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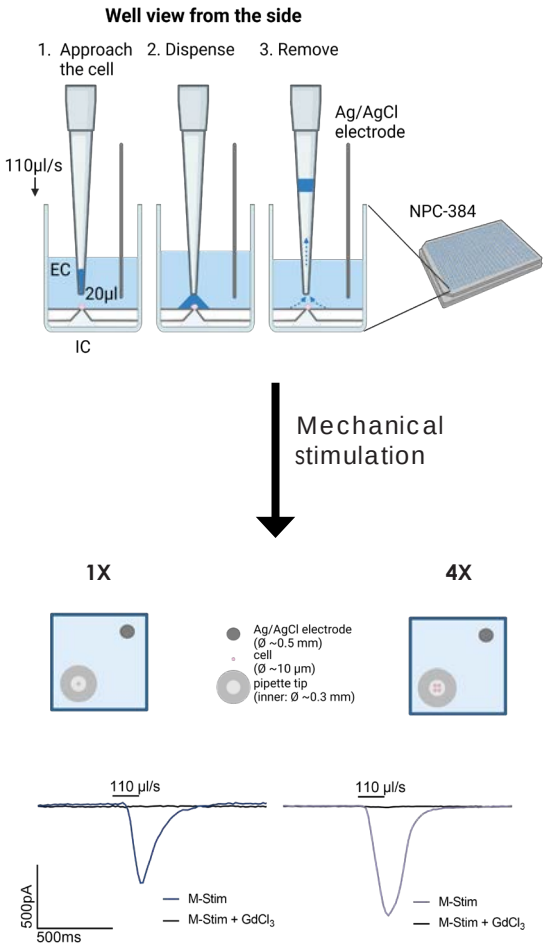

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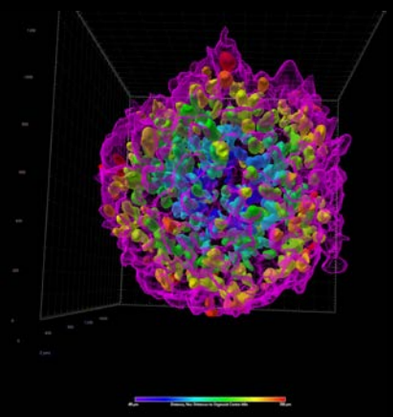

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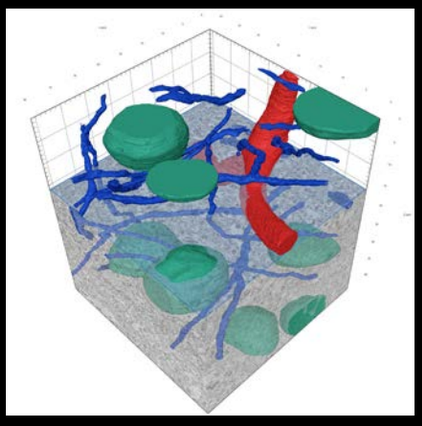

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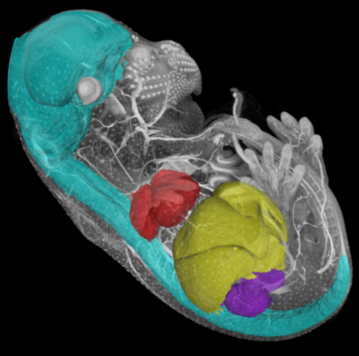

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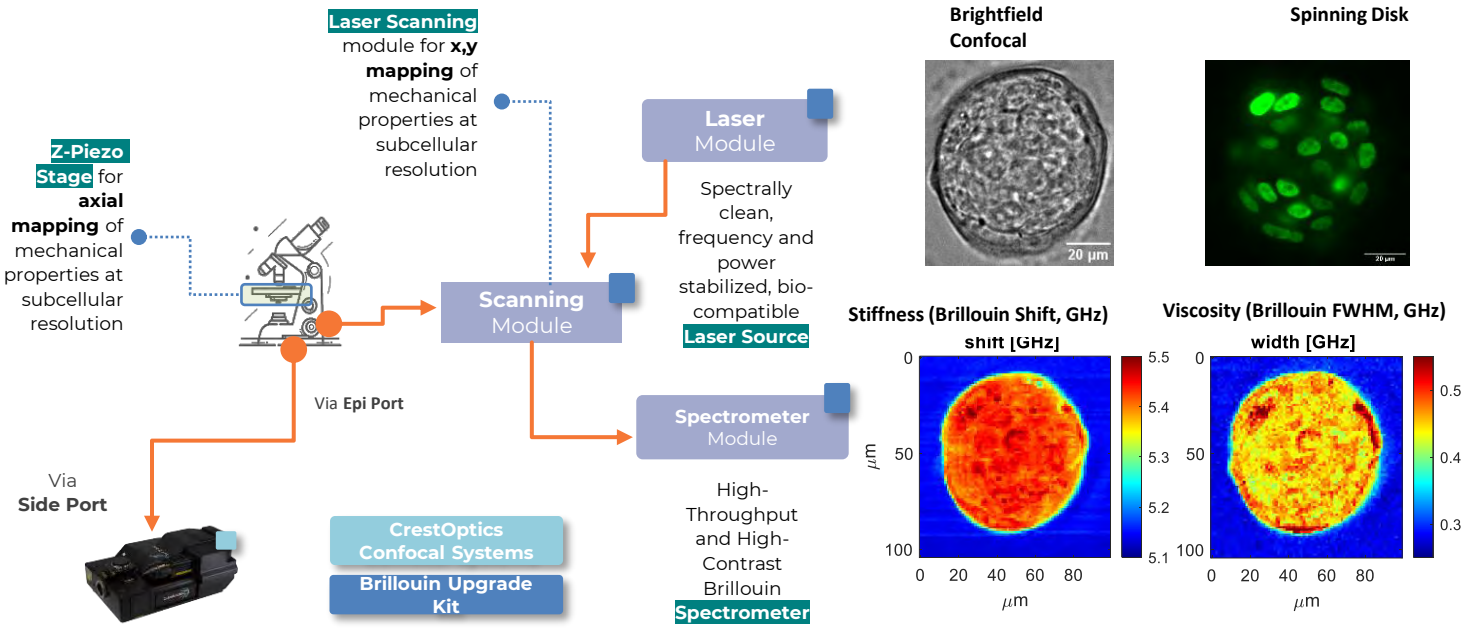

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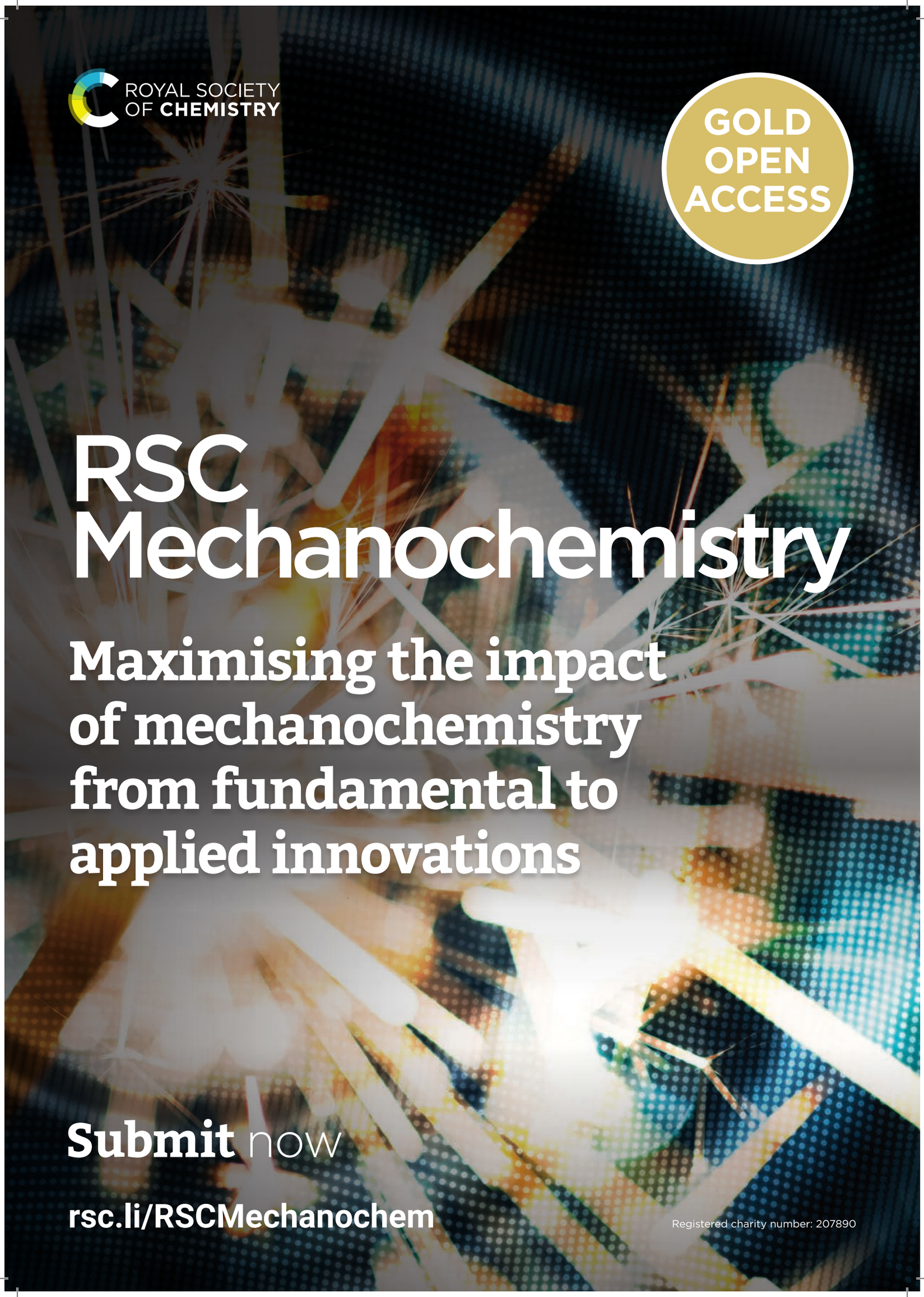
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Plenary Speakers

Innovation for global justice

Patricia Osseweijer[1]
[1]Delft University of Technology, Netherlands

Plenary Session: Patricia Osseweijer, July 13, 2026, 11:00 - 11:45

The transition from a fossil- to a bioeconomy has long been promoted as a way to mitigate climate change by reducing carbon emissions. However, progress has been slow. At the same time, competing uses of biomass - for food, feed, plastics, fuels and chemicals - became the subject of intense public and political debate. The sustainability of biomass production was increasingly questioned, feedstock availability became a major concern, and the renewable products proved often more costly than the fossil products they aimed to replace. These criticisms weakened support for the bioeconomy and shifted attention towards alternative technological pathways. While science and innovation in the bioeconomy domain continued to improve biomass conversion technologies, logistics and market development, transition agendas became increasingly dominated by wind and solar energy and renewed interest in nuclear power with large enthusiasm for hydrogen as novel energy storage system.
This shift risks overlooking the broader societal contributions of research and innovation for the bioeconomy. Sustainable agriculture, including soil and water management and biodiversity conservation, is essential for health, for food and water security, while the responsible use of biomass and waste streams can simultaneously strengthen energy security, rural development and social resilience. Wind, solar and nuclear energy based transitions cannot provide these wider benefits, while hydrogen remains only an energy carrier.
The bioeconomy can therefore be considered to be much more than a substitute for fossil resources. It spans the entire innovation chain, from fundamental research in biological processes and biotechnology to sustainable production systems and circular value chains. Providing valuable insight in life itself and the complex ecological system on our globe. Importantly, biomass utilisation uniquely provides opportunities for improving livelihood and social development for rural communities. However, reaching such objectives requires other design principles and integration with social sciences.
This places an important responsibility on scientists and innovators. Rather than focusing solely on technological performance or carbon reduction, research should be designed from the outset with societal objectives such as human wellbeing, resilience and global justice in mind.
In this lecture, I will examine the assumptions underlying the bioeconomy debate and reflect on lessons from public communication and stakeholder engagement around genetic modification (GM). I argue that scientists have an essential role not only in developing new technologies, but also in considering the societal directions in which they evolve. This requires integrating moral questions ex ante into research and innovation, while engaging more proactively with society, policy and industry. Drawing on several interdisciplinary projects, I will show how scientific research can be organised to maximise technological performance while simultaneously advancing sustainability, social development and global justice.

May the Force be with you! Piezo channels in mechanosensory biology

Ardem Patapoutian[1]
[1]Howard Hughes Medical Institute, Scripps Research, United States

Plenary Session: Ardem Patapoutian, July 13, 2026, 09:00 - 09:45

Mechanotransduction was perhaps the last major sensory modality not understood at the molecular level. Proteins/ion channels that sense mechanical force are postulated to play critical roles in sensing touch/pain (somatosensation), sound (hearing), shear stress (cardiovascular function), etc.; however, the identity of ion channels involved in sensing mechanical force had remained elusive. The Patapoutian lab identified PIEZO1 and PIEZO2, mechanically activated cation channels that are expressed in many mechanosensitive cell types. Genetic studies established that PIEZO2 is the principal mechanical transducer for touch, proprioception, baroreception, bladder, and lung stretch, and that PIEZO1 mediates blood-flow sensing, which impacts vascular development and iron homeostasis. Clinical investigations have confirmed the importance of these channels in human physiology. Current work in Patapoutian continues to explore the role of mechanosensation and interoception in physiology and disease.

The human organ atlas as a resource for open biomedical research

Claire Walsh[1]
[1]University College London, United Kingdom

Plenary Session: Claire Walsh, July 13, 2026, 09:45 - 10:30

Understanding the human body across scales remains one of the central challenges in biomedical research. Clinical imaging can visualise whole organs but lacks microscopic detail, while histology reveals cellular structure but only within small, physically sectioned samples. The Human Organ Atlas was formed to bridge this gap: to create an open, multiscale, three-dimensional reference of intact human organs in health, ageing and disease.
The Atlas grew from the development of Hierarchical Phase-Contrast Tomography, a synchrotron-based imaging approach established through an international collaboration between clinicians, imaging scientists, engineers and data specialists. Initially driven by the urgent need to understand organ-level pathology during the COVID-19 pandemic, the project rapidly evolved into a broader open-science effort. By imaging intact organs non-destructively, while retaining the ability to zoom into selected regions at near-cellular resolution, the Atlas preserves the spatial context that is often lost when organs are reduced to small samples or two-dimensional sections.
This talk will describe the history of how the Human Organ Atlas was formed: from method development and early biological discoveries, to the creation of an open-access data and visualisation platform, and the building of a wider community around this technique. I will discuss how technical work in large-scale data formats, metadata, web-based visualisation and reusable analysis pipelines has made these complex datasets accessible beyond the original imaging teams. I will also highlight how clinical and biological collaborations are turning the Atlas into a resource for health impact, supporting anatomical discovery, disease research, validation of clinical imaging, education, and the development of AI models trained on high-quality, spatially contextualised human data.

Cardiac mechanics to cure cancer

Serena Zacchigna[1]
[1]International Centre for Genetic Engineering and Biotechnology, Italy

Plenary Session: Serena Zacchigna, July 13, 2026, 11:45 - 12:30

The talk will focus on the mechanisms that prevent the spontaneous regeneration of the heart after damage and discuss mechanistic link with the rarity of cardiac cancers, to eventually move to therapeutic solutions to both promote cardiac repair and treat cancer.

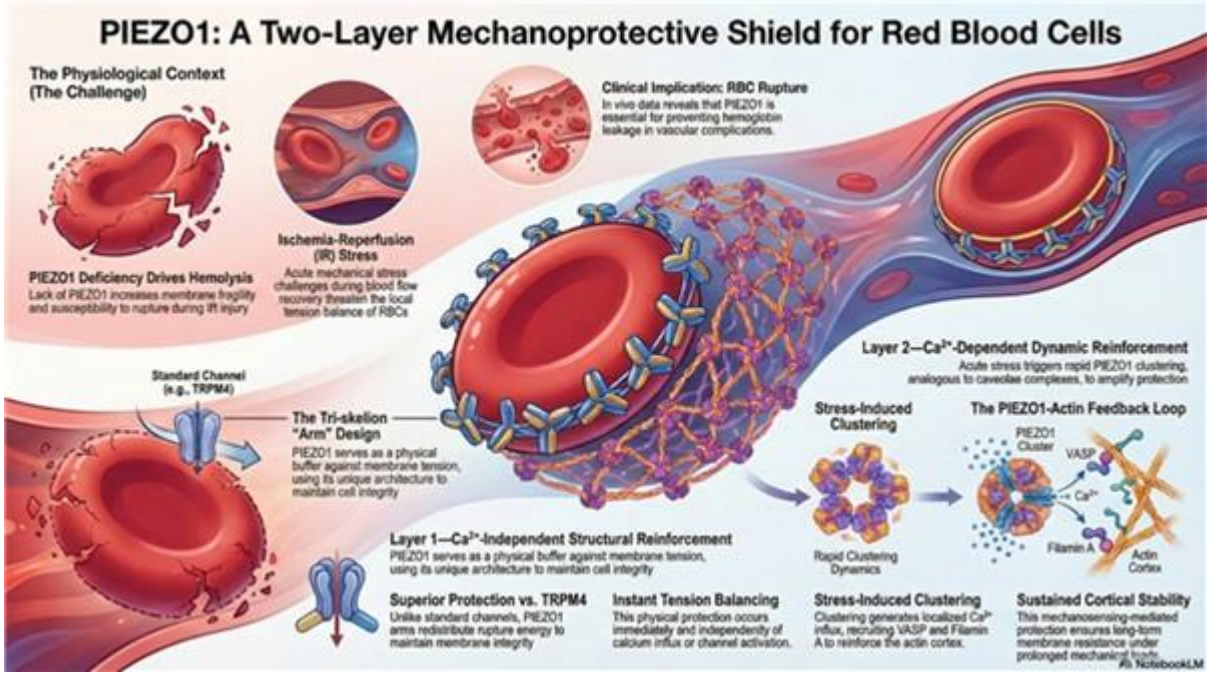
The Physiological Society – PIEZOs Oral Presentations

PIEZO1 adaptively safeguards plasma membrane under mechanical stress through a two-layer mechanoprotective mechanism

Ju Arnold[1,2,3], Jianfang Ren[1,2,3], Yao Wang[1,3], Haoqing (Jerry) Wang[1,2,3], Zhian Yao[1], Naveen Louis[1], Tiana Pelaia[1,2,3], Zijing Zhou[5,6], Qing Li[4], Chia Lun (Mike) Wu[1,2,3], Charles Cox[5]
[1]School of Biomedical Engineering, The University of Sydney, Australia, [2]Heart Research Institute, Australia, [3]Charles Perkins Centre, The University of Sydney, Australia, [4]School of Aerospace, Mechanical and Mechatronic Engineering, The University of Sydney, Australia, [5]Molecular Cardiology and Biophysics Division, Australia, [6]Faculty of Medicine, St. Vincent's Clinical School, University of New South Wales, Australia

Session 4, July 14, 2026, 10:30 - 12:30

The plasma membrane serves as the critical interface between cells and their mechanical environment, continuously enduring physical stresses without catastrophic failure. While PIEZO1 is well recognized as a mechanosensitive ion channel that transduces force into calcium signals, whether its physical presence directly contributes to membrane material properties remains unexplored. Here, we reveal that PIEZO1 safeguards membrane integrity through a hierarchical, two-layer mechanoprotective mechanism. Using a mouse model of gut ischemia-reperfusion injury, we demonstrate that PIEZO1-deficient erythrocytes undergo dramatically increased hemolysis under physiological mechanical stress. Through comprehensive biophysical analysis and molecular dynamics simulations, we divulge that the first layer involves rapid, extracellular calcium-independent protection, where PIEZO1's unique trimeric "triskelion" architecture with extended blade domains dissipates membrane stress by buffering acute tension through force-induced clustering. The second layer engages calcium-dependent positive feedback with the actin cytoskeleton, mediated by VASP, Filamin A, and Calmodulin, which reinforces cortical stability under sustained mechanical load. Critically, pore-dead PIEZO1 mutants retaining the blade architecture preserve membrane integrity, whereas structurally distinct channels lacking peripheral arms fail to confer protection. Overall, our findings establish PIEZO1 as a tunable "smart material" embedded within the plasma membrane, bridging nanoscale structural mechanics with macroscale physiological resilience.



