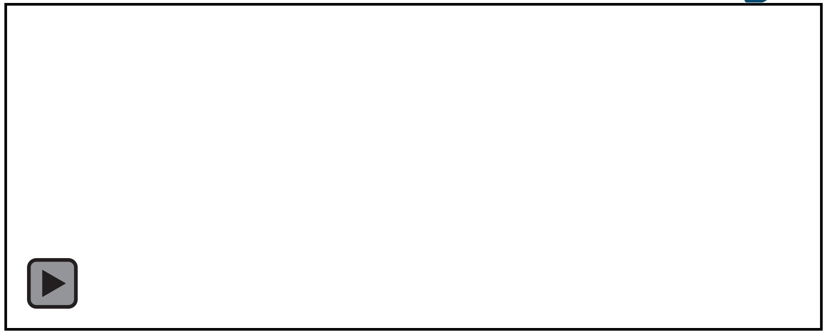
Michael L. Smith

BOSTON UNIVERSITY

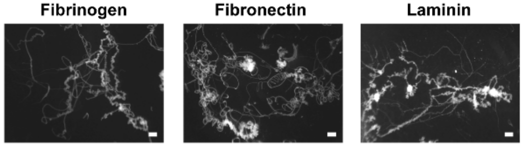


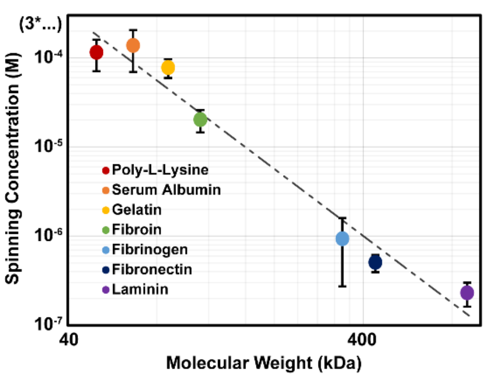
Conformation

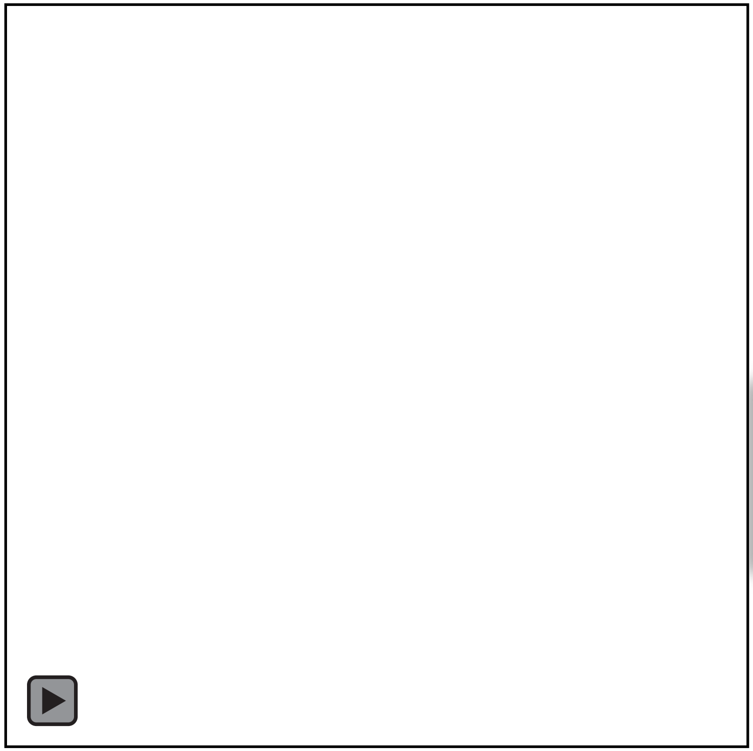
Cell and Growth Factor Binding



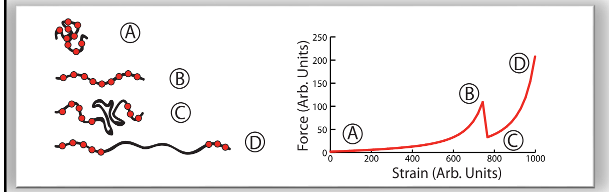
Fabricating Novel ECM Materials







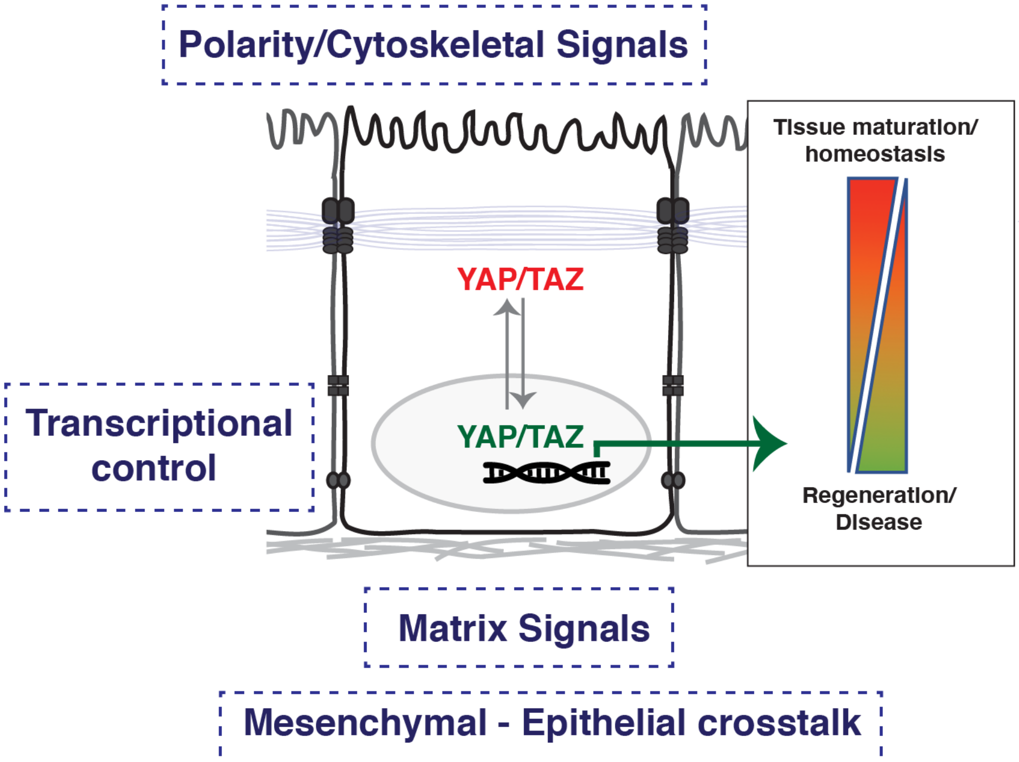
ECM Biomechanics

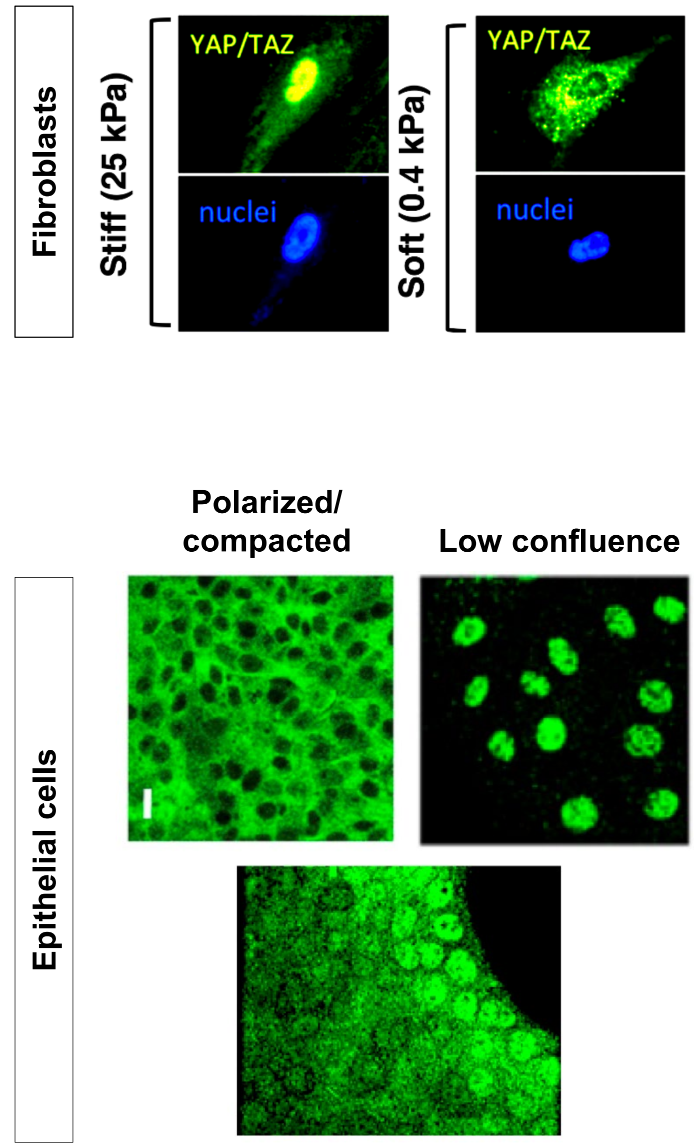


YAP/TAZ Signaling in Development and Disease

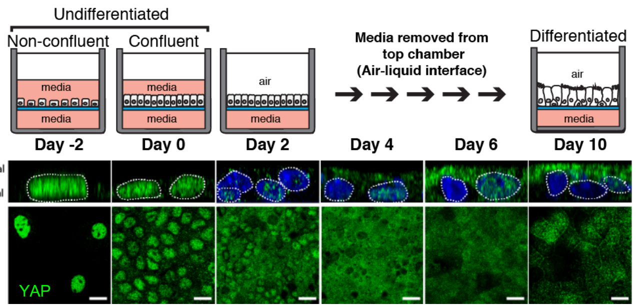
Bob Varelas

Associate Professor
Department of Biochemistry, School of Medicine

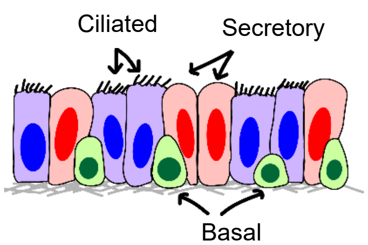

Polarity/Cytoskeletal Signals
YAP/TAZ
YAP/TAZ
Transcriptional control
Tissue maturation/ homeostasis
Regeneration/ Disease
Matrix Signals
Mesenchymal - Epithelial crosstalk


Fibroblasts
Stiff (25 kPa)
YAP/TAZ
nuclei
Soft (0.4 kPa)
YAP/TAZ
nuclei
Epithelial cells
Polarized/ compacted
Low confluence

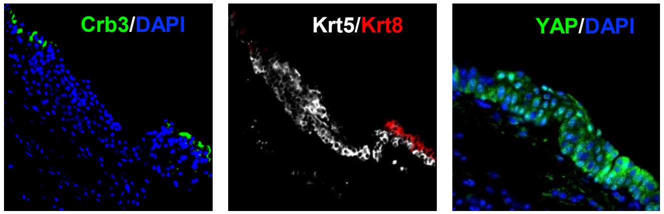
Organ development & homeostasis: cell fate regulation



Airway epithelial stem cell renewal and differentiation

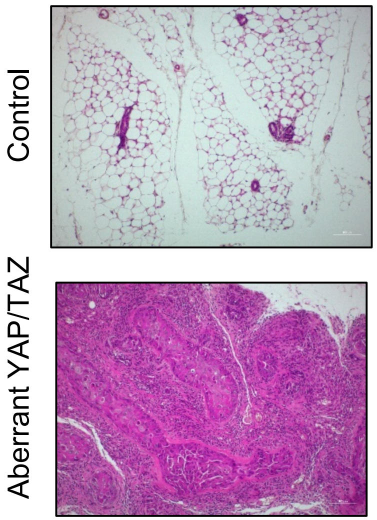


Polarity-mediated homeostasis



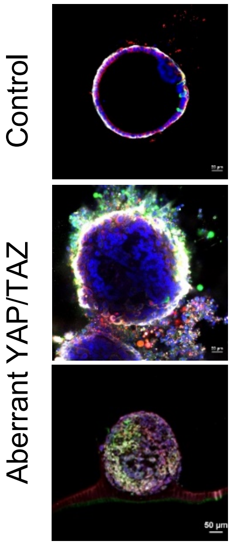
Cancer initiation and progression

In vivo

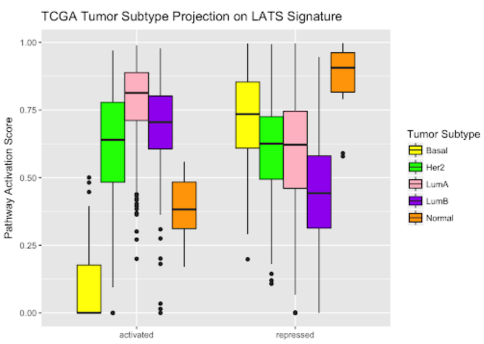


Mammary gland

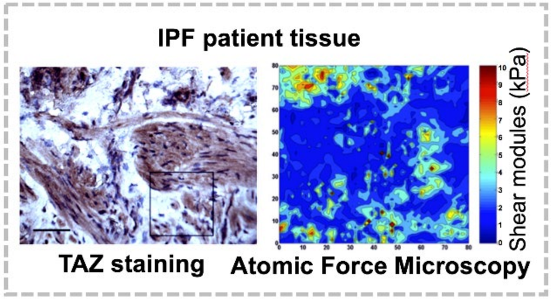
In vitro

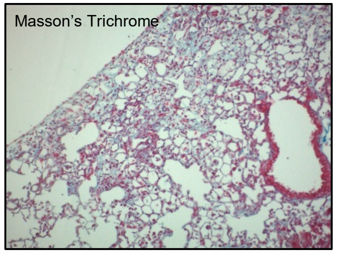


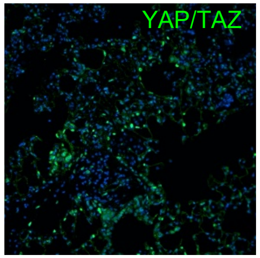
In silico



Tissue regeneration & Fibrosis







Mechanobiology of Heritable Connective Tissue Disease
(*ECM and the 3 Bears*)

