ORAL PRESENTATIONS AT VASCULAR BIOLOGY 2025

REGENERATIVE MEDICINE AND CARDIOVASCULAR REPAIR

02

Transcriptional reprogramming of mitochondrial dynamics in iPSCs-derived endothelial cells

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- iECs have impaired mitophagy and mitochondrial biogenesis.
- Flow increases KLF2 and KLF4 expression, which are involved in mitochondrial function.
- ETV2+KLF2+KLF4 co-expression restores mitochondrial and vascular function.

03

Systematic discovery of collateral artery regulators via cross-species in vivo Perturb-seq

Xiaochen Fan Ph.D.[1,2], Ronghao Zhou[3], Tim F. Shay Ph.D.[4], Pamela E. Rios Coronado Ph.D.[5], Viviana Gradinaru Ph.D.[4], Jesse Engreitz Ph.D.[3,6,2], Kristy Red-Horse Ph.D.[1,7,2]

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- Cross-species analysis reveals why guinea pigs resist ischemia.
- In vivo Perturb-seq platform systematically screens genetic regulators in living mouse brains.
- Druggable targets identified for first therapies enhancing natural bypass formation in patients.

04

Connexin 43 is required for smooth muscle cell driven neointimal hyperplasia

Mark C Renton PhD[1], Meghan W Sedovy PhD[1], Renée Sarmiento[1], Kailynn Roberts[1], Adam Hoch BS[2], Amanda Reynolds BS[2], Clare Dennison PhD[1], Scott R Johnstone PhD[1,2,3]

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- Smooth muscle cells are the predominant neointimal cell in mouse carotid arteries
- Smooth muscle cell-specific Connexin 43 knockout prevents neointima
- Fluorescent reporter mice allow comprehensive profiling of neointimal cell origin

05

Genetic mechanisms in natural variation of coronary artery anatomy across diverse populations

Pamela E. Rios Coronado PhD
Yale University, New Haven, CT, USA

- GWAS of coronary dominance identifies 10 loci associated at genome-wide significance
- CXCL12 is expressed in human fetal hearts at the time dominance is established
- Heterozygous knockout of Cxcl12 alters septal dominance in mice

MICROVASCULAR DYSFUNCTION IN SHOCK

08

Distinct blood and lung proteins drive pulmonary capillary leak in invasively ventilated children

Richard Pierce MD[1], Angeliki Gkaifyllia MD[2], Steven Bruzek MS[3], Vera Ignjatovic PhD[3], Jordan S Pober MD, PhD[4], Anthony Sochet MD[3]
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- Pulmonary edema drives severity of hypoxemic respiratory failure
- Blood and lung fluid differentially alter pulmonary capillary barrier function
- Distinct effects on pulmonary capillary barrier function change over disease course

09

Fluid shear stress modulates the CD44/HA axis of the basal endothelial glycocalyx

Zoe Vittum, Jacqueline O'Donnell, Udaya Rattan B.S., Solomon Mensah PhD
Worcester Polytechnic Institute, Worcester, MA, USA

- The basal glycocalyx contributes to endothelium barrier and mechanotransduction functions.
- The apical and basal glycocalyx are intrinsically linked through the endothelial cell cytoskeleton.
- The presence of CD44 and hyaluronic acid is spatial, temporal, and fluid shear stress dependent.

10

Characterization of the endothelial ADAM10 sheddome identifies novel cleavage substrates during *S. aureus* Hla infection

Danielle N Alfano MD, Byoung-Kyu Cho PhD, Young Ah Goo PhD, Juliane Bubeck Wardenburg MD, PhD
Washington University School of Medicine, St Louis, MO, USA

- The precise molecular mechanisms that underlie microvascular dysfunction in sepsis remain understood
- ADAM10 is the primary sheddase for many protein substrates important in endothelial cell function

- CD99 and endothelial protein C receptor are potential novel ADAM10 substrates during Hla infection

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STAT1 and STING are required for endothelial expression of interferon-stimulated genes in response to an endotoxin challenge

Nina Martino B.S.[1], Alejandro Adam PhD[1], Ramon Bossardi Ramos PhD[1], Fatma Awadalla B.S.[1], Daniel Spindola M.S.[1], Samantha Clark B.S.[1], Peter Vincent PhD[1], Shuhan Lu PhD[1], Pilar Alcaide PhD[2], Erin Sanders PhD[2]
[1]Albany Medical College, Albany, NY, USA. [2]Tufts University, Boston, MA, USA