Intracellular Mechanosensation in GI Smooth Muscle: Piezo1-RyR-BKCa Complexes Amplify Signaling Beyond the Surface

Geoanna Bautista[1], Emily Lieu[1], Stephanie Ugochukwu[1], Joshua Tulman[1], Sal Baker[2], Steven McElroy[1], Manuel Navedo[1], Fernando Santana[1]
[1]University of California, United States, [2]University of Nevada, United States

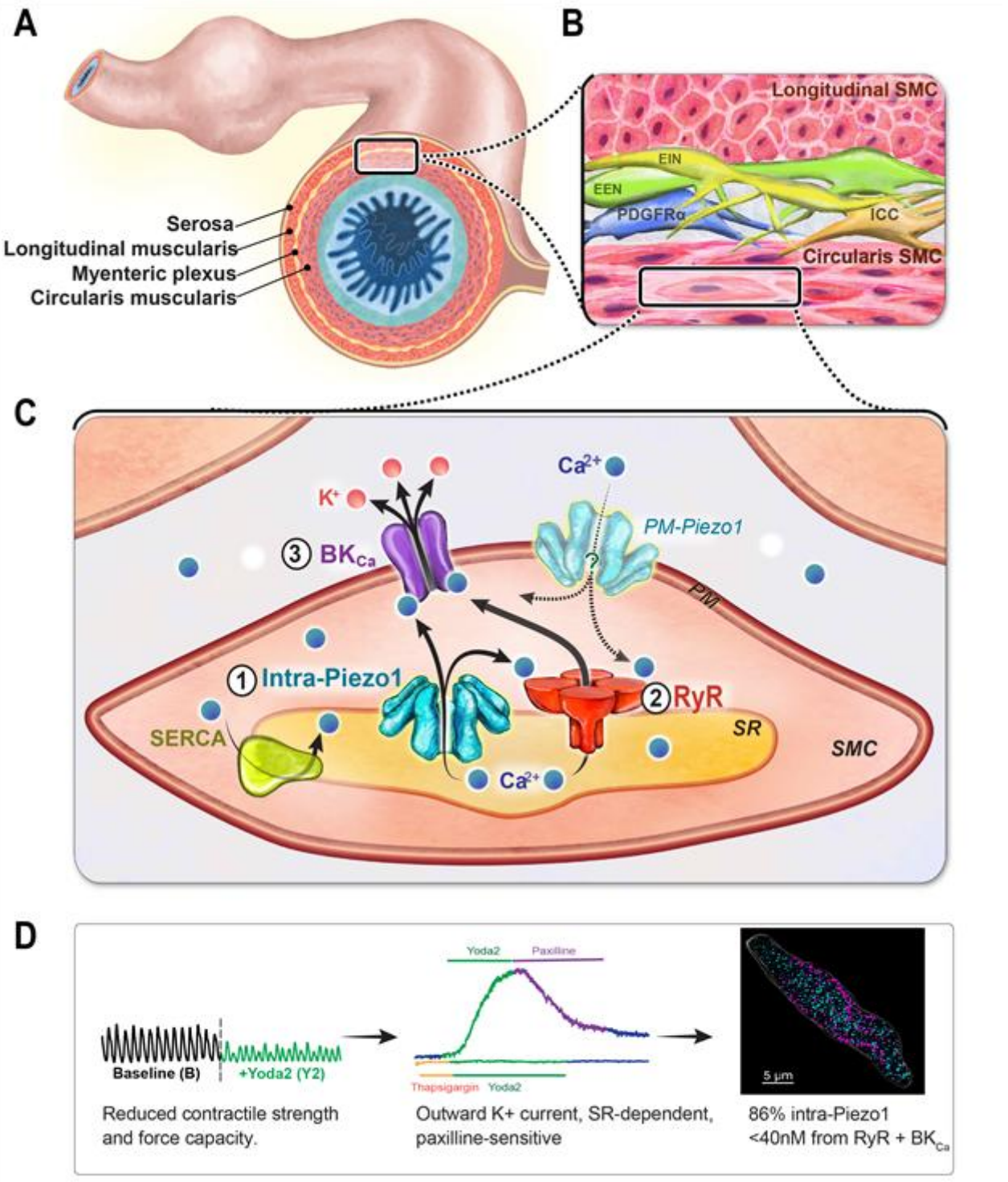
Session 2, July 13, 2026, 16:30 - 17:30

Piezo1-mediated mechanosensation is canonically defined as a plasma membrane (PM) phenomenon. Yet our previous work demonstrated that smooth muscle-specific Piezo1 knockout mice exhibited impaired weight gain, muscle thinning, and ion channel remodeling, along with an unexpected predominant intracellular localization in intestinal smooth muscle cells, challenging this fundamental assumption. This raised a compelling question: Does intracellular Piezo1 (intra-Piezo1) constitute a functionally distinct mechanosensory axis driving intestinal smooth muscle function? We hypothesized that an organelle-based Sensor-Amplifier-Effector complex at the sarcoplasmic reticulum (SR) amplifies mechanotransduction from the inside out.

To test this hypothesis, we combined high-resolution confocal microscopy with 3D surface-based classification, proximity ligation assays (PLA), and patch-clamp electrophysiology on freshly dissociated intestinal smooth muscle cells, alongside functional tissue-level wire myography of peeled intestinal muscularis.

Confocal analysis revealed 86% of Piezo1 clusters were intracellular rather than PM-localized, mirroring the RyR distribution ($p<0.0001$, N=10 mice). PLA confirmed nanoscale physical coassembly (<40 nm) of BKCa-Piezo1 (120.5 ± 105.3 puncta/mm^2) and RyR-Piezo1 (67.6 ± 39.9 puncta/mm^2). Whole-cell patch-clamp recordings demonstrated that Yoda2-induced Piezo1 activation evoked large BK-mediated outward currents that were blocked by paxilline, abolished by thapsigargin, and persisted in 0 mM extracellular Ca^{2+}. At the tissue level, Piezo1 activation reduced contraction amplitude by 57% ($p<0.0001$) and integral force by 56% ($p<0.0001$), with a 152% increase in temporal irregularity ($p=0.0103$; N=12 mice).

Together, these findings redefine the subcellular locus of Piezo1-mediated mechanotransduction and provide a mechanistic basis for the contractile dysregulation observed in smooth muscle-specific knockout animals. Rather than acting solely at the cell surface, Piezo1 also operates within SR-PM junctional microdomains as part of a Sensor-Amplifier-Effector complex that amplifies cellular sensitivity to physical force from the inside out, representing a critical gain-control system that could tune smooth muscle excitability and coordinate gastrointestinal motility.


A
B
Serosa
Longitudinal muscularis
Myenteric plexus
Circularis muscularis
Longitudinal SMC
EIN
EEN
PDGFRα
ICC
Circularis SMC
C
K+
Ca2+
3 BKCa
PM-Piezo1
PM
1 Intra-Piezo1
2 RyR
SERCA
SR
SMC
Ca2+
D
Yoda2
Paxilline
Baseline (B)
+Yoda2 (Y2)
Thapsigargin
Yoda2
5 µm
Reduced contractile strength and force capacity.
Outward K+ current, SR-dependent, paxilline-sensitive
86% intra-Piezo1 <40nM from RyR + BKCa

Understanding the interaction dynamics of PIEZO1 and its auxiliary subunits

Delfine Cheng[1], Zijing Zhou[1,2], Charles D Cox[1,2]
[1]The Victor Chang Research Institute, Australia, [2]The University of New South Wales, Australia
Session 4, July 14, 2026, 10:30 - 12:30

PIEZO channels are calcium-permeable mechanosensitive ion channels present in almost all living cells. We previously identified MyoD-family inhibitor proteins (MDFI, MDFIC, MDFIC2) as auxiliary subunits that modulate PIEZO channel activity across sensory and non-sensory cells. These subunits increase PIEZO channel activation threshold and slow channel inactivation. However, the dynamics of this interaction lacks any meaningful investigation. So, in this study, we explore the membrane associated dynamics of these auxiliary proteins using fixed- and live-cell imaging making use of fusions that connect MyoD-family inhibitor proteins to the small red fluorescent protein miRFP670nano3. To explore the potential for dissociation of these subunits from PIEZO1 channels, we combined imaging with various PIEZO1 channel mutants, including non-functional variants and mutants with redox-sensitive conformations. This allows us to probe the dynamics of the interaction between PIEZO1 and its auxiliary subunits and whether the conformation of PIEZO1 or the calcium it permeates influence how these proteins interact. Our findings suggest that conformational changes in PIEZO1 channels promote the dissociation of their auxiliary subunits, enabling their translocation to the cytosol where they can interact with transcription factors and ultimately, regulate gene expression. This provides the basis for a mechanically induced pathway direct to transcription and suggests MyoD-family inhibitor proteins act as a molecular bridge between mechanotransduction and gene regulation.

PIEZO1 Gain-of-Function Mutations Disrupt Cardiac Function Beyond Iron Overload

Sumei Cui[1]
[1]Shandong University, China

Session 6, July 14, 2026, 16:00 - 17:30

PIEZO1 is a mechanosensitive ion channel that mediates Ca^{2+} signaling in response to cardiomyocyte stretch and contributes to the Frank–Starling mechanism. Gain-of-function (GOF) mutations in PIEZO1 cause hereditary xerocytosis (HX), a hemolytic disorder frequently associated with iron overload. Increasing clinical reports describe cardiomyopathy in HX patients, yet whether PIEZO1 mutations directly affect cardiac function remains unclear.

We identified acute heart failure with severe myocardial iron deposition in a 31-year-old patient carrying the PIEZO1 D669Y variant. While cardiomyopathy in HX has largely been attributed to iron overload, our integrated human and experimental evidence suggests that PIEZO1 GOF may impair cardiac function partly independent of iron accumulation.

Consistently, PIEZO1 M2241R transgenic mice develop hypertrophic cardiomyopathy, and pharmacological PIEZO1 activation similarly induces cardiac hypertrophy. These findings suggest that PIEZO1 mutations may contribute to both hypertrophic and dilated cardiomyopathy. Ongoing genetic screening of cardiomyopathy cohorts aims to identify additional pathogenic PIEZO1 variants and define the underlying mechanisms.

Deletion of Piezo1 in adult cardiomyocytes accelerates cardiac aging and promotes premature mortality

Yang Guo[1,2], Scott Kesteven[1], Delfine Cheng[1,2], Hanzhou Lei[1], Jianxin Wu[1], Evelyn Nadar[1], Jamie Vandenberg[1,2], Zeyan Yu[1,2], Peter Macdonald[1,2,3], Munira Xaymardan[4], Charles Cox[1,2], Michael Feneley[1,2,3], Boris Martinac[1]
[1]Victor Chang Cardiac Research Institute, Australia, [2]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Australia, [3]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Australia, [4]Faculty of Medicine and Health, University of Sydney, Australia

Session 5, July 14, 2026, 14:00 - 15:30

Mechanosensitive Piezo1 channels have emerged as key transducers of mechanical forces in the cardiovascular system. We previously demonstrated that Piezo1 mediates mechanical cues driving pressure overload-induced cardiac hypertrophy. However, its role in maintaining baseline cardiac function and aging remains unclear. Here, we show that conditional deletion of Piezo1 in adult cardiomyocytes results in premature mortality in mice. Hearts lacking Piezo1 exhibited features of accelerated cardiac aging, including increased expression of senescence-associated secretory phenotype markers and a marked attenuation of age-dependent cardiac hypertrophic remodelling, accompanied by reduced activation of pro-hypertrophic Ca2+/calmodulin-dependent protein kinase II (CaMKII).
Aged Piezo1-deficient mice displayed altered Ca2+ handling kinetics together with molecular and functional signatures of electrical remodelling, consistent with lethal cardiac arrhythmias as a likely cause of premature death. While young adult knockout mice maintained normal resting heart rates, progressive sinus bradycardia developed with aging and was associated with pronounced fibrotic remodelling of the right atrium, where Piezo1 expression is highest in the healthy heart. Mechanistically, Piezo1 loss resulted in a substantial reduction in atrial natriuretic peptide (ANP), a key anti-fibrotic factor. In vivo, atrial stretch-induced ANP release was markedly blunted in conditional Piezo1 knockout mice, providing a mechanistic link between mechanical stretch sensing and ANP secretion and explaining progressive aging-associated atrial fibrosis.
Together, these findings identify Piezo1 as a critical mechanosensitive regulator of cardiac homeostasis that enables adaptation to the aging myocardial microenvironment and protects against premature cardiac dysfunction and death.

Conformational coupling between Piezos and TREK/TRAAK force-gated ion channels

Eric Honoré[1]
[1]CNRS, France

Session 8, July 15, 2026, 10:30 - 11:30

Mechanosensitive ion channels (MSCs) play a key role in a variety of physiological functions, including hearing, balance, touch, proprioception, autonomic regulation of blood pressure, urination and breathing. Thus, dysfunction of MSCs is associated with various inherited and acquired diseases. Significant progress has been made in identifying these channels, solving their structure, and understanding the gating of both hyperpolarizing and depolarizing MSCs. Besides prototypical activation by membrane tension, additional gating mechanisms involving channel curvature and/or tethered elements are at play. Mechanoelectrical transduction is mediated by the opening of different types of force-sensitive ion channels, including Piezo1/2 and the TREK/TRAAK K2P channels. Piezo1 curves the membrane locally into an inverted dome that reversibly flattens in response to force application. We show that Piezo1/2 increase TREK/TRAAK current amplitude, slow down activation/deactivation, and remove inactivation upon mechanical stimulation. The up-modulation of TREK/TRAAK channels by Piezos is independent of ionic flow and is attributed to a conformational coupling. This regulation occurs in mouse fibroblasts between endogenous Piezo1 and TREK-1/2, both channel types acting in concert during wound healing. In conclusion, we demonstrate a community effect between different structural and functional classes of mechanosensitive ion channels.

Understanding how lipids regulate PIEZO1 mechanosensitive ion channel

Dr Antreas Kalli[1], Katie Smith, Eulashini Chuntharpursat-Bon[1], Oleksandr Povstyan, Jian Shi[1], David Beech[1]
[1]University of Leeds, United Kingdom

Session 3, July 14, 2026, 09:00 - 10:00

PIEZO1 mechanosensitive ion channel is a key force sensing protein that is a critical mechanical sensor found in the membrane of cells in the cardiovascular and many other systems that include the immune, nervous, reproductive and respiratory systems. For this reason, PIEZO1 serves many diverse roles spanning from blood pressure regulation and immunity in mammals, to root growth in plants. There is increasing evidence that specific lipids e.g. phosphatidyl inositol phosphate (PIP) play a key role in the function of mechanosensitive ion channels and of PIEZO1. However, the mechanism by which lipids regulate PIEZO1 sensitivity to different physiological forces remains poorly understood. In this study, we used a computational approach to model the full-length three-dimensional structure of the human PIEZO1 channel. We used multiscale molecular dynamics simulations at the coarse-grained and atomistic resolutions to simulate the dynamics and interactions of the human PIEZO1 channel with model endothelial membranes. Our results demonstrate an inter-subunit interaction within PIEZO1 mechanosensitive ion channel that is mediated by basic amino acids, with phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) lipid at the interface, termed “handshake” mechanism. This interaction determined the resting configuration of the channel, blade curvature, and compactness. Lab-based studies using electrophysiology confirmed that disruption of the handshake by mutations or $PI(4,5)P_2$ depletion increased the channel’s sensitivity to membrane tension. This new discovery demonstrates that the membrane environment, and in particular anionic lipids such as PIP lipids, is critical to regulate the channel’s mechanical sensitivity in lipid-dependent ways.

Cardiac Mechanosensitivity Underlying Autoregulation of Cardiac Output

Peter Kohl[1]
[1]University of Freiburg, Germany, [2]University of Oxford, UK

Session 7, July 15, 2026, 09:00 - 10:00

The human heart contains ~3 billion cardiomyocytes, and even more non-myocytes. Individual myocytes experience slightly different stress–strain environments (including, but not limited to, spatial and temporal differences between atrial and ventricular chambers, between free walls and septa, as well as along transmural and baso-apical gradients). These differences are overlaid by dynamic undulations in cardiac pre- (approximated by end-diastolic volume) and afterload (~ end-systolic pressure), that occur upon every breath, through changes in posture, during physical activity, or in more sustained challenges such as pregnancy or exposure to different atmospheric pressures such as when diving, when dwelling at high altitudes, or while on an airplane. All these highly dynamic changes affect individual cells in a non-linear manner. In the absence of neuro-muscular junctions that determine the activity levels of skeletal myofibres, the heart relies on auto-regulatory processes that allow cardiomyocytes individually and collectively to adjust their performance to changes in circulatory demand. This rich auto-regulatory landscape works in real time, it is present also in excised hearts (one of the reasons for which transplants work), and it can be detected right through to the level of isolated tissue and single cells. The exact mechanisms underlying cardiac autoregulation remain a subject of intense research. This lecture will provide an overview of current insight into how cardiac mechanosensitivity enables homeodynamic activity of teh heart, matching cardiac output to haemodynamic demand.

Environmental stiffness regulates neuronal maturation via Piezo1-mediated TTR activity

Eva Kreysing[4], Helene Gautier[1], Sudipta Mukherjee[1], Katrin Mooslehner[1], Leila Muresan[5], Daniel Haarhoff[6], Xiaohui Zhao[7], Alexander Winkel[1], Tina Borić[3], Sebastián Vásquez-Sepúlveda[3], Niklas Gampl[2], Andrea Dimitracopoulos[1], Eva Pillai[1], Robert Humphrey[8], Thora Karadottir[8], Kristian Franze[3]

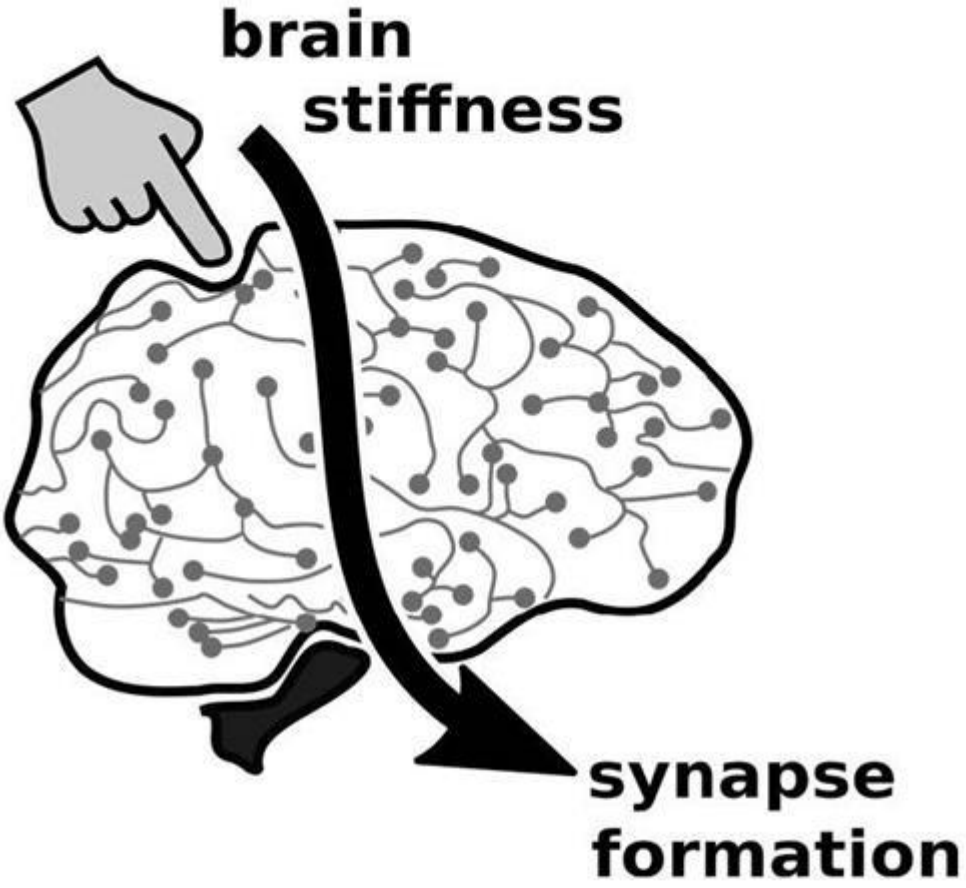
[1]Department of Physiology, Development and Neuroscience, University of Cambridge, United Kingdom, [2]Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, [3]Max-Planck-Zentrum für Physik und Medizin, Germany, [4]University Of Warwick, United Kingdom, [5]Anglia Ruskin University, United Kingdom, [6]Makespace Cambridge Ltd, United Kingdom, [7]Department of Medicine, University of Cambridge, United Kingdom, [8]Cambridge Stem Cell Institute, University of Cambridge, United Kingdom

Session 1, July 13, 2026, 14:00 - 16:00

During the development of the nervous system, neurons grow axons and dendrites to connect with other cells. As neurons become integrated into the neural network, they mature and develop electrical activity. While mechanical interactions between neurons and their environment are critical for axon growth and pathfinding, their role in the electrical maturation of neurons—and thus in the formation of circuits in the developing brain—remains poorly understood.

Here, we identified environmental mechanics as a key regulator of neuronal maturation and discovered the pathway that links tissue mechanics to this process. Using electrophysiology, immunofluorescence, RNA sequencing, and CRISPR Cas9 knockdown in primary rat neurons, we showed that stiffer environments delay electrical maturation via Piezo1 activity, leading to downregulation of transthyretin and delaying synaptogenesis and electrical maturation.

In Xenopus laevis embryos, we found that tissue stiffness was negatively correlated with synapse density, and that stiffening of the brain significantly delays synaptic activity in vivo. Our findings highlight the critical role of mechanical signals in neuronal maturation and suggest that local brain tissue stiffness is a key regulator of circuit formation in the developing brain.


brain
stiffness
synapse
formation

Functional heteromerization of PIEZO channel subunits

Aneesh Chandrasekharan[1], Tharaka Wijerathne[1], Louis-Philippe Guinard[2], Michelle Digman[2], Jerome Lacroix[1]
[1]Western University Of Health Sciences, United States, [2]University of California at Irvine, United States

Session 3, July 14, 2026, 09:00 - 10:00

Mechanosensitive PIEZO channels consist of large, Megadalton-size molecular assemblies of three subunits interacting at their C-terminal pore domain. In mammals, two distinct homologous PIEZO subunits are known to form two distinct homotrimeric channels named PIEZO1 and PIEZO2. Yet, these subunits are structurally similar and are often co-expressed in the same cells, suggesting the possibility that PIEZO1 and PIEZO2 subunits could interact to form functional heterotrimers. To test this hypothesis, we first determined the physical proximity of fluorescent probes inserted intracellularly at the C-terminus of both subunits expressed in mammalian cells. Using bimolecular fluorescence complementation (BiFC), confocal imaging and flow cytometry, we show that the C-terminus of the two homologous subunits come within close enough proximity to complement fluorescence of split mNeonGreen2 (mNG2). To determine whether the PIEZO1/PIEZO2 complex form heteromers with a defined stoichiometry, we next deployed fluorescence lifetime imaging microscopy combined with Förster resonance energy transfer (FLIM-FRET), using blue fluorescent protein 2 (BFP2) as a donor and mNG2 as an acceptor split between two identical subunits. Remarkably, our FLIM-FRET data reveals the existence of PIEZO1-PIEZO2-PIEZO2, but not PIEZO1-PIEZO1-PIEZO2, heterotrimers, consistent with electrophysiology recordings showing that cells co-transfected with our tagged PIEZO1 and PIEZO2 subunits exhibit mechano-currents with a PIEZO2-like inactivation phenotype. Last, to directly evaluate whether heteromeric channels are capable of mechanotransduction, we measured calcium entry in these channels using functional BiFC, employing a split GCaMP as a complemented calcium indicator and BAPTA to chelate non-specific intracellular-calcium ions. Our data validates this novel approach and shows that PIEZO heteromers mediate BAPTA-resistant calcium entry in response to osmotic stimulation. Overall, our study reveals that mammalian PIEZO1 and PIEZO2 subunits form functional heteromeric channels in transfected cells.

