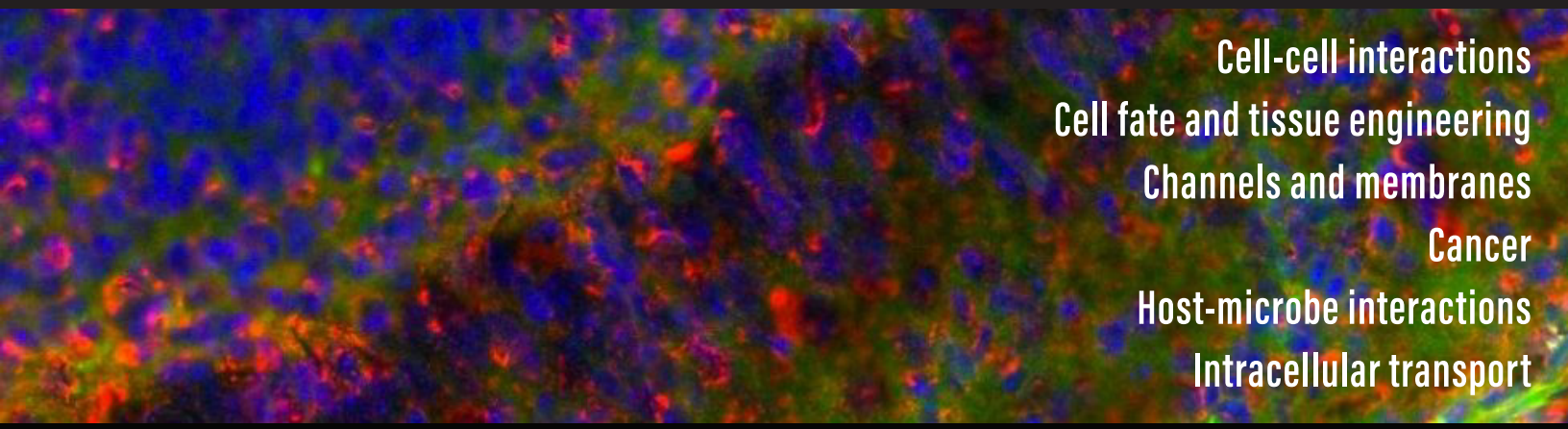
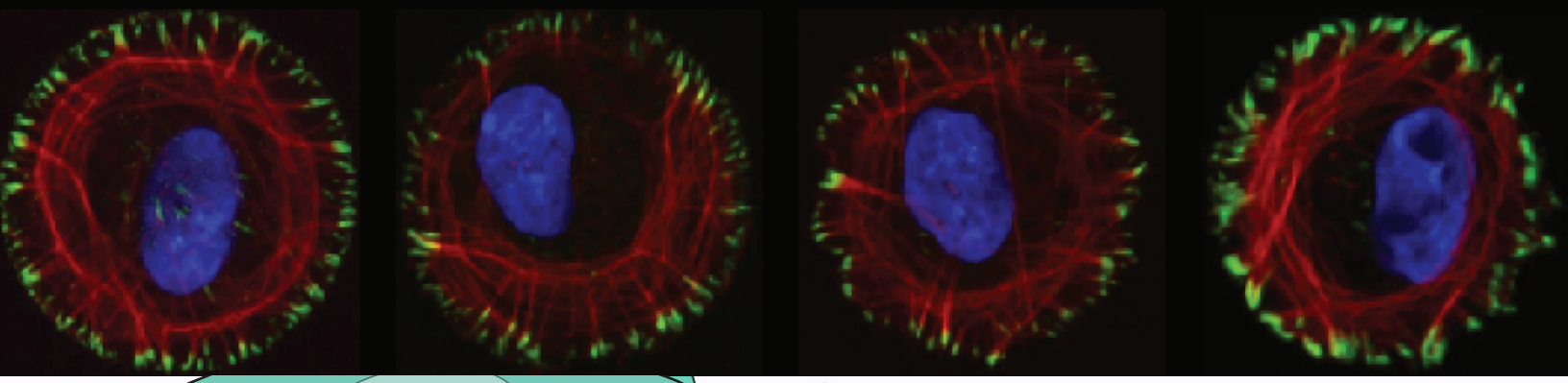
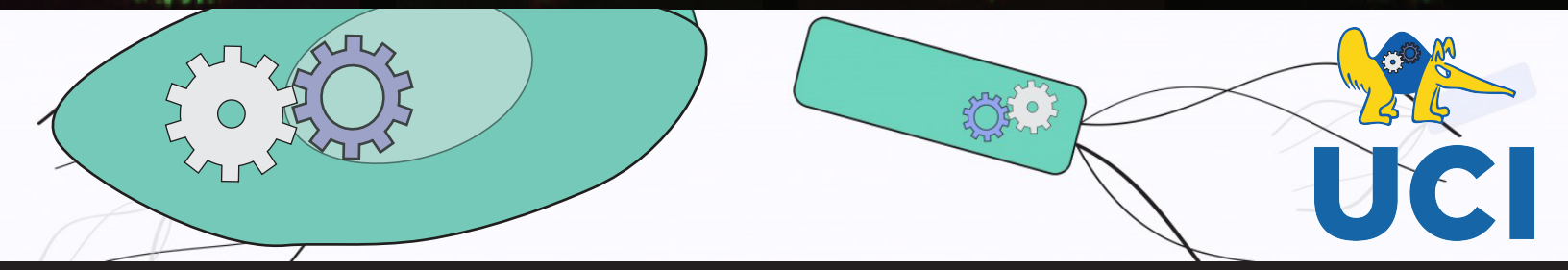
# Mechanobiology Symposium

# The Mechanome in Action






## July 26th-27th, 2018

## University of California, Irvine

Gross Hall Conference Center

## Welcome to the 2018 Mechanobiology Symposium!

In the past few decades, striking progress in biology has come from quantitative understanding of two foundational areas of biology: genetics and biochemistry. However, to us, there is a clear third category: mechanobiology – that is, mechanical forces and the machinery that produces, senses and responds to them. Mechanobiology plays a role in how cells move, divide and organize themselves. Perhaps more surprisingly, research is revealing a role for mechanobiology in how cells communicate and determine their fate, how bacteria and viruses infect their hosts, how we develop into healthy organisms, and how it goes wrong in disease. Experimental tools to study mechanobiology are notoriously difficult to apply to the delicate, wet, salty, crowded, noisy, heterogeneous environment of living systems. Researchers capable of overcoming these challenges, marshaling the tools of physics, engineering, biology, medicine, mathematics and computing, will help establish biomechanics as a third pillar of biology, alongside genetics and biochemistry.

In 2016, the Mechanobiology Symposium was held at UC San Diego. Entitled “Building the Mechanome”, this two-day meeting brought together biologists, computational scientists, mathematicians and physicists who think about different aspects of mechanobiology. Feedback from the attendees was uniformly positive, and UC Irvine offered to host the next meeting in 2018. As a natural next step, we entitle this meeting “The Mechanome in Action” and will highlight many biological functions that mechanobiology is helping elucidate.

Mechanobiology, as a field, tends not to have a single center of mass. Instead, it flourishes in meetings like this one, at the interface of many disciplines. Critical to our ability to hold this meeting are the resources of four Centers based at UC Irvine: The Center for Complex Biological Systems, the Sue and Bill Gross Stem Cell Research Center, the Center for Cancer Systems Biology, and the Center for Multiscale Cell Fate. The latter two centers are new, and we encourage you to be on the lookout for many opportunities these centers will offer the mechanobiology research community. We also benefit from the support of the National Institute of General Medical Sciences and the National Science Foundation, and UC Irvine Office of Research, Cancer Research Institute and the Schools of Engineering, Medicine, and Physical Sciences. Most of all, the success of the meeting and ultimately discovery in the area of mechanobiology depends on the participants. Thank you for attending – Enjoy!

The organizers,

Jun Allard, Department of Mathematics
Tim Downing, Department of Biomedical Engineering
Medha Pathak, Department of Physiology and Biophysics
Albert Siryaporn, Department of Physics

Center for Complex Biological Systems

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Cancer Systems Biology

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# Mechanobiology Symposium: The Mechanome in Action

July 26-27, 2018

Irvine, California, USA

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**The Mechanome in Action: Finding the Pieces, Building the Puzzle**

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**Additional Acknowledgements to:**
The organizers would like to thank Drs. Sidney Golub (Former Director) and Aileen Anderson (Director) of the Sue and Bill Gross Stem Cell Research Center for the generous use of the Gross Hall Conference Center for hosting the Symposium.