- The endothelium responds to endotoxin by inducing an interferon-like response
- STAT1 and STING are required for this IFN-like gene expression
- Shock severity correlates with IFN-like transcription

EPIGENETIC AND POST-TRANSCRIPTIONAL CONTROL OF THE VASCULATURE

14

IL-12 upregulates SETD4 to epigenetically activate atherogenic programs in diabetic aortic endothelial cells

James Shadiow PhD, Tyler Bauer MD, Kevin Mangum MD, PhD, Lindsey Hughes PhD, Sabrina Rocco MS, Moses Nelapudi BS, Rachel Wasikowski MS, He Zhang BS, Amrita D. Joshi PhD, Gabriela Saldana de Jimenez MS, Samuel Buckley BS, Matthew White Jr. BS, Jadie Y. Moon BS, Jorge Reyes-Arbujas BS, Amy Stark PhD, Alex C. Tsoi PhD, Johann E. Gudjonsson MD, PhD, Katherine Gallagher MD
University of Michigan, Ann Arbor, MI, USA

- Identification of SETD4 as a novel epigenetic regulator in diabetic endothelial cells.
- IL-12 drives SETD4 expression and H3K4me1-mediated chromatin modifications for active transcription.
- SETD4 knockdown blocks IL-12-induced expression of adhesion genes (Selp and Itga6).

15

Endothelial cells retain inflammatory memory through chromatin remodeling in a two-hit model of infection-induced inflammation

Daniel Spindola MSc, Amber Bahr, Samantha Clark, Nina Martino, Alejandro P Adam Ph.D., Katherine MacNamara Ph.D., Ramon Bossardi Ramos Ph.D.
Albany Medical College, Albany, NY, USA

- Kidney endothelial transcriptional memory amplifies secondary infection injury
- Endothelial JunB drives chromatin remodeling after sepsis
- Epigenetic regulation of endothelial responses after sepsis

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Loss of the lncRNA DIO3OS promotes caspase activation, mitochondrial dysfunction, and endothelial apoptosis

Chayan Bhattacharya PhD[1], Celestina Agyemang-Dua Ms[1], Miguel Nieto-Hernandez Bs[1], Sydney Rudolph Bs[1], Warlley Cunha Ms[1], sudarshan Anand PhD[2], Cristina Espinosa-Diez PhD[1]

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- DIO3OS prevents Caspase-mediated apoptosis and maintains mitochondrial membrane potential.
- DIO3OS preserves DNA damage response capacity under genotoxic stress.
- DIO3OS may engage RNA-binding protein networks to support vascular integrity.

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PKM2 signaling in HDAC7-mediated lung endothelial barrier dysfunction

Peter Biggs, Anita Kovacs-Kasa, Liselle Simon, Rahul Patil, basmah mohamed, yitzchak zolty, erin eroglu, shweta patil, latika jaiswal, robert batori, david fulton, alexander verin
augusta university, augusta, USA

- HDAC7 export promotes PKM2's shift from metabolism to inflammatory signaling.
- Targeting PKM2's dimer-tetramer balance may protect lung vascular barrier.
- ALI pathogenesis involves HDAC7/PKM2 crosstalk disrupting endothelial integrity.

INFLAMMATION IN SMALL VESSELS

20

BET bromodomain proteins regulate an interferon-like proinflammatory response in the vasculature in Hutchinson-Gilford progeria syndrome

Subati Tuerdi MD, PhD[1], Quanhu Sheng PhD[2], Jonathan D. Brown MD[1]
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- Hutchinson-Gilford progeria syndrome features significant activation of interferon-related pathways.
- Interferon regulatory factor 3 is activated in the aortas of HGPS animals.
- BET bromodomain inhibition, which disrupts proinflammatory transcription, reduces inflammation.

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Fxr1 loss in aging cerebrovascular endothelium impairs desmosome organization and increases nuclear strain

Olivia Durham[1], Amy Kimble[1], Alyssa Sirianni[1], Emily Burrage PhD[1], Jennifer Liddle PhD[2], Jeremy Balsbaugh PhD[2], Evan Jellison PhD[1], Patrick Murphy PhD[1]
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- Blood brain barrier aging
- Brain endothelial junction dysfunction
- Endothelial cell regulation via RNA binding proteins

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Discovering novel regulators of VE-Cadherin from stabilized endothelial adherens junctions using proximity labeling proteomics

Avishek Ghosh PhD[1,2], Timothy Hla PhD[1,2]

[1]Boston Children's Hospital, Boston, MA, USA. [2]Harvard Medical School, Boston, MA, USA

- VE-Cad-TurboID identifies novel protein interactors in blood endothelial cells downstream of S1P
- S1P stimulation relocalizes Numb, an endocytic adaptor away from adherens junctions.
- Numb regulates VE-Cad and S1PR1 levels in endothelial cells.