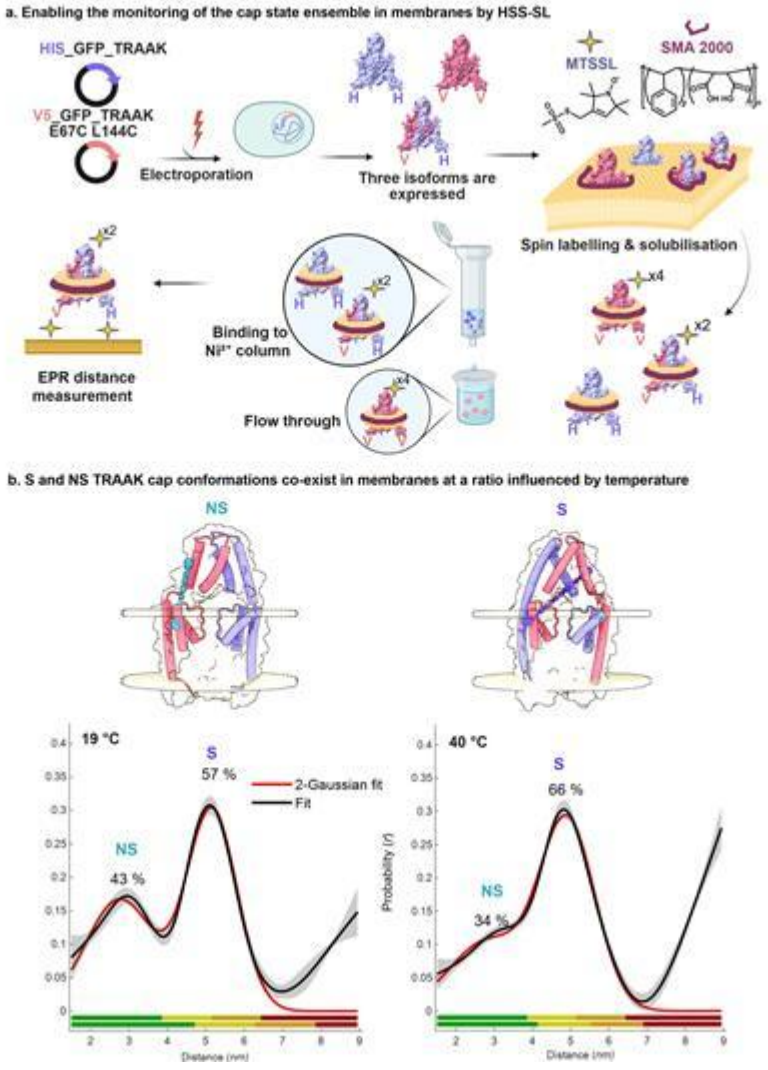
Heterologous spin labelling and DEER spectroscopy reveal K2P channel cap swapping in membranes

Yue Ma[1], Katrin Ackermann[2], Qaiser Waheed[1], Vincent Postis[3], Terry Smith[2], Bela Bode[2], Christos Pliotas[1]
[1]University of Manchester, United Kingdom, [2]University of St Andrews, United Kingdom, [3]University of Dundee, United Kingdom

Session 8, July 15, 2026, 10:30 - 11:30

The potassium two-pore domain (K2P) ion channel TRAAK is expressed in the nervous system and contributes to the regulation of fast action potentials across membranes. Like other K2P channels, TRAAK features a distinctive extracellular cap that can adopt both swapped and non-swapped conformations[1,2]. However, the relative abundance of these two species in native membranes, and the trigger or stimuli that drive the conformational transition remain unclear. Here, we employ pulse dipolar EPR spectroscopy (DEER/PELDOR) in combination with heterologous single-subunit spin labelling to monitor the full conformational ensemble of the TRAAK cap domain in native membranes. We show that the swapped and non-swapped states coexist, quantify their respective populations within the TRAAK ensemble, and find that the swapped conformation dominates, with the ratio being temperature dependent3. Native lipid analysis further reveals that TRAAK selectively associates with and is activated by signalling lipids, while excluding the membrane-abundant phosphatidylcholine lipids from its immediate environment, thereby establishing a distinct microdomain. Our combined methodology provides a robust platform for monitoring and quantifying conformational ensembles and identifying the triggers associated with such transitions in K2P channels and other membrane proteins.

1Brohawn, S. G. et al. Crystal structure of the human K2P TRAAK, a lipid- and mechano-sensitive K+ ion channel. Science (2012).
2Brohawn, S. G. et al. Physical mechanism for gating and mechanosensitivity of the human TRAAK K+ channel. Nature (2014).
3Yue, M. et al. Swapped and non-swapped TRAAK states co-exist in membranes at a ratio influenced by temperature. Nat Commun (2026).


a. Enabling the monitoring of the cap state ensemble in membranes by HSS-SL
HIS_GFP_TRAAK
V5_GFP_TRAAK
E67C L144C
Electroporation
Three isoforms are expressed
MTSSL
SMA 2000
Spin labelling & solubilisation
x2
x4
Binding to Ni2+ column
Flow through
EPR distance measurement
b. S and NS TRAAK cap conformations co-exist in membranes at a ratio influenced by temperature
NS
S
19 °C
S
57 %
NS
43 %
2-Gaussian fit
Fit
40 °C
S
66 %
NS
34 %
Probability (r)
Distance (nm)

Mechanical Control of Sinoatrial Node Activity and Heart Rate

Eilidh MacDonald
[1]University Of Glasgow, United Kingdom

Session 7, July 15, 2026, 09:00 - 10:00

The heart's intrinsic pacemaker, the sinoatrial node (SAN), is precisely regulated, allowing for adaptation of heart rate (HR) to physiological demand. Although HR regulation is generally described as occurring via the autonomic nervous system or circulating hormones, the SAN is also influenced by its exquisite mechano-sensitivity. First described over a century ago, atrial distention with increased venous return immediately increases HR, allowing for beat-by-beat adaptation of SAN activity to mechanical load. This chronotropic response has been demonstrated in excised and transplanted hearts, isolated SAN tissue, and single SAN cells, revealing its intrinsic, myogenic nature. Although the physiological relevance of SAN mechano-sensitivity has been extensively investigated and is highly conserved across vertebrate and invertebrate species, mechanisms of mechanical HR control are poorly understood, with important implications for SAN dysfunction in aging and disease.

Our interspecies results have revealed that the chronotropic response to SAN stretch depends on tissue structure and mechanics. In mouse – one species in which HR is reduced by sustained SAN stretch – the magnitude of change is inversely correlated with SAN stiffness, whereas the opposite is true for zebrafish and rabbit. This appears to relate to species differences in cell and tissue micro-architecture at baseline and when stretched, including collagen crimp / tortuosity and caveolae-mediated membrane reserves. Our current work, using motion-tracking of SAN deformation and optical mapping of membrane voltage, aims to identify whether structural differences result in spatially heterogeneous SAN stretch, and how tissue mechanics relates to stretch-induced changes in electrophysiology, including regional diastolic depolarisation and pacemaker initiation site. Further, recent pharmacological experiments have provided evidence for Piezo1 involvement in SAN stretch responses. Overall, our aim is to combine classic observations of SAN mechano-sensitivity with modern tools to reveal how structural heterogeneity and Piezo1 activation translate SAN stretch into electrophysiological responses that govern HR adaptation.

Cryogenic light microscopy with angstrom precision deciphers structural conformations of PIEZO1 in its native state

Hisham Mazal[1,2], Vahid Sandoghdar[1,2,3]
[1]Max Planck Institute For The Science Of Light, Germany, [2]Max-Planck-Zentrum für Physik und Medizin, Germany, [3]Friedrich-Alexander University of Erlangen-Nürnberg, Germany
Session 4, July 14, 2026, 10:30 - 12:30

The structure of the PIEZO protein, partially resolved by cryo-electron microscopy (cryo-EM), comprises a symmetric trimer. The core of the channel is formed by the C-terminal domain, while the N-terminal side of the protein consists of long transmembrane alpha-helices that create a blade-like feature, curving the membrane into a dome-shaped structure. Transition of PIEZO from a curved to flat conformation is believed to actuate the closed and open states of the channel for ion flow. However, these hypotheses are mostly based on data from proteins in non-native samples. To avoid chemical fixation and synthetic reconstruction, we exploit shock freezing to preserve the sample in its near-native state, which we then study via single-particle cryogenic light microscopy (spCryo-LM). To achieve this, we implement a high-vacuum cryogenic shuttle to transfer shock-frozen unroofed cell membranes in and out of a custom-built cryogenic super-resolution microscope, operating at liquid helium temperature. Our measurements reveal three distinct blade configurations with side lengths of 9, 19, and 34 nm, measured with Angstrom precision. Radius of curvature estimations based on the dome-shaped model suggest that the 19 nm conformation, the most occupied state, represents the relaxed PIEZO1 state as predicted for PIEZO in an asymptotically flat membrane. The shortest distance of these conformations hints toward a more strongly curved dome-shaped structure than previously observed and predicted by AlphaFold III. In addition, our findings indicate that the structure must unbend and form an extended blade in the largest conformation. We believe spCryo-LM can be readily combined with spCryo-EM to extend our studies to other biomolecular complexes in their native states.

Sub-cellular organelle mechano-sensitivity in the beating heart

Eva Rog-Zielinska[1]
[1]University of Freiburg, Germany

Session 2, July 13, 2026, 16:30 - 17:30

The external uniformity of cardiomyocyte contractions emerges from coordination of numerous, spatio-temporally heterogeneous processes, involving specialised sub-cellular nano-domains. Through omnidirectional coupling of electrical activity, calcium fluxes, and mechanical action, cardiomyocytes rapidly adjust to ever-changing physiological demand. It remains unknown how dynamic ultrastructural cross-talk contributes to the cardiac auto-regulatory capacity.
In my research I propose that beat-by-beat auto-regulation of heart function is governed at the nano-scale by a process unique to cardiomyocytes: the rhythmic cycle of cardiomyocyte stretch, contraction, and relaxation. In this concept, the heartbeat is not merely the consequence of cardiomyocyte activity, but an intrinsic regulator that continually modifies nano-domain structure and function in preparation for the next beat.
I combine quasi-time-resolved 3D electron microscopy, sub-cellular functional imaging, artificial intelligence-assisted data synthesis, and computational modelling. I have shown that cardiomyocyte contraction and stretch are associated with beat-by-beat deformation of cardiomyocyte organelles: transverse-axial tubular system (TATS), sarcoplasmic reticulum, mitochondria, microtubules, caveolae, and nuclei. Functionally, I have shown that TATS (a network of surface membrane invaginations that enables close structural coupling of plasma membrane and extracellular fluid with sarcoplasmic reticulum throughout the cell, and thus facilitates rapid contraction upon membrane depolarisation) cyclically deforms during cardiomyocyte stretch and contraction, where the transverse elements become cyclically ‘squeezed’, which is associated with faster luminal content exchange with the bulk extracellular space, an effect that scales up with contraction amplitude and frequency. TATS pumping serves to abolish intraluminal calcium gradients that would otherwise develop deep within TATS as a result of uneven distribution of calcium influx/efflux pathways, and – if left unrectified by deformation-driven pumping – would lead to the loss of the contractile force. Cardiac organelle mechano-sensitivity therefore likely represents a fundamental principle of cardiac physiology, where mechanical modulation of nano-domain structure and function explains how cardiomyocytes adapt rapidly to changes in circulatory demand.

High-Throughput Automated Patch Clamp Method to Enable Drug Discovery on the Force-Sensing Ion Channel Piezo1

Reetta Penttinen[1,2], Nicoletta Murciano[1], Nadine Becker[1], Markus Rapedius[1], David J. Beech[3], Lars Kaestner[2], Vincent Jaquet[4], Nicolas Demaurex[4], Niels Fertig[1], Maria Giustina Rotordam[1]
[1]Nanion Technologies GmbH, Germany, [2]University of Saarland, Germany, [3]University of Leeds, UK, [4]University of Geneva, Switzerland

Session 4, July 14, 2026, 10:30 - 12:30

Cells constantly experience physical forces such as blood flow, stretch, or pressure and they need ways to detect and respond to those forces. Piezo1 is a “force-sensing” ion channel that opens when the cell membrane is mechanically disturbed, allowing ions to flow and triggering downstream signals. Because Piezo1 is important in processes like blood vessel development, red blood cell function, and cancer progression, there is growing interest in finding compounds that can modulate Piezo1 activity. A major challenge is that the most direct way to measure Piezo1 channel activity mechanically (patch clamp electrophysiology) is traditionally slow and difficult to scale for screening many compounds.

We recently developed an automated patch clamp approach called “M-Stim,” which uses rapid, high-flow pipetting in a 384-well format to apply a controlled mechanical stimulus that reproducibly activates Piezo1 currents. In this work, we use M-Stim to test Piezo1 pharmacology in cells engineered to overexpress Piezo1, and cells that endogenously express Piezo1, to measure how effectively a set of Piezo1 inhibitors reduces mechanically evoked currents.

By combining a mechanical trigger with automated, parallel recordings, M-Stim enables faster and more standardized testing across many cells than traditional patch clamp. This makes it a practical tool for discovering and comparing compounds that modulate Piezo1, especially in biologically relevant cell types.

PIEZO1-Dependent Endothelial Mechanotransduction Protects Against Tyrosine Kinase Inhibitor–Induced Cardiotoxicity

Nazish Sayed[1]
[1]Stanford University, United States

Session 1, July 13, 2026, 14:00 - 16:00

Tyrosine kinase inhibitors (TKIs) are widely used in oncology but frequently cause hypertension and cardiotoxicity, limiting their long-term clinical utility. Endothelial mechanotransduction, the ability of endothelial cells to sense and respond to hemodynamic forces, is essential for vascular homeostasis, yet its role in TKI-associated cardiovascular toxicity remained poorly defined. We investigated whether disruption of mechanosensitive signaling underlay TKI-induced cardiotoxicity, focusing on the mechanosensitive ion channel PIEZO1.

Using a multiscale platform integrating human iPSC-derived endothelial cells, 3D engineered cardiac tissues, murine models, and single-cell transcriptomic analyses, we demonstrated that clinically relevant TKIs impaired endothelial alignment to shear stress, reduced nitric oxide bioavailability, compromised barrier integrity, and suppressed angiogenic capacity. These functional abnormalities were accompanied by downregulation of mechanotransduction pathways and reduced PIEZO1 expression.

Importantly, restoration of PIEZO1 activity, through genetic overexpression or pharmacologic modulation, rescued endothelial mechanosensing, reinstated flow-induced alignment, normalized nitric oxide production, and improved barrier and angiogenic function in vitro. In vivo, preservation of PIEZO1-dependent signaling mitigated TKI-induced vascular dysfunction and protected cardiac performance. Cross-platform transcriptomic profiling identified conserved PIEZO1-regulated networks controlling shear stress adaptation, cytoskeletal organization, and endothelial–cardiomyocyte communication.

Together, these findings established impaired endothelial mechanotransduction as a unifying mechanism linking targeted cancer therapy to cardiovascular toxicity and identified PIEZO1 as a key mechanosensitive safeguard. This work advance mechanobiology by connecting force sensing to cardioprotection and highlight PIEZO1-dependent pathways as potential therapeutic targets to prevent therapy-associated cardiovascular injury without compromising anticancer efficacy.

Piezo2 tension sensitivity and its modulation by alternative splicing

Michael Sindoni[1], William Sharp[1], Jorg Grandl[1]
[1]Duke University, United States

Session 5, July 14, 2026, 14:00 - 15:30

Piezo2 is a force-gated ion channel that functions as a sensor of mechanical touch, proprioception, lung inflation, and gut transit. Human Piezo2 contains seven domains that are alternatively spliced in a tissue-specific fashion resulting in the expression of at least 22 distinct variants. Despite the relevance of Piezo2 in human physiology, its sensitivity to membrane tension, and how this fundamental biophysical property is affected by alternative splicing, are unknown. Here, we use cell-attached pressure-clamp electrophysiology combined with differential interference contrast microscopy to quantify the response of Piezo2 to membrane tension and identify the alternatively spliced exon 35 as a domain sufficient to confer high sensitivity to membrane tension and cellular indentation. We further show that physiological variants of Piezo2 sense mechanical forces with distinct sensitivities and dynamic ranges. Together, our findings rationalize how Piezo2 variants may fulfill distinct physiological functions required for somatosensation and interoception.

Hypertensive Pressure Mechanosensing Triggers Transdifferentiation of Vascular Smooth Muscle Cells to Foam Cells

Pamela Swiatlowska[1], William Tipping, Emilie Marhuenda, Paolo Severi, Vitalay Fomin, Zhisheng Yang, Qingzhong Xiao, Duncan Graham, Cathy Shanahan, Thomas Iskratsch
[1]School of Engineering and Materials Science, Queen Mary University of London, United Kingdom

Session 6, July 14, 2026, 16:00 - 17:30

Arterial vascular smooth muscle cells (VSMCs) play central role in the onset and progression of atherosclerosis, where they undergo phenotypic switching by downregulating vSMC-specific genes and transition to a different cell type. Our previous work indicated that vSMC respond to hypertensive pressure and differential extracellular matrix compliance, exhibiting an atherosclerotic phenotype. Our aim here was to study pressure sensing in further detail.
A7R5 rat vSMC were plated on glass or 1kPa-polydimethylsiloxane and subjected to hypertensive pressure (200/120mmHg). Hyperspectral Stimulated Raman Spectroscopy (hsSRS) was applied for lipid imaging. Scratch, proliferation, TUNEL assays and RT-PCR were used to verify the foam cell phenotype. Electroporation, Western-Blot, immunocytochemistry were used to visualize Piezo1 channel. CUT&Tag analysis were applied for Piezo1-driven gene regulation changes. Lamin-associated heterochromatin was visualized with Transmission Electron Microscope. Nanoindentation was used to examine nuclear stiffness. Mouse tissue, primary rat and human vSMC were used to confirm the A7R5 findings.
Following hypertensive pressure stimulation, we observed lipid droplet accumulation in vSMC as indicated by hsSRS ($p>0.05$). Similar result was obtained upon acute vSMC Piezo1, mechanosensitive channel, stimulation ($p>0.01$). Further results demonstrate upregulation of CD68, KLF4, LDLR and downregulation of ABCA1 genes ($p>0.05$), higher proliferation rate ($p>0.001$) and lower cell motility ($p>0.01$).; characteristics specific to foam cells, indicating that Piezo1 $Ca2+$ transients can trigger vSMC-to-foam cell transition. We identified that Piezo1 activation leads to changes in nuclear $Ca2+$ uptake, reactive oxygen signaling, downregulation of histone-3-lysine-9-trimethylation ($p>0.001$) and softer nucleus ($p>0.05$). CUT&Tag experiment confirmed Piezo1-epigenetic regulation of VSMC phenotypic switching.
These results show that vSMC-to-foam cell transition can be triggered by mechanical stimulation.

Tracking mechanosensitive ion channels PIEZO1 and PIEZO2 across scales

Dr Clement Verkest[1]
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Session 1, July 13, 2026, 14:00 - 16:00

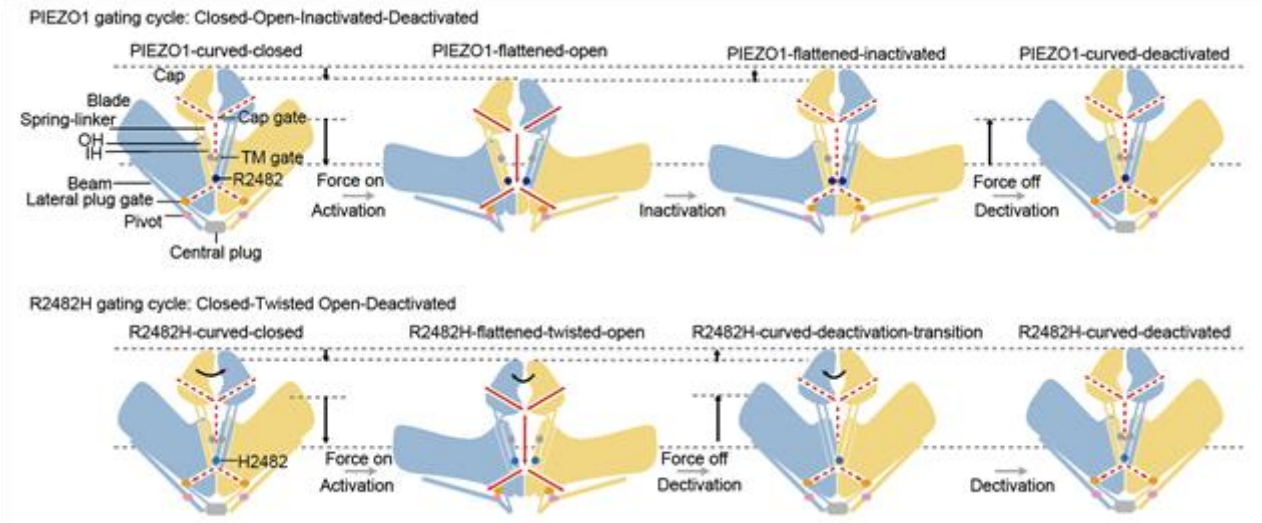
Since their discovery in 2010, the mechanically activated ion channels PIEZO1 and PIEZO2 were shown to be of crucial importance in a variety of cells, tissues and physiological processes (light touch detection, blood pressure control, organs distention, cell migration etc.). High-resolution cryo-EM studies showed that PIEZO1 and PIEZO2 oligomerize as homotrimers and shared a common propeller-shaped quaternary structure. Subsequent structure-guided studies have revealed the role of several structural domains as well as single amino acids and interdomain interactions that control important functional properties, showing similarities but also some differences between the two channels. A central question is how external and internal mechanical forces acting on cellular plasma membrane are transmitted to mechanically-gated PIEZO channels, that convert these forces into biochemical signals. It is therefore crucial to understand the dynamics and subcellular localization of PIEZOs, particularly their interaction with their environment (membrane, cytoskeleton etc.), as those are key regulators of mechanical forces integration and PIEZOs function. Here, using a combination of diffraction limited and super-resolution microscopy in living cells, we have tracked clusters and individual PIEZO1 and PIEZO2 channels, while simultaneously monitoring the actin cytoskeleton or key membrane lipids. As previously observed by us and others, PIEZO1 and PIEZO2 clusters exhibit different types of motions at the plasma membrane (Brownian/mobile diffusion, confined/sub-diffusion). Direct comparison of the two channel clusters did not reveal any major differences. Leveraging the high spatiotemporal resolution of MINFLUX, we observed that PIEZO1 and PIEZO2, at the single channel level, differ significantly regarding their mobility, with PIEZO2 being more prone to confined diffusion. We are currently investigating the cellular and structural basis underlying this difference. Our results should provide new insights into the functional regulation of PIEZOs channels in living cells.

