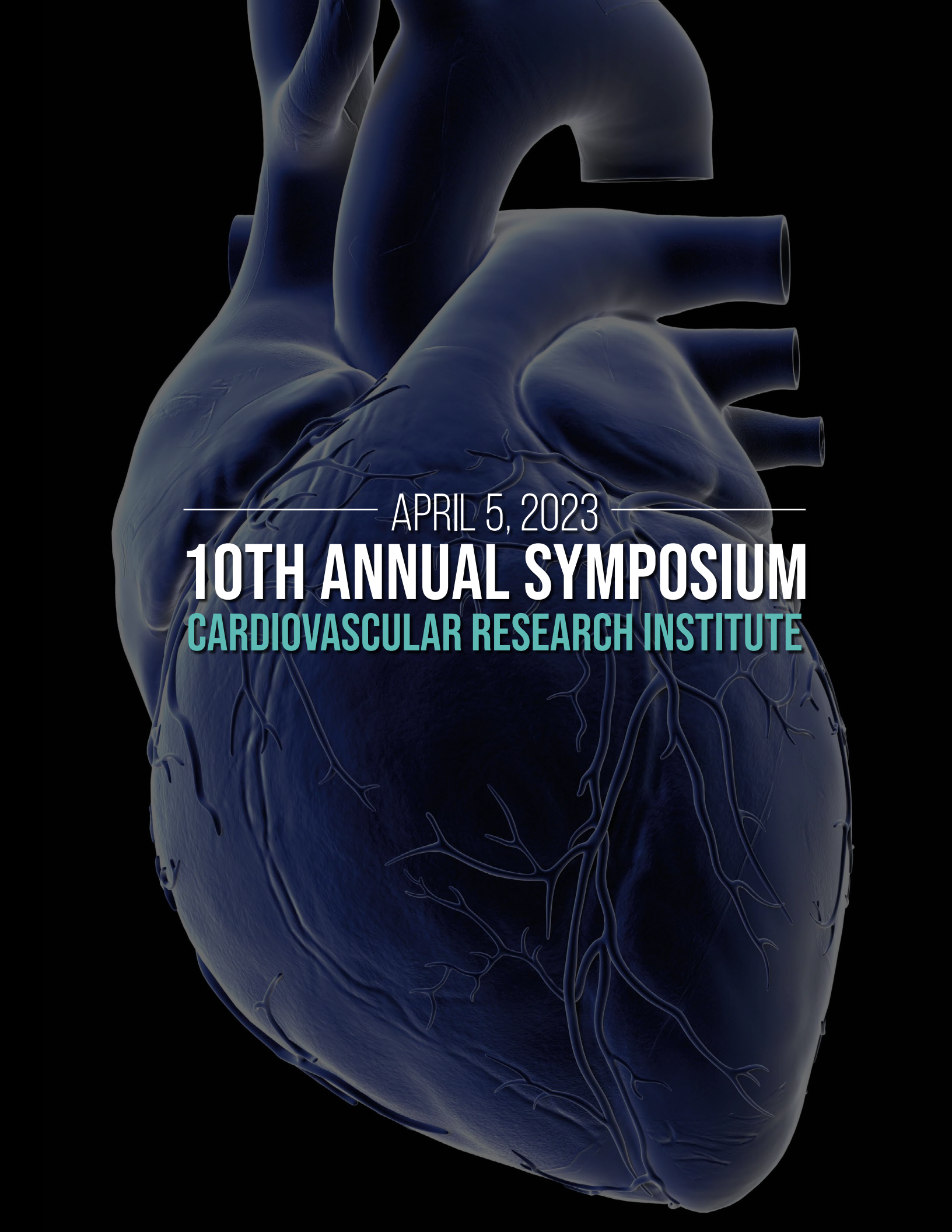

APRIL 5, 2023

10TH ANNUAL SYMPOSIUM

CARDIOVASCULAR RESEARCH INSTITUTE

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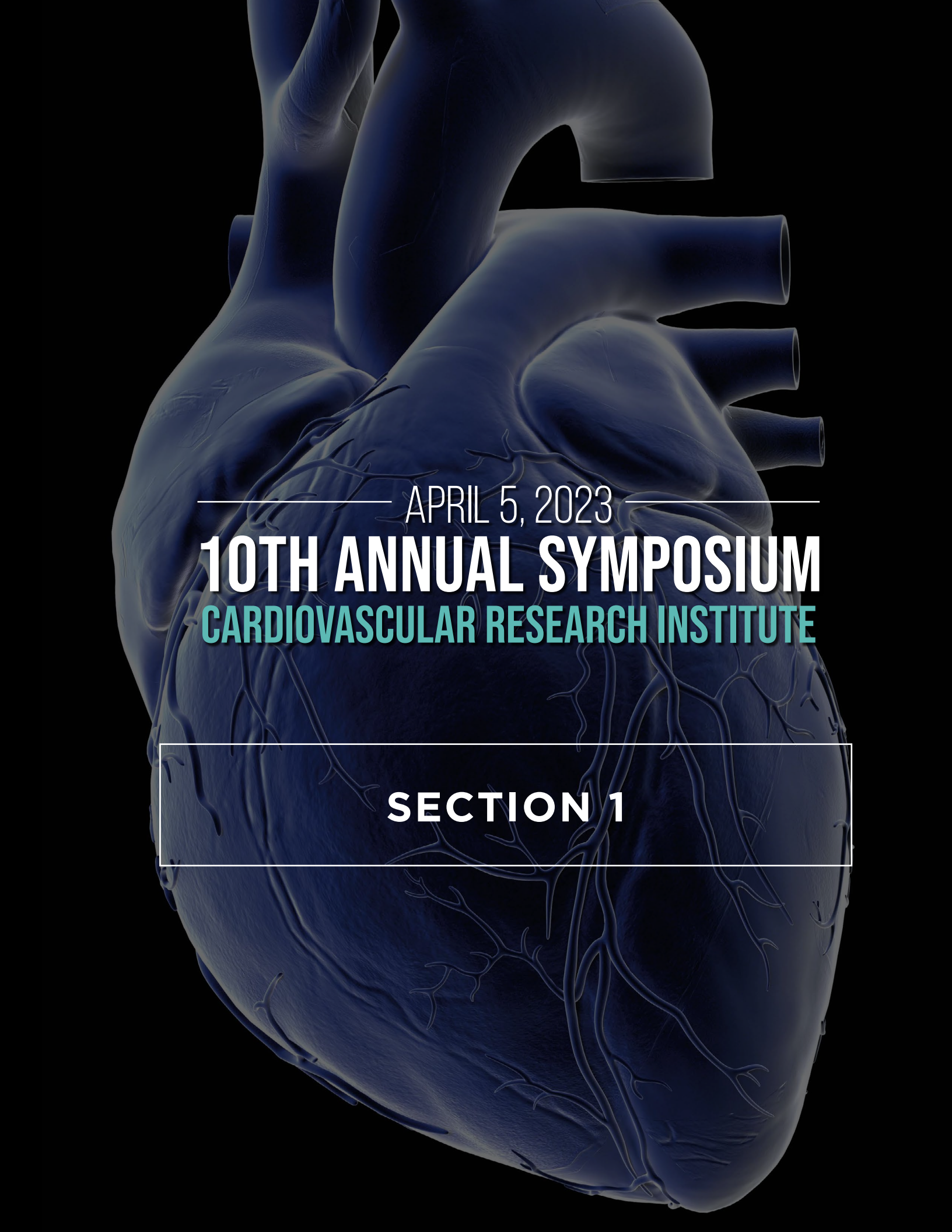


APRIL 5, 2023

10TH ANNUAL SYMPOSIUM

CARDIOVASCULAR RESEARCH INSTITUTE

SECTION 1

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 PROGRAM CHAIR

LILEI ZHANG, M.D., PH.D.
Assistant Professor
Molecular and Human Genetics
Baylor College of Medicine

SYMPOSIUM PROGRAM COMMITTEE

Yuriana Aguilar, Ph.D.
David Durgan, Ph.D.
Amber Eakin
Xiaoming Jia, M.D.
Mirza Umair Khalid, M.D.
William Lagor, Ph.D.
Scott LeMaire, M.D.
Na Li, Ph.D.
Xiao Li, Ph.D.
Jing Liu, M.D.
Richelle Lopez
A.J. Marian, M.D.
Dianna Milewicz, M.D., Ph.D.
Jack Price, M.D.
Jeff Steimle, Ph.D.
Xander Wehrens, M.D., Ph.D.

SESSION CHAIRS

Session I Xinchun Pi, Ph.D.

Session II Joshua Wythe, Ph.D.

Session III Jason Karch, Ph.D.

WELCOME NOTE

FROM THE DIRECTOR

XANDER WEHRENS, M.D., PH.D.

Dear Colleagues,

It is with great pleasure that I welcome you to the 10th 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. The CVRI is also active in expanding training programs in cardiovascular sciences.

This year CVRI is honored to feature two distinguished keynote lecturers at the symposium. Jeffery Molkentin, Ph.D., director of the Division of Molecular Cardiovascular Biology; executive co-director of the Heart Institute and professor of pediatrics at Cincinnati Children's Hospital Medical Center will speak on "Adult stem cells do not regenerate the damaged heart; they mildly rejuvenate it thru inflammation". The event will also feature Dianna Milewicz, M.D., Ph.D.; professor and George H.W. Bush Chair of Cardiovascular Medicine; director of the Division of Medical Genetics and vice-chair of internal medicine at McGovern Medical School at the University of Texas Health Science Center who will speak on "Molecular mechanisms for the vascular disease pleiotropy associated with pathogenic variants in smooth muscle α-actin (ACTA2)". In addition, this year's symposium will have three sessions that spotlight cardiovascular research being done in the Texas Medical Center, and two poster sessions with over 70 abstracts.

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

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

Target Audience
Physicians, Fellows, Residents, Physician Assistants, and Nurses/Nurse Practitioners specializing in cardiovascular research and care, and all other practitioners interested in cardiovascular sciences.

Global Learning Objectives
At the conclusion of the conference, participants should be able to:

- Summarize the novel molecular mechanisms of vascular disease.
- Discuss changes in the immune microenvironment in pediatric heart transplantation.
- Describe lineage determination from stem cell to cardiac progenitors to different types of cardiomyocytes.
- Discuss the regulatory mechanisms that lead to premature onset aging-related cardiovascular diseases observed in cancer survivors and their mitigation strategies.

Educational Methods
Lecture, Panel Discussion, Demonstration, Question and Answer Sessions.

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

Credit Designation
Baylor College of Medicine designates this live activity for a maximum of 7.00 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Dr. Mark L. Entman Award for Excellence in Cardiovascular Education

MARK L. ENTMAN, M.D.
William J. Osher Professor of Cardiovascular Research
Baylor College of Medicine
Scientific Director
DeBakey Heart Center
The Houston Methodist Hospital

The Dr. Mark L. Entman Award for Excellence in Cardiovascular Education was established in 2021 by the CVRI to recognize faculty 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 this prestigious award 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

KEYNOTE SPEAKER

DIANNA MILEWICZ, M.D., PH.D.
Professor and George H.W. Bush Chair of Cardiovascular Medicine
Director, Division of Medical Genetics
Vice-Chair of Internal Medicine
The University of Texas Health Science Center McGovern Medical School

KEYNOTE SPEAKER

JEFFERY D. MOLKENTIN, PH.D.
Director, Division of Molecular Cardiovascular Biology
Executive Co-Director, Heart Institute
Professor of Pediatrics
Cincinnati Children's Hospital Medical Center

JUN-ICHI ABE, M.D., PH.D.
Professor of Cardiology
The University of Texas MD Anderson Cancer Center

REZA ARDEHALI, M.D., PH.D.
Professor and Chief of Cardiology
Baylor College of Medicine

MIHAIL CHELU, M.D., PH.D.
Associate Professor of Cardiology
Baylor College of Medicine

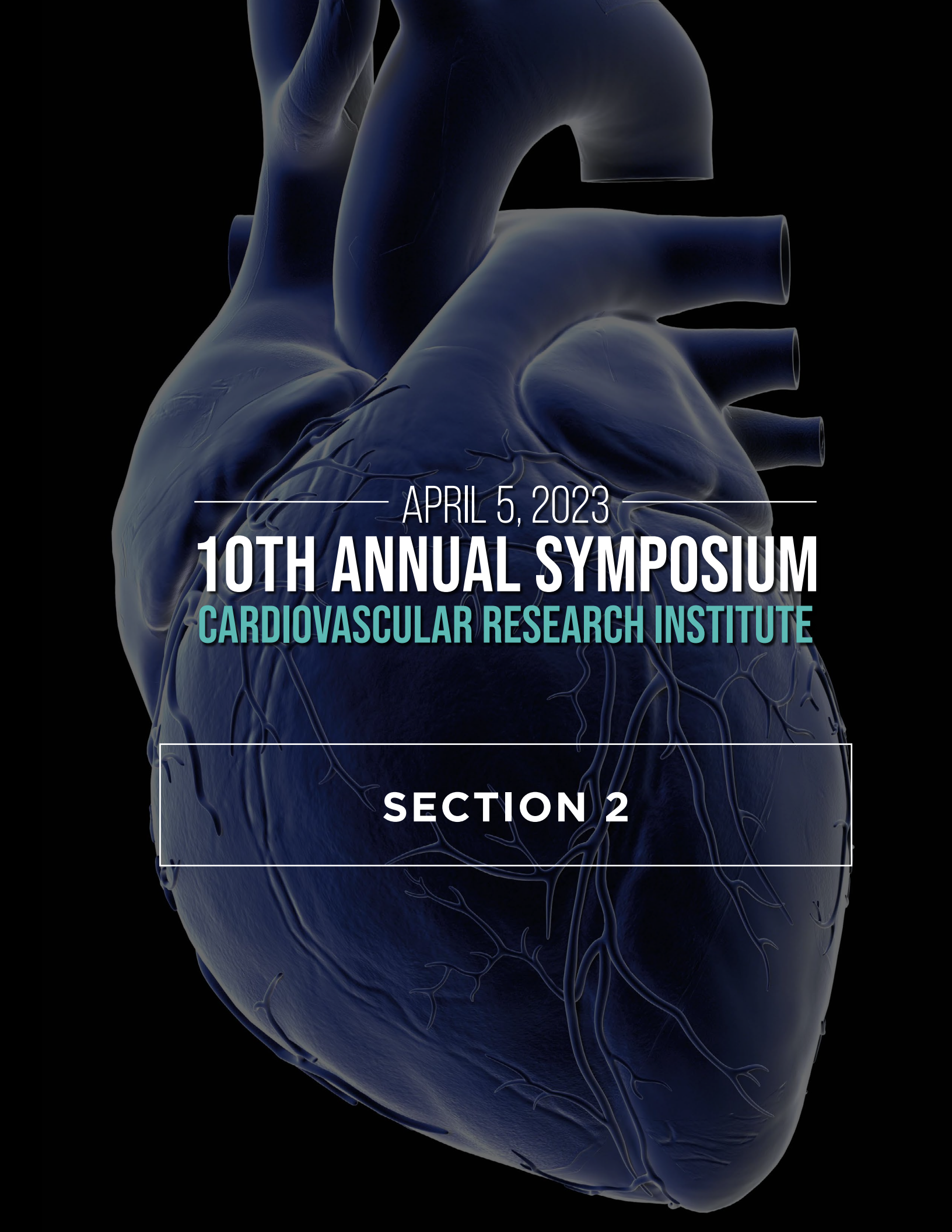
K. JANE GRANDE-ALLEN, PH.D.
Isabel C. Cameron Professor of Bioengineering
Rice University

PRIYATANSH GURHA, PH.D.
Assistant Professor of Cardiovascular Genetic Research
The University of Texas Health Science Center McGovern Medical School

AJITH NAIR, M.D.
Assistant Professor of Cardiology
Baylor College of Medicine

DIWAKAR TURAGA, M.D., PH.D.
Assistant Professor of Pediatrics
Baylor College of Medicine
Texas Children's Hospital

JUN WANG, PH.D.
Associate Professor of Pediatrics
The University of Texas Health Science Center McGovern Medical School



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10TH ANNUAL SYMPOSIUM

CARDIOVASCULAR RESEARCH INSTITUTE

SECTION 2

AGENDA

10TH ANNUAL SYMPOSIUM
CARDIOVASCULAR RESEARCH INSTITUTE
APRIL 5, 2023

8:00 – 8:45	Breakfast and Registration *Poster preview session*
8:45 – 8:55	Opening Remarks and Welcome
9:00 – 9:20	"The Macrophage Landscape Across the Lifespan of a Human Cardiac Allograft"
9:20 – 9:40	"To Beat or Not to Beat: Molecular Regulation of Cardiac Conduction System Homeostasis and Repair"
9:40 – 10:00	"Chromatin remodeling in cardiac reprogramming"
10:00 – 11:00	**Poster Session I**
11:00 – 12:00	"Molecular mechanisms for the vascular disease pleiotropy associated with pathogenic variants in smooth muscle α-actin (ACTA2)" **KEYNOTE LECTURE**
12:00 – 1:30	**Poster Session II** *Lunch throughout*

Biykem Bozkurt, M.D., Ph.D.
Senior Dean of Faculty
Associate Director, CVRI

Diwakar Turaga, M.D., Ph.D.
Assistant Professor of Pediatrics
Baylor College of Medicine
Texas Children's Hospital

Jun Wang, Ph.D.
Associate Professor of Pediatrics
The University of Texas Health Science Center
McGovern Medical School

Reza Ardehali, M.D., Ph.D.
Professor and Chief of Cardiology
Baylor College of Medicine

Dianna Milewicz, M.D., Ph.D.
Professor and President George H.W. Bush Chair of Cardiovascular Medicine
Director, Division of Medical Genetics
Vice-Chair of Internal Medicine
The University of Texas Health Science Center
McGovern Medical School

AGENDA

1:30 – 1:50	"Premature aging in cardio-oncology"
1:50 – 2:10	"Disease modifying Therapies for Cardiomyopathies"
2:10 – 2:30	"Conduction system pacing for cardiac resynchronization therapy: present and future"
2:30– 3:30	"Adult stem cells do not regenerate the damaged heart; they mildly rejuvenate it thru inflammation"
	KEYNOTE LECTURE
3:30 – 3:45	Break
3:45 – 4:05	"Inhibition of Histone Demethylase KDM5 Promotes Cardiomyocyte Maturation"
4:05 – 4:25	"New Models and New Mechanisms for Examining Discrete Subaortic Stenosis"
4:25 – 5:00	**Awards Ceremony and Closing Remarks**
5:00 – 5:30	Reception *Rayzor Lounge*

Jun-ichi Abe, M.D., Ph.D.
Professor of Cardiology
The University of Texas
MD Anderson Cancer Center

Ajith Nair, M.D.
Assistant Professor of Cardiology
Baylor College of Medicine

Mihail Chelu, M.D., Ph.D.
Associate Professor of Cardiology
Baylor College of Medicine

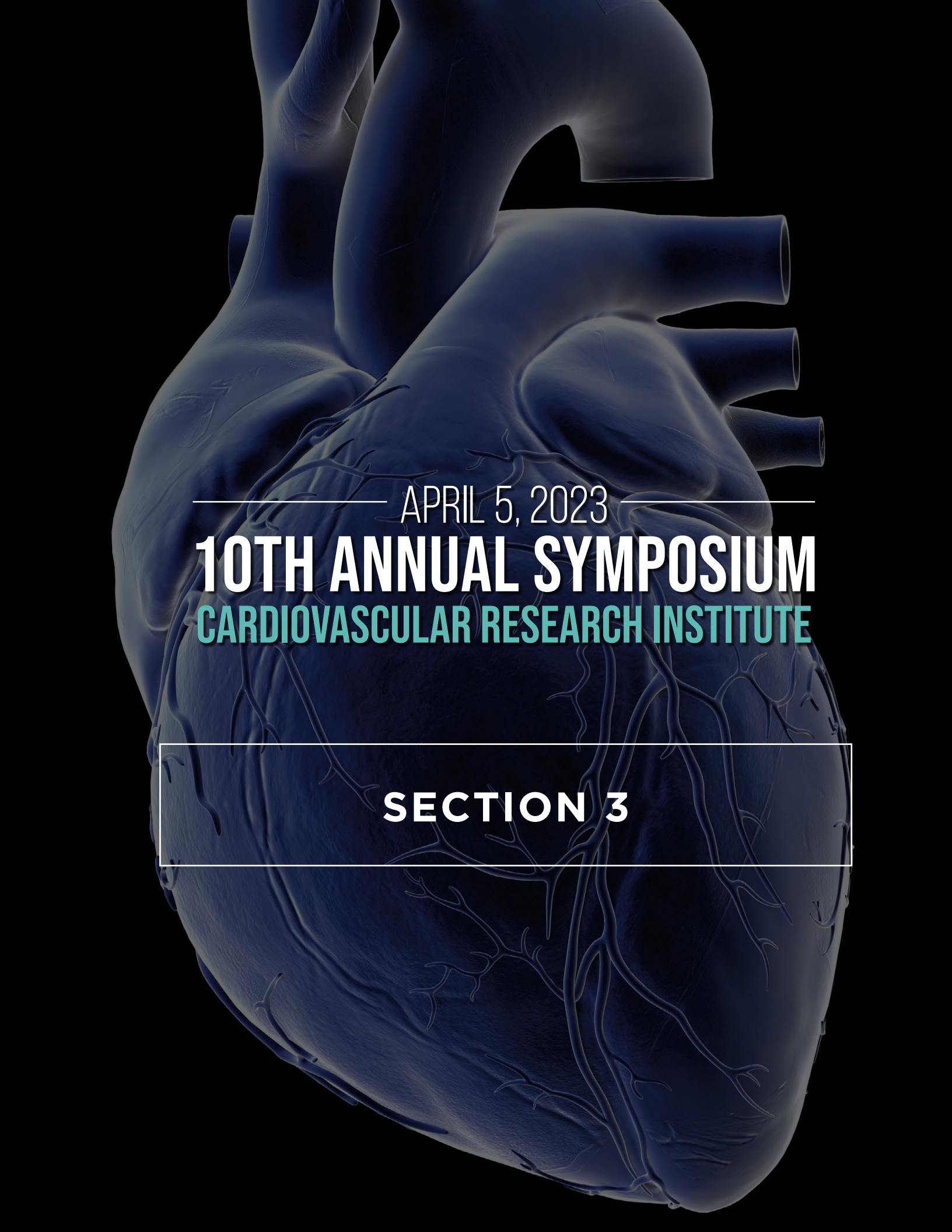
Jeffery Molkentin, Ph.D.
Director, Division of Molecular Cardiovascular Biology
Executive Co-Director, Heart Institute
Professor of Pediatrics
Cincinnati Children's Hospital Medical Center

Priyatansh Gurha, Ph.D.
Assistant Professor of Cardiovascular Genetic Research
The University of Texas Health Science Center
McGovern Medical School

K. Jane-Grande Allen, Ph.D.
Isabel C. Cameron Professor of Bioengineering
Rice University

Na Li, Ph.D.
Associate Professor of Cardiovascular Sciences

Xander Wehrens, M.D., Ph.D.
Professor of Integrative Physiology and Medicine
Director, CVRI



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10TH ANNUAL SYMPOSIUM

CARDIOVASCULAR RESEARCH INSTITUTE

SECTION 3

KEYNOTE SPEAKER

Dianna Milewicz, M.D., Ph.D.

