12TH ANNUAL SYMPOSIUM

Cardiovascular Research Institute

APRIL 9, 2025

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ABOUT THE **CVRI**

CVRI MISSION

The Cardiovascular Research Institute was established in 2012 to enhance collaborative opportunities for research, promote the development of new cardiovascular technologies and to expand training programs in cardiovascular sciences. The CVRI aims to provide administrative and research support to promote synergy for interdisciplinary basic, translational and clinical research.

SYMPOSIUM & SEMINAR COMMITTEE CHAIR

Lilei Zhang, M.D., Ph.D.
Associate Professor
Molecular and Human Genetics
Baylor College of Medicine

SYMPOSIUM & SEMINAR COMMITTEE

David Durgan, Ph.D.
Mirza Umair Khalid, M.D.
Riyad Kherallah, Ph.D.
William Lagor, Ph.D.
Na Li, Ph.D.
Xiao Li, Ph.D.
A.J. Marian, M.D.
James Martin, M.D., Ph.D.
Azeez Mulli, Ph.D.
Jack Price, M.D.
Jeffrey Steimle, Ph.D.
Xander Wehrens, M.D.., Ph.D.
Richelle Ouch
Tyler Robinson

SESSION CHAIRS

SESSION I Michael Bround, Ph.D.
SESSION II Na Li, M.D., Ph.D.
SESSION III Diwakar Turaga, M.D., Ph.D.
SESSION IV Mihail Chelu, M.D., Ph.D.

FROM THE DIRECTOR

Dear Colleagues,

It is with great pleasure that I welcome you to the 12th Annual Symposium of the Cardiovascular Research Institute (CVRI) at Baylor College of Medicine.

The CVRI at Baylor College of Medicine was founded in 2012. One of its core missions is to promote innovative research by facilitating new collaborations across the various BCM departments and affiliated hospitals, as well as throughout other institutions in the Texas Medical Center.

This year, CVRI is honored to feature distinguished keynote speaker Patrick Ellinor, M.D., Ph.D., from Mass General Brigham. Dr. Ellinor is the Executive Director of the Heart and Vascular Institute at Mass General Brigham and a Professor of Medicine at Harvard Medical School. At the Broad Institute of MIT and Harvard, he is an Institute Member and the Director of the Cardiovascular Disease Initiative. His research areas include cardiovascular disease genetics, single cell sequencing, the application of machine learning to cardiac imaging data and the development of new therapies for cardiovascular diseases. He has trained more than 100 students, postdoctoral fellows and junior faculty members over the last 20 years. He was the recipient of an NIH K24 award for more than a decade and he is the co-PI of the T32 award at the MGH. In 2023, he received the Distinguished Scientist Award from the Heart Rhythm Society and the American Heart Association.

On behalf of the organizing committee, I hope you enjoy the symposium and that it provides a great opportunity to meet and network with colleagues and trainees interested in cardiovascular research.

Sincerely,

Xander Wehrens, M.D., Ph.D.
Director, Cardiovascular Research Institute
Baylor College of Medicine

CME INFORMATION

NEEDS STATEMENT

The rapidly evolving landscape of cardiovascular research and technology has created a critical need for healthcare professionals to stay informed about new evidence and emerging innovations. Despite advances in care, significant knowledge gaps and practice deficits persist, particularly in the management of heart failure and care of older adult populations (Wang et al., 2024; Rich et al., 2016). These gaps can lead to suboptimal patient outcomes and decreased quality of life. This symposium aims to address these gaps by showcasing cutting-edge cardiovascular research, facilitating collaboration and providing a platform for discussion on the application of emerging diagnostic and imaging techniques. By translating research into clinical practice, healthcare professionals can improve patient care and outcomes in cardiovascular medicine.

TARGET AUDIENCE

This activity is for physicians, Ph.D. faculty, residents, fellows, medical students, graduate school trainees and other healthcare professionals.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the participant should be able to:

- Describe the impact of genetic mutations on congenital heart disease risk.
- Analyze the potential benefits and limitations of gene editing-based approaches for treating congenital heart disease.
- Evaluate the role of fibrinogen in thromboinflammation and its implications for patient management and outcomes.
- Explain the role of vascular endothelium in maintaining metabolic homeostasis and its impact on cardiovascular health.

EDUCATIONAL METHODS

Lecture

EVALUATION

Evaluation by questionnaire will address program content, presentation, and possible bias.

CME INFORMATION

ACCREDITATION/CREDIT DESIGNATION

Baylor College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Baylor College of Medicine designates this live activity for a maximum of 3.50 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

OBTAINING CREDIT

Two (2) business days after the course, an email will follow from the Baylor College of Medicine, Division of Continuing Professional Development with instructions for completing the evaluation and obtaining your CME Certificate, CE Certificate or Certificate of Attendance.

Contact Information

Baylor College of Medicine
Division of Continuing Professional Development
One Baylor Plaza, MS: BCM 155
Houston, TX 77030-3411

Email: cpd@bcm.edu
Phone: 713.798.8237
Fax: 713.798.7955

Visit our website at **cpd.education.bcm.edu** for information about additional CME activities.

DRUG/DEVICE STATUS DISCLOSURE

Some drugs/devices identified during this activity may have United States Food and Drug Administration (FDA) clearance for specific purposes only or for use in restricted research settings. The FDA has stated that it is the responsibility of the individual physician to determine the FDA status of each drug or device that he/she wishes to use in clinical practice and to use the products in compliance with applicable law.

Baylor College of Medicine requires that all faculty/presenters disclose an unlabeled use or investigational use of pharmaceutical and medical device products, as well as provide adequate scientific and clinical justification for such use. Physicians are urged to fully review all the available data on products or procedures before using them to treat patients.

CME INFORMATION

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITH COMMERCIAL INTERESTS

DISCLOSURE POLICY

Baylor College of Medicine (BCM) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education (CME) for physicians. BCM is committed to sponsoring CME activities that are scientifically based, accurate, current, and objectively presented.

In accordance with the ACCME Standards for Commercial Support, BCM has implemented a mechanism requiring everyone in a position to control the content of an educational activity (i.e., directors, planning committee members, faculty) to disclose any relevant financial relationships with commercial interests (drug/device companies) and manage/resolve any conflicts of interest prior to the activity. Individuals must disclose to participants the existence or non-existence of financial relationships at the time of the activity or within 24 months prior.

In addition, BCM has requested activity faculty/presenters to disclose to participants any unlabeled use or investigational use of pharmaceutical/device products; to use scientific or generic names (not trade names) in referring to products; and, if necessary to use a trade name, to use the names of similar products or those within a class. Faculty/presenters have also been requested to adhere to the ACCME's validation of clinical content statements.

BCM does not view the existence of financial relationships with commercial interests as implying bias or decreasing the value of a presentation. It is up to participants to determine whether the relationships influence the activity faculty with regard to exposition or conclusions. If at any time during this activity you feel that there has been commercial/promotional bias, notify the Activity Director or Activity Coordinator. Please answer the questions about balance and objectivity in the activity evaluation candidly.

All of the relevant financial relationships listed for these individuals have been mitigated

CME INFORMATION

DISCLOSURES

FACULTY	PLANNING COMMITTEE	PRESENTER	DISCLOSURE
Thomas Cooper, M.D. Assistant Professor Baylor College of Medicine		●	Nothing to disclose
Patrick Ellinor, M.D., Ph.D. Executive Director Mass General Brigham Professor of Medicine Harvard Medical School		●	Research Support: Bayer AG; Pfizer; BMS; Novo-Nordisk; Speaker Honorarium: Bayer AG.
Yun Huang, Ph.D. Professor, Associate Director Institute of Bioscience and Technology Texas A&M University		●	Nothing to disclose
Nandan Kumar Mondal, MSc, MPhil, Ph.D. Associate Professor Baylor College of Medicine		●	Nothing to disclose
Hongjie Li, Ph.D. Assistant Professor Baylor College of Medicine		●	Nothing to disclose
Richelle Ouch, BBA Business Operations Sr. Coordinator Baylor College of Medicine	●		Nothing to disclose
Kriti Puri, M.D. Assistant Professor Baylor College of Medicine Texas Children's Hospital		●	Nothing to disclose
Tyler Robinson, BBA Senior Business Operations Associate Baylor College of Medicine	●		Nothing to disclose
Abul Hassan Samee, Ph.D. Associate Professor Baylor College of Medicine		●	Nothing to disclose
Daryl Scott, M.D., Ph.D. Professor Baylor College of Medicine		●	Nothing to disclose
Joseph Spinner, M.D. Assistant Professor of Pediatrics Baylor College of Medicine Texas Children's Hospital		●	Research Support: Enduring Hearts Consultant: Cobicure Advisory Committee: Bayer; Speaker Honorarium: Rocket Pharmaceuticals (ended in the past 24 months)
Xander Wehrens, M.D., Ph.D. – Activity Director Cardiovascular Research Institute Baylor College of Medicine	●	●	Consultant: Rocket Pharmaceuticals, Topic: Heart Disease, Relationships end date: 06/30/2025.
Liang Xie, Ph.D. Assistant Professor Baylor College of Medicine		●	Nothing to disclose

CME INFORMATION

DISCLAIMER

This activity is designed for healthcare professionals for educational purposes. Information and opinions offered by the faculty/presenters represent their own viewpoints. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information.

While Baylor College of Medicine makes every effort to have accurate information presented, no warranty, expressed or implied, is offered. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision making before applying any information, whether provided here or by others, for any professional use.

Faculty/presenters have submitted materials for this syllabus for printing in advance so that you may have an outline or summary of the main points of their presentation. Often this differs from the final version of their slides as faculty/ presenters make revisions up until the day of the meeting.

Additionally, some images (cartoons, drawings and some photographs) shown on the screen may not be present in your educational materials because of publishers' requirements for reprinting of copyrighted images.

NOTICES

Faculty, topics, program schedule, and credit are subject to change.

Audio or videotaping is prohibited without written permission from the Activity Directors and the Division of Continuing Professional Development, Baylor College of Medicine, Houston, Texas.

DR. MARK L. ENTMAN AWARD FOR EXCELLENCE IN CARDIOVASCULAR EDUCATION

Mark L. Entman, M.D.
Distinguished Professor
Emeritus of Medicine,
Biochemistry and Pathology
Baylor College of Medicine

The Dr. Mark L. Entman Award for Excellence in Cardiovascular Education was established in 2021 by the Cardiovascular Research Institute (CVRI) at Baylor College of Medicine to recognize faculty members for outstanding teaching and service in the graduate school curriculum.

In honor of Dr. Entman's extensive contributions to cardiovascular education and research at Baylor College of Medicine, the CVRI will present these prestigious awards at the annual symposium.

Dr. Entman was recruited to Baylor as an Assistant Professor in 1970. He was a Howard Hughes Medical Investigator from 1971-1979. In 1977, Dr. Entman became the Chief of the Section of Cardiovascular Sciences and the Director of the Division of Research of the NHLBI National Research and Demonstration Center (now the DeBakey Heart Center) at Baylor College of Medicine and The Methodist Hospital from 1976-1985. Dr. Entman has been an inspirational leader whose research has spanned a range of topics, including the role of myocardial calcium and sarcoplasmic reticulum function, acute inflammation and myocardial injury, and the chronic inflammatory response in cardiac repair and remodeling.

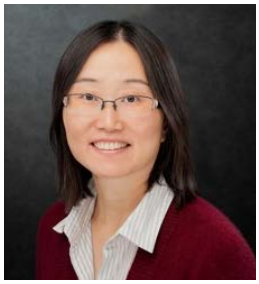
Before joining Baylor faculty, Dr. Entman's training at Duke University involved matriculation in the highly innovative Research Training Program designed to promote the proper background for cellular and molecular research for M.D.'s seeking a career in academic medicine. In 1974, his former mentor at Duke, Dr. Salih Wakil, joined the Baylor faculty as Chairman of Biochemistry and the two collaborated in writing the NIH training grant to establish the M.D./Ph.D. Program at Baylor, of which Dr. Entman was a co-director until 1980. In 1978, Dr. Entman became the Director of the Section of Cardiovascular Sciences in the Department of Medicine and he was paramount in the new development of that program. The core curriculum for the DeBakey Heart Center Graduate Program arose from those efforts and was funded for many years by an NIH training grant which supported an independent graduate program directed by his colleague and close friend, Dr. Julius Allen. The resources of this program also provided the structure of a Basic Science Training program in Pediatric Cardiology at Texas Children's Hospital which was financed by an independent NIH training program.

Dr. Entman has given countless lectures to trainees on the Cardiovascular Sciences Ph.D. Track and has been dedicated to furthering the educational mission at Baylor College of Medicine. Dr. Entman has mentored over 50 physician-scientists and researchers, many of whom are now leading cardiology departments and research programs across the US and world. His enthusiasm and commitment to the educational programs at Baylor College of Medicine is revered among his trainees and peers.

SPEAKERS

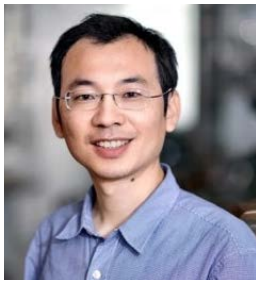
Thomas Cooper, M.D.

Professor
Baylor College of Medicine



Yun Huang, Ph.D.

Professor, Associate Director
Institute of Bioscience and Technology
Texas A&M University



Hongjie Li, Ph.D.

Assistant Professor
Baylor College of Medicine

Nandan Kumar Mondal, MSc, MPhil, Ph.D.

Associate Professor
Baylor College of Medicine

Kriti Puri, M.D.

Assistant Professor
Baylor College of Medicine
Texas Children's Hospital

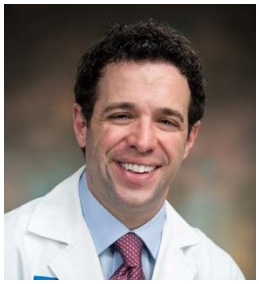
SPEAKERS

Md. Abul Hassan Samee, Ph.D.

Associate Professor
Baylor College of Medicine

Daryl Scott, M.D., Ph.D.

Professor
Baylor College of Medicine

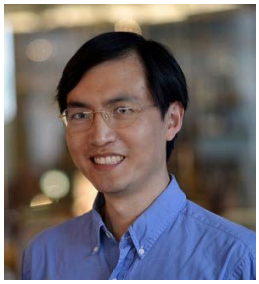


Joseph Spinner, M.D.

Assistant Professor of Pediatrics
Baylor College of Medicine
Texas Children's Hospital

Xander Wehrens, M.D., Ph.D. – Activity Director

Director, Cardiovascular Research Institute
Professor, Baylor College of Medicine



Liang Xie, Ph.D.

Assistant Professor
Baylor College of Medicine

12TH ANNUAL SYMPOSIUM
Cardiovascular Research Institute

8 a.m. — **REGISTRATION**

8:30 a.m. — **WELCOME & OPENING REMARKS**
Xander Wehrens, M.D., Ph.D.
Professor, Department of Integrative Physiology, Medicine/Cardiology
Director, Cardiovascular Research Institute
Baylor College of Medicine

8:40 – 10 a.m. — **SESSION I**

Moderator: Michael Bround, Ph.D.
Assistant Professor, Department of Integrative Physiology
Baylor College of Medicine

8:40 – 9 a.m. — **"Time Flies, How? Unlocking the Secrets of Aging"**
Hongjie Li, Ph.D.
Assistant Professor and CPRIT Scholar, Huffington Center of Aging
Department of Molecular and Human Genetics
Baylor College of Medicine

9 – 9:20 a.m. — **"TET2 Loss-of-Function-Mediated Genome Instability and Clonal Hematopoiesis"**
Yun Nancy Huang, Ph.D.
Professor and Associate Director, Center of Epigenetics and Disease Prevention
Institute of Biosciences and Technology
Texas A&M University

9:20 – 9:40 a.m. — **"SCN5A Dysregulation & Cardiac Manifestations of Myotonic Dystrophy Type 1"**
Thomas A. Cooper, M.D.
Professor, Department of Pathology and Immunology
Baylor College of Medicine

9:40 – 10 a.m. — **"Modulating Regulated Cell Death Pathways & Paradigm Shift for DCD Heart Transplants"**
Nandan Kumar Mondal, MS, MPhil, M.D.
Assistant Professor, Michael E. DeBakey Department of Surgery
Cardiothoracic Transplantation and Circulatory Support
Baylor College of Medicine

10 – 11 a.m. — **POSTER SESSION I**

AGENDA

11 a.m. – Noon	**SESSION II**
	Moderator: Na Li, Ph.D. Professor, Department of Medicine Section of Cardiovascular Research Baylor College of Medicine
11 a.m. – Noon	**KEYNOTE** **"Morphological Profiling to Identify New Genes for Heart Failure"** **Patrick Ellinor, M.D., Ph.D.** Executive Director, Heart and Vascular Institute Mass General Brigham
Noon - 1:20 p.m.	**POSTER SESSION II & LUNCH**
1:20 – 2:20 p.m.	**SESSION III**
	Moderator: Diwakar Turaga, M.D., Ph.D. Assistant Professor, Department of Pediatrics Texas Children's Hospital/Baylor College of Medicine
1:20 – 1:40 p.m.	**"Comparative Modeling of Spatial and Single-Cell Transcriptomics Data"** **Md. Abul Hassan Samee, Ph.D.** Associate Professor, Department of Integrative Physiology Baylor College of Medicine
1:40 – 2 p.m.	**"Iron Deficiency in Children with Heart Disease - Beyond the Blood"** **Kriti Puri, MBBS** Assistant Professor, Department of Pediatrics Divisions of Pediatric Critical Care Medicine and Cardiology Texas Children's Hospital/Baylor College of Medicine
2 – 2:20 p.m.	**"Innovations in Pediatric Heart Transplantation"** **Joseph Spinner, M.D.** Assistant Professor, Department of Pediatrics Baylor College of Medicine Associate Medical Director of Heart Failure and Transplant Texas Children's Hospital
2:20 – 3:20 p.m.	**POSTER SESSION III**

AGENDA

3:20 – 4:20 p.m.	**SESSION IV**
	Moderator: Mihail Chelu, M.D., Ph.D. Professor, Department of Medicine Baylor College of Medicine
3:20 – 3:40 p.m.	**"Unraveling the Mechanisms of Post-Operative Atrial Fibrillation"** **Xander H.T. Wehrens, M.D., Ph.D.** Professor, Department of Integrative Physiology, Medicine/Cardiology Director, Cardiovascular Research Institute Baylor College of Medicine
3:40 – 4 p.m.	**"CRAT Links Cholesterol Metabolism to Innate Immune Responses in the Heart"** **Liang Xie, Ph.D.** Assistant Professor, Cardiovascular Research Institute Section of Cardiovascular Research Department of Medicine Baylor College of Medicine
4 – 4:20 p.m.	**"Using Human Data, Mouse Models and Machine Learning to Identify Novel CHD/CDH Genes"** **Daryl A. Scott, M.D., Ph.D.** Professor, Department of Molecular & Human Genetics Baylor College of Medicine
4:20 – 4:40 p.m.	**AWARDS CEREMONY & CLOSING REMARKS** **Lilei Zhang, M.D., Ph.D** **Xander HT Wehrens, M.D., Ph.D.**
4:40 – 5:15 p.m.	**RECEPTION & POSTER VIEWING**

KEYNOTE SPEAKER
PATRICK T. ELLINOR, M.D., PH.D.

Patrick T. Ellinor, M.D., Ph.D.
Executive Director, Heart and Vascular Institute
Mass General Brigham

Although I was born in a suburb of Boston, I was raised in Cincinnati and graduated from the University of Cincinnati with a degree in Biology. I then moved from the Midwest to the West coast to attend Stanford University for medical and graduate school. My doctoral work focused on the on the structure and function of calcium channels in the laboratory of Dr. Richard Tsien. In 1996, I came to Boston for medical residency at Brigham and Women's Hospital followed by fellowship training in cardiology and cardiac electrophysiology at Massachusetts General Hospital. In 2001, I joined the faculty at MGH and split my time between research and the clinical care of patients with arrhythmias. In 2016, I became the director of the Demoulas Center for Cardiac Arrhythmias at MGH, and I am a Professor of Medicine at Harvard Medical School. At the Broad Institute of MIT and Harvard, I am an Institute Member and the Director of the Cardiovascular Research Initiative. In 2022, I became the acting chief of cardiology and co-director of the Corrigan-Minehan Heart Center at MGH. In 2024, I was named as the inaugural Executive Director of the Heart and Vascular Institute at Mass General Brigham.

I have always been intrigued with human genetics, so my research lab began with an initial focus on trying to identify the genetic basis of early-onset atrial fibrillation. This work in turn led the establishment of the AFGen Consortium, an international group of investigators studying the genetics of atrial fibrillation. In the ensuing years, we have led large-scale genetic analyses for atrial fibrillation and many other cardiovascular diseases. My lab is now largely based at the Broad Institute and has expanded to a wide range of topics that includes cardiovascular disease genetics, disease mechanisms, single cell sequencing, the application of machine learning to cardiac imaging data, and the development of new therapies for cardiovascular diseases.

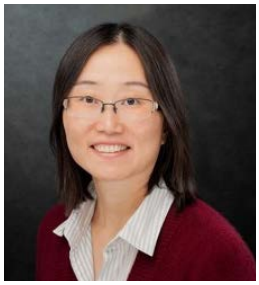
Outside of work, I enjoy spending time with our two boys and our cute, but rather clueless dog as well as reading, sailing, and working as a part-time contractor around the house.

SPEAKER BIOGRAPHIES

Thomas A. Cooper, M.D.

Professor
Department of Pathology and Immunology
Baylor College of Medicine

Dr. Tom Cooper is currently a Professor in the Departments of Pathology and Immunology, Molecular and Cell Biology and Molecular Physiology and Biophysics at Baylor College of Medicine. Tom Cooper obtained his medical degree from Temple University Medical School in Philadelphia, PA then obtained post-doctoral training at the University of California, San Francisco before joining the faculty of Baylor College of Medicine. Dr. Cooper's laboratory uses expertise in RNA biology as well as mouse and cell culture models to investigate the molecular mechanisms by which the RNA gain function in myotonic dystrophy type 1 causes skeletal muscle wasting, cardiac, brain, and gastrointestinal features. Because the toxic RNA gain of function contributing to myotonic dystrophy pathogenesis disrupts postnatal RNA processing transitions, his laboratory also investigates the normal roles of RNA processing in postnatal development of the affected tissues.

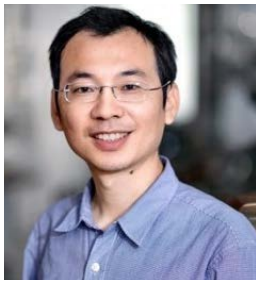


Yun Nancy Huang, Ph.D.