Un-swapping the pore as a structural mechanism for PIEZO1 channelopathy

Chenxi Wang[1,2,3], Ziying Zhang[1,3,4], Xuzhong Yang[1,2,3], Sijia Liu[1,3,4], Jingyi Yuan[1,2,3], Chao Lin[1,3,4], Xiaochun Zhang[2], Boxue Tian[2], Xueming Li[1,3,4], Bailong Xiao[1,2,3]
[1]State Key Laboratory of Membrane Biology, School of Pharmaceutical Sciences, Tsinghua Medicine, Tsinghua University, China, [2]New Cornerstone Science Laboratory, School of Pharmaceutical Sciences, Tsinghua Medicine, Tsinghua University, China, [3]Tsinghua-Peking Center for Life Sciences, Tsinghua University, China, [4]Beijing Frontier Research Center of Biological Structure, Tsinghua University, China

Session 1, July 13, 2026, 14:00 - 16:00

PIEZO1 is a versatile mechanotranduction channel critical for diverse cellular and physiological processes. Gain-of-function mutations, such as R2482H, which slow channel inactivation, are linked to dehydrated hereditary stomatocytosis (DHS) and iron overload. PIEZO1 forms a gigantic bowl-shaped trimer comprising flattenable peripheral blades and a central pore module with a switchable cap. However, the structural dynamics governing its gating process and pathogenesis remain incompletely understood. Here, we determined distinct conformational states of PIEZO1-R2482H in both detergents and proteoliposomes. Remarkably, the R2482H mutation in the central pore induces a conformational change that propagates ~25 nm to the most distal blade, enabling resolution of all 38 transmembrane helices. PIEZO1-R2482H is inherently flatter than wild-type PIEZO1, lowering the gating force and energy barrier and thus explaining its heightened mechanosensitivity. While wild-type PIEZO1 in liposome membrane adopts a flattened and inactivated conformation with its cap in the up-state, the flattened PIEZO1-R2482H has its cap in a down-state and twisted by ~75°. This drastic twist switches the pore module from a swapped to a non-swapped organization, due to disruption of the electrostatic interaction between R2482 and E2133. This twisted conformation of PIEZO1-R2482H hinders the transition to the inactivated and closed state. Instead, it proceeds through a deactivation-transition state characterized by curved blades and a partially twisted cap, thereby explaining the slowed inactivation and deactivation kinetics. Taken together, we reveal the full transmembrane topology and a non-swapped pore conformation induced by R2482H, and propose a structural dynamic model that delineates the distinct gating cycles of activation, inactivation, and deactivation for wild-type PIEZO1 and PIEZO1-R2482H.

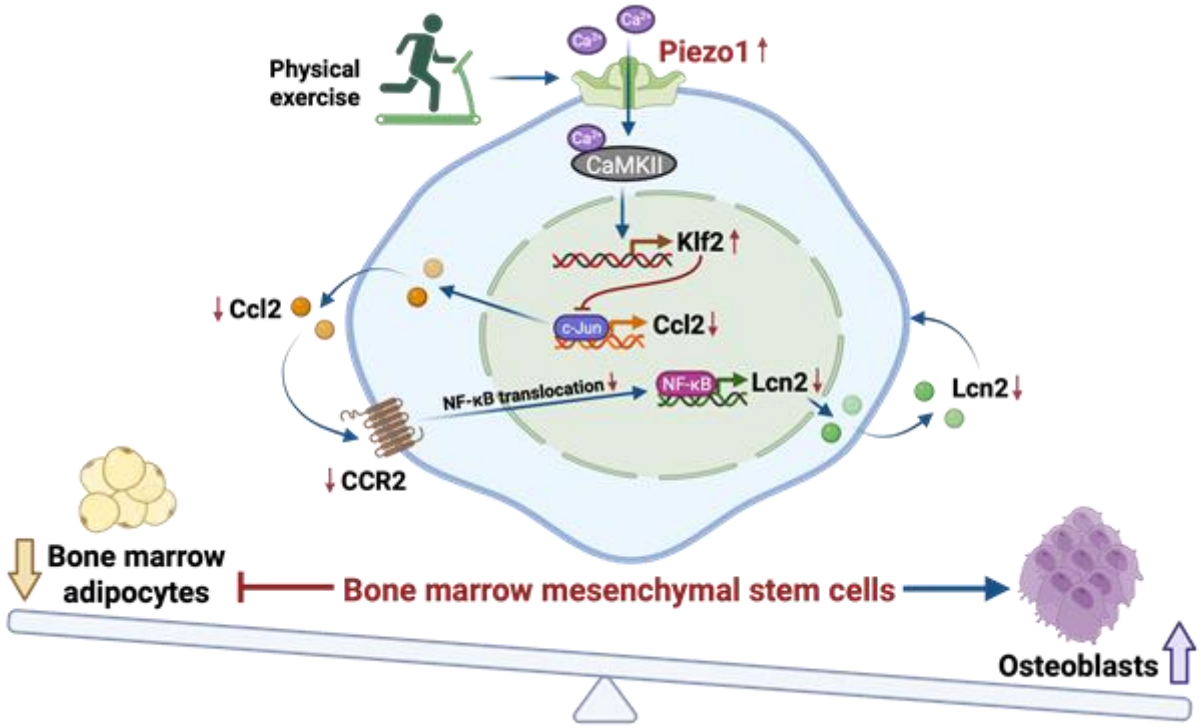


Piezo1 activation suppresses bone marrow adipogenesis to prevent osteoporosis by inhibiting a mechanoinflammatory autocrine loop

Baile Wang[1], Jie Liu[1], Qin Wang[1], Malika Arhatte[2], Lai Yee Cheong[1], Edyta Glogowska[2], Xue Jiang[1], Sookja Kim Chung[1], Leigang Jin[1], Qianxing Hu[1], Yu Wang[1], Eric Honoré[2], Aimin Xu[1]
[1]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong, China, [2]Université Côte d'Azur, Centre National de la Recherche Scientifique, Institut national de la santé et de la recherche médicale, Institut de Pharmacologie Moléculaire et Cellulaire, France

Session 6, July 14, 2026, 16:00 - 17:30

With aging or osteoporosis, bone marrow adipogenesis is increased and inversely correlates with the loss of bone mass. Bone marrow adipocytes are derived from multipotent bone marrow mesenchymal stem cells (BMMSCs), which can differentiate into either fat or bone. BMMSCs are mechanosensitive cells, but how mechanical loading is implicated in the in vivo regulation of bone marrow adipogenesis and its impact on bone remodeling remain poorly understood. Here, we identify the mechanosensitive cationic channel Piezo1 in BMMSCs as a key suppressor of bone marrow adipogenesis by preventing local inflammation, thereby enhancing osteoblast differentiation and bone formation. Mice with a specific Piezo1 invalidation in BMMSCs exhibit osteoporosis and marrow adiposity, together with resistance to the beneficial effects of exercise on bone health. Accordingly, Piezo1-deficient BMMSCs in vitro preferentially differentiate into adipocytes rather than osteoblasts. Invalidation of Piezo1 in BMMSCs enhances the autocrine activation of CCR2 by Ccl2, which further induces lipocalin-2 (Lcn2) production via NF-κB activation, promoting adipocyte differentiation. Conversely, Piezo1 opening induces Klf2 expression through CaMKII, preventing c-Jun activation, Ccl2 production and bone marrow adipogenesis. These findings demonstrate that Piezo1 activation in BMMSCs suppresses bone marrow adipogenesis to maintain bone strength by preventing the Ccl2-Lcn2 inflammatory autocrine loop, thus uncovering a previously unrecognized link between mechanotransduction, inflammation, and cell fate determination.

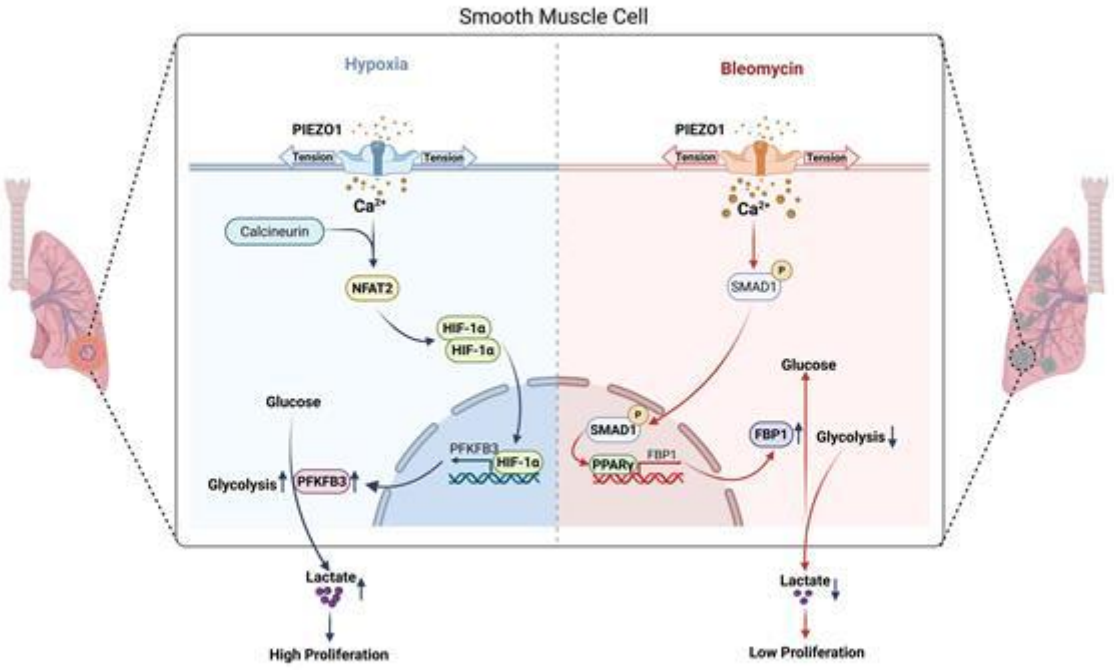


Zonated mechanosensing by PIEZO1 controls liver regeneration

ShengPeng Wang[1]
[1]Xi'an Jiaotong Univ, China

Session 2, July 13, 2026, 16:30 - 17:30

The liver exhibits a marked regenerative capacity organized through distinct zones, yet how tissue mechanics coordinate zonated proliferation remains elusive. We reveal that mechanical cues critically contribute to mouse liver regeneration in a highly region-specific manner through sensing by a subpopulation of mid-lobular hepatocytes, which are characterized by dipeptidyl peptidase-4 (DPP4) expression and represent the key proliferative pool of hepatocytes. PIEZO1 is a primary mechanosensor enriched in zone 2 DPP4+ hepatocytes that integrates biomechanical cues to drive liver regrowth by insulin-like growth factor binding protein 2 (IGFBP2). Genetic disruption of PIEZO1 restrains hepatocyte proliferation and compromises liver regeneration, whereas zonated PIEZO1 gain of function enhances proliferation and accelerates recovery. These findings reveal that DPP4+ mechanosensitive hepatocytes orchestrate liver regrowth through PIEZO1-mediated mechanosensing, establishing a link between tissue mechanics and liver regeneration.



Piezo1-Mediated Mechanotransduction in Endothelial Dysfunction During Dengue Hemorrhagic Fever

Lindsay Whalen[1], Justin Richner[1], Yulia Komarova
[1]University Of Illinois Chicago, United States

Session 6, July 14, 2026, 16:00 - 17:30

Up to 400 million Dengue virus infections occur annually, with a subset progressing to Dengue Hemorrhagic Fever (DHF), a severe complication characterized by vascular leakage, bleeding, and shock. Currently, no effective treatments are available, as vascular leakage develops after viral clearance and is driven by incompletely understood host mechanisms. Clinical evidence has implicated the viral nonstructural protein 1 (NS1) as a key pathogenic factor; exposure to NS1 alone has been shown to disrupt endothelial cell (EC) barriers both in vitro and in vivo through destabilization of VE-cadherin junctions. However, the upstream mechanisms by which NS1 induces EC dysfunction remain unclear. In this project, the molecular signaling events linking circulating NS1 to sustained EC responses are being investigated. NS1 has been found to undergo internalization and to induce calcium influx through Piezo1, a mechanosensitive ion channel. This Ca^{2+} signaling results in disruption of VE-cadherin junctions and suppression of Hippo pathway activity. Under physiological conditions, Hippo signaling maintains EC integrity by restraining the transcriptional co-activator YAP1. When Hippo signaling is suppressed, YAP1 becomes activated, promoting aberrant vascular remodeling and priming ECs for exaggerated responses to secondary stressors, including cytokines and inflammatory mediators. These findings suggest that receptor-mediated internalization of NS1 activates Piezo1-dependent calcium signaling, leading to VE-cadherin destabilization and YAP1-driven endothelial dysfunction, thereby sensitizing endothelial cells to secondary inflammatory stressors and promoting vascular leakage in DHF.

The Physiological Society – PIEZOs Flash Presentations

Mechanosensitive Ion Channel Piezo1 Regulates Osteoclast Differentiation by Activating the Metalloproteinases ADAM10 and ADAM17

Mr. Yunus Benli[1]
[1]Institute Of Molecular Pharmacology, Germany

Flash Talk Session, July 15, 2026, 11:30 - 13:00

Bone remodeling is a continuous process throughout life and serves to adjust bone architecture to meet changing mechanical needs. The mechanosensitive ion channel Piezo1 is known to sense mechanical forces in osteoblasts leading to increased bone formation by these cells. By contrast, the role of Piezo1 in osteoclasts, is less understood. We have recently shown that the constitutive activity of the metalloproteinases ADAM10 and ADAM17 on osteoclast precursor cells limits osteoclast development from precursor cells that differentiate in response to macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL). This is associated with the proteolytic shedding of cell surface expressed receptors for RANKL and M-CSF (RANK and CSF1R, respectively), thereby reducing cellular responsiveness of the cells. In the present study, we investigated whether this regulatory process can be modulated by mechanical forces and signaling through Piezo1. Stimulation of Piezo1 by Yoda1 led to a considerable reduction of osteoclast development in response to M-CSF and RANKL. This was mediated in part by increased activity of ADAM10 and ADAM17 as demonstrated by selective ADAM10 inhibition and ADAM17 knockout. Furthermore, Piezo1 activation reduced RANK and CSF1R surface expression on osteoclast precursor cells again depending on both proteases. Finally, also mechanical compression of the precursor cells diminished RANK and CSF1R surface expression partly involving ADAM10 and ADAM17 activity. These data indicate that ADAM10 and ADAM17 activity is upregulated via the mechanosensitive ion channel Piezo1 leading to enhanced receptor shedding thereby preventing induction of osteoclast differentiation. Also on osteoblasts, we found that stimulation of Piezo1 activates ADAM10 mediated release of RANKL. This implies that less transmembrane RANKL is available on osteoblasts for cell-to-cell stimulation of osteoclasts. Thus, Piezo1 may be locally relevant to limit bone resorption through activation of ADAM10 and ADAM17 which would complement its already well described pro-osteogenic role in osteoblasts.

Actomyosin-dependent PIEZO1-mediated mechanotransduction amplifies aldosterone production

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Adherens junctions (AJs) couple intercellular cadherins to the actomyosin network via αCatenin and are central to sensing mechanical force at cell–cell contacts. The adrenal zona glomerulosa (zG) produces aldosterone in response to increases in intracellular Ca2+ in a highly coordinated manner. In adrenal slices, acute disruption of cadherin binding decreased synchronized intercellular Ca2+ bursts and decreased aldosterone production, suggesting intact AJs support coordinated zG activity. However, how tissue mechanics and intercellular coupling shape zG Ca2+ dynamics and steroidogenesis remains unclear. We hypothesized that AJs transduce mechanical signals through actomyosin to activate mechanosensitive ion channels, thereby amplifying Ca2+ entry and aldosterone production.

To define the downstream mechanotransduction pathway, we combined confocal imaging, atomic force microscopy (AFM), and patch clamping in control, αCatenin-knockout and PIEZO1-knockout human adrenocortical cells (NCI-H295R), and in primary mouse zG cells, and zG-specific mouse models. Upon K+ stimulation (a major physiological secretagogue of aldosterone), cells showed increased actin polymerization (via confocal imaging) and elevated membrane stiffness (via AFM) at cell–cell contact regions, which were blunted when the AJ–actomyosin linkage was disrupted in αCatenin-knockout cells. Pharmacological inhibition of actomyosin (via cytochalasin D, ML7, or blebbistatin) or mechanosensitive channels (via GsMTx4) attenuated K+-evoked Ca2+ influx and aldosterone production in NCI-H295R cells. Conversely, activation of PIEZO1 by Yoda1 induced membrane depolarization, Ca2+ influx, CYP11B2 expression and aldosterone production. Piezo1 deletion in mouse zG cells and NCI-H295R cells reduced K+-stimulated aldosterone production and rendered aldosterone production insensitive to the effects of actomyosin inhibition, consistent with PIEZO1 acting downstream of K+-induced actomyosin contractility.

We propose a mechanotransduction model by which K+-evoked actomyosin-dependent changes in cell–cell junction mechanics activate PIEZO1 to drive Ca2+ signaling and aldosterone production. Our findings establish the zG as a mechanosensitive endocrine tissue and identify an AJ–actomyosin-PIEZO1 axis as a potent regulator of aldosterone production.

Physical mechanism of Piezo1 stiffness sensing

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Cellular membranes play an important role in transducing external and internal mechanical stimuli, such as shear forces and changes in tissue stiffness, into intracellular, biochemical responses. One of the key mechanical properties of the cell surface is effective membrane tension, which is defined as the resistance of the membrane to deformation. Membrane tension contributes to the transduction of mechanical signals via mechanosensitive ion channels embedded in the membrane. The in-plane tension of the lipid bilayer and the interaction of the membrane with the underlying cytoskeleton contribute to the overall tension of the cell surface. Although the membrane to cortex attachment is thought to be the largest contributor to the effective membrane tension, how these parameters interact to transduce mechanical signals is still poorly understood. In particular, how and if a change in tissue stiffness affects the surface mechanics of the cell, which in turn would contribute to the activation of the mechanosensitive ion channel Piezo1, is not yet known. To investigate the dependence of the effective membrane tension on substrate stiffness, I cultured HEK 293T cells and rat embryonic neurons on compliant substrates, and measured the tension with optical tweezers and AFM. To determine whether Piezo1 expression modulates the mechanical response of the cell surface these measurements were also performed in Piezo1 knockout and Piezo1 overexpressed HEK cells, and Piezo1 knockdown neurons. Furthermore, I used pharmacological and genetic approaches to modulate the actin cortex, membrane composition, and membrane to cortex adhesion to characterize their contributions to effective membrane tension. Ultimately, I aim to understand how changes in the effective membrane tension, caused by the changes in tissue stiffness, lead to the activation of Piezo1. This work will contribute to the understanding of how mechanosensitive ion channels are gated, which could have significant implications for drug design in the future.

The Effect of Auditory Conditions on Cognitive Performance and Physiological Responses

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Auditory conditions influence attention and decision processes, making it essential to identify which music types enhance or hinder performance. Optimizing acoustic environments is crucial, as the Yerkes-Dodson law and Arousal Theory suggest that moderate stimulation supports learning acquisition, cognitive performance and wellbeing, whereas extremes may impair task execution and decision-making. These relationships between executive functioning and physiological responses during tasks assessing attention, reaction time, and working memory remain unclear. This study investigates how auditory contexts influence information processing efficiency and decision thresholds under workload by integrating behavioral performance metrics with autonomic measures across structured auditory environments. A controlled within-subject study will compare three music genres: silence (control), classical music (60 BPM) and metal (190 BPM) among 40 high school students (aged 14-16). We developed a web application for participants to complete computer-based reflex, visual search, and mental arithmetic tasks under standardized audio conditions via headphones at 75 dB, with performance evaluated through reaction time and accuracy to assess attention and working memory under load. To record heart rate variability and blood oxygen saturation we built a wrist-based prototype incorporating a MAX30102 photoplethysmography module, with HRV parameters validated against electrocardiography in previous studies. Behavioral and physiological measures will be integrated into the Balanced Integration Score (BIS), reflecting the trade off between speed and accuracy. Differences across auditory conditions will be assessed using linear mixed-effects models to account for within-subject variability. Variations in BIS and physiological measures will be analyzed with the Drift Diffusion Model to estimate drift rate and boundary separation. Low tempo (60 BPM) music is hypothesized to improve performance efficiency without increasing autonomic activation, while high tempo (190 BPM) conditions may decrease reaction time while reducing decision thresholds. Findings are expected to clarify how music tempo modulates cognitive efficiency and psychological activity under cognitive load, especially in educational settings.

The role of Piezo1 in blood-retinal barrier dysfunction

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More than 1 billion people worldwide live with sight loss, with one new person starting to lose their sight every six minutes. Most retinal diseases share common clinical features, such as hyperpermeability and pathological neovascularisation, which stem from inner blood-retinal barrier (iBRB) dysfunction. Vascular endothelial growth factor (VEGF) is the primary driver of iBRB dysfunction. However, anti-VEGFs work in only 50% of patients, highlighting the need for alternative therapeutic targets. From a vascular perspective, disturbances in retinal blood flow characterise the early clinical stages of retinal disorders and cause increased shear stress and endothelial cell (EC) damage. Thus, to uncover the mechanisms of vascular mechanotransduction and increase our understanding of both the maintenance of physiology and the development of disease, we investigated Piezo1, a mechanosensitive calcium (Ca^{2+}) channel whose role in the iBRB functions remains largely unexplored.

To test Piezo activity, primary human retinal endothelial cells (HRECs) were incubated with 2 µM Cal520 AM in Krebs solution for 1h at 37 °C. Treatment of HRECs with Piezo1 agonist Yoda1 induced an increase in the intracellular Ca^{2+} concentration in the form of a single transient, whose amplitude was correlated to Yoda1 concentration. This signal was prevented in most cells when treated without extracellular Ca^{2+}. However, around 20% of cells showed a short single or double transient, indicating heterogeneity in the EC monolayer. Furthermore, 5% of cells responded to Yoda1 after passive depletion of the endoplasmic reticulum in the absence of extracellular Ca^{2+}. Consistent with our data, Piezo1 expression was detected in HRECs via immunocytochemistry. Furthermore, Piezo1 activation stimulated HREC migration in a wound healing assay. Finally, HREC treatment with VEGF induced Ca^{2+} oscillations, whose amplitude and frequency were reduced by preincubation of HRECs with Piezo1 inhibitor Dooku1. In conclusion, our results indicate that Piezo1 plays a relevant role in HREC physiology.

Piezo1 Activation Reduces Coronary Flow in ex vivo-Perfused Mouse Hearts

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Introduction: Adequate tissue perfusion is essential for cardiac function. Piezo1, highly expressed in vascular endothelial cells, acts as a mechanosensor modulating vascular tone via calcium-dependent signalling [Lhomme et al., 2019]. The role of Piezo1 in coronary function remains incompletely understood. We hypothesise that Piezo1-activation by Yoda1 in ex vivo perfused murine hearts increases coronary flow.

Methods: Adult C57BL/6 mouse hearts were Langendorff-perfused using HEPES-buffered saline (perfusion pressure 60 mmHg). Hearts were loaded with the voltage sensitive dye Di-4-ANBDQPQ (10.5 µM) and mechanically uncoupled with blebbistatin (10 µM). Yoda1-containing saline (10 µM, from DMSO-stock) was passed through a 0.22 µm sterile filter to remove any residual Yoda1-crystals as these can block microvessels. Optical maps were acquired every 2 min, while surface electrocardiogram and coronary flow were recorded continuously.

