Advances in Cardiovascular Science and Medicine Through Diversity, Equity, and Inclusion supported by Education, Research, and Technology Innovation

41st North American Section of The International Society for Heart Research

9th North American Section of The International Academy of Cardiovascular Sciences

September 6th – 9th, 2022

Hotel Fort Garry 222 Broadway
Winnipeg, Canada R3C 0R3

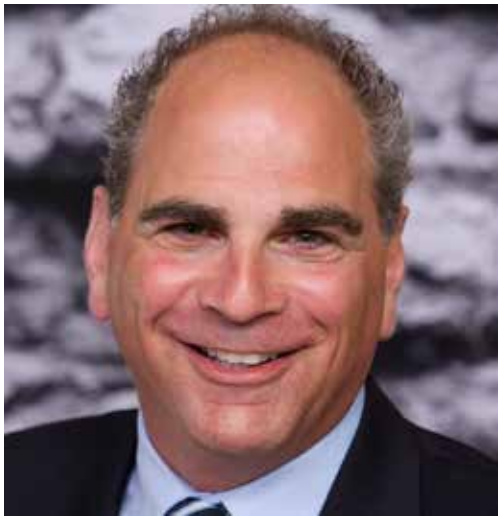
ISHR
North American Section

Institute of Cardiovascular Sciences

International Academy of Cardiovascular Sciences
Education • 1996 • Research

Photo credit: Dan Harper

WELCOME



On behalf of the Organizing and Program Committee I am pleased to welcome you to 9th Meeting of North American Section of the International Academy of Cardiovascular Sciences (IACS) and the 41st International Society for Heart Research (ISHR) meeting on September 6th- 9th, 2022 in Winnipeg, Manitoba, Canada. We are also pleased to welcome the International Union of Physiological Sciences as a symposium sponsor. The theme of the meeting entitled "***Advances in Cardiovascular Science and Medicine Through Diversity, Equity, and Inclusion supported by Education, Research, and Technology Innovation".*** The goal of this scientific meeting is to bring together the top cardiovascular scientists, clinical cardiologists, research fellows and trainees, from all over the world to participate in this scientific forum including Canada, USA, Brazil, Israel, Argentina, Slovakia, Czech Republic, Turkey, France and India.

We would like to acknowledge that the meeting takes place at the historic Fort Garry Hotel, which is located in Treaty 1 territory and that the land on which we gather is the traditional territory of Anishinaabeg, Cree, Oji-Cree, Dakota, and Dene Peoples, and the homeland of the Métis Nation. We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of reconciliation and collaboration.

The meeting will be comprised of 27 scientific symposia with a clinical focus on women's heart health, cardio protection, cardiometabolic diseases, risk factors, oxidative stress, arrhythmogenesis, molecular genetics, prevention, circadian biology, biomaterials and regeneration, heart failure, nutrition, and applied aspects in cardiovascular health care delivery. The scientific program committee did an outstanding job in assembling a stellar line up of expert speakers and integrative aspects of cardiovascular medicine with a special focus on early and midcareer investigator programs. A highlight of the meeting is the highly subscribed poster session and plenary symposiums, named landmark lectures and awards programs. We are particularly proud of the large attendance and strong support of the ISHR and IACS of early and mid-career scientists.

Winnipeg has a rich heritage in performing arts, sports and cultural activities, museums and galleries. It's vibrant night life and international cuisine make it a popular tourist destination for visitors from all over the world. The combination of outstanding speakers, themed symposia and meeting venue will offer a great scientific program. Again, on behalf of the organizing and scientific program committees, ISHR and IACS, I would like to thank you again for attending the conference and wish you a warm welcome to Winnipeg, Manitoba, Canada.

Lorrie A. Kirshenbaum
Conference Chair, Winnipeg, Canada

Conference Chairs/Organizing and Program Committees

Dr. Lorrie A. Kirshenbaum, Conference Chair, Winnipeg, Canada
Dr. Jennifer Van Eyk, Conference Co-Chair, Cedars-Sinai, Los Angeles, USA
Dr. Maria Kontaridis, Conference Co-Chair Masonic Medical Research Institute, Utica, USA
Honourary Chair
Dr. Naranjan S. Dhalla, Winnipeg, Canada

Advisory Board

Grant Pierce - Winnipeg, Canada
Roberto Bolli - Louisville, USA
Gary Lopaschuk - Edmonton, Canada
Elizabeth Murphy - Bethesda, USA
Junichi Sadoshima - Newark, USA
David Lefer - New Orleans, USA
Mark Entman - Houston, USA
Steve Houser - Philadelphia, USA
Joseph Hill - Dallas, USA
AJ Marian - Houston, USA
Jawahar (Jay) Mehta - Little Rock, USA
Peipei Ping - Los Angeles, USA
Noel Bairey Merz - Los Angeles, USA
Richard Kitsis - New York, USA

Organizing Committee Members

Secretary

Michael Czubryt - Winnipeg, Canada

Joint Secretary

Sanjiv Dhingra - Winnipeg, Canada

Committee Members

Peter Nickerson - Winnipeg, Canada
Todd Duhamel - Winnipeg, Canada
Davinder Jassal - Winnipeg, Canada
Inna Rabinovich-Nikitin - Winnipeg, Canada
Pawan Singal - Winnipeg, Canada
Ashish Shah - Winnipeg, Canada
Peter Cattini - Winnipeg, Canada
Pram Tappia - Winnipeg, Canada
Shelley Zieroth - Winnipeg, Canada
Jeffrey Wigle - Winnipeg, Canada
Rakesh Arora - Winnipeg, Canada
Amir Ravandi - Winnipeg, Canada

Conference Coordinators

Local: Kairee Ryplanski, University of Manitoba, Winnipeg, Canada
Local: Mae Villamor, University of Manitoba, Winnipeg, Canada
Off Site: Kelley Brodsky, University of Colorado Anschutz Medical Campus, Aurora, USA

Scientific Committee Members

Secretary

Ross Feldman - Winnipeg, Canada

Joint Secretary

Ian Dixon - Winnipeg, Canada

Committee Members

Anthony Gramolini - Toronto, Canada
Merry Lindsey - Oklahoma, USA
Madhu Anand-Srivastava - Montreal, Canada
Susan Howlett - Halifax, Canada
Mansoor Husain - Toronto, Canada
Maria Kontaridis - Utica, USA
Devendra Agrawal - Los Angeles, USA
Tim McKinsey - Aurora, USA
Tipparaju Srinivas - Tampa, USA
Jennifer Van Eyk - Los Angeles, USA
Buddhadeb Dawn - Las Vegas, USA
Asa Gustafsson - San Diego, USA
Suresh Tyagi - Louisville, USA
Takashi Matsui - Honolulu, USA

Meeting Venue, Fort Garry Hotel, 222 Broadway, Winnipeg, Canada R3C 0R3

Officers and Executive Council of International Academy of Cardiovascular Sciences

(Honourary Life President: Naranjan S. Dhalla)

President:	Roberto Bolli, Louisville, USA
President-Elect:	Grant Pierce, Winnipeg, Canada
Past President:	Bohuslav Ostadal, Prague, Czech Republic
Executive Director:	Naranjan S. Dhalla, Winnipeg, Canada

Executive Council

Michael Czubryt, Winnipeg, Canada

Dragan Djuric, Belgrade, Serbia

Dobromir Dobrev, Essen, German

Ricardo J. Gelpi, Buenos Aires, Argentina

Ramesh K. Goyal, New Delhi, India

Chandrasekharan Kartha, Trivandrum, India

Lorrie Kirshenbaum, Winnipeg, Canada

Melchior L. Lima, Vitoria, Brazil

Gary Lopaschuk, Edmonton, Canada

Naoki Makino, Beppu, Japan

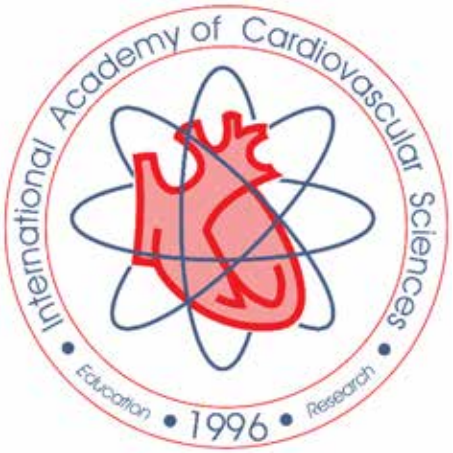
Jawahar (Jay) Mehta, Little Rock, USA

Pawan K. Singal, Winnipeg, Canada

Jan Slezak, Bratislava, Slovak Republic

Andras Varro, Szeged, Hungary Tatiana

Ravingerova, Bratislava, Slovak Republic



International Society for Heart Research
North American Section

Officers and Executive Council	
Program Chair and Co-Chairs:	Lorrie Kirshenbaum (Chair), Jennifer Van Eyk and Maria Kontaridis (Co-Chairs).
Local Organizing Committee:	Kairee Ryplanski and Mae Villamor
Scientific Program Committee:	ISHR NAS Council & Lorrie Kirshenbaum, Jennifer Van Eyk, and Maria Kontaridis (Co-Chairs)
ISHR Officers and Council Members	
President (2022-24):	David Lefer
President-Elect (2022-24):	Timothy Kamp
Past-President (2022-24):	Peipei Ping
Treasurer (2022-24):	Jennifer Davis
Secretary of Recording and Membership (2022-24):	Maria Kontaridis
Executive Committee (EC) US Member (2022-24):	Jennifer Van Eyk
Executive Committee (EC) Canadian Member (2022-24):	Lorrie Kirshenbaum
Executive Secretary:	Kelley Brodsky
Council Members (2018-24):	Hossein Ardehali, John Calvert, Daniel Kelly, Ronglih Liao, & Jil Tardiff.
Council Members (2022-27):	Sam Das, Shirin Doroudgar, Sarah Franklin, Anthony Gramolini, Susan Howlett, Maggie Lam, Jean Bopassa, Hesham Sadek, Susmita Sahoo, & Carmen Sucharov.
MCI Council Leadership:	Maria Kontaridis, Ph.D. (Council Liaison/Council Chair) Rajasekaran Namakkal-Soorappan (Chair) and Nicole Purcell (Vice-Chair).
MCI Program Committee:	Pilar Alcaide, Dominic Del Re, Susmita Sahoo, Sarah Franklin, Michael Tranter, Liming Pei, Mark Kohr, Tim O'Connell, Maggie Lam, Na Li, & Jen Davis.
ECI Council Leadership:	Carmen Sucharov (Council Liaison/Faculty Advisor). Ron Vagnozzi (Chair), Erik Blackwood (Vice Chair).
ECI Program Committee:	Jessica Pfleger, Anja Karlstaedt, Qutuba Karwi, Julia Liu, Catherine (Cat) Makarewich, Thomas Sharp, Michael Zhang, & Rushita Bagchi

24th Annual Institution of Cardiovascular Sciences
Naranjan Dhalla Cardiovascular Awards Day
2022 Award Recipients

Dr. Lorrie Kirshenbaum, Chair, Naranjan Dhalla Cardiovascular Awards Day would like to announce the following awards that will be presented to the award winners at the gala dinner on September 8th, 2022

Robert Beamish Leadership Award
Dr. Andras Varro, Szeged, Hungary

Ken Bowman Research Achievement Award
Dr. Ramesh K. Goyal, New Delhi, India

John Foerster Distinguished Lecture Award
Dr. Vladimir Jakovljevic, Kragujevac, Serbia

Vincenzo Panagia Distinguished Lecture Award
Dr. Miloš P. Stojiljković, Banja Luka, Bosnia and Herzegovina

Institute of Cardiovascular Science Leadership Gold Medal,
Dr. Bohuslav Ostadal, Prague, Czech Republic**,**
Dr. Ranko Škrbić, Banja Luka, Bosnia and Herzegovina and
Dr. Noel Bairey Merz, Los Angeles, USA

Jack Litvack Exemplary Service Award
Ms. Kairee Ryplanski, Winnipeg, Canada

Arnold Naimark Young Investigator Award
Dr. Niketa Sareen, Winnipeg, Canada

Henry Friesen Young Scientist Award
Dr. Weiang Yan, Winnipeg, Canada

Sr. Jacqueline St-Yves Publication Award
Dr. Raghu Nagalingam, Surrey, Canada

Institute of Cardiovascular Sciences Award for Master's Student
Dr. Besher Abual'anaz, Winnipeg, Canada

T. Edward Cuddy Student Award
Mr. Amit Suharenko, Winnipeg, Canada

James S. McGoey Student Award
Ms. Emily Dueck, Winnipeg, Canada

SPONSORS

Special acknowledgment to the individuals and organizations below for their kind contributions and sponsorship to the meeting.