Professor and Associate Director
Center of Epigenetics and Disease Prevention
Institute of Biosciences and Technology
Texas A&M University

Dr. Yun Nancy Huang is a professor and associate director at the center of Epigenetics and Disease prevention at Institute of Bioscience and Technology, and the Department of Translational Medical Sciences at the School of Medicine, Texas A&M University (TAMU). She received her Ph.D. in 2009 and further continued her postdoctoral training as a Leukemia & Lymphoma Society Fellow in Dr. Anjana Rao's group at Harvard Medical School and the La Jolla Institute for Immunology. In 2014, Dr. Huang joined TAMU as the CPRIT scholar. Her research interests are centered on epigenetics, focusing on cardiovascular diseases, cancer and aging. With over 120 peer-reviewed publications garnering 13,500+ citations (H-index of 49), her work has been featured in top-tier journals, including Nature, Nature Cell Biology, Nature Aging, Nature Nano, and Nature Chemical Biology. Dr. Huang's discoveries in epigenetic modifications and their implications in disease have been spotlighted in various media outlets, including American Society of Hematology News and Nature News. Her innovative research earned her recognition as a "Scientist to Watch" by The Scientist Magazine and an American Cancer Society Research Scholar. Her additional accolades include the Rising Star Award from the American Medical Professional Foundation, the Cancer Fighter of Houston Foundation Award, the Excellence in Research Award from TAMU-SOM, and the distinguished Mary Beth Maddox Award and Lectureship by The Academy of Medicine, Engineering & Science of Texas (TAMEST).

SPEAKER BIOGRAPHIES



Hongjie Li, Ph.D.

Assistant Professor and CPRIT Scholar
Huffington Center on Aging
Department of Molecular and Human Genetics
Baylor College of Medicine

Hongjie Li obtained his Ph.D. degree from the University of Rochester under the mentorship of Dr. Henri Jasper and got his postdoctoral training with Dr. Liqun Luo at Stanford University. Hongjie started his lab in 2021 at Baylor College of Medicine (BCM). He is an assistant professor and CPRIT Scholar in Huffington Center on Aging & Department of Molecular and Human Genetics. He pioneered the use of single-cell and single-nucleus RNA sequencing in Drosophila (2017 Cell; 2021a eLife), and has been leading the Fly Cell Atlas project (2022 Science). His lab recently established the Aging Fly Cell Atlas for studying whole organism aging at cellular resolution (2023 Science). His current research focuses on applying single-cell sequencing technologies to understand whole-organism aging and inter-tissue communication during aging. His achievements have been recognized by receiving several awards, including the Stanford Neuroscience Institute Interdisciplinary Award, NIH K99/R00 Award, Cancer Prevention and Research Institute of Texas (CPRIT) Award, Ted Nash Long Life Foundation Award, and NIH Director's New Innovator Award DP2

Nandan Kumar Mondal, MS, MPhil, Ph.D.

Assistant Professor
Michael E. DeBakey Department of Surgery
Cardiothoracic Transplantation and Circulatory Support
Baylor College of Medicine

Dr. Mondal is an Assistant Professor in the Department of Surgery at Baylor College of Medicine. He also holds faculty affiliate positions at Rice University's Center for Applied Algorithms and Regenerative Medicine Research at Texas Heart Institute. With over 20 years of experience as a dedicated basic scientist and biomedical research investigator, Dr. Mondal has committed to making significant contributions to heart failure, heart transplants, circulatory support, and other cardiac surgeries. Dr. Mondal's extensive expertise and training in human subject research, clinical science and translational research, with a particular emphasis on precision medicine, molecular biology, biomedical informatics and machine learning, have positioned him to push the boundaries of what's possible in improving the lives of those suffering from cardiovascular disease. Dr. Mondal has a successful research and teaching career, securing funding as a principal investigator for 10 grants and as a co-investigator for 21, totaling 31 grants. He has published over 100 research articles and conference abstracts. Dr. Mondal has received numerous awards for his excellence in teaching and research, including the prestigious Norton Rose Fulbright Faculty Excellence Award (Teaching & Evaluation), the American Heart Association Innovation Research Award, the Nancy Chang Research Excellence Award, the SOAR Research Mentor Champion Award, the Jay N. Cohn Young Investigator Award, the Satu Somani Scientist Award, and multiple travel and presentation awards. Dr. Mondal leads a diverse research team that includes research coordinators, postdoctoral associates, clinical residents, medical students, summer fellows, visiting learners and undergraduate students

SPEAKER BIOGRAPHIES

Kriti Puri, MBBS

Assistant Professor of Pediatrics
Divisions of Pediatric Critical Care Medicine and Cardiology
Texas Children's Hospital/Baylor College of Medicine

Dr Kriti Puri is a pediatric cardiac intensive care physician and pediatric cardiologist with a special focus on advanced heart failure and mechanical circulatory support. Boarded in both pediatric cardiology and pediatric critical care medicine, she practices in the cardiac intensive care unit as well as on the pediatric heart failure and transplantation service, and is the Clinical Director of the Heart Failure-ICU at Texas Children's Hospital. She also pursues her clinical interests in a research capacity as well, leading several collaborative projects between the critical care and cardiology including critical care practices and outcomes of children in advanced heart failure or on mechanical circulatory support, hematologic aspects of the care of these patients (including anemia, iron deficiency, blood transfusion practices and anticoagulation) and their nutritional support (including specific nutritional deficiencies, undernutrition and obesity). She is also invested in the well-rounded care of children with heart disease and their families and is the cofounder of an early childhood literacy and reading program called "Books@Heart" at the Texas Children's Heart Center in 2021.

Md. Abul Hassan Samee. Ph.D.

Associate Professor
Department of Integrative Physiology
Baylor College of Medicine

Hassan Samee is an Associate Professor in the Department of Integrative Physiology at Baylor College of Medicine. He received his Ph.D. in computer science from the University of Illinois at Urbana Champaign in 2015. He then worked as a Bioinformatics Fellow with Dr. Katherine Pollard at the Gladstone Institutes (University of California San Francisco). Hassan developed biophysical models in his Ph.D. and postdoctoral works to predict the effects of non-coding variants in the human genome. He has broadened his research portfolio after starting his lab at BCM in 2019. Besides working on genetic variants, he is actively developing machine learning models for single cell and spatial transcriptomics data. His lab applies these models in a variety of contexts to elucidate the transcriptional mechanisms underlying disease onset and progression. The overarching goal of Hassan's lab is to explain how genetic variants can lead to pathological outcomes by impacting the function of individual cells and their spatial microenvironment.

SPEAKER BIOGRAPHIES

Daryl A. Scott, M.D., Ph.D.

Professor
Department of Molecular and Human Genetics
Baylor College of Medicine

Dr. Scott received his undergraduate training at Brigham Young University. After graduation, he was accepted to the Medical Scientist Training Program at the University of Iowa. There he completed his M.D. training and also graduated with a Ph.D. degree in genetics. He then moved to the University of Utah where he did a residency in Pediatrics and then to Baylor College of Medicine where he did a second residency in Clinical Genetics. He is currently a board certified in both specialties. After completing his residency training, Dr. Scott joined the Department of Molecular and Human Genetics at Baylor College of Medicine. He is currently a Professor with Tenure. He runs a research laboratory dedicated to identifying the genetic causes of common birth defects with specific emphasis on congenital heart defects and congenital diaphragmatic hernia. As a clinical geneticist, he cares for children with a variety of genetic disorders and collaborates with physicians and scientists from around the world to identify novel disease genes. He is also actively engaged in the training of high school students, undergraduates, medical students, residents, fellows, and MS and Ph.D. graduate students. He and his wife, Apryl, have seven children ranging in ages from 33 to 13. He enjoys camping, hiking, long distance running, cycling and swimming.

Joseph A. Spinner, M.D.

Assistant Professor
Department of Pediatrics
Baylor College of Medicine
Associate Medical Director of Heart Failure and Transplant
Texas Children's Hospital

Dr. Joseph Spinner is a pediatric cardiologist and Associate Director of Pediatric Heart Failure and Transplantation at Texas Children's Hospital. He specializes in the care of children with heart failure, children with cardiomyopathy, children who have undergone placement of a ventricular assist device and children who have undergone a heart transplant. He also serves as the Executive Director of Operations and Co-Chair of the Heart Failure Committee for The Advanced Cardiac Therapies Improving Outcomes Network (ACTION) and on the Scientific Committee of the Pediatric Heart Transplant Society (PHTS).

SPEAKER BIOGRAPHIES

Xander H.T. Wehrens, M.D., Ph.D.

Director, Cardiovascular Research Institute
Professor
Department of Integrative Physiology, Medicine/Cardiology
Baylor College of Medicine

Xander Wehrens, M.D., Ph.D., is the Director of the Cardiovascular Research Institute at Baylor College of Medicine, where he holds the Quigley endowed chair in Cardiology, and is a Professor in the Departments of Integrative Physiology, Medicine, Pediatrics, Neuroscience, and the Center for Space Medicine. Dr. Wehrens is internationally recognized for pioneering translational research on cardiac arrhythmias and heart failure mechanisms. Dr. Wehrens obtained his M.D. and Ph.D. degrees from Maastricht University in the Netherlands. His work at Columbia and subsequently at Baylor has led to the development of several small molecule inhibitors of these ryanodine receptor channels that are currently in preclinical development or clinical trials for catecholaminergic polymorphic ventricular tachycardia. Dr. Wehrens directs a translational research lab that aims to elucidate the mechanism underlying inherited and acquired arrhythmia and cardiomyopathy phenotypes using a wide range of assays utilizing human tissue samples, isolated cardiac cells, and transgenic mouse models.
Dr. Wehrens has served as Associate Director of the Medical Scientist Training Program at Baylor since 2009 and has mentored over 120 trainees in his lab, most of whom are still active in medical research. Dr. Wehrens is also the co-director of a new T32 program for predoctoral students entitled 'Cardiovascular Research and Drug Development'. Finally, Dr. Wehrens is an elected member of the American Society of Clinical Investigation (ASCI) and Association of American Physicians (AAP) and a fellow of the American Heart Association, European Society of Cardiology, International Society for Heart Research and the Heart Rhythm Society. In April 2025, he will receive the Distinguished Scientist Award from the Heart Rhythm Society

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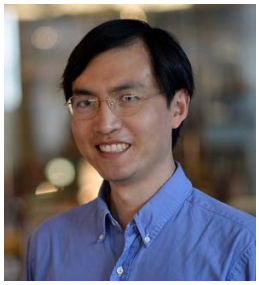

Liang Xie, Ph.D.

Assistant Professor
Cardiovascular Research Institute
Section of Cardiovascular Research
Department of Medicine
Baylor College of Medicine

Dr. Liag Xie, Ph.D., is an Assistant Professor in Medicine in the section of Cardiovascular Research and a faculty member in the Cardiovacular Research Institute. His lab focuses on defining the roles of prolyl hydroxylase domain (PHD) proteins in cardiac function and exploring the molecular mechanisms driving the cardiomyocyte-intrinsic innate immune responses in heart failure. Our goal is to enhance our understanding of heart diseases and provide novel insights into therapeutic strategies for heart failure. Our studies have been supported by multiple grants from NIH and AHA, and our findings have been published in high-impact journals, such as *Nature Metabolism*, *Circulation* and *Journal of Clinical Investigation*.

POSTER SESSION SCHEDULE

SESSION I

10 – 11 a.m.

1	Sarcomere Disassembly Due to Genetic Deletion of Cysteine and Glycine-Rich Protein 3 (Csrp3) Promotes Cardiomyocyte Mitotic Cell Cycle Entry
2	Molecular Mechanism of Cardiac Arrhythmias in TANGO2-Deficiency Models
3	Omics-Based Evidence of Synergistic Ejects Between Electronegative HDL and LDL Subfractions in Compromising Vascular Innate Immunity
4	Optical Mapping of Engineered Heart Tissues
5	Role of Monocytes in Mancreatitis in Hypertriglyceridemia
6	Sex-Specific Differences in Cardiac Aging: Correlation Between Heart Function, Frailty, Anesthesia Recovery and Endurance.
7	Myocardial Compact Zone Re-location Contributes to Left Ventricular Noncompaction
8	Using Metabolomics to Identify Predictive Biomarkers for Thrombotic Complications in Patients with Left Ventricular Assist Devices
9	Role of PAI-1 in Cerebral Amyloid Angiopathy
10	Noninvasive Image-based Assessment of Coronary Artery Plaque Vulnerability Using Computational Biomechanical Modeling
11	Double Bioreactor Assisted Sequential Co-cultivation of An Artery-typical Niche with Native Myocardial Heart Slices to Induce Anti-apoptotic Signaling.
12	Inflammation and JAK/STAT3 Signaling Promote AML Mediated Atrial Fibrillation
13	Profiling Transposable Element Regulation Across Primate Cardiomyocyte DiJerentiation
14	Sphingosine-1-Phosphate as a Target for Myocardial Repair: Activating Proliferative and Regenerative Pathways
15	Ischemic Stroke Induced Cardiac Dysfunction in Mice
16	Role of Junctophilin-2 (JPH2) in the SR-mitochondrial Contacts in Heart Failure
17	Hepatic-derived Eicosanoids Regulate Myelopoiesis and the Pathogenesis of Heart Failure with Preserved Ejection Fraction
18	Cytosolic DNA-STING-IRF3/4 Pathway Mediates Epigenetic Induction of Macrophage Phenotypic Polarization in Acute Thoracic Aortic Aneurysm and Dissection
19	Complement Signaling Orchestrates an Immunosuppressive Microenvironment During Cardiac Renewal
20	Functional Asymmetry of Cardiac Macrophages in Left and Right Atria
21	Altered Cellular Composition and Pro-Inflammatory Signatures in Marfan Syndrome Aortic Tissues
22	SUMO2/3 Excludes YAP5SA from the Nucleus and Inhibits Cardiomyocyte Proliferation
23	YAP Induces a Pro-Renewal Metabolic State in Cardiomyocytes
24	Sex Differences in At

POSTER SESSION SCHEDULE

SESSION II — Noon – 1:20 p.m.

25	Atrial Fibroblast-Derived Macrophage Migration Inhibitory Factor Promotes Atrial Macrophage Accumulation in Postoperative Atrial Fibrillation
26	De Novo Nucleotide Synthesis is Necessary for DNA Damage and Repair in Atheroprone Endothelial Cells
27	CRAT to the Rescue: Enhancing Cardiac Function and Combating NASH
28	Inhibition of BMPER Mitigates Pulmonary Arterial Remodeling by Modulating LRP1-YAP Interaction in Smooth Muscle Cells
29	Anthracyclines Induce Global Changes in Cardiomyocyte Chromatin Accessibility that Overlap with Cardiovascular Disease Loci
30	Novel Approach for Quantitative, Volumetric Assessment of Early Blood Flow Speeds for Early Embryonic Cardiovascular Phenotyping
31	Phosphorylation of RyR2 at Serine 2808 Mediates Atrial Fibrillation in Chronic Kidney Disease
32	Structural-Compositional Interplay of Electronegative Lipoproteins: TEM and Omics Insights into LDL, VLDL and HDL
33	Defining Postnatal Cardiomyocyte Maturation Stages Using a Transcriptional Clock
34	CX-5461 Induces a Gene Expression Signature in Cardiomyocytes that is Shared with Doxorubicin without the Cardiotoxicity
35	ATAD3 is an Essential Component of the Mitochondrial Permeability Transition Pore
36	Closed Loop Solute Transport in Blood Vessels and Organs
37	YAP Defines Glycolytic Microenvironment to Drive Atrial Fibrosis
38	Preventing Nuclear Localization of Junctophilin-2 (JPH2) Attenuates Progression of HF
39	Biomechanics of Functional Mitral Regurgitation: Optimizing the RUFLS Bioreactor for Better Disease Modeling
40	Cardiac Myocyte Cytosolic Self-DNA Contributes to the Pathogenesis of Desmoplakin-cardiomyopathy
41	Gasdermin D Enhances Atrial Arrhythmogenesis by Promoting Mitochondrial Dysfunction
42	Single Cell Transcriptomic Reveals the Heterogeneity of Aortic Fibroblasts During Aortic Disease Development in Mice
43	Calcitonin-induced Matrix Gla Protein Suppresses Fibroblast Activation: Implications for Mitigating Fibrotic Remodeling in Atrial Fibrillation
44	LncRNA Circa Regulates DNA Damage Response and Recovery in the Ischemic Heart
45	Personalized Prognosis: A Blessing or a Burden? Patient Views on Survival Estimates for LVAD Therapy
46	The Added Value of Cardiac MRI in Pediatric Rheumatologic Disorders
47	Tumor Compression-Induced Myocardial Infarction with Non-Obstructive Coronary Arteries
48	Pericardial Mass with Tumor-Associated Thrombi Causing Pericardial Effusion and Right Heart Failure
49	Predicting Acute Ischemic Stroke in Heart Failure Patients with Left Ventricular Assist Devices: The Role of Elevated Plasma Homocysteine and High Mobility Group Box 1 Proteins

POSTER SESSION SCHEDULE

SESSION III — 2:20 – 3:20 p.m.

50	Increased IFN-γ Levels in African American Women Following Ischemic Stroke: A Study of Ethnic Disparities in Plasma Biomarkers
51	Hit Pause: Marked Sinus Pauses and Asystole Leading to Pacemaker Implantation in a Patient with Wieacker-Wolff Syndrome
52	Eject of Osteopathic Manipulative Medicine on Cardiovascular Parameters
53	Anesthetic Management of First BiVACOR Recipient: Total Artificial Heart of the Future
54	Predictors and Outcomes Following a Stroke in Patients Who had an Open Thoracoabdominal Aortic Aneurysm Repair.
55	K2P Potassium Channels Affect Endothelin A Receptor and Vasoreactivity in Idiopathic Pulmonary Fibrosis– Pulmonary Hypertension (IPF–PH) Patients
56	GPCR-β-arrestin Biased Signaling at Angiotensin-II type1 Receptor (AT1R) as a Therapeutic Target for Heart Failure
57	Targeting CTLA-4 with Small Molecules to Modulate T-Cell Responses in Cardiovascular Injury
58	Pathogenic Variants in ACTA2 that Activate Heat Shock Factor 1 Signaling and Cholesterol Biosynthesis in Smooth Muscle Cells Predispose to Premature Atherosclerosis
59	Nanoparticle Contrast-enhanced Imaging of Thoracic Aortopathy and Cardiovascular Pathology in a Mouse Model of Marfan Syndrome
60	The Role of a Domain of Von Willebrand Factor in Inflammation During Rheumatoid Arthritis
61	Increased CCL4 and CCL5 Following Mechanical Thrombectomy: A Plasma Biomarker Study in Ischemic Stroke Patients
62	Targeting Ephrin Receptor Kinase for the Treatment of Endometriosis
63	Steroid Receptor Coactivator Stimulators Mitigate Myocardial Infarction by Reducing Oxidative Stress in Cardiac Fibroblasts and Enhancing Angiogenesis
64	Acta2 Pathogenic Variant Leads to Immature Smooth Muscle Cells and Causes Moyamoya-like Occlusive Cerebrovascular Lesions: Targeting Cellular Metabolism Prevents Disease
65	The Mouse Metabolism and Phenotyping Core Supports Research Investigating Cardiovascular Outcome Measures
66	Oxidized LDL and LOX-1 Mediate ATRIAL Fibrillation Development In Chronic Kidney Disease
67	Discovering Novel Genetic Causes of Hypertrophic Cardiomyopathy using iPSC-Cardiomyocyte Models
68	CD36/FABP5/PPARd Signaling Axis Defines Spontaneously Proliferating Cardiomyocytes in Neonatal Stages
69	Characterization of Lipid Droplets and Inflammation in Foamy Monocytes in Severe Hypertriglyceridemia
70	Integrin-Targeting Hydrogel Coatings to Improve Endothelialization of Vascular Grafts

Poster 1

SARCOMERE DISASSEMBLY DUE TO GENETIC DELETION OF CYSTEINE AND GLYCINE-RICH PROTEIN 3 (CSRP3) PROMOTES CARDIOMYOCYTE MITOTIC CELL CYCLE ENTRY

Kamal A Abou Farraj[1],Riham Abouleisa[1], Tamer Mohamed[1], Abou Bakr Salama[1], Pretty Rose Mathew[1], Marc Dwenger[2], Ghazal Sadri[2], Yazan Almasry[3], Stuti Mehta[3], Maryam Al Attas[3], Dania Ibrahim[3], Arnav Garg[4]

[1]Surgery, Baylor College of Medicine, Houston, TX; [2]Medicine, University of Louisville; [3]Medicine, Alfaisal University; [4]Sciences, University of Texas

Background: Adult cardiomyocytes (CMs) have limited regenerative capacity and rigid a sarcomere structure, whereases neonatal CMs retain regenerative potential with sarcomere disassembly observed during proliferation. Interestingly, our recent study showed that overexpression of 4 cell cycle genes (Cdk1, Cdk4, Ccnb, Ccnd; 4F) induces CM proliferation in vitro and in vivo with observed sarcomere disassembly during anaphase and cytokinesis. Here, we aim to identify the protein controlling sarcomere disassembly during forced CM proliferation.

Materials/Methods: Temporal proteomics and ubiquitin-linked proteomics were conducted on 60-day-old hiPS-CMs transduced with control or 4F adenovirus for 24 h (early mitosis), 48 h (mitotic peak), and 72 h (final stage of division). Csrp3, which interacts with T-Cap and α-actinin at Z-disks, was highly downregulated at 24 and 48 h, returning to baseline at 72 h. Ubiquitination at Csrp3 sites K119 and K113 increased only at 24 h, indicating Csrp3 is actively degraded during mitosis and replenished post-division. To validate Csrp3's role in forced CM proliferation, Csrp3 knockdown (KD) was performed in P7 neonatal mouse CMs (NMCMs) with/without 4F. In 4F-transduced NMCMs, Csrp3 KD elevated PHH3+ CMs (G2/M marker) and mono-nucleated CMs with no effect on EDU+ CMs (G1/S marker), indicating enhanced G2/M entry without altering G1/S.

Results: In vivo, P21 Csrp3KO hearts exhibited disrupted sarcomere structure, increased HW/BW ratio with no change in CM size, and a significant increase in PHH3+ and AurkB+ CMs, indicating increased cell number rather than hypertrophy. RNA sequencing showed upregulation of cell cycle genes, confirmed by RT-PCR. Similarly, Csrp3 KD in human heart slices increased PHH3 + CMs and increased cell cycle gene expression.