Dianna M. Milewicz, M.D. Ph.D. is the President George H.W. Bush Chair of Cardiovascular Medicine, Director of the Division of Medical Genetics and the John Ritter Research Program, and Vice-Chair of the Department of Internal Medicine at McGovern Medical School at the University of Texas Health Science Center at Houston (UTHealth). Dr Milewicz's career focuses on research to identify the genetic and environmental triggers for acute aortic dissections, with an overarching goal of using this information to prevent aortic dissections. In addition, her research has identified the altered genes triggering other vascular diseases and identified the molecular links between the defective genes and the resulting vascular diseases. She also chairs an international aortic consortium (Montalcino Aortic Consortium) to define precision medical care to prevent acute aortic dissections based on the underlying genetic triggers. She has received numerous honors and awards for her research, including Doris Duke Distinguished Clinical Scientist Award, American Heart Association Merit Award, and Rice University Distinguished Alumni Award. She was inducted into the American Society of Clinical Investigation and the Association of American Physicians (AAP; both honorary associations for physician scientists), and currently serves as an AAP Council member. Dr. Milewicz has also participated in educating and increasing awareness for acute aortic dissections, including participating and chairing boards for the John Ritter Foundation, the American Heart Foundation, the Marfan Foundation and the Canadian Genetic Aortic Disorder Association.

KEYNOTE SPEAKER

Jeffery D. Molkentin, Ph.D.

Jeffery D. Molkentin, Ph.D. is a Professor in the Department of Pediatrics, University of Cincinnati and Cincinnati Children's Hospital in the United States of America. He is also the Division Director of Molecular Cardiovascular Biology and co-director of the Heart Institute. He received his B.S. from Marquette University in Milwaukee Wisconsin (USA) in 1989. He then received his Ph.D. from the Medical College of Wisconsin in 1994, after which he performed postdoctoral training with Dr. Eric Olson in Texas (USA) from 1994-1997, followed by his first faculty appointment in 1997 at the Cincinnati Children's Hospital Medical Center of the University of Cincinnati (USA). Dr. Molkentin has published over 420 original articles during this time, he has a Scopus H-index of 125 and Google Scholar h-index of 145. Dr. Molkentin was a Pew Scholar early in his career and a full investigator of the Howard Hughes Medical Institute in the USA from 2008-2021. He has won several awards such as the Louis N. and Arnold M. Katz award to young investigators and more recently the Basic Research Prize, both of the American Heart Association. Dr. Molkentin also won the Lucian Award from McGill University. He has served on NIH study section and was an organizer of various national and international scientific meetings. Finally, Dr. Molkentin has placed 30 of his past trainees into academics as laboratory principal investigators. Research in the laboratory focuses on the identification of candidate genes and signaling pathways involved in cardiac hypertrophy, contractility, cell death, heart failure, fibrosis, regeneration and muscular dystrophy, as well as mitochondria-dependent necrosis.

SPEAKER BIOGRAPHIES

Jun-ichi Abe, M.D., Ph.D.

Dr. Jun-ichi Abe received his medical degree from the Yamagata University in 1987 and went on to pursue his Internal Medicine Residency. He continued his fellowship in cardiology at Mitsui Memorial Hospital in Tokyo, where he focused on interventional cardiology and echocardiography with Dr. Tetsu Yamaguchi. Following medical residency and cardiology fellowship, he was appointed Instructor of Medicine/Cardiology at the University of Tokyo in 1992 with Dr. Kiyoshi Kurokawa. In 1995, Dr. Abe decided to pursue his career in medical research and became senior fellow in cardiology and worked with Dr. Bradford C. Berk at University of Washington (UW), Seattle, WA. Dr. Abe received his Ph.D. degree in Medicine/Cardiology from the University of Tokyo in 1998 under the guidance of Drs. Kiyoshi Kurokawa and Yoh Takuwa. He was then recruited to the University of Rochester as an Assistant Professor in 1999, became Tenured Professor in 2011, and Dean's professor in 2013. In 2014, Dr. Abe joined the faculty of the Department of Cardiology at the University of Texas MD Anderson Cancer Center. He has received grants from the National Institute of Health and American Heart Association. He was a Fellow of American Heart Association (FAHA), Dean's Professor at University of Rochester, Established Investigator of the American Heart Association, and was elected to ATVB Special Recognition Award in Vascular Biology. He has written over 130 scientific papers and book chapters and is a current member of the Editorial Board of several high impact journals.

Reza Ardehali, M.D., Ph.D.

Dr. Reza Ardehali is a physician-scientist investigating the molecular mechanisms regulating cardiovascular development and cardiac fibrosis. My research is focused in two areas: (1) the mechanisms underlying cardiovascular formation during embryonic development and how this information can be applied for regenerative purposes and (2) the developmental origins of cardiac interstitial cells and their contribution to remodeling and scar formation. We recently showed how developmentally diverse cardiac fibroblasts migrate to the heart and whether their origin may affect their reprogramming potential. We demonstrated that microenvironment supersedes developmental origin for fibroblast-to-cardiomyocyte reprogramming. Our findings challenged the current prevailing dogma that the embryonic origin of a cell is the sole determinant of its final differentiation state.

Mihail Chelu, M.D., Ph.D.

Dr. Chelu is an Associate Professor and the Director of Electrophysiology and of Clinical Electrophysiology Research at Baylor College of Medicine. His research interests include: molecular mechanisms of conduction system disease and clinical strategies to treat conduction system disease in different patient populations; molecular mechanisms and genetics of cardiac arrhythmias and cardiomyopathies; developing magnetic resonance imaging protocols to image left atrial scar and characterize biophysics of ablation; and integration of sensors and mobile platforms to monitor, identify disease signatures and determine impact on quality of life. He is the co-PI of a PCORI funded ($31,299,000) large, international, multi-center randomized clinical trial, Left vs Left RCT, testing the comparative effectiveness of His/Left Bundle Branch Pacing in relation to patient centered outcomes (quality of life, heart failure hospitalization, mortality) and comparative safety in relation to device-related complications and re-interventions (e.g. lead dislodgement, infection) relative to standard of care biventricular pacing in patients with heart failure with LVEF≤50% and an indication for cardiac resynchronization therapy (CRT).

K. Jane Grande-Allen, Ph.D.

Jane Grande-Allen is the Isabel Cameron Professor of Bioengineering at Rice University. Her research group investigates the structure-function-environment relationship of soft connective tissues through bioengineering analyses of the extracellular matrix and cell mechanobiology, with a focus on cardiovascular and intestinal diseases, as described in >175 peer-reviewed publications. Dr. Grande-Allen received a B.A. in Mathematics and Biology from Transylvania University in 1991 and a Ph.D. in Bioengineering from the University of Washington in 1998. After postdoctoral research in Biomedical Engineering at the Cleveland Clinic, she joined Rice University in 2003 and was promoted to full professor in 2013. Dr. Grande-Allen is a Fellow of AIMBE, IAMBE, BMES, AAAS, AHA and the Society for Experimental Mechanics. She served on the BMES Board of Directors and Executive Board since 2009. Dr. Grande-Allen is currently a Deputy Editor of Annals of Biomedical Engineering and serves on the research committee for the American Heart Association.

Priyatansh Gurha, Ph.D.

Dr. Gurha is an Assistant Professor at the University of Texas Health Science Center in Houston. Before joining UTHealth, he was a postdoctoral fellow at Baylor College of Medicine's Department of Genetics. His research goals are to understand the molecular processes that coordinately govern gene expression and contribute to heart failure. His present research focuses on determining the function of the KDM5 family of histone lysine demethylases in the cardiac myocyte maturation and the pathological contribution of activation of KDM5 proteins in heart failure.

Ajith Nair, M.D.

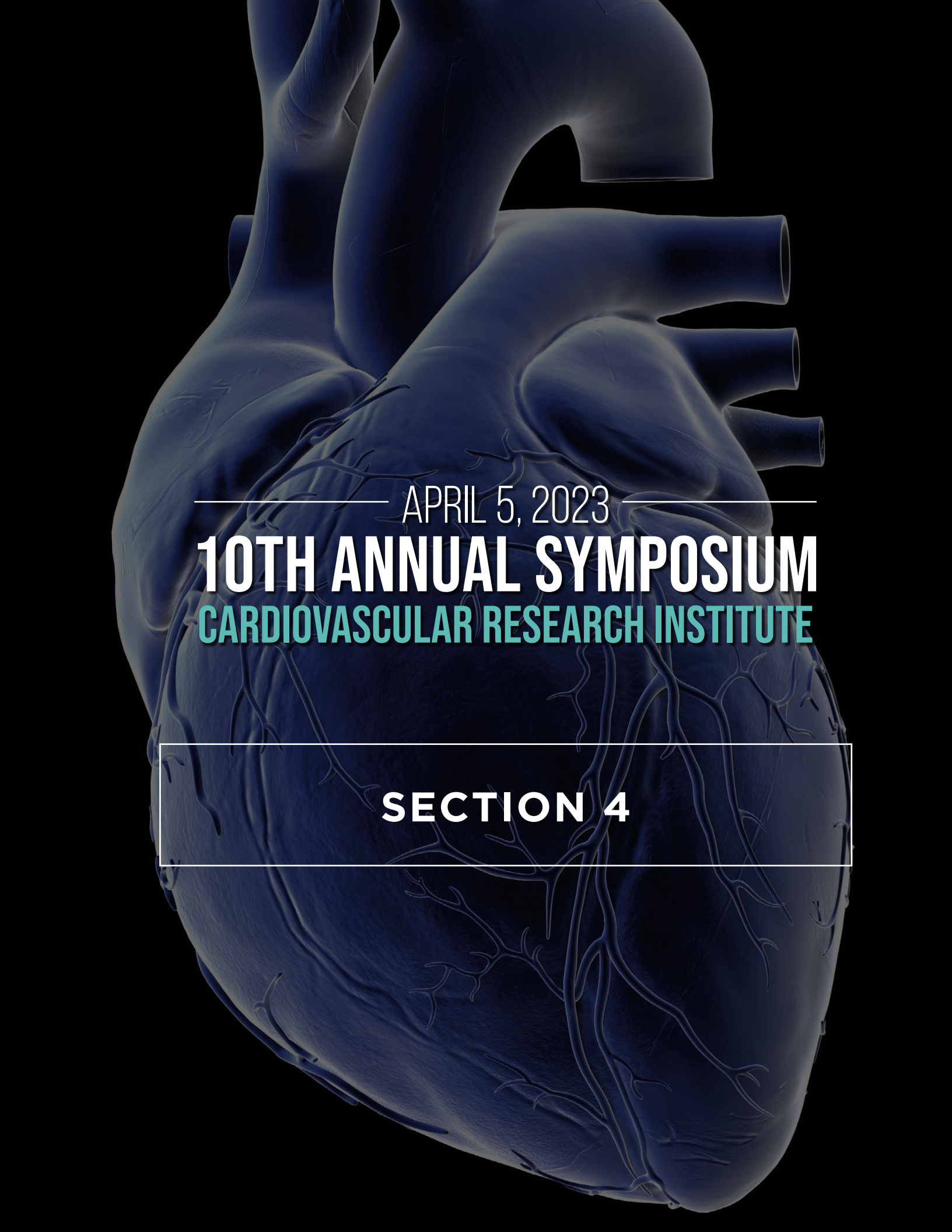
Ajith Nair, M.D. is an advanced heart failure cardiologist with a focus on cardiomyopathies, cardiac transplantation, mechanical circulatory support, and pulmonary arterial hypertension. He earned his medical degree from UT Southwestern and completed internal medicine residency and cardiology fellowship at Icahn School of Medicine at Mount Sinai. He has served in leadership roles at Baylor College of Medicine (BCM) and previously at Icahn School of Medicine at Mount Sinai. He is currently the Director of the Baylor St. Luke's Medical Center Heart Failure Clinic (BCM), Assistant Program Director for the Advanced Heart Failure fellowship program (BCM) and Director of the Pulmonary Hypertension Program (BSLMC). He is dedicated to the education of his peers, fellows, and residents, and he has contributed academically to the field of advanced heart failure. He is currently the principle site investigator for multiple (>8) clinical trials. He has multiple publications in the field of heart failure, cardiomyopathies, mechanical circulatory support and pulmonary hypertension.

Diwakar Turaga, M.D., Ph.D.

Dr. Diwakar Turaga is a physician-scientist with clinical training in pediatric cardiac critical care and research training in stem-cell biology and microscopy. His career objective is to combine clinical work in pediatric cardiac critical care with research in cardiac regenerative medicine. He earned his M.D., Ph.D. degrees from the Washington University, St. Louis and went onto the University of California, San Francisco to continue training with a fellowship in Pediatric Cardiology. From there, he completed a second fellowship at the University of Pittsburgh. Currently, Dr. Turaga is an assistant professor of pediatrics at Baylor and pediatric cardiac critical care specialist at Texas Children's Hospital. He is working on collaborative studies surrounding mechanisms underlying the progression of congenital heart disease.

Jun Wang, Ph.D.

Dr. Jun Wang is a tenured Associate Professor in the Department of Pediatrics at McGovern Medical School at University of Texas Health Science Center at Houston (UTH). She received her Ph.D. degree from the Texas A&M University Health Science Center in 2010. After completing postdoctoral training and being an Assistant Professor at Baylor College of Medicine, Dr. Wang joined UTH in 2018. Wang's lab is mainly focused on studying molecular and genetic regulation of cardiovascular and craniofacial development, diseases and regeneration. Her group uses a combination of various approaches in their study including mouse genetics, physiology studies, genome editing and next generation sequencing techniques. During her career, she is the recipient of many honors and awards such as the Lawrence Bone Research Award, American Heart Association National Career Development Award, NIH K01 Award, The University of Texas System Rising STARs Award and the Women Faculty Forum Rising Star Award.



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10TH ANNUAL SYMPOSIUM

CARDIOVASCULAR RESEARCH INSTITUTE

SECTION 4

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10TH ANNUAL CVRI SYMPOSIUM POSTERS
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10TH ANNUAL CVRI SYMPOSIUM POSTERS

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28 - Aguilar, Y.	34 - Pfortmiller, E.	58 - Mondal, N.
29 - Angelini, A.	35 - Johnson, O.	59 - Xie, B.
30 - Qi, L.	36 - Tsai, C.	
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POSTER SESSION SCHEDULE

Session I

10:00 – 11:00 a.m.

Group 1: Posters 1 - 5

Group 2: Posters 6 - 10

Group 3: Posters 11 - 15

Group 4: Posters 16 - 20

Group 5: Posters 21 - 25

Group 6: Posters 26 - 30

Group 7: Posters 31 - 35

Group 8: Posters 36 - 40

Session II

12:00 – 1:30 p.m.

Group 1: Posters 41 - 45

Group 2: Posters 46 - 50

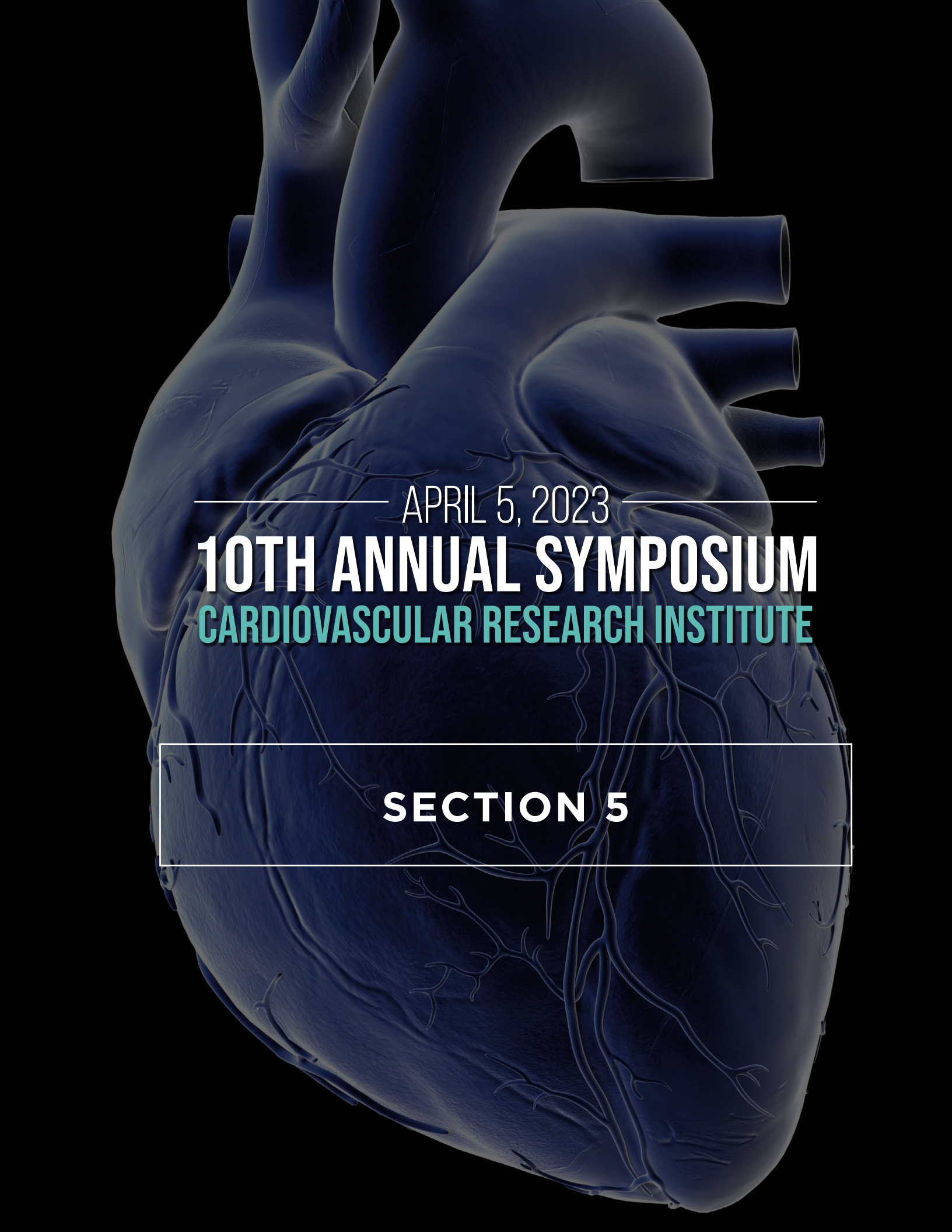
Group 3: Posters 51 - 54

Group 4: Posters 55 - 59

Group 5: Posters 60 - 64

Group 6: Posters 65 - 69

Group 7: Posters 70 - 74



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SECTION 5

ABSTRACTS

Poster Number 1

Postdoctoral Researcher

Cardiac Arrhythmia and Electrophysiology

UNCOVERING THE STRUCTURAL EFFECTS OF RADIOFREQUENCY ABLATION ON THE PAPILLARY MUSCLE-CHORDAE TENDINEAE JUNCTION

Drew Bernard[1], Luis H Victor[2], Christine Cao[1], Skylar Buchan[1], Mathews John[1], Allison Post[1], Deborah Vela[3], Jane Grande-Allen[2], Mehdi Razavi[4]

[1]Department of Electrophysiology Clinical Research and Innovations, Texas Heart Institute, Houston, TX; [2]Department of Bioengineering, Rice University; [3]CV Pathology Research, Texas Heart Institute; [4]Depart of Cardiology, Texas Heart Institute

Background: When targeting papillary muscle ventricular arrhythmias (VA), physicians create more radiofrequency (RF) ablation lesions and use a higher power output, creating excess lesion damage, negatively affecting papillary muscle (PM) function and causing conditions such as mitral regurgitation (MR). We hypothesize that ablating PMs damages internal structures anchoring the chordae tendineae (CT), leading to a compromised PM CT junction and thus structural failure at tensile forces lower than non-ablated papillary muscles.

Materials/Methods: Samples were excised from fresh porcine hearts, 36 PM CT – leaflet sections in total. Half of the samples were then ablated at 50W, 60s, and 30g of force. Samples then underwent tensile testing until failure. The stress-strain curves for each group were analyzed, and each sample underwent histological analysis.

Results: Comparing the ultimate tensile strength (UTS) of each group, the ablated group failed at forces lower than the control group. Histologic sectioning reveals superficial CT insertion, denaturation of collagen fibers in the CT in ablated samples and tearing of the myocardium inferior to the insertion point. Ablated samples failing at the PM appear to have a smaller portion of torn PM and a more friable failure point. The ablated group contained the only samples to fail at or below peak tensile forces seen by the PM during systole within the heart. However, both groups failed at similar locations beyond the CT collagen network at the myocardial tissue, suggesting that tensile properties of the CT were not significantly diminished by the ablation.

Conclusions: RF ablations at the PM create changes in the structure and strength of the PM CT junction that raise concerns for patients that have undergone this treatment. As these findings are restricted to ex vivo samples and histopathologic evaluation on tissues collected acutely after experimentation, future work must be done to establish extended timepoints in vivo to guide clinical practice.

Poster Number 2

Student

Cardiac Arrhythmia and Electrophysiology

RUXOLITINIB AS AN ANTI-ARRHYTHMIC CAMKII INHIBITOR

Lauren E Dorn[1], Oscar Reyes Gaido[2], Nikoleta Pavlaki[2], Mohit Hulsurkar[1], Mark E Anderson[2]

[1]Cardiovascular Research Institute, Dept. of Integrative Physiology, Baylor College of Medicine; [2]Department of Medicine, Johns Hopkins University School of Medicine

Background: Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, responsible for nearly 5.5 million deaths worldwide. Enhanced activity of Ca^{2+}, /calmodulin-dependent protein kinase II (CaMKII) has been implicated in AF pathogenesis. Despite proven benefits of CaMKII inhibition in various preclinical models of AF, translation of CaMKII antagonists into humans has been stymied by low potency, toxicity, and concerns for adverse effects on cognition due to an established role of CaMKII in learning and memory. To address these challenges, we asked if any clinically approved drugs, developed for other purposes, were potent CaMKII inhibitors.

Materials/Methods: Using a modified fluorescent biosensor, CaMKAR (CaMKII Activity Reporter), we performed a drug repurposing screen (4,475 compounds in clinical use) in human cells (HEK293T/17) expressing active CaMKII. One of these drugs, Ruxolitinib, was injected into isolated rodent cardiomyocytes with hyperglycemia-induced AF to test for pacing activity. To test anti-arrhythmic activity in vivo, 8-month-old CREM transgenic mice were monitored for AF with surface ECG at baseline, post-placebo, and post-Ruxolitinib injections. AF was defined as loss of p-waves and irregularly irregular R-R intervals for > 10 seconds.

Results: Ruxolitinib was the most suitable drug based on potency and safety profile among the screened candidates. Ruxolitinib treatment suppressed pacing-induced AF in isolated cardiomyocytes. With CREM mice, at baseline more than 70% of mice were in persistent AF. Mice treated with Ruxolitinib spent 33.6% ± 6.5% of time in AF compared to placebo with 95.2% ± 3.7% time in AF.

Conclusions: The FDA approved drug Ruxolitinib was identified as a potent CaMKII inhibitor. Ruxolitinib may be repurposed for safe and effective restoration of sinus rhythm in patients with AF.

Poster Number 3

Junior Faculty

Cardiac Arrhythmia and Electrophysiology

NOVEL RYR2 BINDING-PARTNERS NDPK-B/C PROMOTE ATRIAL FIBRILLATION THROUGH CALCIUM DYSREGULATION

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Background: Nucleoside diphosphate kinases (NDPKs) transfer a γ-phosphate from NTP to NDP. NDPK-B and -C are critical regulators of cAMP signaling and play an important role in calcium (Ca^{2+},) signaling during heart failure. Since atrial fibrillation (AF) is also associated with impaired cAMP signaling and abnormal Ca^{2+}, handling, we hypothesized that NDPK-B and -C promote AF progression through key cardiac Ca^{2+}, handling proteins by modulating cAMP signaling.