Dr. Gary Lopaschuk - Edmonton, Canada

Dr. Ken Rockwood - Halifax, Canada

Dr. Morris Karmazyn - London, Canada

Dr. Roberto Bolli - Louisville, USA

Dr. Susan Howlett - Halifax, Canada

Bio-Rad Laboratories, Inc.

Canadian Journal of Physiology and Pharmacology

Cardiac Sciences St. Boniface Hospital

Cedars-Sinai Medical Center

Cincinnati Children's Hospital - Heart Institute

Institute of Cardiovascular Sciences

International Academy of Cardiovascular Sciences

International Society for Heart Research

International Union of Physiological Sciences

Journal of Molecular and Cellular Cardiology

Lewis Katz School of Medicine at Temple University

Louisiana State University School of Medicine

Masonic Medical Research Institute

St. Boniface Hospital Foundation, Winnipeg, Canada

The Journal of Cardiovascular Aging

Thomas Jefferson University

University of Alabama

University of California, Los Angeles David Geffen School of Medicine

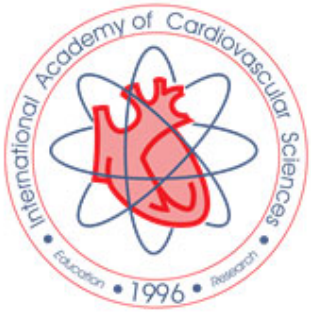
University of Colorado Anschutz Medical Campus

University of Manitoba, Department of Physiology and Pathophysiology

University of Manitoba, Max Rady College of Medicine


ISHR
North American Section


Institute of Cardiovascular Sciences


International Academy of Cardiovascular Sciences
Education
1996
Research


University of Manitoba


BIO-RAD


UAB
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM.


University of CINCINNATI


MASONIC MEDICAL RESEARCH INSTITUTE
MMRI


INTERNATIONAL UNION OF PHYSIOLOGICAL SCIENCES
IUPS
1953


University of Colorado
Anschutz Medical Campus


LSUHealth

The Journal of Cardiovascular Aging

Tuesday, September 6, 2022		
7:00 – 5:00 PM	Registration	Provencher
7:00 – 8:00 AM	Continental Breakfast	Provencher
	Early Career Investigator (ECI) Scientific Symposium **Chairs: Qutuba Karwi and Julia Liu**	Provencher
8:00 – 8:05 AM	Opening remarks	
8:05 - 8:12 AM	**Mateusz Tomczyk** *Sirtuin 3 (SIRT3) Prevents Doxorubicin Induced Dilated Cardiomyopathy: Investigating Mitochondrial Protein Acetylation, Cardiac Lipids and Metabolic Dysfunction*	
8:12 - 8:19 AM	**Kaya Persad** *The Warburg effect is reduced in matured cardiomyocytes due primarily to a decrease in glycolysis.*	
8:19 - 8:26 AM	**Sharon Parkins** *HuR-dependent expression of Wisp1 is necessary for TGFβ-induced cardiac myofibroblast activity*	
8:26 – 8:33 AM	**Cristine Reitz** *Integrative proteomic and phosphoproteomic analysis identifies etiology-specific phosphorylation patterns in the failing human heart*	
8:33 - 8:40 AM	**Qiuyu Sun** *Cardiac glucose oxidation is impaired in heart failure with preserved ejection fraction (HFpEF)*	
8:40 - 8:47 AM	**Matthew Martens** *The Role of Reactive Oxygen Species Modulator 1 (ROMO1) in the Heart*	
8:47 - 8:54 AM	**Sara Puccini** *Homology model of free fatty acids receptor 4 and Gq in complex uncovers the pharmacology of endogenous fatty acid binding and receptor activation*	
8:54 – 9:01 AM	**Adrienne Guarnieri** *Exploring sarcoplasmic reticulum calcium cycling as a thermogenic mechanism in brown adipose tissue*	

9:01 - 9:08 AM	**Ezra Ketema** *CD38 inhibition decreases myocardial glucose utilization and impairs post-ischemic recovery without altering protein acetylation status*	
9:08 - 9:15 AM	**Moriah Turcotte** *Perinuclear β-Adrenergic Receptors are Necessary and Sufficient to Promote Cardiac Hypertrophy*	
9:15 - 9:22 AM	**Tanya Baldwin** *Defining the role of DHHC3 and DHHC7 in cardiac stress signalling*	
9:22 - 9:29 AM	**Simran Pherwani** *Ketones provide an extra source of fuel for the failing heart without impairing glucose oxidation*	
9:30 – 9:45 AM	**Coffee break**	
9:45 – 10:00 AM **10:00 – 11:00 AM**	**ECI Career Development Workshop** **Session Chairs:** **Cat Makarewich, Jessica Pfleger, and Inna Rabinovich-Nikitin** **<u>"Speed Mentoring"</u>** Mentors: Chris Glembotski — Asa Gustafsson Joseph A. Hill — Kimberly Kafka Wally Koch — Maria Kontaridis Jeff Molkentin — Nikki Purcell Sakthi Sadayappan — Jun Sadoshima KC Woufle Mentor Introductions Small group discussion, 10-minute sessions	Provencher
11:00 – 11:30 AM	**Mid-Career Investigator (MCI) Town Hall Meeting**	Provencher
11:30 – 12:00 PM	**MCI Leadership Achievement Award Presentation**	Provencher
12:00 – 1:30 PM	ECI and MCI Joint Box Lunch **<u>(Ticket Required)</u>**	Provencher
1:30 – 3:00 PM	MCI Research Scholarship Award Competition (3 finalists)	Provencher
3:00 – 5:30 PM	Young Investigator Competition Award (YICA)	Provencher

Tuesday, September 6, 2022 **OPENING CEREMONY**		
Chair	**Lorrie Kirshenbaum** (University of Manitoba, Winnipeg, Canada)	
5:30 – 5:35 PM	**Welcome Greetings Dr. Lorrie Kirshenbaum**	Grand Ballroom
5:35 – 5:40 PM	**Honourable Minister Dan Vandal** Government of Canada	
5:40 – 5:45 PM	**Honourable Audrey Gordon** Health Minister, Province of Manitoba	
5:45 – 5:50 PM	**His Worship Mayor Brian Bowman** City of Winnipeg	
5:50 – 5:55 PM	**Peter Nickerson** Dean of Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba	
5:55 – 6:00 PM	**Nicole Aminot** President and CEO, St. Boniface General Hospital	
6:00 – 6:30 PM	**IACS Presidential Address, IACS Lifetime Achievement Award Lecture** **Roberto Bolli** (University of Louisville, Louisville, USA) *Cell therapy for heart failure: challenges and opportunities.*	
6:30 – 7:00 PM	**IACS Medal of Merit Lecture** **Jawahar (Jay) Mehta** (University of Arkansas, Little Rock, USA) *On molecular mechanisms of cardioprotection following myocardial ischemia by mesenchymal stem cell exosomes*	
7:00 – 7:30 PM	**IACS Cardiovascular Landmark Lecture, IACS Lifetime Achievement Award** **Joseph A. Hill** (UT Southwestern Medical Center, Dallas, USA) *Conspiracy of Comorbidities: Meta-inflammation and HFpEF*	
7:30 – 7:45 PM	***Special Recognition*** **Gary Lopaschuk, IACS-NAS President** (University of Alberta, Edmonton, Canada) **Michael Czubryt, IACS-NAS President Elect** (University of Manitoba, Winnipeg, Canada)	
7:45 – 9:30 PM	**Entertainment and Reception**	

Wednesday, September 7th, 2022		
8:00 – 5:00 PM	**Registration**	**Grand Ballroom Foyer**
7:00 – 8:15 AM	**Poster Set up for Poster Session 1** *Posters will remain up all day and removed by 7:30 PM*	Crystal Ballroom
7:00 – 8:20 AM	**Women Health ICS Gold Medal Lecture** ***Speaker*** **Noel Bairey Merz** (Cedars Sinai Medical Center, Los Angeles, USA) *Women and Ischemic Heart Disease: 2022* **Introduced by** **Jennifer Van Eyk** (Cedars-Sinai Medical Center, Los Angeles, USA) **Women Heart Health Breakfast *(Round Table)*** **General admission** **Session Chairs** **Peipei Ping** (University of California Los Angeles, Los Angeles, USA) **Kika (Carmen) Sucharov** (University of Colorado Anschutz Medical Campus, Aurora, USA)	Provencher
7:00 – 8:20 AM	**Continental Breakfast**	Grand Ballroom Foyer

	<u>Symposium 1</u> **Cardiac Signaling in Health and Disease** **Session Chairs:** **John McDermott** (York University, Toronto, Canada) **Mohsin Khan** (Temple University, Philadelphia, USA) ***Speakers:***	Provencher
8:30 – 8:50 AM	**1) Chen Gao** (University of Los Angeles, Los Angeles, USA) *Regulation of RNA metabolism in heart*	
8:50 – 9:10 AM	**2) Wally Koch** (Temple University, Philadelphia, USA) *Novel Interactions of GRKs in the Heart*	
9:10 – 9:30 AM	**3) Nilanjana Maulik** (University of Connecticut, Farmington, USA) *New Molecular Targets of VEGF Signaling in Cardiovascular Disease*	
9:30 – 9:50 AM	**4) Sergio Lavandero** (University of Chile, Santiago, Chile) *New insights in interorganelle communication in the heart*	
9:50 – 10:10 AM	**5) Vaibhav Patel** (University of Calgary, Calgary, Canada) *Endothelial colony-forming cell-derived extracellular vesicles and cardiac repair after myocardial infarction*	

	<u>Symposium 2</u> **IACS Gary Lopaschuk Graduate Students Awards Competition** **Session Chairs:** **Jan Slezak** (Slovak Academy of Sciences Bratislava, Bratislava, Slovakia) **Ashok Srivastava** (University of Montreal, Montreal, Canada) **Jeffrey Wigle** (University of Manitoba, Winnipeg, Canada) ***Speakers***	Gateway/Tache
8:30 – 8:50 AM	**1)Weiang Yan** (University of Manitoba, Winnipeg, Canada)	
8:50 – 9:10 AM	**2)Michelle Di Paola** (University of Toronto, Toronto, Canada)	
9:10 – 9:30 AM	**3)Yena Oh** (University of Ottawa, Ottawa, Canada)	
9:30 – 9:50 AM	**4)Sharon Parkins**	
9:50 – 10:10 AM	**5)Zana Maksimović** (Banja Luka, City in Bosnia and Herzegovina)	

	<u>Symposium 3</u> **Mitochondria in Health and Disease** **Session Chairs** **George Kararigas** (University of Iceland, Reykjavík, Iceland) **Julia Liu** (University of Minnesota, Minneapolis, USA) ***Speakers:***	LaVerendrye
8:30 – 8:50 AM	**<u>IACS, Makoto Nagano Distinguished Achievements Lecture</u>** **1) Richard Kitsis** (Albert Einstein College of Medicine, New York, USA) *The mitochondrial ATP synthase in cardiac biology and disease*	
8:50 – 9:10 AM	**2) Elizabeth Murphy** (National Heart Lung and Blood Institute, Maryland, USA) *Targeting mitochondria to reduce cardiac cell death*	
9:10 – 9:30 AM	**3) Asa Gustafsson** (University of California San Diego, La Jolla USA) *Secretion of Mitochondria as a Cellular Quality Control Mechanism*	
9:30 – 9:50 AM	**4) Jason Karch** (Baylor College of Medicine, Texas, USA) *The molecular triggers and components of the mitochondrial permeability transition pore*	
9:50 – 10:10 AM	**5) Gyorgy Hajnoczky** (Thomas Jefferson University, Pennsylvania, USA) *The mitochondrial calcium uniporter in cardiac health and disease*	