Results: Yoda1 perfusion reduced coronary flow within 10 min from 1.50±0.13 mL/min to 0.47±0.08 mL/min (mean±SD, n=9, $p<0.001$), which partially recovered during a 10min-washout to 0.81±0.23 mL/min ($p=0.03$ vs. Yoda1; $p=0.004$ vs. baseline). During Yoda1-perfusion, 7 of the hearts showed atrio-ventricular (AV) block (4× type-II, 3× type-III). In solvent controls (0.1% DMSO, n=9), coronary flow did not change significantly, and AV-block was observed in 1 heart (type-III). Time-matched saline controls (20 min perfusion, n=4) exhibited no significant flow reduction or AV block. To assess the effect of reduced coronary perfusion, flow was transiently reduced (45% of baseline, n=4), resulting in AV-block in 2 hearts (2× type-II).

Conclusion: These findings suggest that in the coronary vasculature, Piezo1-activation can reduce flow. This effect is not caused by the presence of DMSO. The reduction in coronary flow may underlie the observed AV-block in mouse hearts ex vivo. Further studies will clarify the mechanisms underlying coronary flow reduction by Piezo1-activation.

Lipid Interactions and Membrane Curvature of Arabidopsis thaliana PIEZO1

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PIEZO1 is a trimeric mechanosensitive ion channel characterized by a curved transmembrane architecture composed of a cap domain, a central pore formed by C-terminal transmembrane segments, and peripheral blade regions. While high-resolution structures are available for mouse and human PIEZO1, no experimental structure exists for plant homologues, limiting our understanding of plant mechanotransduction. Arabidopsis thaliana PIEZO1 (AtPIEZO1) is similar in size to mouse PIEZO1 with moderate residue conservation between the two homologues. In this study, we used homology modelling to generated a 3D model of AtPIEZO. Using molecular dynamics simulation at the coarse-grained resolution we inserted AtPIEZO1 in a bilayer that mimics the A. thaliana tonoplast membrane. Our simulations revealed strong interactions between AtPIEZO1 and anionic lipids, particularly phosphatidylinositol (PI), phosphatidylserine (PS), and phosphatidylglycerol (PG). Studies with the human and mouse homologues of PIEZO1 have shown that anionic lipids regulate PIEZO1 mechanosensitivity. As PG lipids are abundant in the tonoplast but absent from mammalian plasma membranes our simulations may suggest plant-specific regulatory mechanisms. Furthermore, our results indicate that AtPIEZO1 induces a shallower membrane deformation compared to mouse PIEZO1, potentially reflecting a distinct force-sensing mechanism. Overall, our results provide new insights into the interactions of AtPIEZO1 that in turn may regulate its function.

Does function follow form? Differences in excitation-contraction coupling of hiPSC-CMs cultured in 3D versus 2D

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Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have become a popular in vitro cardiac model. In recent years, 3D culture (spheroids) has been proposed as an alternative model that may better recapitulate the heart in situ. Understanding the underlying excitation-contraction coupling of hiPSC-CM monolayers and spheroids is essential for their translational application. Therefore, the aim of this study was to characterise excitation-contraction coupling of hiPSC-CM monolayers and spheroids. Commercial hiPSC-CMs were plated as either a monolayer or spheroid. Optical dyes were used to study intracellular calcium and membrane voltage dynamics, and contractility was assessed using an image-based algorithm. Monolayer and spheroid response to electrical stimulation was assessed by increasing field stimulation from 1-4Hz. Both preparations were stained with Wheat Germ Agglutin (WGA) and DAPI to assess cell structure. Finally, the Paci hiPSC-CM model was used to assess the effect of cell size on calcium and voltage dynamics. HiPSC-CM spheroids had a faster spontaneous beat rate (1123 vs 1724ms, p=0.0002), faster calcium rise time (43 vs 69ms, p=0.0067), shorter calcium duration at 50% and 90% (187 vs 167ms, p=0.0096 and 407 vs 521ms, p=0.0238 respectively) and shorter APD90 (149 vs 219ms, $p<0.05$) compared to hiPSC-CM monolayers (Nexp=3, n=12). Spheroids also followed higher rates of electrical stimulation than monolayers (85% of spheroids but only 53% of monolayers, paced up to 3Hz, Nexp=3, n=15-27). Interestingly, cells within a spheroid were ~5X smaller than cells within a monolayer (cell diameter 13 vs 49µm $p<0.0001$, N=13, n=65). however modelling suggests that changes in cell size alone cannot account for the differences in calcium and voltage dynamics observed. Overall, hiPSC-CMs cultured in 3D have distinct functional and structural differences than the same cells cultured in 2D, which is an important consideration when deciding on the optimal cardiac in vitro model for specific translational applications.

The role of PIEZO1 in Purkinje Fibre-mediated arrhythmia development: A study from the whole heart to the nanoscale level

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Premature ventricular contractions originate from the Purkinje fibre (PF) network; however, their underlying mechanism and propagation is unknown. Such answers would be revolutionary for targeting arrhythmia development within ablation therapy. This study looks at the role that PIEZO1, a mechano-sensitive ion channel, has within PF-mediated arrhythmia development.

In accordance with local ethical regulations: (1) Langendorff-perfused, male Wistar rat hearts (N=8) underwent mechanical stimulation by a left ventricular (LV) fluid-filled balloon (100 µL inflation over 2s; maintained for 38s). The LV was perfused with Tyrode then 50 µM Yoda1, a PIEZO1 activator, for 5 minutes, followed by Lugol's. (2) Isolated female Ovine PFs (N=3) were loaded with 10 µM Fura-2 to obtain calcium recordings in the presence and absence of Yoda1 whilst the PF underwent electrical and mechanical stimulation. (3) Isolated male Porcine PFs (N=2) were sectioned (350 µm) and incubated with 10 µM Rhod2; 10 µM blebbistatin and 7.5 µM RH237 for optical mapping recordings (0.5 Hz field stimulation; 35°C). All tissue underwent immunofluorescence staining and 4x expansion microscopy for PIEZO1. Data presented as mean ± SEM; One-Way ANOVA ($P<0.05$).

When the LV was dilated, (1) in the presence of Yoda1, ectopic activations increased 32% (12.21 ± 1.10) compared to Tyrode alone (9.25 ± 0.82), decreasing 75% to 3.09 ± 0.43 after Lugol's. Isolated PFs (2) had an altered calcium transient wavefront upon stretch, which was exacerbated in the presence of Yoda1 (denoted in brackets). Amplitude increased 65% (80%), with a 9% (14%) slower time to peak and 6% (27%) slower time to fall. (3) Voltage and calcium activation was mapped across the PF, with PIEZO1 localised to the PF membrane to correlate function with structure.

We propose PIEZO1 to have a key role in the PF network, its structural heterogeneity being fundamental to the mechanism of arrhythmia development.

Limora: A Synchronized Multimodal System for Real-Time Cognitive Load Monitoring in Educational Environments

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Cognitive load, the total mental effort required to perform a task, is crucial for assessing attention, stress, and learning performance. However, accurate measurement remains challenging as many existing monitors rely on single-sensor or unsynchronized devices, producing incomplete representations of cognitive activity. According to Cognitive Load Theory (Sweller), increased mental effort during complex tasks are reflected in physiological changes such as pupil dilation and autonomic activation, serving as reliable indicators of cognitive effort, yet their synchronized dynamics during academic tasks are rarely analyzed in controlled educational settings.

This study introduces Limora, a synchronized dual-sensor system for cognitive load measurement that simultaneously records pupil diameter and skin conductance. Integrated architecture aligns both data streams through temporal synchronization, enabling cross-modal analysis of physiological responses. Pupillary fluctuations are captured using a webcam integrated with Pupil Capture software, while electrodermal activity is recorded via a Raspberry Pi connected to a Galvanic Skin Response sensor on the middle and index fingers.

40 high schoolers will complete a three-phase protocol using Limora, where stimuli are presented through PsychoPy, generating synchronized event timestamps. Tasks include a baseline fixation, an arithmetic task inducing working-memory load, and a Stroop interference task targeting cognitive stress.

Data will be preprocessed by removing blinks, smoothing, and baseline-correcting pupil signals, while electrodermal activity will be separated into tonic skin conductance level (SCL) and phasic electrodermal response amplitudes (SCR). Mean and peak pupil dilation will indicate attentional effort, whereas SCL and SCR will reflect autonomic arousal. Normality will be assessed using the Shapiro–Wilk test. Repeated-measures ANOVA with Bonferroni-corrected post hoc tests will compare physiological responses across conditions, and Pearson correlation will examine associations between pupil dilation and electrodermal activity. The study aims to determine whether synchronized multimodal physiological signals provide deeper insight into cognitive load than single-sensor measurements, supporting potential applications in educational environments.

The Piezo1-ADAM axis modulates the inflammatory state of dermal keratinocytes via EGFR signaling

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Dermal wound healing is a tightly regulated process that is essential for restoring skin barrier function. This process is strongly influenced by mechanical cues, which are sensed by mechanosensitive ion channels such as Piezo1. The activation of Piezo1 has been shown to modulate inflammatory and regenerative responses during wound repair. A key component in this chain of events is the controlled release of cytokines and growth factors, including chemokines such as IL-8 that recruit immune cells, and epidermal growth factor receptor (EGFR) ligands such as amphiregulin (AREG) to promote keratinocyte proliferation and migration. We have recently shown that proteases of the a disintegrin and metalloproteinase family can be induced subsequent to chemical or mechanical activation of Piezo1 leading to proteolytic cleavage of AREG and its release. In this study, we could show that chemical and mechanical activation of Piezo1 also leads to ADAM-dependent AREG release in dermal keratinocytes. Interestingly, Piezo1 activation also led to increased IL-8 secretion. Although IL-8 is released via the secretory pathway, its release was nonetheless dependent on ADAM activity. This dependency can be explained by the pronounced ADAM mediated release of growth factors and the subsequent activation of EGFR signaling which leads to IL8 gene induction. Together, our findings demonstrate that the Piezo1–ADAM axis controls autocrine and paracrine signaling in keratinocytes in response to mechanical stimulation via growth factor shedding and thereby modulates dermal wound healing.

Pharmacological Activation of PIEZO1 and Inhibition by Benzbromarone in Human Liver Sinusoidal Endothelial Cells

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Background
Liver regeneration following resection is critically dependent on haemodynamic changes within the hepatic microcirculation. Liver sinusoidal endothelial cells (LSECs) are among the first cells exposed to altered portal flow and shear stress. PIEZO1, a mechanosensitive Ca^{2+}-permeable ion channel, has been proposed as a key regulator of flow-mediated signalling and endothelial function. Here, we investigated the functional characteristics and pharmacological modulation of PIEZO1 in human LSECs.

Methods
Intracellular Ca^{2+} responses were measured in human LSECs using Fura-2 and ratiometric fluorescence imaging in a FlexStation III. PIEZO1 activation was induced using Yoda2 and a novel small-molecule agonist (CHR), and EC_{50} values were calculated. Specificity was assessed using siRNA-mediated PIEZO1 knockdown. Benzbromarone was investigated as a potential PIEZO1 inhibitor with relevance to liver toxicity. Benchmark modulators ionomycin and ATP were utilized.

Results
Yoda2 (EC_{50} 469 ± 125 nM) and CHR (EC_{50} 331 ± 248 nM) induced dose-dependent Ca^{2+} influx consistent with PIEZO1 activation. PIEZO1 knockdown attenuated Yoda2 and CHR evoked responses. Benzbromarone inhibited Yoda2-mediated Ca^{2+} influx in a concentration-dependent manner (IC_{50} 362 ± 164 nM) but lacked specificity for PIEZO1 because it also inhibited Ca^{2+} responses triggered by other modulators.

Conclusion

Human LSECs exhibit robust PIEZO1-dependent Ca^{2+} signalling, supporting a mechanistic role for PIEZO1 in hepatic haemodynamic sensing. Benzbromarone strongly attenuates PIEZO1-mediated responses and other Ca^{2+} pathways, effects that may contribute to its liver toxicity. These findings support the hypothesis that PIEZO1 is an important determinant of hepatic blood flow and potential new target for therapeutic intervention to improve blood flow and regeneration in liver disease and surgery.

Decoding vascular aging: Substrate stiffness and shear stress orchestrate endothelial inflammation and remodelling via mechanosensitive pathways

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Vascular aging is a major factor which underlies many cardiovascular diseases including atherosclerosis and myocardial infarctions. Characteristics include stiffening of the vascular wall which disrupts endothelial homeostasis and promotes chronic inflammation, yet the underlying mechanisms remain poorly understood due to technological limitations. Here, we have developed an in vitro microfluidic model to investigate how biomechanical forces, specifically substrate stiffness and shear stress, interact to regulate endothelial cell functions. Using RNA sequencing and functional assays, we found that endothelial cells exposed to both physiologically high levels of shear stress were more sensitive to increases in substrate stiffness in which the cells exhibited a greater number of differentially expressed genes and enhanced activation of inflammatory signalling pathways.

We identified enriched pathways involved in inflammatory signalling and extracellular matrix remodelling due to substrate stiffening. Endothelial cells exposed to high shear stress and increased stiffness showed up-regulation of genes such as ICAM1 and VCAM1 which mediate leukocyte adhesion, and LAMB3 and MMP28 which mediate extracellular matrix remodelling. Importantly, these findings were benchmarked using human aortic tissue which confirmed concordant molecular and histological changes between stiff (aged) and soft (healthy) aortas.

We have also explored the role of mechanosensitive ion channel Piezo1 under the combined effect of shear stress and substrate stiffness in endothelial morphology, senescence, proliferation, and inflammation. Piezo1 facilitated endothelial adaptation to flow and regulation of inflammation under both atheroprotective and atherogenic shear stress levels. In endothelial senescence, Piezo1 contribution was limited to the soft substrate and atheroprotective shear stress.

Ultimately, this validated microfluidic platform provides proof of concept that biomechanical forces characteristic of vascular aging drive endothelial inflammation and vascular remodelling, offering new mechanistic insight and a powerful experimental framework to advance therapeutic strategies targeting vascular stiffness and age-related vascular disease in which the process may involve Piezo1 mechanotransduction.

PIEZO1 Variation in Myofibroblasts Obtained at Open Heart Surgery

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Type 2 diabetes (T2D) commonly contributes to a clustering of inter-related and co-incident cardiovascular disease (CVD) risk factors, in which cardiac fibrosis is a common hallmark. Fibrosis is characterised by excessive extracellular matrix deposition by cardiac fibroblasts (CF), resulting in stiff and less compliant matrices. Mechanical forces activate CF, and PIEZO1, a mechanosensitive, calcium (Ca2+) permeable ion channel has emerged as central to force sensing, maintaining myocardial mechanical properties and efficient pumping by regulating CF. This project aims to characterise PIEZO1 channels in CFs from CVD patients, with or without associated T2D. CF were isolated and cultured from right atrial appendage (RAA) biopsies (N=35) from patients undergoing open heart surgery (IRAS ID 200339). Immunohistochemistry identified a homogenous myofibroblast (myoCF) population. Gene expression analysis outlined collagen and inflammatory markers linked with PIEZO1 signalling in myoCF which differ with CVD severity and type (n=18). Robust Ca2+ entry is triggered by application of Yoda1 or Yoda2, two agonists of PIEZO1 channels (N=33). Preliminary analysis suggests heightened PIEZO1 function in ischemic heart disease and comorbid burden with associated T2D or additional CVD. There is high inter-patient variability potentially due to confounding factors such as sex, age and obesity. In summary, PIEZO1 channels are expressed and functionally active in human myoCF obtained at open heart surgery and there is variability in channel activity, potentially due to type or severity of heart disease or T2D.

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A Human Liver Small-for-size graft (SFSG) Model to Study Mechanosensing in Liver Regeneration and Failure Pathophysiology

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Background
Liver is the only solid organ capable of regeneration after surgical resection or transplantation. This process is hypothesised to be initiated by increased blood flow through the remnant or smaller graft. Mechanosensitive pathways, particularly PIEZO1 ion channels, are proposed to detect hemodynamic changes and initiate signalling. Conversely, excessive portal inflow in a relatively smaller segment can cause mechanical damage leading to liver failure or Small-for-size syndrome. Most current knowledge is based on animal models, limiting translation to human liver physiology.

Methods
Twelve livers from adult donors with negative virology and without extensive steatosis/ fibrosis were perfused using normothermic machine perfusion (NMP). Whole liver NMP at physiological rates was performed for 4 hours, followed by 6 hours of isolated left lateral segment (LLS) NMP at >250mL/min/100g liver tissue to simulate post-surgery hyperperfusion. PIEZO1 agonists (Yoda1/Yoda2), PIEZO1 negative modulator (Dooku1), or nitric oxide synthase inhibitor L NMMA were administered 75 minutes before the end of LLS perfusion. Perfusion parameters, bile production and biochemical measurements were serially recorded. Tissue biopsies were obtained for histology and RNA sequencing. Viability was determined using established hepatocellular criteria for whole liver perfusion and applied to the LLS to evaluate hyperperfusion induced dysfunction.

Results
Median donor age was 52.5 years and median BMI 31.7 kg/m^2. Mean LLS weight was 336.3±107.4 g. Five of 12 livers appeared moderately steatotic. Based on viability criteria, 9 of 12 LLS grafts demonstrated impaired function. Histology showed early changes of portal hypertension (sinusoidal dilatation, congestion, extravasation of RBCs, hepatocyte ballooning) in LLS.

Conclusion

Hyperperfusion of LLS during NMP induced functional impairment and morphological changes consistent with early SFSS, supporting this model as a platform to investigate vascular modulation and mechanosensitive pathways in human liver regeneration. Ongoing transcriptomic and protein analyses will assess differences across whole livers and LLSs for treatment groups.

Propofol Modulates Calcium Signalling in Human Liver Sinusoidal Endothelial Cells: Implications for Mechanotransduction in Liver Surgery

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Background
Propofol-based total intravenous anaesthesia is increasingly used in liver surgery/transplantation due to its potential to reduce hepatic ischemia–reperfusion injury and oxidative stress. However, the underlying cellular mechanisms remain unclear. Recent studies suggest propofol inhibits mechanosensitive PIEZO1 channel, though its effects on native PIEZO1 are unknown. As PIEZO1 plays key roles in liver sinusoidal endothelial cell (LSEC) function and liver regeneration, we investigated whether propofol modulates PIEZO1-mediated Ca^{2+} signaling in human LSECs.

Methods
Primary human LSECs were studied using real-time intracellular Ca^{2+} measurements (FlexStation III) with exposure to Propofol (2,6-Diisopropylphenol) and site of action investigated. Single-injection activation assays were performed for 50 μM/150 μM Propofol. Interactions with the PIEZO1 agonist Yoda2 were assessed using direct application or pre-incubation and sequential protocols. For inhibitory studies, cells were preincubated with Propofol for 30 minutes before stimulation with Yoda2 (3 μM) or exposed to sequential injections of Yoda2 (3 μM) followed by Propofol, keeping final concentration of Yoda2 stable.

Results
Propofol 50 μM produced a mild Ca^{2+} elevation was observed, whereas 150 μM produced a larger yet still slowly developing elevation. This did not depend on extracellular Ca^{2+} and ER Ca^{2+} depletion with Thapsigargin abolished this response. If Yoda2 were applied first, Propofol had a stronger faster effect, suggesting synergistic modulation of Ca^{2+} entry. In contrast, pre-incubation with Propofol attenuated subsequent Yoda2-induced Ca^{2+} responses, indicating potential inhibitory as well as agonist effects on mechanosensitive signalling.

Conclusion
Propofol has strong modulatory effects on Ca^{2+} signaling in human LSECs and PIEZO1 deletion confirmed Yoda2 specificity for PIEZO1 channels. The data indicate intracellular Ca^{2+} release and dual modulation of PIEZO1 channels (inhibition and enhancement), potentially mediated by ER mediated mechanisms, that warrants further investigation. Together these findings highlight important modulatory effects of Propofol on hepatic vasculature that involve PIEZO1 and could be relevant in liver surgery.

The mechanosensitive channel Piezo1 is a mediator of mechanical forces in bone marrow endothelial cells

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

Circulating blood cells are generated in the bone marrow from hematopoietic stem cells that differentiate into all blood cell lineages. Once mature, these cells enter the bloodstream exclusively through specialised sinusoid microvessels. A complex set of mechanical forces is therefore applied to bone marrow sinusoid endothelial cells (BMEC) which express receptors that enable them to sense and adjust to mechanical forces. However, the role of such mechanoreceptors in regulating transmural passage remains unclear. This project aims to characterise the role of stretch-activated channels (SAC) in BMEC.
BMEC from C57BL/6J mice were isolated by enzymatic digestion and sorted based on the phenotype $CD45^{-}$, $F4/80^{-}$, $Ter119^{-}$, $CD31^{+}$, $CD140ab^{-}$, CD105bright. SAC activity was assessed using patch-clamp recordings in a cell-attached configuration. Increasing negative pressure pulses (0 to −80 mmHg) were applied via the pipette to elevate membrane tension. These experiments revealed clear stretch-induced currents, and single-channel analysis suggested the presence of non-selective cation SAC.
To identify the channels involved, RT-qPCR analyses were performed, identifying Piezo1 as the most highly expressed candidate. Consistently, BMEC from Piezo1 gain-of-function mice (R2482H) exhibited larger stretch-induced currents than wild-type controls, confirming its functional contribution. In vitro, confluent BMEC cultures from Piezo1KI/+ mice showed reduced VE-cadherin staining intensity, indicating altered endothelial junction organisation and potential changes in permeability.
Furthermore, bone marrow sections stained for FABP4 and laminin revealed increased vessel diameters and laminin intensity in Piezo1Ki/Ki mice, with thick-section analysis supporting structural vascular alterations. Overall, these findings indicate that BMEC express functional SAC, with Piezo1 playing a central role in regulating endothelial organisation, vascular architecture, and potentially transmigration processes.

PIP2-Dependent Stabilization of PIEZO1 handshake interactions Revealed by molecular dynamics simulations

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

PIEZO1 is a mechanosensitive ion channel essential for processes such as red blood cell volume regulation, vascular development, and the conversion of mechanical stimuli into cellular responses. PIEZO1 is a trimeric complex with a three-bladed, propeller-like architecture embedded in the lipid bilayer, featuring a hydrophobic ion-conducting pore at its center. Its activity is strongly influenced by the surrounding lipid environment, which interacts with multiple regions within the protein and modulates different stages of the gating process. In this work, we study the role of anionic lipids, particularly phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidyl serine (POPS) lipids, as regulators of force sensitivity and intermolecular interactions within the channel. We performed coarse-grained molecular dynamics simulations of the full-length human PIEZO1 embedded in an endothelial-like membrane, totalling 50 μs of simulation time. Our results show that anionic lipids, especially PIP2 and to a lesser extent POPS, mediate an interblade interaction between helices belonging to two adjacent subunits, termed the handshake interactions. These intermolecular contacts shape key global properties of the protein, including protein curvature and compactness. As such they may be key to PIEZO1 force sensitivity and activation.