Materials/Methods: NDPK-B, -C and cAMP levels were measured in atrial biopsy samples from human patients by western blotting and ELISA. NDPK-C was overexpressed in canine atrial cardiomyocytes (cACMs) in vitro and in mouse hearts in vivo, and its overexpression was confirmed by qPCR and western blotting. Spontaneous sarcoplasmic reticulum (SR) Ca^{2+}, release events (SCaEs) were recorded and susceptibility to induced AF was measured by programmed electrical stimulation (PES). Immunoprecipitation (IP)-Proteomics study revealed novel NDPK binding partners.

Results: NDPKc, Gαs and cAMP were upregulated in chronic AF (cAF) patients. Gαs and cAMP levels were upregulated when NDPK-C was overexpressed in cACMs. PES revealed increased AF incidence and duration in mice overexpressing NDPK-C. Overexpression of NDPK-C in mice increased atrial SCaEs (3.45±0.81 vs 0.67±0.11 sparks/100μm/s in control, $P<0.05$), Ca^{2+} transients (4±0.5 a.u., vs 2.8±0.4 a.u., $P<0.05$) and incidence of Ca^{2+}, waves (24% cells, vs 3% in control). IP-Proteomics revealed NDPK-B and -C to be novel RyR2 binding partners.

Conclusions: NDPK-B and -C are regulators of cAMP levels in AF. They increase the susceptibility to induced AF and regulate Ca^{2+}, handling in cACMs and in mouse atria. This increased Ca^{2+}, trafficking was associated with generation of arrhythmogenic SCaEs, revealing a potential novel mechanism underlying the critical role of NDPK-B and -C. Mechanistically, we found that overexpression of NDPK-B and -C results in increased binding to RyR2, suggesting a novel model of RyR2 regulation.

Poster Number 4

Student

Cardiac Arrhythmia and Electrophysiology

MACROPHAGE-MEDIATED INTERLEUKIN-6 SIGNALING DRIVS RYANODINE RECEPTOR-2 (RYR2) CALCIUM LEAK IN POSTOPERATIVE ATRIAL FIBRILLATION

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Background: Postoperative atrial fibrillation (poAF) is transient atrial fibrillation that occurs days after surgery in 33% of cardiac surgery patients. Despite treatment with beta blockers and anticoagulation, poAF patients are at an eight-fold risk of recurrent AF and two-fold risk of mortality. Prior clinical and preclinical studies have demonstrated a key role of systemic inflammation in poAF. Specifically, interleukin (IL)-6 is elevated in the atria and sera of poAF patients and causes abnormal RyR2 calcium (Ca^{2+}, release in isolated rat hearts.

Materials/Methods: To study IL-6 signaling in the context of poAF, we have developed a novel poAF mouse model consisting of atrial pericardiectomy and transient aortic cross-clamping followed by intracardiac burst pacing on postoperative day three to assess poAF inducibility, after which atrial samples were harvested for further characterization.

Results: Our model has a poAF incidence of 38% based on a cohort 131 wild-type mice. We found that macrophages, particularly pro-inflammatory macrophages by flow cytometry CD11b expression, are more prominent in the atria of poAF versus sham mice. Immunohistochemical co-staining experiments further suggest that atrial macrophages produce IL-6R. Indeed, atrial IL-6 and IL-6R protein as well as STAT3 phosphorylation, indicating active IL-6 signaling, are increased by 2.2-fold (P=8.0E-03), 2.0-fold (P=0.030), and 1.3-fold (P=0.020), respectively, in poAF versus sham mice. Atrial cardiomyocytes (ACMs) isolated from poAF mice on postoperative day three have a 3.7-fold (P=1.0E-04) increase in RyR2 Ca^{2+}, leak compared to sham, likely mediated by greater RyR2 serine-2814 phosphorylation, which we observe by western blot (2.0-fold increase in poAF versus sham, P=0.030).

Conclusions: Our data suggest that macrophages infiltrating the atria three days after cardiac surgery produce IL-6R, which activates STAT3 in ACMs, resulting in RyR2 serine-2814 phosphorylation, Ca^{2+}, leak, and arrhythmia.

Poster Number 5

Postdoctoral Researcher

Cardiac Arrhythmia and Electrophysiology

IMPLEMENTATION OF ETHANOL INJECTION TO CREATE A COMPLETE ATRIOVENTRICULAR BLOCK IN A RODENT MODEL

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Background: Complete atrioventricular block (AVB) is an abnormal heart rhythm resulting from a defect in the cardiac conduction system. Patients with complete AVB are at risk of symptoms ranging from syncope or hypotension to cardiovascular collapse or sudden cardiac death. A reliable animal model of complete AVB is essential for understanding the mechanisms underlying the fatal hemodynamic effects and alterations in electrical conductivity associated with this arrhythmia. Most complete AVB models require specialized equipment not available in all laboratories. Here, we evaluated the use of ethanol injections in a systematic surgical approach to create a complete AVB model in rats.

Materials/Methods: We used 8 Sprague Dawley rats (8 weeks old; average weight, 220 ± 30g): 4 rats received a 70% ethanol injection in the AV node, and 4 rats received a similar injection of normal saline (controls). Our surgical approach involved performing a partial sternotomy using the epicardial fat as a landmark for ethanol injections. Animals were followed for 7 and 14 days.

Results: Stable complete AVB was successfully induced in all 4 rats that received ethanol injections, as corroborated by electrocardiogram. Rats in the control group experienced a transient AVB with return to sinus rhythm. No major complications occurred.

Conclusions: Our study found that using 70% ethanol injections in a systematic surgical approach is a reliable, safe, and reproducible way of creating a complete AVB model in rats.

Poster Number 6

Postdoctoral Researcher

Arrhythmias and Channelopathies

LMNA MUTATION AND CARDIAC CONDUCTION DISORDERS

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Background: Cardiac conduction disorders (CCDs), including sick sinus syndrome, atrioventricular block, and bundle branch block are common arrhythmic disorders. CCDs has been associated with mutations of LMNA, which encodes the nuclear envelope protein lamin A and lamin C. However, the mechanistic link between mutated lamin A/C and CCDs is largely unexplored.

Materials/Methods: We identified a nonsense LMNA mutation (c.C673T, p.R225X) in a kindred and was associated with progressive CCDs. We established LMNA-R225X knock in mice, and performed surface ECG recordings, echocardiography in WT and R225X-Het mice aged from 2 to 10 months. We also performed programmed electrical stimulation to induce atrial fibrillation in 2 months old mice. HE staining and Masson's trichrome staining are conducted to study atrioventricular node (AVN) morphology and fibrosis, separately. We dissected AVN from WT and R225X-Homo mice for RNA-seq analysis to find the differentially expressed genes and related signal pathways.

Results: R225X-Het mice developed longer PR interval at 2 months, and exhibited I-AVB at 4 months, III-AVB at 10 months. R225X-Het mice displayed increased susceptibility to AF at 2 months. Echocardiography showed normal ejection fraction and chamber size in 2 months old mice. HE staining showed nuclear morphology change in AVN, and Masson's staining showed increased fibrosis in AVN of 2 months old R225X-Het mice. RNA-seq revealed a total of 2088 differentially expressed genes, of which several genes encoding ion channels involved in pace making activity were significantly downregulated including Kcnd2 (Kv4.2 channel) and Kcnn3 (SK3 channel).

Conclusions: The development of CCDs and atrial arrhythmogenesis in R225X-Het mice is independent from the development of cardiomyopathy, recapitulating the disease progression in LMNA (c.C673T, p.R225X) patients. The nuclear morphology change, AVN fibrosis and impaired function of ion channels of AVN pacemaker cells may cause AVB in R225X KI mice.

Poster Number 7

Postdoctoral Researcher

Arrhythmias and Channelopathies

DOWNREGULATION OF FKBP5 PROMOTES ATRIAL ARRHYTHMOGENESIS

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Background: Atrial fibrillation (AF), the most common arrhythmia, is associated with the downregulation of FKBP5 (encoding FK506-binding protein 5, FKBP5). However, the function of FKBP5 in the heart remains unknown. Here, we elucidate the consequences of cardiomyocyte (CM)-restricted loss of FKBP5 on cardiac function and AF development and study the underlying mechanisms.

Materials/Methods: Right-atrial samples from patients with AF were used to assess the protein levels of FKBP5. A CM-specific FKBP5 knockdown (cKD) mouse model was established by crossbreeding Fkbp5 flox/flox mice with Myh6MerCreMer+ mice. Cardiac function and AF inducibility were assessed by echocardiography and programmed intracardiac stimulation. Histology, optical mapping, cellular electrophysiology, and biochemistry were employed to elucidate the proarrhythmic mechanisms due to loss of CM FKBP5.

Results: FKBP5 protein levels were lower in atrial lysates of patients with paroxysmal AF or long-lasting persistent AF . cKD mice exhibited increased AF inducibility and duration compared with control mice. Enhanced AF susceptibility in cKD mice was associated with the development of action potential alternans and spontaneous Ca^{2+}, waves, and increased protein levels and activity of the Na^{+}/Ca^{2+}, +-exchanger 1 (NCX1), mimicking the cellular phenotype of cAF patients. FKBP5-deficiency enhanced transcription of Slc8a1 (encoding NCX1) via transcription factor hypoxia-inducible-factor 1a (HIF-1a). In vitro studies revealed that FKBP5 negatively modulated the protein levels of HIF-1a by competitively interacting with heat-shock-protein 90 (HSP90). Injections of the HSP90 inhibitor 17-AAG normalized protein levels of HIF-1a and NCX1, and reduced AF susceptibility in cKD mice. Furthermore, the atrial-specific knockdown of FKBP5 was sufficient to enhance AF arrhythmogenesis.

Conclusions: This is the first study to demonstrate a causal role of FKBP5 deficiency in atrial arrhythmogenesis and to establish FKBP5 as a negative regulator of HIF-1a in cardiomyocytes.

Poster Number 8

Junior Faculty

Arrhythmias and Channelopathies

AN INNOVATIVE AND TOTALLY PERCUTANEOUS PIG MODEL OF ACUTE ATRIAL FIBRILLATION INDUCTION

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Background: Atrial fibrillation (AF) is a common disease with the potential for severe comorbidities. Several translational models have been used to study this arrhythmia's mechanisms and develop new devices for treating it. Most translational research models require an open-chest approach to induce AF in large animals, which can be complex to reproduce and may interfere with data on the primary endpoints. We present a totally percutaneous translational model for AF induction.

Materials/Methods: Our model uses a hybrid pharmacological and electrical approach for AF induction. Firstly, we selectively engage the right coronary using a percutaneous approach at the femoral artery. Two electrophysiological catheters are placed for stimulation, one on the right atrium and other at the right ventricle. For AF induction, we administer intravenous neostigmine (2.5mg) in a peripheral vein, followed by intracoronary acetylcholine (0.5mg) directly into the right coronary (pharmacological approach). After the drug administration, a 10 Hz burst pacing is delivered through a right atrial pacing catheter for 1-2 seconds (electrical approach). Because acetylcholine may cause asystole, we support heart contraction with stimulation through the catheter on the right ventricle.

Results: This technique was performed 26 times in two Yorkshire pigs (80.5 ± 0.71 kg) and successfully induced acute atrial fibrillation in all attempts. The average duration of AF was 7 min±33 seconds (standard deviation 3 min±32 sec). The shortest period was 3 minutes and 14 seconds, and the longest was 13 minutes and 45 seconds. The electrophysiological analysis showed a pattern of AF with an average cycle length of 85 ± 36.36 ms. The most common side effect was transient hypotension, which was well tolerated and did not compromise the study results. Ventricular tachycardia or fibrillation did not occur.

Conclusions: This totally percutaneous model of an intracoronary injection of acetylcholine followed by an atrial burst efficiently induced acute AF in pigs.

Poster Number 9

Student

Arrhythmias and Channelopathies

AAV CRISPR/CAS9 GENOME EDITING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

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Background: Autosomal dominant single nucleotide polymorphisms in RYR2 are responsible for 60% of cases of catecholaminergic polymorphic ventricular tachycardia (CPVT). In vivo CRISPR/Cas9-mediated gene editing is a promising strategy that can rescue CPVT by specifically disrupting the mutant RYR2 allele. Our objective was to determine the effectiveness of genome editing mutant RYR2 in both the heart and the central nervous system.

Materials/Methods: We employed a heterozygous mouse model of CPVT harboring the R176Q mutation in RYR2. We generated AAV9-SaCas9 and subcutaneously injected p10 mice. 6 weeks after injection, mice underwent ECG stress testing with isoproterenol, caffeine, and programmed electrical stimulation. Isolated ventricular cardiomyocytes loaded with Fluo4 dye were analyzed by confocal line scanning. Ventricular DNA was processed for next generation deep sequencing. We generated AAVPHPeB-SaCas9 and injected intravenously p21 mice. 6 weeks after injection, mice underwent telemetry implantation and stress testing with isoproterenol and caffeine. An AAV-mCherry reporter was used to verify in vivo editing.

Results: We found that AAV-SaCas9 specifically edited the mutant RYR2 allele and reduced the total RyR2 protein levels. Confocal imaging showed a normalization of RyR2 Ca^{2+} leakage following beta adrenergic stimulation. Systemic AAV9-SaCas9 treatment reduced ventricular arrhythmia susceptibility by 75% without affecting baseline cardiac contractility. CNS penetrating AAV-SaCas9 treatment normalized baseline autonomic dysfunction and reduced duration of ventricular arrhythmia.

Conclusions: CRISPR/Cas9 gene editing can treat CPVT by specifically targeting causative mutation sites in multiple channel domains, reducing mutant allele expression and preventing Ca^{2+} leak. This work brings to the fore genome editing as a method of investigation and potential treatment of heritable neurocardiac disorders.

Poster Number 10

Junior Faculty

Arrhythmias and Channelopathies

INCREASED MYOCARDIAL CAPTURE ACROSS AREAS OF SLOWED CONDUCTION BY PACING FROM A HYDROGEL ELECTRODE

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Background: The efficacy of traditional lead-based systems is limited due to their size. Standard leads are too large to traverse beyond large epicardial vessels, particularly on the left side of the heart where endovascular placement is less practical. Our lab has developed an in-situ curing, biostable, conductive hydrogel, or “liquid wire”, capable of filling venous tributary branches and thus accessing mid-myocardial regions which cannot be captured by standard leads. Electrotherapies delivered via the hydrogel electrode may thus have far greater efficacy due to increased myocardial capture.

Materials/Methods: In acute open chest procedures in three pigs, four different pacing modalities were tested: metal electrode point pacing, a small blob of hydrogel, a pre-cured line of hydrogel on the epicardium, and pacing from the hydrogel electrode in the AIV. ECG tracings were recorded during each pacing modality and compared to baseline sinus rhythm. In another three pigs, acute point pacing and AIV liquid wire pacing were assessed before and after ablation around the AIV to mimic scar tissue using electroanatomical mapping of the epicardium and endocardium.

Results: In comparing the four pacing modalities, hydrogel AIV pacing very clearly mimics the baseline sinus tracing, while all others exhibit a typical inverted QRS morphology. In the mapping comparison, we observe a delay in conduction before and after scar in point pacing as well as a dramatic increase in capture when pacing the hydrogel electrode in the AIV after scar formation.

Conclusions: There is clear evidence that pacing the hydrogel electrode from the AIV mimics native rhythm and can capture across areas of slowed conduction. There is great potential for this pacing modality to eliminate re-entrant arrhythmias that is not possible in point pacing by virtue of pacing across areas of slow conduction and normalizing myocardial synchronization across those zones.

Poster Number 11

Postdoctoral Researcher

Cardiac Regeneration and Stem Cells

SILENCING HIPPO PATHWAY COMPONENTS FOR CARDIAC REGENERATION

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Background: Population aged 65 and up is the fastest growing age group in the world. This growth is likely to correlate with an increase of heart attack events. With the lack of efficient treatment and a poor cardiac self-healing, finding new therapeutic avenues for heart diseases is becoming both urgent and critical.

Materials/Methods: Inducing heart-cell regeneration via RNA therapies is one promising method, and genetic knockdown of different genes of the Hippo pathway shows a major cardiomyocyte proliferation. Our study explored the use of DsiRNAs to transiently manipulate different Hippo pathway components: NF2, Sav1 and Mob1.

Results: We demonstrated that combination knockdowns can promote a more efficient cellular regeneration. More importantly, we established that Mob1 knockdown is more powerful than silencing other Hippo pathway targets.

Conclusions: In conclusion, our study proves that Mob1 can be a viable target for cardiac regeneration using RNA-based therapeutics.

Poster Number 12

Junior Faculty

Cardiac Regeneration and Stem Cells

OPTIMIZED AND STANDARDIZED FABRICATION OF DECELLULARIZED CARDIAC EXTRACELLULAR MATRIX POWDER

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Background: Decellularized extracellular matrix (dECM) preparations have become increasingly important in tissue engineering and regenerative medicine. These preparations are often used in powdered form for a multitude of uses including cell differentiation, drug delivery, 3D printing, and clinical uses. Current chemical processes of decellularized powder generation focus on applying organ specific methods and attempt to decellularize on larger samples – as such, they prolong tissue exposure to chemical detergents risking sample degradation. Our group previously described cardiac dECM powders that we used to successfully guide cardiac fate and regulate metabolic maturation during differentiation of cardiomyocytes from human induced pluripotent stem cells (hiPSC-CMs).

Materials/Methods: Here we report an optimized and standardized fabrication method for generating our cardiac dECM powder based on a novel technique that capitalizes on powdering the lyophilized cadaveric tissue first followed by decellularizing the cadaveric powder.

Results: This new protocol yields product quickly, demonstrates high purity, and, importantly, produces uniform dECM pieces.

Conclusions: This more efficient and reliable fabrication method can be scaled to produce large amounts of dECM powder from any type of organ and can be adapted to GMP-grade conditions to produce a product for therapeutic use.

Poster Number 13

Postdoctoral Researcher

Cardiac Regeneration and Stem Cells

YAP INDUCES A NEONATAL LIKE PRO-RENEWAL NICHE IN THE ADULT HEART

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Background: After myocardial infarction (MI), the heart fails to renew, and the cardiac microenvironment is irreversibly disrupted. Inactivation of the Hippo signaling pathway can rebuild the post ischemic microenvironment and improve cardiac function.

Materials/Methods: We investigated spatially resolved cellular relationships of neonatal and adult renewal-competent hearts to gain insight into inefficient mammalian heart renewal. Spatial transcriptomics (ST) and single-cell sequencing of adult control hearts and hearts expressing YAP5SA, an active version of the Hippo signaling pathway effector YAP, which models heart renewal.

Results: Our experiments revealed a conserved, renewal-competent cardiomyocyte (CM) population in control hearts and amplified in YAP5SA hearts. This CM population was also found in the wildtype, renewal competent neonatal heart after myocardial infarction, as well as the adult human heart. Cardiac fibroblasts (CFs), expressing complement C3, colocalized with these CMs. In YAP5SA hearts and neonatal hearts post-MI, macrophages (MPs) expressing complement receptor C3ar1 also colocalized, creating a pro-renewal niche composed of the CM, CF and MP triad. Both C3 and C3ar1 loss-of-function in YAP5SA hearts similarly suppressed heart renewal, indicating that C3-expressing CFs, C3ar1-expressing MPs, and complement system signaling play a direct role in heart renewal.

Conclusions: Our data reveal that YAP drives co-localization of three cell types, a cellular triad, composed of distinct CMs, CFs, and MPs, to form a neonatal-like niche in the adult heart.

Poster Number 14

Postdoctoral Researcher

Cardiac Regeneration and Stem Cells

ASSESSING THE ROLE OF TOP2B AND P53 IN MEDIATING BREAST CANCER DRUG-INDUCED CARDIOTOXICITY

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Background: Anthracycline Doxorubicin (Dox), which is prescribed in 32% of breast cancer patients, can cause irreversible left ventricular dysfunction and heart failure. Dox intercalates into DNA forming a ternary complex with Top2β. Under physiological conditions, Top2β regulates DNA topology and interacts with CTCF and cohesin at topologically associating domain (TAD) boundaries. The Top2β-Dox-DNA complex induces DNA double-strand breaks, mitochondrial dysfunction and apoptosis by activating p53. p53, Top2B, CTCF and cohesin subunit Rad21 are known to bind to the genome at thousands of locations across cell types. However, the binding profiles of these transcriptional regulators in healthy human cardiomyocytes, and those exposed to Dox is unknown.

Materials/Methods: To gain insight into the mechanisms behind Dox-induced cardiotoxicity, we have developed an iPSC-derived cardiomyocyte model to study the binding of these factors in response to Dox treatment. As a first step towards investigating global binding of these factors in iPSC-CMs, we performed chromatin immunoprecipitation followed by qPCR to determine whether these factors bind at locations identified in other cell types.

Results: We observed enrichment of Top2B binding at the BDH2 promoter, enrichment of CTCF and Rad21 binding at four TAD boundaries, and enrichment of p53 binding at known stress response genes CDKN1A, PUMA, MDM2 and BAX compared to input DNA. To measure p53 binding in response to Dox, we exposed iPSC-CMs to a non-lethal dose of Dox that induces thousands of gene expression changes in 24 hours. p53 binding is increased at the CDKN1A and MDM2 promoters in Dox-treated iPSC-CMs compared to vehicle control, which suggests that Dox treatment leads to the activation of the p53 stress response pathway in these cells.

Conclusions: Using this model, we plan to perform ChIP-seq experiments for these factors in iPSC-CMs to determine the gene regulatory networks activated in response to Dox that may explain the cardiotoxic effects of drug treatment.

Poster Number 15

Postdoctoral Researcher

Cardiotoxicity

TOP2B-INHIBITING BREAST CANCER DRUGS INCLUDING ANTHRACYCLINES AFFECT CARDIOMYOCYTE HEALTH THROUGH A SHARED GENE EXPRESSION RESPONSE SIGNATURE

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Background: Breast cancer drugs, such as the anthracycline (AC) Doxorubicin (DOX), cause off-target effects on the heart in some, but not all, women. Tens of AC and non-AC drugs are approved for breast cancer treatment; therefore, predicting adverse drug reactions could inform on optimal patient treatment. The DNA topology regulator, Top2β, is a target of DOX and mediates DOX-induced cardiotoxicity.

Materials/Methods: To gain insight into breast cancer drug-specific effects on the heart across individuals, we developed an iPSC-derived cardiomyocyte (iPSC-CM) model from six genotyped females. We exposed iPSC-CMs to three AC-based Top2β inhibitors (Top2βi): DOX, Daunorubicin, and Epirubicin; a non-AC-based Top2βi: Mitoxantrone; an unrelated monoclonal antibody against HER2: Trastuzumab (TRA), and a vehicle control.

Results: Experimentally-derived 50% lethal doses of the Top2βi drugs are 1-2.5 uM, within the range observed in cancer patient serum. TRA does not affect viability. We chose a sub-lethal dose (0.5 uM) to measure primary responses to drug treatment at 24 hours. We observe a significant increase in cell stress marker release across drugs and effects on cardiomyocyte contractility in Top2βi-treated cells. Global gene expression data shows that drug treatment accounts for most variation between samples followed by the individual from which samples were derived. Joint analysis across all five drugs reveals two predominant gene expression signatures: Top2βi response genes (5,611) and non-response genes (9,211). Top2βi response genes are enriched in cell cycle, DNA replication, and DNA damage pathways., We performed pairwise comparisons between each drug and vehicle treatment to dissect drug-specific effects. Of the 7,192 genes that respond to DOX, 4.5% are specific to DOX treatment, while 50% are shared across AC drugs.

Conclusions: Our data thus demonstrate that Top2βi affect cardiomyocyte health and induce a shared gene expression response signature.