	<u>Symposium 4</u> **Molecular Basis of Heart Failure** **Session Chair:** **Grant Pierce** (University of Manitoba, Winnipeg, Canada) **Emma Robinson** (University of Colorado, Denver, USA) ***Speakers:***	Grand Ballroom
8:30 – 8:50 AM	**1) Donald Bers** (UC Davis Health, Davis, USA) *Ca and CaMKII signaling in Cardiac Myocytes*	
8:50 – 9:10 AM	**2) Martin Morad** (University of South Carolina, Columbia, USA) *Calcium Signaling Consequences of Mutations in RyR2-Ca2+ binding site expressed in hiPSC-CMs*	
9:10 – 9:30 AM	**3) Charles Hong** (University of Maryland, Baltimore, USA) *Disruption in centrosome remodeling during cardiomyocyte maturation as novel cause of human dilated cardiomyopathy*	
9:30 – 9:50 AM	**4) Litsa Kranias** (University of Cincinnati College of Medicine, Cincinnati, USA) *Cardiac Compartment-Specific Effects of Human Phospholamban Mutations*	
9:50 – 10:10 AM	**5) Francisco Alvarado** (University of Wisconsin-Madison, Madison, USA) *Ryanodine Receptor 2 Dysfunction in Arrhythmogenic Cardiomyopathy*	
10:15 – 10:30 AM	Coffee Break	Mezzanine

	<u>Symposium 5</u> **Naranjan Dhalla Cardiovascular Awards Symposium** **Session Chairs:** **Lorrie Kirshenbaum** (University of Manitoba, Winnipeg, Canada) **Bohuslav Ostadal** (The Czech Academy of Sciences, Prague, Czech Republic) ***Speakers:***	Provencher
10:30 – 10:50 AM	**<u>ICS Awards, Robert Beamish Leadership Award Lecture</u>** **1) Andras Varro** (University of Szeged, Szeged Hungary) *Effect of citrus alkaloids on cardiac potassium channels – possible proarrhythmic implications?*	
10:50 – 11:10 AM	**<u>ICS Awards Ken Bowman Research Award Lecture</u>** **2) Ramesh Goyal** (Delhi Pharmaceutical Science and Research University, Delhi, India) *Emergence of Angiotensin-converting enzyme-2 as a novel target for the treatment of cardiovascular complications.*	
11:10 – 11:30 AM	**<u>IACS Awards Gold Medal Lecture</u>** **3) Bohuslav Ostadal** (Czech Academy of Sciences, Prague, Czech Republic) *Developmental And Sex Differences In Cardiac Sensitivity To Ischemia: The Role Of Mitochondria*	
11:30 – 11:50 AM	**4) Rajasekaran Namakkal-Soorappan** (The University of Alabama at Birmingham, Birmingham, USA) *Atrial remodeling – An early event in proteotoxic heart disease*	
11:50 – 12:10 PM	**5) Jason Dyck** (University of Alberta, Edmonton, Canada) *Cardiac Inflammation in Heart Failure*	

	<u>Symposium 6</u> **Targets for the Prevention of Cardiac Fibrosis** **Session Chairs:** **Roddy Hiram** (University of Montreal, Montreal, Canada) **Ciara Barry** (University of Guelph, Guelph, Canada) ***Speakers:***	Gateway/Tache
10:30 – 10:50 AM	**1) Reza Ardehali** (University of California Los Angeles, Los Angeles, USA) *The role of cardiac pericytes in cardiac fibrosis*	
10:50 – 11:10 AM	**2) Jennifer Davis** (University of Washington School of Medicine, Seattle, USA) *Regulators of Fibroblast Fate & Fibrosis*	
11:10 – 11:30 AM	**3) John Elrod** (Lewis Katz School of Medicine, Philadelphia, USA) *Metabolic control of myofibroblast formation and cardiac fibrosis*	
11:30 – 11:50 AM	**4) Steve Jones** (University of Louisville, Louisville USA) *Metabolic Regulation of the Extracellular Matrix*	
11:50 – 12:10 PM	**5) Zamaneh Kassiri** (University of Alberta, Edmonton, Canada) *The role of TIMPs in atherosclerosis*	

	<u>Symposium 7</u> **Advances in Cardiac Repair, Reprograming and Cell Therapy** **Session Chairs:** **Roberto Bolli** (University of Louisville, Louisville, USA) **Erik Blackwood** (The University of Arizona College of Medicine, Phoenix, USA) ***Speakers:***	LaVerendrye
10:30 – 10:50 AM	**<u>Paul Ganguly Distinguished Award Lecture</u>** **1) Deepak Srivastava** (University of California San Francisco, Gladstone Institute, San Francisco, USA)	
10:50 – 11:10 AM	*Cellular Reprogramming Approaches for Heart Disease* **2) Young-sup Yoon** (Emory University, Atlanta USA)	
11:10 – 11:30 AM	*Directly Reprogrammed Cardiovascular Tissue and Its Cardiac Regenerative Potential* **3) Erik Suuronen** (University of Ottawa, Ottawa, Canada)	
11:30 – 11:50 AM	*Biomaterials, Hydrogels, Cardiovascular Disease* **4) Prasanna Krishnamurthy** (University of Alabama, Birmingham, USA)	
11:50 – 12:10 PM	*Extracellular Vesicles alter Myocardial Inflammation resolution and repair after injury* **5) Jianyi "Jay" Zhang** (University of Alabama at Birmingham, Birmingham, USA) *Bioengineering Approaches to Remuscularize the Myocardial Infarct*	

	<u>Symposium 8</u> **Metabolic Dysfunction in Cardiovascular Abnormalities** **Session Chairs:** **Shuangbo Liu** (University of Manitoba, Winnipeg, Canada) **Kathleen Woulfe** (University of Colorado, Aurora, USA) ***Speakers:***	Grand Ballroom
10:30 – 10:50 AM	**1) Rong Tian** (University of Washington, Seattle, USA) *Metabolic mechanisms of Heart Failure*	
10:50 – 11:10 AM	**2) Joshua Hare** (University of Miami Health System, Miami, USA) *A Novel Class of Drugs for HFpEF*	
11:10 – 11:30 AM	**3) Jeffery Molkentin** (Cincinnati Children's Hospital, Cincinnati, USA) *Human mutation in FLII gene predisposes to genetic cardiomyopathy*	
11:30 – 11:50 AM	**4) Timothy O'Connell** (University of Minnesota, Minneapolis, USA) *Ffar4 attenuates HFpEF through induction of proresolving oxylipin synthesis and attenuation of inflammation*	
11:50 – 12:10 PM	**5) Maria Kontaridis** (Masonic Medical Research Institute, Utica, USA) *Cardiac-specific Deletion of PTP1B Induces a Global Metabolic and Lean Phenotype*	
12:45 – 1:45 PM	**Lunch Break with Special Lecture**	Grand Ballroom

12:45 – 1:45 PM	**ISHR Presidential Lecture** **Session Chair** **David Lefer** (Cedars-Sinai California, Los Angeles, USA) ***Speaker:*** ***Eduardo Marban*** *(*Cedars-Sinai California, Los Angeles, USA) *Deconstructing regenerative medicine: cells, exosomes and bioinspired RNA drugs* **Special Tribute to Dr. Jeffrey Robbins**	Grand Ballroom
12:45 – 1:45 PM	**IACS North American Council Meeting**	Salon A
2:00 – 2:20 PM **2:20 – 2:40 PM** **2:40 – 3:00 PM** **3:00 – 3:20 PM** **3:20 – 3:40 PM**	**Symposium 9** **Advances in Cardiovascular Disease in Women** **Session Chairs:** **Maria Kontaridis** (Masonic Medical Research Institute, Utica, USA) **Inna-Rabinovich-Nikitin** (University of Manitoba, Winnipeg, Canada) ***Speakers:*** **1) Ross Feldman** (University of Manitoba, Winnipeg, Canada) *Sex-specific determinants of heart disease: a cellular perspective* **2) Lea Delbridge** (University of Melbourne, Melbourne, Australia) *Yet more about HFpEF – a female perspective* **3) Raj Kishore** (Temple University, Philadelphia, USA) *Estrogen-independent Gender-specific Dimorphism in Endothelial Progenitor Cell Function* **4) Sarah Rouhana** (University of Guelph, Guelph, Canada) *The Risky Business of Menopause: How perimenopausal changes in the heart shape post-menopausal cardiac risk* **5) Susan Howlett** (Dalhousie University, Halifax, Canada) *Sex-specific effects of frailty on cardiovascular structure and function: insights from preclinical models*	Provencher

	<u>Symposium 10</u> **Roberto Bolli Young Investigator Competition** **Session Chairs** **Michael Czubryt** (University of Manitoba, Winnipeg, Canada) **Devendra Agrawal** (Western University of Health Sciences, Pomona, USA) **Istvan Baczko** (University of Szeged, Szeged, Hungary) ***Speakers:***	Gateway/Tache
2:00 – 2:20 PM	**1) Riham Abouleisa** (University of Louisville, Louisville, USA) *Gene therapy encoding cell cycle factors improves cardiac function in a chronic heart failure rat model*	
2:20 – 2:40 PM	**2) Barbora Kalocayova** (Slovak Academy of Sciences, Bratislava, Slovakia) *Application of molecular hydrogen in the cardiac surgery-associated acute kidney injury*	
2:40 – 3:00 PM	**3) Sathnur Pushpakumar** (University of Louisville, Louisville, USA) *Renal mechanism of preserved ejection fraction*	
3:00 – 3:20 PM	**4) Arun Samidurai** (Virginia Commonwealth University, Richmond, USA) *Dual role of embryonic stem cell derived exosomes in treatment of triple negative breast cancer and improvement of cardiac functions*	
3:20 – 3:40 PM	**5) Srikanth Vallurupalli** (University of Arkansas, Little Rock, USA) *Gender and racial differences in stress induced cardiomyopathy-etiology and biology*	

	Symposium 11 **Proteomics and Proteotoxicity in Cardiovascular Dysfunction** **Session Chairs** **Michael Kapiloff** (Stanford Medicine, Palo Alto, USA) **Tanya Baldwin** (Cincinnati Children's Hospital Medical Center, Cincinnati, USA) ***Speakers:***	LaVerendrye
2:00 – 2:20 PM	**Dennis McNamara Excellence in Science Lecture** **1) Peipei Ping** (University of California Los Angeles, Los Angeles, USA) *A deep learning approach to investigate PTMs: Bridging AI to CV Research*	
2:20 – 2:40 PM	**2) Abhinav Diwan** (Washington University School of Medicine in St. Louis, St. Louis, USA) *Understanding and targeting protein aggregation in cardiomyopathies*	
2:40 – 3:00 PM	**3) Christopher Glembotski** (University of Arizona, Tucson, USA) *The ER as a Nexus of Stress Sensing and Signaling in the Heart*	
3:00 – 3:20 PM	**4) Anthony Gramolini** (University of Toronto, Toronto, Canada) *Global proteomic analysis of mouse and human ventricle: Insights into novel membrane proteins in the myocyte*	
3:20 – 3:40 PM	**5) Jennifer Van Eyk** (Cedars-Sinai, Los Angeles, USA) *Cardiomyocyte heterogeneity: single cell proteomics*	

	<u>Symposium 12</u> **Epigenetics and Cardiac Disease** **Session Chairs** **Angelo Calderone** (University of Montreal, Montreal, Canada) **Danielle Bruns** (University of Wyoming, Laramie, USA) ***Speakers:***	Grand Ballroom
2:00 – 2:20 PM	**1) Maha Abdellatif** (Rutgers New Jersey Medical School, Newark, USA) *Decoding the diet-modulated histone code in the heart*	
2:20 – 2:40 PM	**2) Sarah Franklin** (The University of Utah, Salt Lake City, USA) *Histone Methyltransferases Regulate Cardiac Physiology*	
2:40 – 3:00 PM	**3) Tim McKinsey** (University of Colorado, Aurora, USA) *Targeting HDAC11 to treat cardiometabolic disease*	
3:00 – 3:20 PM	**4) Emma Robinson** (University of Colorado, Aurora, USA) *HDAC11 Regulates Gene Expression and Lipid Droplet-associated protein Myristoylation in Adipocytes*	
3:20 – 3:40 PM	**5) Thomas Vondriska** (University of California Los Angeles, Los Angeles, USA) *How accessibility is related to structure in cardiac chromatin*	
5:30 – 7:00 PM	**Poster Session 1 Reception**	Crystal Ballroom
7:30 – 11:30 PM	**ECI and MCI Joint Social Event** **Appetizers/wine, beer and cocktails** ***Ticket required***	La Roca Restaurant
	Special IACS Dinners by Invitation Only	