Matthew D. Layne

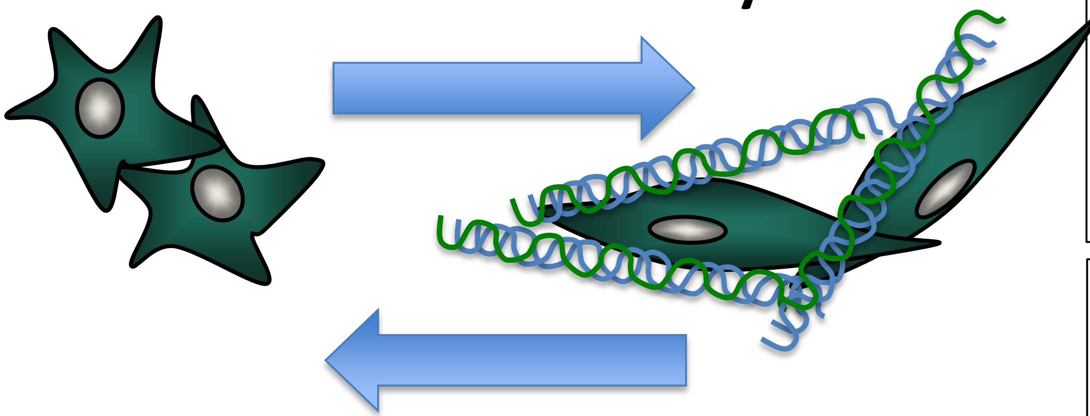
Associate Professor
Biochemistry, BUSM

ECM, Mechanotransduction & Three Bears

Mechanotransduction Drives Fibrosis

"Too Hard" = Fibrosis

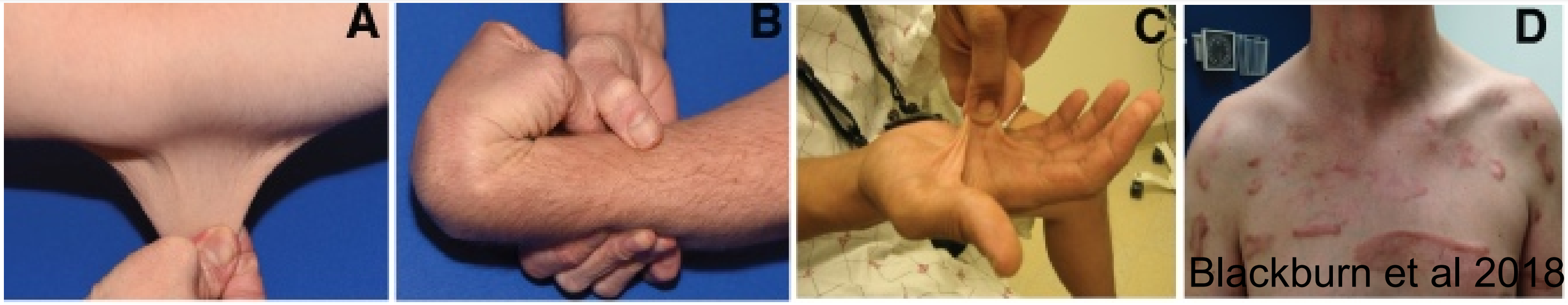
Fibroblasts **Myofibroblasts**



INCREASE TISSUE STIFFNESS
- Increase ECM production
- Increase migration
- Proliferation
- Activates TGFβ

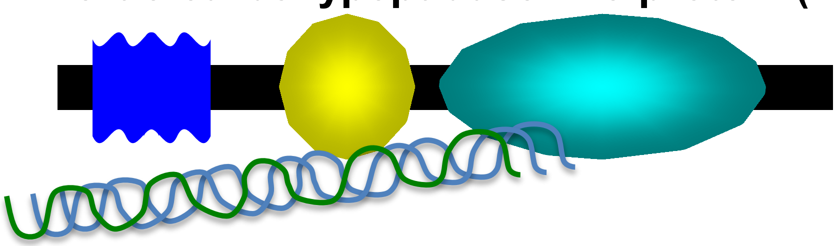
FIBROSIS THERAPY?
- Decrease tissue stiffness
- Reduce ECM production

Connective Tissue Disease "Too Soft" = Ehlers-Danlos Syndrome



- Heritable collagenopathies (~1:2500 people) → collagen fiber defects
- Mutations in collagens I, III, V, XII, processing machinery, & accessory proteins
- ECM structural and assembly defects
- skin hyperextensibility • joint hypermobility • tissue fragility/vascular weakness
- Mechanotransduction disease

Aortic carboxypeptidase-like protein (ACLP/*AEBP1*)



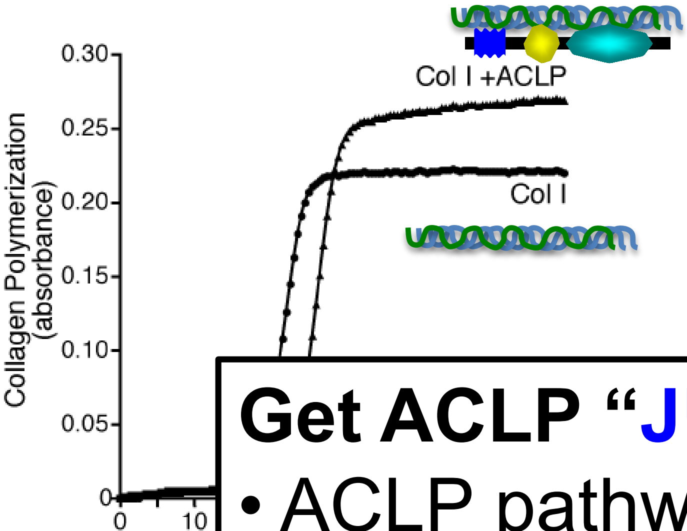
TOO MUCH:
- organ fibrosis
- vascular disease
- cancer?

TOO LITTLE:
- Human ACLP mutations
- Novel EDS variant
- joint laxity
- defective wound healing
- vascular disruption

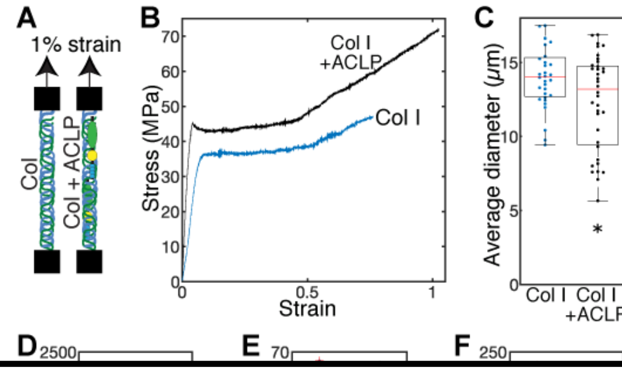
- ECM protein→binds collagens
- Stimulates TGFβ and Wnt signaling

How does ACLP Regulate ECM Assembly and Mechanotransduction?

Collagen assembly



ACLP-ECM mechanical properties

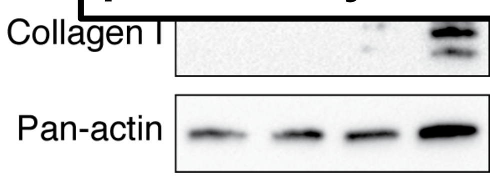


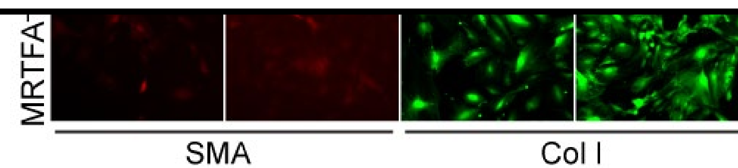
Wet-spun fibers

Gwenn Hoffmann
Michael Smith
Joyce Wong

Get ACLP “JUST RIGHT”

- ACLP pathways tissue fibrosis
- Stromal reaction in cancer
- Differentiation of vascular progenitors
- Increase mechanotransduction signaling pathways to treat EDS



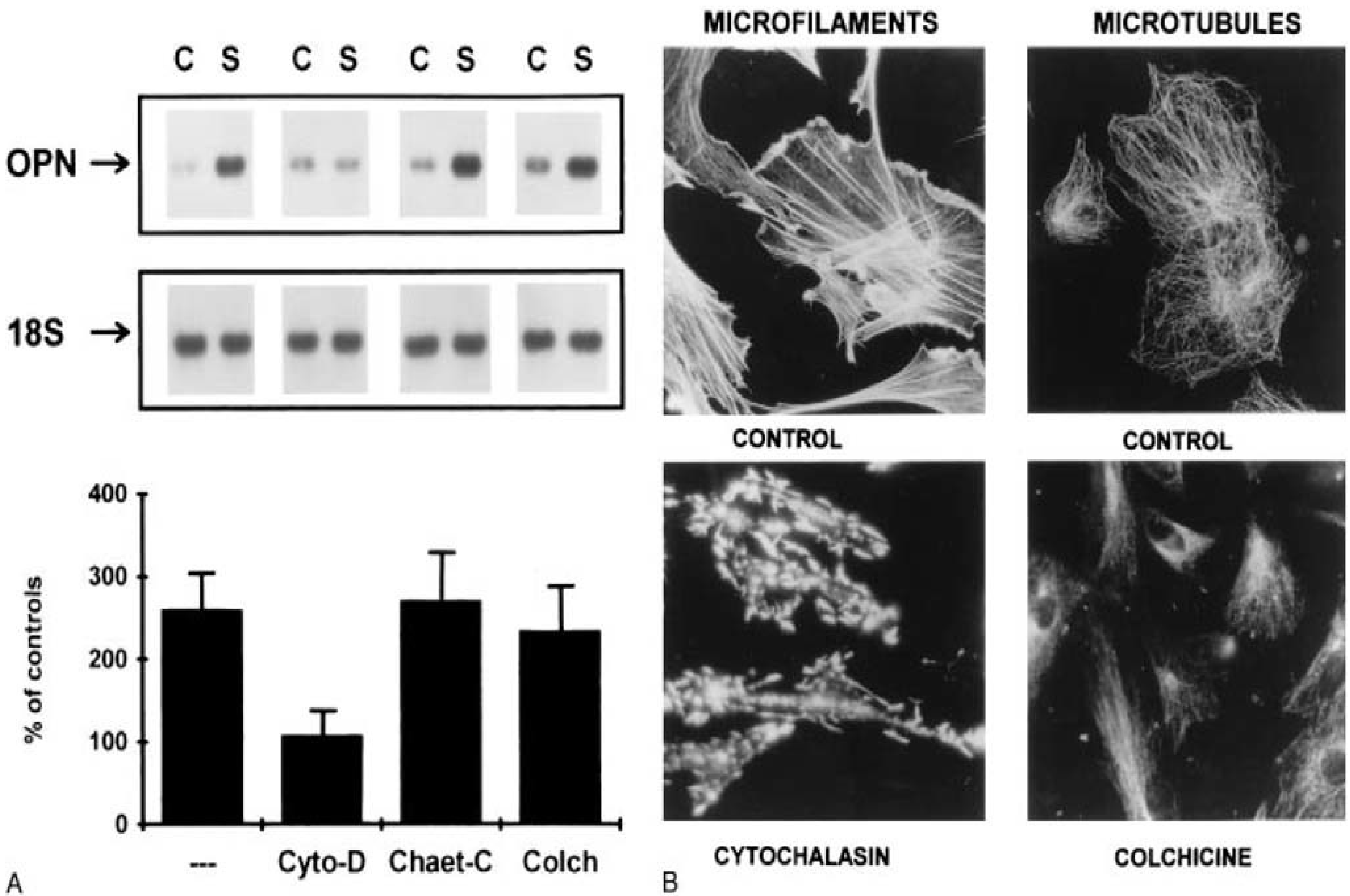


Cytoskeletal Structure Mediates In Vitro Mediated Signaling By Mechanical Stretch