Poster Number 16

Student

Congenital Developmental Heart Disease

YAP AND TAZ ARE REQUIRED FOR NEURAL CREST-DERIVED HEART DEVELOPMENT

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Background: Cardiac neural crest cells (NCCs) make key contributions to the cardiac outflow tract (OFT), valves, and speta. Defects in NCCs cause the most common human birth defect, congenital heart defect (CHD), occurring in 1% of newborns.

Materials/Methods: We specifically deleted Yap and Taz, downstream effectors of the fundamental Hippo-Yap signaling pathway, in NCCs using Wnt1-Cre and Wnt1-Cre2SOR drivers, and correspondingly investigated phenotypical and molecular alterations.

Results: Although all conditional knockout (CKO) mutants with Yap-/- were lethal before E10.5, Yap+/-; Taz-/- CKO mutants produced cardiac defects similar to CHD patient phenotypes including ventricular septal defect (VSD), tetralogy of Fallot, and double outlet right ventricle, varyingly from embryonic day E14.5 to E18.5. In addition, Yap+/-; Taz+/- double heterozygous hearts exhibited external morphology similar to controls, but sectioning revealed mild VSD and vessel aberrations suggesting functional redundancy. Yap+/-; Taz-/- CKO mutants did not show obvious defects regarding cell apoptosis and proliferation in the cardiac OFT. However, both ex vivo cardiac OFT culture and in vitro migration assays indicated an important role for Yap and Taz in regulating NCC migration. Furthermore, analysis of unbiased datasets including RNA-sequencing and CUT&RUN-sequencing reveals potential Yap/Taz novel downstream genes for migration during cardiac development.

Conclusions: Together, our data indicate that Yap and Taz play a critical role in proper cardiac NCC-derived cardiac formation.

Poster Number 17

Student

Congenital Developmental Heart Disease

MECHANOBIOLOGY OF ENDOTHELIAL CELLS IN TURNER SYNDROME BICUSPID AORTIC VALVE DISEASE

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Background: Bicuspid aortic valve disease (BAV) is the most common sexually dimorphic congenital heart deformation (CHD), affecting 1.5% of 46,XY men and 0.5% of 46,XX women. This CHD alters blood flow, such as increased shear stress, and may lead to early onset of aortic valve disease. It's theorized that BAV is heritable, and non-syndromic cases are caused by mutations that impair a conserved pathway called endothelial-mesenchymal transition (endMT). This pathway is critical in heart development and endothelial homeostasis. Its aberrant activation is theorized to contribute to BAV development and adult-onset of vascular aneurysms, and calcific aortic stenosis. BAV is 50x more prevalent in women with Turner syndrome (TS), who are missing all or part of one X chromosome. This suggests that X chromosome mutations contributes to BAV development. However, the molecular dynamics between shear stress in endMT, with respect to X chromosome mutations, has not been elucidated. I hypothesize that genes sensitive to shear stress are inactive/missing in endothelial cells derived from induced pluripotent stem cells (iPSC-ECs) of women with TS and will lead to aberrant activation of endMT.

Materials/Methods: Endothelial behavior was tested by stimulating monolayers of HUVECs and 46,XX TS iPSC-ECs with physiological and pathological shear (0, 5, 15 & 25 dynes/cm2) using a cone-plate bioreactor. The monolayers were characterized for nuclei and actin filament alignment and area after 24 hrs. of shear using fluorescent staining.

Results: HUVECs exhibit actin and nuclei alignment at 5 and 15 dynes/cm2 and is lost at 25 dynes/cm2 compared to the static control. The 46,XX TS IPSC-ECs do not exhibit a cellular response to shear compared to HUVECs. There's a significant decrease in nuclei area with increase shear in HUVECs that's not observed in TS IPSC-ECs.

Conclusions: The results suggest aberrant endothelial behavior of cells derived from TS patients and supports the need for additional studies to further characterize endMT in TS iPSC-ECs.

Poster Number 18

Student

Congenital Developmental Heart Disease

PATHOLOGICAL SHEAR STRESS PROMOTES PRO-INFLAMMATORY MACROPHAGE PHENOTYPE

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Background: Discrete subaortic stenosis (DSS) is a congenital heart disease characterized by fibrotic tissue growth in the left ventricular outflow tract (LVOT), often requiring open-heart surgical correction. The cause of DSS is still unclear, but evidence points to disrupted flow in the LVOT. We hypothesize that the altered shear stress activates a pro-inflammatory response from the endocardial endothelial cells, which attracts macrophages that drive fibrosis of the endocardial tissue. Progress in understanding the cellular mechanisms that lead to DSS formation has been hindered largely by the lack of available model systems that provide insight into the DSS microenvironment. Here, we present an in vitro model system for investigating macrophage behavior in pathological shear stress conditions in the context of DSS.

Materials/Methods: Human monocyte-derived macrophages were harvested and subjected to the following conditions: static, 15 dynes/cm2, or 35 dynes/cm2 for 3 hours, 24 hours, or 48 hours. Shear stress was applied using a cone-and-plate viscometer system, and macrophage phenotype was evaluated through flow cytometry, RT-qPCR, and Luminex.

Results: MDMs exposed to shear stress exhibited a rounder morphology compared to statically-cultured controls. RT-qPCR results showed significant upregulation of TNF-α, and analysis of cytokine release revealed increased secretion of TNF-α, IL-18, fractalkine, and other chemokines. The upregulation of pro-inflammatory factors was evident with both increasing magnitudes of shear and time. Taken together, these results indicate that prolonged shear exposure induced a pro-inflammatory M1 phenotype.

Conclusions: These findings have implications for applications such as in situ vascular graft design, wherein macrophages are exposed to shear and have been shown to affect graft resorption, and further illuminates the role of macrophages in atherosclerosis where shear is directly related to disease outcome. Future studies should evaluate longer timepoints and higher shear rates.

Poster Number 19

Junior Faculty

Congenital Developmental Heart Disease

ASCC2 AS A NOVEL REGULATOR OF CARDIAC DEVELOPMENT

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Background: In humans, congenital heart defects are among the most common birth defects. Congenital muscular dystrophies (CMD) are early onset congenital disorders that can present with cardiac failure. Human loss-of-function alleles of Activating signal co-integrator (ASC) complex members, TRIP4 and ASCC1 were shown to lead to CMD with heart failure in a subset of patients, indicating a novel role for the ASC complex in development and disease. The ASC transcription co-regulator complex consists of TRIP4, ASCC1, ASCC2, and ASCC3.

Materials/Methods: We utilize the KOMP targeted deletion allele, Ascc2tm1d(EUCOMM)Wtsi, to characterize Ascc2 loss-of-function. WISH and qRT-PCR were used for gene expression analysis. Western blotting and co-immunoprecipitation were utilized to determined complex member interactions. Embryos were imaged using μCT, lightsheet, and confocal microscopy. EKG and echocardiography were used to characterize adult cardiac phenotypes.

Results: We found that ASCC2 interacts with other ASC complex members in mouse embryos. Homozygous deletion in Ascc2 results in lethality by embryonic day (E) 9.5. Ascc2 is broadly expressed during early post implantation stages. Ascc2 has the highest expression in the E8.5 heart. Mutant embryos have under-developed hearts, morphological defects and in some cases, complete absence of heart tube formation. Genes required for cardiac mesoderm specification and migration were significant up regulated in Ascc2 mutants, while other mesoderm derived cell markers showed no change. Mesp1 conditional knockout (CKO) of Ascc2 resulted in embryonic lethality and Nkx2.5 CKOs were subviable as adults with morphological and functional cardiac defects.

Conclusions: Loss of Ascc2 during development leads to abnormal heart formation, dysregulation of cardiac progenitor genes, and embryonic lethality. CKO studies suggest that Ascc2 is required in Mesp1 expression cells and functions in Nkx2.5 expressing cells. These data suggest that ASCC2 is an essential regulator of cardiac development.

Poster Number 20

Student

Congenital Developmental Heart Disease

NOVEL METHOD OF DYNAMIC VOLUMETRIC BLOOD FLOW ANALYSIS FOR EARLY EMBRYONIC CARDIOVASCULAR PHENOTYPING

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Background: Congenital heart defects are present in 1.8% of newborns and account for one third of congenital defects. Biomechanical factors are known to regulate cardiac development, but the lack of methods to analyze flow in live embryos limits progress in biomechanical studies. This project aims to develop a novel optical coherence tomography (OCT) based method for volumetric, dynamic, and quantitative analysis of blood flow. This method will be applied to build the first 4D (3D+time) map of early mouse embryonic blood flow and will set a platform for functional cardiovascular phenotyping.

Materials/Methods: Structural OCT imaging was performed on cultured mouse embryos on embryonic day 8.5 (E8.5) volumetrically at 100 Hz as a single volume of 30,000 frames with ~55 frames per heartbeat. The heartbeats are aligned following previously established methods. The new flow speed analysis is based on the duration each pixel detects a particle, particle size statistics, optical microangiography, and the periodicity of the cardiac cycle. Doppler OCT in regions of defined orientation was used as calibration and validation.

Results: We reconstructed the spatially and temporally resolved blood flow profile within the embryonic cardiovascular system with microangiography, particle statistics, and Doppler OCT. The blood flow fluctuation over the heartbeat cycle followed the expected pattern and statistically correlated trend between approaches.

Conclusions: We present a quantitative OCT angiography approach for blood flow analysis in the early mouse embryonic cardiovascular system. This approach will next be applied to build the first 4D quantitative cardiac flow pattern in early embryos. With existing mouse models of congenital heart defects this approach will provide insight into the interplay between genetic and biomechanical factors in cardiac development and disease.

Poster Number 21

Postdoctoral Researcher

CAD, Atherosclerosis, Ischemia

UNUSUAL CASE OF CAROTID ENDARTERECTOMY: OBSTRUCTION BY HYOID BONE

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Background: Hyoid bone compression has shown to be a rare but reported factor in causing carotid vessel disruption. Due to the possibility of persistent or recurrent carotid stenosis and its related complications, definitive management involves surgical correction including carotid endarterectomy and hyoid bone resection. This management has shown a better prognosis than using a stent for carotid artery stenosis due to hyoid bone compression.

Materials/Methods: We describe the case of a 72-year-old male patient presenting to the emergency room with slurred speech and left facial droop. The patient has previously undergone cardiac catheterization in 2019, cardiac defibrillator placement and mitral valve repair. CT scan showed acute MCA territory infarct without haemorrhagic conversion and atherosclerosis of the right carotid bifurcation and proximal right internal carotid artery. CT Angiogram showed anterior cervical fusion between C4 to C6 and compression of the lateral and ventral aspect by the adjacent hyoid bone, requiring open surgery with intraoperative EEG monitoring and resection of the greater horn of the hyoid bone.

Results: Hyoid bone compression of the carotid vasculature should be considered as a rare but possible cause of carotid artery stenosis, dissection or other complications which could lead to TIA or stroke in patients.

Conclusions: Due to the identification of the involvement of the hyoid bone, definitive management in the form of carotid endarterectomy with stem cell patch placement and hyoid bone dissection were performed so as to prevent the recurrence of stenotic changes and its sequelae in this patient. The patient responded to the procedure well.

Poster Number 22

Postdoctoral Researcher

Congenital Developmental Heart Disease

PITX2 IS REQUIRED FOR LEFT-RIGHT EPIGENETIC PATTERNING DURING HEART DEVELOPMENT

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Background: Following left-right symmetry breaking during gastrulation, PITX2 is expressed on the left side of the embryo and gives rise to left-sided structures of the heart like the left atrium (LA). PITX2 is required to confer left-sided identity to the cardiomyocytes (CMs) of the LA, and in its absence, the LA adopts a ride-sided identity. Our recent work describes how decreased Pitx2 perturbs transcription factor networks near PITX2 binding motifs affecting gene transcription in adult LA CMs. That study hinted at a developmental remodeling process at PITX2 sites; however, the mechanism by which this epigenetic inheritance is initiated is unknown. In this work, we test the hypothesis that PITX2-dependent DNA methylation patterning determines the left-sided fate of atrial CMs.

Materials/Methods: We performed whole genome bisulfite sequencing (WGBS) on Pitx2 mutant and control embryonic left and right atrium to profile the DNA methylome. We generated an endogenous epitope-tagged mouse allele of PITX2 and performed cleavage under targets and tagmentation (CUT&Tag) to localize PITX2 binding to DNA in the embryonic LA CMs. We further used this allele to perform immunoprecipitation followed by mass spectrometry (IP-MS) to identity interaction partners of PITX2.

Results: PITX2 binding in LA CMs is associated with regions of low DNA methylation and repressed gene expression. In the absence of PITX2, these regions are methylated, and nearby genes are expressed. PITX2 likely interacts with GATA4 to recruit the TET DNA de-methylases to remove local DNA methylation at FOX, bHLH, and bZIP transcription factor binding sites.

Conclusions: Our work highlights a molecular mechanism for how PITX2 determines left-sided patterning. These left-right asymmetrical patterns persist throughout embryonic development and adult life, which imparts long-lasting transcriptional consequences underlying adult disease susceptibility, such as atrial fibrillation, in the physiologically distinct left from right atria.

Poster Number 23

Postdoctoral Researcher

Aortopathy and Valvular Heart Disease

INFLUENCE OF SOCIOECONOMIC STATUS ON OUTCOMES AFTER LEFT-SIDED VALVE REPLACEMENT FOR INFECTIVE ENDOCARDITIS

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Background: Socioeconomic status (SES) is believed to affect outcomes in patients with infectious endocarditis (IE). We analyzed the influence of SES on mortality, readmissions, and resource utilization after aortic (AVR) or mitral valve replacement (MVR) for patients with IE.

Materials/Methods: The Nationwide Readmissions Database was queried to identify 13,694 patients who underwent AVR or MVR for IE between 01/2016 and 12/2018. A tiered SES metric composed of patient and neighborhood factors stratified patients. Multivariable analysis assessed the impact of SES on risk-adjusted outcomes.

Results: In IE patients, lower SES was more frequent (38% [5,216/13,694]) than higher SES (16% [2,221/13,694]). AVR was more common (69% [9,400/13,694]) than MVR (31% [4,294/13,694]). Patients with lower SES had longer index hospitalization (22 vs 17 days) and higher cost ($84,931 vs $83,826; p<0.001 for both), but similar mortality (6.4% [336/5,216] vs 5.9% [130/2,221]; p=.8) compared to higher SES. Patients with lower SES were less frequently discharged with home health care (26% [1,122/4,396] vs 49% [930/1,897]; p<.001). Lower SES had higher readmission rates at 30-days (22% [955/4,396] vs 17% [330/1,897]; p=.038), 90-days (35% [1,257/3,614] vs 27%; [421/1,580]; p<.001) and within a year (36% [1,860/5,216] vs 27% [606/2,221]; p<.001). Death during readmission was twice as frequent in patients with lower SES (3% [154/5,216] vs 1.5% [34/2,221]; p=.003). Lower SES was an independent predictor of readmission at 30-days (OR 1.42 95% CI [1.10, 1.84]), 90-days (OR 1.44 [1.12, 1.84]) and one year (HR 1.32 [1.14, 1.54]).

Conclusions: SES influences outcomes after valve replacement in patients with IE. Patients with lower SES have longer hospitalizations at greater cost with more frequent readmissions up to 1 year after surgery. Targeted interventions, such as greater use of home health care in patients with lower SES, may reduce readmission and improve outcomes.

Poster Number 24

Student

Congenital Developmental Heart Disease

A CASE SERIES AND LITERATURE REVIEW OF PULMONARY EMBOLISM DETECTION IN FONTAN ANATOMY

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Background: Fontan anatomy is completed to establish a conduit between the caval vasculature and the pulmonary artery thus bypassing the right ventricle. This anatomy increases the risk of thromboembolic events because of direct venous conduit to the PA in addition to decreased flow state. Additionally, congenital heart disease (CHD) often exists with comorbidities like atrial fibrillation (AF) further increasing thromboembolic risk. This complex anatomy poses difficulty for standard CT pulmonary angiogram (CTPA) identification of PE. Limited studies exist optimizing CT for PE visualization in Fontan anatomy. CTPA was insufficient for identification of PE as evidenced by cases we present here of recurrent PE.

Materials/Methods: We present two patients with Fontan anatomy with high clinical suspicion for PE undergoing CTPA with failure of standard PE imaging protocol to clearly identify the Fontan conduit requiring MRI imaging. The cases identified here emphasize the importance of further reviews on the best imaging techniques for timely identification of PE and for establishing standard imaging acquisition protocol in patients with Fontan anatomy.

Results: Overall, these pathologies can manifest in this at-risk population; however, PE is an urgent pathology that can lead to a substantial burden and mortality. Moreover, retrospective analyses found that 20% of patients have significant thromboembolic events with most occurring within the venous circulation and few in the systemic pathways. From the literature search we performed, we identified specialized CT angiography and cardiac magnetic resonance (CMR) imaging as forms of identifying PE in patients who have undergone the Fontan procedure.

Conclusions: In summary, both CT and CMR have their advantages and disadvantages in their roles of diagnosing PE in Fontan anatomy. Simply, dual site CTPA and CMR should be utilized in conjunction for the benefit of identifying PE in patients with Fontan physiology.

Poster Number 25

Postdoctoral Researcher

Congenital Developmental Heart Disease

COMPARING PALLIATION STRATEGIES FOR SINGLE VENTRICLE ANATOMY WITH TRANSPOSED GREAT ARTERIES AND SYSTEMIC OUTFLOW OBSTRUCTION

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Background: Patients with complex single ventricle anatomy with transposed great arteries and systemic outflow obstruction (SV-TGA-SOO) undergo varied initial palliations with ultimate goal of Fontan circulation. We examine contemporary outcomes for the palliative arterial switch operation (pASO) compared with alternate strategies in a similar anatomic cohort.

Materials/Methods: Neonates with SV-TGA-SOO who underwent pASO (n=23), modified Norwood (n=23), or pulmonary artery (PA) banding (n=25) for initial surgical palliation from July 1995 to 2022 were retrospectively reviewed. Clinical outcomes were compared using non-parametric methods and Kaplan-Meier survival analysis.

Results: At a median follow up of 7.9 years (range 2-21.8 years) after pASO, there were no deaths, 83% Fontan completion (n=19), and 1 post-Fontan heart transplant for ventricular dysfunction. 2 patients (9%) had early postoperative coronary complications attributable to pASO, 1 requiring reoperation. At latest follow up, 12 patients had neo-aortic insufficiency (55%, mild to moderate) and 3 had ventricular dysfunction (13%, all mild). Significant differences among the palliation types included weight at operation, bypass and cross-clamp time, postoperative length of stay, time to second stage palliation, and multiple PA reinterventions. Reintervention-free survival in the first interstage period, PA reintervention-free survival, overall survival, Fontan completion, postoperative coronary problems, ventricular dysfunction, and neo-aortic insufficiency at follow-up were similar.

Conclusions: pASO is a reasonable strategy for neonates with SV-TGA-SOO, with excellent mid-term survival and Fontan progression as well as robust preservation of ventricular function and neo-aortic valve competency. Compared with PA banding or modified Norwood, pASO confers PA accessibility for ease of extensive augmentation without increased rates of coronary artery complications.

Poster Number 26

Student

CHF and Cardiomyopathy

THE ROLE OF JUNCTIN (JNC) IN MUSCLE FUNCTION

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Background: Junctin (JNC) is a sarcoplasmic reticulum (SR) transmembrane protein that is a component of excitation-contraction coupling complexes in skeletal muscle triads and cardiac dyads. In humans JNC depletion correlates with dilated cardiomyopathy (DCM), the most prevalent form of cardiomyopathy worldwide. However, whether depletion of JNC is a driver or a consequence of DCM is unknown. JNC is a non-catalytic splice variant of aspartyl-β-hydroxylase (ASPH) gene. Interpretation of the phenotypes of previously reported JNC deficient mice was complicated by the simultaneous ablation of all ASPH isoforms in multiple tissues.

Materials/Methods: We generated a new mouse model with a deletion JNC's 4th exon (designated JNCΔ4). Exon-4 deletion results 90% and 55% decreases in JNC in skeletal and cardiac muscle, respectively, without altering other enzymatic ASPH isoforms.

Results: JNCΔ4 mice display DCM with increased myocardial fibrosis, skeletal muscle weakness, and decreased lean mass. Muscle weakness in JNCΔ4 mice is exacerbated with age. We determined that JNC deficiency decreased SR Ca^{2+} release, increased cytosolic Ca^{2+} levels, and increased excitation contraction-coupled calcium entry (ECCE) via CaV1.1. JNC has a relatively short cytoplasmic domain and, therefore, the mechanism by which JNC modulates both CaV1.1 and RyR1 is unclear. We found that JNC immunoprecipitates to a much greater extent with junctophilin 2 (JPH2) than with RyR1. JPH2 is an SR transmembrane protein that interacts with transverse tubules to stabilize triads/dyads.

Conclusions: One possible role for JNC is to stabilize the interactions of JPH2 with CaV1.1 and RyR1 in skeletal muscle, leading to increased SR calcium release and decreased calcium entry through CaV1.1.

Poster Number 27

Junior Faculty

CHF and Cardiomyopathy

MYOCARDIAL LIPID REGULATION IN JUNCTOPHILIN-2 (JPH2) ASSOCIATED FAMILIAL CARDIOMYOPATHIES

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Background: Cardiomyopathies are one of the leading causes of death worldwide. Abnormal myocardial lipid regulation is one of the critical factors leading to these diseases. Lipids are essential for cardiac metabolism, cellular structure, etc. Therefore, identifying myocardial lipid alteration could be vital in understanding the underlying mechanism of these diseases. JPH2 is a critical regulator of excitation-contraction coupling. Several studies have found inherited mutations in this gene of patients with hypertrophic cardiomyopathy (HCM) and in some cases dilated cardiomyopathy (DCM).

Materials/Methods: Echocardiography assessed cardiac function in mice with the JPH2 missense variant (A399S), identified in patients with HCM, and truncation variant, E640*, found in an Iranian family with early onset DCM. Isolated total lipids from LV of these mice were analyzed using a Vanquish UPLC, a Lumos orbitrap mass spectrometer, and Lipid search software.

Results: Echocardiography revealed HCM characteristics in A339S mice with an increased septum (1.17±0.03mm vs.1.00±0.01mm in WT) and DCM features in E640* mice with increased LV diameter (2.78±0.1mm vs. 2.2±0.16mm in WT). We discovered significantly reduced fatty acid content in both models (49.9±6.6% in A399S and 47.2±5.8% in E640* vs. 100±13.1% in WT), suggesting altered cardiac metabolism. Furthermore, we found reduced ceramides and phospholipids in both models. Interestingly we found significantly increased diglycerides and triglycerides only in HCM, whereas they were unchanged in DCM. However, ChE was only increased in the DCM model. Interestingly, we found a dose-dependent change in the A399S heterozygous and homozygous mice suggesting the potential involvement of JPH2 in lipid regulation.

Conclusions: Our findings discover novel cardiac lipid profiling in HCM and DCM caused by distinct JPH2 variants, which can be critical to identifying potential biomarkers for these diseases. Moreover, this study expands a new paradigm in studying the role of JPH2 in lipid regulation.

Poster Number 28

Student

Cardiac Arrhythmia and Electrophysiology

LOSS OF STRIATED MUSCLE PREFERENTIALLY EXPRESSED GENE (SPEG) KINASE LEADS TO HEART FAILURE DUE TO ABERRANT SARCOPLASMIC RETICULUM CA2+ HANDLING

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Background: Heart failure (HF) afflicts 6.5 million people in US. Ca^{2+} mishandling plays a key role in development of contractile dysfunction in HF. 'Striated muscle preferentially expressed gene' (SPEG) is a novel kinase that phosphorylates RyR2 at S2367 and regulates intracellular Ca^{2+} dynamics. The role of phosphorylation at S2367 in HF progression has not been assessed. Here we hypothesized that SPEG phosphorylation of S2367 on RyR2 ameliorates HF development by reducing aberrant SR Ca^{2+} release.