# Day 1 – Thursday July 26, 2018

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|---|---|
| **8:00 –8:30AM** | **Registration and Continental Breakfast**<br>**Gross Hall, 4th Floor, Thorp Conference Center** |
| 8:30 – 8:35 | Welcome (Medha Pathak) |
| **Session 1: Tissue Organization and Engineering** | |
| 8:35 – 8:55 | *Short Talk – Andrea Cugno (UC San Diego)*<br>"Shape-induced alteration of second messenger dynamics in dendritic spines" |
| 8:55 – 9:15 | *Short Talk – Zachary Reitz (UC Irvine)*<br>"The Adhesome as a Limiting Factor in iPSC Production" |
| 9:15 – 9:55 | Elliot Botvinick (UC Irvine)<br>"Cells establish their own stiffness landscape" |
| 9:55 -10:05 | Opportunity Award Announcement (Tim Downing) |
| 10:05 – 10:10 | Introduction to Speed Dating (Jun Allard) |
| **10:10 – 10:30** | **Coffee Break – Gross Hall** |
| **Session 2: Mechanobiology of Cancer** | |
| 10:30 – 10:50 | *Short Talk – Jesse Placone (UC San Diego)*<br>"Inhibition of mechanical signaling reduces malignant transformation of mammary epithelial cells on a dynamically stiffened matrix" |
| 10:50 – 11:10 | *Short Talk – Amy Rowat (UC Los Angeles)*<br>"Identifying novel targets for cancer therapies through the cell mechanome" |
| 11:10 – 11:50 | Dino Di Carlo (UC Los Angeles)<br>"Physical Phenotyping of Cells for Diagnostics and Drug Discovery" |
| **12:00 – 1:30PM** | **Lunch – Gross Hall** |
| **1:30 – 3:30** | **Poster Session – Sprague Hall**<br>*Odd numbered posters will present from 1:30 – 2:30PM*<br>*Even numbered posters will present from 2:30 – 3:30PM*<br>*Posters may remain on the boards until 4:30PM Friday.* |
| **Session 3: Cell and Tissue Mechanics** | |
| 3:30 – 3:50 | *Short Talk – Mark Alber (UC Riverside)*<br>"Computational study of remodeling of fibrin networks under compression" |
| 3:50 – 4:15 | Arpita Upadhyaya (University of Maryland, College Park)<br>"Cytoskeletal dynamics and mechanosensing in immune cells" |
| 4:15 – 4:55 | Cheng Zhu (Georgia Tech)<br>"Mechanobiology at the molecular level" |
| **4:55 – 5:00** | Acknowledgements and future plans (Albert Siryaporn) |
| **6:00 – 8:00** | **Banquet – Pacific Ballroom, Student Center** |

# Day 2 – Friday July 27, 2018

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| **8:00 –8:30AM** | **Continental Breakfast**<br>**Gross Hall, 4th Floor – Thorp Conference Center** |
| **Session 4: Channels and Membranes** | |
| 8:30 – 8:50 | *Short Talk – Jerome Lacroix (Western University of Health Sciences)*<br>"Activation of Piezo1 with a Small Molecule Agonist" |
| 8:50 – 9:15 | Allen Liu (University of Michigan)<br>"Repurposing mechanosensitive channel to study 3D cell migration" |
| 9:15 – 9:55 | Ardem Patapoutian (The Scripps Research Institute)<br>"Structure and function of PIEZO family of mechanically activated ion channels" |
| **9:55 – 10:15** | **Coffee Break – Gross Hall** |
| 10:15 – 11:15 | **Lightning Talks - Gross Hall**<br><br>Steven Abel (University of TN, Knoxville)<br>Ian Berg (University of IL, Urbana-Champaign)<br>Morgan Chabanon (UC San Diego)<br>George Degen, (UC Santa Barbara)<br>Danial Faghihi-Shahrestani (UT, Austin)<br>Yue Liu, (University of British Columbia)<br>Ali Nematbaksh, (UC Riverside)<br>Asher Preska Steinberg, (Caltech)<br>Arjun Singh Yadaw (Icahn Institute of Medicine, Mount Sinai)<br>Zhuo Yang (UC Los Angeles)<br>Wei-Zheng Zeng (The Scripps Research Institute) |
| **Session 5: Cell Fate and Disease** | |
| 11:15 – 11:35 | *Short Talk – Mehrsa Mehrabi (UC Irvine)*<br>"In Vitro Modeling of Variable Heart Diseases due to Lamin A/C Mutation via Patient induced Pluripotent Stem Cell-derived Cardiomyocytes" |
| 11:35 – 12:00 | Emily Mace (Columbia University, Irving Medical Center)<br>"Defining mechanisms of human NK cell differentiation" |
| **12:00 – 1:30PM** | **Lunch – Gross Hall** |

## Day 2 – Friday July 27, 2018

**Session 6: Cellular Dynamics**

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| 1:30 – 1:50 | *Short Talk – Yizeng Li (Johns Hopkins University)*<br>"Cellular Responses to Different Hydrodynamic Environments" |
| 1:50 – 2:15 | Jing Xu (UC Merced)<br>"Dissecting Intracellular Transport: A Physicist's Perspective" |
| **2:15 – 4:15** | **Poster Session – Sprague Hall**<br>*Odd numbered posters will present from 2:15 – 3: 15 PM*<br>*Even numbered posters will present from 3:15 – 4:15 PM*<br>*Please remember to take your poster with you at the conclusion of this session.* |

**Session 7: Bacterial Physiology**

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| 4:30 – 4:50 | *Short Talk – Bo Li (UC San Diego)*<br>" Spatiotemporal Development of Growing Bacterial Colonies" |
| 4:50 – 5:30 | Gerard Wong (UC Los Angeles) |
| 5:30 – 5:35 | Poster/Speed Dating Awards (Jun Allard/Tim Downing) |
| 5:35 – 5:40 | Closing Remarks (Medha Pathak) |

## *Short Talk Abstracts*

### Shape--induced alteration of second messenger dynamics in dendritic spines

Andrea Cugno [1], Thomas M. Bartol [2], Terrence Sejnowski [2,3], and Padmini Rangamani [1]
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[2] Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, California.
[3] Division of Biological Sciences, University of California, San Diego, San Diego, California

Communication in neurons is a complex cascade of signal transduction where the presynaptic terminals release neurotransmitters that are taken up by the postsynaptic spines to initiate a series of electrical, chemical, and mechanical events. Many of these events are tightly coupled to the dynamics of $Ca^{2+}$, cAMP, and $IP_3$. The spatio-temporal dynamics of second messengers are involved not only in the propagation of action potentials but also in downstream effects such as long-term potentiation (LTP), long-term depression (LTD), and structural plasticity. It is well established that these cognitive process, related to memory formation, involve the change in shape and size of dendritic spines. The morphology of spines is the results of the complex interaction between the mechanical impedance of the plasma membrane and the forces due to different level of polymerization of actin filaments, which in turn is affected by the concentration of second messengers. Dendritic spines come in a variety of shapes — a mature dendritic spine has different mushroom-like shapes, consisting of a thin neck and a spherical or ellipsoidal shaped head and roughly 19% of mature spines have an endoplasmic reticulum (ER).
How does neuronal shape affect function? This question is central to our understanding of neurobiology, learning, and memory formation. We sought to characterize the effect of spine shape and the presence and shape of the ER, on the spatio-temporal dynamics of second messengers. We developed and analyzed a general mathematical model, in which a set of reaction -diffusion partial differential equations with time -dependent mixed boundary conditions were solved to identify how the geometric parameters are related to the spatial dynamics of the second messenger. We then performed sensitivity analyses on the shape of the domains to demonstrate how shape and reaction parameters may induce different distributions of the specific signaling components.
We theoretically showed how shape may induce transient localization of hot and cold spots of concentration of second messengers in specific region of the spine, and thus eventually induce — at least in principle — a different downstream effects, for example with respect to actin dynamics or spine volume change.

### The Adhesome as a Limiting Factor in iPSC Production

Zachary Reitz, Tri Andrew Quoc Phan, Timothy Downing
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Stem cells are known to sense and respond to their mechanical microenvironment. Previous studies have found that cell differentiation is heavily directed by mechanotransduction pathways. Other evidence has implicated the adhesome in several cellular decisions including differentiation and proliferation. Our lab has recently demonstrated that substrate topography can modulate the epigenetic state of mouse fibroblasts and facilitate cell reprogramming. However, the effectors responsible for this phenomenon remain poorly understood. Here, we explore the effects of RNA knockdowns of genes found within the adhesome on somatic cell reprogramming. We hope to use the insights gained from this screen to better understanding the influence of mechanical forces in somatic cell reprogramming.
For this study, we utilized a human fibroblast cell line (hiF-T) containing a doxycycline inducible OKSM gene cassette. Our reanalysis of a previously published RNA-seq time course revealed that 104 adhesomal genes are dynamically expressed during cellular reprogramming. For each of these genes, three shRNAs were designed and virally transduced into hiF-T cells before reprogramming was initiated. The impact of each shRNA was assessed by immunostaining for TRA-1-60, a known pluripotency marker. This allowed the resulting iPSC colonies to be quantified by count and coverage. Here we show over 90% of adhesome shRNA gene knockdowns increased colony count over shRNA controls. Additionally, our shRNA's improved colony count by as much as 27-fold compared to controls. Of the 10% that decreased colony count, none reduced it by more than a 3.8-fold when compared to the controls. Starker observations can be made in terms of colony coverage area, where increases in reprogramming efficiency of over 100-fold were observed. Ultimately, these results suggest a positive correlation between cellular reprogramming efficiency and adhesome gene suppression.
Our study reinforces the importance of mechanotransduction in cellular reprogramming. It also reveals that reprogramming efficiency can be increased by inhibiting the gene expression of many relevant integrin and cadherin adhesome genes. These findings imply that cellular mechanosensing may act as a significant barrier to efficient somatic cell reprogramming. Further study of these mechanisms may enable a better understanding of somatic cell reprogramming and fate regulation more broadly.