Thursday, September 8, 2022

8:00 – 5:00 PM	**Registration**	**Grand Ballroom Foyer**
7:00 – 8:00 AM	**Continental Breakfast**	Grand Ballroom Foyer
7:00 – 8:00 AM	**ISHR - NAS Council Meeting**	Salon A
7:00 – 8:15 AM	**Poster Set up for Poster Session 2** *Posters will remain up all day and removed by 7:30 PM*	Crystal Ballroom
	Symposium 13 **Advances in Heart failure and Therapy** **Session Chairs** **Pawan Singal** (University of Manitoba, Winnipeg, Canada) **Sarah Rouhana** (University of Guelph, Guelph, Canada) ***Speakers:***	Provencher
8:30 – 8:50 AM	**1) David Lefer** (Cedars-Sinai California, Los Angeles, USA) *Hydrogen sulfide signaling in heart failure*	
8:50 – 9:10 AM	**2) Jan Slezak** (Slovak Academy of Sciences, Bratislava, Slovak Republic) *Improving the activity of the transplanted heart and the overall condition of the pigs after perioperative administration of molecular hydrogen*	
9:10 – 9:30 AM	**3) Belma Turan** (University of Ankara, Ankara, Turkey) *Comparisons of pleiotropic-effects of SGLT2 inhibition and GLP-1 agonism on cardiac glucose intolerance in heart dysfunction*	
9:30 – 9:50 AM	**4) Ravichandran Ramasamy** (New York University Grossman Medical Center, New York, USA) *Formin related Diaphanous-1 modulates mitochondrial properties in the ischemic heart*	
9:50 – 10:10 AM	**5) Thomas Netticadan** (University of Manitoba, Winnipeg, Canada) *Potential of cyanidin 3-glucoside in the prevention of cardiovascular disease*	

	Symposium 14 **Metabolic Defects in the Pathogenesis of Heart failure** **Session Chairs** **Amir Ravandi** (University of Manitoba, Winnipeg, Canada) **Qutuba G Karwi** (University of Alberta, Edmonton, Canada) ***Speakers:***	Gateway/Tache
8:30 – 8:50 AM	**Cardiovascular Landmark Lecture, IACS Leadership Award** **1) Gary Lopaschuk** (University of Alberta, Edmonton, Canada) *Cardiac energy metabolism changes in heart failure with preserved ejection fraction*	
8:50 – 9:10 AM	**2) Dale Abel** (UCLA Department of Medicine, Los Angeles, USA) *Metabolites as signals in heart failure*	
9:10 – 9:30 AM	**3) Zoltan Arany** (University of Pennsylvania, Philadelphia, USA) *Cardiac metabolism in human heart failure*	
9:30 – 9:50 AM	**4) Dan Kelly** (University of Pennsylvania, Philadelphia, USA) *Targeting Metabolic Circuits in the Failing Heart*	
9:50 – 10:10 AM	**5) Bradford Hill** (University of Louisville, Louisville, USA) *Role of metabolic cycles in cardiac remodeling*	

	<u>Symposium 15</u> **Signal transduction and Cardiac Dysfunction** **Session Chairs** **Balwant Tuana** (University of Ottawa, Ottawa, Canada) **Alina Bilal** (The University of Arizona College of Medicine, Phoenix, USA) ***Speakers:***	LaVerendrye
8:30 – 8:50 AM	**1) Konstantinos Drosatos** (University of Cincinnati, Cincinnati, USA) *Cardiomyocyte KLF5 induces various types of heart failure*	
8:50 – 9:10 AM	**2) Lama Awad** (Technion Israel of Technology, Haifa, Israel) *Heart failure and cancer: a double-edged sword*	
9:10 – 9:30 AM	**3) Pilar Alcaide** (Tufts University, Boston, USA) *Immune responses in heart failure with reduced and preserved ejection fraction*	
9:30 – 9:50 AM	**4) Sakthivel Sadayappan** (University of Cincinnati College of Medicine, Cincinnati USA) *Fast myosin binding protein-C and cardiac contractility in heart failure*	
9:50 – 10:10 AM	**5) Jody Lee Martin** (UC Davis Health, Sacramento, USA) *The many facets of MLC2 regulation and function in the heart*	

	<u>Symposium 16</u> **Fibrosis in Cardiac Disease** **Session Chair** **Ian Dixon** (University of Manitoba, Winnipeg, Canada) **Sarah Anthony** (Memorial University of Newfoundland, St. John's, Canada) ***Speakers:***	Concert Hall
8:30 – 8:50 AM	**<u>Cardiovascular Landmark Lecture, IACS Leadership Award</u>** **1) Michael Czubryt** (University of Manitoba, Winnipeg, Canada) *Targeting cardiac fibroblast to myofibroblast conversion in heart failure*	
8:50 – 9:10 AM	**2) Michelle Tallquist** (University of Hawaii Manoa, Honolulu, USA) *Signaling pathways that regulate cardiac fibroblast activation*	
9:10 – 9:30 AM	**3) Nikolaos Frangogiannis** (Albert Einstein College of Medicine, Bronx, USA) *TGF-beta in cardiac remodeling*	
9:30 – 9:50 AM	**4) Robert Rose** (University of Calgary, Calgary, Alberta) *Glucagon-like peptide 1 protects against atrial fibrillation in type 2 diabetes mellitus via effects on atrial ion channels and fibrosis*	
10:15 – 10:30 AM	**Coffee Break**	Mezzanine

	<u>Symposium 17</u> **Current Concepts in Calcium Signaling and Genesis of Arrhythmias** **Session Chairs** **Darryl Davis** (University of Ottawa Heart Institute, Ottawa, Canada) **Ronald Vagnozzi** (University of Colorado Anschutz, Aurora, USA) ***Speakers:***	Provencher
10:30 – 10:50 AM	**<u>Grant Pierce Excellence in Science Lecture</u>** **1) Peter Backx** (York University, Toronto, Canada) *Atrial fibrillation induced by chronic atrial stretch requires myocardial-derived tumor necrosis factor (TNF)*	
10:50 – 11:10 AM	**2) Katharine Dibb** (The University of Manchester, Manchester, England) *Atrial t-tubule loss and RyR disorder in heart failure: consequences and recovery*	
11:10 – 11:30 AM	**3) Istvan Baczko** (University of Szeged, Szeged, Hungary) *Transgenic rabbit models of long QT syndromes: implications for arrhythmia prediction and testing novel therapeutic modalities*	
11:30 – 11:50 AM	**4) Yael Yaniv** (Technion - Israel Institute of Technology, Haifa, Israel) *Atrial function and dysfunction: An age perspective*	
11:50 – 12:10 PM	**5) Glen Tibbits** (Simon Fraser University, Burnaby, Canada) *The role of SK ion channel variants and atrial fibrillation*	

	Symposium 18 **Cardiac Signaling in Genetic Diseases** **Session Chairs** **Larry Fliegel** (University of Alberta, Edmonton, Canada) **Jessica Pfleger** (Virginia Tech University, Virginia, USA) ***Speakers:***	Gateway/Tache
10:30 – 10:50 AM	**James Willerson Excellence in Science Lecture** **1) Buddhadeb Dawn** (University of Nevada, Las Vegas, USA) *Reparative potential of discarded materials*	
10:50 – 11:10 AM	**Jawahar (Jay) Mehta Clinical Scientist Award Lecture** **2) Ali Marian** (University of Texas Health Sciences Center, Houston, USA) *Desmoplakin – associated cardiomyopathies*	
11:10 – 11:30 AM	**3) Yajing Wang** (Thomas Jefferson University, Philadelphia, USA) *Decoding Pathologic Communications between Ischemic Cardiomyocytes and Adipocytes*	
11:30 – 11:50 AM	**4) Xin-Liang Ma** (Thomas Jefferson University, Philadelphia, USA) Targeting Adiponectin Receptor 1 Phosphorylation against Ischemic Heart Failure	
11:50 – 12:10 PM	**5) Leslie Leinwand** (University of Colorado Boulder, Boulder, USA) *Targeting the Sarcomere in Genetic Diseases of Heart and Skeletal Muscle*	

	<u>Symposium 19</u> **Prevention of Heart Disease** **Session Chairs** **Amarjit Arneja** (Vancouver, Canada) **Anureet Shah** (California State University, Los Angeles, USA) ***Speakers:***	LaVerendrye
10:30 – 10:50 AM	**1) Rakesh Kukreja** (Virginia Commonwealth University School of Medicine, Richmond, USA) *Beyond Erectile Dysfunction - Phosphodiesterase 5 Inhibitors in Cardioprotection and Other Clinical Disorders*	
10:50 – 11:10 AM	**2) Melchior Lima** (Federal University of Espirito Santo, Vitoria, Brazil) *Vascular reactivity in no-touch technique of harvesting of the saphenous veins in CABG – a potential role of perivascular fat on graft vasoactivity.*	
11:10 – 11:30 AM	**3) Anureet Shah** (California State University, Los Angeles, USA) *Effectiveness of some vitamins in the prevention of cardiovascular disease*	
11:30 – 11:50 AM	**4) Mukesh Nandave** (Delhi Pharmaceutical Sciences and Research University, New Delhi, India) *Repurposing of Drugs for Myocardial Ischemia from an Academic Perspective*	
11:50 – 12:10 PM	**5) Pram Tappia** (Asper Clinical Institute, Winnipeg, Canada) *Cardioprotection by dietary amino acids in diabetes*	

	<u>Symposium 20</u> **Cardiac Remodeling, Senescence and Cell Death** **Session Chairs** **Kishore Pasumarthi** (Dalhousie University, Halifax Canada) **Liming Pei** (Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA) ***Speakers:***	Concert Hall
10:30 – 10:50 AM	**1) Ghassan Bkaily** (University of Sherbrook, Sherbrook, Canada) *Short- and long-term effects of high insulin level in aging ventricular cells*	
10:50 – 11:10 AM	**2) Douglas Lewandowski** (Ohio State College of Medicine, Columbus, USA) *Cardioprotective versus adverse metabolic remodeling*	
11:10 – 11:30 AM	**3) Takashi Matsui** (University of Hawaii at Manoa, Honolulu, USA) *Ferroptosis in LV remodeling following acute myocardial infarction*	
11:30 – 11:50 AM	**4) Dinender Singla** (University of Central Florida, Orlando, USA) *BMP-7 attenuates Sarcopenia and Adverse Muscle Remodeling in Diabetic Mice via Alleviation of Inflammation and Pyroptosis*	
11:50 – 12:10 PM	**5) Katherine Yutzey** (Cincinnati Children's Hospital, Cincinnati, USA) *Molecular Mechanisms of Postnatal Cardiomyocyte Cell Cycle Arrest*	
12:45 – 1:45 PM	**Lunch**	Grand Ballroom
12:45 – 1:45 PM	**IACS World Section Council Meeting**	Salon A

	<u>Symposium 21</u> **Advances in Cardiovascular Medicine** **Session Chairs:** **Rimpy Dhingra** (University of Manitoba, Winnipeg, Canada) **Abhishek Mishra** (Bhopal, Madhya Pradesh, India) ***Speakers:***	Gateway/Tache
2:00 – 2:20 PM	**1) Harpal Buttar** (Health Canada and University of Ottawa, Ottawa, Canada) *Pathophysiology of atherosclerosis and hypertension: Preventive role of dietary interventions, physical activity and smoking cessation*	
2:20 – 2:40 PM	**2) Antoinette Blackman** (Instituto Cardiovascular Sao Francisco de Assis, Brasilia, Brazil) *Assessment of Autonomic nervous system in patients subclinical hypothyroidism*	
2:40 – 3:00 PM	**3) Gisel Diaz** (University of La Plata School of Sciences, La Plata, Argentina) *Cardiac pathologies and NHE1: toward drug repurposing*	
3:00 – 3:20 PM	**4) Henrique B Furtado** (Universidade Federal do Tocantins, Heart Surgery Institute, Palmas, Brazil) *Valvular Heart Surgery Update- Research bringing us Health and Happy*	
3:20 – 3:40 PM	**5) Paul Ganguly** (Alfaisal University, Riyadh, Saudi Arabia) *Cardiovascular sciences: Role of research in medical education*	

	Symposium 22 **Translational Medicine in Cardiovascular Disease** **Session Chairs** **Ajit Singh** (Victoria, Canada) **Cat Makarewich** (Cincinnati Children's Hospital, Cincinnati, USA) ***Speakers:***	LaVerendrye
2:00 – 2:20 PM	**Amarjit Arneja Distinguished Award Lecture** **1) Gavin Oudit** (University of Alberta, Edmonton, Canada) *The value of a tissue bank explanted human hearts. Insight into biology, pathogenesis and novel therapies*	
2:20 – 2:40 PM	**2) Devendra Agrawal** (Western University of Health Sciences, Pomona, USA) *TLR-4 Inhibition Attenuates Neointimal Hyperplasia and Plaque Vulnerability after Intimal Injury in the Carotid artery in Hypercholesterolemic Yucatan Microswine*	
2:40 – 3:00 PM	**3) Ashok Srivastava** (University of Montreal, Montreal, Canada) *Role of histone deacetylase 5 in angiotensin ii-induced egr-1 expression and hypertrophy in vascular smooth muscle cells*	
3:00 – 3:20 PM	**4) Madhu Anand-Srivastava** (University of Montreal, Montreal, Canada) *Sirtuin1 and regulation of blood pressure*	
3:20 – 3:40 PM	**5) Hugh Scully** (University of Toronto, Toronto, Canada) *Physicians as leaders in the new World of Healthcare*	
3:40 – 4:00 PM	**6) Amanda King** (Bay Medical Centre, Castries, Saint Lucia) *Lupus and cardiovascular disease*	