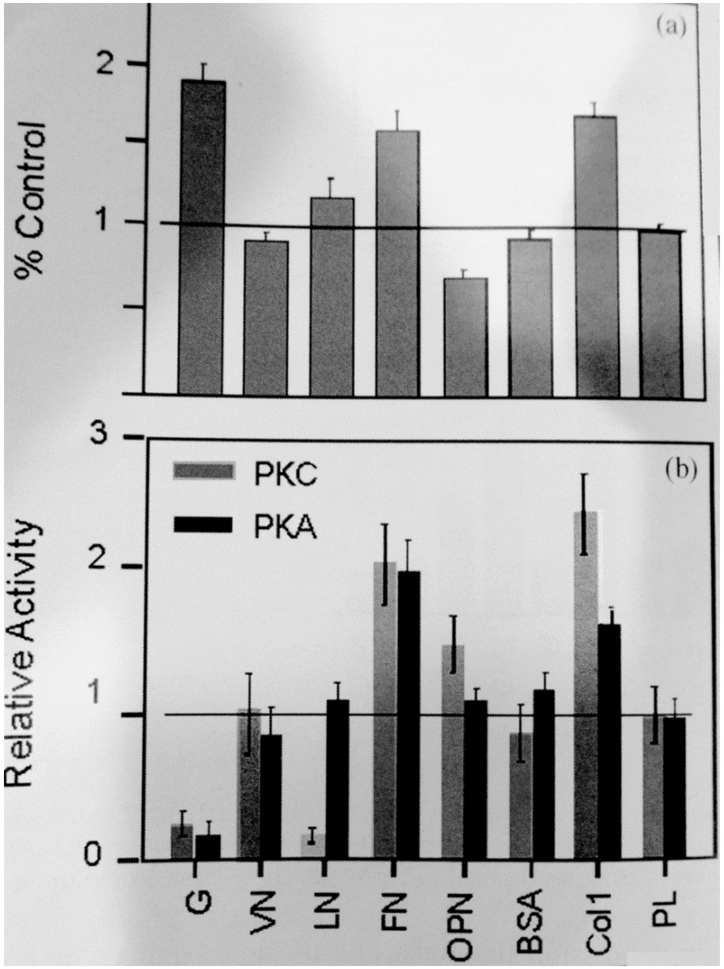
Louis C. Gerstenfeld, PhD

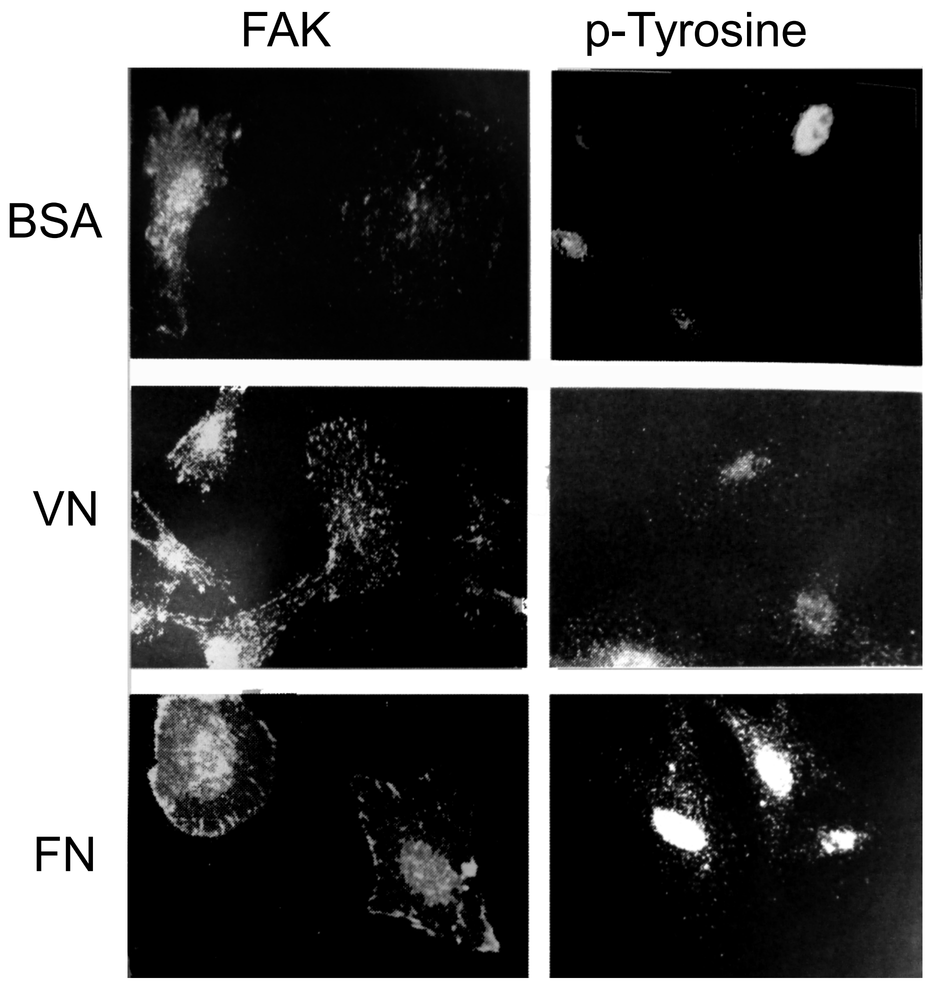
Professor Orthopedic Surgery
Adjunct Professor Mechanical Engineering

Intact Actin Cytoskeleton but not Microtubule Structure is Needed to Facilitate Stretch Mediated Gene Upregulation in Osteoblasts



Selective Ligand Integrin Based Interactions Mediates Specific Kinase Activation and Focal Adhesion Kinase Cellular Organization





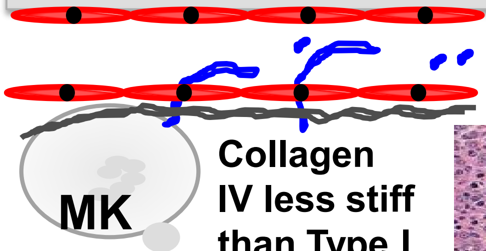
Mechanobiology of Marrow Tissue in Health and Pathology

Katya Ravid

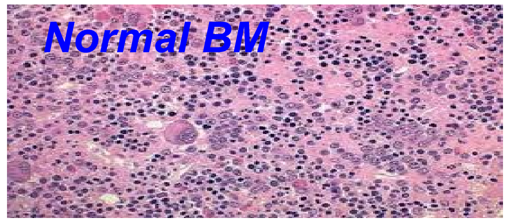
Professor of Medicine, Biochemistry and Biology
Department of Medicine, School of Medicine

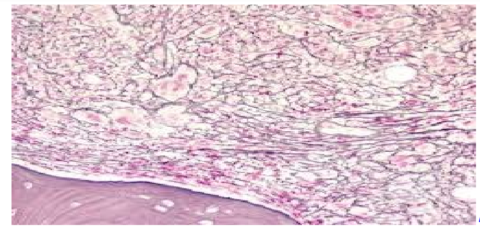
Work presented here was/is co-supported by a Fulbright Research Scholar Award and ANR in collaboration with Catherine Leon/ INSERM

- Platelets play key roles in thrombosis, hemostasis, cardiovascular disease, etc.
- Platelets are released from their precursor cell, the megakaryocyte (**MK**) in the bone marrow **(BM)**; The BM is heterogeneous: composition & stiffness



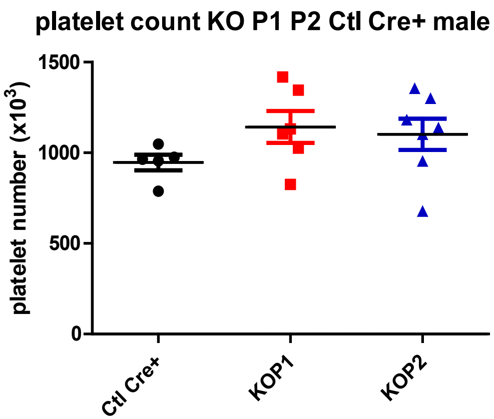
On a stiffer BM, MKs release less platelets. **Why and How?**

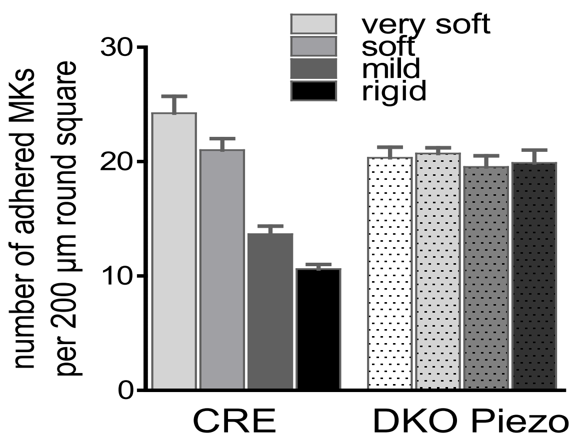


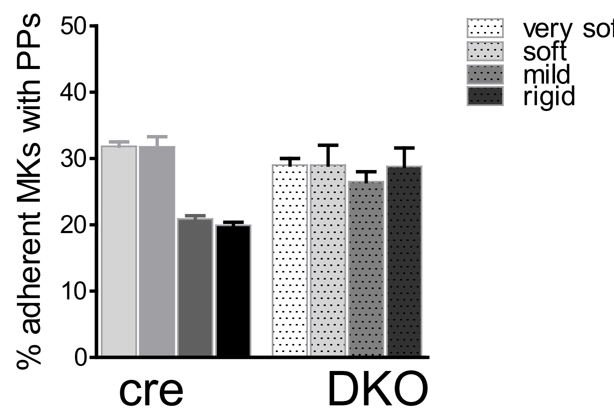


Myelofibrotic BM= very stiff= reduced platelets

- We identified **Piezo 1/2** mechanosensetive cation channels as expressed on MKs, and dys-regulated in disease such as MK-associated Myelofibrosis;
- To probe for functional significance, we collaboratively engineered mice in which **Piezo1/2 is knocked out in MKs and platelets**







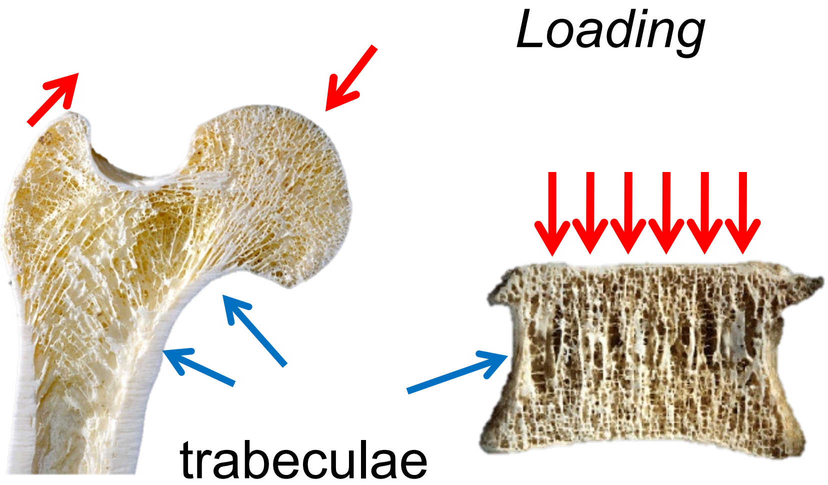
Cytoskeletal & transcriptome changes in response to Piezo-mechanosensing?