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Novel vascular remodeling and endothelial activation in CADASIL-derived blood vessel organoids

Kevin Emmerich, Elisa Ferrante, Manfred Boehm
National Institutes of Health, Bethesda, MD, USA

- CADASIL is due to dominant Notch3 variants but canonical Notch3 signaling is unaffected
- In CADASIL-derived vascular organoids, mural cells undergo major ECM remodeling compared to controls
- Late-stage CADASIL organoids express increased vascular activation markers ICAM1, MCAM and VCAM1

MECHANOSENSING AND MECHANOTRANSDUCTION IN THE VASCULATURE

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Investigating a Mechanotransduction role for EHD2

Jasper S Farrington PhD, Aaryn J David bachelors of science, Talen G niven PhD, Erich Kushner PhD
University of Denver, Denver, colorado, USA

- Caveolae buffer mechanical strain in endothelial cells during morphogenesis
- EHD2 maintains polarized caveolae localization in 2D and 3D endothelial contexts
- EHD2 modulates Rac1/RhoA signaling, impacting vascular sprouting and morphogenesis

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Vascular smooth muscle LIM kinase inhibition attenuates tissue transglutaminase-dependent actin polymerization induced by mechanical stretching

Olubodun M. Lateef M.Sc.[1,2], Francisco I. Ramirez-Perez Ph.D.[1], Gavin Power M.Sc.[1,3], Marc Augenreich M.Sc.[1,3], Jaume Padilla Ph.D.[1,3,4], Luis A. Martinez-Lemus DVM, Ph.D[1,2,5]
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- Stretching-induced F-actin formation and VSMC stiffening require TG2 activity.

- TG2 and LIMK inhibition attenuates stretching-induced increases in F-actin and VSMC stiffness.
- LIMK inhibition abrogates arterial stiffening in isolated mesenteric arteries treated with L-NAME.

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Mechanosensitive BBB modeling reveals glycocalyx-driven neurovascular damage

Nicholas R O'Hare BS[1], Benjamin D Peck BS[1], Lucas McCauley[1], Karina Millican BS[1], Eno E Ebong PhD[1,2]
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- The glycocalyx is a multifunctional regulator of brain microvessel integrity.
- Mechanosensitive blood–brain barrier model enables discovery of glycocalyx - driven mechanisms.
- Different glycocalyx proteins have distinct roles in maintaining BBB stability

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Endothelial Nucleoporin93 maintains Sun1 expression for proper flow-induced cellular alignment

Julia Michalkiewicz[1,2], Tung D Nguyen PhD[1,2], Minsoo Kim MS[1], Michael A. Winek MS[1], Monica Y. Lee PhD[1,2]
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- Shear stress induces the formation of nuclear actin/LINC/lamin (ALL) lines in ECs.
- Nup93 loss reduces Sun1 levels, impairing flow-induced ALL line formation and actin alignment.
- Restoring Sun1 rescues flow alignment, identifying a Nup93-Sun1 axis in EC mechanotransduction.

ADVANCED MOLECULAR MECHANISMS IN VASCULAR MATRIX REMODELING

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Functional profiling of SCAD-associated genes reveals disruption of ECM and cell morphology in human vascular cells

Emily E Bramel PhD[1], Carmen Diaz Verdugo PhD[1], Avanthi Raghavan MD[1,2], Tiffany R Bellomo MD[1,2], Whitney Hornsby PhD[2], Sara Haidermota BS[2], Patrick T Ellinor MD, PhD[1,2], Pradeep Natarajan MD, MMSc[1,2], Mark E Lindsay MD, PhD[1,2]
[1]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [2]Massachsetts General Hospital, Boston, MA, USA

- SCAD gene deletions alter ECM structure and cell morphology in human fibroblasts and VSMCs.
- High-content imaging links gene loss to features of arterial fragility.
- Functional profiling reveals shared and distinct effects of SCAD genes in vascular cells.