Materials/Methods: We developed a cardiac-specific SPEG conditional knock-out mouse (SPEGcKO) by injecting Spegfl/fl mice with AAV9-TNT-Cre. To test role of RyR2-S2367 phosphorylation in HF, we crossed SPEGcKO with RyR2-S2367D (phospho-mimetic) mice to generate a rescue mouse (SPEGcKO-S2367D). Cardiac function was assessed from echocardiograms recorded at 4, 8, and 12w post-injections. SPEG protein levels were measured by Western blot (WB). Cardiomyocytes were isolated to assess intracellular Ca^{2+} dynamics.

Results: SPEGcKO mice have decreased EF at 12w vs SPEGcKO-S2367D mice (24.4□1.45 vs 42.8□4.48). To confirm mice had SPEG protein reduced, we did WBs and saw relative to WT (1±0.21), both Cre injected SPEGcKO (0.28±0.08) and SPEGcKO-S2367D mice (0.21±0.04) had reduced SPEG. Relative to WT, SPEGcKO mice had decreased S2367 phosphorylation of RyR2 (1±0.08 vs 0.47±0.09). At 8w, there was a significant increase in Ca^{2+} transient amplitude in SPEGcKO relative to WT (0.94+0.06 vs 0.61+0.06), which was reduced in SPEGcKO-S2367 (0.71+0.05).

Conclusions: Our data reveal that reduced SPEG phosphorylation of RyR2 is critical in HF progression. Specifically, cardiac function can be protected in SPEGcKO mice by mimicking the RyR2 site-specific phosphorylation at S2367. SPEG is critical for RyR2 phosphorylation at S2367 and its loss leads to HF by dysregulating intracellular Ca^{2+} release. Thus, modulating SPEG activity or directly modifying RyR2 phosphorylation at S2367 may provide new therapeutic opportunities for HF treatment

Poster Number 29

Postdoctoral Researcher

Heart Failure and Cardiomyopathy

A DEFECTIVE EXTRACELLULAR MATRIX/KINDLIN-2/ACTIN/ERK MECHANOSENSING PATHWAY AFFECTS FIBROBLAST-TO-MYOFIBROBLAST TRANSITION IN THE OLD MALE HEART

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Background: In the aging heart, changes in extracellular matrix (ECM) composition contribute to myocardial dysfunction. Specifically, ECM can affect cellular function and phenotype via regulatory crosstalk called mechanosensing. For example, in response to ECM tension, fibroblasts mature into myofibroblasts, expressing contractile actin fibers enriched in α-smooth muscle actin (α-SMA). In the aging male heart, even though ECM becomes stiffer, cardiac fibroblast maturation is drastically impaired. We thus hypothesized that an altered mechanosensing pathway might be involved in the specific phenotype of the old male cardiac fibroblasts.

Materials/Methods: To test our hypothesis, primary adult mouse cardiac fibroblasts (from young or old male vs. female mice) were cultured on a 2-D surface (secreted ECM) or on 3-D matrices (decellularized mouse hearts).

Results: We first found that actin polymerization and polarization were both drastically impaired in the old male cells, and the α-SMA level was significantly reduced. Then, we determined that ECM composition affected the fibroblast phenotype, especially the expression of Kindlin-2, an adaptor that connects ECM and the actin cytoskeleton. When Kindlin-2 levels were manipulated via siRNA interference, young fibroblasts developed an old-like fibroblast phenotype, whereas Kindlin-2 overexpression in old fibroblasts reversed the defective phenotype. Finally, we found that Extracellular Regulated Kinases 1 and 2 (ERK1/2) were overactivated in the old male fibroblasts. Actin polymerization and α-SMA expression were rescued in old cells pretreated with ERK inhibitor without affecting Kindlin-2 expression. However, Kindlin-2 overexpression attenuated ERK1/2 overactivation in the old cells. In contrast, cardiac fibroblasts from old female mice retain an operant mechanosensing pathway.

Conclusions: In conclusion, our results suggest that the Kindlin-2/ERK/actin/α-SMA mechanosensing axis in the cardiac fibroblasts is sex and age sensitive.

Poster Number 30

Postdoctoral Researcher

Heart Failure and Cardiomyopathy

NOVEL REV-ERB SPECIFIC AGONIST SLU-1799 IMPROVES LEFT VENTRICULAR DYSFUNCTION AFTER PRESSURE OVERLOAD IN MICE

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Background: Circadian clock plays a vital role in heart health and diseases. The nuclear receptor Rev-erbα/β are key components of the circadian clock and play critical roles in cardiac remodeling after pressure overload. However, widely used REV-ERB agonist SR9009 has recently been reported to have off-target effects in several model systems. This study aims to test the effect of a structurally distinct, novel REV-ERBα/β agonist (SLU-1799) on left ventricular (LV) dysfunction and remodeling after pressure overload.

Materials/Methods: Twenty-four wild-type (WT) C57BL/6J mice underwent Sham or transverse aortic constriction (TAC) surgery at the age of 9 weeks. After TAC, mice were injected with SLU-1799 at a dose of 20 mg/kg/day or Vehicle at zeitgeber time ZT2 for 6 weeks. Echocardiography was performed before TAC and 1w, 2w, 4w and 6w after TAC. The same strategy was performed in the mice with cardiac-specific Rev-erbα/β total knockout (cTKO) to verify target specificity of SLU-1799. Mice hearts were harvested 6w after TAC. Single Nuclei RNA-Seq and metabolomics were conducted in heart tissues of WT mice.

Results: 6 weeks after TAC, WT mice in the 1799-TAC group showed a significantly improved LV ejection fraction and lower LV mass comparing to WT mice in the Vehicle-TAC group. Both the cross-section sizes of the cardiomyocytes and the fibrosis area were smaller in WT mice of the 1799-TAC group comparing to the vehicle group. However, in cTKO mice SLU-1799 did not show any effect. Multiple changes in metabolomics and snRNAseq have been observed and further analysis is underway.

Conclusions: Novel Rev-erb agonist SLU-1799 improves LV dysfunction and ameliorates cardiac hypertrophy and fibrosis post pressure overload in mice in a Rev-erb dependent fashion, supporting a critical role of core clock factor Rev-erb in cardiac remodeling as well as the further development of SLU-1799 as a proto-drug for heart failure. The molecular mechanism of Rev-erb in cardiac remodeling is currently under investigation.

Poster Number 31

Postdoctoral Researcher

Heart Failure and Cardiomyopathy

NUMB FAMILY PROTEINS REGULATE LEFT VENTRICULAR COMPACTION

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Background: Left ventricular noncompaction (LVNC) is a type of cardiomyopathy. We and others previously found that the ablation of the endocytic adaptor protein Numb and its homolog Numbl, collectively known as Numb Family Proteins (NFPs), at early stage causes defects in trabeculation and compaction, resulting in embryonic lethality. In this study, we found that NFPs deletion in heart at later stage causes LVNC cardiomyopathy.

Materials/Methods: We applied aMHC-Cre to delete NFPs to generate double knockout (ADKO); applied ECHO to determine the pathophysiology of LVNC, the heart structure and functions, and ECG to determine heart arrhythmia; applied mCherry:Numb knockin mouse line to determine Numb subcellular localization, and mass spectrometry to determine proteins that interact with Numb, and autophagy reporter and electron microscopy (EM) to determine the functions of NFPs in autophagy.

Results: The ADKO heart displayed an anatomical feature of LVNC starting at about two-months-old, and showed a progressive reduced diastolic and systolic function starting at four-months-old. The ADKO hearts display the major clinical features of LVNC with arrhythmia, thrombosis, and sudden death starting at about seven-month-old. EM images show that the cardiomyocytes of the ADKO display a significant accumulation of damaged mitochondrial and larger sizes of the autophagosome, confirmed by the LC3-GFP reporter. Numb binds to the proteins involved in endocytosis and autophagy. Multiple proteins failed to localize to specific compartment, and ubiquitin-conjugated protein level was significantly increased in ADKO hearts.

Conclusions: NFPs deletion in cardiomyocytes interferes the endocytosis and autophagic flux, resulting in the abnormal compartment of multiple proteins and increased levels of ubiquitin-conjugated protein. Our studies suggest that NFPs mediated endocytosis and autophagy are essential for left ventricular compaction; LVNC can be both congenital and acquired.

Poster Number 32

Postdoctoral Researcher

Heart Failure and Cardiomyopathy

LNCRNA CIRCA PROTECTS AGAINST POST MYOCARDIAL INFARCTION REMODELING BY COUNTERACTING HNRNPA1 FUNCTION IN THE 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) which indicates its potential function in the disease modeling process.

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) RNA sequencing and replicate multivariate analysis of transcript splicing (rMATS) In vitro CM ischemic assay

Results: 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. Mechanistically, we found that Circa is primarily localized in the nuclei where it associates with components or regulators of the spliceosome, including hnRNPA1. Circa null mice showed hundreds of aberrantly spliced transcripts both at baseline and post MI in the heart. Besides, Circa and hnRNPA1 oppositely regulates CM death from ischemia induced cell death in vitro. Furthermore, Circa counteracts hnRNPA1 induced CM death and the inhibitory function was associated with reduction of the stress granule formation under stress and the formation of nuclear phase separation with Circa and hnRNPA1 containing structure in the nuclear.

Conclusions: In conclusion, our study suggests that LncRNA Circa may regulate the stress response of hnRNPA1 to protects CM from ischemic injury.

Poster Number 33

Student

Heart Failure and Cardiomyopathy

IN PATIENTS WITH MASSIVE AND SUB-MASSIVE PULMONARY EMBOLISM, DOES ULTRASOUND-ACCELERATED ENDOVASCULAR THROMBOLYSIS (USAT) PROVIDE BETTER CLINICAL AND SAFETY OUTCOMES IN COMPARISON TO STANDARD CATHETER DIRECTED THROMBOLYSIS (CDT)?

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Background: CDT exceeded systemic thrombolytic therapy in terms of safety and efficacy outcomes. Lately, USAT has been considered an effective therapy for patients with sub-massive and massive pulmonary embolism. However, studies directly comparing USAT and CDT is limited especially given the fact that USAT may not be widely available. This study's objective is to compare the efficacy of USAT and CDT in patients with massive and sub-massive pulmonary embolism by performing an aggregate data meta-analysis.

Materials/Methods: An extensive time-unlimited literature search was performed using PubMed, EMBASE and Cochrane databases. Final search resulted in 6 studies comparing USAT and CDT. Baseline demographic and clinical variables as well as procedural details were collected from all these studies. Outcomes of interest were pulmonary artery systolic pressure (PASP) and RV/LV ratio before and after treatment, total tissue plasminogen activator (tPA) dose, and in-hospital length of stay and mortality between the two groups. Meta-analyses were performed using Review Manager 5.3 (Cochrane Collaboration). Effect size was calculated using Mean Difference with 95% confidence intervals and random effects model was employed.

Results: These studies reported a total of 425 patients (222 in USAT and 203 in CDT groups). Baseline demographic and clinical variables were comparable between the two groups. There was no difference in the total dose of tPA used between the two groups (mean difference 0.77mg). In efficacy, three studies had available data and showed significant reduction in the PASP and RV/LV ratio with USAT and CDT, but no significant difference between them (P = 0.36 and 0.39, respectively). There was no significant statistical difference for in-hospital length of stay (mean difference 0.81 days) and mortality between CDT and USAT (P-value=0.22).

Conclusions: CDT and USAT were comparable in total dose of tPA, in efficacy with significant reduction in PASP, RV/LV ratio, and in all-cause mortality and hospital length of stay.

Poster Number 34

Student

Heart Failure and Cardiomyopathy

CHARACTERIZING THE CARDIOMYOCYTE RESPONSE TO A PANEL OF DIVERSE STRESSORS

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Background: Cellular stress responses (CSRs) seek to ensure cell survival in exposure to stressors, though unsuccessful resolution of stress leads to damage or cell death. Cardiomyocytes (CMs) are vulnerable to stress due to a limited capacity to regenerate – any damage is nearly irreversible. Loss of CMs is associated with impaired cardiac function and development of cardiovascular disease (CVD). CVD susceptibility is complex with both genetic and environmental factors, though the relative contribution of genetics versus environment is not fully understood.

Materials/Methods: As a first step towards understanding the genetic basis of CSRs, we have developed an in vitro model of induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). To capture a series of CSRs, we exposed iPSC-CMs to a range of concentrations of agents known to induce the unfolded protein response (UPR), DNA damage response (DDR), innate immune response (IMR), and a response to manmade chemicals (MCR), which has unclear cellular effects.

Results: We observe a 50% reduction in cell viability after 24 hours of high concentrations of two MCR (acrylamide, PFOA) and two DDR (doxorubicin, mitoxantrone) stressors, and 25% reduction in UPR (tunicamycin, thapsigargin), DDR (nutlin-3), and MCR (BPA) stressors. No effects on cell viability were observed following IMR stressor (TNFα, IFNγ, and LPS) exposure across concentrations. To investigate initial transcriptional changes consistent with CSR induction, concentrations below the calculated LD50 value of each stressor were selected. qPCR assays of iPSC-CMs exposed to chosen concentrations show mRNA expression changes of CSR-associated response genes such as CDKN1A (DDR), DDIT3 (UPR), IL-6 (IMR), and PPARA (MCR) at 2 to 8 hours of exposure, suggesting induction of each CSR type.

Conclusions: With this model, we aim to measure global gene expression changes and identify regulatory regions to gain insight into genetic elements which mediate effects of differing CSRs in the context of CVD susceptibility.

Poster Number 35

Student

Heart Failure and Cardiomyopathy

INVESTIGATING THE CELLULAR AND MOLECULAR RESPONSE TO HYPERGLYCEMIA IN IPSC-DERIVED CARDIOMYOCYTES

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Background: Hyperglycemia is both a diagnostic hallmark and promoter of various diabetes-related pathologies. In cardiovascular tissue, prolonged hyperglycemia can lead to a type of cardiovascular disease (CVD) called diabetic cardiomyopathy (DCM) in some individuals. Because most CVDs are irreversible, understanding susceptibility to DCM is critical to early diagnosis and risk mitigation. Individual susceptibility to DCM can be assessed before the onset of cardiac pathology by determining genetic risk. Gene-by-environment (GxE) interactions, differential responses to the same environmental perturbation between cells of different genotypes, can be utilized to find disease-relevant variants that may inform genetic risk to DCM. Before functional genetic variants can be isolated, an in vitro model of hyperglycemia must be generated.

Materials/Methods: Three Induced Pluripotent Stem Cell (iPSC) lines were used to generate iPSC-derived cardiomyocytes (iPSC-CM). Given that increased blood glucose concentrations are associated with increased risk for the development of DCM in diabetic individuals, we use glucose as an environmental perturbation relevant to DCM. RNA-Seq was used to measure global gene expression to capture the molecular response to glucose, while Ca^{2+} Imaging, and mitochondrial superoxide fluorescence were used to measure the cellular response to glucose and contextualize the RNA-Seq data.

Results: iPSC-CMs were generated at high sample purities, as measured by the expression of cardiac-specific troponin T. 1,513 genes were differentially expressed (DE) within two hours of high glucose exposure. Many DE genes were found to be involved in ER stress, ROS production, protein metabolism and inflammation. Ca^{2+} imaging showed arrhythmogenicity of iPSC-CMs due to hyperglycemia after 2 hours. Hyperglycemia increased mitochondrial superoxide production at 24 hours.

Conclusions: We have generated an in vitro model of glucose dysregulation iPSC-CMs to model DCM where features of glucose dysregulation can be captured.

Poster Number 36

Postdoctoral Researcher

Heart fibrosis

HIPPO PATHWAY IN CARDIAC FIBROBLASTS REGULATES FIBROBLAST DIFFERENTIATION INTO OSTEOCHONDROPROGENITOR-LIKE CELL STATE DURING HEART FIBROSIS

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Background: Cardiac fibrosis impairs heart function and has been linked to various cardiovascular diseases. However, the cellular and molecular mechanisms underlying cardiac fibrosis are not well defined. Recent studies showed that the Hippo pathway in cardiac fibroblasts (CFs) regulates fibrosis and inflammation. Here, we investigated how Hippo deficient CFs interact with immune cells to regulate their cell state transition during cardiac fibrosis.

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

Results: From the snRNA-seq and ST data analyses, we found that Lats1/2CKO CFs differentiate into osteochondroprogenitor-like (OCP-like) cells. Consistently, expressions several OCP markers, including Sox9, Collagen 2a1 and Runx2, was detected in Hippo deficient CFs by in situ hybridization and immunostaining. In the ST and immunostaining data, OCP-like cells colocalized with macrophages, suggesting communications between two cell types. Indeed, several ligand receptor pairs were identified from the snRNAseq and further validated. To investigate the role of macrophages in this context, we blocked macrophage expansion pharmacologically and found that OCP marker expressions were greatly reduced in Hippo deficient CFs, indicating that macrophages are required for CF differentiation into OCP-like cell state.

Conclusions: Our findings support that Hippo deficient CFs-incuded macrophage expansion is critical for Hippo deficient CF differentiation into OCP-like cells to promote cardiac fibrosis.

Poster Number 37

Junior Faculty

Moyamoya disease/smooth muscle cell development

NUCLEAR SMOOTH MUSCLE A-ACTIN IS CRITICAL FOR SMOOTH MUSCLE CELL DIFFERENTIATION

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Background: Pathogenic variants in ACTA2, encoding α-smooth muscle actin (SMA), predispose to thoracic aortic aneurysms. A subset of these ACTA2 variants, notably missense variants causing substitution for arginine 179 (R179), also predispose to childhood-onset cerebrovascular disease characterized by occlusion of the distal internal carotid arteries and small vessel disease.

Materials/Methods: We reprogrammed dermal fibroblasts from ACTA2 p.R179 patients (n=3) and controls (n=4) into induced pluripotent stem cells, then differentiated them into smooth muscle cells (SMCs). We also made a smooth muscle-specific conditional knock-in mouse model of the Acta2 p.R179C mutation, termed Acta2SMC-R179C/+.

Results: We identified that nuclear localization of SMA is impaired with R179 mutations. Because nuclear SMA has not previously been characterized, we confirmed that SMA is localized to the nucleus in wildtype (WT) SMCs, is enriched in the nucleus over β-actin with differentiation of SMCs, and associates with the promoters of SMC contractile genes. ACTA2 p.R179 patients SMCs and SMCs explanted from Acta2SMC-R179C/+ mice are less differentiated than control SMCs and have increased expression of pluripotency-associated genes, increased proliferation, and in creased migration. Although the mutation is heterozygous, these cells show a dominant negative impact on nuclear SMA function. scRNA-seq analysis of aortic tissue from our Acta2SMC-R179C/+ mouse model confirms decreased differentiation of SMCs as a key phenotype associated with this mutation, and the transcriptional changes correlate with altered chromatin accessibility determined by ATAC-sequencing.

Conclusions: Taken together, we have identified a novel role for SMA in the nucleus driving differentiation of SMCs, and our data supports that defects in this nuclear role drive cellular phenotypes consistent with the cerebrovascular disease seen in ACTA2 p.R179 patients.

Poster Number 38

Postdoctoral Researcher

Ocular Vascular Disease

INHIBITION OF CHOROIDAL NEOVASCULARIZATION BY ANTI-SCG3 GENE THERAPY

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Background: Applications of anti-VEGF gene therapy for the treatment of choroidal neovascularization (CNV) are constrained by safety concerns involving chronic suppression of healthy retinal vessels and neurons. Anti-angiogenic therapy against secretogranin III (Scg3) selectively inhibits pathological angiogenesis without affecting healthy vasculatures or neurons and any detectable side effects.

Materials/Methods: Recombinant adenovirus-associated virus (AAV) expressing aflibercept (AAV-aflibercept), anti-Scg3 Fab (AAV-anti-Scg3 Fab) or mCherry (AAV-mCherry) was constructed and analyzed for binding activity to VEGF and Scg3 by ELISA. AAV was intravitreally injected into C57BL/6J mice on Day 0. Expression of recombinant aflibercept and anti-Scg3 Fab in the retina was detected by Western blot on Day 30. Mice received laser photocoagulation on Day 30 to induce CNV (4 spots/eye). On Day 35, CNV leakage was detected and quantified by fluorescein angiography (FA). Choroids were isolated on Day 37 and stained with Alexa Fluor 488-isolectin B4 (IB4) to label choroidal vessels for CNV quantification.

Results: AAV-mediated expression of FLAG-tagged aflibercept and anti-Scg3 Fab in mouse retinas was verified by Western blot. AAV-aflibercept and AAV-anti-Scg3 Fab significantly inhibited CNV leakage intensity and area size with similar efficacies, as quantified by FA. Additionally, both AAVs significantly reduced CNV 3D volume and lesion size, as detected by IB4 staining with similar high efficacy. Control AAV-mCherry was without effect on CNV by all measurements.

Conclusions: Intravitreal administration of AAV-anti-Scg3 Fab inhibits laser-induced CNV with similar efficacy to AAV-aflibercept. AAV-anti-Scg3 Fab represents a novel alternative to anti-VEGF gene therapy for wet age-related macular degeneration by providing long-term safety advantages and circumventing frequent intravitreal injections.

Poster Number 39

Aortopathy and Valvular Disease

Postdoctoral Researcher

DYNAMIC SMOOTH MUSCLE CELL PHENOTYPIC TRANSITION DURING HUMAN THORACIC AORTIC DISEASE PROGRESSION --- FROM COMPENSATION IN AORTIC ANEURYSM TO DECOMPENSATION IN AORTIC DISSECTION

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Background: Progression of ascending thoracic aortic aneurysm (ATAA) to dissection (ATAD) carries a high risk of mortality. In this study, we compared molecular and cellular events in smooth muscle cells (SMCs) that drive disease progression from ATAA to ATAD.

Materials/Methods: We performed single-cell RNA sequencing (scRNA-seq) of ascending aorta from patients with ATAA (3 women, 6 men), ATAD (3 women, 6 men) and non-diseased organ donor control subjects (3 women, 5 men). We performed scRNA-seq and single cell analysis of accessible chromatin (scATAC-seq) on diseased mouse models induced by angiotensin II (AngII) and beta-aminopropionitrile (BAPN) (public data).

Results: Profound SMC phenotypic transition from contractile to extracellular matrix (ECM)-contractile SMCs (p=0.036) was observed in ATAA that was associated with 389 differentially expressed genes (DEGs) enriched in ECM organization (p=2.30E-07) and muscle contraction (p=1.08E-06). In contrast, a significant switch from contractile to inflammatory SMCs (p=0.04) was detected in ATAD that was associated with 773 DEGs enriched in pro-inflammatory signaling (p=5.05E-08). Single-cell regulatory network inference and clustering analysis suggested that several transcription factors (e.g., MEF2C [OR=7.41, p=3.23E-32], JUND [OR=6.07, p=3.37E-56], NFE2L2 [OR=12.35, p=0.0034]) drive genes in ECM organization and muscle contraction in ATAA, while other transcription factors (e.g., HIF1A [OR=30.68, p=1.57E-24], MYC [OR=19.53, p=1.08E-256], ATF4 [OR=12.61, p=2.23E-73]) promote pro-inflammatory genes in ATAD. The transition to ECM producing phenotype and their potential drivers (e.g. Jund and Nfe2l2) were confirmed in mouse models.

Conclusions: Our data suggest differential SMC phenotypic transitions in aortic diseases with transition to ECM producing-contractile SMCs in ATAA but to pro-inflammatory SMCs in ATAD. These separate transitions are controlled at the epigenetic level by different sets of transcriptional factors.