Osteocytes Mechano-Transduction

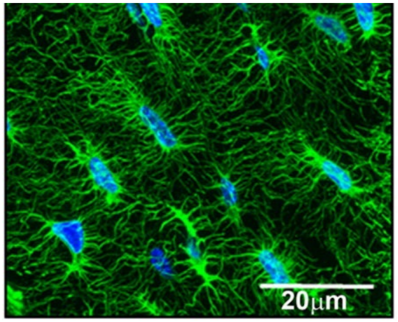
Paola Divieti Pajevic MD, PhD

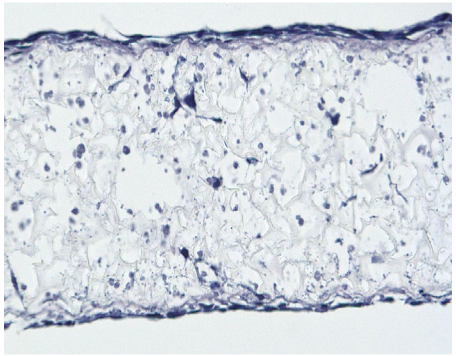
Associate Professor
Molecular and Cell Biology, GSDM

Bone adaptation to mechanical loading



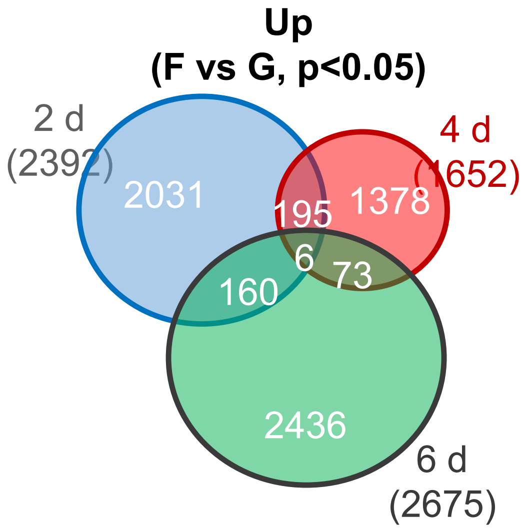
Our laboratory investigates the effects of hormones (PTH), intracellular signaling (Gs alpha) and mechanical forces (gravity) on skeletal homeostasis





In vitro model

1) Osteocytic cell line
2) Simulated microgravity
3) Microgravity (ISS-OSTEO4)
4) Fluid flow shear stress
5) CRISPR/Cas9 for gene editing



In vivo model

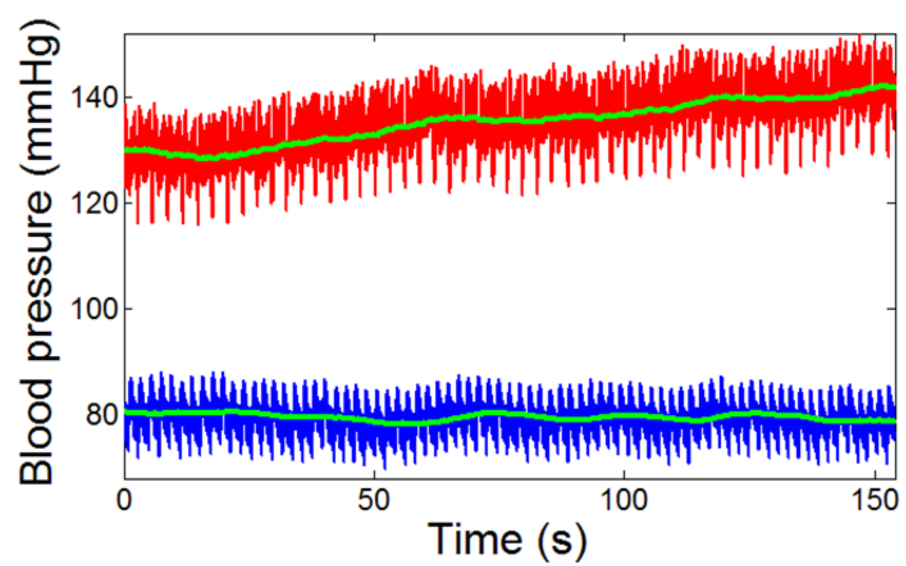
1) Hind limb unloading (tail suspension)

http://divietipajeviclab.com

Fluctuation-Driven Mechanotransduction Regulates Mitochondrial Structure and Function

Béla Suki

Professor
Biomedical Engineering, College of Engineering



• Fluctuations accompany life and change with disease.

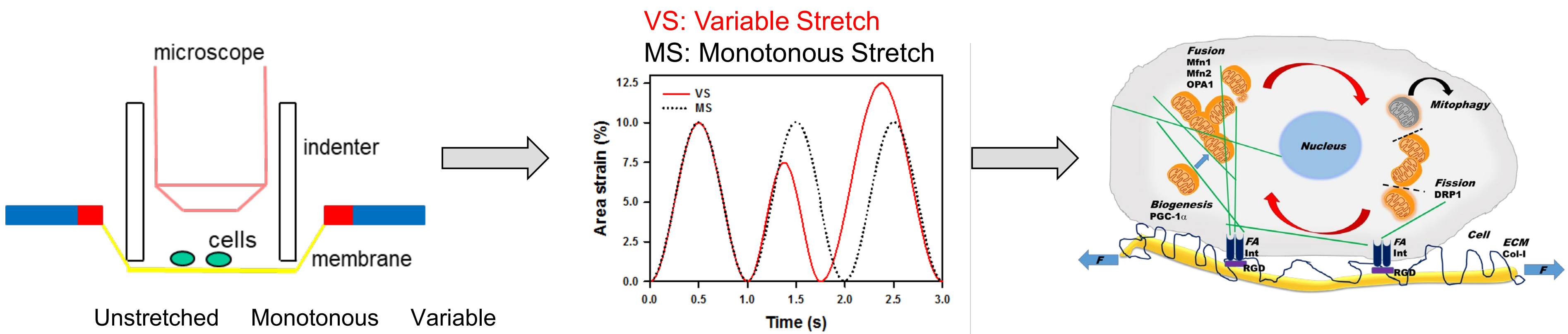
• Breathing, the heart rate, blood pressure, muscle contraction and body movements generate variabilities.

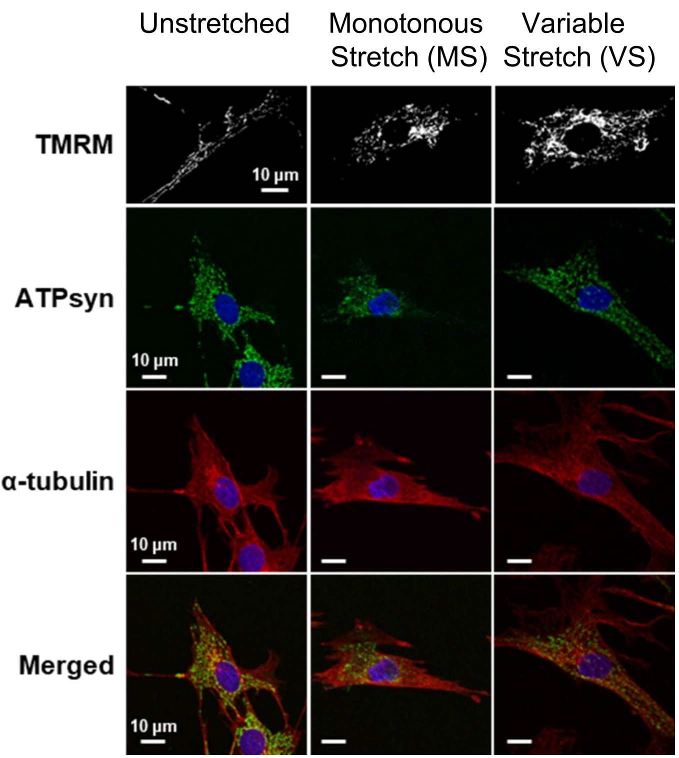
• Stretch/pressure/force that adherent cells are exposed to in the body will show similar variabilities.

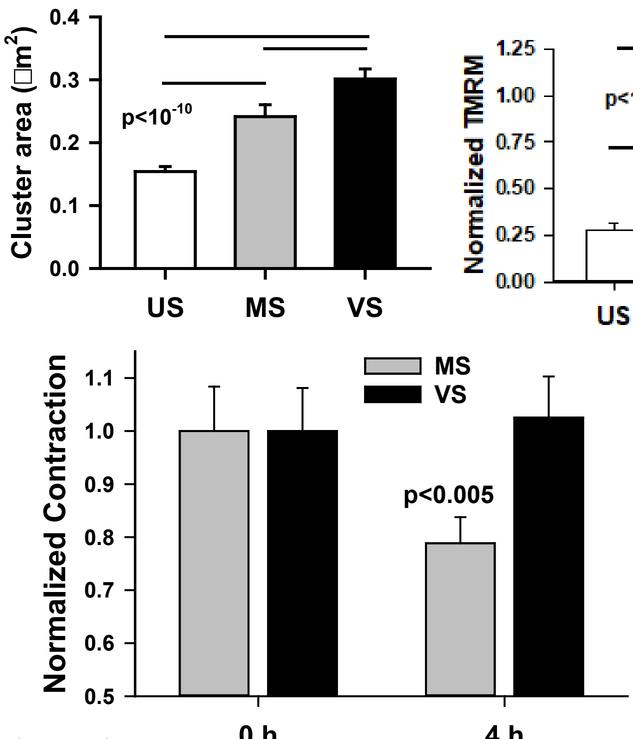
• Over hundreds of millions of years of evolution, cells must have adapted to such fluctuations.

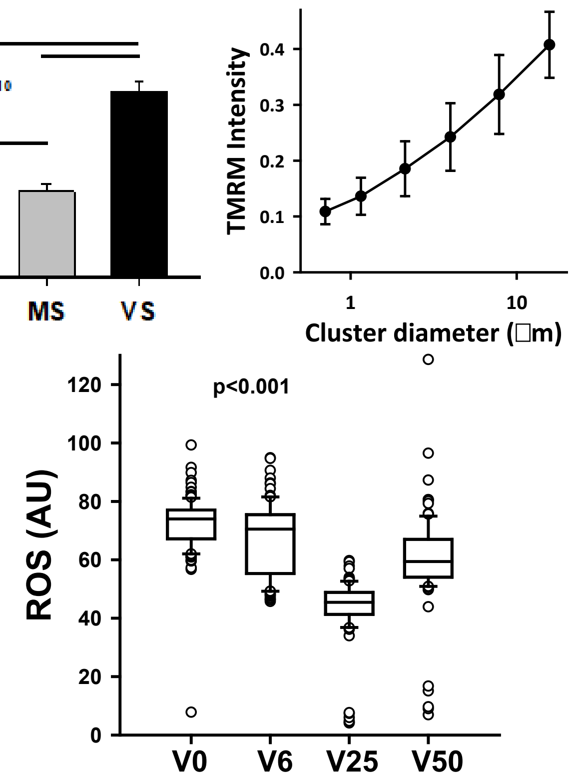
• ***We hypothesize that all cell functions that are affected by mechanical forces will be sensitive to fluctuations in mechanical stimuli, called Fluctuation-driven Mechanotransduction.***

• If variability was built into cell function when multicellular life evolved ~2B years ago, then variability in stretch should affect the most ancient cellular process, the generation of energy in the form of ATP!









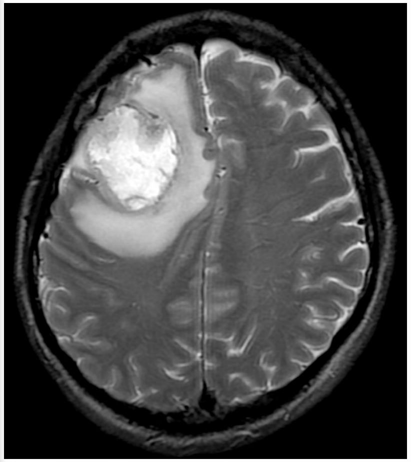
Bartolák-Suki et al. Nature Materials (2015)

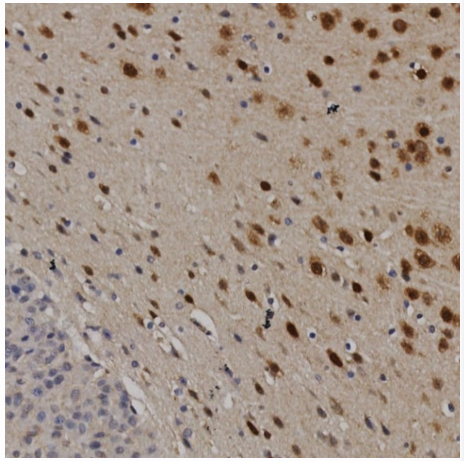
Neurological Dysfunction Associated to Mechanical Stresses at the Brain-Tumor Interface

Hadi T. Nia

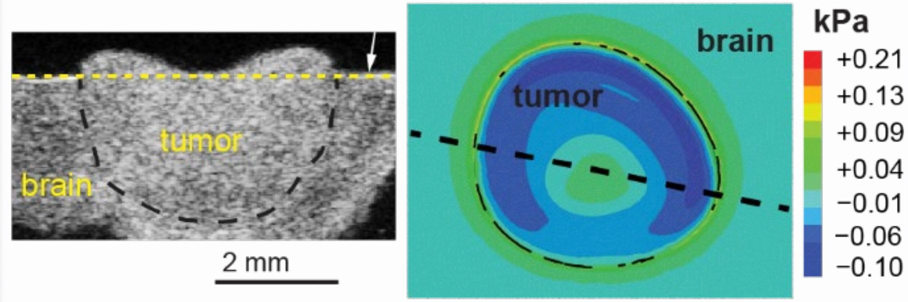
Assistant Professor
Department of Biomedical Engineering

Main hypothesis: compressive mechanical stresses at the brain-tumor interface cause neurological dysfunction





What are the magnitude of the mechanical stresses at the tumor-brain interface?