## Inhibition of mechanical signaling reduces malignant transformation of mammary epithelial cells on a dynamically stiffened matrix

Jesse K. Placone [2*], Matthew G. Ondeck [1*§], Aditya Kumar [2*], Christopher M. Plunkett [2], Bibiana F. Matte [2,5], Kirsten C. Wong [2], Daehwan Kim [3], Laurent Fattet [3], Jing Yang [3,4], and Adam J. Engler [1,2,4,6]
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[5] Department of Oral Pathology, Federal University of Rio Grande do Sul; Porto Alegre, RS, Brazil
[6] Sanford Consortium for Regenerative Medicine; La Jolla, CA USA 92037
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Mammary epithelial cells (MECs) are classically known to respond to stiff biomaterials by transitioning to a more mesenchymal state. While this is akin to stiff mammary tumors, breast cancer fibrosis is a dynamic process that results in stiffness increasing from normal ~150 to 5000+ Pascal over months to years. To more accurately mimic the onset of tumor-associated fibrosis, MECs were cultured on methacrylated-hyaluronic acid hydrogels, whose stiffness that can be dynamically modulated from “normal” to “malignant,” utilizing two-stage polymerization. MECs form and remain as polarized acini but begin to decompose and resemble a mesenchymal morphology upon matrix stiffening. However, both the degree of matrix stiffening and culture time prior to stiffening play a large role in acinar transformation as in both cases, a subset of acini remained insensitive to local matrix stiffness. Acini transformation depended neither on size nor cell density and MECs did not exhibit “memory” of prior niche when serially cultured through cycles of soft and stiff matrix. Instead transforming growth factor β (TGFβ) and YAP activation appeared to modulate stiffness-mediated signaling; when both signals were blocked, collective MEC transformation was reduced in favor of single MECs transforming and migrating away from acini. These data indicates a more complex interplay of time-dependent biomaterial stiffness signaling, acinar structure, and soluble cues that regulate MEC transformation than previous models suggested.

## Identifying novel targets for cancer therapies through the cell mechanome

Amy C. Rowat [1,] Navjot Kaur Gill [1], Bobby Tofig [2], Barbie Taylor-Harding [3], Yen-Wei Chen [1], Kate Lawrenson [2], Beth Y. Karlan [2], Xia Yang [1], Robert Damoiseaux [2]
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[2] Molecular Shared Screening Resource, UCLA, Los Angeles, CA
[3] Women’s Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Cell mechanotype impacts the ability of cells to deform through narrow gaps and thus may have consequences for clinically significant phenotypes in cancer progression such as invasion and metastatic potential. While specific known mechanoregulators, such as actin and microtubules, are well-studied, a systems-level understanding of cell mechanotype has been lacking. High throughput screening provides a powerful tool to determine molecular mechanism, but libraries contain ~$10^3$ small molecules, and measurements of cell deformability are typically acquired sequentially, which limits scale-up and their potential for screening applications. To address this bottleneck, we invented and developed the filtration-based parallel microfiltration (PMF) screening method (Qi et al Sci Reports 2015). PMF is based on the ability of cells to deform through micron-scale pores in response to pressure-driven flow; to achieve high sample throughput we fabricate custom devices that interface with 96 well plates. More deformable cells passage through the pores more quickly than less deformable cells, resulting in a larger filtrate volume, which is quantified using a plate reader; this unprecedented level of throughput enabled us to screen 1280 FDA-approved compounds to identify molecules that cause cisplatin-resistant ovarian cancer cells to be less deformable. We identified 67 top hits that cause a statistically significant decrease in the deformability of cisplatin-resistant cells compared to vehicle-treated control. Follow-up assays reveal the top 6 hits do not consistently affect cell viability, proliferation, or cell cycle, but that all top candidates decrease cell invasion. These findings indicate that mechanotype screening may identify modes of action for compounds that could be synergistic to existing chemotherapeutics, such as cisplatin, which primarily affect cell proliferation and promotes apoptosis. In addition, we use bioinformatics approaches to analyze the targets and pathways of the top 20 hits, which reveals key drivers of cellular mechanotype. Thus, findings from the mechanotype screen provide systems-level insight into the types of molecules and pathways that regulate cell mechanotype and open new avenues for considering the breadth of molecules and pathways that regulate cell deformability.

## Computational study of remodeling of fibrin networks under compression

Mark Alber [1,3],Samuel Britton [1], Oleg Kim [1,2], Rustem Litvinov [2], John Weisel [2]
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Fibrin network is one of the major structural components of both physiological blood clots and pathological thrombi. Mechanical and structural properties of fibrin network contribute to clot mechanical stability and determine its deformation under pressure from blood flow. Computational study of dynamical deformations of fibrin networks under compression demonstrate that dramatic remodeling of a clot observed in experiments is based on bending and reorientation of individual fibers as well as fiber-fiber non-covalent linkage. Structures of the network used in model simulations are generated from data gleaned from confocal microscopy images of in vitro fibrin clots. Fibrin polymers are modeled using the Worm-Like-Chain (WLC) model. The simulated network is governed by the Langevin equation. Upon network compression, non-covalent interactions between fibers result in dynamic variation of network architecture. These interactions significantly affect mechanical response of the network at high degrees of compression, ultimately resulting in clot stiffening. Simulation results match experimental data in both fiber linking rates and network densification under different compression rates. Finally, the model is used to predict how stress propagates through the network and how rearrangement and linking of fibrin fibers affects clot stiffening.

## Activation of Piezo1 with a Small Molecule Agonist

Jerome Lacroix [1], Wesley Botello-Smith [2], Yun Luo [2]
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Piezo1 and Piezo2 are homotrimeric mechanosensitive ion channels which transduce mechanical stimuli into electrochemical signals in a variety of cells and tissues of vertebrate organisms. Piezo-mediated mechanotransduction signaling plays a central role in a myriad of developmental and physiological processes and has been associated with several pathological conditions including nociceptive pain, lymphedema, cancer and anemia. Selective pharmacological modulation of Piezo homologs with small molecules would constitute a promising therapeutic avenue to treat Piezo-related pathologies and a powerful laboratory tool to dissect their biological contribution. Here, we investigate the molecular mechanism by which Yoda1, the only known isoform-selective Piezo modulator, activates Piezo1 but not Piezo2. To this aim, we used a chimeric approach to create a minimal Yoda1-insensitive Piezo1 variant, allowing us to identify a minimal protein region necessary for Yoda1-mediated activation. We next sought to determine whether Yoda1 sensitivity is abolished in hybrid channels containing wild-type Piezo1 and Yoda1-insensitive chimeric subunits. By characterizing cells co-expressing both subunits in defined ratios using calcium imaging and patch-clamp recordings, we show that the presence of a single Yoda1-sensitive subunit per trimeric channel is sufficient for chemical activation by Yoda1. To uncover the structural mechanism by which the agonist interacts with and activates Piezo1, we performed an all-atom molecular dynamic simulation of the mouse Piezo1 channel in the presence of multiple Yoda1 ligands. Our current >4 microsecond-long simulation reveals an anticipated local membrane curvature centered around the channel pore in agreement with experimental data and indicates the existence of two putative agonist binding sites strategically located near our chimera region.

## In Vitro Modeling of Variable Heart Diseases due to Lamin A/C Mutation via Patient induced Pluripotent Stem Cell-derived Cardiomyocytes

Mehrsa Mehrabi [1], Mira Asad [1], Danielle Beker [1], Halida Widyastuti [2], Cecilia Nguyen [2], Linda A. Mccarthy [1], Michael V. Zaragoza [2], Anna Grosberg [1]
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**Introduction:** Nucleus is an important organelle that stores DNA. Therefore, any changes in the nucleus can impact gene expression and downstream mechanisms. Nuclear lamina is a mesh like layer under inner membrane of nuclear envelope, which interacts with nuclear cytoplasm and cytoskeleton. Nuclear lamina plays very important role in gene expression, DNA replication, signal transduction, and maintaining the shape and stability of the nucleus. Nuclear lamina is composed of lamin A and lamin C proteins that are encoded by the Lamin A/C gene (LMNA). Changes in shape and stability of nuclei due to LMNA mutation can affect signal transduction and mechanical signaling. Although, almost all the nucleated cells in the human body have lamin A/C, there are patients with heart diseases caused by LMNA mutation, and the mechanism of such mutation-disease causation remain mystery. To study this, we propose to explore if it is possible to recapitulate the pathological phenotype in vitro by utilizing patient iPSC-derived cardiomyocytes to understand the correlation among the gene profile, structure, and function.
**Methods:** We have used in vitro tissue engineering techniques to interrogate the iPSC-derived cardiomyocytes' tissue structures and function. Patient's and control's fibroblasts (from skin biopsy) were reprogrammed to iPSCs and differentiated to cardiomyocytes, and the intracellular structures were analyzed. Moreover, cells function was evaluated by the "Heart-on-a-Chip" device based on the muscular thin film technology. The dynamics of the tissue constructs were analyzed for frequency response and stress as a function of time.

**Results:** Our data shows significant differences between iPSC-derived cardiomyocytes of patients and controls in frequency and active stress. Patients' tissues do not respond to external electrical stimulation, which can be due to LMNA mutation and could be a cause of heart disease initiation.

**Conclusion:** Since, patients have severe symptoms exclusively in the heart, investigating individual specific iPSC-derived cardiomyocytes can provide understanding of changing cells architecture and function caused by the mutation. By further investigating the structural and functional differences between patients and controls iPSC- derived cardiomyocytes, we can find the downstream mechanisms of LMNA mutation consequences in heart and find the proper treatments through drug screening and the other techniques.

## Cellular Responses to Different Hydrodynamic Environments

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Cells in vivo live in diverse physical environments that provide mechanical cues for cells to deform, migrate, and carry out their biological function. For example, cell migration on 2D surfaces is mostly driven by forces from actin polymerization and focal adhesions, whereas cells in confined geometries can be driven by water permeation. Water flux also plays an important role in epithelial monolayers, where directed transport from the apical to the basal surface can generate epithelial domes. While the role of the cell substrate in directing cell movement has been explored, we have recently found that the fluid properties in the cell surroundings also can generate dramatic cell response during cell migration. For example, in our experiments we find that cells protrude more and migrate faster in high viscous media; the velocity of cell migration scales with the viscosity of the media. In addition, viscous medium reduces actin retrograde flow within the lamellipodial. On the modeling side, we have developed a two-phase mathematical model that describes the motion of the cytosol and the actin-network components during cell migration. We explore the interplay of actin-driven and water-driven cell migration, and show that the former mechanism is important on 2D substrates while the later mechanism is more important in confined spaces. The transition from actin-driven to water-driven cell migration depends on the coefficient of the external hydraulic resistance, which varies with the mechanical properties of the external fluid and the geometry of the cell surroundings. The model has implications on early embryonic development, morphogenesis, and cancer cell metastasis.