Conclusions: Findings indicate Csrp3 is crucial for sarcomere disassembly during CM proliferation. Deleting Csrp3 disrupts CM sarcomere structure and enhances CM mitotic cell cycle entry.

Poster 2

MOLECULAR MECHANISM OF CARDIAC ARRHYTHMIAS IN TANGO2-DEFICIENCY MODELS

Adeniyi G Adeleye[1], William Whitfield[1], Lilei Zhang[2], Christina Miyake[3], Na Li[1]

[1]Medicine/Cardiovascular Research, Baylor College of Medicine, [2]Molecular and Human Genetics, Baylor College of Medicine, [3]Pediatrics, Baylor College of Medicine

Background: TANGO2 deficiency disease (TDD) is associated with metabolic crises and cardiac arrhythmias. The molecular mechanisms underlying TDD-associated arrhythmogenesis remain unclear. Natural history studies suggest that cardiac crises could be mitigated by the supplementation of vitamin B9, which is involved in lipid metabolism. We hypothesize that TANGO2 deficiency promotes ventricular arrhythmias by disrupting lipid homeostasis.

Materials/Methods: Cardiac phenotype was assessed in Tango2-/- knockout (KO) mice using echocardiography and programmed electrical stimulation following a vitamin B deficient (VBD) diet for 5 days, with or without B9 supplementation. To evaluate the impact of TANGO2 levels on stress markers, we assessed ATF6$\alpha\beta$ and autophagic markers (LC3α, LC3β, pERK) in a heterologous system with $TANGO_2$ overexpression

Results: While there were no apparent changes in cardiac function or structure, KO mice were more prone to pacing-induced ventricular tachycardia (VT) after VBD compared to the WT-VBD group. B9-supplementation completely prevented VT development in KO mice. Telemetry ECG recording revealed increased heart rate variability during a 10-hour fasting period in KO mice compared to WT controls, which was restored after B9-supplemented water. Western blot analysis showed reduced Nav1.5, elevated Cav1.2 protein levels, and increased lipid stress markers PLIN5 and LDHA in the ventricles of KO mice. Overexpression of $TANGO_2$ in HEK293 cells increased ATF6α under oxidative stress and enhanced lipid accumulation, while knockdown in AC16 cells upregulated LC3α, LC3β, and pERK.

Conclusions: Our findings suggest that TDD promotes arrhythmogenesis through a vitamin B9-associated metabolism mechanism, which remains unclear. TANGO2 regulates lipid homeostasis and plays a role in stress response and ion channel stability. Future studies will examine how its deficiency disrupts ion channel trafficking via lipid turnover, contributing to arrhythmias.

Poster 3

OMICS-BASED EVIDENCE OF SYNERGISTIC EFFECTS BETWEEN ELECTRONEGATIVE HDL AND LDL SUBFRACTIONS IN COMPROMISING VASCULAR INNATE IMMUNITY

Huan-Hsing Chiang[1], Wen-Li Hsu[2], Ming-Hsien Tsai[3], Darren G Woodside[4], Chu-Huang Chen[1], Omer Akyol[1]

[1]Molecular Cardiology Research Laboratories, Vascular and Medicinal Research, Texas Heart Institute; [2]Regenerative Medicine and Cell Therapy Research Center, Kaohsiung Medical University; [3]Department of Child Care, National Pingtung University of Science and Technology; [4]Molecular Cardiology Research Laboratories, Texas Heart Institute

Background: Emerging evidence suggests that lipoprotein particle quality plays a crucial role in atherogenesis. HDL and LDL can be fractionated into five subclasses (H1-H5 and L1-L5) with the least electronegative H1 and L1 exhibiting cardioprotective properties, whereas the most electronegative H5 and L5 display harmful, dysfunctional characteristics. This study examines the effects of L5 and H5 on endothelial cell (BAEC) and monocyte (THP-1) viability. We hypothesize that L5 directly induces cytotoxicity in both cell types, while H5 exacerbates these effects, potentially driving inflammatory and atherogenic pathways in atherosclerosis.

Materials/Methods: H5 and L5 were fractionated by anion-exchange chromatography. For lipidomics, H5 and L5 were characterized by LC-MS. Cells were treated with 50 µg/mL of L1, L5, H1, and H5 for 24 hours. THP-1 cell viability was assessed using a fluorescence-based method. Image-based cytometric quantification was performed using a cell analysis system. Transcriptomic analysis was conducted on BAECs treated with H1 and H5 to identify differentially expressed genes.

Results: Lipidomic analysis indicated higher triglycerides, lower phosphatidylcholine, and increased oxidized phospholipids in H5 and L5 versus H1 and L1. H5 slightly and L5 moderately reduced cell viability, while their combination significantly decreased cell numbers and viability. In contrast, H1 and L1 enhanced cell proliferation. Transcriptomics linked H5 to changes in cell cycle regulation, senescence, DNA damage response, and chromosome organization.

Conclusions: The distinct lipidomic and transcriptomic profiles of H1, H5, L1, and L5 underscore their divergent roles in vascular biology. H5 and L5 synergistically impair vascular innate immunity and promote atherosclerosis by reducing cell viability, while H1 and L1 support cell proliferation, reflecting a non-cytotoxic, nutrient-providing function. These findings underscore lipoprotein subclasses' role in vascular dysfunction and atherogenesis.

Poster 4

OPTICAL MAPPING OF ENGINEERED HEART TISSUES

Matthew Fiedler[1], Alejandra Vasquez Limeta[1], Leah Carter[1], Ernesto A Reyes Sanchez[1], Francisco Altamirano[1]

[1]Cardiovascular Sciences, Houston Methodist, Houston, TX

Background: Conventional cellular and animal models have long contributed to our knowledge of cardiac physiology but struggle to faithfully recapitulate the complex molecular underpinnings of human cardiac electrophysiology. Optical mapping is a widely used and powerful technique allowing simultaneous action potential (AP) and intracellular calcium (Ca) measurement. However, it remains a technically demanding experimental approach with challenges relating to tissue preparation, system operation, and data interpretation. Moreover, existing applications are relegated to cellular and animal models with limited relevance to human electrophysiology.

Materials/Methods: To address these limitations, we leveraged and modified the open-source milliPillar platform to generate human-engineered heart tissues (EHTs) for robust optical mapping. We developed a reproducible protocol to evaluate AP and Ca alterations using a custom 3D-printed adapter that delivers point electrical stimulation through a pair of platinum electrodes.

Results: Here, we present preliminary data demonstrating: 1) strong AP and Ca coupling and signal propagation, 2) a decrease in AP duration 80 (APD80) and increased conduction velocity with increasing stimulation frequency, 3) AP shortening with nifedipine, and 4) AP prolongation with E-4031 (a hERG potassium channel blocker).

Conclusions: This integrated approach overcomes a critical barrier to human cardiac electrophysiological investigation, providing a reliable, accessible, and clinically relevant platform vital for mechanistic study and preclinical therapeutic development.

Poster 5

ROLE OF MONOCYTES IN PANCREATITIS IN HYPERTRIGLYCERIDEMIA

Feng Gao[1], Benjamin Litchfield[1], Jing Xi[1], Jason C Mills[2], Ballantyne Christie[1], Huaizhu Wu[1]

[1]Medicine, Baylor College of Medicine; [2]Section of Gastroenterology and Hepatology, Baylor College of Medicine

Background: Hypertriglyceridemia (HTG) exacerbates acute pancreatitis (AP), characterized by heightened inflammation. Monocytes, especially Ly-6clow monocytes (Ly6cM), uptake triglycerides, transforming into proinflammatory foamy monocytes. However, the specific role of Ly6cM in HTG-induced pancreatitis (HTGP) remains unknown.

Materials/Methods: Apoc3Tg mice and littermate controls (WT) were fed a high-fat diet (HFD) for 12 weeks. Monocyte phenotypes were assessed via flow cytometry before/after cerulein-induced AP (8 hourly i.p. injections, 5 µg/kg). Pancreas, liver, and lungs were collected after AP induction and analyzed using H&E/IF staining.

Results: Compared to controls, Apoc3Tg mice displayed significantly higher levels of triglyceride (2011 ± 91.14 mg/dL in Apoc3Tg vs 117.6 ± 13.34 mg/dL in WT, $P<0.05$) and cholesterol (613.7 ± 21.23 mg/dL in Apoc3Tg vs 311.3 ± 31.19 mg/dL in WT, $P<0.05$). H&E staining revealed that Apoc3Tg developed more severe pancreatitis than WT (H&E staining score, $P<0.05$). Flow cytometric analysis showed higher side scatter in Ly6cM of Apoc3Tg mice compared to WT ($P<0.05$). Additionally, the expression levels of adhesion molecules and chemokine receptors, including VLA-4, CD11C, CD11A, and CX3CR1, were significantly elevated on Ly6cM of Apoc3Tg mice vs WT ($P<0.05$). Notably, following AP induction, the proportion of Ly6cM, but not Ly-6chigh monocytes were significantly decreased ($P<0.001$) and expression levels of VLA-4, CD11C, CD11A, and CX3CR1 on Ly6cM were all reduced. Immunofluorescence analysis showed that Apoc3Tg mice compared to WT littermates had increased macrophage infiltration, along with high CD11C expression, in the pancreas.

Conclusions: Our results suggest that HTG enhances lipid accumulation and alters the phenotypes of circulating monocytes, particularly Ly-6Clow monocytes. These changes promote monocyte infiltration into the pancreas and exacerbate AP, highlighting a crucial role of Ly-6Clow monocytes in HTGP.

Poster 6

SEX-SPECIFIC DIFFERENCES IN CARDIAC AGING: CORRELATION BETWEEN HEART FUNCTION, FRAILTY, ANESTHESIA RECOVERY AND ENDURANCE

Grecia G Garcia-Marquez[1], Thuy Pham[1], George E. Taffet[1], Katarzyna A. Cieslik[1]

[1]Medicine, Houston Methodist

Background: Cardiovascular dysfunctions are associated with aging. By 2050, the population over 65 years is expected to triple. This demographic shift highlights the importance of understanding how different organs respond to aging and whether these processes vary between males and females. Our hypothesis suggests that there are distinct sex-specific responses in cardiac aging, requiring differentiated approaches to enhance health span and lifespan through effective management and treatment strategies. Additionally, our study explores the potential of non-invasive markers as indicators of cardiac function in aged populations.

Materials/Methods: We examined the correlation between post-anesthesia recovery time, frailty index, wire hanging endurance test, and cardiac parameters obtained by echocardiography and Doppler imaging (under 1.5% isoflurane anesthesia) in 25-26 month-old mice. The first three parameters constitute markers of "whole-body resilience". We employed matrix analysis with non-parametric Spearman correlation and two-tailed p-values to examine associations between these variables.

Results: Our data analysis revealed significant population heterogeneity, demonstrating distinct patterns of sexual dimorphism in the correlations between cardiac and functional parameters. In males, increased frailty was associated with cardiac hypertrophy. In females, hyperdynamic hearts and ventricular thickening correlated with prolonged anesthesia recovery times, while an inverse correlation was observed between physical endurance and systolic parameters.

Conclusions: These findings suggest that anesthesia recovery time, wire hanging test, and frailty index are associated with different cardiac parameters in aged male and female mice. This underscores that the implications of cardiovascular aging differ between sexes and highlights the importance of considering sex as a biological variable (SABV) in geroscience research.

Poster 7

MYOCARDIAL COMPACT ZONE RE-LOCATION CONTRIBUTES TO LEFT VENTRICULAR NONCOMPACTION

Hongyan Guo[1], Luqi Zhao[1], Yangyang Lu[1], Richard A Bond[1], Mingfu Wu[1]

[1]Pharmacy/Pharmacology, University of Houston, Houston, TX

Background: Left ventricular non-compaction (LVNC) is a rare cardiomyopathy marked by excessive trabeculation and a thinner ventricular wall. It is the third most common cardiomyopathy in children, with 47% mortality. Due to the lack of suitable mouse models and unclear pathogenesis, effective therapies for LVNC are still lacking. Therefore, this study aims to establish an LVNC mouse model to explore the pathogenesis and etiology underlying LVNC formation.

Materials/Methods: An LVNC mouse model was established by administering DrugX to pregnant females via minipump, with embryos examined at E17.5 for LVNC features. To investigate the cellular mechanisms underlying LVNC formation, genetically modified mouse lines, including a compact-zone-specific Hey2CreERT2/+ line, a trabecular-specific Cited1DreERT2/+ line, and dual reporter lines, were used to track cellular behaviors during pathogenesis. Additionally, RNA deep sequencing was performed on DrugX-induced LVNC and control hearts to explore the molecular mechanisms involved.

Results: 1. Embryos exposed to DrugX exhibited LVNC characteristics, with a trabecular zone-to-compact zone ratio of 10, compared to 2 in PBS-treated mice at E17.5. 2. Lineage tracing showed that compact zone cells migrated into the trabecular zone, forming recessed trabeculae, while Cited1DreERT2/+-labeled cells were primarily localized to trabecular tips. 3. A distinct population co-labeled by Hey2CreERT2/+ and Cited1DreERT2/+ relocated to the trabeculae, contributing to deep intertrabecular recess formation. 4. GO analysis and genetic models confirmed that DrugX-induced LVNC is Adrbs1/2-dependent.

Conclusions: This study provides evidence that LVNC formation is closely associated with the relocation of the compact cardiomyocytes, especially the double-positive cells labeled by Hey2CreERT2/+and Cited1DreERT2/+, from the compact zone to the trabecular zone. Moreover, Adrbs1/2-related signaling pathways play a crucial role in this process.

Poster 8

USING METABOLOMICS TO IDENTIFY PREDICTIVE BIOMARKERS FOR THROMBOTIC COMPLICATIONS IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES

Adel M Hassan[1], Shiyi Li[1], Iván Murrieta-Álvarez[1], Ismael Garcia[1], Nandan Kumar Mondal[1]

[1]Surgery/Cardiothoracic Transplantation & Circulatory Support, Baylor College of Medicine

Background: End-stage heart failure patients undergoing left ventricular assist device (LVAD) implantation often face thrombotic complications (TC) such as pump thrombosis, venous thromboembolism, and ischemic stroke. This study used untargeted plasma metabolomics to identify potential biomarkers predictive of TC.

Materials/Methods: In an existing cohort of 100 LVAD patients, a subgroup of 25 patients was investigated. This exploratory study included 8 patients who developed TC within 6 months of LVAD implantation, as well as 17 patients who did not experience TC during the same period. Untargeted plasma metabolomics using LC-MS/MS was conducted on day 0 (pre-LVAD) and day 7 (post-LVAD). A comprehensive, web-based tool, MetaboAnalyst was used to train classifiers to distinguish TC vs No TC. Enrichment analysis was conducted using parent classes in the Human Metabolome Database (HMDB).

Results: TC occurred between days 35 and 140. Among 1473 metabolites, 35 differed between TC vs No TC in pre-LVAD plasma and 73 in post-LVAD plasma. The classifiers had an area under the curve (AUC) of 0.704-0.741. Key markers included glucuronides and methylephedrine, which were increased in TC; and metabolites of tramadol, acetaminophen, and caffeine, which were decreased in TC. Enrichment analysis showed differences in O-glucuronides, 6-oxopurines, and aralkylamines ($p<0.05$). In heatmap clustering, O-glucuronides formed a single cluster with elevated levels in patients who would develop TC and 6-oxopurines formed a small cluster with lower levels in TC, but aralkylamines were not grouped together.

Conclusions: Drug metabolites like caffeine, tramadol, and acetaminophen on day 7 influenced TC risk for up to 140 days. Increased glucuronide levels in TC patients suggested overactive glucuronidases, which would metabolize warfarin and predispose to subtherapeutic anticoagulation and therefore thrombosis. Further metabolic studies may help to personalize thrombosis prevention in LVAD patients.

Poster 9

ROLE OF PAI-1 IN CEREBRAL AMYLOID ANGIOPATHY

Joey Hernandez[1], Aleena Lukose[1], Vasilia E Kyriakopoulos[1], Carson Finger[1], Gomana Emara[1], Bharti Manwani[1]

[1]Neurology, UT Health Science Center, Houston, TX

Background: Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder defined by the accumulation of amyloid in small- and medium-sized cerebral arteries, leading to intracerebral hemorrhages and vascular dementia. Plasmin, a member of the fibrinolytic pathway, is known to degrade and clear both aggregated and non-aggregated Aβ. The serine protease plasmin is formed from cleavage of plasminogen (an inactive zymogen) by tissue plasminogen activator (tPA), which is, in turn, inhibited by plasminogen activator inhibitor-1 (PAI-1). Plasma levels of PAI-1 have been found to be elevated in Alzheimer's disease. The objective of this study was to explore the effects of PAI-1 gene deletion on CAA.

Materials/Methods: Transgenic mice (TgSwDI, mouse model of CAA) were bred with PAI-1$^{-/-}$ (PAI-1 complete deletion) mice for two generations to produce homozygous TgSwDI/PAI-1$^{-/-}$ knockout mice. Radial Arm Water Maze (RAWM) was used to assesses spatial learning memory in mice, with longer latency to reach the escape arm indicating worse memory at 12 months of age.

Results: Aging female TgSwDI/PAI-1$^{-/-}$ mice show a trend towards improved spatial learning memory (25±8.6 sec, decreased latency) on the RAWM as compared to TgSwDI females, 40±12 sec), p=0.07, n=6/gp. Male mice exhibited no such benefit, p>0.1, highlighting a sex-specific effect of PAI-1 knockout.

Conclusions: Our data demonstrates a trend towards female-specific neuroprotection in CAA mice with PAI-1 knockout. Experiments in our lab are ongoing to increase the n in this study and also to study the up and downstream mechanisms.

Poster 10

NONINVASIVE IMAGE-BASED ASSESSMENT OF CORONARY ARTERY PLAQUE VULNERABILITY USING COMPUTATIONAL BIOMECHANICAL MODELING

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Background: Coronary Artery Disease (CAD) is a leading cause of death worldwide, caused by the buildup of atherosclerotic plaque in the coronary arteries. Over time, these plaques may rupture, leading to acute coronary syndrome (ACS), such as heart attack and sudden cardiac death. Due to this risk, the ability to identify "vulnerable plaques"—those with a high risk of rupture—is essential for developing effective strategies for the diagnosis, prevention, and treatment of CAD. Recent advances in imaging technology and deep learning image segmentation have enabled the application of computational medicine to overcome the current limitations of conventional approaches to risk assessment. It is now possible to construct detailed, patient-specific models of the heart from noninvasive Coronary Computed Tomography Angiography (CCTA), which can be used for biomechanical assessment of plaque vulnerability to predict rupture and ACS.

Materials/Methods: Previous studies have indicated that high stresses in the fibrous cap are associated with an increased risk of rupture. In this work, we identify the key contributing factors of high stresses in the fibrous cap to gain a biomechanical understanding of vulnerable plaques. A patient-specific biomechanical model using noninvasive CCTA and computational solid mechanics is developed for stress analysis of the plaque. Finally, the model is used in a retrospective study of 209 lesions to identify biomechanical predictors of ACS and evaluate the potential clinical utility of biomechanical assessment of coronary lesions.

Results: Our results show that biomechanics plays a key role in the prediction of plaque rupture and ACS, and noninvasive estimates of stresses in the fibrous cap have potential as predictive metrics.

Conclusions: Noninvasive biomechanical assessment of coronary plaques using computational biomechanics may improve identification of culprit lesions for ACS and simplify the interpretation of risk factors for individual lesions.

Poster 11

DOUBLE BIOREACTOR ASSISTED SEQUENTIAL CO-CULTIVATION OF AN ARTERY-TYPICAL NICHE WITH NATIVE MYOCARDIAL HEART SLICES TO INDUCE ANTI-APOPTOTIC SIGNALING

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Background: We outline a project to stimulate endothelial cells to cardiomyocyte EC-CM crosstalk in heart slices by nitric oxide NO via the sequential pulsatile perfusion of two bioreactors. In previous work, we showed that helical shaped microstructures induced artery typical EC alignment and spiral flow in artificial vascular grafts. With our first bioreactor BR1, we want to proceed with these findings by adding a pulsatile flow profile to provide physiological wall shear stress WSS stimulation for NO production. Previous studies showed further that by mechanical and electrical stimulation, vital in vitro cultivation of heart slices could be markedly prolonged. However, as vital time in culture is precious for clinically relevant cardiotoxicity testing, further prolonging it is highly warranted.

Materials/Methods: BR1 aims to build an artery-typical niche for EC, to provide the media with NO before passing it to the heart slice bioreactor BR2. The needed flow dynamics in BR1 will be double used in BR2 to mechanically stimulate the myocardial tissue. As NO production is known to be crucial for EC-CM crosstalk, in our model, we hope to employ the complex EC-CM interactions to the heart slice cultivation model and modulate them by different processing strategies.

Results: The goal is the induction of anti-apoptotic signaling in BR2 by adjusting the WSS in BR1. Planned results will be parameters for the arterial niche like hyaluronidase and NO production, Trans Endothelial Electrical Resistance assessment and contrasting's to created WSS in BR1 as well as to levels of EC derived anti apoptotic markers in the heart slices in BR2. The vital time in culture will be evaluated by metabolic activity assays in BR2 as well as the level of myocardial functionality as shown by Multielectrode Array assessment.

Conclusions: Conclusions will be leaned on the success of our approach to impact myocardial functionality in cultivated heart slices over time via the modulation of EC-CM crosstalk.

Poster 12

INFLAMMATION AND JAK/STAT3 SIGNALING PROMOTE AML MEDIATED ATRIAL FIBRILLATION

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Background: The number of cancer survivors is increasing with advanced treatment and care, many of whom develop cardiac comorbidities, including atrial fibrillation (AF). These studies show a correlation between cancer therapies and AF (onco-AF); however, the underlying pathways remain unknown, mainly due to the lack of animal models enabling cause-and-effect studies. Our long-term goal is to uncover the mechanisms underlying onco-AF by establishing novel mouse models.

Materials/Methods: We established a model of onco-AF by grafting acute myeloid leukemia (AML) into C57/BL6J mice and assessed their susceptibility to AF. RNA-seq was performed from the atria of AML-mice and bioinformatic analyses were used to reveal the altered genetic landscape.