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Role of endothelial Nck1 in atherosclerosis

Cyrine Ben Dhaou PhD, Wayne Orr PhD
LSU Health Shreveport, Shreveport, LA, USA

- Endothelial Nck1 deletion lowers plaques and inflammation despite greater weight gain.
- Nck1 loss reduces endothelial inflammation without affecting angiogenesis or perfusion.
- Nck1 drives inflammation via PERK–eIF2α–ATF3; ATF3 loss mimics Nck1 deletion effects.

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BMP1 coronary disease causality and mechanisms of disease risk

João P. Monteiro PhD, Markus Ramste MD, PhD, Quanyi Zhao PhD, Matthew D. Worssam PhD, Brian Palmisano MD, PhD, Chad Weldy MD, PhD, Daniel Li MD, Wenduo Gu PhD, Ramendra K. Kundu PhD, Trieu Nguyen PhD, Thomas Quertermous MD
Stanford University, Stanford, CA, USA

- BMP1 expression is inversely correlated to CAD risk
- BMP1 drives ECM remodeling through the TGF-β1 pathway
- BMP1 loss risks fibrous cap weakening and rupture.

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CRK/CRKL regulate embryonic angiogenesis by maintaining formation of tip cells and modulating MAP4K4 signaling in mammals

Lijie Shi Ph.D., Gloria Stoyanova MS, Hansoo Song Ph.D., Jennifer T. Aguilan Ph.D., Simone Sidoli Ph.D., Bernice Morrow Ph.D.
Albert Einstein College of Medicine, Bronx, NY, USA

- Crk/Crkl are required in endothelial cells for embryonic angiogenesis and blood vessel integrity.
- Crk/Crkl regulate endothelial tip cell formation during mouse embryonic angiogenesis.
- CRK/CRKL may regulate angiogenesis and blood vessel integrity via modulating MAP4K4/cJUN signaling.

NEUROINFLAMMATION

38

Pde4b activity and vascular association correlate with immune-like oligodendrocytes in chronic stress

Miguel M Madeira PhD[1], Zachary Hage PhD[1], Dimitris Koliatsis BS[1], Laurel E Schappell MS[1], Neil Nadkarni MD[1], Antonis E Koromilas PhD[2], Styliani E Tsirka PhD[1]
[1]Stony Brook University, Stony Brook, NY, USA. [2]McGill University, Montreal, Quebec, Canada

- Pde4b links stress to immune-like oligodendrocytes via cAMP and ISR pathways.
- Vascular proximity associates with pro-inflammatory oligodendrocyte morphology.

- Pde4 inhibition blocks IFNγ-driven MHCII and may restore oligodendrocyte health.

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Myeloid β2-adrenergic receptors mediate neuroimmune signaling to prime aortic stiffness

Jae Min Cho[1], Khoa Vu[1], Seul-Ki Park[1], Enbo Zhu[1], Peng Zhao[1], Yang Kevin Xiang[1], Ying H Shen[2], Mark W Chapleau[3], Tzung Hsiai[1]
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- β2-AR signaling in macrophages activates adventitia fibroblast activation and aortic stiffness
- Exercise reduces Ang II–induced neuroimmune activation and extracellular matrix deposition
- Myeloid-specific β2-AR deletion mitigates aortic remodeling and pulse wave velocity increases

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Microglia and neutrophils reciprocally mediate unique post-stroke spatial patterning independent of infarct topology

Laurel E Schappell MS, Miguel M Madeira PhD, Meiyi Tang PhD, Stella E Tsirka PhD, Neil A Nadkarni MD
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- Microglia and neutrophils follow cell-specific recruitment patterns in acute ischemic stroke.
- Innate immune cell spatial patterning is not confined to the boundaries of neuronal injury.
- Microglial localization is influenced by the degree of neutrophil infiltration.

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A high-throughput human Blood-brain barrier (BBB)-on-a-chip model for drug discovery of anti-inflammatory and barrier restoring agents for neurological disorders

Jade Admiraal[1,2], Arya Leksimi Nair[1], Linda Groenendijk[1], Roos Overdevest[1], Tania Fowke[1], Rumaisha Annida[1], Nick Saites[1], Orsola Mocellin[1], Helga de Vries[2], Nienke Wevers[1]
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- Human T cell migration and adhesion analyzed under inflammatory BBB conditions
- High-throughput microfluidic platform models BBB dysfunction and repair
- Anti-inflammatory biologics reduce T cell adhesion in inflamed BBB-on-chip model

BLOOD VASCULAR DEVELOPMENT

44

The metabolism-regulated transcription factor FOXO1 links nutrient deprivation to the establishment of artery identity