Investigating effects of actomyosin mechanics on rapid permeability changes in epithelium

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

Epithelial tissues form important barriers in our bodies. Tight junctions (TJs), cell-cell adhesions located at the apical region of epithelial cells, play a central role in the formation of the epithelial barrier. TJs have a role in regulating paracellular transport of ions, molecules, and small proteins. They are large protein complexes containing transmembrane proteins, e.g. claudins, which link the cells together, and cytoplasmic scaffolding proteins, e.g. ZO-1 and ZO-2, through which TJs connect to actomyosin cytoskeleton. TJs form a dynamic barrier, allowing the cells to regulate paracellular transport, yet the role of scaffolding proteins in this behavior is not fully understood. A recently developed microscopic epithelial barrier measurement method (zinc-based ultrasensitive microscopic barrier assay, ZnUMBA) provides a high-resolution, junction-level view of barrier dynamics based on a zinc indicator intensity.

To study the role of ZO-1 and ZO-2 in the barrier dynamics, we applied ZnUMBA to MDCK II cells. The method allowed us to record rapid increases in junction intensity, indicating leaks of zinc through the dynamic barrier. We analyzed the duration and frequency of the leak events in wild type (WT), ZO-1 knockout (KO), ZO-2 KO, and ZO-1 overexpressing MDCK cell lines. We found that ZO-1 KO decreased the leak frequency compared to WT, whereas ZO-1 overexpression and ZO-2 KO increased leak duration compared to WT. In addition, we investigated the role of actomyosin cytoskeleton in the observed leaks. Using drugs to alter myosin II activity did not affect the leak duration or frequency in WT nor ZO-1 KO cell lines. However, actin depolymerization decreased the leak number detected in WT. Our results show that the scaffolding proteins and changes in actomyosin have an effect on the TJ dynamics, but further studies are required.

Understanding PIEZO1 channel conservation across species

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

The PIEZO protein family are transmembrane mechanosensitive cation ion channels, situated in the plasma membrane. These proteins have been shown to have biological relevance across organisms including blood cell volume regulation, cardiovascular development and mediating somatosensory neurons. PIEZO channel have previously been identified in early eukaryotes across multiple kingdoms, including Animalia and Protozoa, indicating it likely evolved in the common eukaryotic ancestor. The homologous of PIEZO subunits vary widely in size, with differences of approximately 1500 residues. Despite this diversity, there has been limited research examining the conservation of PIEZO as a whole protein. Evolutionary analysis can be a powerful tool for understanding its physiological history and fitness advantages. In this study we use phylogenetic comparison of all available full-length Animalia sequences of PIEZO, allowing us to identify structurally conserved regions relevant to function. Our analysis suggests that the evolutionary trajectory of PIEZO indicated early division of invertebrates and later detachment of fish from the remaining vertebrate classes. The protein's sequence conservation was seen to increase moving toward the C-terminal part of the protein across the Animalia kingdom. This was exemplified through the high conservation of the proteins C-terminal regions (anchor domain, transmembrane pore and C-terminal domain) likely reflecting the preservation of its ion conductance function. In contrast, N terminal blade and C terminal extracellular domain show lower conservation. This novel understanding of diverging aspects of PIEZO1 could enhance our understanding of physiological functions of PIEZO1 that have previously been undetermined.

PIEZO1-Mediated Mechanosensing Drives Selective Ultrasound-Induced Cytotoxicity in Pancreatic Cancer Cells

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, characterized by a mechanically altered tumor microenvironment (TME) and aberrant ion channel expression. Among the mechanosensitive players in PDAC, PIEZO1 has emerged as a key mediator of mechanotransduction, yet its role in ultrasound-induced cytotoxicity remains unexplored.
In this work, we investigated the effects of Low Intensity Continuous Ultrasound across a frequency range of 1–5 MHz on PANC-1 pancreatic cancer spheroids. Ultrasound stimulation was delivered using a custom-built setup featuring two interchangeable transducers, designed to ensure the most homogeneous acoustic pressure delivery across the tested frequency range. Cytotoxicity was quantified by LDH release assay, revealing a strong frequency-dependent response with a peak cytotoxicity of 45.02 ± 0.5% at 3.5 MHz ($p < 0.01$). Critically, no cytotoxic response was observed in non-tumoral control models, including Human Pancreatic Ductal Epithelial (HDPE) cells (0.00% ± 0.0) and RLT-PSC pancreatic stellate cells (~0% at all frequencies tested), demonstrating a selective effect on cancer cells.
To investigate the molecular basis of this selectivity, we focused on mechanosensitive ion channels as primary candidates. The applied acoustic pressures (1–3 kPa) fall well below the cavitation threshold, placing the stimulation regime within a non-cavitational mechanical index. This makes direct membrane mechanosensing — rather than cavitation-driven damage — the most plausible cytotoxic mechanism, pointing to PIEZO1 as a key transducer. PIEZO1 is overexpressed in PDAC, and its contribution to the observed response was assessed through pharmacological modulation using the agonist Yoda1 and the inhibitor GsMTx4.
Collectively, these results suggest that PIEZO1-mediated mechanosensing plays a central role in the selective cytotoxic response of PDAC cells to low-intensity ultrasound, opening new perspectives for ultrasound-based therapeutic strategies in pancreatic cancer.

Bridging Disciplines: A Research Oriented Neuroscience Curriculum for Secondary Education

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

While neuroscience courses are traditionally reserved for higher education, introducing these concepts in secondary school cultivates analytical skills, scientific literacy, and interdisciplinary thinking. This presentation outlines the "Introduction to Neuroscience", which is a multidisciplinary elective course developed over the past five years at Hisar School for secondary students (Grades 11–12 only). By integrating principles from physics, biology, mathematics, computer science, and psychology, the curriculum illustrates how these convergent fields collaboratively solve real world problems, ranging from cognitive health to technological innovation. Core modules include fundamental neuroanatomy, neurotransmitter dynamics, neuroplasticity, neuroimaging, and neuromarketing. The course follows an inquiry based, research oriented approach with a strong focus on developing critical thinking. Students transition from acquiring theoretical foundations to investigating empirical studies through case studies. Alongside lecture based lessons, students also take part in activities such as the Stroop task and split brain case studies, which help them see cognitive processes in action. Students also receive formal training in research and learn how to use academic databases such as Google Scholar, Semantic Scholar, and Consensus. It helps them break down complex texts and stay actively engaged with the material, making advanced research more accessible. Throughout the course, research assignments are often presented as academic or poster presentations, allowing students to share their work in a structured scientific format. This presentation will outline the course design, discuss how inquiry based learning is implemented at the secondary level, and show how early exposure to research practices supports students' confidence, analytical skills, and academic readiness.

Role of PEZO-1 in Maintenance of the Germline Stem Cell Population in Caenorhabditis elegans

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Flash Talk Session, July 15, 2026, 11:30 - 13:00

Stem cells are essential for the development and maintenance of tissues. Germline stem cells (GSCs), in particular, sustain the reproductive capacity as well as modulate systemic aging of an organism. The population of germline stem/progenitor cells in Caenorhabditis elegans is maintained by their single-cell niche, known as the Distal Tip Cell (DTC), and their numbers gradually decline as the worms age. PEZO-1, the homolog of the mammalian mechanosensitive ion channel Piezo in C. elegans, is extensively expressed throughout the gonad and in all stages of germ cells within the organism. Additionally, PEZO-1 is necessary for proper ovulation and fertilization in the proximal gonad of worms. However, its potential role in the distal gonad, where the stem cells reside, remains unclear.
I am investigating the role of PEZO-1 in maintaining the germline stem/progenitor cells in the distal part of the gonad in C. elegans. While perturbing the levels of PEZO-1 did not demonstrate any measurable effect on the morphological attributes of the niche, I observed that the loss of PEZO-1 directly impacted the germline stem cell population as worms aged. We are currently exploring the possible pathway through which PEZO-1 regulates the stem cell dynamics. This study will enhance our understanding of the mechanical regulation of stem cells broadly, with a specific focus on GSCs, and will provide valuable insights into the role of mechanics in aging phenotypes.

The Physiological Society – PIEZOs Poster Presentations

Mechanosensitive Ion Channel Piezo1 Regulates Osteoclast Differentiation by Activating the Metalloproteinases ADAM10 and ADAM17

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Poster Session A, July 15, 2026, 14:00 - 15:30

Bone remodeling is a continuous process throughout life and serves to adjust bone architecture to meet changing mechanical needs. The mechanosensitive ion channel Piezo1 is known to sense mechanical forces in osteoblasts leading to increased bone formation by these cells. By contrast, the role of Piezo1 in osteoclasts, is less understood.
We have recently shown that the constitutive activity of the metalloproteinases ADAM10 and ADAM17 on osteoclast precursor cells limits osteoclast development from precursor cells that differentiate in response to macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL). This is associated with the proteolytic shedding of cell surface expressed receptors for RANKL and M-CSF (RANK and CSF1R, respectively), thereby reducing cellular responsiveness of the cells. In the present study, we investigated whether this regulatory process can be modulated by mechanical forces and signaling through Piezo1. Stimulation of Piezo1 by Yoda1 led to a considerable reduction of osteoclast development in response to M-CSF and RANKL. This was mediated in part by increased activity of ADAM10 and ADAM17 as demonstrated by selective ADAM10 inhibition and ADAM17 knockout. Furthermore, Piezo1 activation reduced RANK and CSF1R surface expression on osteoclast precursor cells again depending on both proteases. Finally, also mechanical compression of the precursor cells diminished RANK and CSF1R surface expression partly involving ADAM10 and ADAM17 activity. These data indicate that ADAM10 and ADAM17 activity is upregulated via the mechanosensitive ion channel Piezo1 leading to enhanced receptor shedding thereby preventing induction of osteoclast differentiation. Also on osteoblasts, we found that stimulation of Piezo1 activates ADAM10 mediated release of RANKL. This implies that less transmembrane RANKL is available on osteoblasts for cell-to-cell stimulation of osteoclasts. Thus, Piezo1 may be locally relevant to limit bone resorption through activation of ADAM10 and ADAM17 which would complement its already well described pro-osteogenic role in osteoblasts.

Actomyosin-dependent PIEZO1-mediated mechanotransduction amplifies aldosterone production

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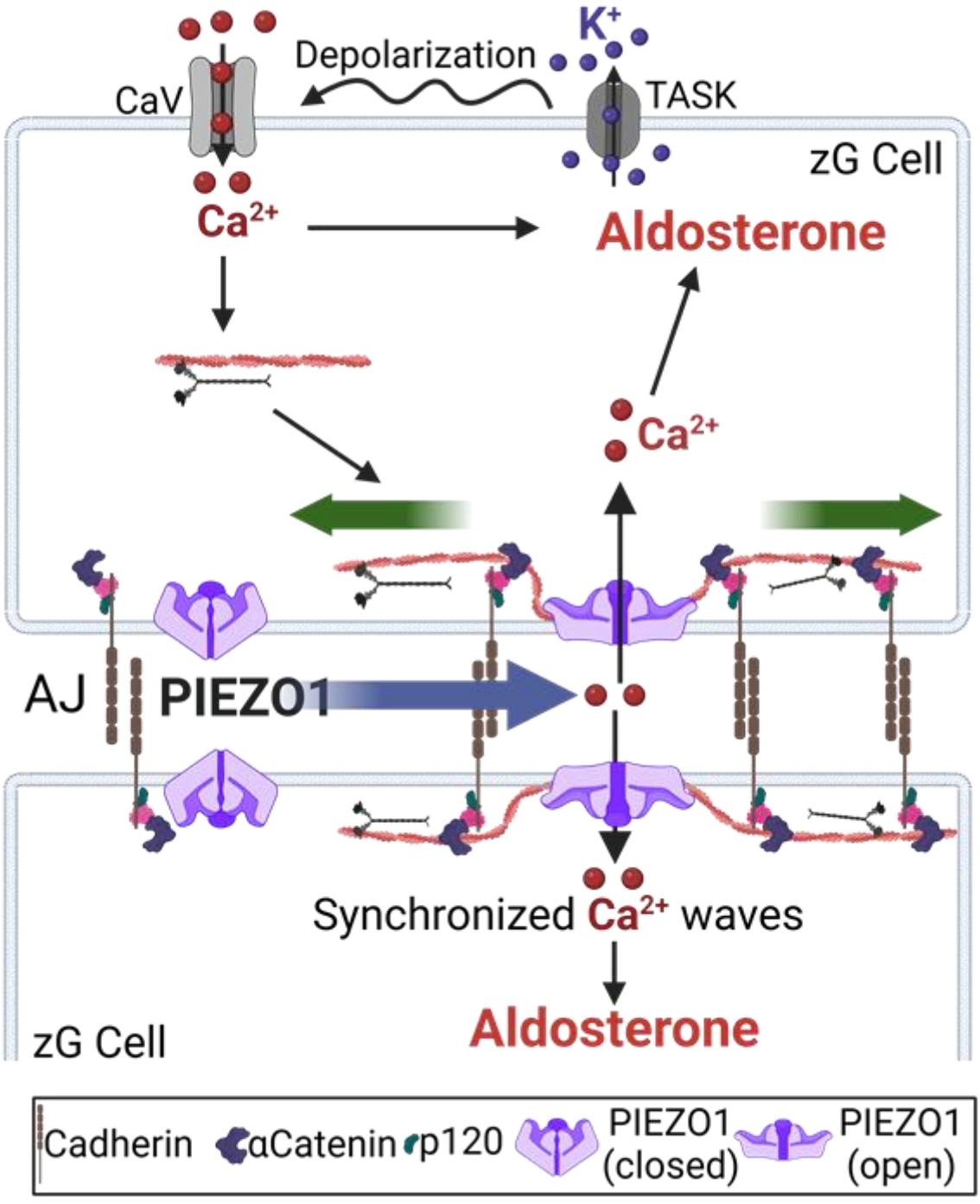
Poster Session A, July 15, 2026, 14:00 - 15:30

Adherens junctions (AJs) couple intercellular cadherins to the actomyosin network via αCatenin and are central to sensing mechanical force at cell–cell contacts. The adrenal zona glomerulosa (zG) produces aldosterone in response to increases in intracellular Ca2+ in a highly coordinated manner. In adrenal slices, acute disruption of cadherin binding decreased synchronized intercellular Ca2+ bursts and decreased aldosterone production, suggesting intact AJs support coordinated zG activity. However, how tissue mechanics and intercellular coupling shape zG Ca2+ dynamics and steroidogenesis remains unclear. We hypothesized that AJs transduce mechanical signals through actomyosin to activate mechanosensitive ion channels, thereby amplifying Ca2+ entry and aldosterone production.

To define the downstream mechanotransduction pathway, we combined confocal imaging, atomic force microscopy (AFM), and patch clamping in control, αCatenin-knockout and PIEZO1-knockout human adrenocortical cells (NCI-H295R), and in primary mouse zG cells, and zG-specific mouse models. Upon K+ stimulation (a major physiological secretagogue of aldosterone), cells showed increased actin polymerization (via confocal imaging) and elevated membrane stiffness (via AFM) at cell–cell contact regions, which were blunted when the AJ–actomyosin linkage was disrupted in αCatenin-knockout cells. Pharmacological inhibition of actomyosin (via cytochalasin D, ML7, or blebbistatin) or mechanosensitive channels (via GsMTx4) attenuated K+-evoked Ca2+ influx and aldosterone production in NCI-H295R cells. Conversely, activation of PIEZO1 by Yoda1 induced membrane depolarization, Ca2+ influx, CYP11B2 expression and aldosterone production. Piezo1 deletion in mouse zG cells and NCI-H295R cells reduced K+-stimulated aldosterone production and rendered aldosterone production insensitive to the effects of actomyosin inhibition, consistent with PIEZO1 acting downstream of K+-induced actomyosin contractility.

We propose a mechanotransduction model by which K+-evoked actomyosin-dependent changes in cell–cell junction mechanics activate PIEZO1 to drive Ca2+ signaling and aldosterone production. Our findings establish the zG as a mechanosensitive endocrine tissue and identify an AJ–actomyosin-PIEZO1 axis as a potent regulator of aldosterone production.


CaV
Depolarization
K+
TASK
zG Cell
Ca2+
Aldosterone
Ca2+
AJ
PIEZO1
Synchronized Ca2+ waves
Aldosterone
zG Cell
Cadherin
αCatenin
p120
PIEZO1 (closed)
PIEZO1 (open)

Physical mechanism of Piezo1 stiffness sensing

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Poster Session A, July 15, 2026, 14:00 - 15:30

Cellular membranes play an important role in transducing external and internal mechanical stimuli, such as shear forces and changes in tissue stiffness, into intracellular, biochemical responses. One of the key mechanical properties of the cell surface is effective membrane tension, which is defined as the resistance of the membrane to deformation. Membrane tension contributes to the transduction of mechanical signals via mechanosensitive ion channels embedded in the membrane. The in-plane tension of the lipid bilayer and the interaction of the membrane with the underlying cytoskeleton contribute to the overall tension of the cell surface. Although the membrane to cortex attachment is thought to be the largest contributor to the effective membrane tension, how these parameters interact to transduce mechanical signals is still poorly understood. In particular, how and if a change in tissue stiffness affects the surface mechanics of the cell, which in turn would contribute to the activation of the mechanosensitive ion channel Piezo1, is not yet known. To investigate the dependence of the effective membrane tension on substrate stiffness, I cultured HEK 293T cells and rat embryonic neurons on compliant substrates, and measured the tension with optical tweezers and AFM. To determine whether Piezo1 expression modulates the mechanical response of the cell surface these measurements were also performed in Piezo1 knockout and Piezo1 overexpressed HEK cells, and Piezo1 knockdown neurons. Furthermore, I used pharmacological and genetic approaches to modulate the actin cortex, membrane composition, and membrane to cortex adhesion to characterize their contributions to effective membrane tension. Ultimately, I aim to understand how changes in the effective membrane tension, caused by the changes in tissue stiffness, lead to the activation of Piezo1. This work will contribute to the understanding of how mechanosensitive ion channels are gated, which could have significant implications for drug design in the future.

The Effect of Auditory Conditions on Cognitive Performance and Physiological Responses

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Poster Session A, July 15, 2026, 14:00 - 15:30

Auditory conditions influence attention and decision processes, making it essential to identify which music types enhance or hinder performance. Optimizing acoustic environments is crucial, as the Yerkes-Dodson law and Arousal Theory suggest that moderate stimulation supports learning acquisition, cognitive performance and wellbeing, whereas extremes may impair task execution and decision-making. These relationships between executive functioning and physiological responses during tasks assessing attention, reaction time, and working memory remain unclear. This study investigates how auditory contexts influence information processing efficiency and decision thresholds under workload by integrating behavioral performance metrics with autonomic measures across structured auditory environments. A controlled within-subject study will compare three music genres: silence (control), classical music (60 BPM) and metal (190 BPM) among 40 high school students (aged 14-16). We developed a web application for participants to complete computer-based reflex, visual search, and mental arithmetic tasks under standardized audio conditions via headphones at 75 dB, with performance evaluated through reaction time and accuracy to assess attention and working memory under load. To record heart rate variability and blood oxygen saturation we built a wrist-based prototype incorporating a MAX30102 photoplethysmography module, with HRV parameters validated against electrocardiography in previous studies. Behavioral and physiological measures will be integrated into the Balanced Integration Score (BIS), reflecting the trade off between speed and accuracy. Differences across auditory conditions will be assessed using linear mixed-effects models to account for within-subject variability. Variations in BIS and physiological measures will be analyzed with the Drift Diffusion Model to estimate drift rate and boundary separation. Low tempo (60 BPM) music is hypothesized to improve performance efficiency without increasing autonomic activation, while high tempo (190 BPM) conditions may decrease reaction time while reducing decision thresholds. Findings are expected to clarify how music tempo modulates cognitive efficiency and psychological activity under cognitive load, especially in educational settings.

The role of Piezo1 in blood-retinal barrier dysfunction

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Poster Session A, July 15, 2026, 14:00 - 15:30

More than 1 billion people worldwide live with sight loss, with one new person starting to lose their sight every six minutes. Most retinal diseases share common clinical features, such as hyperpermeability and pathological neovascularisation, which stem from inner blood-retinal barrier (iBRB) dysfunction. Vascular endothelial growth factor (VEGF) is the primary driver of iBRB dysfunction. However, anti-VEGFs work in only 50% of patients, highlighting the need for alternative therapeutic targets. From a vascular perspective, disturbances in retinal blood flow characterise the early clinical stages of retinal disorders and cause increased shear stress and EC damage. Thus, to uncover the mechanisms of vascular mechanotransduction and increase our understanding of both the maintenance of physiology and the development of disease, we investigated Piezo1, a mechanosensitive calcium (Ca2+) channel whose role in the iBRB functions remains largely unexplored.
To test Piezo activity, primary human retinal endothelial cells (HRECs) were incubated with 2 µM Cal520 AM in Krebs solution for 1h at 37°C. Treatment of HRECs with Piezo1 agonist Yoda1 induced an increase in the intracellular Ca2+ concentration in the form of a single transient, whose amplitude was correlated to Yoda1 concentration. This signal was prevented in most cells when treated without extracellular Ca2+. However, around 20% of cells showed a short single or double transient, indicating heterogeneity in the EC monolayer. Furthermore, 5% of cells responded to Yoda1 after passive depletion of the endoplasmic reticulum in the absence of extracellular Ca2+. Consistent with our data, Piezo1 expression was detected in HRECs via immunocytochemistry. Furthermore, Piezo1 activation stimulated HREC migration in a wound healing assay. Finally, HREC treatment with VEGF induced Ca2+ oscillations, whose amplitude and frequency were reduced by preincubation of HRECs with Piezo1 inhibitor Dooku1. In conclusion, our results indicate that Piezo1 plays a relevant role in HREC physiology.

Mechanosensor PIEZO1-mediated endothelial nitric oxide synthase phosphorylation. Is WNK the missing link?

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Poster Session A, July 15, 2026, 14:00 - 15:30

Background: PIEZO1 is a mechanosensor expressed by human umbilical endothelial cells (HUVECs). Its activation results in rapid endothelial nitric oxide synthase (eNOS) phosphorylation at serine site 1177 (Ser1177) independent of protein kinase B (AKT). The serine-threonine kinase linked with this rapid PIEZO1-mediated eNOS phosphorylation is unknown. This study aimed to investigate with no lysine kinases (WNK1-4) as responsible candidates in this pathway.