Results: We found, for the first time, that AML-mice have a 55.6% susceptibility to AF, compared to 9.1% in control mice. GSEA analysis of the RNA-seq data revealed TNFα mediated inflammatory pathway to be the most activated pathway in the atria of AML-mice. RT-qPCR analysis confirmed increased expression of TNFα in AML-mice (2.2 fold, $p=0.008$). Since macrophages are one of the largest sources of TNFα, we assessed if there was increased expression of macrophage marker F4/80 in the atria of AML-mice. Indeed, F4/80 mRNA was increased in AML-mice (2.0 fold, $p<0.001$). Furthermore, we found an increase in the mRNA levels of macrophage recruiting chemokine CCL2 in AML-mice (2.1 fold, $p=0.004$). Similarly, elevated expression of STAT3 was observed in AML-mice. Furthermore, RT-qPCR revealed increased expression of fibrotic marker Col1 (2.8 fold, $p=0.001$), and myofibroblast marker alpha smooth muscle actin Acta2a in AML-mice (2.5 fold, $p=0.004$), indicating increased fibrosis in the atria of the AML-mice.

Conclusions: Our results show that AML itself is a risk factor for AF. This increased susceptibility to onco-AF is likely driven by macrophage mediated inflammation via increased TNFα secretion that activates STAT3 signaling and promotes fibrosis in the atria of AML.

Poster 13

PROFILING TRANSPOSABLE ELEMENT REGULATION ACROSS PRIMATE CARDIOMYOCYTE DIFFERENTIATION

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Background: Humans and chimpanzees differ in their anatomy and physiology despite their genomes being approximately 98% identical. Differential gene regulation is the major driver of the phenotypic differences between these closely related species. Transposable Elements (TEs) comprise fifty percent of primate genomes and can contribute to gene regulation within and between species. However, their relative contribution appears to differ between pluripotent and somatic cell types.

Materials/Methods: To study the evolutionary dynamics of TE regulation during development, we utilize an in vitro system to differentiate iPSCs of human and chimpanzees into beating cardiomyocytes. We collected cells at four stages of differentiation (pluripotent cells, mesoderm, cardiac mesoderm and terminal cardiomyocytes), which were defined by over 50% of the cell population expressing stage-specific markers by flow cytometry in both species. Gene expression was measured through RNA-sequencing and to study TE regulatory dynamics, we profiled the enrichment of H3K27ac, a marker of active regulatory regions, by Cleavage Under Targets and Tagmentation (CUT&Tag).

Results: Global gene expression data reveals that differentiation stage is the largest contributor to variation in the data followed by species. We detected tens of thousands of H3K27ac regions within orthologous regions that cluster by differentiation stage. H3K27ac regions that are observed across differentiation stages (stage-invariant) are more likely to be conserved across species than regions that are observed in a subset of stages (stage-variant). Conserved stage-variant regions are more likely to overlap a TE than conserved stage-invariant regions.

Conclusions: These results suggest TE contribution to stage-specificity. We are collecting data from additional individuals to investigate the species-specificity of TE regulation during cardiomyocyte differentiation.

Poster 14

SPHINGOSINE-1- PHOSPHATE AS A TARGET FOR MYOCARDIAL REPAIR: ACTIVATING PROLIFERATIVE AND REGENRATIVE PATHWAYS

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Background: Cardiomyocytes (CMs) have limited proliferative capacity, challenging myocardial renewal after ischemic injury. Identifying molecular regulators is crucial for developing regenerative heart failure therapies. Sphingosine-1-phosphate (S1P), a bioactive lipid, is recognized for its ability to modulate cell survival, migration, and proliferation across various organ systems. However, its role in CM renewal and cardiac repair is not completely understood.

Materials/Methods: This study explores the effects of S1P on CM proliferation via the Hippo-YAP signaling pathway and examines its interaction with key regenerative signaling pathways, including Notch, Wnt, and mTOR. We investigated the impact of S1P on rat Cardiomyocyte-like cells (CM-like) and human induced pluripotent stem cell-derived CMs (hiPSC-CMs) through proliferation assays and transcriptomic analyses.

Results: Our findings reveal that S1P triggers cell-cycle re-entry in CM-like cells within 8 hours. From a mechanistic standpoint, S1P decreases YAP phosphorylation, facilitating its translocation into the nucleus. An EdU incorporation assay demonstrated that S1P promotes CM renewal in hiPSC-CMs within 24 hours. Additionally, RNA sequencing analysis indicated that S1P influences various regenerative pathways, which are critical for CM renewal and differentiation. Furthermore, S1P enhanced the expression of angiogenesis-related genes, highlighting its potential role in vascular remodeling following myocardial injury.

Conclusions: Our findings identify S1P as a powerful inducer of CM proliferation, positioning it as a promising therapeutic target for myocardial regeneration. By modulating regenerative signaling pathways, S1P orchestrates a complex network that supports cardiac repair. With clinically approved drugs targeting S1P signaling, these insights enable targeted regenerative strategies for ischemic heart disease and heart failure.

Poster 15

ISCHEMIC STROKE INDUCED CARDIAC DYSFUNCTION IN MICE

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Background: Acute ischemic stroke patients with cardiac complications have increased in-hospital mortality. The cardiac complications have been attributed to pre-existing comorbidities like coronary artery disease, cardiomyopathy, arrhythmia, to name a few. Aging is a known risk factor for both stroke and myocardial injury. Interestingly, ischemic injury to the brain in itself may lead to cardiac injury. However, the post-stroke brain-heart interaction is not well defined. This study was designed to fill this gap in our knowledge.

Materials/Methods: C57BL/6J young (3 months) and aged (18 months) male mice were subjected to 60 minutes of middle cerebral artery occlusion (MCAO). Electrocardiography (ECG) and echocardiography (ECHO) measurements were performed at four time points: pre-stroke (day 0, D0) and post-stroke day 3 (D3), 7 (D7), and 14 (D14) and were analyzed using a generalized estimated equation method with a post hoc group comparison test at each time point, Bonferroni correction.

Results: There was a significant decrease in cardiac output after stroke in aged but not young mice at D3, as compared to baseline (young, D0: 18.5±1.6ml/min vs. D3:16.6±5.16 ml/min, n=8, p=0. 0038; aged, D0 25.4±6.86 ml/min vs. D3, 16.8±6.8 ml/min, n=6, p=0.0038). Cardiac output normalized to baseline by adjusting heart rate and stroke volume in young but remained significantly low in aged mice even at D14. Interestingly, left ventricular mass decreased significantly after stroke in aged mice at day 3, 118.4±23.2 mg compared to baseline 160.7±22.9 mg. There was no significant change in LV mass in young mice.

Conclusions: Our data indicates that cardiac output decreases after stroke in aged mice. Interestingly, there is a significant decrease in left ventricular mass and ventricular wall thickness in aged mice after MCAO, indicating cardiac atrophy. We speculate this may be secondary to cardiac ischemia caused by stroke.

Poster 16

ROLE OF JUNCTOPHILIN-2 (JPH2) IN THE SR-MITOCHONDRIAL CONTACTS IN HEART FAILURE

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Background: Heart failure affects millions of individuals and is characterized by both contractile and metabolic dysfunction, leading to impaired cardiac output. JPH2, an intermembrane protein, is essential for maintaining the spatial organization of the plasmalemma and sarcoplasmic reticulum (SR) within junctional membrane complexes (JMCs), ensuring efficient excitation-contraction coupling. Recent studies in a pulmonary hypertension model suggest that JPH2 interacts with mitofusin-2 (MFN2), a known SR–mitochondria tether, to regulate mitochondrial function in the right ventricle. However, whether JPH2 plays a direct role in maintaining SR-mitochondria structural integrity and its impact on mitochondrial function remain largely unexplored.

Materials/Methods: Transmission electron microscopy (TEM) quantified SR-mitochondria distance. Seahorse extracellular flux analysis measured mitochondrial respiration.

Results: Proteomic analysis of crude mitochondrial fractions, along with western blotting of mitochondria-associated membrane (MAM) fractions, confirmed JPH2 localization at SR-mitochondrial contact sites. Electron microscopy of left ventricular tissue revealed a significant increase in SR-mitochondrial distance in JPH2-mutant hearts, accompanied by an accumulation of dysfunctional rod-shaped mitochondria and reduced mitochondrial Ca^{2+} uptake. Seahorse metabolic analysis demonstrated a marked reduction in oxygen consumption rate (OCR) in both JPH2-mutant murine cardiomyocytes and JPH2-deficient iPSC-derived cardiomyocytes. Additionally, JPH2 deficiency resulted in a significant increase in mitochondrial ROS generation. Collectively, these findings establish JPH2 as a critical regulator of SR-mitochondrial tethering, essential for maintaining mitochondrial Ca^{2+} homeostasis and metabolic function.

Conclusions: These findings establish JPH2 as a critical regulator of SR-mitochondrial contacts in the heart. Targeting JPH2-dependent SR-mitochondrial interactions may provide a novel therapeutic strategy for heart failure.

Poster 17

HEPATIC-DERIVED EICOSANOIDS REGULATE MYELOPOIESIS AND THE PATHOGENESIS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Background: Heart Failure with preserved Ejection Fraction (HFpEF) is a leading cause of morbidity and mortality. A common comorbidity of HFpEF is Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), suggesting that metabolic dysfunction in the liver may contribute to the development of HFpEF. Liver arachidonic acid (AA)-derived metabolites, including epoxyeicosatrienoic acid (EET) and dihydroxyeicosatrienoic acid (DHET), play critical roles regulating cardiac inflammation. EETs are generated from AA by cytochrome p450 (CYP2C) and rapidly hydrolyzed by soluble epoxide hydrolase (sEH) into DHET. However, the role of these enzymes and their metabolites in the axis of MASLD and HFpEF are unclear.

Materials/Methods: We generated mice deficient in Cyp2c29, which is the most abundant CYP2C isoform in liver. Mice were treated with high-fat diet (HFD) and N-Nitro-L-arginine methyl ester hydrochloride (L-NAME) for 10 weeks to induce HFpEF. Longitudinal assessments included measurements of blood pressure and echocardiography. Terminal endpoints comprised of liver and serum EET and DHET levels and markers of inflammation, fibrosis, and fat accumulation in the liver and heart.

Results: HFpEF treatment led to reductions in liver CYP2C and EET levels with a concomitant increase in sEH and ratio of DHET to EET. Unexpectedly, loss of Cyp2c29 attenuated liver steatosis and lipid peroxidation. This was associated with reduced monocyte recruitment to the heart and improved cardiac function. Similarly, pharmacologic inhibition of sEH during HFpEF abrogated monocyte mobilization to the heart. Treatment of mice with exogenous DHET alone was sufficient to increase abundance of monocytes and their progenitors in bone marrow reservoirs, which required hypoxia inducible factor signaling in monocytes.

Conclusions: Taken together, our data reveals a causal role for hepatic-derived eicosanoids in regulating monocytes and cardiac inflammation in the axis of MASLD and HFpEF and support further exploration of therapeutic potential.

Poster 18

CYTOSOLIC DNA-STING-IRF3/4 PATHWAY MEDIATES EPIGENETIC INDUCTION OF MACROPHAGE PHENOTYPIC POLARIZATION IN ACUTE THORACIC AORTIC ANEURYSM AND DISSECTION

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Background: Sporadic acute thoracic aortic aneurysm and dissection (ATAAD) involves severe inflammation and macrophage infiltration into the aortic wall. However, the mechanisms driving pro-inflammatory macrophage phenotypes remain unclear. This study explores the epigenetic regulation of macrophage polarization in ATAAD.

Materials/Methods: Single-cell RNA sequencing (scRNA-seq) of human ATAAD macrophages, along with scRNA-seq, spatial RNA-seq, and single-cell ATAC-seq (scATAC-seq) of aortic macrophages in angiotensin II (Ang II)-induced ATAAD mice, was performed. In vitro studies investigated the role of the cGAMP-STING-IRF3 pathway in epigenetic macrophage regulation. Macrophage-specific Sting or Irf4 deletion was assessed in ATAAD mice.

Results: scRNA-seq identified diverse macrophage (MΦ) subsets, including pro-inflammatory, phagocytic/anti-inflammatory, and reparative/healing MΦs. ATAAD aortic MΦs showed increased pro-inflammatory and reduced phagocytic populations, confirmed by spatial transcriptomics. scATAC-seq revealed epigenetic reprogramming with enhanced chromatin accessibility at pro-inflammatory genes and reduced accessibility at phagocytic loci. Transcription factors (TFs) such as IRF3 were implicated in driving pro-inflammatory differentiation. In cultured monocytes/MΦs, dsDNA from damaged aortic cells acted as danger signals, activating cytosolic DNA/cGAMP-STING-IRF3/IRF4 signaling to promote pro-inflammatory chromatin remodeling. Macrophage-specific Sting or Irf4 deletion mitigated Ang II-induced ATAAD in mice.

Conclusions: Aortic stress epigenetically drives pro-inflammatory macrophage polarization, contributing to aortic inflammation and ATAAD progression. The STING-IRF3/IRF4 pathway is a critical regulator of this process, presenting a potential therapeutic target for ATAAD.

Poster 19

COMPLEMENT SIGNALING ORCHESTRATES AN IMMUNOSUPPRESSIVE MICROENVIRONMENT DURING CARDIAC RENEWAL

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Background: After myocardial infarction (MI), adult mammalian hearts fail to regenerate, and the cardiac microenvironment is irreversibly disrupted. In contrast, MI in neonatal mammals induces proliferation of existing CMs, resulting in near-complete cardiac renewal with minimal fibrosis. We found that C3, the central component of the innate immune complement pathway, is increased in epicardial cells (EpiCs) and cardiac fibroblasts (CFs) after neonatal MI.

Materials/Methods: We used single-cell RNA-sequencing combined with spatial transcriptomics to examine the cellular relationships within the microenvironment of regenerating neonatal murine hearts. We conditionally knocked out C3 in EpiCs and CFs of murine hearts to determine the role of C_3 in neonatal cardiac renewal.

Results: Loss of C3 in EpiCs and CFs resulted in a metabolic shift towards oxidative phosphorylation, aberrant activation of interferon-mediated signaling, increased fibrosis, and impaired cardiac function after neonatal MI.

Conclusions: These results indicate that C3 and the complement pathway are required for conditional a pro-renewal immunosuppressive microenvironment during cardiac renewal.

Poster 20

FUNCTIONAL ASYMMETRY OF CARDIAC MACROPHAGES IN LEFT AND RIGHT ATRIA

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Background: The left atrium (LA) and right atrium (RA) differ in physiology due to distinct hemodynamic and tissue environments. The RA, exposed to systemic circulation, faces greater oxidative stress and immune challenges, potentially influencing disease susceptibility, particularly atrial fibrillation (AFib). However, a detailed molecular comparison of atrial cell diversity in adult models is lacking. We hypothesize that RA and LA differ in cellular composition and immune microenvironment, impacting atrial homeostasis and disease risk.

Materials/Methods: We performed single-nucleus RNA sequencing (snRNA-seq) on healthy adult mouse atria to characterize cardiac cell diversity. Spatial transcriptomics validated findings in situ, and human snRNA-seq reanalysis confirmed conservation across species. To assess macrophage function, we conducted electrophysiological studies in Ccr2 knockout (Ccr2-KO) mice, which lack the chemokine receptor Ccr2 required for macrophage recruitment.

Results: We identified distinct cell states in fibroblasts, endothelial cells, epicardial cells, and macrophages. RA stromal cells showed higher metabolic activity, oxidative stress, and immune gene expression. RA macrophages were enriched in pro-inflammatory monocyte-derived macrophages (MoMPs), while LA had more anti-inflammatory tissue-resident macrophages (TRMPs), a pattern conserved in human hearts. Ccr2-KO mice exhibited an 80% reduction in RA MoMPs, increased AFib susceptibility, and impaired atrioventricular conduction.

Conclusions: The RA is a metabolically active environment with heightened basal inflammation, requiring immune surveillance maintained by abundant MoMPs. Balancing immune and metabolic activity is crucial for atrial health and a potential target for AFib treatment.

Poster 21

ALTERED CELLULAR COMPOSITION AND PRO-INFLAMMATORY SIGNATURES IN MARFAN SYNDROME AORTIC TISSUES

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Background: Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by mutations in the FBN1 gene. Aortic enlargement, a hallmark of MFS, can progress to dissection that is life-threatening. Understanding the molecular and cellular processes of aortic enlargement is crucial for identifying therapeutic targets to prevent disease progression.

Materials/Methods: We performed single-cell RNA sequencing (scRNA-seq) on aortic tissues from MFS patients (n=9) and age-matched non-aneurysmal diseased controls (n=10).

Results: MFS aortas exhibited significantly smaller populations of smooth muscle cells (SMCs) and fibroblasts but higher numbers of macrophages and T lymphocytes. Principal component analysis revealed distinct gene expression profiles in fibroblasts and macrophages from MFS patients compared to controls. Consistently, these two cell types displayed the highest number of differentially expressed genes in MFS. Genes that are involved in the response to misfolded proteins, such as DNAJB4 and HSP90AA1, were reduced in both fibroblasts and macrophages in MFS. Additionally, compared with control tissue, fibroblasts in MFS showed increased expression of genes in extracellular matrix organization, chemotaxis, and antigen presentation, while macrophages exhibited higher levels of genes associated with antigen processing, T lymphocyte activation, and cytokine production. Cell-cell interaction analysis suggested that fibroblasts acted as stronger signal senders, while T lymphocytes were more active signal receivers in MFS.

Conclusions: Key characteristics of the structurally vulnerable aortic wall in MFS patients include decreased SMC and fibroblast populations, increased macrophage and T lymphocyte populations, and pro-inflammatory features in fibroblasts and macrophages.

Poster 22

SUMO2/3 EXCLUDES YAP5SA FROM THE NUCLEUS AND INHIBITS CARDIOMYOCYTE PROLIFERATION

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Background: Adult mammals, including humans, have limited cardiomyocyte (CM) regeneration, so cardiac injuries, such as myocardial infarction (MI), cause permanent damage and impaired heart function, leading to heart failure. In adult hearts, Hippo signaling is active and prevents CM proliferation by repressing the YAP1 transcription co-factor. However, a constitutively active form of YAP1, known as YAP5SA, bypasses this regulation and promotes adult CM proliferation in mice. We aimed to understand how YAP5SA nuclear and cytoplasmic localization contribute to CM proliferation and find interactors that regulate this process.

Materials/Methods: We used co-immunoprecipitation (Co-IP) and mass spectrometry (MS) immunofluorescence (IF) staining and western blotting (WB) to determine YAP5SA subcellular localizatio and its interactors. We then used pharmacologic reagents, adeno-associated viruses, and genetic mous models to determine if inhibition of SUMO2/3, a YAP5SA interactor, affects subcellular YAP5SA localizatio and CM proliferation.

Results: Using Co-IP and MS, we found SUMO2/3 to be a YAP5SA interactor and upregulated in YAP5SA-expressing hearts. We confirmed the interactions using IF and WB. IF showed colocalization of YAP5SA and SUMO2/3, which moved from the nucleus into the cytoplasm over six days after tamoxifen-induced activation of YAP5SA. To assess the role of SUMO 2/3 in CM proliferation, we inhibited SUMOylation and found increased nuclear YAP5SA, sarcomere disassembly, and cell cycle activity in CMs.

Conclusions: These findings suggest that SUMOylation plays a crucial role in regulating the nuclear localization of YAP, and its inhibition may improve the efficacy of YAP-based therapeutics for cardiac renewal.

Poster 23

YAP INDUCES A PRO-RENEWAL METABOLIC STATE IN CARDIOMYOCYTES

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Background: Cardimyocytes possess a limited capacity for renewal contributing to the pathogenesis of heart failure. Neonatal rodent and porcine models possess the ability to regenerate CMs following injury; however, CM regeneration rapidly declines with CM maturation, suggesting an inhibitory network between cellular maturation and proliferation in CMs. During this maturation process, CMs undergo a metabolic shift from predominantly glycolysis towards increased reliance on fatty acid oxidation (FAO) in the mature state. While such metabolic state is required to meet the increased energetic demands during heart maturation, it establishes a barrier to CM proliferation.

Materials/Methods: We explored how YAP induces metabolic remodeling through transcriptomic (snRNA-seq) and metabolomic analyses in mice. By using lipidomic analysis, we demonstrated how YAP induces metabolic reprogramming by remodeling the balance of fatty acid catabolism and anabolism. Following ATAC-seq, DNA footprinting, and transcriptional profiling (RNA-seq), we aim to discover the key transcription factors that YAP interrupts to reprogram the CM metabolic states.

Results: We found that YAP directs metabolic remodeling from mature CM to neonatal-like CM metabolic state and illustrate how fatty acid metabolism functions in proliferating CMs. We found that YAP reduced CM fatty acid utilization, driving fatty acid anabolism and phospholipid biosynthesis. We identified that YAP transcriptional activity inhibits the cardiac maturation transcription factor MEF2A genome wide, resulting in decreased gene expression of CM maturity pathways. Perturbing MEF2A transcriptional activity can serve as a strategy to interrupt the CM maturation program and restore regenerative capacity of the heart.

Conclusions: Our research endeavors to provide a comprehensive understanding of the balance of CM metabolic maturation and proliferation to overcome the barriers of heart regeneration, offering novel insights into the potential for therapeutic intervention in heart failure.

Poster 24

SEX DIFFERENCES IN ATRIAL SUBSTRATE FIBROSIS IN ATRIAL FIBRILLATION

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Background: Atrial fibrillation (AF) is the most common arrhythmia that leads to morbidity and mortality due to cardioembolic events, leading to stroke and dementia. While the exact pathogenesis of AF remains unclear, emerging evidence suggests atrial remodeling (fibrosis) and inflammation to be the niche of altered electrical activity. This risk is notably higher in elderly women, who are also more likely to experience severe consequences from AF, including disability or death. There is a large gap in our understanding of the pathogenesis of sex differences in AF and the objective of this study was to understand these mechanisms.

Materials/Methods: Cardiac tissue from C57BL/6J aged (18 months) male and female mice was stained with Masson's trichrome stain and ImageJ was used to quantify the area of fibrosis. We also collected human autopsy atrial tissue from patients with AF and controls and similarly analyzed using Masson's Trichrome stain to detect fibrosis. Patient demographics were collected from electronic health records at Memorial Hermann.

Results: We found that aged female mice had increased fibrosis in the atrial tissue (2.02±0.25, n=12) as compared with aged males, (5.24±1.12, n=9), p=0.01. This suggests increased atrial tissue remodeling in aged females. In the human autopsy samples, we compared control and AF atrial tissue samples for fibrosis and found a trend towards increased fibrosis in patients with AF (3.1±2.1) as compared to control patients (1.9±0.), p=0.08, n=4/gp.

Conclusions: Our data suggests that aged females have increased atrial remodeling and fibrosis as compared to males. We are still collecting human atrial tissue samples to detect sex differences in fibrosis and inflammation and preliminary data suggests increased atrial fibrosis in patients with AF, supporting our work in animal models. Future studies on cardiac inflammation on human histology samples will further shed light on these mechanisms.