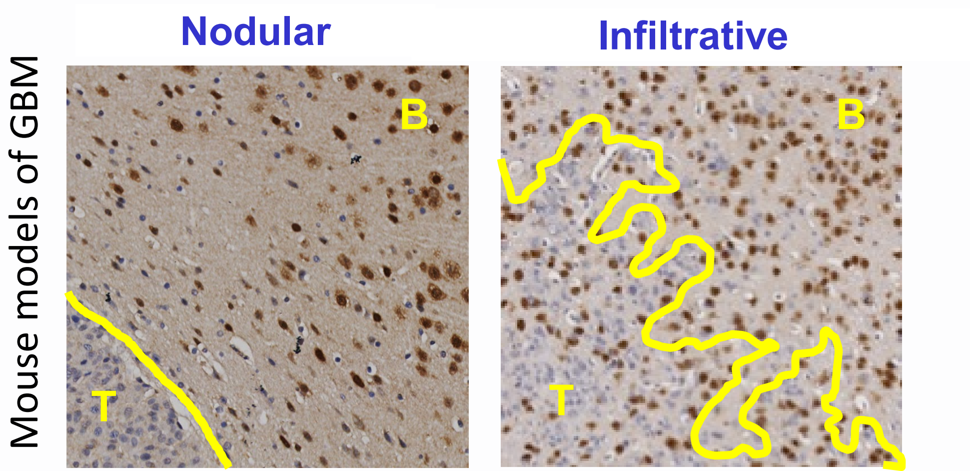


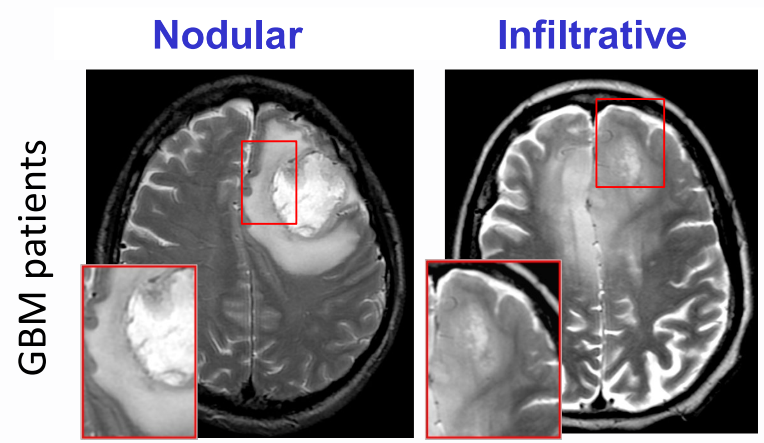
Using planar-cut method

H.T. Nia, et al, *Nature Biomed. Eng.* 2017

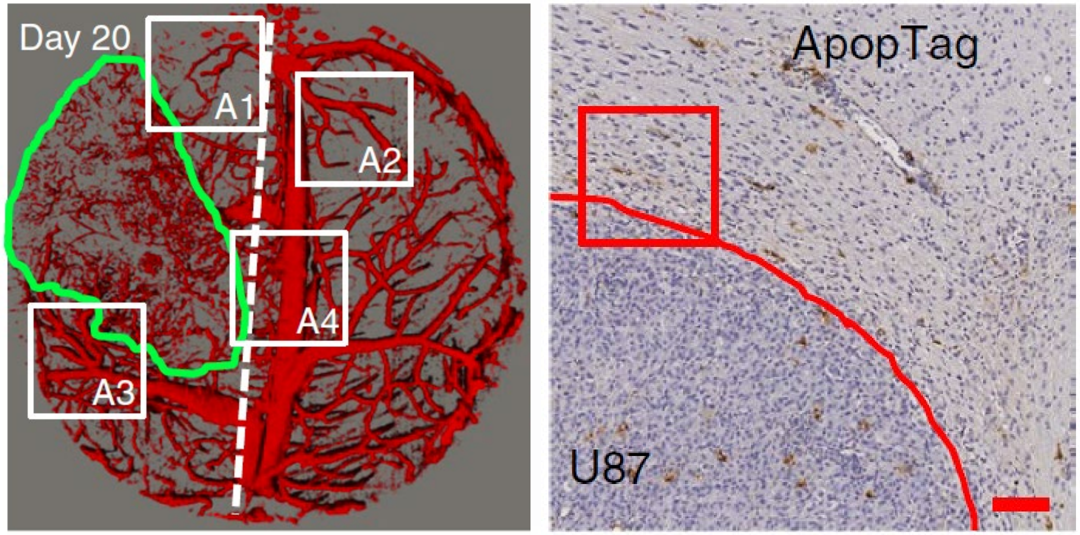
H.T. Nia*, M. Datta*, et al, *Nature Protocols* 2018

What are the origins of these stresses? Role of growth pattern

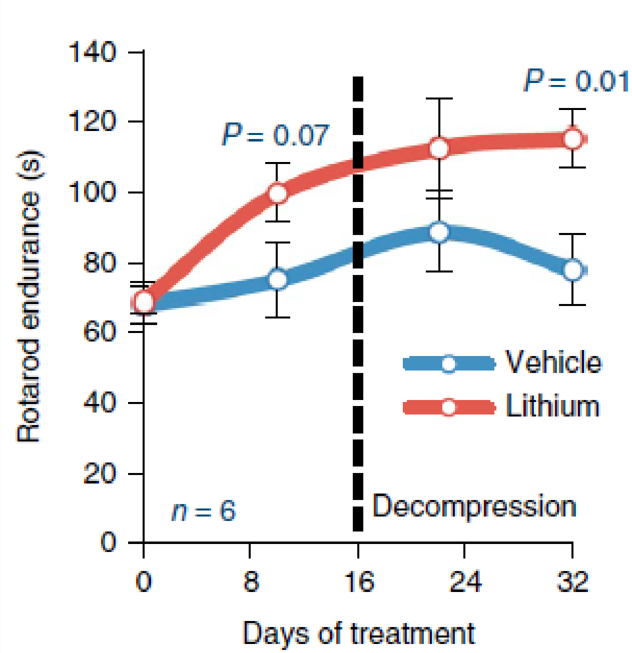


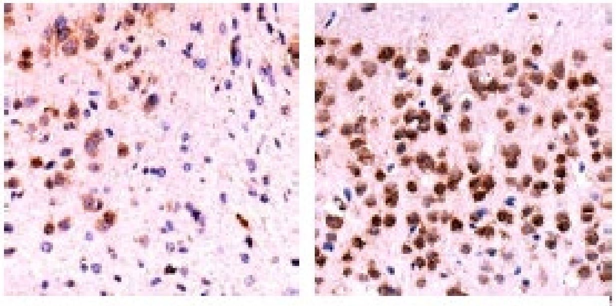


What are the consequences of these mechanical stresses?

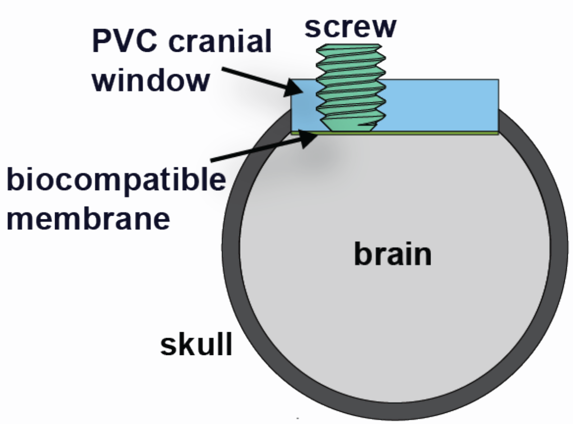


How can we target the effect of the mechanical stresses?



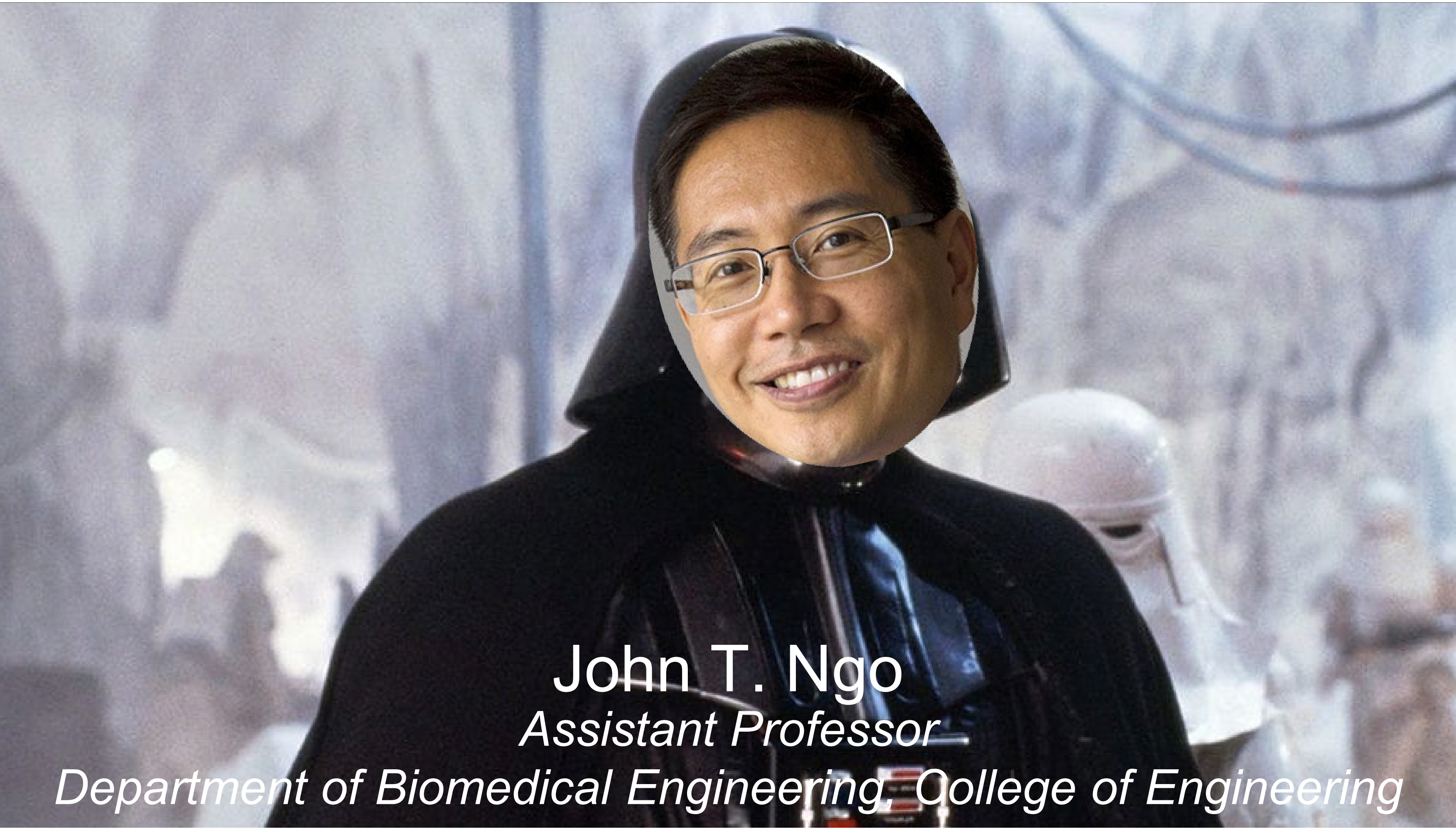


How to decouple mechanical from biological stresses at the tumor-brain interface?



G. Seano*, H. T. Nia*, et al, *Nature Biomed. Eng.* 2019

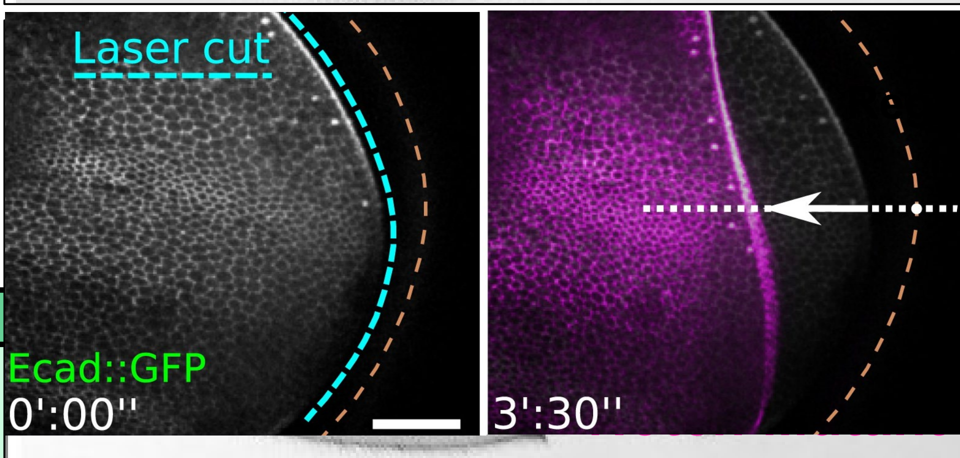
Probing and Programming How Cells Sense Force

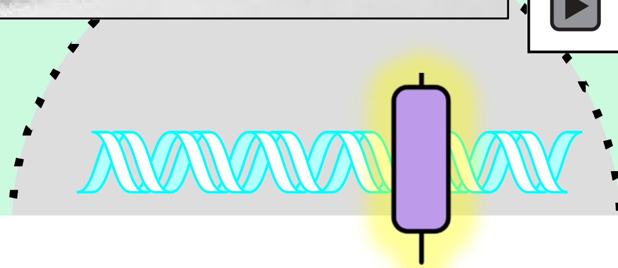


How do cells sense and interpret mechanical force?