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- FOXO1 is essential for arterial but not venous endothelial cell specification.
- FOXO1 acts during differentiation but is not required to maintain artery identity.
- Acute FOXO1 depletion via dTAG reveals temporal control of arteriovenous fate

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Pioneer factor ETV2 safeguards endothelial cell specification by recruiting the repressor REST to restrict alternative lineage commitment

Danyang Chen Ph.D., Xiaonuo Fan, Ninghe Sun Ph.D., Kai Wang Ph.D., Liyan Gong Ph.D., Juan M. Melero-Martin Ph.D., William T. Pu M.D.
Boston Children's Hospital, Boston, MA, USA

- Single-cell analyses defined the mechanisms by which ETV2 drives endothelial cell specification.
- We identified cofactors that cooperate with ETV2 in EC specification, including the activator GABPA.
- Our study highlights ETV2 recruiting repressors REST to suppress alternative lineage commitment.

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Artery formation is mediated by Esm1+ endothelial cells

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- Our work identifies a critical mechanism of fetal and postnatal artery development.
- Findings could be important for vascular syndromes characterized by insufficient arterial function.
- Arterial progenitor cells have conserved but also organ-specific properties.

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Endothelial Ovol1 regulates angiogenesis via Slug

Kapil Thapa[1], Brandon Burow[1], Shawn Sutherland[1,2,3], Christopher Hughes[4], Jennifer Fang[1]
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- Ovol1 transcriptionally regulates Slug in endothelial cells.
- Ovol1 regulates sprouting angiogenesis in a Slug-dependent manner.
- Ovol1 is required for tumor angiogenesis but is dispensable for developmental angiogenesis.

VASCULAR EXTRACELLULAR MATRIX BIOENGINEERING

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Biological sex influences long term remodeling outcomes of compliance matched vascular grafts

Katarina M Martinet, David R Maestas PhD., Keishi Kohyama MD., Jackie Avila, Leon Min, Reyhaneh Gholami, Kang Kim PhD., William R Wagner PhD., Jonathan P Vande Geest PhD.
University of Pittsburgh, Pittsburgh, PA, USA

- Vascular smooth muscle cell remodeling
- Compliance matched tissue engineered vascular grafts
- Sex as a biological variable

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From human genetics to therapeutics: RNA nanomedicine for cardiovascular and metabolic disease

Yun Fang
The University of Chicago, Chicago, IL, USA

- Human genetics guide vascular regulator selection, boosting cardiovascular drug success
- Polymer/lipid nanoparticles deliver nucleic acids to inflamed endothelium, reducing atherosclerosis.
- Targeting genetic vascular pathways restores homeostasis and alters disease course.

EMERGING TOPICS IN MICROCIRCULATION

55

Paracrine regulation of angiogenesis and coronary microvascular function by cardiac-specific isoform Friend of GATA 2 (FOG2S)

Mansi Kumar MSE, Varun Kanangat, Samantha Wu, Madison George, Donna Conlon PhD, Marie Guerraty MD, PhD
University of Pennsylvania, Philadelphia, PA, USA

- Little is known about the role of FOG2S in vascular biology.
- FOG2S is a cardiomyocyte-specific isoform of FOG2 which regulates angiogenesis in a paracrine manner
- Cardiomyocyte FOG2S regulates coronary microvascular structure and function in vivo.

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Investigating stimuli that elicit pericyte-capillary dissociation in skeletal muscle

Mark A Danesh, George Nader, Anthony Scimè, Tara L Haas
York University, Toronto, Ontario, Canada

- Injury-specific pericyte response - Pericytes activate in ischemic but not cardiotoxin injury
- Novel ex vivo model to assess mechanisms regulating pericyte fate
- Pericyte-capillary interaction is critical to regulating pericyte behaviour

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Calcium influx via Cx43 hemichannels directs eNOS internalization and endothelial hyperpermeability

Pia C Burboa PhD, Veronica A Kuzdowicz MS, Stefany Ordenes MS, Daniela Canales, Mauricio A Lillo PhD
Rutgers New Jersey Medical School, Newark, NJ, USA

- Cx43-HCs boost Ca^{2+} influx, driving Cx43-eNOS–Cav-1 internalization and barrier loss
- Inhibiting Cx43-HCs blocks hyperpermeability without affecting eNOS activation
- Cx43 hemichannel is anything but a “simple pore.”