Poster 25

ATRIAL FIBROBLAST-DERIVED MACROPHAGE MIGRATION INHIBITORY FACTOR PROMOTES ATRIAL MACROPHAGE ACCUMULATION IN POSTOPERATIVE ATRIAL FIBRILLATION

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Background: Macrophage migration inhibitory factor (MIF) is a cytokine with macrophage chemoattractant properties. Prior studies reported MIF to be involved in atrial fibrosis and sarcoplasmic reticulum calcium mishandling, but no studies have assessed MIF in postoperative AF (poAF). We previously demonstrated that pro-inflammatory macrophages play a fundamental role in poAF development. Here, we explored the role of MIF as an upstream driver of atrial macrophage recruitment after cardiac surgery.

Materials/Methods: Using our published poAF mouse model, we conducted single-cell RNA sequencing (scRNAseq) comparing atrial non-myocytes from mice with poAF (TAF) versus sham. We collected pericardial fluid (PF) from human patients 24-h after cardiac surgery as a surrogate of local cardiac inflammation and used this PF to challenge THP-1 monocytes in vitro.

Results: Using our scRNAseq dataset, we found MIF to be a top cell-cell communication pathway in TAF versus sham mice. To test whether MIF signaling is necessary for atrial macrophage recruitment after cardiac surgery, we inhibited MIF using 4-IPP, which attenuated postoperative atrial macrophages (2.0-fold, P=0.024), poAF incidence (5.2-fold, P=0.036), and poAF duration (9.3-fold, P=0.037). To assess the translatability of our findings, we assessed MIF levels in the PF of human patients 24-h after open-heart surgery and found that PF MIF levels were greater in patients with versus without poAF (1.7-fold, P=0.038). To definitively show that PF MIF was necessary for monocyte activation and recruitment, we challenged THP-1 monocytes with PF from poAF patients and found that MIF inhibition was sufficient to attenuate PF-induced monocyte activation.

Conclusions: Altogether, MIF is necessary for atrial macrophage recruitment after cardiac surgery and poAF. Given that an early MIF surge likely plays a key role in poAF, PF MIF may portend prognostic utility for poAF, and perioperative MIF inhibition may attenuate atrial macrophage recruitment and poAF.

Poster 26

DE NOVO NUCLEOTIDE SYNTHESIS IS NECESSARY FOR DNA DAMAGE AND REPAIR IN ATHEROPRONE ENDOTHELIAL CELLS

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Background: Endothelial cell (EC) metabolism is tightly regulated by hemodynamic changes to protect them from atherogenic injury induced by disturbed flow (d-flow) and other atherogenic risk factors. Therefore, characterizing the role of flow-induced metabolic reprogramming is important to develop new treatments for atherosclerosis and similar diseases. Currently, the effect of proatherogenic d-flow on EC nucleotide metabolism, including de novo purine and pyrimidine synthesis, remains under explored. ATIC and CAD are critical enzymes for de novo purine synthesis and pyrimidine synthesis, respectively. We investigated the role of ATIC and CAD-mediated de novo nucleotide metabolism in atheroprone ECs.

Materials/Methods: scRNA-seq and bulk RNA-seq were used to analyze metabolic gene expression in atheroprone ECs. Primary ECs were cultured to investigate the role of nucleotide synthesis in DNA damage. EC-specific Atic knockout mice were generated and utilized to examine its role in two atherosclerosis models.

Results: (i) scRNA-Seq analysis results showed that DNA damage response was increased in ECs exposed to d-flow, this was accompanied by increased ATIC-mediated de novo purine synthesis and CAD-mediated de novo pyrimidine synthesis; (ii) Knockdown of ATIC or CAD with siRNA aggravated EC DNA damage, apoptosis and EC permeability induced by d-flow or other atherogenic factors; (iii) Supplement of nucleobases can rescue ATIC KD-mediated DNA damage and apoptosis in ECs; (iv) MYC, predicted high stringency binding with ATIC promoter, was highly expressed in d-flow induced ECs and MYC knockdown reduced the increased ATIC expression in d-flow induced ECs; (v) The atherosclerotic lesion size was markedly increased in EC-specific Atic deficient mice in atherosclerosis.

Conclusions: ATIC and CAD-mediated de novo nucleotide synthesis in ECs supply nucleotides to repair DNA damage and preserve EC barrier integrity in vulnerable atheroprone regions and ultimately protect against the development and progression of atherosclerosis.

Poster 27

CRAT TO THE RESCUE: ENHANCING CARDIAC FUNCTION AND COMBATING NASH

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Background: Increased hepatic de novo lipogenesis contributes to heart failure progression via lipotoxicity, metabolic inflexibility, and systemic inflammation. However, hypertriglyceridemia limits the use of pharmacological ACC inhibitors as a monotherapy. CRAT (carnitine acetyltransferase) facilitates the transfer of acetyl groups between CoA and carnitine, allowing acetylcarnitine to shuttle between mitochondria and cytosol. Depletion of carnitine acetyltransferase (CRAT) promotes cholesterol catabolism through bile acid synthesis pathway in cardiomyocytes, but weather overexpression is effective for improving cardiac function and treating NASH is unknown.

Materials/Methods: Here, we characterize a new mouse model with AAV-CRAT overexpression in hepatocytes, which improves diastolic dysfunction in the heart, as assessed via echocardiography, and reduces blood glucose, cholesterol, and triglycerides, measured through serum analysis using commercially available kit protocols. We divided the mice into four groups: a control (GFP) group on normal chow, a control (GFP) group on a high-fat diet, a CRAT group on normal chow, and a CRAT group on a high-fat diet.

Results: We observed improved diastolic function, blood glucose levels, cholesterol, and triglycerides in the AAV-CRAT group. Carnitine acetyltransferase (CRAT) exists as a single gene product but has multiple isoforms due to alternative targeting sequences that direct it to different subcellular compartments. These isoforms play key roles in acetyl-CoA metabolism and energy regulation. We are studying the localization and differential expression of CRAT isoforms in the heart and liver, which will help us better understand their role in energy metabolism and their potential impact on metabolic regulation and disease processes.

Conclusions: Enhancing CRAT activity may improve metabolic efficiency and heart health preventing heart failures and ischemic conditions.

Poster 28

INHIBITION OF BMPER MITIGATES PULMONARY ARTERIAL REMODELING BY MODULATING LRP1-YAP INTERACTION IN SMOOTH MUSCLE CELLS

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Background: Bone morphogenetic protein (BMP)-binding endothelial regulator (BMPER) is a secreted protein that is highly expressed in endothelial cells (ECs). It regulates the BMP pathway during the vascular development and adulthood. Mutations in the BMP pathway are recognized as risk factors for pulmonary arterial hypertension (PAH)-Group 1 pulmonary hypertension (PH). However, BMPER's roles in PAH remain unknown.

Materials/Methods: We assessed BMPER expression in PAH patient samples and examined its role in vascular remodeling using in vivo and in vitro approaches.

Results: BMPER level was elevated in PAH lung tissues and significantly associated with pulmonary vascular resistance. However, no increase was observed in patient plasma. Global and EC-specific depletion of BMPER in a mouse model of hypoxia-induced PH displayed attenuation in pulmonary artery smooth muscle cell (PASMC) proliferation, a hallmark of pulmonary vascular remodeling, and reduced right ventricular pressures. Conversely, adeno-associated virus-assisted BMPER overexpression targeted to the pulmonary endothelium led to the spontaneous development of PH. Mechanistically, BMPER promoted YAP (yesassociated protein 1) activation through release of YAP sequestration by LRP1 (low density lipoprotein receptor-related protein 1), a BMPER endocytic receptor, in the membrane of PASMCs. Moreover, the protective effect of BMPER depletion can be reversed by simultaneous depletion of LRP1 in mice with hypoxia-induced PH

Conclusions: Collectively, these results implicate secreted BMPER as a discrete regulator for pulmonary vascular remodeling and suggest its inhibition as a new potential therapeutic strategy against PH.

Poster 29

ANTHRACYCLINES INDUCE GLOBAL CHANGES IN CARDIOMYOCYTE CHROMATIN ACCESSIBILITY THAT OVERLAP WITH CARDIOVASCULAR DISEASE LOCI

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Background: Breast cancer drugs including anthracyclines (ACs) and Trastuzumab increase the risk for cardiovascular diseases (CVD) such as atrial fibrillation (AF) and heart failure (HF) that ultimately affect the heart muscle. These CVD are associated with hundreds of genetic variants in non-coding regions of the genome. However, how these drugs affect the non-coding genome of the heart and CVD risk loci is unknown.

Materials/Methods: We therefore measured global chromatin accessibility across iPSC-derived cardiomyocytes from four individuals treated with the ACs, Doxorubicin, Epirubicin, and Daunorubicin, a related non-AC, Mitoxantrone, and the monoclonal antibody Trastuzumab, or a vehicle control for three and 24 hours.

Results: We identified 155,557 high-confidence regions of open chromatin across 48 samples where the major sources of variation are associated with drug type and time. Jointly modeling the data revealed three accessibility response signatures denoted as early-acute, early-sustained, and late that correspond to 65,844 regions that open or close in response to drug treatment. Sequences associated with drug-induced chromatin opening contain motifs for DNA damage-associated transcription factors including p53 and ZBTB14, and associate with increases in active histone acetylation and gene expression. 21 AF- and HF-associated SNPs directly overlap with regions associated with drug-induced opening. A shared intronic HF and AF SNP, rs3176326, that is also an eQTL for CDKN1A in heart tissue, associates with increased chromatin accessibility, histone acetylation and CDKN1A expression in response to all ACs.

Conclusions: Our results demonstrate large-scale changes in chromatin accessibility in cardiomyocytes treated with ACs, which correspond to several regions harboring CVD risk loci.

Poster 30

NOVEL APPROACH FOR QUANTITATIVE, VOLUMETRIC ASSESSMENT OF EARLY BLOOD FLOW SPEEDS FOR EARLY EMBRYONIC CARDIOVASCULAR PHENOTYPING

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Background: The biomechanical force of early blood flow is vital to proper heart development, yet studying patterns of blood flow during early cardiovascular development remains limited by existing technologies. Imaging embryonic heart movement in mouse models is possible using optical coherence tomography (OCT), but no established method can quantify speed throughout the early heart and vasculature. By integrating our lab's recent live heart imaging methods and developing a new approach to speed measurements, this project enables spatially and temporally resolved measurement of blood flow speeds in embryonic mice as the heart beats and presents the first quantitative, volumetric map of blood flow speeds in the embryonic cardiovascular system.

Materials/Methods: Our approach integrates live embryo culture, high-speed structural OCT imaging, cardiodynamic synchronization, segmentation of blood flow based on speckle variance between subsequent heartbeats, and a novel speed analysis method based on the duration that each pixel detects a particle, particle size statistics, and the periodicity of the cardiac cycle. The presented example was imaged on embryonic day 8.5 (E8.5) volumetrically at 100 fps with ~55 frames per heartbeat.

Results: The newly developed method was first validated by Doppler OCT in a yolk sac vessel, then applied to the whole cardiovascular system. This method quantifies patterns of blood flow over the heartbeat, accurately measures steady flow speed in regions of known flow and reveals spatial differences in flow speed dynamics.

Conclusions: We present the first quantitative reconstruction of the early blood flow pattern in beating embryonic heart and early cardiovascular system. Our novel method allows direction-independent analysis of early blood flow speeds in cultured mouse embryos. This new capability enables biomechanical studies of early blood flow, functional phenotyping over developmental milestones, and investigation of the regulatory effects of circulation in early heart development.

Poster 31

PHOSPHORYLATION OF RYR2 AT SERINE 2808 MEDIATES ATRIAL FIBRILLATION IN CHRONIC KIDNEY DISEASE

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Background: Atrial Fibrillation (AF) is the most common sustained arrhythmia and is frequent in chronic kidney disease (CKD) patients. AF can be caused by calcium (Ca^{2+}) dysregulation in cardiomyocytes. Ca^{2+} dysregulation is usually caused by altered ryanodine receptor 2 (RyR2) phosphorylation at serines 2808, 2814, or 2367 by protein kinase A (PKA), calmodulin kinase type II (CaMKII) or striated-muscle preferentially expressed (SPEG), respectively.

Materials/Methods: CKD was induced in mice by 5/6 nephrectomy. Pacing electrical stimulation studies were used to analyze AF incidence in CKD mice. Intracellular Ca^{2+} handling was analyzed by confocal microscopy in isolated atrial cardiomyocytes (ACMs). Western blotting was used to study RYR2 phosphorylation. Ca^{2+} handling in transgenic mice lacking 2808 phosphorylation (S2808A) was analyzed.

Results: Ca^{2+} spark frequency (CaSF) was greater in the CKD mice with AF (CKD-AF) compared to sham ($P<0.01$) and CKD in sinus rhythm (CKD-SR) ($P<0.001$). Sparks were wider in CKD-AF than in Sham ACMs ($P<0.001$). No changes in Ca^{2+} transient amplitudes (CaT) were observed in CKD-AF. CaT decay time (tau) was significantly higher in CKD-AF than in Sham ($P<0.01$) and CKD-SR ($P<0.001$) ACMs, suggesting slower SERCA2a activity. No changes were observed in sarcoplasmic reticulum Ca^{2+} load in CKD-AF while it was smaller in CKD-SR ACMs ($P<0.01$). Caffeine-induced CaT tau was smaller in CKD-AF than Sham ($P<0.05$) and CKD-SR ACMs ($P<0.01$), suggesting faster sodium/calcium exchanger (NCX) activity in CKD-AF ACMs. Only RyR2 phosphorylation at Ser2808 was significantly decreased in CKD-AF atria compared to Sham and CKD-SR ($P<0.05$) suggesting that PKA is potentially responsible of these alterations. ACMs from S2808A mice recapitulated similar Ca^{2+} mishandling to CKD-AF mice.

Conclusions: In conclusion, reduced phosphorylation is RyR2 at S2808 might be responsible for intracellular Ca2+ dysregulation in ACMs from CKD-AF mice, highlighting PKA as possible therapeutic target to prevent AF in CKD patients.

Poster 32

STRUCTURAL-COMPOSITIONAL INTERPLAY OF ELECTRONEGATIVE LIPOPROTEINS: TEM AND OMICS INSIGHTS INTO LDL, VLDL, AND HDL

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Background: During myocardial ischemia, cardiomyocytes rely on lipids for energy, increasing metabolic stress. Lipoproteins play a key in this process, but their modifications under ischemia remain unclear. This study aims to clarify these changes using TEM and omics, providing insights into how lipoprotein remodeling impact ischemic heart disease and guide potential therapeutic strategies.

Materials/Methods: LDL, VLDL, and HDL subfractions from healthy donors were isolated via sequential density-gradient ultracentrifugation coupled with anion-exchange chromatography, yielding five subclasses (L1-L5, V1-V5, and H1-H5) with L5, V5, and H5 as the most electronegative in each class. Across subfractions, molecular characterization of lipid species and protein cargo was achieved through high-resolution mass spectrometry-based lipidomics and shotgun proteomics with rigorous analytical validation ensuring reproducibility.

Results: High-resolution transmission electron microscopy (TEM) revealed size heterogeneity among electronegative lipoprotein subclasses, with L5, V5, and H5 exhibiting larger diameters and irregular surface morphology compared to less electronegative counterparts. Lipidomic analysis showed higher triglyceride and lower phosphatidylcholine levels in these subclasses, while proteomics identified consistent enrichment of the atherogenic apo(a), apoCIII, and apoJ, indicating distinct structural and compositional features that may influence their functional properties.

Conclusions: The study reveals a correlation between lipoprotein electronegativity and structural-compositional remodeling in L5, V5 and H5 subfractions, supporting distinct functional properties. The similarity between L5 and V5 suggests a potential metabolic link, with L5 possibly being a descendant of V5. These findings highlight the role of lipoprotein electronegativity in cardiovascular pathophysiology, emphasizing its impact on both arterial and cardiomyocytic homeostasis.

Poster 33

DEFINING POSTNATAL CARDIOMYOCYTE MATURATION STAGES USING A TRANSCRIPTIONAL CLOCK

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Background: During postnatal development, cardiomyocytes undergo metabolic, sarcomeric, and cell cycle changes during the transition from fetal to adult cardiomyocytes. These biological changes have great impacts on injury response, with injury in an early postnatal state leading to a regenerative injury response, while injuries after cardiomyocyte maturation result in hypertrophic or fibrotic injury response. However, the mechanisms that govern maturation and act as a barrier to entry for cardiomyocyte proliferation are still not well defined.

Materials/Methods: We aimed to characterize the transcriptional states and regulators throughout postnatal cardiomyocyte maturation. Isolating cardiomyocyte nuclei and performing RNAseq across postnatal development we identified that cardiomyocyte maturation is not linear but rather occurs in a stepwise fashion with three key transition times. The three transitions occur between postnatal day 1 (P1) to P3, P5 to P7, and P11 to P21. Using this data set, we generated a transcriptional clock using a linear regression model to score cardiomyocytes based on transcriptional age.

Results: Our model was tested using published data sets, followed by examining how maturation perturbations could shift the transcriptional age of cardiomyocytes. Specifically, we perturbed maturation using YAP5SA, a constitutively active version of the transcriptional effector Yap1 that has been previously demonstrated to promote cardiomyocyte proliferation. Treating mice with cardiomyocyte specific YAP5SA via adeno-associated virus 9 we observed a significant decrease in transcriptional age of cardiomyocytes compared to controls.

Conclusions: Our study provides a novel understanding of postnatal cardiomyocyte maturation by defining distinct stages of postnatal cardiomyocyte maturation rather than a gradual linear progression. Additionally, we generated a transcriptional clock that can be utilized by the field to examine how genetic perturbations may impact cardiomyocyte maturation state.

Poster 34

CX-5461 INDUCES A GENE EXPRESSION SIGNATURE IN CARDIOMYOCYTES THAT IS SHARED WITH DOXORUBICIN WITHOUT THE CARDIOTOXICITY

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Background: CX-5461 is a chemotherapeutic drug that is in clinical trials for the treatment of solid tumors enriched for DNA-repair deficiencies. While CX-5461 was initially described as an RNA pol I inhibitor, it has recently been shown to be a topoisomerase II poison that primarily targets TOP2B. Anti-cancer drugs such as Doxorubicin (DOX) also target TOP2B which can result in cardiotoxicity. It has therefore been suggested that CX-5461 may also induce cardiotoxicity.

Materials/Methods: We therefore designed a study to investigate the effects of CX-5461 on iPSC-derived cardiomyocytes from six individuals. We compared the cellular and molecular response to CX-5461 and DOX at 0.1 and 0.5 uM concentrations at 3, 24 and 48 hours post-treatment.

Results: CX-5461 is less cardiotoxic than DOX based on cell viability measurements 24 hours following treatment (LD50 DOX = 0.65 uM, CX-5461 = 9.98 uM). Similarly, the proportion of cells expressing the DNA damage marker γ-H2AX 24 hours post sub-micromolar drug treatment is higher in DOX-treated cells (DOX = 90%, CX-5461 = 6%). Consistent with the strong cellular effects of DOX, transcriptomic analysis between DOX and a vehicle control identified thousands of gene expression changes. In contrast CX-5461 induced 441 gene expression changes across drug concentrations and time. Comparison of gene expression drug response trajectories over time reveals response signatures that are shared between CX-5461 and DOX, and specific to DOX. There are no CX-5461 unique signatures. Shared response genes correspond to pathways related to the cell cycle and DNA replication. A total of 33 genes in loci associated with DOX-induced cardiotoxicity show gene expression changes in response to DOX and only one gene (GPSM2) in response to CX-5461.

Conclusions: Our results indicate that CX-5461 treatment of cardiomyocytes induces gene expression changes that mirror some of those induced by DOX, but these effects do not coincide with the cardiotoxicity observed with DOX treatment.

Poster 35

ATAD3 IS AN ESSENTIAL COMPONENT OF THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE

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Background: Coronary heart disease is the leading cause of death in the U.S., with over 800,000 adults experiencing a heart attack annually. During myocardial infarction (MI), coronary artery obstruction deprives the myocardium of oxygen, disrupting cellular Ca^{2+} homeostasis. This results in elevated cytoplasmic Ca^{2+} levels and subsequent mitochondrial Ca^{2+} accumulation. Once mitochondrial matrix Ca^{2+} reaches a critical threshold, the mitochondrial permeability transition pore (mPTP) opens, leading to mitochondrial membrane depolarization, swelling, ATP depletion, and ultimately, mPTP-dependent necrosis—a key driver of ischemic injury in the heart. Although several mPTP regulators have been identified, no single genetic ablation has completely prevented mPTP activation, and the pore-forming component remains unknown. We hypothesize that we have identified a novel essential component of the mPTP and inhibiting this component will confer cardioprotection during ischemia/reperfusion (I/R) injury.

Materials/Methods: Through a genome-wide screen for novel cell death regulators, we identified ATAD3, an inner mitochondrial membrane ATPase, as a potent inducer of cell death. To investigate its role in ischemic heart disease, we generated a cardiac-specific ATAD3 knockout mouse.

Results: Deletion of ATAD3 exhibited significant cardioprotection during I/R injury. Mechanistically, ATAD3 deletion completely inhibited mPTP opening during Ca^{2+} overload, and prevented mitochondrial swelling—a phenomenon also observed in a liver-specific ATAD3 knockout model.

Conclusions: To our knowledge, ATAD3 is the first essential component of the mPTP identified. These findings highlight the therapeutic potential of targeting ATAD3 to inhibit mPTP opening, reduce infarct size, and preserve cardiac function following MI.

Poster 36

CLOSED LOOP SOLUTE TRANSPORT IN BLOOD VESSELS AND ORGANS

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Background: Hypoplastic left heart syndrome (HLHS) is a congenital heart disease that causes oxygenated blood to mix with deoxygenated blood, resulting in death. This raises a critical need to accurately model the transport of oxygen in blood vessels and organs throughout the human body to improve outcomes in patients with HLHS.

Materials/Methods: Previously, numerical reduced models have been created to solve for blood flow and concentration of one solute. These models reduce the dimensions of the vessels and organs to improve computational efficiency. This work extends the models from open network of blood vessels to closed loops and includes organs. Appropriate transmissibility conditions at each vessel junction and organ bed are constructed, that are based on balance laws. The class of interior penalty discontinuous Galerkin methods is used for the spatial discretization of the models. The blood flow equations are discretized in time using a two-stage Runge-Kutta scheme and we solve for the momentum of the blood and cross-sectional area of the vessel first. We then discretize the solute transport equation in time using a forward Euler scheme and solve for the oxygen concentration.

Results: We test several networks of vessels and organs as part of the numerical experiments. The conservation of solute mass is of important consideration and the proposed method and numerical results are indeed shown to conserve solute mass.