	<u>Symposium 23</u> **Cardiac Regeneration and Biomaterials** **Session Chairs** **Alireza Rafieerad** (University of Manitoba, Winnipeg, Canada) **Glen Tibbits** (Simon Fraser University, Burnaby, Canada) ***Speakers:***	Concert Hall
2:00 – 2:20 PM	**1) Rajasingh Johnson** (The University of Tennessee Health Science Center, Memphis, USA) *Non-invasively generated iPSC-derived cells for cardiovascular disease therapy*	
2:20 – 2:40 PM	**2) Timothy Kamp** (University of Wisconsin, Wisconsin, USA) *Human iPSC-derived Cardiac Progenitor Cells for Myocardial Repair*	
2:40 – 3:00 PM	**3) Charles Murry** (University of Washington, Washington, USA) *Regenerating the Human Heart with Stem Cells*	
3:00 – 3:20 PM	**4) James Martin** (Baylor College of Medicine, Houston, USA) *Hippo signaling in heart regeneration*	
3:20 – 3:40 PM	**5) Sanjiv Dhingra** (University of Manitoba, Winnipeg, Canada) *Allogeneic Stem Cells and Immunomodulatory Biomaterials for Cardiac Regeneration*	
3:40 – 4:00 PM	**6) Ren-Ke Li** (Toronto General Hospital Research Institute, Toronto, Canada) *Synergistic Effects of Conductive Biomaterial and Cardiomyocytes in Cardiac Graft to Improve Electrical Propagation and Synchronize Cell Contraction for Heart Repair*	
4:00 – 4:15 PM	Coffee Break	Mezzanine

	<u>Symposium 24</u> **Mitochondria, Cardiac Dysfunction and Protection** **Session Chairs** **Elissavet Kardami** (University of Manitoba, Winnipeg, Canada) **Nicole Purcell** (Huntington Medical Research Institutes, Pasadena, USA) ***Speakers:***	Provencher
4:15– 4:20 PM	**<u>Howard Morgan Distinguished Achievements Award Lecture</u>** **1) Junichi Sadoshima** (Rutgers New Jersey Medical School, New York, USA) *The role of thioredoxin 1 in the ischemic heart*	
4:20 – 4:40 PM	**2) Hossein Ardehali** (Northwestern University School of Medicine, Chicago, USA) *Role of mitochondrial binding of hexokinases in the development of HFpEF*	
4:40 – 5:00 PM	**3) Kika (Carmen) Sucharov** (University of Colorado Anschutz Medical Campus, Aurora, USA) *The secretome and its effects on pathologic remodeling and mitochondrial dysfunction*	
5:00 – 5:20 PM	**4) Federica del Monte** (Medical University of South Caroloina, Charleston, USA) *Molecular Diversity in Alzheimer's Cardiomyopathy*	
5:20 – 5:40 PM	**5) Delphine Baetz** (Claude Bernard University Lyon, Lyon, France) *Mild therapeutic hypothermia protects from acute and chronic renal ischemia-reperfusion injury*	

	<u>Symposium 25</u> **Advances in Cardiovascular Medicine** **Session Chairs** **Thomas Netticadan** (University of Manitoba, Winnipeg, Canada) **Glen Pyle** (University of Guelph, Guelph, Canada)	Gateway/Tache
4:00 - 4:20 PM	**1) Tami Martino** (University of Guelph, Guelph, Canada) *Benefits of Circadian Rhythms on Cardiovascular Disease and Recovery*	
4:20 – 4:40 PM	**2) Tobias Eckle** (University of Colorado Anschutz Medical Campus, Aurora, USA) *The Circadian-Hypoxia Link*	
4:40 – 5:00 PM	**3) Martin Young** (University of Alabama at Birmingham Alabama, Birmingham, USA) *Circadian Regulation of Cardiac Physiology and Pathology*	
5:00 – 5:20 PM	**4) Inna-Rabinovich-Nikitin** (University of Manitoba, Winnipeg, Canada) *Regulation of mitochondrial autophagy and cell survival by the circadian gene Clock in cardiac myocytes during ischemic stress*	
5:20 – 5:40 PM	**5) Srinivas Tipparaju** (University of South Florida, Tampa, USA) *Protecting the diabetic heart*	

	<u>Symposium 26</u> **Chromatin Remodeling/ER Stress Signaling** **Session Chairs** **John Seubert** (University of Alberta, Edmonton, Canada) **Joelle Trepanier** (University of Montreal, Montreal, Canada) ***Speakers:***	LaVerendrye
4:00 – 4:20 PM	**1) Kathleen C. Woulfe** (University of Colorado, Aurora, USA) *Acetylation and sarcomeric function*	
4:20 – 4:40 PM	**2) Suresh Tyagi** (University of Louisville School of Medicine, Louisville USA) *Epigenetic Mechanism of Growth Retardation During Development and Disease*	
4:40 – 5:00 PM	**3) Manuel Rosa-Garrido** (University of Alabama at Birmingham, Birmingham, USA) *Chromatin Structure Dynamics During Treatment of Cardiac Disease*	
5:00 – 5:20 PM	**4) Marek Michalak** (University of Alberta, Edmonton, Canada) *Non-canonical function of IRE1α links ER stress sensor to cardiac excitation-contraction (E-C) coupling*	

	<u>Symposium 27</u> **Mechanisms of Cardiac Signaling, Aging and Cardiomyopathy** **Session Chairs** **Lea Delbridge** (University of Melbourne, Melbourne, Australia) **Abhay D. Srivastava** (University of Manitoba, Winnipeg, Canada)	Concert Hall
4:00 – 4:20 PM	**1) John McDermott** (York University, Toronto, Canada) *The MEF2A Transcription Factor Interactome in Cardiomyocytes*	
4:20 – 4:40 PM	**2) Eric Thorin** (Montreal Heart Institute Research Center, Montreal, Canada) *Genes, aging, longevity…and then, senescence came along*	
4:40 – 5:00 PM	**3) Anthony Rosenzweig** (Harvard University, Cambridge, USA) *Lnc'ing Exercise to Cardiovascular Benefits*	
5:00 – 5:20 PM	**4) Izhak Kehat** (Technion Israel of Technology, Haifa, Israel) *Imaging of localized translation in cardiomyocytes*	
5:30 – 7:15 PM	**Poster Session 2 Reception**	Crystal Ballroom
7:30 – 11:00 PM	**Gala Dinner, Award Ceremonies and Closing Remarks**	Grand Ballroom
Friday, September 9, 2022		
	Departure	

Poster Session 1:
Wednesday September 7th 5:30-7:00 pm
Judges: Dr. Paul Ganguly and Dr. Asa Gustafasson

P001
Sex-dependent survivorship in periostin knockout mice following post-myocardial infarction.
Besher Abual'anaz[1,2,3], Sunil Rattan[1,2,3], Ian Dixon[1,2,3]
[1]Institute of Cardiovascular Sciences, Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [3]Rady Faculty of Health Sciences, Max Rady College of Medicine, Winnipeg, Canada

P002
Scleraxis' Role in Arterial Stiffness in a Mouse Model of Hypertension.
Danah Alhattab[1,2], Teri Moffat[1], Allison Ledingham[1], Michael Czubryt[1,2]
[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada

P003
Nocturnal arterial hypotension and non-arteritic ischemic optic neuropathy: a Meta-Analysis study.
Antoinette Blackman[1,2], Nubia Faria[3], Matheus Moreira[4], Isabella Domingos[5], Marcelo Lopes[6], Natalia Barros[5]
[1]Centro Univeritário de Brasilia CEUB, Brasilia, Brazil. [2]Instituto Cardiovascular São Franciso de Assis, Belo Horizonte, Brazil. [3]Centro Universitário de Brasilia -CEUB, Brasilia, Brazil. [4]Universidade Federal do Rio Grande do Norte - UFRN, Natal, Brazil. [5]Centro Universitário de Brasilia - CEUB, Brasilia, Brazil. [6]Centro Universitário de Brasilia, Brasilia, Brazil

P004
Scleraxis is Required for Induction of GLS1 Expression in Cardiac Myofibroblasts.
Sikta Chattopadhyaya[1,2], Raghu S. Nagalingam[1,2], D. Allison Ledingham[1], Teri L. Moffatt[1], Danah S. Al-Hattab[1,2], Pavit Narhan[1], Matthew T. Stecy[1], Kimberley A. O'Hara[1], Michael P. Czubryt[1,2]
[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

P005
Understanding the role of Adenosine 2B receptor in macrophages.
Fatima Deuna, Peisan Lew, Robin da Silva
University of Manitoba, Winnipeg, Canada

P006

Sarco(endo)plasmic reticulum membrane protein REEP5 regulates subcellular structure and function in the heart.

Michelle Di Paola[1,2], Uros Kuzmanov[1,2], Cristine J. Reitz[1,2], Allen C.T. Teng[1,2], Anthony O. Gramolini[1,2]
[1]Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada. [2]Translational Biology and Engineering Program, Ted Rogers Centre for Heart Research, Toronto, Canada

P007

Cardiac remodeling induced by early postnatal abdominal aorta constriction in rats: sex differences in heart function and geometry.

Jaroslav Hrdlicka[1], Veronika Olejnickova[2,3], Frantisek Papousek[2], Milana Peskova[2], Eva Zabrodska[4], Jan Neckar[2]
[1]Laboratory of Developmental Cardiology, Institute of Physiology, Prague, Czech Republic. [2]Laboratory of Developmental Cardiology, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic. [3]Institute of Anatomy, First Faculty of Medicine, Charles University, Prague, Czech Republic. [4]nstitute of Anatomy, First Faculty of Medicine, Charles University, Prague, Czech Republic

P008

Angiogenic and cardiac reparative effects of endothelial colony forming cells derived exosomes in myocardial infarction.

Anshul Jadli, Karina Gomes, Ananya Parasor, Noura Ballasy, Monica Surti, Darrell Belke, Methsala Wijesuriya, Paul Fedak, Vaibhav Patel
University of Calgary, Calgary, Canada

P009

Defining the role of DHHC3 and DHHC7 in cardiac stress signaling.

Tanya Baldwin[1], Matthew Brody[2], Yasuhide Kuwabara[1], Weiqi Zhang[3], Jeffery Molkentin[1]
[1]Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [2]University of Michigan, Ann Arbor, USA. [3]University of Munster, Munster, Germany

P010

ATF6 Regulates ANP Secretion and Endocrine Function of Atrial Myocytes.