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Rapid activation of TRPV4 channels by aldosterone in mouse and human vascular smooth muscle cells

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- Aldosterone increases TRPV4 currents in freshly isolated vascular SMC within seconds.
- Aldosterone activation of TRPV4 channels in SMCs occurs through MR signaling.
- Aldosterone activation of TRPV4 channels in SMCs occurs in male and female mice, and in humans.

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Understanding the process and signaling of coronary collateral growth in adult heart by single-cell RNA sequencing

Jian Shi MS[1], Iyanuoluwa Ogunmiluyi MS[1], Molly Enrick BS[1], Bevelyn glen Eglen MS[1], Abygail Deemer[2], Taylor Jansky[2], Yang Wang[3], Blessing Nagy[1], Liya Yin[4]
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- stimuatlion coronary collateral growth in adult hearts
- cardioprotection in ishemic heart diseases
- scRNA seq in coronary vascular development

60

Poor lysosome acidification blunts BK_{Ca} channel activity in the cerebral vasculature of male *5x-FAD* mice

Paige E. Martin MS, Felipe D. Polk, Paulo W. Pires PhD

University of Arizona, Tucson, Arizona, USA

- Lysosomes of cerebral vascular smooth muscle cells in male 5x-FAD mice are poorly acidified.
- Poor lysosomal acidification in CVSMC leads to decreased Ca2+ sparks and BKca activity.
- Recovery of lysosomal acidification partially recovers Ca2+ sparks and BKca activity in CVSMC.

LYMPHATIC VASCULAR DEVELOPMENT

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Adm and Ackr3 regulates cardiac lymphatic vessel formation during zebrafish heart development and regeneration

Xidi Feng, Huiyu Chen, Yuhan Sun, Sean Yan, Ching-ling Lien
Children's Hospital Los Angeles, Los Angeles, CA, USA

- Transcriptomic analysis on zebrafish fish hearts reveals potential regulatory targets for LECs.
- Ackr3a in epithelium regulate Adm signaling in zebrafish cardiac lymphatic development.
- Pre-existing lymphatic affects immune cell clearance during heart regeneration.

65

Erg deletion in lymphatic endothelium protects against bleomycin-induced lung fibrosis

Arun Narota PhD, Tapiwa Muvavarirwa BS, Adri Chakroborty PhD, Maria Trojanowska PhD
Arthritis & Autoimmune Diseases Center, Boston University School of Medicine, Boston, MA, USA

- Erg deletion in LECs improves lymphatic drainage and reduces lung inflammation post-injury.
- Erg-CKO mice show reduced fibrosis and ECM deposition after bleomycin-induced lung injury
- HGF–c-MET axis is upregulated in Erg-deficient LECs, supporting anti-fibrotic lymphatic remodeling

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A novel role for second heart field progenitors in lymphovenous valve formation

Christina Vyzas MA[1], AnnJosette Ramirez PhD[2], Yunping Guo MS[3], Sophie Astrof PhD[3]
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- SHF-derived cells transit through the cardinal vein to contribute to the venous layer of LVVs.
- The expression of Vegfr2 and Prox1 in the SHF are important for proper LVV formation.

- SHF defects causing congenital heart disease may also precipitate abnormal LVV development.

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Metabolic mechanisms regulating lymphatic vascular development

Pengchun Yu Ph.D.
Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

- mTORC1 sustains PROX1 expression and controls lymphatic capillary and collecting vessel development
- Lymphatic endothelial mTORC1 controls glycolysis and glutaminolysis through MYC–HK2/GLS signaling
- Ablation of MYC or HK2/GLS in LECs impairs lymphatic capillary and collecting vessel formation

INNOVATIONS IN VASCULAR TISSUE ENGINEERING

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Kidney organoid vascularization using inducible endothelial cells from human pluripotent stem cells

Yonglin Zhu Ph.D.[1,2], Daniel Tremmel Ph.D.[1,2], Liyan Gong Ph.D.[1,2], Xiang Li Ph.D.[1,2], Umji Lee Ph.D.[1,2], Gwang-Bum Im Ph.D.[1,2], Alex Barutis B.S.[1], Juan Melero-Martin Ph.D.[1,2]
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- Inducible ETV2 activation enables nephron progenitor cell conversion into endothelial cells.
- Induced endothelial cells significantly improve kidney organoid vascularization.
- Podocyte-specific CXCL12 expression directs vascular ingrowth.