## Quantitative anatomy of growing bacterial colonies

Bo Li [2,*], Mya Warren [1,o], Hui Sun [1,2,3,o], Yue Yan [2,4], Jonas Cremer [1], Terence Hwa [1,*]
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A three-dimensional computational model is developed to describe the growth of simple bacterial colonies on agar. The model incorporates the elements of nutrient diffusion, elastic and dissipative cell-cell, cell-agar interactions, and a unique cell-level description of surface tension which provides the cell-agar adhesion force. With a single set of parameters, the model captures key observed features of colony growth dynamics by non-motile *E. coli* cells on hard agar surfaces, from the initial single-layer growth, through buckling, to the steady expansion of a macroscopic colony. The captured features include the conic shape of the colony, the linear growth of both the colony radius and height in time, and their dependencies on the cell growth rates in different growth medium. The latter observations are particularly valuable as they allow discrimination among different models of colony growth. Analysis of the model output reveals a disc-like growth zone at the bottom of the colony, whose thickness, set by nutrient penetration from the bottom, determines the rate of vertical colony growth. The rate of radial colony growth is instead controlled by planarly oriented cells located as a thin layer at the outer perimeter of the colony, with the width of the region set by a buckling transition which reorients interior cells vertically. Our model predicts the width of this radial expansion zone, which determines the radial growth rate and hence the colony morphology, to be crucially dependent on cell-level surface tension and dynamic cell-agar friction. Overall, the model provides a versatile platform for mechanistic investigations of the influences of metabolic and environmental factors (e.g., agar characteristics and ambient humidity) on the growth and morphology of bacterial colonies.

## *Lightning Talk and Poster Abstracts*

### 1. Force-Induced Ultrasensitive Responses at Cell-Cell Interfaces

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[2] National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville, TN

One of the central problems in immunology involves molecular recognition at cell-cell interfaces. Fascinating recent experiments have revealed that mechanical forces regulate processes by which B cells identify molecular signatures of pathogens. Although B cells can be activated by soluble antigens, B cells *in vivo* are activated predominantly by antigens attached to membrane surfaces: In such cases, B cells use mechanical forces generated by myosin motors to discriminate between antigens of similar binding affinity and to internalize portions of the antigen-presenting surface. However, it remains unclear how collective dynamical processes at the B-cell surface are shaped by membrane and actomyosin mechanics. In this work, we develop hybrid computational models that account for key biophysical properties of immune-cell interfaces, including stochastic receptor-ligand binding kinetics, membrane mechanics, and actin-mediated forces on the membrane. We use the models to assess the number of antigens engaged by B cell receptors (BCRs) as a function of BCR-antigen binding affinity. Membrane deformations and actin-dependent forces lead to ultrasensitive responses with a threshold affinity that increases as the bending rigidity of the antigen-presenting membrane increases. This is in contrast with the broad response expected for purely two-dimensional reaction-diffusion processes. Additionally, increased actin-mediated forces sharpen the response curve and shift the threshold to larger binding affinities. We show that receptor clustering is a key intermediate step in the process and characterize a critical cluster size as a function of membrane bending rigidity. Taken together, our work elucidates how mechanical forces and membrane deformations enhance antigen discrimination at B-cell surfaces, and we conclude by discussing our results in the broader context of antigen discrimination in adaptive immunity.

### 2. Spatially Defined 3D Microtissue Arrays for Investigating Microenvironment Impact on Liver Progenitor Cell Differentiation

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Decoding the regulatory roles of cues in the tissue microenvironment requires models that can adequately recapitulate in vivo conditions. Traditional 2D techniques often fail to mimic the appropriate cell-cell and cell-matrix interactions, motivating the rise of 3D culture systems. Three-dimensional suspension aggregates or bulk encapsulation in animal-derived gels provide limited control over tissue geometry and mechanical properties, which impacts the distribution of cellular forces. To address these limitations, we are implementing a 3D microtissue platform that enables improved control over tissue geometry and an enhanced capability for performing downstream cellular fate measurements including higher throughput analyses. Utilizing bipotential mouse liver progenitor (BMEL) cells, we are applying this platform to study liver progenitor cell differentiation into hepatocytes or cholangiocytes (biliary type). This differentiation process underlies liver development, regeneration, and disease. In our studies, a microscale master with arrays of the desired geometries is fabricated using a 3D printer or photolithography, which is then used to mold PEG-Acrylate substrates containing wells of the given geometry. Cells are seeded and cultured, with the multicellular geometries dictated by these micromolded wells. At distinct time points of differentiation, tissues are immunostained and imaged using fluorescence confocal microscopy. Confocal image stacks are processed using MATLAB to trace cells and identify phenotype and location, demonstrating a 3D immunocytometry framework. With this highly adaptable platform, we have successfully fabricated arrays of spatially-defined BMEL cell microtissues of various geometries including cylinders and toroids with outer diameters of 200-500 um and inner diameters of 25-300 um. Finite element simulations predict that cell traction stress concentrations develop at the tissue edges in these geometries, dependent on boundary conditions. When stained for hepatocytic makers (albumin, HN4α) and cholangiocytic markers (osteopontin, sox9), BMEL cells exhibit both phenotypes distributed across the 3D microtissues. Preliminary results suggest that cell fate is influenced by tissue geometry, with the frequency of osteopontin-positive cells increasing by approximately 3- fold near the outer edge in 400um cylinder tissues, while remaining more uniform across the toroid tissues, with a modest increase (approximately 1.5-fold) at the edges. Overall, these studies are providing key insights into the microenvironmental regulation of liver progenitor differentiation.

## 3. Interplay between curvature-inducing proteins and intracellular membrane structures: application to biologically relevant minimal surfaces

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An astonishing variety of membrane structures can be observed in the cellular environment, both at the plasma membrane and at the organelles. These morphologies are intricately related to biological functions, enabling and regulating fundamental cellular processes. Yet the membrane composition in curvature-inducing proteins allowing to shape these structures remain challenging to assess. We ask, given a cellular membrane structure, what is the distribution and concentration of curvature inducing proteins necessary to maintain this shape? We propose a theoretical approach based on Helfrich model extended for lipid-protein interaction, that allows us to compute the field of spontaneous curvature that sustains a given membrane structure at mechanical equilibrium. We demonstrate this approach by investigating the role of spontaneous curvature in minimal surfaces, which include catenoids — relevant to vesicle trafficking, tubulation, and nuclear pores — and helicoids — relevant to endoplasmic reticulum ramps. In these cases, the shape equation reduces to a variable-coefficient Helmholtz equation for the spontaneous curvature, where the source term is proportional to the local Gaussian curvature. Importantly we show the existence of energy barriers associated with geometrical variations of the membrane structure, pointing out the need for a coordinated action of at least two distinct curvature-inducing proteins, in agreement with experimental observations of necking processes.

## 4. Simulation of Rare Events in the Diffusion of Molecules on Crowded Cell Surfaces

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Many spatial molecular processes exhibit a wide range of timescales, which means that specialized rare-event algorithms are necessary to make simulation of processes of interest tractable. In particular, rare events may be important in the spatiotemporal dynamics of molecules diffusing on cell membranes. Large surface molecules present in a crowded region of the cell surface can impede the formation of a cell-cell interface. For example, it has been estimated that large surface molecules must evacuate from a ~100 nm region on the surface of T cells in order to allow for the T cell to interact with its target and initiate activation. Evacuation of a region this size by diffusion becomes increasingly rare with increasing surface crowding. To study this evacuation process, we apply the Weighted Ensemble rare-event sampling algorithm. The mean first passage time to evacuation versus number of molecules, N, in a region grows exponentially as N increases. Simulations revealed that the mean first passage time depends sensitively on the timestep in the Brownian Dynamics model of diffusion, due to the fleeting nature of the target (evacuated) state. The fleeting nature of the target state furthermore presented challenges to implementing standard Weighted Ensemble methods. We present methods to address these challenges, which could be adaptable to simulation studies of other systems with multiscale spatiotemporal dynamics.

## 5. Membrane-associated intrinsically disordered signaling proteins can exhibit emergent cooperativity, even under symmetric reversible kinetics

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Recent evidence has demonstrated that the intrinsically disordered regions of signaling molecules can be more than just flexible linkers of functional domains, but rather confer non-linear functionality themselves. As a specific example, the T Cell Receptor zeta chain has been suggested to dynamically dissociate from the membrane upon receptor triggering, allowing it to become further phosphorylated. This implies a delicate balance: For membrane dissociation to have a substantial impact, the membrane must significantly occlude tyrosines from kinases, but not so much that initial triggering is inhibited. We present a general model of a multi-site disordered signaling molecule in simplified, theta-solvent, freely-jointed chain dynamics. We use this model to study the zeta chain association with the membrane. We find that for a wide range of molecular properties, the zeta-chain can be membrane-associated yet still accessible to kinases, and accessibility is dramatically increased upon phosphorylation. This leads to cooperativity of phosphorylation that allows membrane-association to serve as an effective binary switch in the signal transduction cascade. Surprisingly, we find that cooperativity persists even if phosphatases, and thus dephosphorylation, are assumed to operate with identical molecular features as the kinases. Our work adds to a growing body of research suggesting that disordered regions themselves may act as modules in signal transduction cascades.