Poster Number 40

Clinical Fellow

Aortopathy and Valvular Heart Disease

ROLE OF GSDMD-MEDIATED PYROPTOSIS IN AORTIC ANEURYSM AND DISSECTION FORMATION

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Background: Loss of vascular smooth muscle cells (SMCs) contributes to aortic aneurysm and dissection (AAD) formation, though the underlying mechanisms remain poorly understood. Pyroptosis is a form of lytic cell death triggered by cleavage of gasdermin D (GSDMD); its N'-terminal creates a cell membrane pore that causes lysis. We hypothesized that pyroptosis contributes to AAD formation and explored whether it can create pores in nuclear and mitochondrial membranes.

Materials/Methods: The effect of SMC-specific Gsdmd knockout (KO) in mice on AAD formation was determined by comparing SMC-Gsdmd KO (n=30) and littermate controls (n=10) challenged with angiotensin II for 7 days. We examined the effect of intraperitoneal injection of necrosulfonamide (NSA), a GSDMD inhibitor, in the same murine model (vehicle, n=20; NSA, n=15). In the groups, we compared incidence of AAD and a subcategory, severe AAD (comprised of dissection, rupture, or intramural hematoma). Mechanisms of GSDMD activation were investigated in cultured human aortic SMCs.

Results: Compared to challenged control mice, challenged KO mice had a significantly decreased incidence of aortic dissection (p=.007) and rupture (p=.008). Challenged mice treated with NSA had a significantly reduced incidence of AAD (p=.002) and severe AAD (p=.005), compared with challenged control mice receiving a vehicle. In cultured SMCs, full length/inactive GSDMD was found in the cytoplasm and nuclear membrane of unchallenged cells, however the N'-terminal was found at the cell, mitochondrial, and nuclear membranes after challenge.

Conclusions: Our findings suggest GSDMD-mediated pyroptosis is involved in AAD formation. In our mouse model, SMC-Gsdmd KO reduced the incidence of dissection and rupture; administration of NSA reduced AAD incidence. We showed that N'-GSDMD accumulates at the nuclear and mitochondrial membranes in stressed SMCs. This suggests that GSDMD is a potential therapeutic target for patients with aneurysms below threshold for or not amenable to surgical repair.

Poster Number 41

Postdoctoral Researcher

Cardiac Arrhythmia and Electrophysiology

SPEG MEDIATES INCREASED ATRIAL FIBRILLATION INCIDENCE IN CHRONIC KIDNEY DISEASE

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Background: Chronic kidney disease (CKD) is a major public health problem. CKD is a risk factor of cardiovascular morbidity and mortality due to the increased incidence of atrial fibrillation (AF). AF onset is known to be the consequence of cardiomyocyte intracellular calcium (Ca^{2+} mishandling where increased ryanodine receptor type 2 (RyR2) activity causes triggered activity. RyR2 activity is regulated by phosphorylation of serine 2367 (S2367) by the 'striated muscle preferentially expressed protein' (SPEG). Reduced RyR2 phosphorylation at S2367 increases the risk of AF. We hypothesized that changes in atrial SPEG underly the increased risk of AF in CKD patients.

Materials/Methods: The experimental 5/6 nephrectomy model was used to mimic CKD disease in mice. AF inducibility was determined using intracardiac programmed electric stimulation. Echocardiography was used to analyze cardiac structure. RYR2 phosphorylation and SPEG levels were measured by western blotting.

Results: CKD mice showed increased serum phosphate (14.1±1.4 vs 9.3±0.4mg/dL; $p<0.01$) and urea (30.5±1.1 vs 20.9±0.4 mg/dL; $p<0.001$) vs sham controls. AF incidence was 4-fold higher in CKD vs sham mice (60 vs 14.2%; $p<0.05$). CKD mice showed longer P waves (14.3±0.4 vs 12.5±0.3; $p<0.01$) and greater increase of left atrial size than sham mice (35.0±7.5 vs 13.9±4.6; $p<0.05$). Ejection fraction was slightly reduced in CKD mice after 6 weeks of CKD progression (57.9±0.6 vs 61.7±0.8%; $p<0.001$) while no changes were observed in sham mice. SPEG levels were decreased in atria from CKD mice compared to sham (0.57±0.1 vs 1.00±0.1; $p<0.01$). Finally, RyR2 phosphorylation at S2367 was reduced in CKD mice atria (0.60±0.1 vs 1.00±0.1 in sham; $p=0.098$).

Conclusions: This study shows for the first time that SPEG levels are decreased in atria from CKD mice, associated with increased RyR2 activity leading to increased AF incidence. Thus, we propose increasing SPEG activity as a possible therapeutic target to reduce the increased incidence of AF in CKD patients.

Poster Number 42

Postdoctoral Researcher

Cardiac Arrhythmia and Electrophysiology

NLRP3 / IL-1B PATHWAY PROMOTES ATRIAL ARRHYTHMIAS IN CHRONIC KIDNEY DISEASE

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Background: Chronic kidney disease (CKD) is associated with higher risk of atrial fibrillation (AF). The mechanistic link between CKD and AF remains elusive. Interleukin (IL)-1, a main effector of 'NLR-family pyrin domain-containing 3' (NLRP3) inflammasome activation, is a key modulator of conditions associated with inflammation.

Materials/Methods: An established 'two-stage nephrectomy' protocol was used to create CKD in 8 weeks old wildtype (WT) and Nlrp3-/- mice. For the IL-1β neutralization studies, 3 weeks after the 2nd nephrectomy, WT-CKD mice were injected weekly with anti-IL-1β antibody or IgG as control for 3 weeks.

Results: Circulating IL-1β levels were elevated in CKD-patients with AF (vs CKD-patients in sinus rhythm, $P<0.05$). NLRP3-activity was enhanced in atria of CKD-patients. To elucidate the NLRP3/IL-1β pathway in the pathogenesis of CKD-induced AF, we used a CKD mice model. EP study revealed that WT-sham (14.3% n=7) and Nlrp3-/--sham (14.3%, n=7) mice had low incidence of induced-AF, whereas WT-CKD (85.7%, n=7) mice were more susceptible to AF. IL-1β levels in serum and atrial tissue was increased in WT-CKD mice compared with the WT-sham mice ($P<0.05$). Left atrial dimension was increased in WT-CKD mice (vs WT-sham mice, $P<0.001$), which was attenuated in Nlrp3-/--CKD mice ($P<0.001$). Percentage of fibrosis in atria tissue was increased in WT-CKD mice compared with the WT-sham ($P<0.01$). Neutralizing anti-IL-1β antibodies effectively reduced IL-1β levels (WT-CKD-IgG vs WT-CKD-anti-IL-1β , $P<0.01$), normalized left atrial dimensions(WT-CKD-IgG vs WT-CKD-anti-IL-1β , $P<0.05$), reduced fibrosis (WT-CKD-IgG vs WT-CKD-anti-IL-1β, $P<0.05$) and the incidence of inducible-AF(WT-CKD-IgG vs WT-CKD-anti-IL-1β, $P<0.05$).

Conclusions: These data demonstrate that CKD creates a substrate for AF development by activating the NLRP3 inflammasome in atria, associated with structural remodeling and development of a substrate for AF-maintenance. Neutralizing IL-1β antibodies might be beneficial to prevent AF caused by CKD.

Poster Number 43

Clinical Fellow

Cardiac Arrhythmia and Electrophysiology

INTERPRETING THE ECG IN PATIENTS WITH CHEST PAIN WHO HAVE RIGHT BUNDLE BRANCH BLOCK

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Background: Right bundle branch block (RBBB) has been associated with poorer prognoses in patients with known acute coronary syndrome. The most up-to-date guidelines recommend that patients with RBBB (whether known prior or presumed new) and suspected ischemia should be managed with urgent coronary angiography, with or without percutaneous coronary intervention as indicated. Further guidance when assessing patients with ischemic symptoms and RBBB is needed.

Materials/Methods: A 65-year-old female with atrial fibrillation and heart failure with preserved ejection fraction presented with baseline ECG interpreted as normal sinus rhythm, premature atrial complexes, right bundle branch block, bifasicular block, and nonspecific ST and T wave abnormality. However, ST-elevations in leads V1 and V2, ST-elevation of aVR and widespread ST depressions in the lateral leads were missed.

Results: Non-urgent coronary angiography found a severe calcific lesion of 80% in the proximal left anterior descending (LAD) and 80% occlusion of the mid and distal LAD, requiring drug-eluting stent placement in the proximal LAD. ECG two days after presentation showed sinus rhythm, RBBB and left anterior fascicular block with ST elevation in I, aVL, aVR and V1-V2 and ST depression in the inferior leads + V5-V6. Course was complicated by pulseless electrical activity cardiac arrest with return of spontaneous circulation after cardiopulmonary resuscitation and high-grade atrioventricular block heart block for which she had a dual chamber pacemaker with LBB pacing implanted.

Conclusions: It is crucial to understand the typical morphology of RBBB on ECG in order to look for deviations that may be suggestive of underlying ischemic disease. Any degree of ST-elevation in the anterior leads and/or ST-elevation of lead aVR with ST-depressions in the lateral leads in a patient with RBBB is suggestive of significant LAD disease, and should be considered a STEMI equivalent to be treated with urgent angiography.

Poster Number 44

Postdoctoral Researcher

Arrhythmias and Channelopathies

N-TERMINAL GASDERMIN D EXACERBATES AF SUSCEPTIBILITY

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Background: We recently demonstrate that activated NLRP3 inflammasome in cardiomyocytes (CMs) is sufficient to promote a pro-arrhythmic substrate for atrial fibrillation (AF) development. However, whether and which downstream effector of NLRP3 inflammasome activation mediates AF pathogenesis remains to be determined. The aim of this study is to elucidate the role of the cleaved N-terminal gasdermin D (GSDMDNT), a main NLRP3-inflammasome effector, in AF development.

Materials/Methods: Atrial CM-specific overexpression of GSDMDNT mouse model was developed by injecting the C57Bl/6 mice with the atrial-specific AAV9 virus (AAV9-ANF-GSDMDNT, aGSDMDNT) or AAV9-ANF-Flag virus as control (aCtl).

Results: 4 weeks after AAV9 injection, the protein level of GSDMDNT was 2.5 times higher in atria of aGSDMDNT than that of aCtl mice, but not in ventricles. Programmed intracardiac stimulation revealed that the AF susceptibility was significantly increased in aGSDMDNT mice compared with aCtl mice (72.7% vs 18.8%, $P<0.01$). Echocardiography showed that atrial size and ventricular EF% were similar between aGSDMDNT and aCtl mice. Optical mapping studies showed that atrial effective refractory period (AERP) was reduced, while the conduction velocity was unchanged in aGSDMDNT mice. Shortening of AERP was associated with the upregulation of the ultra-rapid inward-rectifier K^+ channel in aGSDMDNT mice. Surprisingly, the overexpression of GSDMDNT in aGSDMDNT mice did not cause excessive cell death – a known function of GSDMDNT in immune cells by forming the lytic membrane pores. We transfected H9C2 cells with either GSDMDNT or the mutated GSDMDNT-mut lacking the pore-forming ability and found that GSDMDNT-mut alleviated the activation of NLRP3 inflammasome in H9C2 cells upon LPS stimulation.

Conclusions: Our results suggest that GSDMDNT could directly enhance AF pathogenesis by an unrecognized pyroptosis-independent functions in CMs.

Poster Number 45

Postdoctoral Researcher

Cardiac Arrhythmia and Electrophysiology

PERICARDIAL CUTTING TOOL FOR PERICARDIAL ADHESIONS

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Background: Pericardial adhesions develop in patients' hearts after surgical cardiac intervention or infection. Epicardial ablation may be a laborious task for surgeons due to the presence of pericardial adhesions, making advancement of surgical tools into target areas within the heart difficult and dangerous, resulting in longer procedure times and, in the worst cases, invasive surgery. The objective is to design and test a device that will safely cut through pericardial adhesions without compromising the pericardium and epicardium for epicardial access procedures.

Materials/Methods: The cutting tool prototype blade design consists of a moving, pivoting blade and a stationary blade. The motion from the stepper motor, designed with adjustable parameters, such as rotations per minute (RPM) and angle range, rotates the moving blade around the pivot point. The final prototype was tested on a silicone heart with adhesion mimics made from sponge segments and on excised porcine fibrous tissue from a cardiac procedure. Motor parameters for testing were an angle range of 5 and RPMs starting from 50 increasing to 400 in increments of 50. The performance of the cutting tool on the test rig was compared to that of a sheath.

Results: The cutting tool cuts through tissue and artificial adhesions at any RPM greater than 50 with an angle range of 5. RPMs greater than 100 result in lower cutting times and less force to advance the device through adhesion. The cutting tool cuts through adhesions without damaging the pericardium or epicardium while the sheath is unable to cut through adhesion or mimic.

Conclusions: The pericardial cutting tool has proven efficacy and safety on both ex-vivo tissue and benchtop model. The next step is to perform pre-clinical testing to further validate the safety of the device.

Poster Number 46

Clinical Fellow

CAD, Atherosclerosis, Ischemia

EARLY DISCHARGE AFTER CORONARY ARTERY BYPASS GRAFTING: A NATIONWIDE READMISSIONS ANALYSIS

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Background: Analysis of early discharge after Coronary Artery Bypass Grafting (CABG) and readmissions has been limited on a national scale. We hypothesized that early discharge after CABG would not lead to increased readmissions compared to routine discharge.

Materials/Methods: The Nationwide Readmissions Database was queried to identify patients who underwent CABG between 01/2016 and 12/2018. Early discharge was defined as length of stay (LOS) <5 days; routine discharge as 5-10 days. Patients were excluded with hospital courses indicative of complicated stays: LOS >10 days, discharge to care facilities or with home health, and urgent cases. Propensity score matching was performed to compare outcomes (30- and 90-day readmissions, cost, readmission mortality). Kaplan-Meier analysis estimated freedom from readmission within a calendar year.

Results: During the study period 91,861 patients underwent CABG with uncomplicated postoperative course. Of these 31% (28,790/91,861) were discharged early and 69% (63,071/91,861) routine. In a propensity matched cohort of 56,610 patients, readmission rates were lower after early discharge at 30 days (5.2% [1,362/26,232] vs 6.5% [1,650/25,494]; p<.001), 90 days (8.8% [1,911/21,688] vs 10.6% [2,198/20,770]; p<.001) and within a calendar year (log-rank p<.001). Index-hospitalization cost was higher with routine discharge ($32,859 vs $26,676; p<.001). Mortality on readmission and readmission cost were similar after routine versus early discharge, however readmission length of stay was higher after routine discharge (3 days vs 2 days; p<.001). Infection, the most common cause of readmission, was higher after routine discharge (18% [648/3,651] vs 14% [469/3,235], p=.016).

Conclusions: In uncomplicated patients, early discharge does not lead to increased readmissions after CABG. Patients discharged early are less likely to be readmitted and have a lower incidence of infection as a cause of readmission. These results suggest that early discharge efforts are safe in this patient population.

Poster Number 47

Student

CAD, Atherosclerosis, Ischemia

RISK FACTORS ASSOCIATED WITH POST-OPERATIVE CARDIAC EVENTS FOLLOWING ARTHROPLASTY

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Background: Post-operative cardiac events are of significant concern in patients undergoing total hip and knee arthroplasty (THA and TKA, respectively), particularly with pre-operative risk factors present. This study investigates adverse cardiac events following total joint replacements and analyzes contributing risk factors.

Materials/Methods: We queried the TriNetX database for THA and TKA patients in the United States between January 1, 2017 and January 1, 2022. We stratified these patients by those with prior cardiac risk factors. We subsequently compared the risk of developing an adverse cardiac event within three months of joint replacement surgery between at-risk patients and non-risk patients. Adverse cardiac events were defined as either a clinically significant troponin elevation, acute myocardial infarction (MI), or heart failure. Results were analyzed using chi-square analysis with $p<0.01$ considered significant.

Results: Initial queries resulted in 80,544 THA patients and 112,531 TKA patients for investigation. A total of 19,733 patients of the THA cohort had a history of at least one of the studied risk factors. A total of 34,052 patients of the TKA cohort had a history of at least one of the studied risk factors. Patients with at least one cardiac risk factor were significantly more likely to experience troponin elevation, acute MI, and heart failure within three months of their total hip replacement. Similarly, patients with at least one cardiac risk factor were significantly more likely to experience troponin elevation, acute MI, and heart failure within three months of their total knee replacement. All differences were found to be statistically significant.

Conclusions: Risk stratification for complications following orthopedic procedures is important to minimize adverse outcomes. This investigation identifies key risk factors that significantly increase risk of adverse cardiac events three months following THA or TKA, highlighting the need to consider risk factors prior to joint replacement surgery.

Poster Number 48

Clinical Fellow

CAD, Atherosclerosis, Ischemia

INCRETINS AND CARDIAC AUTONOMIC FUNCTION IN YOUTH WITH OBESITY ACROSS THE GLYCEMIA SPECTRUM

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Background: Incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have been related to vascular function with variable effects depending on obesity status in adults. The relationship of incretins to vascular function in youth is unclear. We hypothesized that endothelial and cardiac autonomic dysfunction (CAD) are related to lower GLP-1 and GIP in response to glucose ingestion in youth with dysglycemia compared with those overweight (OW) or normal weight (NW) and normal glucose tolerance (NGT).

Materials/Methods: Adolescents [50 male/52 female; 15.6±1.8 yrs; 24 NW-NGT, 22 OW-NGT, 27 prediabetes and 29 with type 2 diabetes (T2D)] underwent assessment of body composition (DXA scan), 2-hour oral glucose tolerance test (OGTT) with calculation of whole body insulin sensitivity index (WBISI), area under the curve (AUC) of glucose (BG), GLP-1 and GIP. Reactive hyperemia index (RHI), and heart rate variability (HRV), were measured by peripheral arterial tonometry. For HRV, a higher LF/HF (low frequency to high frequency ratio) is indicative of CAD with loss of parasympathetic tone and decreased HRV.

Results: The ratios of AUC-GLP-1 and AUC-GIP to AUC-BG were lower in the groups with dysglycemia compared NGT groups ($p=0.016$ and 0.001, respectively). GLP-1 and GIP were not related to RHI. Fasting and AUC-GLP-1, but not GIP, negatively related to LF/HF ($r=-0.37$, $p=0.002$ and $r=-0.43$, $p<0.001$ respectively). In a linear regression model with LnLF/HF as the dependent variable, AUC-BG ($b=0.31$, $p=0.04$) and AUC-GLP-1 ($b=-0.44$,$p=0.002$) contributed to the variance in LnLF/HF independent of %body fat, hs-CRP, WBISI, age, sex, race-ethnicity and Tanner stage ($R2= 0.27$, $p=0.04$).

Conclusions: Youth with obesity and dysglycemia have impaired incretin response. Glycemia is negatively, whereas GLP-1 is positively associated with HRV after accounting for adiposity, WBIS and inflammation. GLP-1 may be an important determinant of CA function in youth with obesity across the glycemia spectrum.

Poster Number 49

Student

CAD, Atherosclerosis, Ischemia

PARADOXICAL EMBOLISM INDUCED MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERIES - A RARE PHENOMENON

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Background: Patent foramen ovale (PFO) is a rare cause of myocardial infarction with non-obstructive coronary arteries (MINOCA), representing only 0.51% of its underlying etiologies. We present a rare case of MINOCA with concurrent ischemic stroke due to PFO.

Materials/Methods: A 45-year-old male with no medical history presented to our institution with chest pain, dizziness, and transient vision loss. Despite elevated troponins on admission, coronary angiography showed non-obstructive coronary artery disease (CAD). Given concomitant neuro-ocular symptoms, MRI of brain was pursued, findings of which were consistent with acute embolic infarct involving the posterior circulation territory. The simultaneous occurrence of MINOCA and stroke raised concerns for paradoxical embolism. Initial transthoracic echocardiogram showed evidence of right-to-left shunt; subsequent transesophageal echocardiogram confirmed the presence of a PFO, thus establishing paradoxical embolism as the likely cause of our patient's presentation. He was initiated dual antiplatelet therapy, and, ultimately, underwent PFO closure.

Results: The presence of right to left shunting in the setting of acute myocardial infarction with non-occlusive CAD supported the diagnosis of paradoxical embolism induced MINOCA (PE-MINOCA). Patient was started on Aspirin and Clopidogrel. subsequently underwent PFO closure to prevent recurrence of paradoxical embolism. To date he remains free of further thromboembolic events.

Conclusions: The concurrent occurrence of MINOCA and systemic thromboembolic event should raise the clinical suspicion of intra-cardiac shunting. Early repair of the defect could potentially prevent future embolic events. Although guidelines for secondary prevention of MINOCA is lacking, PE-MINOCA is a unique etiology where secondary prevention can be accomplished.

Poster Number 50

Postdoctoral Researcher

CAD, Atherosclerosis, Ischemia

A NOVEL APPROACH FOR TREATING RADIAL ARTERY THROMBOSIS USING ACOUSTIC PULSE WAVE THROMBOLYSIS

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Background: Radial artery complications following access for cardiac or peripheral interventions are uncommon. When symptomatic, intervention is warranted. Here, we describe a novel approach to this problem by utilizing acoustic-mediated catheter-directed thrombolysis using the EKOSonicEndovascular System (EKOS) which is a minimally invasive, less traumatic adjunct to angioplasty with good long term outcomes. This is one of the first reports of using EKOS for this purpose.

Materials/Methods: A 51-year-old female underwent cardiac catheterization for chest pain and a positive stress test. She was referred to the cardiovascular surgeon after two weeks with non-resolving pain in the fingers and proximal weakness in the affected hand, swelling in her forearm and inability to tightly grasp objects with that hand. Urgent non-invasive testing with an arterial Doppler of her left upper extremity demonstrated occlusion of the entire left radial artery. A CT angiogram of the left upper extremity confirmed flush occlusion of the left radial artery with a patent ulnar artery with incomplete cross-filling into the radial artery through the palmar arch. We inserted an EKOS catheter sheath through which the ultrasonic component was inserted. After an initial 2 mg TPA injected as a bolus, TPA was run at 1mg/hr for 18 hours before bringing her back the next day.

Results: An angiogram done after removing the EKOS catheter system showed resolution of flow in the artery. A 3-month follow up Ultrasound shows a patient radial artery.

Conclusions: The case described above shows the effectiveness of acoustic pulses in restoring radial artery circulation when mechanical thrombectomy and percutaneous angioplasty have failed, especially in subacute occlusions or when presentation is delayed. Guidelines and standard of care for managing radial artery occlusion are scarce and this approach using the EKOSonic system describes a new, safe and effective method to approach.

Poster Number 51

Junior Faculty

Coronary Artery Disease and Atherosclerosis

OBSTRUCTIVE SLEEP APNEA-INDUCED HYPERTENSION IS ASSOCIATED WITH INCREASED GUT AND NEUROINFLAMMATION

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Background: Obstructive sleep apnea (OSA) is an independent risk factor for the development of hypertension (HT). We have previously demonstrated that OSA induces gut dysbiosis. Recent studies have demonstrated that gut dysbiosis can induce a pro-inflammatory response of the host resulting in peripheral- and neuro-inflammation, key factors in the development of HT. We hypothesized that OSA induces inflammation in the gut that contributes to neuroinflammation and HT.

Materials/Methods: OSA was induced in 8-week-old male rats (60 apneas/hour). After two weeks of apneas, lymphocytes were isolated from aorta, brain, cecum, ileum, mesenteric lymph node (MLN), and spleen for flow cytometry. To examine the role of IL-17, a monoclonal antibody was administered to neutralize IL-17. Lymphocytes originating from the gut were tracked by labeling with carboxyfluorescein succinimidyl ester dye. IL-10 was administered by gavaging the rats with L.reuteri producing bacteria engineered to produce IL-10 every day during the two weeks of apneas.