Methods: HUVECs were cultured and treated with and without WNK1-4 and WNK1 inhibitors for 30 minutes prior to stimulation with PIEZO1 agonist Yoda1 (2μM) for 1 minute or dimethyl sulphoxide (DMSO) as control. Western blot to measure eNOS phosphorylation was conducted using mouse anti-eNOS-pS1177 and total eNOS for each treatment condition. To investigate the impact of WNK 1-4 and WNK1 inhibitors on PIEZO1 activity, a calcium flux assay was undertaken. Sample size N=3.

Results: In Western blot analysis, there was a reduction in eNOS phosphorylation following treatment with WNK1-4 and WNK1 inhibitors ($p<0.05$). A significant but smaller reduction in Yoda-1 mediated PIEZO1 calcium flux following treatment with WNK1-4 and WNK1 inhibitors ($p<0.05$) was also seen.

Conclusion: Findings of this work provide novel insights into the potential responsible serine-threonine kinase involved in PIEZO1-mediated eNOS phosphorylation. However, as inhibitors are also shown to reduce PIEZO1-mediated calcium influx, further work is required to investigate the eNOS phosphorylation effects.

Piezo1 Activation Reduces Coronary Flow in ex vivo Perfused Mouse Hearts

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Poster Session A, July 15, 2026, 14:00 - 15:30

Introduction: Adequate tissue perfusion is essential for cardiac function. Piezo1, highly expressed in vascular endothelial cells, acts as a mechanosensor modulating vascular tone via calcium-dependent signalling [Lhomme et al., 2019]. The role of Piezo1 in coronary function remains incompletely understood. We hypothesise that Piezo1 activation by Yoda1 in ex vivo perfused murine hearts increases coronary flow.

Methods: Adult C57BL/6 mouse hearts were Langendorff-perfused using HEPES-buffered saline (perfusion pressure 60 mmHg). Hearts were loaded with the voltage sensitive dye Di-4-ANBDQPQ (10.5 µM) and mechanically uncoupled with blebbistatin (10 µM). Yoda1-containing saline (10 µM, from DMSO-stock) was passed through a 0.22 µm sterile filter to remove any residual Yoda1-crystals as these can block microvessels. Optical maps were acquired every 2 min, while surface electrocardiogram and coronary flow were recorded continuously.

Results: Yoda1 perfusion reduced coronary flow within 10 min from 1.50±0.13 mL/min to 0.47±0.08 mL/min (mean±SD, n=9, $p<0.001$), which partially recovered during a 10min-washout to 0.81±0.23 mL/min ($p=0.03$ vs. Yoda1; $p=0.004$ vs. baseline). During Yoda1-perfusion, 7 of the hearts showed atrio-ventricular (AV) block (4× type-II, 3× type-III). In solvent controls (0.1% DMSO, n=9), coronary flow did not change significantly, and AV-block was observed in 1 heart (type-III). Time-matched saline controls (20 min perfusion, n=4) exhibited no significant flow reduction or AV block. To assess the effect of reduced coronary perfusion, flow was transiently reduced (45% of baseline, n=4), resulting in AV-block in 2 hearts (2× type-II).

Conclusion: These findings suggest that in the coronary vasculature, Piezo1-activation can reduce flow. This effect is not caused by the presence of DMSO. The reduction in coronary flow may underlie the observed AV-block in mouse hearts ex vivo. Further studies will clarify the mechanisms underlying coronary flow reduction by Piezo1-activation.

Lipid Interactions and Membrane Curvature of Arabidopsis thaliana PIEZO1

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Poster Session A, July 15, 2026, 14:00 - 15:30

PIEZO1 is a trimeric mechanosensitive ion channel characterized by a curved transmembrane architecture composed of a cap domain, a central pore formed by C-terminal transmembrane segments, and peripheral blade regions. While high-resolution structures are available for mouse and human PIEZO1, no experimental structure exists for plant homologues, limiting our understanding of plant mechanotransduction. Arabidopsis thaliana PIEZO1 (AtPIEZO1) is similar in size to mouse PIEZO1 with moderate residue conservation between the two homologues. In this study, we used homology modelling to generated a 3D model of AtPIEZO. Using molecular dynamics simulation at the coarse-grained resolution we inserted AtPIEZO1 in a bilayer that mimics the A. thaliana tonoplast membrane. Our simulations revealed strong interactions between AtPIEZO1 and anionic lipids, particularly phosphatidylinositol (PI), phosphatidylserine (PS), and phosphatidylglycerol (PG). Studies with the human and mouse homologues of PIEZO1 have shown that anionic lipids regulate PIEZO1 mechanosensitivity. As PG lipids are abundant in the tonoplast but absent from mammalian plasma membranes our simulations may suggest plant-specific regulatory mechanisms. Furthermore, our results indicate that AtPIEZO1 induces a shallower membrane deformation compared to mouse PIEZO1, potentially reflecting a distinct force-sensing mechanism. Overall, our results provide new insights into the interactions of AtPIEZO1 that in turn may regulate its function.

Does function follow form? Differences in excitation-contraction coupling of hiPSC-cardiomyocytes cultured in 3D versus 2D

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Poster Session A, July 15, 2026, 14:00 - 15:30

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have become a popular in vitro cardiac model. In recent years, 3D culture (spheroids) has been proposed as an alternative model that may better recapitulate the heart in situ. Understanding the underlying excitation-contraction coupling of hiPSC-CM monolayers and spheroids is essential for their translational application. Therefore, the aim of this study was to characterise excitation-contraction coupling of hiPSC-CM monolayers and spheroids. Commercial hiPSC-CMs were plated as either a monolayer or spheroid. Optical dyes were used to study intracellular calcium and membrane voltage dynamics, and contractility was assessed using an image-based algorithm. Monolayer and spheroid response to electrical stimulation were assessed by increasing field stimulation from 1-4Hz. Both preparations were stained with Wheat Germ Agglutin (WGA) and DAPI to assess cell structure. Finally, the Paci hiPSC-CM model was used to assess the effect of cell size on calcium and voltage dynamics. HiPSC-CM spheroids had a faster spontaneous beat rate (1123 vs 1724ms, p=0.0002), faster calcium rise time (43 vs 69ms, p=0.0067), shorter calcium duration at 50% and 90% (167ms vs 187, p=0.0096 and 407 vs 521ms, p=0.0238 respectively) and shorter APD90 (149 vs 219ms, $p<0.05$) compared to hiPSC-CM monolayers (Nexp=3, n=12). Spheroids also followed higher rates of electrical stimulation than monolayers (85% of spheroids but only 53% of monolayers, paced up to 3Hz, Nexp=3, n=15-27). Interestingly, cells within a spheroid were ~5X smaller than cells within a monolayer (cell diameter 13 vs 49µm $p<0.0001$, N=13, n=65). however modelling suggests that changes in cell size alone cannot account for the differences in calcium and voltage dynamics observed. Overall, hiPSC-CMs cultured in 3D have distinct functional and structural differences than the same cells cultured in 2D, which is an important consideration when deciding on the optimal cardiac in vitro model for specific translational applications.

The role of PIEZO1 in Purkinje Fibre-mediated arrhythmia development: A study from the whole heart to the nanoscale level

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Poster Session A, July 15, 2026, 14:00 - 15:30

Premature ventricular contractions originate from the Purkinje fibre (PF) network; however, their underlying mechanism and propagation is unknown. Such answers would be revolutionary for targeting arrhythmia development within ablation therapy. This study looks at the role that PIEZO1, a mechano-sensitive ion channel, has within PF-mediated arrhythmia development.

In accordance with local ethical regulations: (1) Langendorff-perfused, male Wistar rat hearts (N=8) underwent mechanical stimulation by a left ventricular (LV) fluid-filled balloon (100 µL inflation over 2s; maintained for 38s). The LV was perfused with Tyrode then 50 µM Yoda1, a PIEZO1 activator, for 5 minutes, followed by Lugol's. (2) Isolated female Ovine PFs (N=3) were loaded with 10 µM Fura-2 to obtain calcium recordings in the presence and absence of Yoda1 whilst the PF underwent electrical and mechanical stimulation. (3) Isolated male Porcine PFs (N=2) were sectioned (350 µm) and incubated with 10 µM Rhod2; 10 µM blebbistatin and 7.5 µM RH237 for optical mapping recordings (0.5 Hz field stimulation; 35°C). All tissue underwent immunofluorescence staining and 4x expansion microscopy for PIEZO1. Data presented as mean ± SEM; One-Way ANOVA ($P<0.05$).

When the LV was dilated, (1) in the presence of Yoda1, ectopic activations increased 32% (12.21 ± 1.10) compared to Tyrode alone (9.25 ± 0.82), decreasing 75% to 3.09 ± 0.43 after Lugol's. Isolated PFs (2) had an altered calcium transient wavefront upon stretch, which was exacerbated in the presence of Yoda1 (denoted in brackets). Amplitude increased 65% (80%), with a 9% (14%) slower time to peak and 6% (27%) slower time to fall. (3) Voltage and calcium activation was mapped across the PF, with PIEZO1 localised to the PF membrane to correlate function with structure.

We propose PIEZO1 to have a key role in the PF network, its structural heterogeneity being fundamental to the mechanism of arrhythmia development.

Limora: A Synchronized Multimodal System for Real-Time Cognitive Load Assessment in Educational Environments

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Poster Session A, July 15, 2026, 14:00 - 15:30

Cognitive load, the total mental effort required to perform a task, is crucial for assessing attention, stress, and learning performance. However, accurate measurement remains challenging as many existing monitors rely on single-sensor or unsynchronized devices, producing incomplete representations of cognitive activity. According to Cognitive Load Theory (Sweller), increased mental effort during complex tasks are reflected in physiological changes such as pupil dilation and autonomic activation, serving as reliable indicators of cognitive effort, yet their synchronized dynamics during academic tasks are rarely analyzed in controlled educational settings.

This study introduces Limora, a synchronized dual-sensor system for cognitive load measurement that simultaneously records pupil diameter and skin conductance. Integrated architecture aligns both data streams through temporal synchronization, enabling cross-modal analysis of physiological responses. Pupillary fluctuations are captured using a webcam integrated with Pupil Capture software, while electrodermal activity is recorded via a Raspberry Pi connected to a Galvanic Skin Response sensor on the middle and index fingers.

40 high schoolers will complete a three-phase protocol using Limora, where stimuli are presented through PsychoPy, generating synchronized event timestamps. Tasks include a baseline fixation, an arithmetic task inducing working-memory load, and a Stroop interference task targeting cognitive stress.

Data will be preprocessed by removing blinks, smoothing, and baseline-correcting pupil signals, while electrodermal activity will be separated into tonic skin conductance level (SCL) and phasic electrodermal response amplitudes (SCR). Mean and peak pupil dilation will indicate attentional effort, whereas SCL and SCR will reflect autonomic arousal. Normality will be assessed using the Shapiro–Wilk test. Repeated-measures ANOVA with Bonferroni-corrected post hoc tests will compare physiological responses across conditions, and Pearson correlation will examine associations between pupil dilation and electrodermal activity. The study aims to determine whether synchronized multimodal physiological signals provide deeper insight into cognitive load than single-sensor measurements, supporting potential applications in educational environments.

The Piezo1-ADAM axis modulates the inflammatory state of dermal keratinocytes via EGFR signaling

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Poster Session A, July 15, 2026, 14:00 - 15:30

Dermal wound healing is a tightly regulated process that is essential for restoring skin barrier function. This process is strongly influenced by mechanical cues, which are sensed by mechanosensitive ion channels such as Piezo1. The activation of Piezo1 has been shown to modulate inflammatory and regenerative responses during wound repair. A key component in this chain of events is the controlled release of cytokines and growth factors, including chemokines such as IL-8 that recruit immune cells, and epidermal growth factor receptor (EGFR) ligands such as amphiregulin (AREG) to promote keratinocyte proliferation and migration. We have recently shown that proteases of the a disintegrin and metalloproteinase family can be induced subsequent to chemical or mechanical activation of Piezo1 leading to proteolytic cleavage of AREG and its release. In this study, we could show that chemical and mechanical activation of Piezo1 also leads to ADAM-dependent AREG release in dermal keratinocytes. Interestingly, Piezo1 activation also led to increased IL-8 secretion. Although IL-8 is released via the secretory pathway, its release was nonetheless dependent on ADAM activity. This dependency can be explained by the pronounced ADAM mediated release of growth factors and the subsequent activation of EGFR signaling which leads to IL8 gene induction. Together, our findings demonstrate that the Piezo1–ADAM axis controls autocrine and paracrine signaling in keratinocytes in response to mechanical stimulation via growth factor shedding and thereby modulates dermal wound healing.

Piezo1 in PASMCs: Critical for Hypoxia-Induced Pulmonary Hypertension Development

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Poster Session B, July 15, 2026, 16:00 - 17:30

Pulmonary hypertension (PH) is a life-threatening and progressive, but yet incurable disease. The hallmarks of PH comprise sustained contraction and excessive proliferation of pulmonary arterial smooth muscle cells (PASMCs). A major stimulus to which PASMCs are exposed during PH development is altered mechanical stress. Mechanosensitive ion channels, such as Piezo1, perceive such mechanical stimuli and translate them
into various cellular responses. Thus, the objective of the present study was to elucidate the specific role of Piezo1 in PASMCs for PH-development and progression. Taking advantage of PASMCs from idiopathic pulmonary arterial hypertension (IPAH)-patients and two mouse strains characterized by SMC-specific Piezo1 knock-out, we assessed the SMC-specific role of Piezo1 in PH-development and progression via experiments in isolated, perfused and ventilated mouse lungs, wire myography and proliferation assays. In vivo function of SMC-specific Piezo1 knockout was evaluated upon induction of chronic hypoxia-induced PH (CHPH) in these mice with insights into pulmonary vascular cell senescence. Piezo1 expression and proliferation was enhanced in PASMCs from IPAH-patients and mouse PASMCs upon hypoxic exposure. SMC-specific Piezo1-deletion prevented the hypoxia-induced increase in proliferation. Moreover, Piezo1-knockout reduced hypoxic pulmonary vasoconstriction (HPV) in isolated, perfused and ventilated mouse lungs, pulmonary arteries and hemodynamic measurements in vivo. Consequently, Piezo1-deficient mice were significantly protected against CHPH-development with ameliorated right heart hypertrophy and improved hemodynamic function. In addition, distal pulmonary capillaries were preserved in the Piezo1-knockout mice, associated with a lower number of senescent endothelial cells.
This study provides evidence for Piezo1 expressed in PASMCs being critically involved in the pathogenesis of PH - most likely by controlling pulmonary vascular tone, pulmonary arterial remodeling, and associated lung capillary rarefaction due to endothelial cell senescence.

Pharmacological Activation of PIEZO1 and Inhibition by Benzbromarone in Human Liver Sinusoidal Endothelial Cells

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Background
Liver regeneration following resection is critically dependent on haemodynamic changes within the hepatic microcirculation. Liver sinusoidal endothelial cells (LSECs) are among the first cells exposed to altered portal flow and shear stress. PIEZO1, a mechanosensitive Ca^{2+}-permeable ion channel, has been proposed as a key regulator of flow-mediated signalling and endothelial function. Here, we investigated the functional characteristics and pharmacological modulation of PIEZO1 in human LSECs.

Methods
Intracellular Ca^{2+} responses were measured in human LSECs using Fura-2 and ratiometric fluorescence imaging in a FlexStation III. PIEZO1 activation was induced using Yoda2 and a novel small-molecule agonist (CHR), and EC_{50} values were calculated. Specificity was assessed using the mechanosensitive channel inhibitor GsMTx4 and siRNA-mediated PIEZO1 knockdown. Benzbromarone was investigated as a potential PIEZO1 inhibitor with relevance to liver toxicity. Benchmark modulators ATP, ionomycin, thapsigargin and VEGF were comparators.

Results
Yoda2 (EC_{50} 469 ± 125 nM) and CHR (EC_{50} 331 ± 248 nM) induced dose-dependent Ca^{2+} influx consistent with PIEZO1 activation. GsMTx4 attenuated Yoda2 and CHR evoked responses at 10 μM concentration, as did PIEZO1 knockdown. Benzbromarone inhibited Yoda2-mediated Ca^{2+} influx in a concentration-dependent manner (IC_{50} 395 ± 300 nM) but lacked specificity for PIEZO1 because it also inhibited Ca^{2+} responses triggered by other modulators.

Conclusion

Human LSECs exhibit robust PIEZO1-dependent Ca^{2+} signalling, supporting a mechanistic role for PIEZO1 in hepatic haemodynamic sensing. Benzbromarone strongly attenuates PIEZO1-mediated responses and other Ca^{2+} pathways, effects that may contribute to its liver toxicity. These findings support the hypothesis that PIEZO1 is an important determinant of hepatic blood flow and potential new target for therapeutic intervention to improve blood flow and regeneration in liver disease and surgery.

Decoding vascular aging: Substrate stiffness and shear stress orchestrate endothelial inflammation and remodelling via mechanosensitive pathways

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Poster Session B, July 15, 2026, 16:00 - 17:30

Vascular aging is a major factor which underlies many cardiovascular diseases including atherosclerosis and myocardial infarctions. Characteristics include stiffening of the vascular wall which disrupts endothelial homeostasis and promotes chronic inflammation, yet the underlying mechanisms remain poorly understood due to technological limitations. Here, we have developed an in vitro microfluidic model to investigate how biomechanical forces, specifically substrate stiffness and shear stress, interact to regulate endothelial cell functions. Using RNA sequencing and functional assays, we found that endothelial cells exposed to both physiologically high levels of shear stress were more sensitive to increases in substrate stiffness in which the cells exhibited a greater number of differentially expressed genes and enhanced activation of inflammatory signalling pathways.

We identified enriched pathways involved in inflammatory signalling and extracellular matrix remodelling due to substrate stiffening. Endothelial cells exposed to high shear stress and increased stiffness showed up-regulation of genes such as ICAM1 and VCAM1 which mediate leukocyte adhesion, and LAMB3 and MMP28 which mediate extracellular matrix remodelling. Importantly, these findings were benchmarked using human aortic tissue which confirmed concordant molecular and histological changes between stiff (aged) and soft (healthy) aortas.

We have also explored the role of mechanosensitive ion channel Piezo1 under the combined effect of shear stress and substrate stiffness in endothelial morphology, senescence, proliferation, and inflammation. Piezo1 facilitated endothelial adaptation to flow and regulation of inflammation under both atheroprotective and atherogenic shear stress levels. In endothelial senescence, Piezo1 contribution was limited to the soft substrate and atheroprotective shear stress.

Ultimately, this validated microfluidic platform provides proof of concept that biomechanical forces characteristic of vascular aging drive endothelial inflammation and vascular remodelling, offering new mechanistic insight and a powerful experimental framework to advance therapeutic strategies targeting vascular stiffness and age-related vascular disease in which the process may involve Piezo1 mechanotransduction.

Novel soft robotic cell-stretching device alters PIEZO1 expression in cardiac strain profiles

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Poster Session A, July 15, 2026, 14:00 - 15:30

The myocardium regulates its own mechanical properties by sensing the mechanical forces it generates and experiences. These forces are altered in disease states, challenging us to understand the molecular mechanisms underpinning this mechanosensing. Cardiac fibroblasts (CF) are the primary regulator of extracellular matrix and other mechanical determinants. Mechanical forces activate CF and PIEZO1, a mechanosensitive, calcium permeable ion channel, has emerged as pivotal in sensing and maintaining myocardial mechanical properties and efficient pumping (McGrane et al 2025).

Soft robotics present new opportunities to deliver physiologically relevant mechanical cues to cells, offering advantages over artificially static and stiff tissue-culture plastic substrates for detailed molecular and biochemical analysis. CellQ-Twin is a novel, low-cost, pneumatically driven soft robotic cell stretcher device, developed in-house for applying bio-realistic and patient-relevant mechanical strain waveforms to cultured cells.

Primary human ventricular fibroblasts were plated onto soft substrates in the CellQ-Twin and 10% radial stretch applied at 0.5 Hz, 1.0 Hz or 1.5 Hz for 4 hours. Brightfield images were taken post-adhesion and post-stretching and RT-qPCR employed to measure a panel of fibrotic and mechanically regulated genes. Preliminary gene expression analysis highlighted several genes that were regulated differentially depending on stretch protocols. PIEZO1 expression showed ability to adapt to mechanical forces.

The data highlights the potential for CellQ-Twin to deliver mechanically related insights into health and disease and supports the idea of PIEZO1's centrality in cardiac mechanical adaptation.

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PIEZO1 Variation in Myofibroblasts Obtained at Open Heart Surgery

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Poster Session B, July 15, 2026, 16:00 - 17:30

Type 2 diabetes (T2D) commonly contributes to a clustering of inter-related and co-incident cardiovascular disease (CVD) risk factors, in which cardiac fibrosis is a common hallmark. Fibrosis is characterised by excessive extracellular matrix deposition by cardiac fibroblasts (CF), resulting in stiff and less compliant matrices. Mechanical forces activate CF, and PIEZO1, a mechanosensitive, calcium (Ca2+) permeable ion channel has emerged as central to force sensing, maintaining myocardial mechanical properties and efficient pumping by regulating CF. This project aims to characterise PIEZO1 channels in CFs from CVD patients, with or without associated T2D. CF were isolated and cultured from right atrial appendage (RAA) biopsies (N=35) from patients undergoing open heart surgery (IRAS ID 200339). Immunohistochemistry identified a homogenous myofibroblast (myoCF) population. Gene expression analysis outlined collagen and inflammatory markers linked with PIEZO1 signalling in myoCF which differ with CVD severity and type (n=18). Robust Ca2+ entry is triggered by application of Yoda1 or Yoda2, two agonists of PIEZO1 channels (N=33). Preliminary analysis suggests heightened PIEZO1 function in ischemic heart disease and comorbid burden with associated T2D or additional CVD. There is high inter-patient variability potentially due to confounding factors such as sex, age and obesity. In summary, PIEZO1 channels are expressed and functionally active in human myoCF obtained at open heart surgery and there is variability in channel activity, potentially due to type or severity of heart disease or T2D.

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Pilot investigation of PIEZO1 in endothelial to mesenchymal transition (EndMT) of human umbilical vein endothelial cells

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Poster Session B, July 15, 2026, 16:00 - 17:30

Background: Fetal growth restriction (FGR) is a condition associated with increased rates of preterm delivery and stillbirth. In placentas from FGR pregnancies, placental fibrosis is seen. EndMT is a process whereby the phenotype of endothelial cells shifts to a mesenchymal-type with increased potential for fibrosis. PIEZO1 is a mechanosensor linked with fibrosis in human disease. The role of PIEZO1 in EndMT is not well studied but is perhaps protective. This pilot study aims to explore the relationship between PIEZO1 and EndMT in placental endothelial cells.