## 6. Development of medical adhesives based on siderophore analogs

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There is a need to develop improved biocompatible adhesives for use in the human body, including dental and surgical adhesives. While biomedical adhesives have been developed (*e.g.*, cyanoacrylates and fibrin sealants), they are brittle or poorly biocompatible.[1] Therefore, the development of a robust, biocompatible tissue-glue is of great clinical interest. In this study, we compare adhesion forces and energies between symmetric thin films of collagen type-1 (Col-1) in the presence or absence of highly adhesive siderophore analogs [2] using a Surface Forces Apparatus (SFA). Siderophore analogs are synthetic mimics of small molecule bacterial iron chelators, and have recently been shown to bind strongly to inorganic aluminosilicate substrates.[2] Here, we show that siderophore analogs mediate robust adhesion between Col-1 substrates that are models for tissue. Interestingly, we do not observe adhesion when replacing Col-1 for fibronectin, another important extracellular matrix component.
For Col-1 films in buffer, we observe very weak adhesion forces, $F_{ad}$ < 5 mN/m ($-E_{ad}$ < 1 mJ/m2). Adsorption of TLC siderophore analogs to the Col-1 films significantly increases the force of adhesion, $F_{ad}$, to > 50 mN/m ($-E_{ad}$ > 10 mJ/m2). This strong adhesion persists over repeated cycles of loading and unloading. Our findings suggest that siderophore inspired molecules might be a preferable alternative to existing bio-adhesives for us in the body.
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## 7. Toward a Light-Actuated Membrane Tension Pulsation System for Understanding Mechanosensitive Membrane Protein Dynamics

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Mechanosensitivity is one of the properties shared by a wide variety of cells in many different organisms ranging from bacteria to mammals. The dependence of stretch-activated membrane protein functions on membrane tensions enable cells to sense and convert mechanical stimuli into biochemical signals. Systematic investigation of the membrane tension dependent protein dynamics will advance our understanding of the mechanism of mechanotransduction in biological systems. Single molecule studies of membrane proteins over the last decade have focused almost exclusively on understanding membrane protein functions in the absence of mechanical stimuli. To fill this knowledge gap, we propose using a photoswitchable lipid Bis-azo Phosphatidylcholine (BAPC) for single-molecule study of membrane proteins under rhythmic membrane tension. BAPC lipid membranes can be switched between tightly- and loosely-packed states by an optical-induced conformational change of each BAPC lipid molecule. Stretched membranes have loose lipid packings and consequently, faster diffusion constants compared to relaxed membranes. Therefore, the BAPC lipid membranes can recapitulate the periodic change of membrane tension in a tension exposed biological systems such as the heart. We have measured the diffusion constants of our photoswitchable lipid membranes in both conformations using FRAP experiments along with single particle tracking analysis of cholesterol-functionalized DNA origami rafts. In both assays, our preliminary results show that UV excitation increases the membrane fluidity of the photoswitchable lipids (56±0.9% change of rate of fluorescence recovery; N = 4). Current efforts are focused on incorporating mechanosensitive proteins, such as the bacterial mechanosensitive ion channel of large conductance (MsCL), as a proof of the utility of the system. Photoswitchable lipid bilayers may provide an enabling tool for increasingly complex functional and structural study of mechanosensitive membrane proteins at the single-molecule level. Photoswitchable lipid bilayers may provide a powerful tool that allow researchers to characterize the functional and structural dynamics of mechanosensitive membrane proteins for tackling increasingly complex mechanobiology questions at single-molecule level.

## 8. Modulating Metabolism and Cell Migration Through Adhesion-Mediated Contractility

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Cell-surface interactions are important for improving the lifetime of biomedical implants. Adhesion to surfaces is regulated through focal adhesions (FAs)--contact points to the substrate. One way to control cell adhesion is to use surfaces with nano-textures that are on the same size scale as the FAs, which could more clearly reveal the dynamics of FAs than surfaces without this granularity. Cells on nanopillared and nanolined surfaces adhere and migrate differently than cells on flat surfaces. How these associations occur is not well characterized and therefore, not well understood. Advances in fluctuation correlation microscopy have opened the possibility of measuring spatial-temporal protein interactions in living cells. In this study, we used the number and molecular brightness analysis to monitor the protein assembly and disassembly of FA complexes. We have found that FA proteins are stacked at a higher z-position when formed on our nanolines (L860). In addition, we used a vinculin FRET tension sensor (VinTS) to study how the rearrangement on L860 affects cellular tension. We report that cells on L860 experience higher tension than those on flat. Insight into how proteins assemble with respect to their local landscapes will provide information about cell coordination, motility and invasiveness. In addition to focal adhesion dynamics we hypothesized that cancer cells sense their microenvironment and respond to biophysical cues resulting in active signal transduction networks through ion channels and integrin proteins. New evidence shows that the extracellularmatrix (ECM) signaling cascades may increase glucose uptake leading to altered metabolic states. While is it known that tumor cells stiffen the ECM as the tumor progression occurs, a direct relationship between ECM stiffness and altered metabolism has not been explicitly measured. Here we apply the phasor approach to fluorescence lifetime imaging microscopy (FLIM) as a novel method to measure metabolic alteration as a function of ECM mechanics. Our results show that MDA-MB231 exhibit a decreased fraction of bound NADH (indicative of glycolysis) with increasing substrate density. Inhibition of cell contractility with Y27632 or blebbistatin showed shifts towards a higher free NADH fractional contribution (indicative of oxidative phosphorylation, OXPHOS). All other cell lines showed little to no change in fraction bound NADH on the varying collagen densities. We also conducted metabolism inhibition studies to confirm the shift from OXPHOS to glycolysis and vise-versa on the phasor plot. These results show that the phasor/FLIM approach is a powerful method in monitoring metabolism and mechanics that may improve our understanding in the potential roles it has in cell invasion. This work is supported by the National Institutes of Health grant P41-GM103540.

## 9. A Phase-Field Theory for Modeling the Effects of Mechanical Stress in Tumor Growth

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**Introduction:** Mechanical stresses of the solid phase of a tumor play a vital role in the expansion, invasion, and metastasis of tumors. These stresses mainly arise due to heterogeneous tumor growth and the effect of surrounding tissue confinement, and moderate the development of solid tumors by lowering the proliferation rate and inducing apoptosis of the tumor cells. This contribution focuses on developing a multiscale model to simulate the effect of mechanical stress in avascular model of tumor growth at the tissue scale, while accounting for a range of important cell and subcellular interactions.
**Methods:** The model is developed based on continuum mixture theory coupling diffusion (nonlocal phase-field) with deformation (hyperelastic) responses of multiple interacting constituents. The mixture theory also accounts for balance laws at the microscale (subcellular and cellular scale interactions) in addition to the macroscale balance laws (tissue level). Special attention is given to model the effects of mechanical deformation in tumor progression. In this regard, growth effects and their interaction with the deformation are included in the model through physically and mathematically consistent construction. Finite element implementation of the highly nonlinear model and the numerical experiments are also presented.
**Results:** The simulation results indicate the capability of the proposed model to capture major characteristics of tumor growth and decline in living tissue. Additionally, the computational model enables addressing the significant inhibitory effects of the external mechanical stresses produced by the surrounding tissues on tumor progression.
**Conclusion:** We demonstrate that the developed phase-field theory and the numerical implementations provide a novel computational tool for tumor growth predictions. Ongoing studies are attempting to calibrate and validate the model using various experiments.
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## 10. Piezo1 calcium flickers localize to hotspots of cellular traction forces

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Piezo channels transduce mechanical stimuli into electrical and chemical signals to powerfully influence development, homeostasis, and regeneration. Due to their location in the plasma membrane, they are positioned to transduce both external mechanical forces in the environment as well as internal forces generated by cells. While much is known about how Piezo1 responds to externally-applied mechanical forces, its response to cell-generated forces that are vital for cellular and organismal physiology is poorly understood. Here we show that actomyosin-based cellular traction forces activate Piezo1 in proximal regions to generate transient and local $Ca^{2+}$ flickers in the absence of externally-applied mechanical force. Myosin II motors provide the mechanical force required for Piezo1 activation: pharmacological agents that either augment or inhibit Myosin II contractility produce a corresponding change in Piezo1 flickers. Further, although Piezo1 channels diffuse readily in the plasma membrane and are widely distributed across the cell, flicker activity is enriched in spatially constrained regions at force-producing adhesions. We propose that Piezo1-mediated $Ca^{2+}$ flickers allow spatial segregation of mechanotransduction events within cells, and that Piezo1 diffusion allows a few channel molecules to efficiently respond to transient and localized mechanical stimuli throughout the entire cell surface.

## 11. Measuring fluctuations of reconstituted collagen fiber under tension using optical tweezers and reflection confocal microscopy

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Collagen is the most abundant protein in the human body and is an important structural component of the extracellular matrix. Reconstituted collagen hydrogels are used in 3D cell cultures to mimic the *in vivo* environment. Measuring forces within a network of collagen fibers inside a 3D culture is challenging. Techniques such as atomic force microscopy cannot go below the surface and traction force microscopy has difficulty due to the nonlinear and heterogeneous material properties. We observed unlabeled reconstituted bovine pepsin extracted collagen using confocal reflection microscopy as tension is applied to the fiber using optical tweezers. The aim of this project is to find differences in reflection confocal images of fibers under varying tensions in order to determine force propagation in unlabeled biological fibrous networks. This work is important for understanding cellular interactions with the extracellular environment.