Conclusions: The numerical scheme developed in this work is shown to conserve solute mass analytically and numerically.

Poster 37

YAP DEFINES GLYCOLYTIC MICROENVIRONMENT TO DRIVE ATRIAL FIBROSIS

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Background: In failing hearts, cellular metabolism and tissue microenvironment are significant altered despite that the underlying mechanisms remain unclear. Cardiac fibrosis, a common pathophysiology associated with various heart diseases, occurs from the excess deposition of extracellular matrix by cardiac fibroblasts (CFs). Inactivation of Hippo pathway in CFs lead to YAP activation that promotes fibrosis and inflammation. How CF YAP regulates metabolism and cell-cell communications are yet to be explored.

Materials/Methods: To study the role of Hippo pathway in CFs, we conditionally knocked out Lats1/2 specifically in the CFs of mouse hearts (Lats1/2CKO). We then performed metabolic approaches, single-nucleus RNA sequencing (snRNA-seq) and spatially resolved transcriptomic profiling (ST) of Lats1/2CKO and control hearts. To identify the cell-cell communications between Lats1/2CKO CFs and other cell types, we performed ligand-receptor analysis of the snRNA-seq data. The functions of Lats1/2CKO CFs sending and receiving signals were tested by pharmacologic inhibitors.

Results: Metabolic approaches, snRNA-seq and ST analyses revealed that Hippo-deficient CFs activated glycolysis and increased cell plasticity during fibrosis and inflammation. Glycolysis inhibition abolished Hippo-deficient CF proliferation and fibrosis. To investigate the role of macrophages (Mac) in this context, we blocked Mac expansion pharmacologically and found that Hippo-deficient CF proliferation, cell plasticity and fibrosis were significantly reduced, suggesting that Macs promoted Hippo-deficient CF proliferation, plasticity and fibrosis. Sequencing analyses and functional studies showed that Macs secreted insulin-like growth factor 1 (IGF1) to activate IGF1 signaling in Hippo-deficient CFs to induce cell proliferation and fibrosis.

Conclusions: CF YAP upregulates glycolysis and promotes CF-Mac communications to induce CF plasticity, fibrosis and inflammation.

Poster 38

PREVENTING NUCLEAR LOCALIZATION OF JUNCTOPHILIN-2 (JPH2) ATTENUATES PROGRESSION OF HF

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Background: JPH2 is essential to maintaining the cardiac junctional membrane complex and efficient excitation-contraction coupling. We showed that a novel C-terminal fragment of JPH2 (JPH2-CTP) is significantly elevated in both pressure overload- and ischemia-induced heart failure (HF). Notably, JPH2-CTP translocates to the nucleus and may promote maladaptive remodeling through alternative splicing (AS) regulation. We hypothesize that preventing JPH2-CTP nuclear localization mitigates HF progression.

Materials/Methods: Ischemia was induced in mice by ligating the left anterior descending coronary artery for 30 min, followed by reperfusion. Pressure overload was induced in mice using transverse aortic constriction (TAC). Confocal microscopy with Zeiss LSM-880 was used to image JPH2-CTP in primary cardiomyocytes.

Results: Nuclear localization of JPH2 using a C-terminus-specific antibody was observed in primary cardiomyocytes isolated from an ischemia-reperfusion model. JPH2-CTP localization was found in discrete nuclear speckles, confirmed by co-localization with nuclear speckle marker SC35. Proteomics and co-IP revealed that JPH2-CTP interacts with C1QBP, a subunit of splicing factor 2 (SF2). Inhibition of SF2-mediated AS of target genes (CaMKIIδ, cTnT, and ZASP) has been shown to mitigate maladaptive remodeling in HF. Inactivating the nuclear localization signal (NLS) within JPH2-CTP using 5 alanine (5A) substitutions prevented JPH2 nuclear translocation. Likewise, blockage of JPH2-CTP nuclear localization in NLS-5A mice coincided with prevention of maladaptive CaMKIIδ AS. Slower disease progression, decreased mortality, and reduced cardiac remodeling were observed in NLS-5A knock-in mice with TAC.

Conclusions: Overall, our study demonstrates that blocking nuclear translocation of JPH2-CTP mitigates HF progression likely via regulation of CaMKIIδ AS. Analysis of AS events in these protected mice through RNA seq could provide critical insights into the nuclear function of JPH2 and pave the way for novel therapies for HF.

Poster 39

BIOMECHANICS OF FUNCTIONAL MITRAL REGURGITATION: OPTIMIZING THE RUFLS BIOREACTOR FOR BETTER DISEASE MODELING

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Background: Functional mitral regurgitation (FMR) is a form of mitral regurgitation (MR) caused by underlying heart disease that distorts the geometry of the mitral valve (MV) annulus and/or papillary muscles. The resulting increased tensile forces throughout the leaflets and chordae tendineae lead to abnormal coaptation during systole, leading to the backflow of blood, or regurgitation. FMR is the least studied form of MV disease, and even less is known about FMR from a biomechanical perspective. Our group has developed a pseudo-physiological flow loop system, RUFLS, to study the effects of altered MV geometry on mitral valve tissue by reproducing disease hemodynamics. RUFLS is capable of sterile, long-term culture of porcine mitral valves at physiological pressures and near physiological flow (3L/min). Using a model that mimicked FMR hemodynamics and valve geometry (5mm apical + 5mm lateral displacement, 65% larger annular area), our group has previously shown that FMR-conditioned MVs became stiffer, more brittle, and less extensible after 1 week.

Materials/Methods: While previous work with RUFLS has provided big-picture insights into the remodeling process that occurs, more needs to be done to further understand the response of MV tissue to these mechanical changes. To address this gap and more accurately generate clinically relevant results, we have been improving upon the current RUFLS bioreactor to address design limitations.

Results: For example, the current bioreactor only accommodates a flat MV annulus ring, when in reality the annulus is more saddle-shaped. Optimizing the RUFLS model into a more anatomically precise flow loop system will allow us to better capture the mechanistic pathways that result in remodeling of the MV, a topic that is still very understudied.

Conclusions: In the end, these improvements will allow us to translate our findings into clinically significant applications such as investigating potential therapeutics that can be developed to treat FMR before it is too late.

Poster 40

CARDIAC MYOCYTE CYTOSOLIC SELF-DNA CONTRIBUTES TO THE PATHOGENESIS OF DESMOPLAKIN-CARDIOMYOPATHY

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Background: Mutations in the DSP gene, encoding desmoplakin (DSP), cause DSP-cardiomyopathy, which is characterized by extensive myocardial fibrosis, cell death, inflammation, and premature death. There is no effective treatment for DSP cardiomyopathy. Recent data implicated increased DNA double-stranded breaks (DSBs) and consequent activation of the nuclear and cytosolic DNA Damage Response (DDR) pathways in a subset of hereditary cardiomyopathies. Whereas activation of the nuclear DDR leads to cell cycle arrest and cell death; activation of the cytosolic DDR, which occurs in response to the release of DNA, activates CGAS-STING1 pathway. We determined the activation and the role of the cytosolic DNA-sensing protein (CDSP) pathway in the pathogenesis of DSP-cardiomyopathy.

Materials/Methods: • Cytosolic nDNA and mtDNA were detected using immunofluorescence staining and PCR. • Activation of the CGAS-STING1 pathway were analyzed through RNA sequencing and immunoblotting. • A genetic blockade of the CGAS pathway was introduced by deleting the Mb21d1 gene encoding CGAS in the DSP-deficient mice to assess its impact on survival, cardiac function, myocardial fibrosis, and cell death.

Results: • DSP-deficient mice exhibited premature death, severe cardiac dysfunction, myocardial fibrosis, and increased pro-inflammatory cytokines. • Cytosolic self-DNA were significantly elevated in these mice. • Cytosolic DNA-sensing protein (CDSP) pathway is activated in the cardiac myocytes of DSP cardiomyopathy. • Blocking CGAS improved survival, reduced myocardial fibrosis, decreased cell death, and improved cardiac function.

Conclusions: • Cytosolic self-DNA (nDNA and mtDNA) is increased in cardiac myocytes in DSP-cardiomyopathy and activates the CGAS-STING1 pathway, which induces the expression of pro-inflammatory genes involved in cardiac dysfunction, cell death, and fibrosis. • Genetic blockade of the CDSP pathway significantly mitigates the disease phenotypes, suggesting CGAS as a potential therapeutic target in cardiomyopathy.

Poster 41

GASDERMIN D ENHANCES ATRIAL ARRHYTHMOGENESIS BY PROMOTING MITOCHONDRIAL DYSFUNCTION

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Background: Atrial fibrillation (AF), the most common arrhythmia, is linked to atrial inflammasome activation. The cleaved N-terminal GSDMD (NT-GSDMD), a downstream effector of the activated inflammasome pathways, reportedly can promote the programmed cell death known as pyroptosis. Although the NT-GSDMD protein level is elevated in atrial tissues of AF patients, its role in AF remains unclear.

Materials/Methods: AAV9 was employed to establish ACM-restricted overexpression of NT-GSDMD and the pore-forming defective mutant NT-GSDMD (AAA) in mice. AF susceptibility and the pro-arrhythmic substrate were assessed with echocardiography, programmed intracardiac stimulation, optical mapping, histology, flow cytometry, and immunostaining.

Results: ACM-restricted overexpression of NT-GSDMD in mice increased susceptibility to pacing-induced AF. The NT-GSDMD pore formation is associated with increased IL-1β production, promoting macrophage infiltration. On the other hand, up-regulating 'endosomal sorting complexes required for transport'-mediated membrane-repair mechanisms prevented inflammatory cell death in ACMs. Up-regulated NT-GSDMD directly targeted mitochondria, increasing mitochondrial reactive oxygen species (ROS) generation, which triggered proarrhythmic calcium-release events. The NT-GSDMD-induced arrhythmogenesis was mitigated by the mitochondrial-specific antioxidant MitoTEMPO. The AAA-mutant NT-GSDMD lacking pore-formation capability failed to cause mitochondrial dysfunction or induce atrial arrhythmia. Genetic ablation of Gsdmd prevented AF development in the mouse model of spontaneous AF.

Conclusions: Active NT-GSDMD could induce IL-1β release and mitochondrial dysfunction, creating an AF substrate. This study uncovers a non-pyroptotic role for GSDMD that is associated with the enhanced atrial arrhythmogenesis. Either GSDMD inhibition or reducing ROS production might have the anti-AF potential.

Poster 42

SINGLE CELL TRANSCRIPTOMIC REVEALS THE HETEROGENEITY OF AORTIC FIBROBLASTS DURING AORTIC DISEASE DEVELOPMENT IN MICE

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Background: Aortic fibroblasts are highly dynamic cell populations and critical in repair and remodeling in aortic aneurysm and dissection (AAD). However, their molecular and cellular changes in response to aortic stress remain poorly understood. In this study, we aimed to test the hypothesis that aortic fibroblasts change their phenotypes in response to challenge by performing single-cell RNA seq analysis of aortic tissues from a mouse model of sporadic AAD.

Materials/Methods: We utilize a mouse model of sporadic AAD induced by angiotensin II (AngII) infusion in wild-type mice. To capture the early response of aortic cells to aortic stress, we performed single-cell RNA-seq from ascending aortas at the day 7 time point. 16,187 qualified cells were analyzed by Seurat, edgeR, and Monocle package in R.

Results: We identified 7 aortic fibroblast subsets: extracellular matrix (ECM) producing fibroblasts, myofibroblasts, Tnfrsf11bhigh fibroblasts, 2 clusters of mesenchymal progenitor cells (MPCs), pro-inflammatory fibroblasts, and Cd14+ fibroblasts. These subsets showed specific gene expression patterns indicating their putative functions (eg, increased collagen synthesis and ECM organization in ECM fibroblasts, increased proliferation and migration in Tnfrsf11bhigh and pro-inflammatory fibroblasts, and increased cell adhesion and cell junction organization in myofibroblasts and MPCs). Pseudotime analyses suggest Tnfrsf11b is important in fibroblast trajectory differentiation. Pro-inflammatory and Cd14+ fibroblasts were found almost exclusively in AngII-infused mice compared with saline-infused control.

Conclusions: Aortic fibroblasts showed marked phenotypic heterogeneity and changes in gene expression during aortic stress, suggesting specialized functions of fibroblast subsets.

Poster 43

CALCITONIN-INDUCED MATRIX GLA PROTEIN SUPPRESSES FIBROBLAST ACTIVATION: IMPLICATIONS FOR MITIGATING FIBROTIC REMODELING IN ATRIAL FIBRILLATION

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Background: Background: Atrial fibrosis, driven by fibroblast activation and excessive extracellular matrix deposition, promotes conduction heterogeneity and atrial fibrillation (AF) progression. Cardiomyocyte-derived calcitonin (CT) inhibits atrial fibroblast (ACF) activity, preventing arrhythmogenic substrate development. Proteomics and transcription factor binding analysis identified Matrix Gla Protein (MGP) as a CT-responsive target putatively regulated by PBX1, yet the broader anti-fibrotic relevance of MGP remains elusive. We hypothesize that PBX1 contributes to CT-induced MGP expression and MGP suppresses fibroblast activation.

Materials/Methods: MGP expression was examined in mouse ACFs via immunocytochemistry and in atrial tissue from CREM-Tg mice (spontaneous AF model) using immunoblotting (IB). CT-induced MGP expression was confirmed by qPCR and IB. The role of PBX1 in mediating CT-induced MGP regulation was tested through pharmacological inhibition. PBX1 nuclear translocation was analyzed using immunostaining. Lentiviral MGP knockdown/overexpression in 3T3 fibroblasts assessed fibroblast activation via proliferation (BrdU assay) and activation markers (α-SMA, COL1A1, FN1).

Results: MGP expression was unchanged in 2-month CREM-Tg mice but reduced at 7 and 12 months versus wild type ($p < 0.05$), inversely correlating with COL1A1 (Pearson's $r = -0.581$, $p = 0.048$) and showing a suggestive inverse correlation with FN1 (Pearson's $r = -0.427$, $p = 0.166$). In mouse ACFs, CT upregulated MGP expression ($p < 0.05$), which was blocked by PBX1 inhibition ($p < 0.05$). CT promoted PBX1 nuclear translocation. MGP knockdown exacerbated TGFβ-induced fibrotic marker expression (αSMA, COL1A1, FN1) and basal proliferation ($p < 0.05$), whereas MGP overexpression attenuated these responses ($p < 0.05$).

Conclusions: Our data suggest PBX1 involvement in calcitonin-induced MGP upregulation, and MGP suppresses fibroblast activation. Targeting MGP may mitigate atrial fibrosis, warranting in vivo validation for AF therapy.

Poster 44

LNCRNA CIRCA REGULATES DNA DAMAGE RESPONSE AND RECOVERY IN THE ISCHEMIC HEART

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Background: Disruption of circadian rhythm is associated with cardiovascular diseases, but the exact molecular mechanism remains elusive. Via transcriptional profiling of murine hearts, we discovered a cardiac specific circadian lncRNA Circa, which is uniquely expressed in the cardiomyocytes (CM) of the adult mouse heart. Circa expression is increased postnatally and diminished after stress such as myocardial infarction (MI). Circa null mice exhibit exaggerated infarct and reduce cardiac function after MI. Ectopic expression of Circa protects CM from ischemia injury in vitro and reversed the exaggerated MI phenotype in Circa null mice.

Materials/Methods: Mouse MI surgery (permanent ligation of the left anterior descending coronary artery) and Echocardiogram (Echo) Masson's trichrome staining Primary neonatal & adult cardiomyocytes isolation RNA immunoprecipitation (RIP) RNA Affinity Purification (RAP) Biotinylated RNA pull down assay Mass spectrometry Proximity ligation in situ hybridization (PLISH) In vitro CM ischemic assay Microscopy study

Results: Mechanistically, we found that Circa is primarily localized in the nuclei where it associates with chromatin and RNA binding proteins, including hnRNPA1(A1). Under hypoxia, there is an increased hnRNPA1 translocation to the cytosol, which leads to a concomitant increased cytosolic export and degradation of Circa. The nuclear Circa is critical in reducing the RPA foci formation and R-loop signal induced by hypoxia stress. The down-regulated R-Loop and RPA signal in the MI border zone by Circa is associated with less sustained immune cell infiltration during the recovery stage, which may limit infarct expansion.

Conclusions: In conclusion, our study suggests that LncRNA Circa may regulate DNA damage response and reduce the immunogenic signaling produced from the R-loop structure to down-regulate inflammation level and enhance the ability of the heart to recover from the MI induced damage.

Poster 45

PERSONALIZED PROGNOSIS: A BLESSING OR A BURDEN? PATIENT VIEWS ON SURVIVAL ESTIMATES FOR LVAD THERAPY

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Background: End-stage heart failure patients face difficult decisions: transplant, mechanical circulatory support, or palliative care. Personalized survival estimates (PSEs) offer predictions specifically tailored to a patient's characteristics (e.g. genetics, past medical and surgical history, lifestyle, and current health status). PSEs allow clinicians to provide patients with precise information about their risk profiles when engaging in shared decision-making. Yet, given their novelty, little is known about stakeholder perspectives upon receiving PSEs. How do patients understand, weigh, and respond emotionally to them?

Materials/Methods: As part of a 5-year, multi-institutional study, our research team developed a patient-facing calculator to communicate PSEs to advanced heart failure patients considering left ventricular assist device (LVAD) therapy. In partnership with 7 clinical sites nationwide, we conducted structured interviews with 24 patients considering LVAD therapy. Interviews documented patients' recall and attitudes towards receiving PSEs at 1- and 2-years w/wo LVAD. Interviews were audio-recorded, transcribed, and analyzed using a mixed-methods approach.

Results: Specific recall of PSEs was quite low amongst participants, but a majority (79%) demonstrated high 'gist understanding' of LVAD therapy and its various implications. Most patients (62%) reported their PSEs were "very" or "somewhat" helpful in deciding whether to get an LVAD. About half (52%) said that receiving PSEs made them more likely to get an LVAD, while 38% said it had no impact and 10% (2 people) said it made them less likely. Finally, most (77%) reported a positive emotional reaction, while 24% reported a negative one, and 10% were neutral.

Conclusions: Ours is among the first empirical studies to examine patients' perceptions of personalized risk communication in high-stakes clinical decision making. Our findings suggest patients are receptive to PSEs, though more research is warranted in this growing area of precision medicine.

Poster 46

THE ADDED VALUE OF CARDIAC MRI IN PEDIATRIC RHEUMATOLOGIC DISORDERS

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Background: Systemic Lupus Erythematosus, Systemic Scleroderma, and Mixed Connective Tissue Disease are three common rheumatologic conditions with systemic, multi-organ pathologies. Cardiac presentations of these conditions are known to occur, but optimal surveillance strategy for cardiac complications is not well defined. Echocardiography is the most widely utilized modality for assessing cardiac function in patients with concerns for cardiac symptoms. Cardiac MRI may offer additional insights into myocardial edema and fibrosis. However, data on its utility in pediatric patients with rheumatologic disorders remain limited.

Materials/Methods: We conducted a retrospective study of pediatric patients with SLE, SSc and MCTD who received care at Texas Children's Hospital from 2014 to 2022. Inclusion criteria encompassed all patients who underwent both cardiac MRIs and echocardiogram within three months. Baseline demographic characteristics were recorded and right and left ventricular function were assessed by both modalities. Evidence of myocardial edema and scar/fibrosis on MRI was documented. Chart review was performed to evaluate changes in management following cardiac MRI.

Results: A total of 11 patients met inclusion criteria with a median age of 16 years old and at the time of cardiac MRIs and median disease duration of 1.5 years. Ten were female. Echocardiography identified abnormal ventricular function in 5/11 patients, all of whom had findings confirmed by cardiac MRIs. In addition, cardiac MRIs detected more severe ventricular dysfunction in 4 patients, myocardial edema in 2, and fibrosis in 2. All three patients with edema and/or fibrosis noted on cardiac MRI underwent escalation of immunotherapy, suggesting a clinical impact of these findings.

Conclusions: Cardiac MRI in pediatric patients with SLE, SSc and MCTD provided additional insights beyond echocardiography, identified more severe ventricular dysfunction and detected myocardial edema and fibrosis, which influenced treatment decision.

Poster 47

TUMOR COMPRESSION-INDUCED MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERIES

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Background: Pulmonary artery intimal sarcoma (PAIS) is a rare entity with a 0.001-0.003% prevalence. Clinical manifestations and diagnostic characterizations are similar to that of pulmonary thromboembolism, with a high recurrence rate despite surgical resection and chemoradiotherapy. Due to the aggressive nature of malignancy, myocardial infarction with non-obstructive coronary artery (MINOCA) is a potential life-threatening complication from mass compression or emboli. Here, we present a clinical vignette of inferior myocardial infarction (MI) due to tumor compression.
Materials/Methods: A 38-year-old woman with recurrent, metastatic PAIS status post pneumonectomy and chemotherapy presented with acute chest pain and dyspnea concerning for acute coronary syndrome. Electrocardiogram was notable for ST elevation in leads III and aVF with reciprocal ST depression in leads I and aVL. Troponins peaked at 824 ng/L and transthoracic echocardiogram (TTE) revealed new akinetic inferolateral and posterior wall motion abnormality. Coronary CT angiography showed distal right coronary artery occlusion proximal to the bifurcation of the posterior left ventricular (PLV) and posterior descending artery. A large centrally necrotic soft tissue mass filling the entire left hemithorax was evidenced on chest CT.
Results: Left heart catheterization showed distal PLV artery occlusion and inability of guidewire advancement. Repeat TTE demonstrated a large compressive mass at the left ventricular posterior wall. Given the recurrence and extent of tumor invasion, she was not a candidate for surgical resection or additional chemotherapy and eventually transitioned to comfort care.
Conclusions: We describe an atypical case of tumor compression leading to MINOCA. The etiology was due to the large compressive mass, leading to compromised coronary artery perfusion. Early recognition and surgical intervention are critical to prevent delayed treatment of MI. Clinicians should maintain a high index of suspicion as overall prognosis remains unfavorable.

Poster 48

PERICARDIAL MASS WITH TUMOR-ASSOCIATED THROMBI CAUSING PERICARDIAL EFFUSION AND RIGHT HEART FAILURE

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Background: A myxofibrosarcoma is a rare and aggressive soft tissue sarcoma, which often metastasizes to the lungs, lymph nodes, and bone. It can also spread to the heart and surrounding pericardium, resulting in pericardial effusion or arrhythmias that favor a poor prognosis. Here, we describe a clinical vignette of a new pericardial mass invading the right ventricular outflow tract (RVOT) with tumor-associated thrombi.