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Hemodynamic cues promote hierarchical vascular remodeling and maturation in *in vitro* model of perfusable vascular organoids

Yu Jung Shin Ph.D[1], Yuexin Xu Ph.D[2], Rachel Wellington Ph.D[2], Sam Rayner M.D[1], Christian Mandrycky Ph.D[1], Kyle Loh Ph.D[3], Brandon Hadland M.D/Ph.D[1], Ying Zheng Ph.D[1]
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- Perfusable hVO-microvessel sustain prolonged survival of vascular organoid in vitro.
- Distinct pressure- and flow-driven vascular remodeling in perfusable vascular organoid.
- Arterio-venous capillary network specification during vascular organoid development and remodeling.

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Organ-on-Chip model of the microcirculation in AAA recapitulates aspects of disease

Philipp C Hauger[1], Karlijn B Rombouts[1], Marc Vila Cuenca[2], Max C Overboom[1], Jan Willem Buikema[1], Kak Khee Yeung[1], Valeria V Orlova[2], Peter L Hordijk[1]
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- Development of a novel 3D organ-on-chip co-culture model of the microcirculation in AAA
- Patient derived VSMCs maintain a disease phenotype in vitro and mimic AAA features in a 3D model
- We propose this VoC as alternative to current in vivo models to improve therapeutic translatability

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Reconstructing native soluble cues to enhance endothelial cell maturation in bioengineered whole lung vascular model

Yongdae Yoon PhD, Shannon kirk BS, Konstantin Birukov MD, PhD, Yifan Yuan PhD
University of Maryland School of Medicine, Baltimore, Maryland, USA

- scRNAseq identifies key L/R pairs in the human lung microenvironment.
- Adrenomedullin improves vascular integrity and reduces anti-inflammatory responses.
- Adrenomedullin improves native endothelial phenotypes and functions in engineered vascular models.

HEALTH DISPARITIES AND THE MICROCIRCULATION

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Endothelial-derived Neuregulin 1 modulates pericytes function in heart failure with preserved ejection fraction

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- Neuregulin 1 is upregulated in HFpEF patients
- Endothelial-specific overexpression of NRG1 in mice reduces pericyte coverage and pericyte number
- NRG1 induces pericyte dysfunction by reducing viability and adhesion capacity of pericytes in vitro

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FoxO1 protects female endothelial cells from mitochondrial dysfunction, DNA damage and oxidative stress

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- Endothelial cells behave in a sex-specific manner.
- FoxO1 is necessary in preventing endothelial dysfunction in female endothelial cells.
- Endothelial-specific knockdown of FoxO1 results in whole-body metabolic changes.

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Iron regulates endothelial NO signaling via endothelial a-globin

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- Iron deficiency increases endothelial nitric oxide in female mice via loss of endothelial a-globin
- Males have a higher level of active a-globin than females.
- Genetic deletion of a-globin from the endothelium results in males phenocopying females.

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Matrix Gla protein expression in pericytes and myofibroblasts contributes to renal fibrosis

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- MGP expression is negatively associated with renal function.
- Pericytes in healthy kidneys and myofibroblasts in fibrotic kidneys are the major source of MGP.
- Loss of MGP attenuates renal fibrosis followed by folic acid injury.

METABOLISM AND VASCULAR DYSFUNCTION

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HIV Nef extracellular vesicles impair macrophage efferocytosis via epigenetic regulation of Btk-NFκB-MerTK to promote atherosclerosis

Sarvesh Chelvanambi[1], Julius Decano[1], Yuto Nakamura[1], Constance Delwarde[1], Cassandra Clift[1], Francesca Bartoli-Leonard[1], Prabhash Jha[1], Adrien Lupieri[1], Takashi Enomoto[1], Joan Matamalas[1], Shin Mukai[1], Diego Santinelli-Pestana[1], Rile Ge[1], Mary Whelan[1], Katelyn Perez[1], Shiori Kuraoka[1], Shannan Ho Sui[2], Ira Tabas[3], Sasha Singh[1], Elena Aikawa[1], Masanori Aikawa[1]
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- HIV viral protein Nef persists within extracellular vesicles (EV) even in ART treated HIV patients.
- Nef EV reprogram macrophage heterogeneity through epigenetic regulation.
- Nef EV impairs efferocytosis capabilities of macrophage to promote atherosclerosis.

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Resolvin D2 limits senescent cell accumulation in atherosclerotic plaques

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- Resolvin D2 mediates inflammation resolution in atherosclerosis and limits its progression.
- Senescent cell accumulation and necrosis in plaques is reduced with the help of Resolvin D2.
- In vitro senescent cells are efficiently cleared when incorporating Resolvin D2 as a treatment.