## 12. Quantification of the mechanical properties of subcellular structures reveals that non-mitotic nuclei are passively distributed within epithelial cells

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Changes within the mechanical structure of organs during development occur on multiple time scales and are embedded within the spatial tissue domain. As a result, measuring stress and other mechanical properties within a tissue and the physical properties of subcellular structural components remain experimentally challenging. Consequently, a quantitative understanding of the mechanics of organ formation requires developing computational models validated by experimental measurements. Furthermore, experimental images of developing tissues often suffer from non-ideal orientations, which adds to the challenge of identifying spatial coordinates of subcellular structures. Here we have developed semi-automated segmentation pipelines for rapid extraction of nuclear positions and surface curvatures, which allows the user to account for image rotation. This framework has been applied successfully to cross sections of the *Drosophila* wing disc pouch epithelium. We then pharmacologically removed the extracellular matrix of the wing disc and show that this component applies lateral compression on the tissue, which results in cell elongation and contributes to asymmetric nuclear positioning along the apical-basal axis of epithelial cells. Additionally, we have quantified the spatial variation of tension between cells using laser-ablation techniques. These experiments provide important constraints to calibrate a predictive subcellular element model of epithelial organ shape. Together, these results highlight the utility of quantitative subcellular feature extraction from experimental data in the development of biological models.

## 13. Quantitative structural mechanobiology of blood clot contraction

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The volume shrinkage of blood clots named clot contraction (retraction) that determines the final size and structure of a mature clot is an essential part of blood clotting. Platelet-driven clot contraction is important for hemostasis and wound healing as well as for restoring the blood flow past otherwise obstructive thrombi within a vessel. While it has been demonstrated that platelets and fibrin are necessary for contraction of clots, much less is known about how individual platelets or small platelet aggregates exert contractile force on individual fibrin fibers and how this tension causes collapse of the entire filamentous network and reduction of clot volume. The studies described so far define the components necessary for clot contraction, but the physical mechanism is still unknown. In other words, what is the physical action of platelets that causes contraction of the clot and what structural alterations in fibrin occur during cell-based clot contraction? To gain insight into the structural reorganization of the extracellular matrix underlying platelet-driven clot contraction biomechanics, we used high-resolution confocal microscopy and rheometry to perform concurrent 3D dynamic structural and mechanical measurements of the platelet-fibrin meshwork over the course of clot contraction. We paid special attention to the elementary steps of clot contraction in the real time scale by visualizing single contracting platelets bound to an individual fibrin fiber and their effects on remodeling of the entire fibrin network powered by multiple contracting platelets.

## 14. Stochastic averaging for multiple cooperative and antagonistic molecular motors

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We study a system of stochastic differential equations which describe the procession of multiple molecular motors carrying a cargo along a microtubule. For cooperative motors we can obtain, through averaging principles, effective statistics for motor velocities for several models of motor attachment and detachment. The assumption of various time scales needed to obtain accurate averaging estimates are no longer valid with antagonistic motors systems. We discuss methods for overcoming such difficulties, and conclude with simulations comparing various models.

## 15. Extensions of the wave-pinning model for cellular polarization and localized patterns

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Cellular polarization is essential for a variety of cell behaviors, including chemotaxis and directed motion. Understanding the mechanism behind polarization is therefore of great interest. The wave-pinning model was proposed by Mori et al (2008) as a caricature of cellular polarization in eukaryotic cells. The model is simple enough to understand mathematically. For the types of cells of interest, polarization of regulatory proteins (GTPase) plays an important role in triggering morphological response in the cell. In this project, we explore the possible behaviors exhibited by two extensions to the wave-pinning model that include interactions of GTPase with the actin cytoskeleton. We study the extended model numerically, and explore its bifurcation properties. We also explain its biological significance in real cells.

## 16. Compression Force Promotes Breast Cancer Cell Invasion via Opening Stretch-Activated Ion Channels

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Compression force is a feature of tumor microenvironment that is thought to promote the invasive phenotype of cancer cells. However, the process by which cancer cells convert mechanical stimuli into biochemical responses leading to the changes in cell invasion is not fully understood. Caveolae and stretch-activated ion channels which can be regulated by membrane tension and initiate calcium signaling are believed to orchestrate cancer cell functions in response to biochemical and physical stimuli, thereby controlling cell proliferation, migration, and invasion. We hypothesize that compression force can increase membrane tension which leads to disassembly of caveolae and open stretch-activated ion channels, resulting in cell signaling that leads to enhanced cell migration and cell invasion. We have previously established functional expression of bacterial mechanosensitive channel of large conductance (MscL) in mammalian cells as a new experimental platform. In the present work, we examined breast cancer MDA-MB-231 cells with or without MscL-GFP and Calvin-1-GFP under different compressive stresses. Our results show that compression force induces: 1) the opening of MscL in a compressive stress-dependent manner; 2) the disassembly of caveolae; 3) an immediate increase in intracellular [$Ca^{2+}$]; 4) an increase in migration and invasion; 5) an increase in the number of invadopodia and matrix gelatin degradation, and finally 6) the activation of PI3K, Akt, FAK,ERK and Src signaling pathways. We also found that gadolinium attenuates the increase in intracellular [$Ca^{2+}$], migration, and invasion induced by compression force, suggesting that stretch-activated ion channels play a significant role in response of cancer cells to compression force. Taken together, our data links compression force to the activation of PI3K/Akt/FAK and ERK/Src signaling pathways via membrane tension-mediated disassembly of caveolae and the opening of stretch-activated ion channels.

## 17. Epigenetic regulation during topography-induced cardiomyocyte maturation

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Current therapy strategies for heart failure have concentrated on regenerative medicine. Although promising, cardiomyocytes differentiated from stem cells often retain properties of immature cells. It was recently shown that neonatal rat ventricular myocytes (NRVMs), when seeded on patterned substrates that mimic the anisotropic structure of the native myocardium, had a gene expression closer to mature cardiomyocytes than when seeded on an unpatterned (isotropic) substrate. Our lab and others have demonstrated that substrate topography can influence cell behavior through epigenetic mechanisms. Understanding how NRVM maturity is affected by topography through epigenetics can therefore be beneficial for future tissue engineering applications. We aim to characterize differences in the epigenetic landscape that are induced through surface topography and assist in cardiomyocyte maturation.

Primary NRVMs were plated onto coverslips patterned with fibronectin stamped either over the entire coverslip (isotropic surface) or patterned into spaced lines (anisotropic surface). To understand how DNA methylation may be involved in cardiomyocyte maturation, cells were then treated with RG108, a DNA methylation inhibitor, for either 24 or 48 hours. Coverslips were then fixed and stained to reveal the nuclear, actin, and sarcomere structures of the cells. Following image acquisition, the orientational order parameter (OOP), which returns a value between zero (unorganized tissue) and one (perfectly aligned), was calculated. We observed that cells seeded on anisotropic surfaces, when treated with RG108 for 24 hours, had a sarcomere OOP of 0.09, while non-treated controls exhibited a sarcomere OOP of ~0.5. Interestingly, this value returned to 0.42 in the 48-hour treatment condition. This apparent delay in sarcomere OOP could suggest that RG108 is slowing down cardiomyocyte maturity. This deviation from control OOP values, however, was not present in isotropic cells or in actin OOP for both conditions. Finally, the effect of topography on histone modifications was tested for by staining cells for H3K4me3. We observed that some cells exhibited nuclear localization of the histone modification, while others had it dispersed in the cytoplasm. Analysis of OOP between nuclear and non-nuclear H3K4me3-containing cells, however, did not show any significant difference for both sarcomere and actin, in any of the studied conditions.

## 18. Assessing Continuous Z-line Length as a Metric for Cardiac Function

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The heart is organized into laminar sheets of cardiac fibers - myofibrils[1]. Furthermore, the structural remodeling of the myofibrils contributes to declined cardiac function in a diseased heart[2]. Within a myofibril, each sarcomere produces a contractile force parallel to the actin fibrils and ideally perpendicular to its z-lines, which are the boundaries between sarcomeres[3]. Because many sarcomeres work together to produce the force necessary for cardiac contractions, their spatial organization affects the heart's ability to pump blood[4]. Therefore, measuring/quantifying precise sarcomere organization is an essential part of understanding the mechanisms that influence cardiac function. Based on qualitative experimental observations, it is hypothesized that cardiac tissues with sarcomeric z-lines that are registered between myofibrils tend to produce a greater contractile force. This hypothesis is supported by looking at single myofibrils in isolated cells[5]. Additionally, visibly shorter z-lines are considered a hallmark of immature stem-cell derived cardiac tissue. Based on these qualitative experimental observations, the degree of continuity and/or registration of sarcomeric z-lines is expected to correlate with cardiac force production that deviates from existing predictions. In this work, we measure the distance over which z-lines from multiple myofibrils are continuous, termed the continuous z-line length. The continuous z-line length can be automatically and accurately measured from images of alpha-actinin stained cardiac tissue using the pixel and orientation information. The continuous z-line length has the potential to be used as a tool to better compare tissues and differentiation methods across labs and contribute a robust understanding of how tissue level structure affects the hearts mechanical function.

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## 19. Mechanical effect on growth and morphology of epithelial cells during early development

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Uncontrolled epithelial growth and dysregulation of epithelial morphology underlie more than ninety percent of tumors. Epithelia serve a critical role as barriers between the environment and internal structures of organs. The growth and morphogenesis of epithelia must be carefully controlled through coordination of cellular properties. Mechanical properties are an important regulator during the development. However, how the mechanical properties in the cell scale contribute to growth and morphogenesis in the tissue scale is still poorly understood. Here, we introduce a subcellular element particle-based model to predict the mechanical properties of epithelial cells to investigate their contribution to the proliferation and morphology in cell and tissue scale. The developed model consists of three sets of nodes: internal nodes represent inner organelles, membrane nodes represent cortex and membrane of cells, and extracellular nodes represent the extracellular matrix. These three classes of nodes interact through distinct potential energy functions. Our model incorporates subcellular properties such as cytoplasmic pressure, cortical stiffness, cell adhesion and interactions between the cell membrane and nucleus. We also account for the mechanical interaction between the extracellular matrix and epithelial cells. We found that cytoplasmic pressure is the main driver of cell's expansion in mitotic phase, while cortical stiffness and cell-cell adhesion are contributors to the roundness of cells before division. Recently, we have extended the model to predict the curvature profile of epithelial cells. Our results show that the level of contraction in the extracellular matrix significantly contributes to the curvature profile of epithelia. To validate this prediction, tissue mechanics were measured experimentally in *Drosophila* wing imaginal discs, an established biophysical model of epithelial organ development. Furthermore, both computational predictions and experiments establish that the relative cells' nucleus position contributes to the curvature profile. The right curvature profile of wing disc is essential for wing eversion, the next stage of wing development. Aberrant folding and bending of epithelia can lead to cyst formation, which occurs during early cancer progression.