Materials/Methods: An 84-year-old male with a right suprapatellar myxofibrosarcoma with metastases to the right inguinal lymph node and lung presented with hypotension and large pericardial and pleural effusions concerning for cardiac tamponade. He obtained a pericardiocentesis and required pressors after his hypotension did not resolve. On subsequent CT and MRI imaging of his chest, he was found to have a 10-centimeter infiltrative pericardial mass into the conus and tumor-associated thrombus with an additional thrombus in the right ventricle (RV). Radiology Oncology saw the patient and felt radiation therapy was an option, but the patient did not tolerate it and developed delirium. He was transitioned to hospice thereafter.

Results: The patient was on anticoagulation for atrial fibrillation (AF) and new RV thrombi, but was also found to have a large pericardial effusion. There was concern that continuing anticoagulation would lead to further expansion of the pericardial effusion and hemorrhage. Because of the size of the pericardial mass and its infiltrative nature, the fear was that he would develop complete obstruction of the RVOT. He also developed significant bruising across his chest that extended to his back while on heparin. A risk-benefit discussion was made within the various treatment teams, and anticoagulation was terminated despite his thrombi and AF indications.

Conclusions: There are risks and benefits to anticoagulation in the course of poor prognoses. Thus, early detection of malignancy progression is imperative to provide patient-centered care and respect the patients' goals of care.

Poster 49

PREDICTING ACUTE ISCHEMIC STROKE IN HEART FAILURE PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES: THE ROLE OF ELEVATED PLASMA HOMOCYSTEINE AND HIGH MOBILITY GROUP BOX 1 PROTEINS

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Background: Left ventricular assist devices (LVADs) can lead to neurological complications despite technological advancements. Among newer continuous flow (CF) LVADs, the early postoperative stroke incidence is 6.3% (0.294 events per patient-year). Elevated plasma homocysteine (Hcy) is a risk factor for acute ischemic stroke (AIS) and can trigger High Mobility Group Box 1 (HMGB1) release. We investigated systemic changes in these markers before and after LVAD implantation and their link to post-LVAD AIS.

Materials/Methods: We screened 100 LVAD patients (2020–2022) for post-LVAD neurological dysfunction, identifying six who developed AIS within 90 days. Blood samples were collected 24 hours pre-LVAD and on post-implantation day 7. Hcy and HMGB1 levels in AIS patients were compared with 25 patients without neurological dysfunction, bleeding, or thrombosis (No-AIS group).

Results: Pre-LVAD, AIS patients had higher Hcy ($p<0.001$) and trended toward higher HMGB1 ($p=0.064$). Post-LVAD, only AIS patients showed increased Hcy and HMGB1 ($p<0.001$). The percentage change in these markers was significantly higher in AIS patients (2.5- and 6.9-fold increases for Hcy and HMGB1, respectively). The percent change analysis indicated that 71% of patients had an Hcy increase, and 65% had an HMGB1 increase, with a more pronounced rise in AIS patients. In a post-LVAD AIS prediction model, Hcy and HMGB1 changes had AUC values of 0.855 (95% CI: 0.51–0.998) and 0.989 (95% CI: 0.925–1.00), after adjusting for age, diastolic blood pressure, diabetes, and one-year mortality.

Conclusions: Heart failure patients with post-LVAD AIS exhibited elevated pre-LVAD levels of Hcy and HMGB1, followed by significant increases after surgery. Monitoring these biomarkers may facilitate early AIS prediction, enhancing risk stratification and personalized management strategies. Routine pre- and post-LVAD monitoring of Hcy and HMGB1 could improve stroke prevention in this patient population. A large cohort study is needed to confirm these initial findings.

Poster 50

INCREASED IFN-Γ LEVELS IN AFRICAN AMERICAN WOMEN FOLLOWING ISCHEMIC STROKE: A STUDY OF ETHNIC DISPARITIES IN PLASMA BIOMARKERS

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Background: Stroke outcomes vary with ethnicity, with immune response markers like interferon-gamma (IFN-γ) playing a significant role in stroke pathophysiology. IFN-γ, a proinflammatory cytokine produced by T cells and natural killer (NK) cells, regulates immune responses by activating macrophages and promoting inflammation. Given the worse stroke outcomes experienced by African Americans, we hypothesized that IFN-γ levels may vary with sex and ethnicity post stroke.

Materials/Methods: Plasma samples were collected from stroke patients admitted to Memorial Hermann Hospital, Houston by UTHealth biobank within 24 hours of admission and analyzed for IFN-γ levels using ELISA. Patients were stratified by sex and ethnicity (Black, Hispanic, White) and multilinear regression analysis was conducted to examine the adjusted associations.

Results: The mean age of patients was 63.6 years, 35% were women, 88% had hypertension, 47% had diabetes mellitus, and 53% had hyperlipidemia. In men, no significant differences in plasma IFN-γ levels were observed across ethnic groups. However, in women (n=21), IFN-γ levels varied significantly by ethnicity, p=0.04. African American women had the highest IFN-γ levels, 4.0±1.7 pg/mL, followed by Hispanic 2.6±1.6 pg/mL, and White women 1.5±0.8 pg/mL. Pairwise comparisons showed a significant difference between African American and White women (p=0.04), but no difference between Hispanic and White women, p=0.62. This association held true when adjusted for other co-morbidities in the multilinear model.

Conclusions: The higher IFN-γ levels observed in African American women likely reflects an exaggerated proinflammatory response to stroke in women. This heightened response may contribute to worse stroke outcomes. The absence of such differences in men suggests a potential sex-specific inflammatory response to stroke. Further research is needed to investigate the correlation between IFN-γ levels and clinical outcomes in African American women.

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HIT PAUSE: MARKED SINUS PAUSES AND ASYSTOLE LEADING TO PACEMAKER IMPLANTATION IN A PATIENT WITH WIEACKER-WOLFF SYNDROME

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Background: Wieacker-Wolff Syndrome is an X-linked recessive disorder caused by loss-of-function mutations in the zinc-finger ZC4H2 gene. This disorder has been reported in less than 150 individuals and leads to multisystem disease including skeletal and neurodevelopmental abnormalities. Single case reports of bradycardia have been reported but not well described. We present a case of a child with recurrent, prolonged sinus pauses with asystole and bradycardia, ultimately requiring single chamber pacemaker implantation.

Materials/Methods: A 22-month-old with Wieacker-Wolff Syndrome due to hemizygous ZC4H2: c.593G>A, p.R198Q and multiple congenital anomalies (hypotonia, seizures, facial dysmorphisms, feeding intolerance, vesicoureteral reflux, orthopedic abnormalities) presented in acute respiratory failure in the setting of viral illness. He had repeated bradycardia, and sinus pauses with both vagal stimulation (oral suctioning) and agitation. Two events required cardiopulmonary resuscitation (CPR). He underwent uncomplicated epicardial single chamber pacemaker placement

Results: In prior literature, eight males have been reported with the p.R198Q variant. Of these, two suffered cardiac arrest in setting of bradycardia requiring CPR and six had unexplained death at a young age. One surviving case received a pacemaker. These arrests and deaths have not been reported in other cases to our knowledge

Conclusions: This case highlights the importance of recognizing specific variants that may cause more severe disease and how therapeutic interventions may differ. Although rare, electrophysiologists should recognize this specific ZC4H2 variant (hemizygous ZC4H2: c.593G>A, p.R198Q) may increase risks of profound bradycardia, extended sinus pauses, cause cardiac arrest, and early, unexplained deaths. Together these finding suggest pacemaker placement is warranted among male patients with the p.R198Q variant.

Poster 52

EFFECT OF OSTEOPATHIC MANIPULATIVE MEDICINE ON CARDIOVASCULAR PARAMETERS

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Background: Osteopathic Manipulative Treatment (OMT) has the potential of offering new therapeutic perspectives for managing hemodynamic instability by incorporating its principle of self-healing to achieve homeostasis. This project evaluated the effect of OMT on baseline heart rate, blood pressure, radial artery diameter (D(ra)), and oxygen saturation (SaO_2), as well as on heart rate and blood pressure recovery, vasodilation (DD(ra)) and oxygen saturation in response to exercise.

Materials/Methods: Ten healthy subjects were randomized to receive either OMT (n=5) or sham (n=5) treatment three times over a period of one week, on day 1, day 3 and day 7. All subjects performed exercise (standard stationary bike stress test to 80% of maximal heart rate predicted for age) on days 1 and 7. All cardiovascular parameters (HR, BP, D(ra) and SaO_2) were measured at baseline and after exercise on day 1 and day 7.

Results: OMT was associated with decreased blood pressure after exercise (mean post-exercise systolic BP was 171 mmHg on day 1 vs. 154 mmHg on day 7, $p<0.05$) and improved HR recovery (mean post-exercise HR was 129/min on day 1 vs. 121/min on day 7, $p<0.05$). Radial artery diameter increased to a similar extent on both day 1 (28%) and day 3 (25%) in response to exercise in subjects who received OMT but not in those receiving the sham treatment, suggesting that OMT may induce vasodilation independent of known effects of exercise.

Conclusions: These results suggest that OMT may ameliorate pathological cardiovascular responses to stressors and support its role as an adjunct treatment in patients with cardiovascular disease (CVD) or with risk factors for CVD to provide holistic care.

Poster 53

ANESTHETIC MANAGEMENT OF FIRST BIVACOR RECIPIENT: TOTAL ARTIFICIAL HEART OF THE FUTURE

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Background: Biventricular (BiV) heart failure (HF), cardiogenic shock (CS), & multiorgan failure clinically coincide, and patient and healthcare burdens are immense. A total artificial heart (TAH) offers bridge-to-transplant (BTT) therapy for orthotopic heart transplant (OHT). This case outlines the first human implantation of BiVACOR, a TAH undergoing FDA early feasibility trials. The goal is to highlight novel applications of tenured concepts in physiology & pharmacotherapies which mitigated clinical entanglements leading to a successful outcome.

Materials/Methods: A 57-year-old male with NICM, HF, & acutely worsening CS from Lamin-A (LMNA) mutation was awaiting OHT. Multiorgan failure persisted despite escalating mechanical circulatory support (MCS) & IV inotropy. The patient was evaluated, and approved, for the first BiVACOR TAH. Pre-CPB course was uneventful. Total intravenous anesthetic (TIVA) was exclusively used. During CPB, uninterrupted ventilation with ½ Vt and recruitment breathing every 30 minutes was employed while RR & PEEP were unchanged. Therapeutic bronchoscopy was performed prior to CPB liberation. Post-CPB, vasoplegia & coagulopathy resolved with blood products, K-Centra, & methylene blue. The team opted for delayed sternal closure (DSC); TEE probe was maintained post-op. During ICU handoff, BiVACOR flows were 5.6 LPM, patent pulmonary veins with midline interatrial septum (IAS) were observed via TEE. Uncomplicated Sternal closure POD1 & subsequent OHT POD8 were performed.

Results: A successful perioperative outcome in the first patient BiVACOR implantation as BTT hinges on minimizing right circuit resistance (RCR) & left circuit resistance (LCR) to increase forward flow. Multidisciplinary collaboration is paramount. Analysis of marginal gains is needed.

Conclusions: The need for a durable TAH cannot be overstated for decompensating HF patients. Ultimately, undocumented discoveries currently outweigh known certainties, and BiVACOR patient zero provided new insight into TAH therapeutic possibilities.

Poster 54

PREDICTORS AND OUTCOMES FOLLOWING A STROKE IN PATIENTS WHO HAD AN OPEN THORACOABDOMINAL AORTIC ANEURYSM REPAIR

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Background: Post-operative stroke is of special interest in cardiac surgery due to the potentially devastating neurologic complications. However, contributors to a stroke after an open thoracoabdominal aortic aneurysm repair (TAAAR) are understudied.

Materials/Methods: Data from 3,765 patients undergoing an open TAAAR between the years 1986-2024 from a single practice were analyzed. Patients with a transient stroke were excluded. We leveraged multivariable logistic regression for modeling, and an alpha of 0.1 was used for model inclusion. We used these methods to identify contributors to a patient's odds of both stroke and mortality following a stroke. Finally, considering only elective patients, we built a predictive model using factors known preoperatively for stroke following a TAAAR.

Results: In the cohort, 91 patients (2.4%) had a stroke, with 60.4% of those having an operative death. 76.3% of those strokes were ischemic and 26.9% were hemorrhagic. Several factors were contributors to a higher odd of stroke in the complete cohort and a higher odds of operative death following a stroke. Notably, new onset atrial fibrillation was a predictor of an increased odds of stroke (OR=1.51, P=0.095). For mortality, three factors were predictors of a higher risk of mortality following a stroke: aortic dissection (2.73, 0.04), a prior aortic repair (3.14, 0.056), and a repair requiring bypass graft of the visceral or renal arteries (2.89, .04). Finally, 6 factors were predictive of a persistent stroke in elective repairs: age (1.03, .01), a prior history of a stroke (2.14, 0.01), chronic kidney disease (1.58, 0.08), BMI (1.07, 0.006), a symptomatic aneurysm (1.72, 0.03), and a Crawford extent II repair (2.93, <0.001).

Conclusions: In this study we built several models to identify patients receiving TAAAR at greater risk of stroke and death following a stroke. This data has the benefit of aiding comprehensive patient counseling and identifying more vulnerable patients in the post-operative setting.

Poster 55

K2P POTASSIUM CHANNELS AFFECT ENDOTHELIN A RECEPTOR AND VASOREACTIVITY IN IDIOPATHIC PULMONARY FIBROSIS–PULMONARY HYPERTENSION (IPF–PH) PATIENTS

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Background: Pulmonary Hypertension (PH) is a pulmonary vasculature disorder that is characterized by remodeling and muscularization of the smaller, distally located pulmonary arterioles leading to elevated pressure in the lung arteries. PH occurs in more than 46% of IPF cases and it is the main cause of IPF mortality. Two-pore potassium channels (K2P) play a role in controlling the pulmonary membrane's electrical properties (transmembrane potential) by regulating K^+ leakage and Ca^{2+} influx levels. K2P channels contribute to the development of distal resistance-vessel vasculopathy through interactions with G protein coupled receptor (GPCR) signaling pathways. The GPCR ligand endothelin-1 (ET-1) is an endogenous vasoconstrictor that binds to the endothelin A (ETA) receptor, it increases $[Ca^{2+}]_i$, which raises pulmonary vascular resistance.

Materials/Methods: PVSMCs were isolated from different anatomic locations of IPF-PH patients and cadaveric normal subjects. The distal PVSMCs were isolated from the fifth and the sixth degree of the lung while the proximal PVSMCs were isolated from the main pulmonary artery. To investigate the ETA receptor density, cells were stimulated with ET-1 and then fixed and immunostained with an ETA receptor antibody. Total internal reflection fluorescence microscopy (TIRF) was used to visualize the receptor on the cell surface. Intracellular calcium $[Ca^{2+}]_i$ signaling was measured using Fluo-4 AM dye.

Results: The distal PVSMCs of IPF-PH revealed downregulation of one of the candidates' K2P genes compared to proximal PVSMCs. The ET-A receptor density was statistically upregulated when stimulated with ET-1 in a dose-response manner in the distal PVSMCs when compared to the proximal IPF-PH cells. Also, distal IPF-PF PVSMCs displayed a statistical increase in the $[Ca^{2+}]_i$ levels

Conclusions: The pathophysiological role of K2P channels in PVSMCs highlight these channels as a novel target of therapy in PH.

Poster 56

GPCR-B-ARRESTIN BIASED SIGNALING AT ANGIOTENSIN-II TYPE1 RECEPTOR (AT1R) AS A THERAPEUTIC TARGET FOR HEART FAILURE

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Background: β-arrestin signaling from G protein-coupled receptors plays a critical role in facilitating dual-modality signaling, affecting the function of cardiomyocytes. AT1R operates through both the classical Gαq-dependent pathway and the β-arrestin-mediated pathway. While Gαq-dependent pathways may contribute to harmful hypertrophy, AT1R can also activate β-arrestin signaling which promotes cell survival during acute cardiac injury. By using a biased agonist that preferentially activates β-arrestin signaling, we can achieve cardioprotective effects while inhibiting detrimental G protein signaling. We have successfully synthesized such a biased agonist and hypothesize that our novel AT1R β-arrestin biased peptide agonist enhances cardiac function and provides cardioprotection in HF by facilitating β-arrestin-mediated signaling.

Materials/Methods: We utilized AC16-CMs, human-induced pluripotent stem cells (hiPSC) induced CMs, and then later in vivo mouse myocardial infarction. AT1R desensitization and internalization, protein expression assays, transcriptomic analyses, proliferation assays, and inflammation assays will be performed. Contractile properties will be evaluated using our IonOptix Multi-Cell Lite system by measuring sarcomere length, Ca2+ transients, and membrane potential (Vm) in response to the β-arrestin-biased AT1R peptide agonist and compared to AngII and other peptide controls.

Results: Our novel β-arrestin-biased AT1R peptide agonist successfully demonstrated the recruitment of β-arrestin at the AT1R while inhibiting Gαq recruitment in AC16-CMs. AC16-CMs and hiPSC-CMs will be subjected to various treatments to induce the phenotype of an ischemic model of HF and our peptide is being further evaluated for its potential to mitigate or prevent ischemic damage.

Conclusions: This study aims to define the role of β-arrestin in mediating cardiac protection, proliferation, and contractility. By achieving this, we will establish β-arrestin biased signaling as a potential therapeutic target for alleviating HF.

Poster 57

TARGETING CTLA-4 WITH SMALL MOLECULES TO MODULATE T-CELL RESPONSES IN CARDIOVASCULAR INJURY

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Background: T-cell activation plays a critical role in the fibrotic and inflammatory responses following cardiovascular injury. CTLA-4, a key T cell inhibitory receptor, has been implicated in modulating post-injury immune responses, with its dysregulation contributing to maladaptive fibrosis and chronic inflammation. While antibody-based immune checkpoint inhibitors for CTLA-4 have been extensively explored in oncology, their application in cardiovascular disease remains underinvestigated. In addition, antibody-based CTLA-4 inhibitors carry significant risks, including systemic toxicities. To develop a safer and more precise therapeutic approach, we aimed to identify small-molecules that could modulate T-cell activation in a controlled manner via CTLA-4 interaction.

Materials/Methods: We expressed and purified the extracellular domains of CTLA-4 and its ligands, CD86 and CD80, in human cells. The stability and functionality of these proteins were confirmed via dendritic cell binding assays and thermal shift analyses. To identify potential small-molecule modulators, we utilized a DNA-encoded library (DEL) comprising over four billion unique compounds. Candidate molecules were synthesized through a multi-step process involving repeated purification and rigorous structural validation to confirm their purity and identity. Biophysical assays were conducted to assess the binding interactions of these compounds with CTLA-4, CD80, and their complex.

Results: We identified highly specific small molecules that target CTLA-4, CD80, and the CTLA-4/CD80 complex. Molecules that selectively engage the CTLA-4/CD80 complex have the potential to enhance immunosuppression, thereby mitigating maladaptive fibrotic responses following cardiovascular injury. Biophysical analyses confirmed the binding interactions of these compounds, establishing a strong foundation for further investigation.

Conclusions: These findings underscore the potential of small-molecule checkpoint modulators as novel therapeutic agents for cardiovascular disease.

Poster 58

PATHOGENIC VARIANTS IN ACTA2 THAT ACTIVATE HEAT SHOCK FACTOR 1 SIGNALING AND CHOLESTEROL BIOSYNTHESIS IN SMOOTH MUSCLE CELLS PREDISPOSE TO PREMATURE ATHEROSCLEROSIS

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Background: ACTA2 pathogenic variants predispose to thoracic aortic disease, and a subset of variants lead to early-onset atherosclerotic cardiovascular disease (ASCVD). The molecular pathway linking misfolded smooth muscle α-actin (SMA) monomers to augmented atherosclerosis-associated smooth muscle cell (SMC) phenotypic modulation can be modeled in vitro by stably expressing the ACTA2 p.R149C variant in Acta2-/- SMCs.

Materials/Methods: The Montalcino Aortic Consortium patient registry was used to identify cases with ACTA2 pathogenic/likely pathogenic missense variants. These patients were surveyed and/or their medical records reviewed to identify cases with early-onset ASCVD. The variants for these cases, as well as other recurrent ACTA2 missense variants, were individually expressed in Acta2-/- SMCs, and transcript and protein levels, heat shock factor 1 (HSF1) activation, HMG-CoA reductase expression and activity, cholesterol ester levels, and downstream SMC phenotypic modulation were assessed.

Results: Early-onset ASCVD included coronary artery disease, peripheral vascular disease, and atherosclerotic plaques identified by imaging in the arch, descending, or abdominal aorta, along with the celiac, iliac, renal, or vertebral arteries. Twelve ACTA2 variants were identified to be associated with early-onset ASCVD. Early-onset ASCVD was correlated with HSF1 activation ($p = 0.0178$), cellular cholesteryl ester levels ($p = 0.0012$), and having one family member with the specific ACTA2 pathogenic variant who had early-onset ASCVD ($p=0.0002$).

Conclusions: Molecular assays assessing the pathogenic molecular mechanism that leads to early-onset ASCVD can identify which ACTA2 pathogenic variants will trigger this condition. Ultimately, this information informs precision medical care for individuals with ACTA2 pathogenic variants, with the ultimate goal of preventing vascular diseases.

Poster 59

NANOPARTICLE CONTRAST-ENHANCED IMAGING OF THORACIC AORTOPATHY AND CARDIOVASCULAR PATHOLOGY IN A MOUSE MODEL OF MARFAN SYNDROME

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Background: Marfan syndrome (MFS) patients often develop severe cardiovascular complications, including thoracic aortic aneurysm and dissection (TAAD). The Fbn1mgR/mgR (mgR) mice are a widely accepted model of MFS for studying aortic abnormalities. However, in vivo imaging-based phenotyping of cardiovascular abnormalities remains unexplored in this model. In this work, we utilized high-resolution nanoparticle contrast-enhanced computed tomography (nCECT) for in vivo imaging of thoracic aortopathy and cardiac abnormalities in mgR mice.

Materials/Methods: In vivo nCECT was performed in mgR (n=25) and wild-type (WT) (n=8) littermate control mice. Pre-contrast scans were followed by serial whole-body nCECT from 6 weeks to 6 months of age. nCECT scans were acquired within an hour of IV liposomal-iodine contrast (1.2 g I/kg). Aortic diameter was measured at 64±4 days-old mice to assess thoracic aortopathy (dilatation and aneurysm). nCECT images were analyzed for aortic and cardio-respiratory abnormalities in mgR mice.