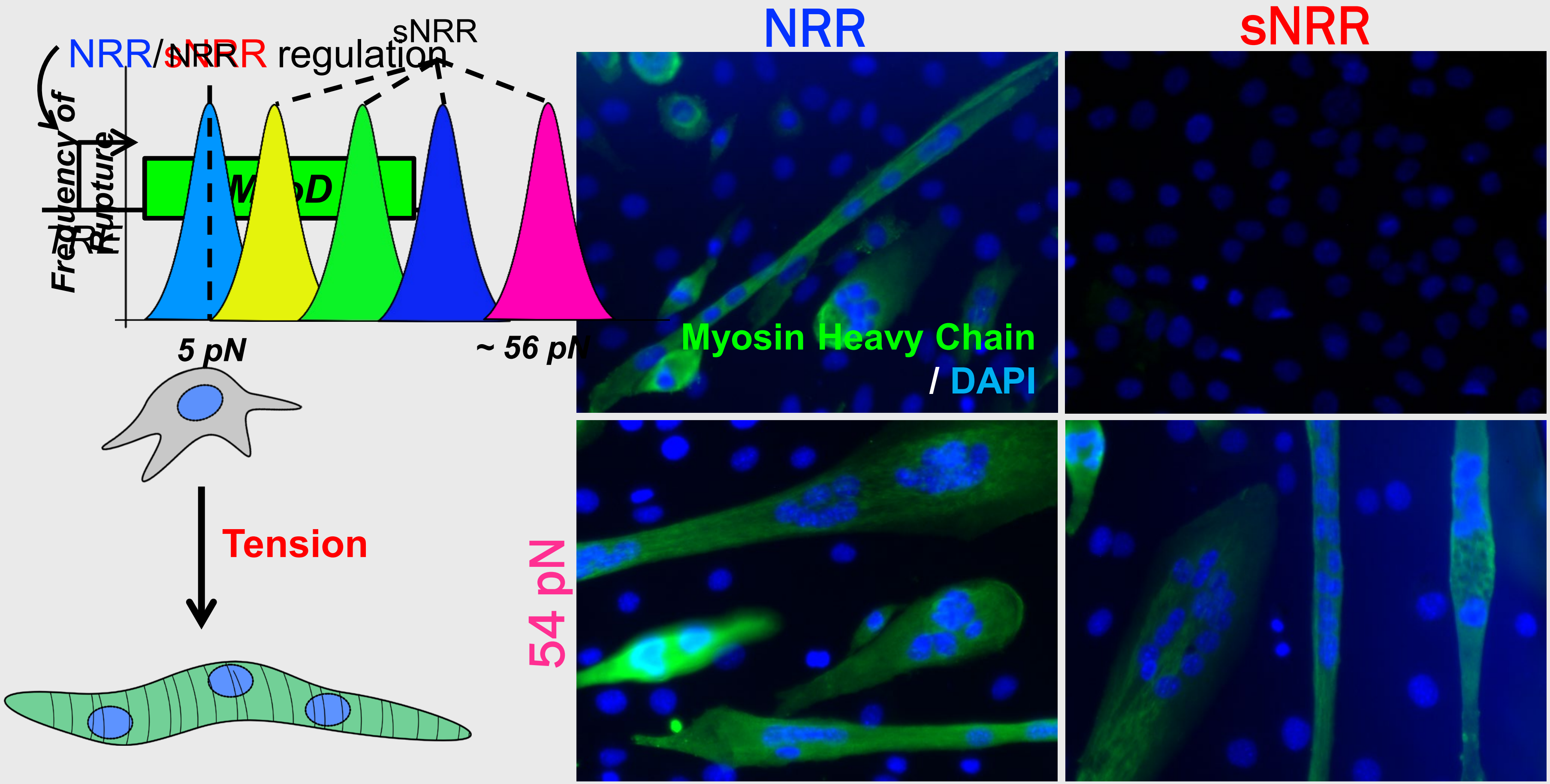
Notch mediates cell-cell communication

Notch Activation Requires 2 Inpu
1) Ligand binding
2) Tension





Synthetic Mechanobiology for Directing Myogenic Differentiation in Engineered Fibroblasts

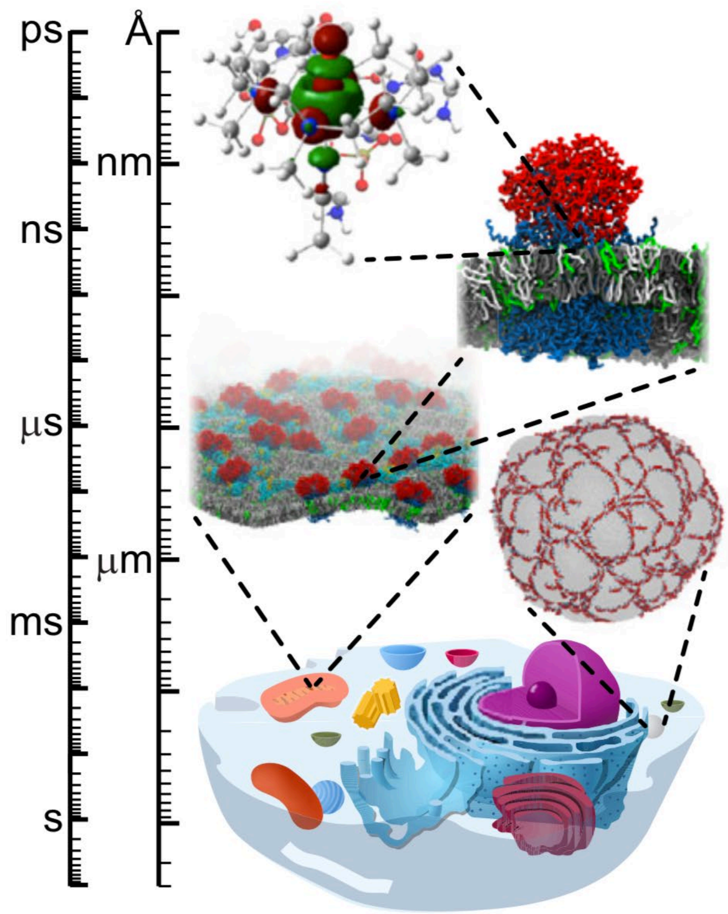


Multi-Scale Computations for Mechanobiology

Qiang Cui

Professor
Department of Chemistry
College of Arts & Sciences

MULTI-SCALE COMPUTATIONAL MODELS IN BIOLOGY



Quantum

- Chemical reactions
- Spectroscopies

All-atom

- Protein structure/dynamics
- Materials properties
- Protein-membrane interfaces

Coarse-grained

- Protein assembly
- Local membrane bending

Supra-coarse-grained

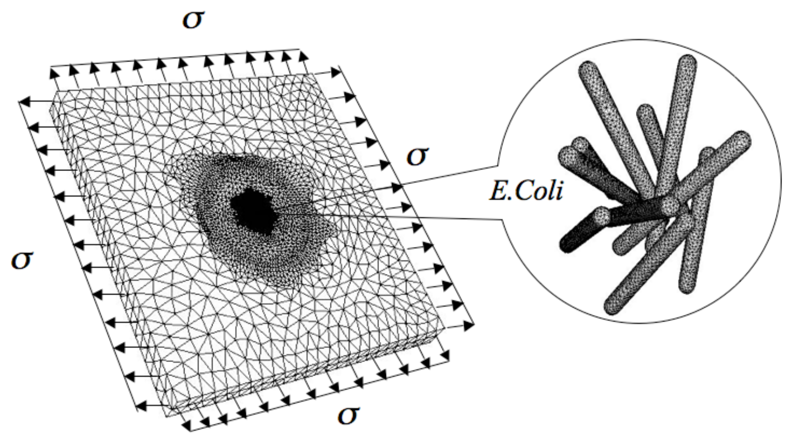
- Larger scale remodeling
- Other collective behaviors
- Domain formations

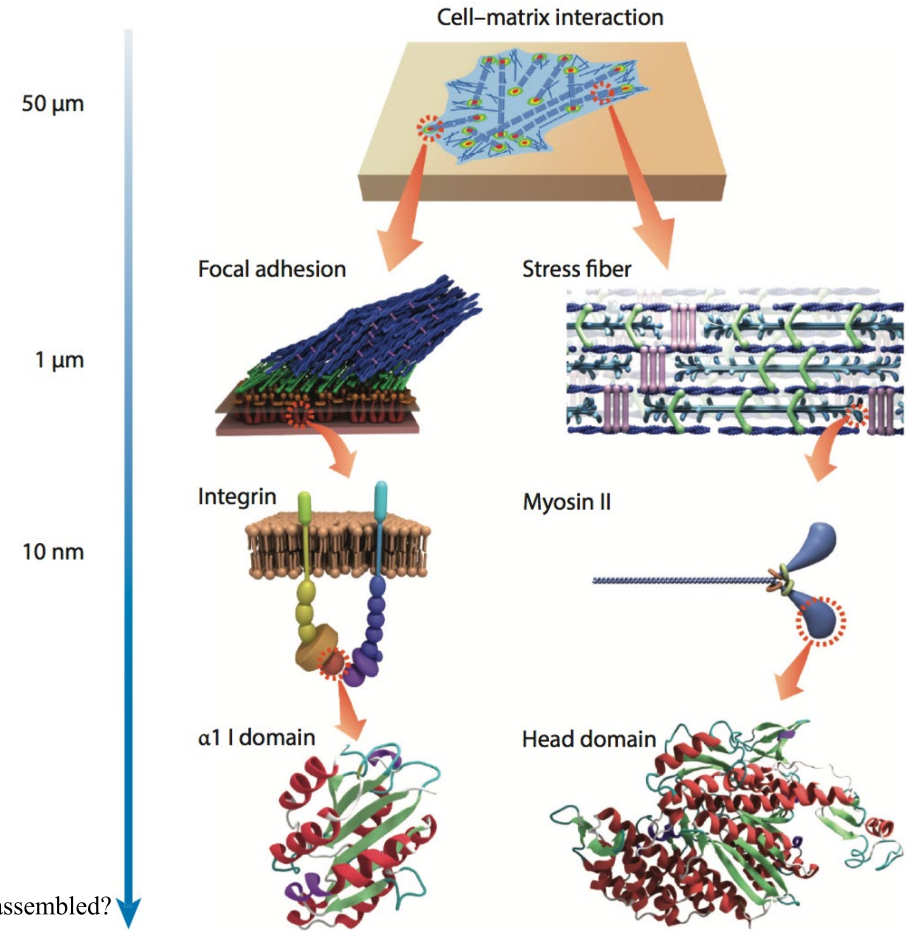
Continuum

- Tabulations, scission
- Coupled w/ rxn-diffusion
- …

S. Marrink et al. ('16)

TOWARDS LARGER-SCALE PHENOMENA





is a stress fiber assembled?

does matrix rigidity regulate gene expression?

Which level of rigidity does a cell sense on a highly heterogeneous matrix?

How does a cell distinguish between 2D and 3D environments?

w/ X. Chen, *Biophys. J.* ('06; '09); *J. Mech. Biomol.* ('18)

H. J. Gao et al. *Annu. Rev. Biophys.* ('15)

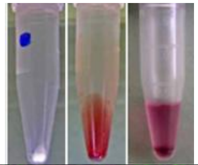
How Structural and Geometric Heterogeneity Shape Local ECM Mechanics?