## 20. Imaging T Lymphocyte Calcium Dynamics Using a Ratiometric tdTomato-GCaMP6f Transgenic Reporter Mouse

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Calcium is an essential cellular messenger that regulates numerous functions in living organisms. Currently available synthetic calcium indicators such as fura-2 and fluo-4 are unsuitable for long-term studies due to leakage out of cells, and fluorescent protein-based GECI such as GCaMP6 (non-ratiometric) are problematic for calcium imaging in motile cells where fluorescence changes resulting from movement may be indistinguishable from actual changes in calcium levels. Here, we describe development and characterization of "Salsa6f", a fusion of GCaMP6f and tdTomato optimized for cell tracking while monitoring cytosolic calcium. We created a transgenic mouse strain in which Salsa6f is expressed under cell-specific genetic control in Cre-driver strains using the Rosa26-Cre recombinase system, and we have used this system to monitor cytosolic calcium in CD4-Salsa6f T cells. Salsa6f expression is non-perturbing; we saw no effects of Salsa6f expression in T cell surface phenotype, cell proliferation, differentiation, homing, and motility in the lymph node. Salsa6f is distributed uniformly throughout the cytosol; its exclusion from the nucleus provides reliable and selective reporting of cytosolic calcium signaling. We describe single cell calcium signals reported by Salsa6f during T cell receptor activation in naïve T cells, Th17 cells and regulatory T cells, and calcium signals mediated in T cells by an activator of mechanosensitive Piezo1 channels. Transgenic expression of Salsa6f enables ratiometric imaging of calcium signals in complex tissue environments found *in vivo*. Two-photon imaging of migrating T cells in the steady-state lymph node revealed both cell-wide and localized sub-cellular calcium transients ("sparkles") as cells migrate. Altogether, our results demonstrate the sensitivity, brightness, uniformity of labelling, and ease of detecting calcium signals in moving T cells using Salsa6f.

## 21. Phosphorylation of NudE and its role in regulating dynein forces of intracellular organelles

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Molecular motor proteins transport membrane bound vesicles, regulatory factors, and other cargos to their destination on the tracks called microtubules and actin filaments inside the cell. The Cytoplasmic Dynein motor is found on the majority of intracellular vesicles, and moves cargos towards the microtubule minus ends. How is transport tuned to achieve specific local demands? The motors functions are thought to be altered by phosphorylation, either of the motors themselves, or of their co-factors. Using lipid droplets in COS1 cells as a model system, we previously reported that dynein-driven motion shows force adaptation in response to increased load. Using biochemical and biophysical tools, we have now identified the molecules involved in regulation of dynein forces during force adaptation, which I will discuss in detail.

## 22. Mathematical approaches to investigate diversity of myofibroblast in Dupuytren's disease

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Dupuytren's disease (DD) is an ill-defined commonly occurring fibroproliferative disorder affecting the palms of the hands. The disease is prevalent in individuals of Northern European Caucasian origin. DD tissues can be classified into several stages according to their cellularity; the nodule and the cord. The nodule is described as a highly vascularized tissue containing a large number of fibroblasts, with a high percentage being myofibroblasts, as recognized by their expression of α-smooth muscle actin. The cord however, is relatively avascular and acellular, collagen-rich with few myofibroblasts. There are different opinions regarding the origin and development of this aspect of the DD phenotype, either viewing the nodule as developing into the cord as the disease progresses over time or, the two structures as representing independent stages of the disease.
We designed and performed a study in which the nodule and the cord were considered as two separate entities, as if arisen from separate precursor cells. Gene-expression profiles were compared between diseased Dupuytren's tissue biopsies (nodules and cords) and corresponding healthy tissue (the transverse palmar fascia adjacent to the diseased site) from the same patients. We also compared these gene-expression profiles with those from the carpal ligamentous fascia from healthy individuals not affected with DD.
We adopt a systems biology approach to investigate DD and propose a new method for analyzing gene expression dataset that reduces the number of false positives compared to traditional techniques. Our method leverages the massive amount of publicly available gene expression datasets to establish robust logical relationships between genes and compare it to the differentially expressed genes in DD samples. We develop mathematical models based on the logical relationships. The combination of logical analysis and pathway oriented approach highlights key molecules that are suggestive that DD may arise from innate inflammation related to autoimmunity but may be also be co-activated by other factors e.g. trauma, mechanical stress, other external/internal factors etc.

## 23. Recovery of cellular tractions in three-dimensional matrices

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Tractions exerted by cells on extra-cellular matrices (ECM) play a crucial role in many biological processes such as wound healing, angiogenesis and metastasis, as well as in many basic cellular functions such as biochemical signaling, proliferation and differentiation. Traction forces are typically quantified through traction force microscopy (TFM), where the displacement of selected markers inside of the ECM is measured, and is then utilized to reconstruct the traction field by solving an inverse problem. However, most applications of this technique have thus far assumed that the ECM exhibits a linear elastic behavior and undergoes infinitesimal deformations[1], regardless of the fact that strains generated by cellular tractions can be as large as 100% in the ECM. In this work, we propose a robust and efficient TFM approach accounting for geometric and material nonlinearities in the ECM[2], thus leading to more accurate reconstructions of cellular tractions. In particular, the TFM problem is formulated as an inverse problem, where the goal is to find the traction field that minimizes the difference between predicted and measured displacement fields. In the minimization procedure, our method requires—at each iteration—the solution of a forward nonlinear hyperelastic problem in the stressed (current) configuration of the ECM (where the geometry of the cell surface is known), as well as of an adjoint problem, in order to evaluate the gradient of the objective function. We will present results for encapsulated single cells interacting with the hydrogel matrix. Our results suggest that it is crucial to incorporate the nonlinear effects when solving the TFM problem, while significant errors could be made if the nonlinear effects are neglected.

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## 24. Polymers compress the colonic mucus hydrogel

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While the majority of recent work on the gut has focused on the microbiome and biological regulation of the gut, little is known about the physicochemical interactions that shape this environment. The mammalian gut abounds in soft materials such as polymers (e.g. dietary fibers, food additives, therapeutic polymers, and mucins) and colloidal matter (e.g. microbes and therapeutic particles). We have found experimentally that soluble polymers can compress the colonic mucus hydrogel, which is a critical barrier that mediates host-microbe interactions and protects against pathogens. We found that these polymer-mucus interactions could be described using a simple, mean-field Flory-Huggins model. In both our experiments and numerical calculations, we found that the amount of hydrogel de-swelling increases with polymer concentration and size. This framework can be used to make predictions about how different polymer solutions will affect the structure of mucus.

## 25. Dynamic Balance between vesicle transport and microtubule growth enables steady neurite outgrowth

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Axonal regeneration after nerve injury often ends in failure of neurite outgrowth due to the formation dystrophic bulbs the mechanisms underlying the formation of dystrophic bulbs are not well understood. We hypothesized that dystrophic bulb formation may be due to quantitative imbalances between the processes involved and tested this hypothesis computationally and experimentally Whole cell responses like neurite outgrowth are complex because they involve many subcellular processes (SCPs) that function in a coordinated manner. To understand how balance between SCPs is essential for steady neurite outgrowth, such that formation of dystrophic bulbs is avoided we developed computational models and tested predictions experimentally. Neurite outgrowth involves three types of subcellular processes (SCPs): production of membrane components, vesicle transport that delivers membrane to the growth cone and microtubule growth that regulates extension of the neurite shaft. Mathematical modeling and simulations show that redundancies between lower level sibling SCPs within each type produce robustness of higher level SCPs. In contrast, higher level SCPs characteristic of each type need to be strictly coordinated and cannot compensate for each other. From these models we predicted the effect of SCPs involved vesicle fusion as well as microtubule growth on the formation of dystrophic bulbs. siRNA ablation experiments verified these predictions. We conclude that whole cell dynamics requires strict balance between the higher-level SCPs involved and imbalances can terminate whole cell responses, such as neurite outgrowth

## 26. Avoiding a parametrectomy in patients with early cervical cancer based on an evaluation of biological indicators in the parametrium

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Objective: To assess apoptosis and the expression of biological indicators in different centrifugal sites of the parametrium in patients with cervical cancer and to suggest a basis for triaging a group of patients for whom type III radical hysterectomy may not be needed. We also provide preoperative triaging markers.
Methods: A prospective study of 124 patients with cervical squamous cell carcinoma stage IB1 though IIA1 who underwent type III radical hysterectomy and pelvic lymphadenectomy. Apoptosis and expression of biological indicators at different centrifugal sites of the parametrium were detected by TdT-mediated dUTP nick-end labeling, immunohistochemistry, western blot, and enzyme-linked immunosorbent assays.
Results: The expression levels of vascular endothelial growth factor, cytokeratin 19, high-risk human papillomavirus 16 and/or 18, and squamous cell carcinoma antigen (SCC-Ag) tended to decrease with increasing centrifugal distance from the parametrium, which were correlated with clinical stage, invasive depth of the cervix, and lymph node metastasis. Apoptosis and the expression of the biological indicators at the 2 cm centrifugal site from the cervix in the cardinal ligament and sacral ligament and at 3 cm in the vagina were not different between the "the early group" (stage IB1, ≤ 1/2 invasive depth of cervix and negative lymph node metastasis) and the normal control group. Sensitivity was 75.7% and specificity was up to 100% using serum SCC-Ag 2.45 ng/ml as the cut-off value for triage. Sensitivity was 97.3% and specificity was 71.4% when a tumor size of 1.5 cm was considered the optimal triage cut-off value.
Conclusions: Patients triaged into "the early group" with stage IB1, ≤ 1/2 invasive depth of the cervix, and negative lymph node metastasis should be selected for a less radical parametrectomy, while a vaginal resection is still recommended for those > 3 cm. Preoperative serum SCC-Ag and tumor size were effective preoperative triaging markers.