Erik A Blackwood[1], Alina S Bilal[1], Donna J Thuerauf[2], Alice Zemljic-Harpf[3], Scott A Hahn[1], Sean N Noudali[1], Hemal H Patel[3], Christopher C Glembotski[1]
[1]University of Arizona College of Medicine – Phoenix, Phoenix, USA. [2]San Diego State University, San Diego, USA. [3]University of California San Diego, San Diego, USA

P011
Myocardial protein citrullination as a novel mechanism of sex-specific cardiac aging.
Aykhan Yusifov[1], Kathleen Woulfe[2], Brian Cherrington[1], Danielle Bruns[1]
[1]University of Wyoming, Laramie, USA. [2]University Colorado-Anschutz Medical Campus, Aurora, USA

P012
p38 MAPK signaling in mononucleated ventricular cardiomyocytes translates to the acquisition of an inflammasome phenotype and concomitant inhibition of cell cycle re-entry.
Mariana Kebbe[1,2], Patrice Naud[1], Angelo Calderone[1,2]
[1]Montreal Heart Institute, Montreal, Canada. [2]Department of Pharmacology and Physiology, Universite de Montreal, Montreal, Canada

P013
Early Renal Denervation Protects Against Diastolic Dysfunction in Rodent Model of Heart Failure with Preserved Ejection Fraction.
Jake Doiron[1,2], Zhen Li[1,2], Kyle LaPenna[1,2], Daniel Kapusta[1,2], Traci Goodchild[1,2], David Lefer[1,2]
[1]Louisiana State University Health Sciences Center New Orleans, New Orleans, USA. [2]Cardiovascular Center of Excellence, New Orleans, USA

P014
Angiotensin II-induced cardiac hypertrophic remodeling is attenuated by inhibition of Peptidyl arginine deiminases (PADs) activity.
Takeshi Ijichi[1], Rakhi Pandey[2], Niveda Sundararaman[2], Martin Thomas[3], Etai Koronyo[4], Jonathan Kirk[3], Eduardo Marbán[2], Jennifer Van Eyk[2], Justyna Fert-Bober[2]
[1]Tokai University School of Medicine, Tokai, Japan. [2]Cedars Sinai, Los Angeles, USA. [3]Loyola University, Chicago, USA. [4]UC Berkeley, Berkeley, USA

P015
The Effects of Daily Swim Exercise Duration on Cardiac Responses and Atrial Fibrillation.
Renée Gorman, Nazary Polidovitch, Robert Lakin, Ryan Debi, Jhonny Mendoza, Peter Backx
York University, Toronto, Canada

P016
Exploring sarcoplasmic reticulum calcium cycling as a thermogenic mechanism in brown adipose tissue.
Adrienne R. Guarnieri, Sarah R. Anthony, Michael Tranter
University of Cincinnati, Cincinnati, USA

P017

Next-generation α-1-adrenergic receptor antagonists without cardiotoxic side-effects for the treatment of hypertension.

Chastity L. Healy, Ingrid Rodriguez Aragon, Yuk Y. Sham, Timothy D. O'Connell
University of Minnesota, Minneapolis, USA

Judges: Dr. Eric Thorin and Dr. Carmen Sucharov

P018

Lichen *Xanthoparmelia stenophylla* ameliorates doxorubicin-induced cardiotoxicity in rats.

Jovana Jeremic[1], Aleksandar Kocovic[1], Slobodanka Mitrovic[1], Jasmina Sretenovic[1], Nedeljko Manojlovic[1], Perica Vasiljevic[2], Marijana Andjic[1], Nevena Draginic[1,3], Dejan Baskic[1], Vladimir Zivkovic[1], Vladimir Jakovljevic[1,3]
[1]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]Faculty of Sciences and Mathematics, University of Niš, Nis, Serbia. [3]1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation

P019

Protective effect of molecular hydrogen on the heart and the whole body in simulated heart transplantation.

Branislav Kura[1], Barbora Kalocayova[1], Vladan Hudec[2], Matej Ondrusek[2], Ivo Gasparovic[2], Rastislav Sramaty[2], Jaroslav Luptak[2], Michal Hulman[2], Jan Slezak[1]
[1]Centre of Experimental Medicine, Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovakia. [2]Department of Cardiac Surgery, Faculty of Medicine, National Institute of Cardiovascular Diseases, Comenius University, Bratislava, Slovakia

P020

Activation of ATF6α signaling pathway in doxorubicin associated cardiomyopathy and its attenuation by IL-10.

Akshi Malik[1], Ashim K Bagchi[2], Davinder S Jassal[3], Pawan K Singal[1]
[1]Institute of Cardiovascular Sciences, department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, USA. [3]Institute of Cardiovascular Sciences, department of Internal Medicine, University of Manitoba, Winnipeg, USA

P021
Potential of cyanidin 3-glucoside in the prevention of cardiovascular disease.
Basma Aloud[1], Pema Raj[1], Jason McCallum[2], Chris Kirby[2], Heather Blewett[1], Jeffrey Wigle[3], Thomas Netticadan[1]
[1]Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, Canada. [2]Charlottetown Research and Development Centre, Charlottetown, Canada. [3]Institute of Cardiovascular Sciences, Winnipeg, Canada

P022
Alternative Splicing Targets Death Gene Bnip3 to Endoplasmic Reticulum for Cell Survival.
Inna Rabinovich-Nikitin, Hongying Gang, Rimpy Dhingra, Vicky Margulets, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

P023
Dual Role of Embryonic Stem Cell Derived Exosomes in Treatment of Triple Negative Breast Cancer and Improvement of Cardiac Function.
Arun Samidurai[1], Anindita Das[1], Donatas Kraskauskas[1], Karthikeya Bhoopathi[1], Bei Zhang[1], Amy Olex[1], Jinze Liu[1], Bin Hu[1], Jennifer Koblinski[1], Dinender Singla[2], Rakesh Kukreja[1]
[1]Virginia Commonwealth University, Richmond, USA. [2]University of Central Florida, Orlando, USA

P024
Reduced cyclooxygenase 2 levels result in the loss of immunoprivilege of allogeneic mesenchymal stem cells following hypoxia.
Niketa Sareen[1], Ejlal Abu-El-Rub[1], Hania I. Ammar[2], Weiang Yan[1], Glen Lester Sequiera[1], Meenal Moudgil[1], Elika Verma[1], Sanjiv Dhingra[1]
[1]University of Manitoba, Winnipeg, Canada. [2]Cairo University, Cairo, Egypt

P025
The effects of Amiodarone and Dronedarone on heart function and redox balance of isolated hypertensive rat hearts.
Ivan Srejovic[1,2], Stefan Simovic[3], Jovana Jeremic[4], Vladimir Zivkovic[1,2], Maja Nikolic[1], Slobodanka Mitrovic[5], Vladimir Jakovljevic[1,6]
[1]University of Kragujevac, Faculty of Medical Sciences, Department of Physiology, Kragujevac, Serbia. [2]I.M. Sechenov First Moscow State Medical University, Department of Pharmacology of the Institute of Biodesign and Complex System Modelling, Moscow, Russian Federation. [3]University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia. [4]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia. [5]University of Kragujevac, Faculty of Medical Sciences, Department of Pathology, Kragujevac, Serbia. [6]I.M. Sechenov First Moscow State Medical University, Department of Human Pathology, Moscow, Russian Federation

P026

Cardiac-specific branched-chain aminotransferase (BCATm$^{Cardiac-/-}$) deletion exacerbates adverse cardiac hypertrophy in heart failure.

Qutuba Karwi[1], Liyan Zhang[1], Cory Wagg[1], Keshav Gopal[2], Kim Ho[1], Jody Levasseur[1], Qiuyu Sun[1], Sai Panidarapu[1], John Ussher[2], Jason Dyck[1], Gary Lopaschuk[1]
[1]Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada. [2]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

P027

CD38 inhibition decreases myocardial glucose utilization and impairs post-ischemic recovery without altering protein acetylation status.

Ezra Ketema, Qutuba G. Karwi, Liyan Zhang, Gary D. Lopaschuk
Cardiovascular Research Centre, Department of Pediatrics, University of Alberta, Edmonton, Canada

P028

Transcriptional Blueprint of the Postnatal Atrioventricular Conduction system.

Yena Oh[1,2], Rimshah Abid[1,2], David Cook[2,3], Jin G. Park[4], Barbara Vanderhyden[2,3], Nikhil Munshi[5], Kyoung-Han Kim[1,2]
[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada. [3]Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, Canada. [4]Virginia G. Piper Center for Personalized Diagnostics, Biodesign Institute, Arizona State University, Tempe, USA. [5]Center for Regenerative Science and Medicine, UT Southwestern Medical Center, Dallas, USA

P029

Chamber-specific atrial and ventricular structural and arrhythmogenic remodeling in response to chronic volume overload in a mouse model of aortic regurgitation.

Robert Lakin[1], Nazari Polidovitch[1], Xueyan Liu[1,2], Ryan Debi[1], Parashar Bhatt[1], Simona Yakobov[1], Peter Backx[1]
[1]York University, Toronto, Canada. [2]China-Japan Union Hospital of Jilin University, Changchun, China

P030

Nitrosothiol Signaling Dysfunction is Driven by GSNOR in the Pathogenesis of Heart Failure with Preserved Ejection Fraction.

Kyle LaPenna[1], Zhen Li[1], Jake Doiron[1], Thomas Sharp[1], Huijing Xia[1], Karl Moles[1], Amelia Haydel[1], Timothy Allerton[2], Ravi Patel[3], Sanjiv Shah[3], Traci Goodchild[1], David Lefer[1]
[1]LSU Health Sciences Center, New Orleans, USA. [2]Pennington Biomedical Research Center, Baton Rouge, USA. [3]Northwestern University Feinberg School of Medicine, Chicago, USA

P031
PSAT1 Promotes Serine Synthesis Pathway and Cardiac Regeneration Post-Myocardial Infarction.

Ajit Magadum[1], Vandana Mallaredy[1], Rajika Roy[1], Zhongjian Cheng[1], Vagner O C Rigaud[1], Celio X.C. Santos[2], Chunlin Wang[1], Mohsin Khan[3], Ajay Shah[2], Walter Koch[3], Raj Kishore[3]
[1]Center for Translational Medicine, Lewis Katz School of Medicine, Temple University., Philadelphia, USA. [2]King's College London British Heart Foundation Centre, School of Cardiovascular Medicine & Sciences, London, USA. [3]Center for Translational Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, USA

P032
Transforming growth factor β-dependent regulation of cardiomyocyte maturation.

Rachel Minerath[1], Kelly Grimes[1], Michelle Sargent[1], Allen York[1], Yasuhide Kuwabara[1], Anthony Saviola[2], Christina Alfieri[1], Kirk Hansen[2], Katherine Yutzey[1], Jeffery Molkentin[1]
[1]CCHMC, Cincinnati, USA. [2]UC Denver, Aurora, USA

P033
Enalapril reduces frailty and increases MAPK expression in heart and muscle in aging male mice, even when drug is deprescribed.

Manish Mishra[1], Alice E Kane[2], Susan E. Howlett[1]
[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA

P034
Exploring the role of metformin on cardiac function in PAI-1 deficient mice.

Serena Pulente[1,2], Sweta Gupta[3], Magdalena Lewandowski[3], Amy Shapiro[3], Kyoung-Han Han[1,1], Erin Mulvihill[2,4]
[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]University of Ottawa, Ottawa, Canada. [3]Indiana Hemophilia & Thrombosis Center, Indianapolis, USA. [4]Univeristy of Ottawa Heart Institute, Ottawa, Canada

Judges: Dr. Robert Rose and Dr. Maha Abdellatif

P035
Determining the Role of Zeb1 and Zeb2 in Cardiac Fibroblast Activation.

Rohini Suresh[1,2], Jessica McBride[1,2], Nicolas Leclerc[1,2], Jeffrey Wigle[1,2]
[1]Department of Biochemistry and Medical Genetics, Winnipeg, Canada. [2]Institute of Cardiovascular Sciences, St. Boniface Hosp. Albrechtsen Res Centre, Winnipeg, Canada

P036
Curcumin mitigates heart function, oxidative stress and proinflammatory cytokine levels in rats with rheumatoid arthritis.

Tamara Nikolic Turnic[1,2], Andjela Milojevic-Samanovic[1], Katarina Djordjevic[1], Igor Ilic[3], Marko Folic[1], Vladimir Zivkovic[1], Ivan Srejovic[1], Jovana Jeremic[1], Nevena Jeremic[1], Vladimir Jakovljevic[1,2]
[1]University of Kragujevac, Kragujevac, Serbia. [2]IM Sechenov University, Moscow, Russian Federation. [3]Clinical Center Kragujevac, Kragujevac, Serbia

P037
Identification of Fkbp8 as a Novel Interacting Partner to PLN in Mouse Hearts.

Ava Vandenbelt[1,2], Allen Teng[1,3], Marjan Tavassoli[1,3], Anthony Gramolini[1,3]
[1]Translational Biology and Engineering Program, Ted Rogers Centre for Heart Research, Toronto, Canada. [2]Faculty of Kinesiology & Physical Education, University of Toronto, Toronto, Canada. [3]Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada

P038
Lipidomic predictors of coronary no reflow.

Arun Surendran[1,2,3], Umar Ismail[4], Negar Atefi[1], Ashim K Bagchi[4], Pawan K Singal[4] Ashish Shah[4,5], Michel Aliani[2], and Amir Ravandi[1,4,5]
[1]Cardiovascular Lipidomics Laboratory, St. Boniface Hospital, Albrechtsen Research Centre, Winnipeg, Canada, [2]Faculty of Agricultural and Food Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada, [3]Mass Spectrometry and Proteomics Core Facility, Rajiv Gandhi Centre for Biotechnology, Kerala, India, [4]Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada, [5]Section of Cardiology, Department of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

P039
One-year outcomes in patients who underwent coronary intravascular shockwave lithotripsy for highly-calcified coronary lesions.