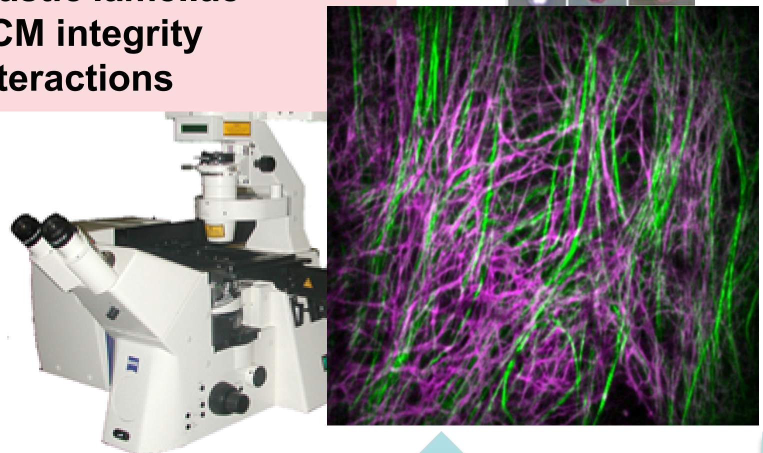
Katherine Yanhang Zhang

Professor
Department Mechanical Engineering
College of Engineering

Coupled Experimental and Modeling Approach

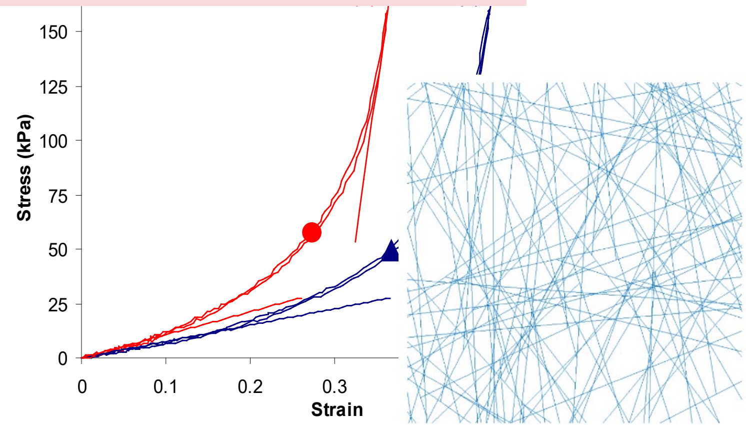
Microstructure
Elastin, collagen fiber
Elastic lamellae
ECM integrity
Interactions





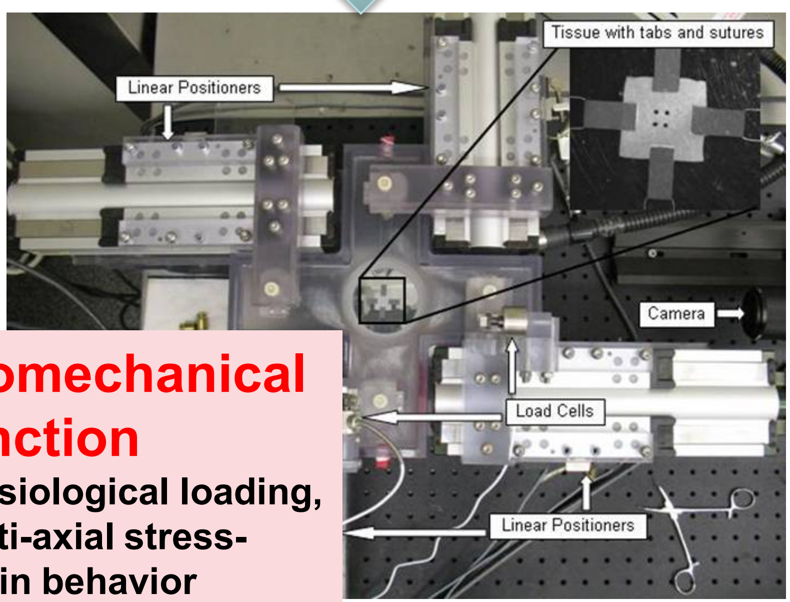
Input

Structure-based constitutive model



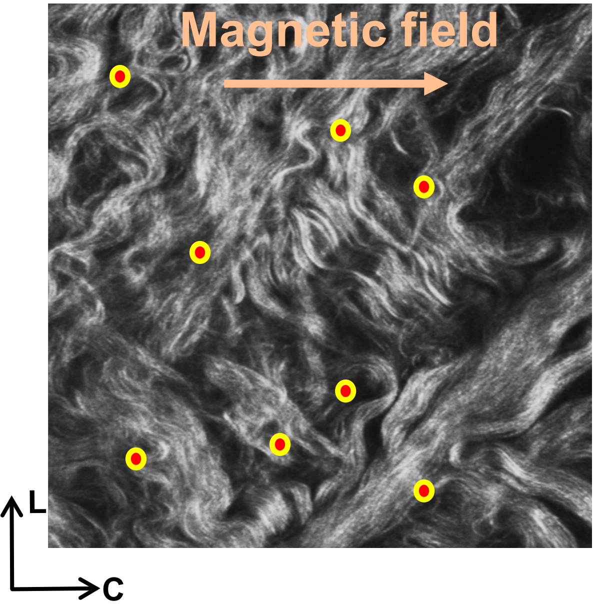
Model calibration & validation

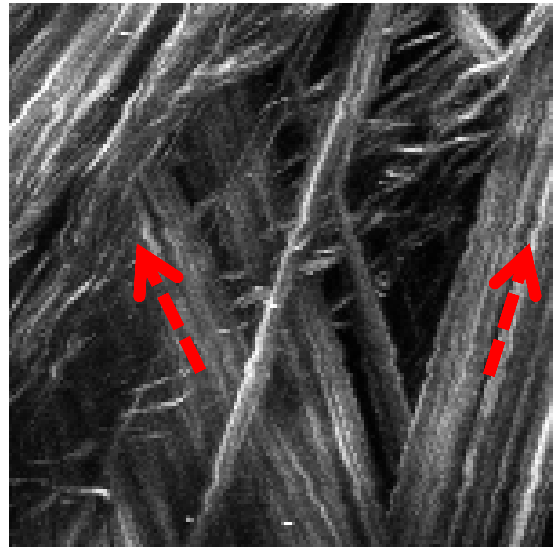
Structure-function

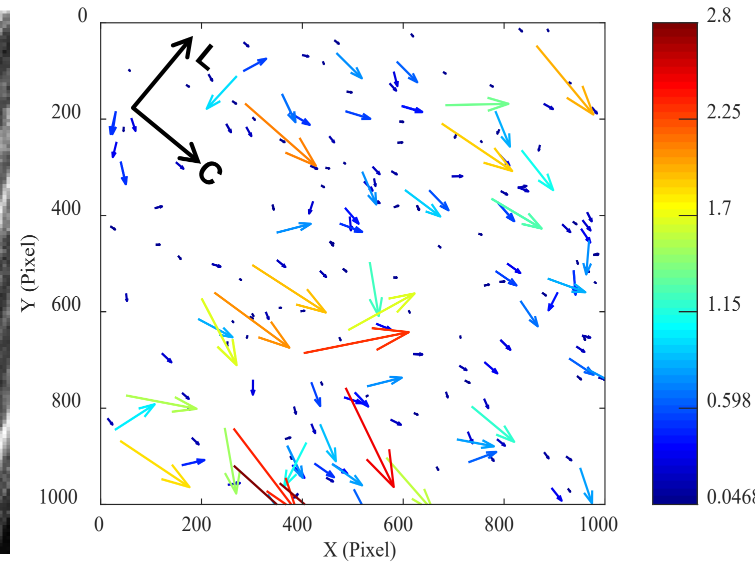


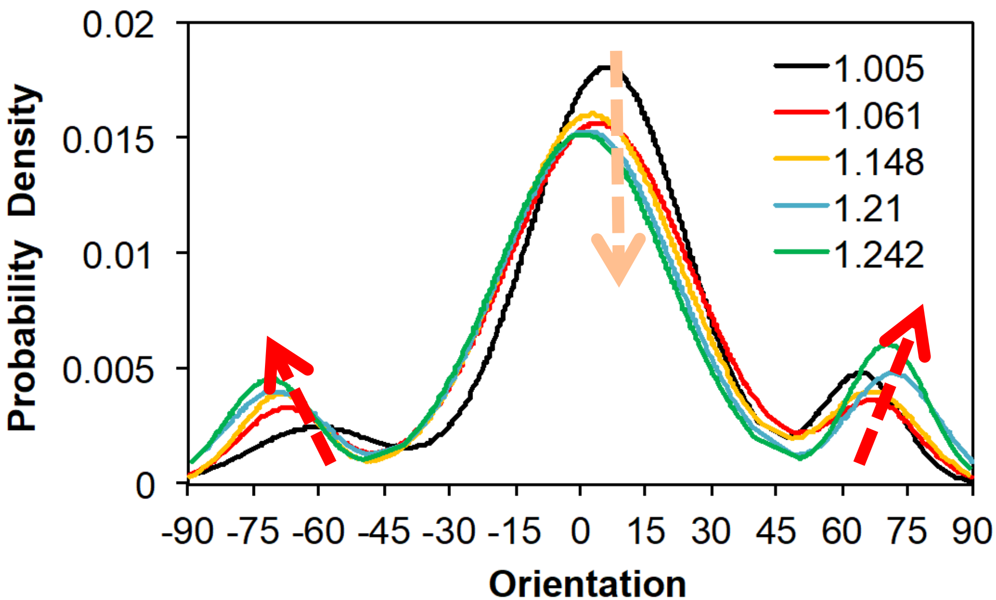
Biomechanical function
Physiological loading, multi-axial stress-strain behavior

How do different ECM constituents and cells contribute and modify the dynamic behavior of arteries?





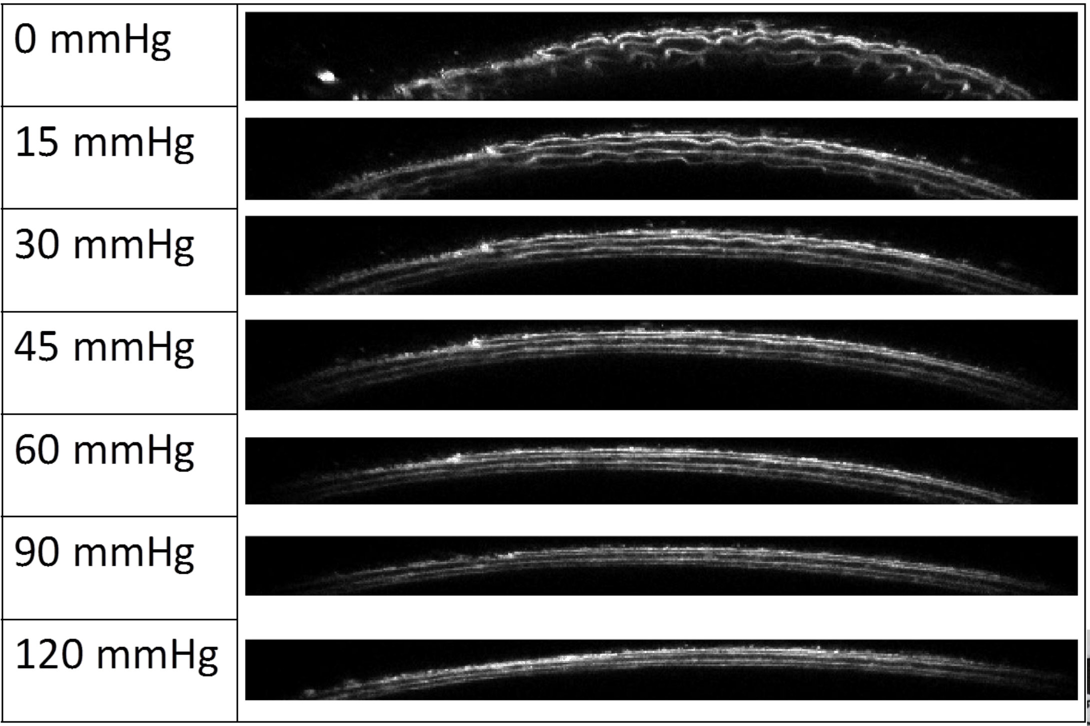


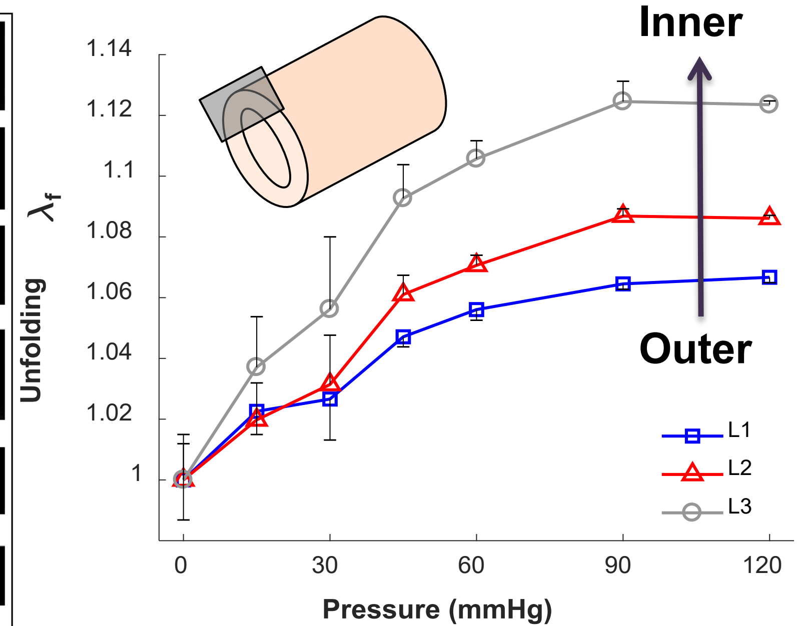


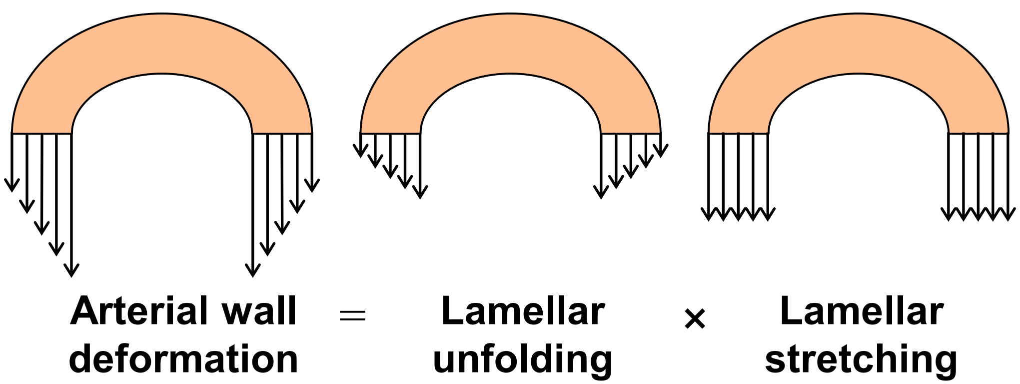
Fiber orientation and recruitment play important roles in dictating the local ECM properties.