## 27. Blood Pressure Sensing in Baroreceptors is Mediated by Mechanosensors PIEZO1 and PIEZO2

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Abstract text: Blood pressure (BP) is tightly regulated to ensure that the body is optimally prepared to meet varied daily activity demands. Mechanisms that change blood volume play an important role in long-term BP regulation. In the short term (within seconds and minutes), BP regulation is initiated primarily by baroreceptors, a class of sensory neurons within the nodose and petrosal ganglia that are stretch sensitive, and have peripheral projections in the walls of the aorta and carotid sinus. Activation of these baroreceptors trigger a neuronal feedback mechanism that exerts acute control over heart rate and blood pressure via the autonomic nervous system. Importantly, compromised baroreceptor function can predict resistant hypertension, heart failure, and myocardial infarctions in the long term. Although the baroreceptor reflex has been described for more than 80 years, questions regarding the molecular identity of the baroreceptor mechanosensors remain. Here we show that mechanically activated ion channels PIEZO1 and PIEZO2 are together required for baroreceptor mechanosensitivity. Genetic ablation of both Piezo1 and Piezo2 in the nodose and petrosal ganglia abolishes the phenylephrine-induced baroreflex and aortic depressor nerve activity. Awake, behaving animals that lack Piezo1 and Piezo2 have labile hypertensive BP and increased blood pressure variability, consistent with phenotypes observed in humans with baroreflex failure. Moreover, optogenetic activation of $Piezo^{2+}$ sensory afferents is sufficient to initiate the baroreceptor reflex in adult mice. These findings suggest that PIEZO1 and PIEZO2 are the long-sought baroreceptor mechanosensors that are critical for acute blood-pressure control. Our findings will enable a mechanistic understanding of common cardiovascular pathologies associated with baroreceptor dysfunction.

## 28. Mechanoresponsive stem cells to target cancer metastases through biophysical cues

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Despite decades of effort, little progress has been made to improve the treatment of cancer metastases. We present a mechanoresponsive cell system (MRCS) which targets the specific biophysical cues of the tumor microenvironment *in vivo* to selectively identify and treat cancer metastases. MRCS leverages the central role of the mechanoenvironment in cancer metastasis by using mechanosensitive promoter–driven mesenchymal stem cell (MSC)–based vectors, which selectively home to and target cancer metastases in response to specific mechanical cues to deliver therapeutics to effectively kill cancer cells, as demonstrated in a metastatic breast cancer mouse model. Our data show MRCS is specifically activated by the specific cancer–associated mechano-cues of the tumor niche, and suggest a strong correlation between collagen cross-linking and increased tissue stiffness at the metastatic sites. MRCS indicates that biophysical cues, specifically matrix stiffness, are appealing targets for cancer treatment due to their long persistence in the body, making them refractory to the development of therapeutic resistance. Our MRCS can serve as a platform for future diagnostics and therapies targeting aberrant tissue stiffness in conditions such as cancer and fibrotic diseases, and can elucidate mechanobiology in the cellular microenvironment *in vivo*.

## 29. An integrin $\alpha_{IIb}\beta_3$ intermediate affinity state mediates biomechanical platelet aggregation

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Integrins are important receptors mediating cell adhesion and mechanosensing. Their structure-function relationship remains incompletely understood, despite that it is fundamental to cell biology and of great significance to tissue engineering, cell therapy and diseases. Using combined approaches of dual biomembrane force probe, microfluidics and cone-and-plate rheometry, we applied precisely-controlled mechanical stimulation to isolated platelets and identified an intermediate state of integrin $\alpha_{IIb}\beta_3$ activation that is characterized by an extended-closed conformation, and affinity and bond lifetimes for ligands that are intermediate between the well-known inactive and active states. This intermediate state is induced by GPIbα via a distinct mechano-signaling pathway. It potentiates $\alpha_{IIb}\beta_3$ outside-in mechano-signaling and facilitates intermediate-to-active state transition, necessary for mechanical affinity maturation. Our work identifies an important role for the $\alpha_{IIb}\beta_3$ intermediate affinity state in promoting biomechanical platelet aggregation. Moreover, they suggest the existence of distinct $\alpha_{IIb}\beta_3$ activation states in response to biomechanical and biochemical stimuli.

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# Opportunity Awards

Awards will support travel for a team of two or three graduate students or postdocs for travel to the other's respective lab to work on a new collaboration. A broad topic related to mechanobiology will be announced at the MechBio conference.

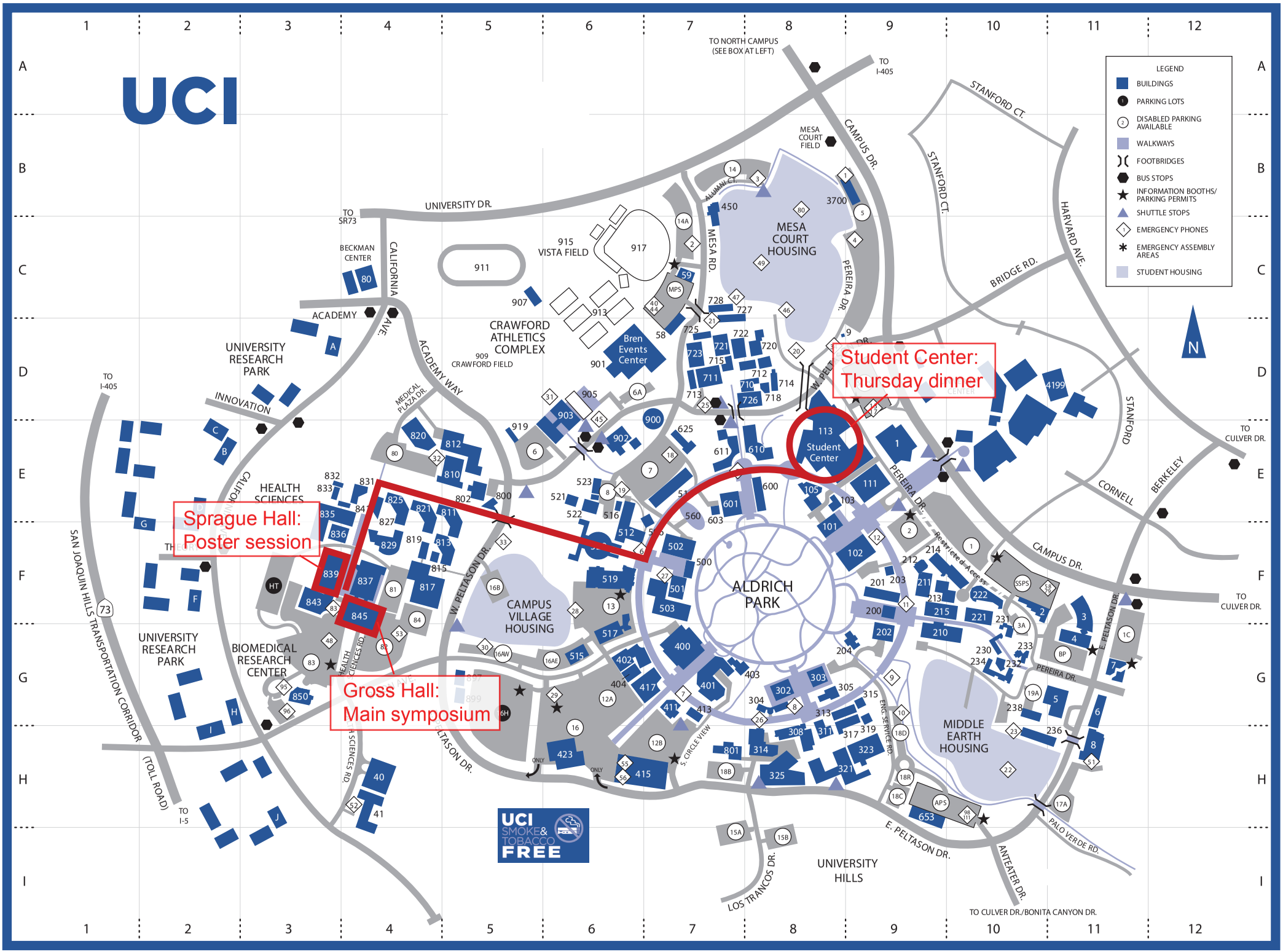
To be eligible, graduate students or postdocs must co-submit a single abstract (350 words or less) that addresses the topic before the end of the conference (**July 27th at midnight) by email to mechbio@uci.edu with the subject [Opportunity Award]**.

By August 10, 2018 at midnight, the proposers must co-submit a complete proposal (3 pages or less) and each proposer must submit an advisor support form (available at http://sites.uci.edu/mechbio2018/opportunity-awards/). A member from each of the submitting labs must have attended the symposium, the labs must be from different institutions, and must not have co-published before.

The announcement of the award recipients will be made by emailing the award recipients and the faculty mentors of the award recipients, and through a posting on the conference website.

After one year, the winning teams will produce a progress report submitted to the Organizers. After two years, the teams will be invited to present their final research at the next MechBio Symposium, which will be held in 2020.

# UCI Campus Core




OCTOBER 2016

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