Methods: Cultured human umbilical vein endothelial cells (HUVECs) were treated with TGF-β and IL1-β for 48hrs with and without PIEZO1 knockdown by RNA interference under static and shear stress conditions. EndMT was investigated using flow cytometry, immunocytochemistry and Western blotting.

Results: After knockdown, a potential increase was seen in the mesenchymal marker N-cadherin between Day 0 and Day 2. However, immunocytochemistry did not show increases in mesenchymal markers (alpha-SMA and vimentin) or decrease in endothelial markers (CD31 and CD144). Western blotting did not show an increase in collagen-1 after 2 days of treatment.

Conclusion: Overall, this pilot study did not support the idea of EndMT regulation by PIEZO1. However, this could be due to a limited sample size of 3 and short (2 day) EndMT induction period. Further work is required to optimise the experimental protocol and explore the relationship between PIEZO1 and EndMT in endothelial cells from FGR placentas.

A Human Liver Small-for-size graft (SFSG) Model to Study Mechanosensing in Liver Regeneration and Failure Pathophysiology

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Poster Session A, July 15, 2026, 14:00 - 15:30

Background:
Liver is the only solid organ capable of regeneration after surgical resection or transplantation. This process is hypothesised to be initiated by increased blood flow through the remnant/smaller graft. Mechanosensitive pathways, particularly PIEZO1 ion channels, are proposed to detect hemodynamic changes and initiate signalling. Conversely, excessive portal inflow in a relatively smaller segment can cause mechanical damage leading to liver failure or Small-for-size syndrome. Most current knowledge is based on animal models, limiting translation to human liver physiology.

Methods:
Twelve livers from adult donors with negative virology and without extensive steatosis/fibrosis were perfused using normothermic machine perfusion (NMP). Whole liver NMP at physiological rates was performed for 4 hours, followed by 6 hours of isolated left lateral segment (LLS) NMP at >250mL/min/100g liver tissue to simulate post-surgery hyperperfusion. PIEZO1 agonists (Yoda1/Yoda2), PIEZO1 negative modulator (Dooku1) or nitric oxide synthase inhibitor L-NMMA were administered 75 minutes before the end of LLS perfusion. Perfusion parameters, bile production and biochemical measurements were serially recorded. Tissue biopsies were obtained for histology and RNA sequencing. Viability was determined using established hepatocellular criteria for whole liver perfusion and applied to the LLS to evaluate hyperperfusion induced dysfunction.

Results:
Median donor age was 52.5 years and median BMI 31.7 kg/m^2. Mean LLS weight was 336.3±107.4 g. Five of 12 livers appeared moderately steatotic. Based on viability criteria, 9 of 12 LLS grafts demonstrated impaired function. Histology from first 4 livers showed early changes of portal hypertension (sinusoidal dilatation, congestion, extravasation of RBCs, hepatocyte ballooning) in LLS.

Conclusion:
Hyperperfusion of LLS during NMP reproducibly induced functional impairment and morphological changes consistent with early SFSS, supporting this model as a platform to investigate vascular modulation and mechanosensitive pathways in human liver regeneration. Ongoing transcriptomic and protein analyses will assess differences across whole livers and LLSs for treatment groups.

Propofol Modulates Calcium Signalling in Human Liver Sinusoidal Endothelial Cells: Implications for Mechanotransduction in Liver Surgery

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Poster Session A, July 15, 2026, 14:00 - 15:30

Background:
Propofol-based total intravenous anaesthesia is increasingly used in liver surgery and liver transplantation following clinical and experimental studies that suggest it may attenuate hepatic ischemia–reperfusion injury and reduce oxidative stress. However, the cellular mechanisms underlying these protective effects remain incompletely understood. Emerging evidence indicates that propofol inhibits the mechanically activated PIEZO1 channel expressed in HEK293T cells but the relevance to native PIEZO1 is unclear. PIEZO1 is pivotal in liver sinusoidal endothelial cells (LSECs) and liver regeneration and other hepatobiliary functions. Here, we explored whether Propofol alters PIEZO1-related Ca^{2+} signalling in human LSECs.

Methods:
Primary human LSECs were studied using real-time intracellular Ca^{2+} measurements (FlexStation III) with exposure to Propofol (2,6-Diisopropylphenol). Single-injection activation assays were performed for 50 µM and 150 µM Propofol. Interactions with the PIEZO1 agonist Yoda2 or a novel PIEZO1 agonist (CHR) were assessed using direct application or pre-incubation and sequential protocols. For inhibitory studies, cells were preincubated with Propofol for 30 minutes before stimulation with Yoda2/CHR (3 µM) or exposed to sequential injections of Yoda2/CHR (3 µM) followed by Propofol, keeping final concentration of Yoda2/CHR stable.

Results:
Propofol induced striking Ca^{2+} responses in LSECs. At 50 µM, a mild Ca^{2+} elevation was observed, whereas 150 µM produced a larger yet still slowly developing elevation. If Yoda2/CHR were applied first, Propofol had a stronger and faster effect, suggesting synergistic modulation of Ca^{2+} entry. In contrast, pre-incubation with Propofol attenuated subsequent Yoda2-induced Ca^{2+} responses, indicating potential inhibitory as well as agonist effects on mechanosensitive signalling.

Conclusion:
Propofol has strong modulatory effects on Ca^{2+} signalling in human LSECs. They include complex changes in PIEZO1-related Ca2+ events, including inhibitory and enhancing effects that warrant further investigation. These findings suggest important modulatory effects of Propofol on hepatic vasculature that involve PIEZO1 and could be relevant in liver surgery.

The mechanosensitive channel Piezo1 is a mediator of mechanical forces in bone marrow endothelial cells

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Poster Session B, July 15, 2026, 16:00 - 17:30

Circulating blood cells are generated in the bone marrow from haematopoietic stem cells that differentiate into all blood cell lineages. Once mature, these cells enter the bloodstream exclusively through specialised sinusoid microvessels. Bone marrow endothelial cells (BMEC) are therefore exposed to complex mechanical forces and express receptors that enable them to sense and adapt to these stimuli. However, the role of such mechanoreceptors in regulating transmural passage remains unclear. This project aims to characterise the role of stretch-activated channels (SAC) in BMEC.
BMEC from C57BL/6J mice were isolated by enzymatic digestion and sorted based on the phenotype $CD45^{-}$, $F4/80^{-}$, $Ter119^{-}$, $CD31^{+}$, $CD140ab^{-}$, CD105bright. SAC activity was assessed using patch-clamp recordings in a cell-attached configuration. Increasing negative pressure pulses (0 to −80 mmHg) were applied via the pipette to elevate membrane tension. These experiments revealed clear stretch-induced currents, and single-channel analysis suggested the presence of non-selective cation SAC.
To identify the channels involved, RT-qPCR analyses were performed, identifying Piezo1 as the most highly expressed candidate. Consistently, BMEC from Piezo1 gain-of-function mice (R2482H) exhibited larger stretch-induced currents than wild-type controls, confirming its functional contribution. In vitro, confluent BMEC cultures from Piezo1KI/+ mice showed reduced VE-cadherin staining intensity, indicating altered endothelial junction organisation and potential changes in permeability.
Furthermore, bone marrow sections stained for FABP4 and laminin revealed increased vessel diameters and laminin intensity in Piezo1Ki/Ki mice, with thick-section analysis supporting structural vascular alterations. Overall, our findings show that functional SAC are expressed in BMEC plasma. Among these channels, Piezo1 is the most highly expressed and may potentially regulate the organization of endothelial junctions and vascular architecture. Further investigations will allow assessment of the involvement of Piezo1 in BMEC responses to mechanical signals induced by mature hematopoietic cells as well as the consequences for their overall transmigration.

PIP2-Dependent Stabilization of PIEZO1 handshake interactions Revealed by molecular dynamics simulations

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PIEZO1 is a mechanosensitive ion channel essential for processes such as red blood cell volume regulation, vascular development, and the conversion of mechanical stimuli into cellular responses. PIEZO1 is a trimeric complex with a three-bladed, propeller-like architecture embedded in the lipid bilayer, featuring a hydrophobic ion-conducting pore at its center. Its activity is strongly influenced by the surrounding lipid environment, which interacts with multiple regions within the protein and modulates different stages of the gating process. In this work, we study the role of anionic lipids, particularly phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidyl serine (POPS) lipids, as regulators of force sensitivity and intermolecular interactions within the channel. We performed coarse-grained molecular dynamics simulations of the full-length human PIEZO1 embedded in an endothelial-like membrane, totalling 50 μs of simulation time. Our results show that anionic lipids, especially PIP2 and to a lesser extent POPS, mediate an interblade interaction between helices belonging to two adjacent subunits, termed the handshake interactions. These intermolecular contacts shape key global properties of the protein, including protein curvature and compactness. As such they may be key to PIEZO1 force sensitivity and activation.

Investigating effects of actomyosin mechanics on rapid permeability changes in epithelium

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Epithelial tissues form important barriers in our bodies. Tight junctions (TJs), cell-cell adhesions located at the apical region of epithelial cells, play a central role in the formation of the epithelial barrier. TJs have a role in regulating paracellular transport of ions, molecules, and small proteins. They are large protein complexes containing transmembrane proteins, e.g. claudins, which link the cells together, and cytoplasmic scaffolding proteins, e.g. ZO-1 and ZO-2, through which TJs connect to actomyosin cytoskeleton. TJs form a dynamic barrier, allowing the cells to regulate paracellular transport, yet the role of scaffolding proteins in this behavior is not fully understood. A recently developed microscopic epithelial barrier measurement method (zinc-based ultrasensitive microscopic barrier assay, ZnUMBA) provides a high-resolution, junction-level view of barrier dynamics based on a zinc indicator intensity.

To study the role of ZO-1 and ZO-2 in the barrier dynamics, we applied ZnUMBA to MDCK II cells. The method allowed us to record rapid increases in junction intensity, indicating leaks of zinc through the dynamic barrier. We analyzed the duration and frequency of the leak events in wild type (WT), ZO-1 knockout (KO), ZO-2 KO, and ZO-1 overexpressing MDCK cell lines. We found that ZO-1 KO decreased the leak frequency compared to WT, whereas ZO-1 overexpression and ZO-2 KO increased leak duration compared to WT. In addition, we investigated the role of actomyosin cytoskeleton in the observed leaks. Using drugs to alter myosin II activity did not affect the leak duration or frequency in WT nor ZO-1 KO cell lines. However, actin depolymerization decreased the leak number detected in WT. Our results show that the scaffolding proteins and changes in actomyosin have an effect on the TJ dynamics, but further studies are required.

FFA4 inverse agonism and Piezo1 agonism regulate cellular mechanics of 3T3-L1 adipocytes

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Metabolite-sensing GPCRs, such as FFA4, have emerged as key regulators of cellular physiology, particularly in adipocytes. However, other cellular pathways such as mechanotransduction have now been shown to have a significant role in adipogenesis and adipocyte function. Yoda1, a selective agonist of the mechanosensitive ion channel Piezo1, provides a valuable tool to dissect the role of mechanotransduction in adipocyte biology. In this study, we investigated how investigated inverse agonism of FFA4 and its role in modulating cellular mechanics. This study also looks at Piezo1 agonism and its modulatory role in adipogenesis and GPCR expression. Using 3T3-L1 adipocytes, we demonstrate that Yoda1 treatment throughout differentiation can cause varied phenotypic and genotypic changes which is greatly dependent on the Yoda1 concentration, thus the level of Piezo1 activation, used. These results suggest Yoda1-mediated Piezo1 activation has a significant role in mediating adipogenesis where low or high activation can direct differentiating cells down differing cell lineages. Treatment with AH7614, an inverse agonist of FFA4, showed reduced adipogenesis with increased cell stiffness, suggesting that FFA4 inverse agonism regulates intracellular mechanics. These findings suggest that Piezo1 activation and FFA4 inverse agonism serve a modulatory role in adipocyte signalling, suggesting a possible link between the two signalling pathways

Understanding PIEZO1 channel conservation across species

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The PIEZO protein family are transmembrane mechanosensitive cation ion channels, situated in the plasma membrane. These proteins have been shown to have biological relevance across organisms including blood cell volume regulation, cardiovascular development and somatosensory neuronal activity. PIEZO channels have previously been identified in early eukaryotes across multiple kingdoms, including Animalia and Protozoa, indicating they likely evolved in the common eukaryotic ancestor. PIEZOs vary widely in size, with differences of approximately 1500 residues. Despite this diversity, there has been limited research examining the conservation of PIEZOs. Evolutionary analysis can be a powerful tool for understanding physiological history and fitness advantages. In this study we used phylogenetic comparison of all available full-length Animalia sequences of PIEZO1, allowing us to identify structurally conserved regions relevant to function. Our analysis suggests that the evolutionary trajectory of PIEZO involved early division in invertebrates and later detachment in fish from the remaining vertebrate classes. The protein's sequence conservation was seen to increase moving toward the C-terminal part of the protein across the Animalia kingdom. This was exemplified through the high conservation of the protein's C-terminal regions (anchor domain, transmembrane pore and C-terminal domain) likely reflecting the preservation of its ion conductance function. In contrast, N terminal blade and C terminal extracellular domain show lower conservation. This novel understanding of diverging aspects of PIEZO1 could enhance our understanding of physiological functions of PIEZO1 that have previously been undetermined.

PIEZO1-Mediated Mechanosensing Drives Selective Ultrasound-Induced Cytotoxicity in Pancreatic Cancer Cells

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, characterized by a mechanically altered tumor microenvironment (TME) and aberrant ion channel expression. Among the mechanosensitive players in PDAC, PIEZO1 has emerged as a key mediator of mechanotransduction, yet its role in ultrasound-induced cytotoxicity remains unexplored.
In this work, we investigated the effects of Low Intensity Continuous Ultrasound across a frequency range of 1–5 MHz on PANC-1 pancreatic cancer spheroids. Ultrasound stimulation was delivered using a custom-built setup featuring two interchangeable transducers, designed to ensure the most homogeneous acoustic pressure delivery across the tested frequency range. Cytotoxicity was quantified by LDH release assay, revealing a strong frequency-dependent response with a peak cytotoxicity of 45.02 ± 0.5% at 3.5 MHz ($p < 0.01$). Critically, no cytotoxic response was observed in non-tumoral control models, including Human Pancreatic Ductal Epithelial (HDPE) cells (0.00% ± 0.0) and RLT-PSC pancreatic stellate cells (~0% at all frequencies tested), demonstrating a selective effect on cancer cells.
To investigate the molecular basis of this selectivity, we focused on mechanosensitive ion channels as primary candidates. The applied acoustic pressures (1–3 kPa) fall well below the cavitation threshold, placing the stimulation regime within a non-cavitational mechanical index. This makes direct membrane mechanosensing — rather than cavitation-driven damage — the most plausible cytotoxic mechanism, pointing to PIEZO1 as a key transducer. PIEZO1 is overexpressed in PDAC, and its contribution to the observed response was assessed through pharmacological modulation using the agonist Yoda1 and the inhibitor GsMTx4.
Collectively, these results suggest that PIEZO1-mediated mechanosensing plays a central role in the selective cytotoxic response of PDAC cells to low-intensity ultrasound, opening new perspectives for ultrasound-based therapeutic strategies in pancreatic cancer.

High-Throughput Automated Patch Clamp Method to Enable Drug Discovery on the Force-Sensing Ion Channel Piezo1

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Cells constantly experience physical forces such as blood flow, stretch, or pressure and they need ways to detect and respond to those forces. Piezo1 is a “force-sensing” ion channel that opens when the cell membrane is mechanically disturbed, allowing ions to flow and triggering downstream signals. Because Piezo1 is important in processes like blood vessel development, red blood cell function, and cancer progression, there is growing interest in finding compounds that can modulate Piezo1 activity. A major challenge is that the most direct way to measure Piezo1 channel activity mechanically (patch clamp electrophysiology) is traditionally slow and difficult to scale for screening many compounds.

We recently developed an automated patch clamp approach called “M-Stim,” which uses rapid, high-flow pipetting in a 384-well format to apply a controlled mechanical stimulus that reproducibly activates Piezo1 currents. In this work, we use M-Stim to test Piezo1 pharmacology in cells engineered to overexpress Piezo1, and cells that endogenously express Piezo1, to measure how effectively a set of Piezo1 inhibitors reduces mechanically evoked currents.

By combining a mechanical trigger with automated, parallel recordings, M-Stim enables faster and more standardized testing across many cells than traditional patch clamp. This makes it a practical tool for discovering and comparing compounds that modulate Piezo1, especially in biologically relevant cell types.

Bridging Disciplines: A Research Oriented Neuroscience Curriculum for Secondary Education

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While neuroscience courses are traditionally reserved for higher education, introducing these concepts in secondary school cultivates analytical skills, scientific literacy, and interdisciplinary thinking. This presentation outlines the "Introduction to Neuroscience", which is a multidisciplinary elective course developed over the past five years at Hisar School for secondary students (Grades 11–12 only). By integrating principles from physics, biology, mathematics, computer science, and psychology, the curriculum illustrates how these convergent fields collaboratively solve real world problems, ranging from cognitive health to technological innovation. Core modules include fundamental neuroanatomy, neurotransmitter dynamics, neuroplasticity, neuroimaging, and neuromarketing.

The course follows an inquiry based, research oriented approach with a strong focus on developing critical thinking. Students transition from acquiring theoretical foundations to investigating empirical studies through case studies. Alongside lecture based lessons, students also take part in activities such as the Stroop task and split brain case studies, which help them see cognitive processes in action. Students also receive formal training in research and learn how to use academic databases such as Google Scholar, Semantic Scholar, and Consensus. It helps them break down complex texts and stay actively engaged with the material, making advanced research more accessible. Throughout the course, research assignments are often presented as academic or poster presentations, allowing students to share their work in a structured scientific format.

This presentation will outline the course design, discuss how inquiry based learning is implemented at the secondary level, and show how early exposure to research practices supports students' confidence, analytical skills, and academic readiness.

Role of PEZO-1 in Maintenance of the Germline Stem Cell Population in Caenorhabditis elegans

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Stem cells are essential for the development and maintenance of tissues. Germline stem cells (GSCs), in particular, sustain the reproductive capacity as well as modulate systemic aging of an organism. The population of germline stem/progenitor cells in Caenorhabditis elegans is maintained by their single-cell niche, known as the Distal Tip Cell (DTC), and their numbers gradually decline as the worms age. PEZO-1, the homolog of the mammalian mechanosensitive ion channel Piezo in C. elegans, is extensively expressed throughout the gonad and in all stages of germ cells within the organism. Additionally, PEZO-1 is necessary for proper ovulation and fertilization in the proximal gonad of worms. However, its potential role in the distal gonad, where the stem cells reside, remains unclear.
We are investigating the role of PEZO-1 in maintaining the germline stem/progenitor cells in the distal part of the gonad in C. elegans. While perturbing the levels of PEZO-1 did not demonstrate any measurable effect on the morphological attributes of the niche, we observed that loss of PEZO-1 directly impacted the germline stem cell population as worms aged. We are currently exploring the possible pathway through which PEZO-1 regulates the stem cell dynamics. This study will enhance our understanding of the mechanical regulation of stem cells broadly, with a specific focus on GSCs, and will provide valuable insights into the role of mechanics in aging phenotypes.

PIEZO2 and mouthfeel: discovery of PIEZO2 pharmacology from complex herbal mixtures

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PIEZO2 is the principal mechanotransduction channel mediating touch, proprioception, and interoception, yet its contribution to oral somatosensation, including texture perception and tactile aspects of mouthfeel, remains poorly defined. Notably, numerous dietary and botanical compounds elicit tingling, numbing, or other mechanosensory-like oral sensations, suggesting that constituents of complex ingestible mixtures may directly modulate the activity of neurons expressing PIEZO2. To investigate this, we screened 30 herbal liqueurs with documented complex mouthfeel properties for effects on PIEZO2 activity using FM 1-43 uptake as a functional readout. Multiple preparations inhibited PIEZO2-dependent dye loading. Fractionation of Chartreuse Végétal by preparative HPLC, guided by the FM 1-43 uptake assay, followed by NMR-based structure elucidation, identified Compound 1 as the principal active constituent. In heterologous expression systems, Compound 1 inhibited both PIEZO2-dependent FM 1-43 uptake and mechanically evoked currents (IC_{50} = 62 μM). In vivo, local administration of Compound 1 attenuated mechanical sensitivity in corneal blink reflex and hindpaw von Frey assays. Compound 1 did not alter Hargreaves thermal nociception thresholds or TRPV1- and TRPM8-mediated currents, consistent with a mechanism selective for mechanically activated channels. These findings identify complex herbal liqueurs as an underexplored source of PIEZO2-active natural products and establish a framework for linking such compounds to oral mechanosensation.

Chronic Treatment with Hydrogen Sulfide Donor, GYY4137, Mitigates Aging-Induced Abnormal Reactivity in Rat Corpus Cavernosum

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Background: It has been shown that hydrogen sulfide (H2S) has an important role in regulating vascular homeostasis and to be involved in several physiological effects in the body. GYY4137 is a slow-release H2S donor. The aim of this study was to investigate the protective role of H2S in erectile dysfunction in an aged murine model. Method: Male SD rats used in this study were divided into three groups (n = 8/group): Group 1 control (10 weeks old) ; Group 2 older (aged; 30 weeks old). Group 3 older (aged) rats + GYY4137 (50 mg/kg). The animal's body weights were re-measured before sacrificing the animals. Following sacrifice, corpus cavernosum (CC) was isolated and mounted in organ bath to examine their reactivity by measurement of changes in isometric tension to vasoactive agonists (phenylephrine (PE), carbachol or sodium nitroprusside (SNP)). Ascending concentrations of PE were applied to establish a cumulative concentration response curve. Relaxant responses induced by carbachol, or SNP were also tested. CC tissues were pre-contracted first with PE, then relaxant effects to carbachol or SNP were examined. Results: Results showed that CC strips from aged rats produced a significant increase in contractile response to PE compared to control rats ($P < 0.05$), while treatment with GYY4137 50 mg/kg resulted in reduced contractility of aged CC compared to aged-non treated rats. In addition, the relaxant response to carbachol was significantly attenuated in CC from aged animals compared to controls ($P < 0.05$). Response to carbachol in CC from GYY4137-treated aged rats was significantly improved. The relaxant response to SNP was not significantly different in the three animal groups. Conclusion: The findings of this study suggest a promising role of hydrogen sulfide as a potential novel approach in treatment or prevention of cavernosal abnormal reactivity associated with aging.