Results: OSA led to a significant decrease in T regulatory (Treg) cells along with an increase in TH17 in the ileum, cecum, and brain. Neutralization of IL-17 significantly reduced BP, decreased IL-10 levels in plasma, increased Tregs, and decreased TH1 cells in ileum, cecum, and brain of OSA rats. TH1, TH2, and TH17 cells from the Peyer's patches were found to migrate to MLN, spleen, and brain with increased frequency in OSA, as compared to sham, rats. In preliminary studies, administration of IL-10 significantly reduced BP, and decreased inflammation in gut and brain.

Conclusions: OSA induces a pro-inflammatory response in the gut and brain that involves IL-17. Our findings suggest that gut dysbiosis may serve as the trigger for gut and neuroinflammation, and treatment strategies to prevent or reverse gut dysbiosis may prove useful in reducing neuroinflammation and HT.

Poster Number 52

Postdoctoral Researcher

Coronary Artery Disease and Atherosclerosis

A PATHOGENIC VARIANT IN SMOOTH MUSCLE (SMC) ALPHA-ACTIN AUGMENTS ATHEROSCLEROSIS BY HEAT SHOCK FACTOR 1 ACTIVATION AND CHOLESTEROL-DRIVEN PHENOTYPIC MODULATION OF SMCS

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Background: The variant p.Arg149Cys in ACTA2, which encodes smooth muscle cell-specific alpha-actin, predisposes to thoracic aortic disease and early onset coronary artery disease in individuals without cardiovascular risk factors. This study investigated how this variant drives increased atherosclerosis.

Materials/Methods: Apoe-/- mice with and without the p.Arg149Cys variant were fed a high fat diet for 12 weeks, followed by evaluation of atherosclerotic plaque formation and single cell transcriptomics analysis. Smooth muscle cells explanted from Acta2R149C/+ and wildtype mouse ascending aortas were used to investigate atherosclerosis-associated SMC phenotypic modulation.

Results: Hyperlipidemic Acta2R149C/+Apoe-/- mice have a 2.5-fold increase in atherosclerotic plaque burden compared to Apoe-/- mice with no differences in serum lipid levels. At the cellular level, misfolding of the R149C alpha-actin activates heat shock factor 1, which increases endogenous cholesterol biosynthesis and intracellular cholesterol levels through increased HMG-CoA reductase expression and activity. The increased cellular cholesterol in Acta2R149C/+ smooth muscle cells induces endoplasmic reticulum stress and activates PERK-ATF4-KLF4 signaling to drive atherosclerosis-associated phenotypic modulation in the absence of exogenous cholesterol, while WT cells require higher levels of exogenous cholesterol to drive phenotypic modulation. Treatment with the HMG-CoA reductase inhibitor pravastatin successfully reverses the increased atherosclerotic plaque burden in Acta2R149C/+Apoe-/- mice.

Conclusions: These data establish a novel mechanism by which a pathogenic missense variant in a smooth muscle-specific contractile protein predisposes to atherosclerosis in individuals without hypercholesterolemia or other risk factors. The results emphasize the role of increased intracellular cholesterol levels in driving smooth muscle cell phenotypic modulation and atherosclerotic plaque burden.

Poster Number 53

Student

Coronary Artery Disease and Atherosclerosis

A COMPUTATIONAL STUDY OF THE EFFECT OF 3D PLAQUE SHAPE ON LOCAL HEMODYNAMICS AND PLAQUE INSTABILITY

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Background: Roughly 70% of heart attacks occur when unstable atherosclerotic plaques, so called vulnerable plaques, rupture and release their lipid content into the blood stream forming a thrombus in the coronary arteries, inducing myocardial infarction. Hemodynamic features near vulnerable plaques are known to affect plaque instability. Plaque ulcerations are known to occur in areas of high wall shear stress (WSS), while highly positive wall shear stress gradients (WSSG) are known to affect the endothelial cell alignment on the plaque cap, weakening its fracture toughness and increasing rupture risk. We have developed a computational workflow to enable a comprehensive parametric study detailing the effect of 3D plaque shape on local hemodynamics in a patient-specific coronary artery tree and its implications for plaque instability.

Materials/Methods: Parameterized geometric 3D plaque models were created within a coronary artery tree reconstructed from imaging data using an in-house vascular modeling pipeline that leverages a robust algorithm development plugin called Grasshopper within the CAD software package Rhinoceros. By adjusting the axial and proximal/distal symmetry parameters while keeping the plaque length and degree of stenosis fixed, 9 representative plaque models were generated. The unsteady Navier-Stokes equations were solved within an isogeometric analysis framework.

Results: Results show that while the maximum velocity is unaffected by plaque shape for the same degree of stenosis, WSS and WSSG are varied by as much as 22.8% and 57.7%, respectively, among the cases considered. The proximally skewed plaque model with an axial offset has the most vulnerable combination of high WSS and high positive WSSG, and a majority of plaque rupture is predicted to occur in the upstream location, as seen in clinical observations.

Conclusions: The tool developed could potentially identify surrogate markers for plaque instability, ultimately leading to non-invasive diagnosis of vulnerable plaques at risk of rupture.

Poster Number 54

Postdoctoral Researcher

Coronary Artery Disease and Atherosclerosis

BIOMARKERS OF CARDIOVASCULAR INFLAMMATION IN ELECTRONIC CIGARETTE SMOKERS: SYSTEMATIC REVIEW

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Background: Electronic cigarette use has become increasingly popular as a perceived safer alternative to traditional tobacco products. However, concerns exist about the health effects of e-cigarettes, particularly regarding their impact on inflammatory biomarkers and cardiovascular health. This study aims to systematically review the available literature to investigate the evidence of the association between exposure to e-cigarettes and inflammatory biomarkers.

Materials/Methods: The study used a comprehensive search of four electronic databases, including MEDLINE OVID, Embase, Web of Science, and the Cochrane Library. Manuscripts were included if they had a randomized controlled trial or observational design, adult human subjects, at least one studied group included e-cigarette use, and measured the biomarkers of interest. A total of 13 manuscripts (N=9,560) were included in the final data extraction.

Results: We found that e-cigarette use was associated with elevations in heart rate and blood pressure. However, changes in inflammatory biomarkers among e-cigarette users, including IL-6 and IL-8, were inconsistent across studies. 10 of the 13 studies found e-cigarette users had higher inflammatory markers compared to non-smokers. Additionally, e-cigarette smokers showed a significant increase in other inflammatory biomarkers, such as Interferon-gamma, 2,3-d-Thromboxane 2, uric acid, matrix metalloproteinase-9, intercellular cell adhesion molecule-1, desmosine, endothelial growth factor, and vascular endothelial growth factor. Most studies reported an improvement in the inflammatory profile among traditional tobacco product smokers who switched to the exclusive use of e-cigarettes. Overall, high-sensitivity C-reactive protein levels were higher among e-cigarette smokers compared to non-smokers. Furthermore, it was determined that concentrations of Nitric oxide were lower after exposure among those who had never smoked or used e-cigarettes.

Conclusions: There is a clear inflammatory effect associated with e-cigarette use.

Poster Number 55

Junior Faculty

Heart Failure and Cardiomyopathy

DEVELOPMENT OF THE FULLY IMPLANTABLE PEDIATRIC VENTRICULAR ASSIST DEVICE

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Background: The drastic shortage of donor hearts has necessitated mechanical circulatory support to help the failing heart pump blood until a new heart becomes available. However, the Berlin Heart EXCOR is too large to be implanted, leading to severe infection. Therefore, there is a need to develop a safer, fully implantable pediatric ventricular assist device (VAD) to improve pediatric survival.

Materials/Methods: The VAD consists of a maglev motor, the core of the drive unit, and a pump using the motor. We first design and optimize the shape of the motor using 3D CAD and the FEM magnetic field analysis. The target size of the impeller's outer diameter is 40 mm, a total height of about 40 mm, and a target rotation speed of 8,000 rpm.

Results: According to the analytical results, we manufactured the maglev motor, which drives the VAD. Then, we designed and implemented the controller for performance evaluation. The prototype achieved stable magnetic levitation/rotation control up to about 15,000 rpm in the air. In the proposed structure, the maglev motor actively controls the rotation axis direction; however, the radial direction stability relies on passive restoring force. The radial vibration amplitude increases near the resonance frequency when the rotor is accelerated; however, the viscosity of the blood improves radial stability.

Conclusions: To develop the VAD, we worked on developing a maglev motor. The motor was designed based on magnetic field analysis. A prototype was fabricated and achieved stable magnetic levitation control in the air. In the future, we will work on further improving stability and reducing power consumption. Furthermore, we will design and fabricate a pump impeller and pump casing, measure the pump characteristics, and clarify that the proposed maglev pump has the performance to be applied to the VAD.

Poster Number 56

Junior Faculty

Heart Failure and Cardiomyopathy

CRAT LINKS CHOLESTEROL METABOLISM TO INNATE IMMUNE RESPONSES IN THE HEART

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Background: Chronic inflammation is associated with increased risk and poor prognosis of heart failure (HF)1,2. However, clinical trials to target inflammation in HF patients have mostly proven unsuccessful3,4, reflecting the lack of understanding of the precise mechanisms that provoke the sustained inflammation in the failing heart.

Materials/Methods: Here we report that deficiency in carnitine acetyltransferase (CRAT), a key player of metabolic flexibility, induces mitochondrial DNA (mtDNA) stress and triggers cell-intrinsic type I interferon response.

Results: Mechanistically, depletion of CRAT promotes cholesterol catabolism through bile acid synthesis pathway, leading to intracellular accumulation of 7 alpha-hydroxyl-3-oxo-4-cholestenoic acid (7-HOCA). 7-HOCA is sufficient to promote mtDNA release into cytosol and induce the expression of interferon-stimulated genes. In contrast, inhibition of bile acid synthesis pathway completely blocks type I interferon response. Furthermore, type I interferon response elicited by CRAT deficiency leads to a substantial increase in AIM2 expression and activation of DNA-sensing AIM2 inflammasome, which in turn promotes caspase-1 activation, proteolytic maturation of IL-1beta and cardiomyocyte pyroptosis.

Conclusions: Genetic deletion of cardiomyocyte CRAT in mice results in myocardial inflammation and dilated cardiomyopathy, which can be reversed by combined deletion of caspase-1. Collectively, we have identified a mechanism by which cardiac energy metabolism, cholesterol homeostasis and cardiomyocyte intrinsic innate immune responses are interconnected via CRAT-mediated bile acid synthesis pathway, which contributes to chronic myocardial inflammation and HF progression.

Poster Number 57

Postdoctoral Researcher

Heart Failure and Cardiomyopathy

NOVEL PAN-ERR AGONISTS AMELIORATE HEART FAILURE THROUGH ENHANCING CARDIAC FATTY ACID METABOLISM AND MITOCHONDRIAL FUNCTION

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Background: Cardiac metabolic dysfunction is a hallmark of heart failure. Estrogen related receptors ERRα and ERRγ are essential regulators of cardiac metabolism. Therefore, activation of ERR could be a potential therapeutic intervention for heart failure. Though several ERR agonists have been previously developed, no study has demonstrated their potential utility for heart failure treatment in vivo. In addition, pan-ERR agonist that targets all three ERR isoforms (ERRα/β/γ) has not been reported.

Materials/Methods: Two structurally distinct pan-ERR agonists, SLU-PP-332 (332) and SLU-PP-915 (915) were chemically synthesized. Transaortic constriction (TAC) was performed to induce heart failure in adult male mice. Cardiac function was assessed by echocardiography. In vitro study was performed in neonatal rat ventricular myocytes (NRVMs).

Results: Both 332 and 915 treatment significant improved cardiac function but failed to prevent cardiac hypertrophy in mouse after 6-week TAC. Mechanistically, RNA-seq and metabolomics analysis revealed ERR agonism predominantly activates OXPHOS and fatty acid/lipid metabolism-related pathways both in vitro and in vivo. In vitro oxygen consumption rate measurement showed ERR agonism elevated the maximal respiratory capacity using either pyruvate or palmitate as substrate, indicating an upregulation of oxidative metabolism. Autophagy was also induced by ERR agonists in NRVMs. Importantly, both in vitro knockdown and in vivo knockout experiments suggest that ERRγ is the main mediator of ERR agonism-induced transcriptional regulation that leads to cardioprotection against heart failure. ERR agonism also led to downregulation of cell cycle and developmental pathways in NRVMs, which was partially mediated by E2F1.

Conclusions: ERR agonists maintain oxidative metabolism, which confers cardiac protection against pressure overload-induced heart failure in vivo. Our results provided direct pharmacological evidence supporting further development of ERR agonists as novel heart failure therapeutics.

Poster Number 58

Junior Faculty

Heart Failure and Cardiomyopathy

URINE EXOSOME AS A LIQUID BIOPSY FOR KIDNEY HEALTH ASSESSMENT IN HEART FAILURE PATIENTS UNDERGOING CONTINUOUS-FLOW LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

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Background: Precise, mechanistic characterization of kidney health states in LVAD recipients is important to ameliorating adverse outcomes. Current assessments provide limited information about kidney parenchymal health before or after LVAD implantation. Urine exosomes released by kidney and urinary tract cells, have shown promise in assessing kidney pathology in other disease states. We performed an exploratory study assessing kidney health in LVAD recipients using urine exosome isolation and protein biomarkers of kidney health and function.

Materials/Methods: Urine was collected and exosome was isolated from 16 patients received LVAD (HeartMate III) from 1/2022-9/2022, immediately pre-implantation and on post operative day 7. Protein markers (AQP1, NGAL, NHE3, ATF3, and fetuin A) previously found to be associated with kidney health, were studied on urine exosomes. Relationships of exosome protein levels and important baseline clinical characteristics (presence of kidney dysfunction, defined as eGFR<60 ml/min/1.73m2, and hemodynamic instability, defined as INTERMACS profile 1 or 2) were assessed. Biomarker levels were normalized, and median levels were used for group comparisons.

Results: For the 16 LVAD recipients (median age 61 yrs., 81% male), 8 had baseline eGFR below 60, and 8 were INTERMACS profile 1 or 2. Persons with baseline low kidney function had higher levels of NHE3, Fetuin A, and NGAL (fig.1A). Persons with hemodynamic instability had higher levels of AQP1, Fetuin A, and ATF3 (fig.1B). In assessing biomarker changes with changes in serum creatinine level (from pre-op to POD 7), NGAL had the highest correlation.

Conclusions: This pilot study is the first to study urine exosomes in LVAD recipients. The results showed biomarker level changes that are generally in accordance with prior studies assessing urine exosomes in other acute and chronic kidney disease situations. Thus, we have demonstrated the feasibility of studying urine exosomes as a non-invasive way to investigate kidney health in LVAD recipients.

Poster Number 59

Student

Heart Failure and Cardiomyopathy

YAP MEDIATES CARDIAC PROLIFERATION IN TEAD-INDEPENDENT MECHANISMS

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Background: Myocardial infarction (MI) is a leading cause of death worldwide. During an MI, the contractile myocardium experiences reduced blood flow causing expansive cell death. Since adult mammalian hearts lack regenerative capacity, MI damage is permanent followed by heart failure. However, recent studies have demonstrated that the neonatal mouse heart exhibits transient regenerative potential within the first 7 days, suggesting a regulatory mechanism that prevents the adult from initiating a regenerative response to cardiac injury. The Hippo signaling pathway negatively regulates mammalian cardiac regeneration by inhibiting the activity of downstream effector YAP. However, YAP5SA, which completely bypasses Hippo pathway regulation, results in YAP hyper-transcriptional activity and heart overgrowth.

Materials/Methods: In this work, we aim to investigate the TEAD-independent mechanisms of YAP in promoting cardiomyocyte (CM) division and renewal. We generated another YAP protein named YAP6SA, which can not only skip Hippo pathway inhibition, but also lose the interaction with TEADs. We apply AAV9-based over-expression system to study the YAP regulatory role on cardiomyocyte proliferation.

Results: We found that this modified YAP is well tolerated in vivo, and it still promotes cardiomyocyte cell cycle progression and improves cardiac repair post ischemia injury. Compared to the YAP5SA, YAP6SA has decreased transcriptional activities with the upregulated genes only involved in cytoskeleton remodeling. We also identify the YAP6SA interactors and found that they regulate multiple cellular activities. Therefore, we assume that YAP6SA has cytoplasmic functions in a post-transcriptional manner.

Conclusions: The active YAP has TEAD-independent mechanisms on enhancing cardiomyocyte proliferation and can promote cardiac regenerative responses post ischemia injury. Our work will uncover novel functions of YAP and improve YAP therapeutics in myocardial infarction, finally benefiting human heart health.

Poster Number 60

Student

ENERGY METABOLISM DYNAMICS IN SMOOTH MUSCLE CELLS OF SPORADIC AORTIC ANEURYSMS AND ACUTE DISSECTIONS

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Background: Ascending thoracic aortic aneurysms (ATAA) and their progression to acute dissection (ATAD) are associated with high risk of mortality. Metabolic pathways can regulate disease progression, so we investigated transcriptomic profiles of energy metabolism in smooth muscle cells (SMCs) of human aortic tissue. We hypothesized that metabolic activity in SMCs is different in ATAA and ATAD tissues compared to non-diseased controls.

Materials/Methods: We performed single-cell RNA sequencing analysis of ascending aortic tissue from 9 patients with ATAA without dissection, 9 patients with ATAD (dissected and pre-dissected areas collected separately), and 8 non-diseased organ donor control subjects. Within the SMC cluster, we compared expression of metabolic genes via differentially expressed gene analysis as well as metabolic flux and metabolite accumulation using single-cell flux estimation analysis (scFEA) between control, ATAA, and ATAD groups.

Results: Tricarboxylic acid (TCA) cycle-related genes (e.g., SDHB, MDH2) and mitochondria-encoded oxidative phosphorylation genes were upregulated in ATAA SMCs and downregulated in ATAD SMCs compared to controls. Both fatty acid beta-oxidation-related gene expression (e.g., ACADL, HADH) and fatty acid oxidation flux were lower in dissected ATAD compared to control (both $p<0.001$). Glycolytic genes (e.g., ENO1, HK1) and glycolytic activity were upregulated in ATAA SMCs vs controls ($p<0.001$) and in ATAD SMCs vs controls ($p<0.001$). Finally, we observed progressively increased expression of anaerobic respiration-related gene LDHA from control to ATAA ($p<0.001$) and ATAA to ATAD ($p<0.001$) that was associated with greater lactate accumulation.

Conclusions: Increased TCA cycle and oxidative phosphorylation activity in ATAA and decreased activity in ATAD suggest a compensatory response in SMCs of ATAA that is not sustained in ATAD. As fatty acid oxidation activity is also decreased in ATAD, energy demands were met by increased glycolysis and reliance on anaerobic metabolism in ATAD.

Poster Number 61

Postdoctoral Researcher

Aortopathy and Valvular Disease

CRITICAL ROLE OF ENDOTHELIAL INJURY IN THE INITIATION OF AORTIC DISSECTION

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Background: Endothelium forms a protective barrier and maintains vascular hemostasis. However, the role of endothelial injury in aortic aneurysms and dissections (AAD) remains poorly understood. The receptor-interacting protein kinase 3 (RIP3)-mediated necroptosis and gasdermin D (GSDMD)-meditated pyroptosis trigger necrotic cell death. In this study, we tested the hypothesis that endothelial cell (EC) death induced by necroptosis and pyroptosis contributes to AAD formation.

Materials/Methods: Endothelial integrity and gene expression were examined in ascending aortic tissues from ascending thoracic aortic aneurysm (ATAA) patients (n=8) and organ donor controls (n=4) by single-cell transcriptome analysis. The effects of EC death on AAD formation were determined in EC-specific Rip3 knockout mice (EC-Rip3-/-) and EC-specific Gsdmd knockout mice (EC-Gsdmd-/-) in sporadic AAD models induced angiotensin II (Ang II) infusion. Endothelial hyperpermeability was detected by Evans blue staining and nanoparticle-mediated contrast-enhanced CT (n-CECT), which is hypersensitive to early-stage endothelial injury.

Results: Single-cell transcriptome and immunostaining analyses revealed significant upregulation of pro-death genes (e.g., RIP3 and GSDMD), but downregulation of cell junction genes (e.g., TJP1 and GJA1) in ECs of ATAA patients compared with controls. In the sporadic AAD model, endothelial injury and hyperpermeability were detected 2-5 days after Ang II infusion and were associated with intramural nanoparticle accumulation, elastic fiber fragmentation, microdissection, and macrophage infiltration. Importantly, EC-Rip3-/- mice and EC-Gsdmd-/- mice showed preserved EC barrier function, reduced nanoparticle accumulation and microdissection, and a trend reduction in AAD incidence. Blocking necroptosis/pyroptosis by necrosulfonamide treatment reduced the incidence and severity of AAD.

Conclusions: Endothelial injury and subsequent barrier dysfunction cause blood component infiltration, leading to microdissection and AAD formation.

Poster Number 62

Student

Aortopathy and Valvular Heart Disease

OUTCOMES OF THORACOABDOMINAL AORTIC ANEURYSM REPAIR IN PATIENTS WITH A PRIOR MYOCARDIAL INFARCTION

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Background: Patients with prior myocardial infarction (MI) often undergo thoracoabdominal aortic aneurysm (TAAA) repair; however, there is a paucity of data regarding outcomes in such patients. Thus, we aimed to compare outcomes after TAAA repair in patients with and without a prior MI.

Materials/Methods: From 1986-2022, we performed 3737 TAAA repairs. Of these, 706 (18.9%) were in patients with prior MI. We used multivariable logistic regression to identify predictors of operative death in the overall group of patients and in those with a prior MI. Propensity score matching (PSM) analyzed preoperative and select operative variables to create matched groups of patients with or without a prior MI (n=706 pairs). Late survival was determined using Kaplan-Meier analysis and compared with a log rank test.

Results: Overall, operative mortality was 8.5%; this was elevated in patients with MI compared to those without (11.0% vs 7.9%; P=.01), although this difference was insignificant on multivariable analysis (P=.1). In patients with prior MI, multivariable analysis showed that aortic rupture (odds ratio (OR)=1.25, P<.001), aortic dissection (OR=1.06, P=.01), cerebrovascular disease (OR=1.07, P=.01), increasing aortic clamp time (per min) (OR=1.002, P=.003), chronic kidney disease (OR=1.07, P=.004), and incidental splenectomy (OR=1.10, P=.01) were predictors of operative death. In the PSM cohort, the MI group had a higher rate of operative death (11.0% vs 7.6%, P=.04) and ventricular arrhythmia (5.5% vs 2.3 %, P=.002), but there was not a significant difference in survival at 10 years (29.3%±3.7% non-MI vs 24.9%±3.5% MI; P=.1).

Conclusions: After TAAA repair, matched prior MI patients had higher rates of early death and postoperative ventricular arrhythmia. For patients with a prior MI, operative risk is increased by preoperative and operative factors, with rupture being most predictive.

Poster Number 63

Clinical Fellow

Congenital Developmental Heart Disease

SUBAORTIC MEMBRANE IN AN ADULT: DIAGNOSTIC AND THERAPEUTIC APPROACH TO THE ASYMPTOMATIC PATIENT

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Background: Congenital Subvalvular aortic stenosis (SAS) is most commonly caused by a ridge of tissue called a subaortic membrane (SAM). Most SAMs are detected in childhood, but, when the degree of left ventricular outflow tract (LVOT) obstruction and individual level of physical activity allow the patient to remain functional, SAM is diagnosed in adults who are asymptomatic or have nonspecific symptoms. We report a 47 year old female with limited activity and severe obesity undergoing work up of a pancreatic lesion who was found to have a systolic murmur. Echocardiographic imaging confirmed the presence of a SAM causing high-grade obstruction (peak gradient of 64mmHg).