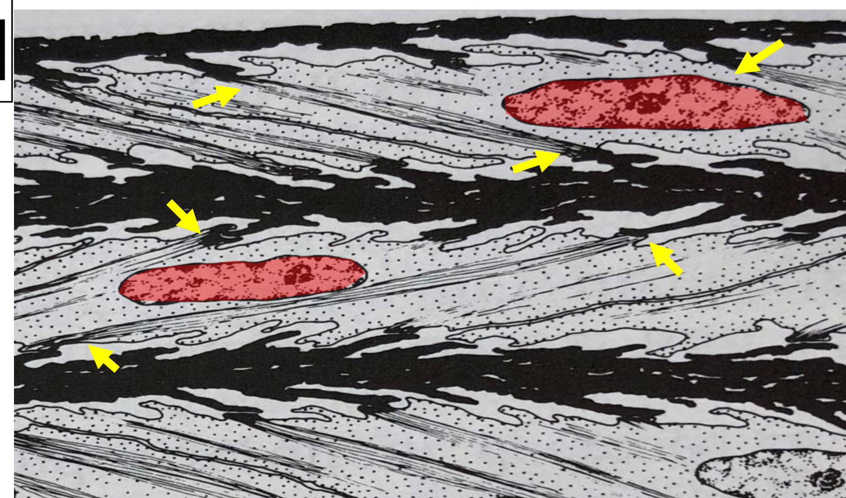
Complex structural and mechanical interplay in multi-scale ECM mechanics

(Li et al., J Mech Behav Biomed Mater, 2018)









The waviness gradient of elastic lamellar layers plays an important role in equalizing local circumferential stretch/stress.

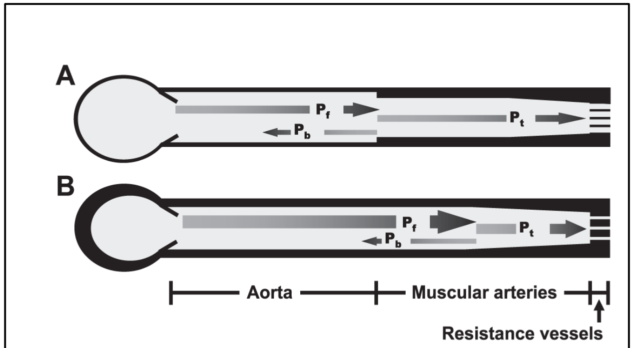
(Yu et al., J Royal Society Interface, 2018)

Capitalizing on Mechanobiology to Prevent Vascular Dementia

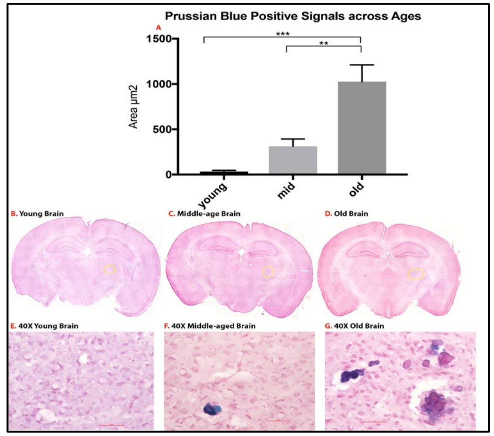
Kathleen Morgan

Professor
Health Sciences, Sargent College

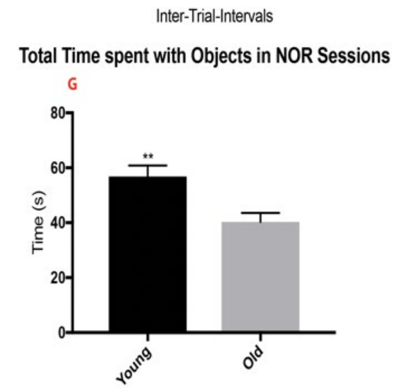
Concept 1: Our aortas get stiffer as we age and this is bad for our brains



Mitchell GF et al JAP 2010



Mouse model –Y. Wang, Zikopoulous, et al

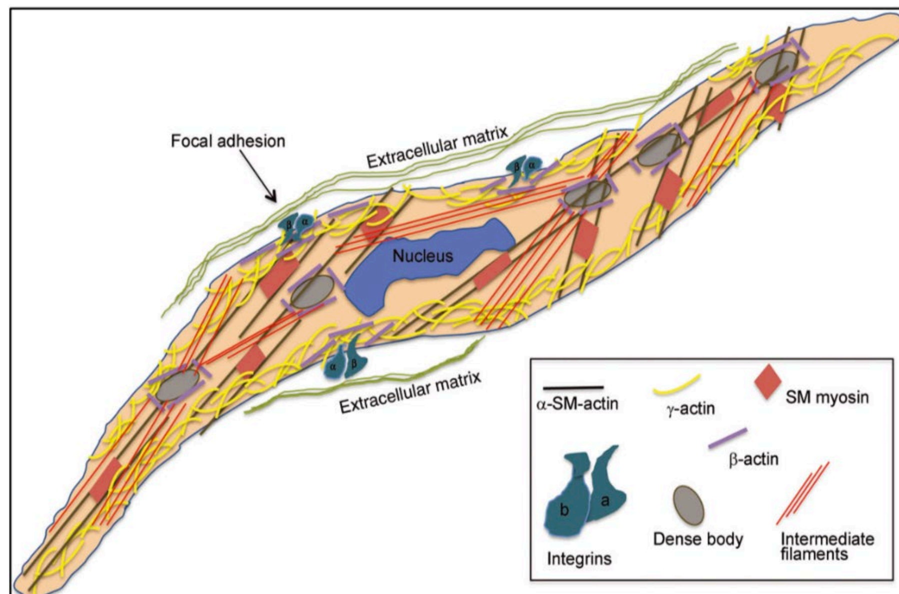


Wang, Kantak et al

- **Molecular Mechanisms of aging-induced Aortic stiffness:**
  - independent of atherosclerosis
  - precedes hypertension
  - matrix is a factor
  - dVSMC is an equally large factor

There are at least 3 components to cellular stiffness:

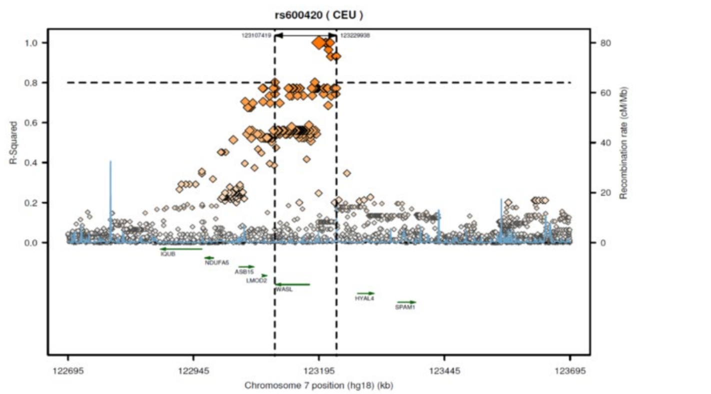
1. Contractile Filament Activation
2. Actin Polymerization
3. Focal Adhesion Dynamics



Yamin & Morgan J.Phys 2012

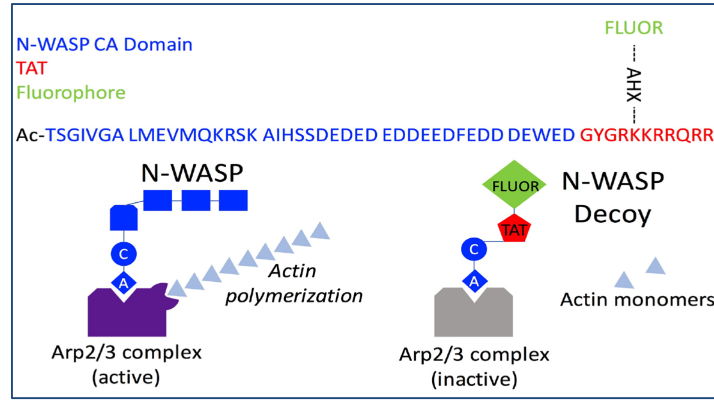
Concept 2: Focal Adhesion Proteins are Associated with Aortic Stiffness AND We Can Decrease Aortic Stiffness with Microbubble–Loaded decoy peptides

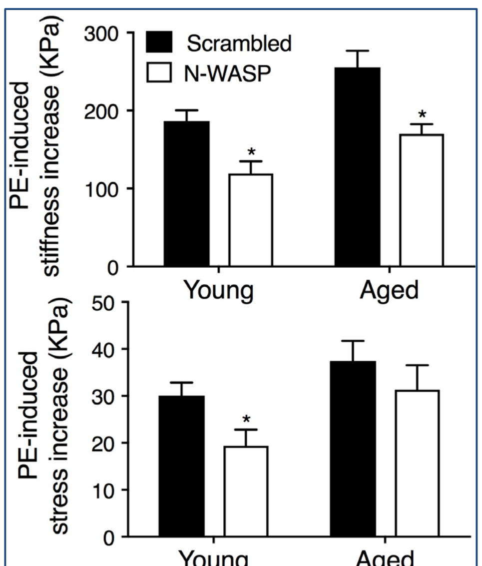
Human Linkage Disequilibrium between Aortic Stiffness and Polymorphisms in the Focal Adhesion WASL gene.



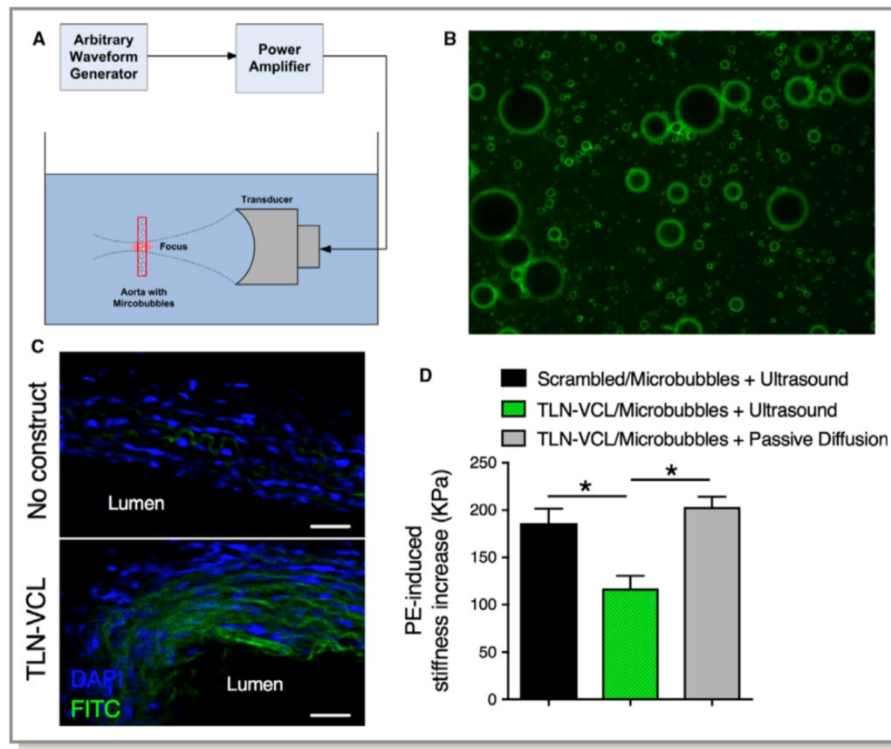
AortaGen Consortium Aortic Stiffness ARC

Strategy of decoy peptide design





Nicholson et al 2018



Upcoming Events

For more details: bu.edu/research/events

Research on Tap:

Please email research@bu.edu with topic suggestions for next year

Research How-To:

How to Secure Funding from the Department of Defense
Wednesday, April 10, 2019 | 3-5 pm