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Extracellular matrix-related genes, such as Cthrc1, are potential targets in pulmonary hypertension

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- scRNA-seq identifies molecular signature of SMC expansion (e.g., enhanced ECM pathways) with PH.
- Pharmacological or genetic CTHRC1 inhibition reduces pulmonary vascular remodeling, RVH and PH.
- Overexpression of CTHRC1 in SMCs promotes distal pulmonary arteriole muscularization and PH.

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Putrescine synthesis drives smooth muscle cell differentiation in a myocardin-dependent manner

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- Reductions in putrescine correlate with atherosclerosis progression and plaque instability in humans
- Putrescine limits phenotypic modulation of SMC by driving myocardin expression
- Putrescine deficiency in SMCs worsens pathologic vascular remodeling and drives atherosclerosis

GENETICS IN VASCULAR INFLAMMATION

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The tryptophan metabolite indoxyl sulfate promotes vascular dysfunction by impairing anti-atherogenic macrophage functions in chronic kidney disease

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- Indoxyl sulfate, a tryptophan-derived uremic toxin, impairs key macrophage functions
- Indoxyl sulfate suppresses the GAS6-STAT6 axis to drive macrophage and vascular dysfunction
- Clinical correlation confirms Indoxyl sulfate-GAS6 link in CKD patients

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TMEM16F regulates multiple aspects of the endothelial cell response to inflammation

Allison Gabbert PhD, Kobe Tray BA, Ivan Aivasovsky MD, Alec Schmaier MD/PhD
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- TMEM16F regulates the expression of over 1000 genes. Many are involved in inflammatory signaling.
- TMEM16F is required for cytokine expression in cell and mouse models of inflammation.
- TMEM16F may regulate cell cycle progression through upregulation of G2/M checkpoint inhibitors.

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Interleukin-1 receptor-activated Kinase-1 in disturbed flow-induced vascular remodeling and atherosclerosis progression

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- IRAK1 in d-flow-induced Atherogenic EndMA
- IRAK1 inhibition reduces plaque burden and inflammation in atherosclerosis
- Targeting IRAK1 stabilizes atherosclerotic lesions

GENETIC DRIVERS OF VASCULAR MALFORMATIONS

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Signaling changes in LOH cells contribute to loss of vessel integrity in Hereditary Hemorrhagic Telangiectasia

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- modeling patient biallelic loss
- mouse models of HHT
- signaling profiles of cells in AVMs

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Loss of TBX4 alters smooth muscle contractility and induces endothelial dysfunction in pulmonary arterial hypertension

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- TBX4 mutations change gene expression and function in smooth muscle cells (SMCs).
- TBX4-deficient SMCs cause endothelial dysfunction via disrupted BMP and Notch signaling.
- Increasing TMEM100 in endothelial cells decreases the proliferation of co-cultured TBX4-mutant SMCs.

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MYC-induced hypertranscription contributes to brain arteriovenous malformation

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- Endothelial cells with KRAS-G12V mutation are in a state of hypertranscription.
- Increased ribosome biogenesis, global RNA, and protein synthesis in mutant endothelial cells..
- MYC identified as a regulator of hypertranscription in endothelial cells expressing KRAS-G12V.

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MEK signaling represents a viable therapeutic vulnerability of KRAS-driven somatic brain arteriovenous malformations

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- KRAS mutations in endothelial cells drive bAVM vascular remodeling via MAPK/ERK signaling cascade.
- MRI shows that the MEK inhibitor trametinib may stabilize or regress existing bAVMs in mice.
- ECs within bAVMs display defects in flow responsiveness and junctional protein localization.

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Endothelial Notch4 and Notch1 in retinal angiogenesis

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- Endothelial Notch4 and endothelial Notch1 share overlapping roles in vascular sprouting.
- Endothelial Notch4 has a distinct role from Notch1 in regulating vascular remodeling.
- Endothelial Notch4 may be involved in angiocrine signaling to perivascular cell populations.

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An endothelial SOX18-mevalonate pathway axis enables novel targeted therapies for vascular anomalies

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- The SOX18-MVP-axis as a central endothelial metabolic regulator enabling drug repurposing
- Novel pleiotropic effects of β-blockers and statins inhibit vasculogenesis and angiogenesis
- Statins demonstrate clinical benefit to treat infantile hemangioma and venous malformations