Evan J Wiens[1,2], Sarah Gibbs[1], Kunal Minhas[1,2]
[1]Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, [2]Section of Cardiology, University of Manitoba, Winnipeg, Manitoba

P040
Resting and exercise-augmented hemodynamic evaluation in heart failure patients with preserved ejection fraction.

Olivia Pieroni, Emelissa Valcourt, Karen Alvarez, Mohammad Zahurul Islam, Amir Ravandi, Shelly Zieroth, Ashish H Shah
St. Boniface Hospital; University of Manitoba, Winnipeg, MB, Canada

P041
Single nucleus transcriptomics: Apical resection prolonged cardiomyocyte regenerative window in neonatal swine hearts.
Yuji Nakada
The University of Alabama, Birmingham, USA

P042
HuR-dependent expression of Wisp1 is necessary for TGFβ-induced cardiac myofibroblast activity.
Sharon Parkins[1], Lisa Green[1], Sarah R Anthony[1], Adrienne Guarnieri[1], subhan Khalid[2], Onur Kanisicak[1], Mike Tranter[1]
[1]University of Cincinnati collage of medicine, Cincinnati, USA. [2]University of Cincinnati, Cincinnati, USA

P043
Study of L-glutamine supplementation on function and metabolism of the diabetic heart and muscle in mice.
Anna Pfister[1,2], Michelle Wintzinger[2], Karen Miz[2], Manoj Panta[2], Mattia Quattrocelli[2,3]
[1]North Carolina State University, Raleigh, USA. [2]Division of Molecular Cardiovascular Biology, Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, USA

P044
Perinuclear Ryanodine Receptors Modulate Calcineurin Mediated Gene Expression.
Sofia Possidento[1], Moriah Turcotte, Ph.D.[1], Hrishikesh Thakur, MS, M.Sc.[2], Michael Kapiloff, M.D., Ph.D.[2], Kimberly Dodge-Kafka, Ph.D.[1]
[1]University of Connecticut Health Center, Farmington, USA. [2]Stanford University, Stanford, USA

P045
Crossing a Fine Line: Disrupted intracellular calcium handling in the myocardium of a mouse model of perimenopause.
Ciara Barry[1], Sarah Rouhana[1], Jessica Braun[2], Mia Geromella[2], Val Fajardo[2], Glen Pyle[1]
[1]University of Guelph, Guelph, Canada. [2]Brock University, St. Catharines, Canada

P046
Integrative proteomic and phosphoproteomic analysis identifies etiology-specific phosphorylation patterns in the failing human heart.
Cristine Reitz[1], Marjan Tavassoli[1], Da Hye Kim[1], Sina Hadipour-Lakmehsari[1], Saumya Shah[2], Allen Teng[1], Andrew Emili[3], Gavin Oudit[2], Uros Kuzmanov[1], Anthony Gramolini[1]
[1]University of Toronto, Department of Physiology, Ted Rogers Centre for Heart Research, Toronto, Canada. [2]University of Alberta, Department of Medicine, Edmonton, Canada. [3]Boston University, Department of Biology and Biochemistry, Boston, USA

P047
The Pause Before the Storm: Identifying Cardiac Molecular Changes in a Mouse Model of Menopause.

Sarah Rouhana[1], Ciara Barry[1], Jessica Braun[2], Mia Geromella[2], Val Fajardo[2], W Glen Pyle[1]
[1]Laboratory of Molecular Cardiology, Department of Biomedical Sciences, University of Guelph, Guelph, Canada. [2]Department of Kinesiology and Centre for Bone and Muscle Health, Brock University, St. Catharines, Canada

P048
Cardiac glucose oxidation is impaired in heart failure with preserved ejection fraction (HFpEF).

Qiuyu Sun, Berna Güven, Cory Wagg, Amanda Oliveira, Heidi Silver, Ander Arana, Brandon Chen, Qutuba Karwi, Faqi Wang, Liyan Zhang, Jason Dyck, Gavin Oudit, Gary Lopaschuk
Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

P049
Tmem65 is critical for the structure and function of the intercalated discs in mouse hearts.

Allen Teng[1], Liyang Gu[1], Michelle Di Paola[1], Robert Lakin[2], Zachary Williams[3], Aaron Au[1], Wenliang Chen[2], Neal Callaghan[1], Farigol Hakem-Zadeh[1], Yu-Qing Zhou[1], Meena Fatah[4], Diptendu Chatterjee[4], Jane Jourdan[3], Jake Liu[1], Craig Simmons[1], Thomas Kislinger[1], Christopher Yip[1], Peter Backx[2], Robert Gourdie[3], Robert Hamilton[4], Anthony Gramolini[1]
[1]University of Toronto, Toronto, Canada. [2]York University, Toronto, Canada. [3]Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, USA. [4]Hospital for Sick Children, Toronto, Canada

P050
Elucidating the molecular mechanisms and cellular specificity of HDAC inhibitor efficacy in diastolic dysfunction.

Joshua Travers[1], Sara Wennersten[1], Marcello Rubino[1], Jessica Schwisow[1], Eric Jonas[1], Rui Fu[1], Ryan Sheridan[1], Harrison Smith[2], Rachel Hirsch[2], Lauren Vanderlinden[3], Ying-Hsi Lin[1], Ilaria Ferrari[1], Doron Regev[1], Kimberly Demos-Davies[1], Rushita Bagchi[1], Evgenia Dobrinskikh[1], Maria Cavasin[1], Luisa Mestroni[1], Christian Steinkuhler[4], Charles Lin[5], Steven Houser[6], Amrut Ambardekar[1], Brisa Pena[1], Kathleen Woulfe[1], Maggie Lam[1], Ronald Vagnozzi[1], Michael Bristow[1], Timothy McKinsey[1]
[1]University of Colorado Anschutz Medical Campus, Aurora, USA. [2]Baylor College of Medicine, Houston, USA. [3]Colorado School of Public Health, Aurora, USA. [4]Italfarmaco SpA, Milan, Italy. [5]Kronos Bio, San Mateo, USA. [6]Temple University, Philadelphia, USA

P051

Perinuclear β-Adrenergic Receptors are Necessary and Sufficient to Promote Cardiac Hypertrophy.

Moriah Turcotte, Ph.D[1], Hrishikesh Thakur, MS, M.Sc.[2], Michael Kapiloff, M.D., Ph.D[2], Kimberly Dodge-Kafka, Ph.D[1]
[1]University of Connecticut Health Center, Farmington, USA. [2]Stanford University, Stanford, USA

P052

Loss of free fatty acid receptor 4 impairs left ventricular functional recovery after ischemia reperfusion.

Michael Zhang[1], Sergey Karachenets[2], Chastity Healcy[2], Timothy O'Connell[2]
[1]University of Minnesota, Minneapolis, USA. [2]University of Minnesota, Minneapolis, USA

Poster Session 2:
Thursday September 8th 5:30-7:15 pm
Judges: Dr. Ian Dixon and Dr. Zamaneh Kassiri

P053
GENE THERAPY ENCODING CELL CYCLE FACTORS IMPROVES CARDIAC FUNCTION IN A CHRONIC HEART FAILURE RAT MODEL.

Riham Abouleisa[1], Abou-Bakr Salama[1], Qinghui Ou[1], Xian-Liang Tang[1], Hania Abdelhafez[1], Amie Woolard[2], Dana Hammouri[1], Sarah Cayton[3], Roberto Bolli[1], Tamer Mohamed[1]

[1]University of Louisville, Louisville, USA. [2]Georgetown college, Georgetown, USA. [3]Transylvania University, Lexington, USA

P054
MXene quantum dots promote maturation of induced pluripotent stem cells derived cardiomyocytes.

Keshav Narayan Alagarsamy, Leena Regi Saleth, Alireza Rafieerad, Abhay Srivastava, Weiang Yan, Niketa Sareen, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

P055
CANFLAX: Can flaxseed “milk” prevent broken hearts in women with breast cancer?

Vibhuti Arya[1], Lana Mackic[1], Sara Telles-Langdon[1], David Y.C. Cheung[1], Paris R. Haasbeek[2], Danielle Desautles[3], Vallerie Gordon[3], Jeffrey Graham[3], Susan Green[3], Debjani Grenier[3], Christina Kim[3], Saroj Niraula[3], Maclean Thiessen[3], Marshall Pitz[3], Davinder S. Jassal[1,3,4]

[1]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Faculty of Science, University of Manitoba, Winnipeg, Canada. [3]Section of Oncology, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada. [4]Section of Cardiology, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

P056
Lady’s bedstraw extract as a novel cytoprotective agent against doxorubicin-induced cardiotoxicity in rats.

Jovana Bradic[1], Jovana Jeremic[1], Vladimir Jakovljevic[2,3], Marijana Andjic[1], Marina Tomovic[1], Marina Nikolic[1]

[1]Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [3]Department of Human Pathology, 1st Moscow State Medical, University IM Sechenov, Moscow, Russian Federation

P057
Mitochondrial Autophagy and Cell Survival is Regulated by the Circadian Clock Gene in Cardiac Myocytes during Ischemic Stress.
Molly Crandall[1], Inna Rabinovich-Nikitin[1], Tami Martino[2], Lorrie Kirshenbaum[1]
[1]University of Manitoba, Winnipeg, Canada. [2]University of Guelph, Guelph, Canada

P058
NF-κB Signaling Regulates Mitochondrial Permeability Transition Pore Opening of Cardiac Myocytes via Cyclophilin D (CypD) Modulation.
Rimpy Dhingra, Matthew Guberman, Victoria Margulets, Floribeth Aguilar, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

P059
Dual Mitophagy and Necrosis Dependent Pathways Functionally Couple Mitochondrial Death protein Bnip3 to Doxorubicin Cardiomyopathy.
Matthew Guberman, Rimpy Dhingra, Victoria Margulets, Floribeth Aguilar, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

P060
Is DHA beneficial or not for your blood vessels: Concentration and growth state dependent effects of DHA on endothelial cells.
Shiqi Huang[1,2], Carla Taylor[1,2], Peter Zahradka[1,2]
[1]University of Manitoba, Winnipeg, Canada. [2]Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, Canada

P061
Adipose tissue expression of HuR modulates cardiac pathology via adipose tissue-derived extracellular vesicles.
Sarah Anthony, Adrienne Guarnieri, Lisa Green, Sam Slone, Rohan Desarapu, A. Phillip Owens, Onur Kanisicak, Michael Tranter
University of Cincinnati, Cincinnati, USA

P062
Chronic Testosterone Deficiency Increases Late Inward Sodium Current and Promotes Triggered Activity in Ventricular Myocytes from Aging Male Mice.
Shubham Banga[1], Manish Mishra[1], Susan Howlett[1,2]
[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Medicine (Geriatric Medicine), Dalhousie University, Halifax, Canada

P063

The Selenoprotein, VIMP, Selectively Regulates a Newly Defined Non-Canonical Form of Proteasomal Degradation at the ER to Modulate Cardiac Hypertrophy.

Erik Blackwood[1], Lauren MacDonnell[1], Donna Thuerauf[2], Alina Bilal[1], Christopher Glembotski[1]
[1]University of Arizona College of Medicine, Phoenix, USA. [2]San Diego State University, San Diego, USA

P064

Rapamycin treatment reveals a sexually dimorphic pattern of scar expansion of the infarcted adult rat heart; potential relationship between mTOR and K_{ATP} channels.

Aya Al-Katat[1], Lucie Parent[1,2], Maxime Lorenzini[1], Celine Fiset[1,3], Angelo Calderone[1,2]
[1]Montreal Heart Institute, Montreal, Canada. [2]Department of Pharmacology and Physiology, Universite de Montreal, Montreal, Canada. [3]Faculty of Pharmacy, Universite de Montreal, Montreal, Canada

P065

Characterizing the effects of βARKct-S670A mutation in mitochondrial mechanisms of heart failure pathophysiology.

Heidi Cho, Kimberly Ferrero, J. Kurt Chuprun, Erhe Gao, Walter Koch
Lewis Katz School of Medicine at Temple University, Philadelphia, USA

P066

Deficiency of 3-Mercaptopyruvate Sulfurtransferase Exacerbates Heart Failure with Preserved Ejection Fraction.

Jake Doiron[1,2], Zhen Li[1,2], Kyle LaPenna[1,2], David Lefer[1,2]
[1]Louisiana State University Health Sciences Center New Orleans, Department of Pharmacology, New Orleans, USA. [2]Cardiovascular Center of Excellence, New Orleans, USA

P067

Unique Mitochondrial Gene Profiles in Activated Cardiac Fibroblasts.