Materials/Methods: A multidisciplinary team determined that addressing the LVOT obstruction prior to the pancreatic lesion would most decrease her risk of significant perioperative events. The LVOT was approached via hemisternotomy under hypothermic circulatory arrest. The valve leaflets were gently retracted and the SAM visualized. A Freer elevator was used to lift the thickened endocardial tissue. This and the underlying 2mm muscular component were both resected.

Results: Transesophageal echocardiography (TEE) confirmed successful resection with an LVOT mean gradient of 12mmHg decreased from 18mmHg.

Conclusions: Physical exam and 2-D echocardiography can be sufficient to diagnose a SAM. The level of anatomic detail and ability to visualize the dynamic motion of the LVOT is enhanced with 3-D imaging. In patients with severe obesity, imaging is key for operative planning aimed at mitigating risk. There are no medical therapies for SAS and surgical resection is indicated for symptomatic patients and those with peak gradient ≥50mmHg in order to prevent ventricular remodeling. Multidisciplinary teams should guide the timing in asymptomatic patients with high grade obstruction who require significant interventions and consider upfront resection to reduce the risk of sudden cardiac death.

Poster Number 64

Clinical Fellow

Aortopathy and Valvular Heart Disease

OUTCOMES AND PREDICTORS OF EARLY MORTALITY AFTER OPEN CRAWFORD EXTENT III THORACOABDOMINAL AORTIC ANEURYSM REPAIR: DO WOMEN DIFFER FROM MEN?

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Background: Crawford extent III thoracoabdominal aortic aneurysm (TAAA) repairs are considered less morbid than more extensive TAAA repairs. We aimed to identify predictors of major complications after open extent III TAAA repair and explore differences between men and women.

Materials/Methods: In this retrospective study, 732 patients (median age 69 years [Q1,3: 61,74]) who underwent extent III repair (1990-2021) were stratified by sex (306 women [41.8%], 426 men [58.2%]). Statistical models identified independent predictors of operative mortality and adverse events (comprising operative death or persistent stroke, paraplegia, paraparesis, and renal failure). Competing risk analyses were completed comparing relative rates of survival and freedom from repair failure or reintervention in men and women.

Results: Operative mortality was 8.7% (women 10.8% vs men 7.3%; P=.1), and adverse events occurred in 16.8% of patients (women 20.6% vs men 14.1%; P=.02). Predictors of operative mortality were female sex, larger maximal aortic diameter, chronic kidney disease, chronic symptoms, longer cross-clamp time, and more packed red blood cell (pRBCs) units transfused. Female sex, chronic kidney disease, longer cross-clamp time, branch-vessel stenting, and more pRBC units transfused independently predicted adverse events. Elective operation predicted better operative survival and fewer adverse events. Women and men did not differ significantly in late survival (P=.3) or freedom from repair failure (P=.9).

Conclusions: Open extent III repair remains a durable approach for TAAA repair but carries notable risk of operative mortality and adverse events. Female sex independently predicts operative mortality and adverse events; however, long-term survival is comparable between men and women. These insights into the extent III repair patient population could be used to revise treatment guidelines and, thus, to improve patient outcomes.

Poster Number 65

Postdoctoral Researcher

Congenital Developmental Heart Disease

EVOLUTION OF SURGICAL REPAIR OF INTRASEPTAL ANOMALOUS LEFT CORONARY ARTERY WITH MYOCARDIAL ISCHEMIA

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Background: Anomalous aortic origin of the left coronary artery with intraseptal course is a rare coronary anomaly associated with increased risk of myocardial ischemia. The role and techniques for surgical intervention are evolving, with numerous novel surgical techniques for this challenging anatomy reported in the last 5 years. We report our single center experience with surgical repair of intraseptal anomalous left coronary artery in the pediatric population, including clinical presentation, evaluation, and short- to mid-term outcomes.

Materials/Methods: All patients with coronary anomalies presenting to our institution undergo standardized clinical evaluation. Five patients aged 4 to 17 years underwent surgical intervention for intraseptal anomalous aortic origin of the left coronary artery between 2012 and 2022. Surgical techniques included coronary artery bypass grafting (n=1), direct reimplantation with limited supra-arterial myotomy via right ventriculotomy (n=1), and transconal supra-arterial myotomy with right ventricular outflow tract patch reconstruction (n=3).

Results: All patients had evidence of hemodynamically significant coronary compression and 3 had evidence of inducible myocardial ischemia preoperatively. There were no deaths or major complications. Median follow up was 6.1 months (range 3.1 – 33.4 months). Patients who underwent supra-arterial myotomy (with or without reimplantation) had improved coronary flow and perfusion based on stress imaging and catheterization data.

Conclusions: Surgical approaches to intraseptal anomalous left coronary artery with evidence of myocardial ischemia continue to evolve, with new techniques demonstrating promising improvement in coronary perfusion. Further studies are warranted to determine long-term outcomes and refine indications for repair.

Poster Number 66

Junior Faculty

Congenital Developmental Heart Disease

SOX7 INTERACTS GENETICALLY WITH WNT4 TO MODULATE ENDOCARDIAL-TO-MESENCHYMAL TRANSITION AND MESENCHYMAL CELL PROLIFERATION IN THE ENDOCARDIAL CUSHIONS OF THE DEVELOPING AV CANAL

Andres Hernandez-Garcia[1], Katherine E Katherine E. Pendleton[1], Sangbae Kim[1], Yumei Li[1], Bum Jun Kim[1], Hitisha P Zaveri[1], Valerie K Jordan[1], Cecilia Ljungberg[2], Rui Chen[1], Rainer B Lanz[3], Daryl A Scott[1]
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Background: SOX7 is a transcription factor-encoding gene located in chromosome 8p23.1 region that is recurrently deleted in individuals with ventricular septal defects (VSDs). We hypothesized that SOX7 functions in the endocardium by regulating the expression of endothelial-to-mesenchymal transition (EndMT) related genes.

Materials/Methods: To verify if Wnt4 interacts with Sox7 to modulate EndMT, we created standard and conditional Sox7 knockout mice. Embryos were harvested for phenotypic, histology, cell density, collagen gel, RNA-In Situ Hybridization (RNA-ISH), and RNA-seq analysis.

Results: We have shown that Sox7-/- embryos die of heart failure around E11.5. Here, we demonstrate that these embryos have hypocellular endocardial cushions (ECs) with severely reduced numbers of mesenchymal cells (MCs). Ablation of Sox7 in the endocardium also resulted in hypocellular ECs, and we observed VSDs in rare E15.5 Sox7flox/-;Tie2-Cre and Sox7flox/flox;Tie2-Cre embryos that survived to E15.5. In atrioventricular explant studies, we showed that SOX7 deficiency leads to a severe reduction in EndMT. RNA-seq studies performed on E9.5 Sox7-/- heart tubes revealed severely reduced Wnt4 transcript levels confirmed by RNA-ISH. Wnt4 is expressed in the endocardium and promotes EndMT by acting in a paracrine manner to increase the expression of Bmp2 in the myocardium. Both WNT4 and BMP2 have been previously implicated in the development of VSDs in individuals with SERKAL and SSFSC1 syndromes. To provide additional evidence that SOX7 and WNT4 function within the same pathway, we determined the density of MCs in the ECs of E10.5 mouse embryos. Consistent with our hypothesis, Wnt4+/-; Sox7+/- double heterozygous have reduced numbers of MCs in their ECs compared to heterozygous and wild type controls.

Conclusions: Our results provide evidence that SOX7, WNT4 and BMP2 deficiency can contribute to the development of VSDs in humans with 8p23.1 deletion and highlight the probability of genetic interactions when interpreting genetic test results.

Poster Number 67

Junior Faculty

Resource, Tool Development, and SIDS

THE MOUSE METABOLISM AND PHENOTYPING CORE: RESOURCES TO CHARACTERIZE YOUR MICE AND DEVELOP ASSAYS

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Background: The Mouse Metabolism and Phenotyping Core provides access to equipment and expertise for the characterization of whole animal and organ systems phenotypes within rodent models.

Materials/Methods: An array of equipment, methods, and analysis tools for interrogating cardiovascular outcome measures (ultrasound, ECG, telemetry) and comorbidities related to other organ systems (XRay, indirect calorimetry assessment of metabolism, assessment of metabolism-associated blood parameters) are available to the users of the core. Additionally, datasets produced by the core as part of the International Mouse Phenotyping Consortium are accessible to through a web portal managed by the IMPC. Finally, the core can also assist in the development of novel assays and analysis methods - an automated neonate autoresuscitation reflex assay to model Sudden Infant Death Syndrome developed in collaboration with the lab of Russell Ray, enables screens for environmental and genetic exposure risks that may contribute to Sudden Infant Death Syndrome.

Results: 1) Use of the core facilitates the acquisition of a wide array of outcome measures permitting thorough characterization of animal models of cardiovascular disease. 2) The IMPC dataset also provides researchers access to first-pass assessment of an assortment of genetic knockouts. 3) Technology development projects enable improvements to methods to provide higher-throughput data collection/analysis and improved standardization.

Conclusions: The Mouse Metabolism and Phenotyping Core serves the researchers at Baylor College of Medicine, the Texas Medical Center, and the wider research community.

Poster Number 68

Junior Faculty

A.I. Algorithm

EVALUATING CHATGPT'S POTENTIAL AS AN AUTOMATIC CHATBOT IN HEALTHCARE: A COMPARISON OF RESPONSES TO REAL CARDIOVASCULAR DISEASE QUESTIONS

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Background: ChatGPT is an artificial intelligence language model that can generate human-like responses to textual inputs. It has been trained on a large corpus of medical data, including medical textbooks, journals, and other relevant medical literatures. In this study, we aimed to evaluate ChatGPT's potential as an automatic chatbot in healthcare by testing its response to real patient questions.

Materials/Methods: We randomly selected 25 cardiovascular questions from the patient Q&A part in The Texas Heart Institute's website(https://www.texasheart.org/heart-health/heart-information-center/frequently-asked-patient-questions/) and input them into ChatGPT(Open AI, https://chat.openai.com) to compare its responses with those of real doctors. The questions were categorized into general information about disease/drugs or healthcare education (13 questions) and specific concerns with clinical results about the disease diagnosis, prognosis, or treatment (12 questions).

Results: Our results showed that ChatGPT provided highly readable and human-like responses to all questions. For general questions, it correctly answered 12 out of 13 questions with more detailed information provided than the doctors. However, for specific clinical questions, ChatGPT only reached 6 corrected answers and tended to provide general information while skipping specific clinical decision requests. Nonetheless, the interactive features of the system allowed users to ask related questions continuously to obtain more specific answers.

Conclusions: Our study demonstrates that ChatGPT has great potential as an automatic chatbot in the healthcare field, particularly for health education and disease prevention. It could be a great relief for doctors and a reliable 24/7 on-demand medical resource for patients. Although it underperformed in clinical decision-making, it could be improved through continuous input training. Meanwhile, more clinical decision-guided training is necessary to further optimize its performance in this area.

Poster Number 69

Postdoctoral Researcher

Angiogenesis

SUBCONJUNCTIVAL INJECTION OF ANTI-SCG3 HUMANIZED ANTIBODY INHIBITS CORNEAL NEOVASCULARIZATION

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Background: There is currently no approved drug therapy for corneal neovascularization (CoNV). Anti-angiogenic drugs against vascular endothelial growth factor (VEGF) have been used off-label to treat CoNV but with potential side effects on corneal epithelium and nerves. Secretogranin III (Scg3) was recently discovered as a disease-restricted angiogenic factor, and Scg3-neutralizing antibodies have been developed for disease-targeted therapy of other ocular angiogenic diseases with significant safety advantages. The purpose of this study is to determine and compare the efficacy of anti-Scg3 and anti-VEGF to treat CoNV in mice.

Materials/Methods: Alkali burn was performed on C57BL/6J mice to induce CoNV. Mice were treated subconjunctivally with anti-Scg3 humanized antibody (hAb), anti-VEGF drug aflibercept or phosphate buffered saline (PBS). To evaluate treatment efficacy, corneal images were taken on Days 5, 7, and 10 post alkali burn and analyzed for CoNV score and total length of new vessels. Corneas were harvested on Day 10, immunostained for blood and lymph vessels and imaged by confocal microscopy.

Results: Anti-Scg3 hAb significantly reduced total length of alkali burn-induced new corneal vessels by 78%. Aflibercept had similar efficacy to inhibit total length of new vessels by 60%. Immunostaining of corneas confirmed that anti-Scg3 hAb markedly reduced corneal blood vessels and lymph vessels in alkali-burned corneas with similar efficacy to that of aflibercept treatment. In contrast, PBS control had no detectable therapeutic activity.

Conclusions: These findings suggest that anti-Scg3 hAb and aflibercept significantly inhibit CoNV with similar efficacy. In light of the disease-targeting property of anti-Scg3 hAb to selectively inhibit pathological angiogenesis with undetectable adverse effects on healthy vessels, neurons and epithelium, our findings warrant further investigation to compare the efficacy and safety of anti-Scg3 and aflibercept for anti-angiogenic therapy of CoNV.

Poster Number 70

Postdoctoral Researcher

CAD, Atherosclerosis, Ischemia

MITOCHONDRIAL TRANSCRIPTION FACTOR-A (TFAM) PLAYS AN IMPORTANT ROLE IN VASCULAR INJURY BY MULTIPLE SUBCELLULAR TARGETING SIGNALS

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Background: Mitochondrial transcription factor A (TFAM) is a master regulator of mitochondrial biogenesis that enhances mitochondrial DNA replication and transcription. In this study, we aimed to test the hypothesis that TFAM plays an important role in protecting smooth muscle cells (SMCs) and preventing the formation of aortic aneurysms and dissections (AADs).

Materials/Methods: We examined TFAM expression in SMCs in human aortic tissue samples from patients with sporadic ascending aortic aneurysms (ATAA, n=10), acute ascending aortic dissections (ATAD, n=10), and non-diseased organ donor controls (n=8). We determined the role of TFAM in AAD development by comparing AAD incidence in SMC-specific knockout mice (SMC-Tfam-/-, n=41) and their littermate controls (SMC-Tfam+/+, n=50) in a sporadic AAD model induced by challenging mice with angiotensin II infusion. We also examined the regulation of TFAM and its role in mitochondrial function and cell function in cultured SMCs.

Results: Our single-cell transcriptome and immunostaining analysis showed that TFAM expression in SMCs was significantly higher in human AAD samples compared to controls ($P<0.02$). In our AAD mouse model, SMC-Tfam-/- mice displayed a significantly higher incidence of AADs ($p=0.04$) compared to SMC-Tfam+/+ controls. SMC-Tfam-/- mice also showed an increased induction of cell death pathways in SMCs and a relative loss of SMCs. Differential gene expression analysis revealed a downregulation of oxidative phosphorylation and tricarboxylic acid cycle related genes in challenged Tfam-/- mice compared to challenged WT mice. Furthermore, we detected TFAM not only in mitochondria but also in SMC nuclei. Inducing oxidative stress in SMCs (using H_2O_2) induced TFAM nuclear translocation.

Conclusions: Our findings suggest that TFAM plays a crucial role in protecting SMCs and preventing the development of AADs.

Poster Number 71

Student

CAD, Atherosclerosis, Ischemia

INCREASE IN CD11B POSITIVE INFLAMMATORY CELLS IN CARDIOEMBOLIC AND CRYPTOGENIC STROKES: A STUDY OF THROMBI FROM STROKE PATIENTS

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Background: 25-40% of ischemic strokes are cryptogenic or strokes of undetermined etiology. Determination of stroke etiology can be challenging and requiring long term monitoring for occult atrial fibrillation. Inflammation (monocytes/ macrophages driven) and fibrosis in the atrial substrate may leads to atrial fibrillation/ cardioembolic strokes. We hypothesized that clots collected from patients with cardioembolic stroke during thrombectomy will have increased myeloid derived inflammatory cells as compared to other stroke etiologies.

Materials/Methods: 54 thrombi were obtained during mechanical thrombectomy in patients with ischemic strokes after consent. They were formalin fixed, embedded, sliced and stained with CD11b, a marker for myeloid derived cells. Mean of five 20x images from two slices per patient was quantified by image J and used for analysis. Relationship between stroke etiology (TOAST) and number of CD11b positive cells was assessed using Mann-Whitney U test and multilinear regression models.

Results: Mean patient age was 64.2±12.5 years, 33.3% were women, 81.5% had hypertension, 22.2% had diabetes mellitus, and 37% had hyperlipidemia. Thrombi with cardioembolic etiology had significantly higher number of CD11b positive cells (248.2±137.4, n=27) as compared to strokes from large artery atherosclerosis (133.3±95.7, n=11), p=0.02. Cryptogenic strokes also had significantly higher number of CD11b positive cells, (212.1± 104.8, n=13) when compared to strokes from large artery atherosclerosis, p=0.04, n=11, even after controlling for hypertension, hyperlipidemia, heart disease, diabetes mellitus and age. No difference was seen in CD11b positive cell numbers between cardioembolic and cryptogenic strokes, p=0.4.

Conclusions: Cardioembolic and cryptogenic stroke thrombi have increased CD11b positive cells as compared to strokes from large artery atherosclerosis. The shared histology of cardioembolic and cryptogenic strokes suggests that many of the cryptogenic strokes may be due to undiagnosed cardioembolism.

Poster Number 72

Postdoctoral Researcher

CAD, Atherosclerosis, Ischemia

SMOOTH MUSCLE CELL-SPECIFIC PERICENTRIN GENE DEFICIENCY LEADS TO AUGMENTED PHENOTYPIC MODULATION AND ATHEROSCLEROSIS IN MICE

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Background: Biallelic loss-of-function pathogenic variants in the centrosomal scaffolding protein pericentrin (PCNT), lead to microcephalic osteodysplastic primordial dwarfism type II (MOPDII), with patients exhibiting onset of coronary artery disease in their 20's with no risk factors. Smooth muscle cell. Vascular smooth muscle cells represent upto 70% of plaque cells by undergoing phenotypic modulation in response to atherogenic stimuli. We hypothesize that smooth muscle cell-specific PCNT gene deletion augments atherosclerotic burden in mice.

Materials/Methods: Hyperlipidemia in mice was induced by AAV-PCSK9DY injection and 12 weeks of high fat diet.

Results: We demonstrated that mice with smooth muscle cell (SMC)-specific Pcnt-deficiency, KO mice (PcntSMC-/-) exhibit ~2.5-fold higher atherosclerotic plaque burden compared to controls. Immunostaining revealed severe loss of medial SMCs in KO mice and MOPDII patient aortic tissue and significantly higher levels of markers of atherosclerosis-associated phenotypic modulation of SMCs in mouse lesions, driven in part by cholesterol, further activating ER stress and PERK-ATF4-KLF4 signaling. Explanted KO SMCs had all three arms of an unfolded protein response activated, and gene expression changes consistent with SMC modulation, either at baseline or with exposure to minimal amounts of exogenous cholesterol, whereas the WT SMCs showed these changes only when exposed to high levels of cholesterol. KO SMCs uniquely exhibited elevated expression and activity of heat shock factor 1 (HSF1) at baseline, which increased HMG-CoA reductase (Hmgcr) expression and activity, resulting in increased cellular cholesterol biosynthesis and cholesterol ester levels, in turn activating ER stress and augmenting SMC modulation. Finally, treatment with the HMGCR inhibitor, pravastatin, attenuates atherosclerosis in KO mice.

Conclusions: In conclusion, our results reveal a novel mechanism by which the loss of Pcnt in SMC augments SMC modulation and drives premature onset atherosclerosis.

Poster Number 73

Junior Faculty

Congenital Developmental Heart Disease

GYG DEFICIENCY RESCUES THE HEART FAILURE PHENOTYPE OF PGM1 NULL MIDGESTATION MOUSE EMBRYOS

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Background: Mammalian hearts that function in low oxygen environments (i.e. embryonic, fetal, and failing hearts) primarily use glucose metabolism as an energy source instead of fatty acid oxidation, which requires significant amounts of oxygen. Phosphoglucomutase 1 (PGM1) converts Glucose-1-P to Glucose 6-P for glycolysis and loss of Pgm1 leads to Congenital Disorder of Glycosylation 1t. Glycogenin (GYG) induces the priming step for glycogenesis and loss of Gyg leads to Glycogen Storage Disease XV. We hypothesized that GYG and PGM1 balance the cardiac needs for glycogenesis and glycolysis.

Materials/Methods: We utilized KOMP mouse lines, including knockout alleles for Gyg as well as the CRISPR-Cas9 derived Pgm1 allele. Individual and compound crosses of these alleles were generated. Offspring from genetic crosses were collected and subjected to a variety of techniques, such as viability assays, phenotyping, LacZ staining, histology, in situ hybridization (ISH), qPCR, and western blot analysis.

Results: Gyg and Pgm1 gene products were undetectable in homozygous mutants. LacZ staining of GygTm1b heterozygous embryos showed that Gyg is expressed specifically in the developing heart at E8.5 and midgestation stages. Whole mount ISH of Pgm1 showed expression in the mesoderm and cardiac mesoderm at E7.5 and cardiac expression at E8.5. Viability assays conducted on Pgm1 null embryos show lethality by E12.5, whereas Gyg null embryos died in perinatal stages. At E10.5 and E11.5, Pgm1 null embryos exhibit pericardial edema and poor yolk sac vasculature, hallmarks of embryonic heart failure. Intercrosses of Pgm1 and Gyg demonstrated that Gyg heterozygosity does not perturb the Pgm1 null phenotype. Homozygous loss of Gyg rescued the Pgm1 phenotype at E12.5.

Conclusions: Disruption of the mouse Gyg or Pgm1 gene results in lethality at perinatal and midgestation stages, respectively. Gyg and Pgm1 are co-expressed in the embryonic heart at E8.5. Disruption of both genes results in a rescue of the Pgm1 phenotype at E12.5.

Poster Number 74

Student

Arrhythmias and Channelopathies

GENETIC TESTING REANALYSIS OF HERITABLE ARRHYTHMIA DISORDERS

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Background: Sudden cardiac death disorders (SCDD) are caused by alternations in cardiac genes that can be identified through genetic testing. Genetic variants can be later reclassified and upgraded or downgraded in status which can impact care. This amplifies the potential risk for misdiagnosis and can result in patients once thought to be normal to have SCDD. Changes in variant status and how potential changes would affect care have yet to be studied. Our objectives are to evaluate the association between diagnostic results of initial SCDD genetic testing and subsequent changes in clinical care and to identify the diagnostic yield of genetic results at initial testing and reclassification.

Materials/Methods: This is a single-center retrospective study of 301 pediatric patients (<18y) between 2007-2018 with suspected SCDD who underwent genetic testing. Variants were classified as diagnostic, variant of unknown significance, or non-diagnostic. Changes in patient care were assessed using logistic regression and diagnostic yield was evaluated using binomial confidence intervals.

Results: In the overall cohort, probands with a diagnostic variant at initial testing had 4.44 times the odds of having changes in care in anti-arrhythmic therapy and had 5.94 times the odds of having changes in lifestyle modification compared to individuals with a non-diagnostic variant at initial testing. Diagnostic yield of diagnostic variants increased from initial testing (22.9%) to reclassification (53.5%) in the overall cohort.

Conclusions: Diagnostic variants identified at initial genetic testing were associated with changes in clinical care in the areas of anti-arrhythmic therapy and lifestyle modifications. Diagnostic yield of diagnostic variants increased from initial testing to reclassification in the overall cohort. The potential alteration of medical care and its psychosocial impact on the patient illustrate the clinical relevance of and the imperative need to further investigate variant reclassification.

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