Results: In vivo nCECT in mgR mice enabled imaging of cardiovascular abnormalities similar to those seen in MFS patients. mgR mice demonstrated aortic enlargement (84%), tortuosity (80%), and valve degeneration (28%). Imaging-derived diameter measurements showed significantly larger ascending aorta (2.32±0.6 vs. 1.30±0.2 mm) and aortic root (2.44±0.7 vs. 1.54±0.3 mm) in mgR compared to WT mice. Majority of ascending aortic enlargement progressed to aneurysmal development (17/21, 81%). 68% (17/25) of mgR mice died prematurely out of which 29% had aortic rupture. Cardiomegaly (72%), aortic valve calcification (36%), and diaphragmatic hernia (32%) were also demonstrated on nCECT imaging of MFS mice.

Conclusions: nCECT enabled in vivo imaging of thoracic aortopathy and cardiovascular pathology in Fbn1mgR/mgR mice. This is the first study demonstrating in vivo 3D visualization of multiple MFS-like phenotypes contributing to the high mortality of MFS mice.

Poster 60

THE ROLE OF A DOMAIN OF VON WILLEBRAND FACTOR IN INFLAMMATION DURING RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting 18 million people worldwide as of 2019. This disease occurs when immune cells attack the lining of the joints and cause joint damage and systemic inflammation that increases thrombosis and can lead to major cardiovascular events such as myocardial infarction and stroke. Current therapeutics for RA are broadly immunosuppressive, and many even include the risk of cardiovascular complications.

Materials/Methods: I hypothesize that the recombinant A2 domain of von Willebrand Factor reduces inflammation by modulating the pathogenic functions of T cells in RA in addition to decreasing excessive blood clotting. Experiments proposed in Aim 1 will identify the activation pathways inhibited by A2, investigate possible receptors, and examine if A2 affects T cell migration and T cells found in the synovial fluid of patients with RA. Experiments in Aim 2 will determine the efficacy of treatment with the A2 protein in two rodent models of RA. Animal trials will be conducted to determine the efficacy of A2 treatment compared to a common RA therapy. We will use immunohistochemistry, MRI, flow cytometry, and micro-Computed Tomography to assess inflammation, joint damage, and clot accumulation in these models.

Results: The recombinant A2 domain of the blood clotting protein von Willebrand Factor (VWF) reduces thrombosis, and our preliminary data shows that rats with the pristane-induced arthritis model of RA treated with the A2 protein have both reduced blood clots and reduced disease severity. The A2 protein co-localizes with CD3+ cells in spleens from rats injected with A2 and inhibits the proliferation of human T cells in vitro.

Conclusions: Uncovering the effects of the A2 protein on T cells and rodent models of RA is highly significant for finding a therapeutic that reduces both inflammation and thrombosis to help the millions of patients who have this painful and debilitating autoimmune disease.

Poster 61

INCREASED CCL4 AND CCL5 FOLLOWING MECHANICAL THROMBECTOMY: A PLASMA BIOMARKER STUDY IN ISCHEMIC STROKE PATIENTS

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Background: Mechanical thrombectomy is the standard of care for patients with acute ischemic stroke due to large vessel occlusion and has been associated with improved outcomes. However, not all patients with successful reperfusion experience good functional outcomes. Investigating the post-reperfusion inflammatory milieu could provide valuable insights into the mechanisms that influence stroke outcomes. We hypothesized that successful reperfusion may cause distinct cytokine/ chemokine profiles.

Materials/Methods: Plasma samples were collected from patients with ischemic stroke that were admitted to Memorial Hermann Hospital, Houston by UTHealth biobank. Multiplex was used to analyze the plasma samples for levels of 48 cytokines and chemokines. The relationship between thrombectomy (TICI 2b and above) and analytes was assessed.

Results: The mean age of patients was 63.3 years, 54% were women, 87% had hypertension, 44% had diabetes mellitus, and 54% had hyperlipidemia. CCL4 (MIP-1β) levels were significantly higher in patients that underwent thrombectomy 55.7±17.4 pg/ml, n=14 vs. the ones that did not undergo this procedure, 39.5±20.6 pg/ml, p=0.01, n=40. Similarly, CCL-5 (RANTES) levels were elevated in patients with acute ischemic stroke that underwent thrombectomy 368.6±275.1 vs. others, 216.5±156.3, p=0.01. These remained significant after adjusting for co-morbidities.

Conclusions: Our study suggests that MIP-1β (CCL4) and RANTES (CCL5) are significantly elevated in ischemic stroke patients that underwent successful reperfusion by mechanical thrombectomy. CCL4 or MIP-1β (macrophage inflammatory protein -1) is a chemoattractant for monocytes in injured tissue. CCL5 or RANTES (regulated on activation, normal T-cell expressed and secreted) is also a chemokine secreted by T cells and monocytes and directly interacts with CCL4. CCL4 and CCL5 may contribute to the post-ischemia reperfusion inflammatory response, potentially influencing outcomes after reperfusion therapies such as mechanical thrombectomy.

Poster 62

TARGETING EPHRIN RECEPTOR KINASE FOR THE TREATMENT OF ENDOMETRIOSIS

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Background: Endometriosis, defined as the abnormal appearance of endometrial tissues outside of the uterine cavity, not only causes dysmenorrhea and chronic pelvic pain, but it also leads to infertility and increased risk for ovarian cancer. Currently, treatment options for endometriosis are limited and are associated with significant challenges, including limited efficacy, fertility concerns, and recurrent symptoms. Our goal is to identify and develop additional therapeutic targets and treatment options for endometriosis.

Materials/Methods: We identified EPHA2 and EPHA4 kinases as potential non-hormonal therapeutic targets for endometriosis based on their significantly elevated expression levels in the endometriotic lesions compared to controls. To discover potent and selective small molecules that inhibit the kinase activity of EPHA2/4, we screened around 5 billion compounds using a DNA-encoded chemistry technology (DEC-Tec) approach. Hit compound (CDD-2693) and optimized compound (CDD-3167) were tested for biological activity in 12Z, an endometriotic epithelial cell line, and patient-derived organoids.

Results: Hit compounds displayed a pico/nanomolar potency in inhibiting EPHA2/4 kinase domains in vitro and demonstrated potent inhibition of ephrin-mediated activation of EPHA2/4 in 12Z cells. To test the therapeutic potential of our inhibitors in the context of inflammation, given one of the hallmarks of endometriosis is to induce a pro-inflammatory state in the ectopic lesions, we examined the expression level of PTGS2, a pro-inflammatory gene, upon the treatment of our inhibitors during an IL-1b challenging assay. Both compounds decreased the PTGS2 expression in the presence of IL-1b. We further validated the therapeutic effect in patient-derived endometrial organoids. Organoids treated with the CDD compounds showed a significant decrease in diameters after 72 hours of treatment.

Conclusions: We developed selective ephrin receptor inhibitors, and we exemplify the use of these inhibitors for endometriosis treatment.

Poster 63

STEROID RECEPTOR COACTIVATOR STIMULATORS MITIGATE MYOCARDIAL INFARCTION BY REDUCING OXIDATIVE STRESS IN CARDIAC FIBROBLASTS AND ENHANCING ANGIOGENESIS

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Background: In our previous study, we demonstrated that MCB-613 and its derivatives, potent small molecule stimulators of steroid receptor coactivators (SRCs), mitigate cardiac dysfunction post-myocardial infarction (MI) and provide lasting protection against adverse remodeling. In this study, we aimed to identify the molecular and cellular injury responses after MI in vivo and the oxidative stress response in vitro. We propose that SRC activation in cardiac fibroblasts (CFs) plays a crucial role in protecting against fibrosis.

Materials/Methods: We conducted LAD MI mouse model with MCB-613-10-1 treatment, sectioned the hearts at various intervals, then carried out immunostaining. Damage was induced in isolated CFs of mouse heart with or without presence of MCB-613-10-1. Additionally, CFs were fixed and performed with immunostaining. The GSH level was tested by GSH/GSSG-Glo assay. Cell viability was measured by WST-1 assay. Chick egg assay was conducted for angiogenesis assay.

Results: Our findings show that a marker of oxidative stress, 8-OHdG is decreased in CFs in the infarct areas at 24 hours post-MI, indicating that MCB-613-10-1 protects against oxidative stress-induced DNA damage. Additionally, MCB-613-10-1 reduced 8-OHdG and 4-HNE levels in CFs with H_2O_2-induced damage, and we observed an increase in total glutathione (GSH) levels, which enhances CF resilience to oxidative stress. Furthermore, cell viability was elevated with MCB-613-10-1 treatment, and ferroptosis induced by erastin was rescued by MCB-613-10-1 in CFs. We also found that CD31-positive and lectin-positive cells were increased in the infarct area 72 hours post-MI. Finally, we show that SRC activation in a chick egg angiogenesis assay stimulates a robust increase in vessel area over time by both direct and paracrine mechanisms.

Conclusions: SRC stimulation protects against oxidative stress and promotes angiogenesis, making it a potential therapeutic target for attenuating pathological remodeling after MI.

Poster 64

ACTA2 PATHOGENIC VARIANT LEADS TO IMMATURE SMOOTH MUSCLE CELLS AND CAUSES MOYAMOYA-LIKE OCCLUSIVE CEREBROVASCULAR LESIONS: TARGETING CELLULAR METABOLISM PREVENTS DISEASE

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Background: Moyamoya disease (MMD) leads to progressive occlusion of the distal internal carotid arteries (ICAs), causing childhood-onset strokes. The molecular mechanisms driving ICA occlusions remain unclear. Pathogenic ACTA2 variants altering arginine 179 are linked to childhood-onset strokes with MMD-like ICA occlusions. These mutations impair smooth muscle cell (SMC) differentiation, increasing their migratory capacity. Metabolic dysfunction may contribute, suggesting that targeting cellular metabolism could be therapeutic.

Materials/Methods: A smooth muscle cell-specific inducible knock-in mouse model (Acta2SMC-R179C/+) was created, incorporating the mutation into 67% of aortic SMCs. The metabolic and functional characteristics of mutant SMCs, including differentiation, migration, and glycolytic flux, were assessed. Nicotinamide riboside (NR) was used to enhance oxidative phosphorylation (OXPHOS), and its effects were evaluated in Acta2SMC-R179C/+ and wildtype (WT) mice following left carotid artery (Lcal) injury.

Results: Mutant Acta2R179C/+ SMCs showed impaired differentiation, maintained stem cell-like properties, and exhibited increased migration and glycolytic flux. NR promoted differentiation and reduced migration. Acta2SMC-R179C/+ mice developed higher mortality, increased incidents of strokes, occlusive lesions, behavioral deficits, and neuron loss in brain post-Lcal injury, unlike WT mice. NR treatment mitigated occlusions, reduced stroke-associated mortality, and prevented behavioral deficits and neuron loss in mice.

Conclusions: Immature, migratory SMCs contribute to MMD-like occlusive lesions. Driving SMC differentiation through metabolic modulation by NR reduces stroke risk and vascular abnormalities in Acta2SMC-R179C/+ mice. NR treatment is a promising approach to attenuate ACTA2 R179C mutation-related vascular pathology.

Poster 65

THE MOUSE METABOLISM AND PHENOTYPING CORE SUPPORTS RESEARCH INVESTIGATING CARDIOVASCULAR OUTCOME MEASURES

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Background: The Mouse Metabolism and Phenotyping Core provides access to equipment and expertise for characterizing whole-animal and organ system phenotypes in rodent models.

Materials/Methods: The facility houses various imaging equipment, including ultrasound, X-ray, and MRI machines, along with instruments for indirect calorimetry, metabolism-related blood parameter assessment, pulmonary and cardiac signal monitoring, and implanted telemetry. The core assists laboratories in collecting data for their animal phenotyping projects.

Results: For example, the core supports the NIH funded Knockout Mouse Project (KOMP), part of the International Mouse Phenotyping Consortium's initiative aimed at creating a comprehensive public resource of mice with null mutations in every gene of the mouse genome. The core contributes to the initial phenotypic characterization of these mutant mouse lines including assessment of ECG and echocardiography. The core also provides equipment and technician time on a fee-for-service basis for projects such as an interrogation of cardiovascular phenotypes following Trypanosoma cruzi infection and modification of outcomes following candidate interventions.

Conclusions: The core supports the phenotyping needs of labs at BCM and the wider scientific community.

Poster 66

OXIDIZED LDL AND LOX-1 MEDIATE ATRIAL FIBRILLATION DEVELOPMENT IN CHRONIC KIDNEY DISEASE

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Background: Atrial fibrillation (AF) is the most common sustained arrhythmia and increased in chronic kidney disease (CKD) patients. CKD patients show increased oxidative stress, a risk factor for AF. Oxidized low-density lipoprotein (oxLDL) is commonly used as a marker of lipid oxidative damage. LOX-1 is a receptor for oxLDL expressed in cardiomyocytes. Whether LOX-1 is involved in AF onset in CKD is still unknown.

Materials/Methods: Levels of oxLDL were measured in dialysis CKD patients in sinus rhythm (SR) and AF. Pacing electrical stimulation was used to assess the incidence of AF in CKD mice. Single-nuclei RNA sequencing was performed in atria samples from Sham, CKD-SR and CKD-AF mice. Left atria size was assessed by echocardiography. Western blotting was used to measure LOX-1 and pSTAT3 in human and mice atrial samples. Confocal microscopy was used to analyze calcium handling in atrial cardiomyocytes (ACM). LOX-1 was pharmacologically inhibited with BI-0115 and genetically by AAV9-ANF-Cre and AAV9-CAG-floxSTOP-shLOX1.

Results: CKD-AF patients showed higher serum oxLDL levels ($P<0.001$) and OXY-Score ($P<0.001$) than CKD-SR. Serum oxLDL was also higher in CKD-AF than Sham mice ($P=0.025$). LOX-1 expression was increased in atria from CKD patients ($P<0.05$) and in CKD-AF mice ($P<0.05$). Function enrichment analysis showed cardiac muscle contraction and calcium signaling were altered in ACMs from CKD-AF mice. CKD-AF mice showed atrial enlargement ($P<0.05$) and increased diastolic Ca^{2+} leak ($P<0.001$). Atria from CKD-AF showed increased pSTAT3 levels compared to Sham ($P<0.01$). LOX-1 blockade by BI-0115 and shLOX1 prevented AF development in CKD. Furthermore, LOX-1 blockade prevented increased diastolic Ca^{2+} leak ($P<0.05$) and increased pSTAT3 ($P<0.001$).

Conclusions: In conclusion, CKD-AF mice show atrial enlargement and Ca^{2+} mishandling that might be responsible of AF onset. LOX-1 blockade prevented both alterations and reduced inducibility of AF, highlighting LOX-1 receptor as a possible target to prevent AF in CKD patients.

Poster 67

DISCOVERING NOVEL GENETIC CAUSES OF HYPERTROPHIC CARDIOMYOPATHY USING IPSC-CARDIOMYOCYTE MODELS

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Background: Hypertrophic Cardiomyopathy (HCM) is a genetic disease characterized by the thickening of the heart's walls, especially those of the left ventricle. This makes it difficult for the heart to contract and to pump blood, causing complications such as atrial fibrillation and cardiac arrest. This disease has few symptoms - sometimes, the first clinical presentation is sudden death. Its genetic causes are also poorly understood. Thus, it is critical to determine potential genetic signs of HCM to detect it early.

Materials/Methods: The Lichtarge Lab at Baylor College of Medicine used evolutionary action (EA) algorithms on data from 473 HCM patients to determine ten genes that are likely to cause HCM if defective. After a preliminary screen, we found five genes that are likely contributors to HCM when defective: REST, DUSP6, FBLIM1, TYK2, and GATA5. We used CRISPR-Cas9 systems to knock out each of these genes in induced pluripotent stem cells (iPSCs), then differentiated these cells into cardiomyocytes. We then used their relative size and heartbeat amplitude to determine if these cells displayed signs of HCM compared to positive and negative controls. In this way, we evaluate each of these genes' relationship with HCM.

Results: We created CRISPR-Cas9 KO of the top candidate genes for further validation and the work is in progress. We found similar to prototypical HCM model (MYH7 R403Q), homozygous deletion of TYK2 leads to hypercontractility of the cardiomyocytes comparing to its isogenic controls, which is considered the key driver of concentric hypertrophy.

Conclusions: Combining novel machine learning tools and large dataset, we were able to identify and confirm novel genetic causes for HCM.

Poster 68

CD36/FABP5/PPARD SIGNALING AXIS DEFINES SPONTANEOUSLY PROLIFERATING CARDIOMYOCYTES IN NEONATAL STAGES

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Background: Spontaneously cycling cardiomyocytes (CMs) represent a rare and unique population in the neonatal heart with the potential to drive cardiac regeneration in adulthood. While previous studies have observed their existence, the mechanisms regulating their cell cycle activity remain poorly understood. Here, we aim to identify the signaling axis that define the spontaneously proliferating CMs in the neonatal stage.

Materials/Methods: We utilized single-cell RNA sequencing, bulk RNA sequencing, and spatial transcriptomics to identify the molecular drivers of CMs cell cycle. Spatial metabolomics identified alterations in metabolites. knockout, and transgenic animal models were used to confirm the hypothesis.

Results: Single-cell RNA sequencing of neonatal mice CMs at P1 (NMCMs-P1) identified CD36 as a marker of the spontaneously proliferating CMs. CD36 global and CMs-specific knockout mice (CD36KO, CD36CKO) exhibited smaller hearts, impaired CM proliferation, and limited regeneration. Bulk-RNAseq in CD36KO and CD36CKO showed downregulation of cell cycle genes, as well as FABP5, PPARδ, and RXRs. Spatial transcriptomics for P1 wild-type (WT) mice hearts identified and localized a subpopulation of CMs with high cell cycle activity and co-expression of CD36, FABP5, and PPARδ. Spatial metabolomics revealed a decrease in CD36KO and CD36CKO cardiac intracellular contents of retinyl-ester. At Nano molar concentrations, retinoic acid (RA) enhanced the cell cycle activity of WT-P1 NMCMs but not the CD36KO. Knockdown of FABP5 abolished the RA effect on CM proliferation, while its overexpression enhanced the cell cycle activity. Crossbreeding CD36KO mice with PPARδ-cardiac specific overexpressing mice rescued the proliferative phenotype, restoring CM proliferation and regenerative capacity after apical resection in P1 to the WT levels.

Conclusions: Spontaneously cycling neonatal CMs are marked by CD36 expression in which CD36/FABP5 functions to direct RA to activate PPARδ axis and drive spontaneous cell cycle activity.

Poster 69

CHARACTERIZATION OF LIPID DROPLETS AND INFLAMMATION IN FOAMY MONOCYTES IN SEVERE HYPERTRIGLYCERIDEMIA

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Background: Hyperlipidemia causes lipid droplet (LD) accumulation in circulating monocytes, leading to the formation of foamy monocytes, which may contribute to atherosclerosis through pro-inflammatory and migratory cues. We characterized monocyte LDs and phenotypes in hypertriglyceridemia (HTG).

Materials/Methods: Mice with HTG and hypercholesterolemia (HCH) (apoC3tgLdlrKO fed western diet [WD]), HCH alone (LdlrKO fed WD), HTG alone (apoC3tg fed WD), C57BL/6 mice fed WD or normal diet (ND), and humans with severe HTG were studied. Monocytes were analyzed for LDs and phenotypes by automated quantitative confocal microscopy, flow cytometry and scRNA-seq.

Results: Among all mouse groups, those with HTG and HCH had the highest LD accumulation in monocytes, primarily in CD36+/Ly-6Clow nonclassical monocytes, as shown by flow cytometry. HTG mice alone had greater LD accumulation in CD36+ monocytes than C57BL/6 controls. Confocal microscopy showed ~80% of CD36+ and ~25% of CD36− monocytes in HTG and HCH mice—or in either condition alone—contained LDs. Foamy monocytes in HTG and HCH mice had the highest LD number (7.0 ± 0.7/cell) and size (11.0 ± 0.3 μm²), compared to 6.5 ± 1.1/cell and 9.9 ± 2.5 μm² in HCH mice and 2.7 ± 0.4/cell and 1.0 ± 0.3 μm² in C57BL/6 controls. In humans with severe HTG, ~25% of monocytes contained LDs, versus <10% in healthy controls. ~40% of CD16+ foamy monocytes in HTG had >4 LDs/cell, while >80% in controls had only 1 LD/cell. Compared to controls, HTG and HCH mice and severe HTG patients had higher CD11a/CD11c surface levels and intracellular IL-1β/TNFα in CD36+ or CD16+ monocytes. scRNA-seq identified 10 monocyte clusters, revealing upregulated lipid metabolism and inflammatory genes in Ly-6Clow/CD36+ vs. Ly-6Chi/CD36− monocytes in HTG and HCH.

Conclusions: HTG induces LD formation and increases inflammation in circulating monocytes, particularly CD36+ monocytes in mice and CD16+ monocytes in humans, which may contribute to atherosclerosis.

Poster 70

INTEGRIN-TARGETING HYDROGEL COATINGS TO IMPROVE ENDOTHELIALIZATION OF VASCULAR GRAFTS

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Background: Small-caliber synthetic vascular grafts are prone to thrombotic failure due to inadequate endothelialization. Despite advances in biomaterials, current synthetic grafts fail to match the performance of autologous vein grafts in coronary artery bypass grafting (CABG) surgery. This study investigates an integrin-targeting hydrogel coating designed to enhance endothelialization and thromboresistance in synthetic vascular grafts.

Materials/Methods: The sheep underwent preoperative imaging to estimate carotid artery diameter for size-matching with multilayer coil-reinforced grafts. After arterial dissection, end-to-end anastomosis was performed using continuous 7-0 prolene sutures. Hemostasis was confirmed, and digital subtraction angiography (DSA) was performed to assess baseline luminal dimensions and cerebral perfusion. Graft patency was monitored using Doppler ultrasonography at 5 hours, postoperative day (POD) 7, POD14, and prior to the final procedure.

Results: Two sheep (body weight: 65 ± 10 kg, left carotid artery inner diameter: 6 ± 0.3 mm) were included. In the first case, the animal survived for 14 days with weekly ultrasound follow-ups. The graft remained patent on day 7; however, by day 14, intraluminal thrombosis was detected, leading to graft occlusion. More frequent ultrasound follow-ups were scheduled to enhance monitoring in the second case. Additionally, aggressive anticoagulation was administered. No significant intraluminal thrombosis was observed before the postoperative day (POD) 25; however, intermittent intraluminal faint thrombi were noted during the final five days, which was resolved by increasing the anticoagulation regimen.

Conclusions: This study investigates an integrin-targeting hydrogel-coated vascular graft to promote endothelialization and prevent thrombotic failure in small-caliber synthetic grafts. Early results in the ovine model show short-term patency and thromboresistance. Further studies are needed to evaluate long-term performance and clinical viability.