Alexandra Garvin[1], Joshua Talboom[2], Matthew De Both[2], Matthew Huentelman[2], Merry Lindsey[3], Taben Hale[1]
[1]University of Arizona College of Medicine, Phoenix, USA. [2]The Translational Genomics Research Institute, Phoenix, USA. [3]Meharry Medical College, Nashville, USA

P068
Identification of nuclear localization signal (NLS) in Rbm20 and its role in Rbm20 nucleocytoplasmic transport and the development of dilated cardiomyopathy (DCM).

Zachery Gregorich[1], Yanghai Zhang[1], Kavish Khinsar[1], Mohammad Abdullah Khan[1], Camila Urbano Braz[1], Yang Liu[1], Timothy Hacker[1], Henk Granzier[2], Wei Guo[1]
[1]University of Wisconsin-Madison, Madison, USA. [2]University of Arizona, Tucson, USA

P069
Histone Demethylase KDM5 Regulates Maturation of iPSC-Cardiac Myocytes.

Manisha Deogharia, Ali J Marian, Priyatansh Gurha
University of Texas Health Sciences Center at Houston, Houston, USA

Judges: Dr. Tim Kamp and Dr. Timothy McKinsey

P070
Therapeutic tools to increase energy expenditure and activate browning of white adipose tissue.

Nevena Jeremic[1,2], Marina Rankovic[3], Jovana Jeremic[3], Jovana Bradic[3], Ivan Srejovic[3], Slobodanka Mitrovic[3], Vladimir Jakovljevic[3,4]
[1]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation. [3]Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia. [4]Department of Human Pathology, 1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation

P071
IDENTIFYING SOCIAL FACTORS THAT MAY LIMIT EARLY DISCHARGE IN LOW-RISK ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION.

Sandeep Krishnan[1], Gabriella Niemcyzk[1], Christopher Parr[1], Yixiu Liu[2], Thang Nguyen[1], Lorraine Avery[3], John Ducas[1], Shuangbo Liu[1]
[1]Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada. [2]Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada. [3]Cardiac Sciences Manitoba, St. Boniface Hospital, Winnipeg, Canada

P072
Influence of oxime K870 and obidoxime on survival and cardiorespiratory parameters in rats poisoned with paraoxon.
Žana M. Maksimović[1], Ranko Škrbić[2], Miloš P. Stojiljković[2]

[1]Centre for Biomedical Research, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina. [2]Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina

P073
Early success and cost-effectiveness of a social media campaign to reduce pre-hospital delays in patients with possible acute coronary syndrome.
Harram Memon, Kirsten Marshall, Emily Czaplinski, Rob Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
St. Boniface Hospital, Winnipeg, Canada

P074
Delayed Symptom Onset-to-first Medical Contact in ST-segment Elevation Myocardial Infarction is Associated with Mortality.
David Nelson, Kirsten Marshall, Yixiu Liu, Robert Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
University of Manitoba, Winnipeg, Canada

P075
Factors Associated with Delay in STEMI Patients Seeking Medical Attention.
David Nelson, Kirsten Marshall, Yixiu Liu, Ashish Shah, Robert Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
University of Manitoba, Winnipeg, Canada

P076
Renal mechanism of preserved ejection fraction.
Sathnur Pushpakumar, Subir Kumar Juin, Irina Smolenkova, Suresh Tyagi
University of Louisville, Louisville, USA

P077
Immunoengineered Tantalum Carbide MXene Quantum Dots for Prevention of Transplant Vasculopathy.
Weiang Yan, Alireza Rafieerad, Keshav Narayan Alagarsamy, Abhay Srivastava, Niketa Sareen, Rakesh Arora, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

P078
Caloric restriction attenuates sinoatrial node dysfunction and atrial arrhythmogenesis in aged and frail female mice.
Lockhart Jamieson[1], Megan McRae[1], Robert Rose[2]
[1]Libin Cardiovascular Institute, Calgary, Canada. [2]Libin Cardiovascular Institute, Calgary, Canada

P079
Cardiomyocyte-derived signaling factors are responsible for heart-fat communication and mediate the development of cardiometabolic disease.
Stephanie Kereliuk, Kenneth Gresham, Walter Koch
Center for Translational Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, USA

P080
IRX5 is the major regulator of ventricular transmural heterogeneity in the healthy and diseased heart.
Saif Dababneh[1,2], Yena Oh[1,3], Julie Pan[1,3], Gavin Oudit[4,5,6], Peter Backx[7,8], Kyoung-Han Kim[1,3]
[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]MD/PhD Program, Faculty of Medicine, University of British Columbia, Vancouver, Canada. [3]Department of Cellular and Molecular Medicine, Facultu of Medicine, University of Ottawa, Ottawa, Canada. [4]Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada, Edmonton, Canada. [5]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada. [6]Department of Physiology, University of Alberta, Edmonton, Canada. [7]Department of Biology, Faculty of Science, York University, Toronto, Canada. [8]Toronto General Research Institute, University Health Network, Toronto, Canada

P081
Novel Synthetic Analogs of Omega-3 Fatty Acids Demonstrate Cardioprotective Properties.
Joshua Kranrod[1], Ahmed Darwesh[1], Wesam Bassiouni[1], Liye Fang[1], John Falck[2], John Seubert[1]
[1]University of Alberta, Edmonton, Canada. [2]UT Southwestern Medical Center, Dallas, USA

P082
Impaired S-Nitrosoglutathione Reductase (GSNOR) Activity Promotes Nitrosative Stress in Cardiometabolic HFpEF.
Kyle LaPenna[1], Zhen Li[1], Karl Moles[1], Jake Doiron[1], Thomas Sharp[1], Huijing Xia[1], Amelia Haydel[1], Timothy Allerton[2], Sanjiv Shah[3], Ravi Patel[3], Traci Goodchild[1], David Lefer[1]
[1]LSU Health Sciences Center, New Orleans, USA. [2]Pennington Biomedical Research Center, Baton Rouge, USA. [3]Northwestern School of Medicine, Chicago, USA

P083
Effects of Cardiac Deletion of Essential MCU Regulator (EMRE) in the Short and Long Term.
Hector Chapoy Villanueva, Jae Hwi Sung, Jackie Stevens, Peyton Nelson, Michael Zhang, Timothy O'Connell, DeWayne Townsend, Julia Liu
University of Minnesota, Minneapolis, USA

P084
The Role of Reactive Oxygen Species Modulator 1 (ROMO1) in the Heart.
Matthew Martens[1,2], Seyed Amirhossein Tabatabaei Dakhili[1], Claudia Holody[1], Heidi Silver[1,2], Mourad Ferdaoussi[1,2], Mihir Parikh[1,2], Helene Lemieux[1], Gavin Oudit[1,2], John Ussher[1], Robert Screaton[3,4], Jason Dyck[1,2]
[1]University of Alberta, Edmonton, Canada. [2]Cardiovascular Research Center, Edmonton, Canada. [3]University of Toronto, Toronto, Canada. [4]Sunnybrook Research Institute, Toronto, Canada

P085
Atrial Natriuretic Peptide promotes differentiation of Cx40 expressing cardiomyocytes by targeting cellular metabolic pathways.
Abhishek Mishra, Mahtab Tavasoli, Christopher McMaster, Kishore Pasumarthi
Dalhousie University, Halifax, Canada

P086
Impact of age and sex on the expression of common reference genes in ventricular muscle from aging C57BL/6 mice.
Manish Mishra[1], Susan E Howlett[2,3]
[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Pharmacology, Dalhousie University, Halifax, Canada. [3]Department of Medicine (Geriatric Medicine), Dalhousie University, Halifax, Canada

Judges: Dr. Vaibhav Patel and Dr. Timothy McKinsey

P087
Development of induced pluripotent stem cell based clinical trial selection platforms for patients with metabolic disorders.
Abhay Srivastava, Glen Lester Sequiera, Niketa Sareen, Weiang Yan, Keshav Narayan Alagarsamy, Elika Verma, Michel Aliani, Cheryl Rockman-Greenberg, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

P088

Is flaxseed equivalent and/or synergistic with ACE inhibition in the treatment of chemotherapy mediated cardiotoxicity?

Sara M. Telles-Langdon[1], Vibhuti Arya[1], David Y. C. Cheung[1], Paris R. Haasbeek[2], J. Alejandro Austria[1], James Thliveris[3], Pawan K. Singal[1], Davinder S. Jassal[1,4]
[1]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Faculty of Science, University of Manitoba, Winnipeg, Canada. [3]Department of Human Anatomy and Cell Sciences, University of Manitoba, Winnipeg, Canada. [4]Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

P089

Gender and racial differences in stress induced cardiomyopathy- etiology or biology?

Srikanth Vallurupalli
University of Arkansas for Medical Sciences, Little Rock, USA

P090

Immunoengineered Tantalum Carbide MXene Quantum Dots for Prevention of Transplant Vasculopathy.

Weiang Yan, Alireza Rafieerad, Keshav Narayan Alagarsamy, Abhay Srivastava, Niketa Sareen, Rakesh Arora, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

P091

Attenuation of oxidized phospholipid activity decreases infarct size in a porcine model of ischemia/reperfusion injury.

Aleksandra Stamenkovic[1,3], Grant N. Pierce[1,3], Joseph L. Witztum[2], Sotirios Tsimikas[2], Amir Ravandi[1,3]
[1]Institute of Cardiovascular Sciences, St. Boniface Hospital, [2]Division of Cardiovascular Sciences, University of California San Diego, La Jolla, CA, USA. [3]Departments of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada

P092

Resting and exercise-augmented hemodynamic evaluation in heart failure patients with reduced ejection fraction: Identification of outcome associated markers.

Emelissa Valcourt, Olivia Pieroni, Karen Alvarez, Mohammad Zahurul Islam, Hilary Bews, Amir Ravandi, Shelly Zieroth, Ashish H Shah
St. Boniface Hospital; University of Manitoba, Winnipeg, MB, Canada

P093

Cardiomyocyte Krüppel-Like Factor 5 accounts for myocardial ischemia/reperfusion injury.

Nikolaos Mylonas[1], Effimia Maria Zacharia[2], Christine J. Pol[3], Ioannis D. Kyriazis[3], Matthew Hoffman[3], Alycia Hildebrand[3], Ira J. Goldberg[4], Vincent W. Yang[5], Agnieszka B. Bialkowska[5], Erhe Gao[3], John Elrod[3], Konstantinos Drosatos[1]
[1]Metabolic Biology Laboratory, Department of Pharmacology & Systems Physiology, College of Medicine, University of Cincinnati, Cincinnati, OH, USA. [2]Cardiology Division of the Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. [3]Center for Translational Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA. [4]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA. [5]Department of Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA

P094

Expanding the GRK-5 Interactome.

Morgan Pantuck[1], Sudarsan Rajan[1], Eric Barr[1], Jessica Ibetti[1], Joanne Garbincius[1], Ryan Coleman[2], Kurt Chuprun[1], Walter Koch[1]
[1]Temple University, Philadelphia, USA. [2]University of Colorado Denver, Colorado, USA

P095

The Warburg effect is reduced in matured cardiomyocytes due primarily to a decrease in glycolysis

Kaya Persad, Donna Andre, Berna Guven, Madeline Houncaren, Liyan Zhang, Jalene Greenwood, Gary Lopaschuk
Cardiovascular Research Center, Department of Pediatrics, University of Alberta, Edmonton, Canada

P096

Ketones provide an extra source of fuel for the failing heart without impairing glucose oxidation.

Simran Pherwani, David Connolly, Qutuba Karwi, Michael Carr, Kim Ho, Cory Wagg, Qiuyu Sun, Liyan Zhang, Jody Levasseur, Heidi Silver, Jason Dyck, Gary Lopaschuk
Cardiovascular Research Centre, University of Alberta, Edmonton, Canada

P097

Homology model of free fatty acids receptor 4 and Gq in complex uncovers the pharmacology of endogenous fatty acid binding and receptor activation.

Sara Puccini, Timothy O'Connell, Yuk Sham
University of Minnesota, Minneapolis, USA

P098

Timing reconverts glucocorticoid pharmacology for heart metabolism through cardiomyocyte-autonomous mechanisms.

Michelle Wintzinger[1], Manoj Panta[1], Karen Miz[1], Ashok Prabakaran[1], Hima Bindu Durumutla[1,2], Mattia Quattrocelli[1,2]
[1]Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [2]University of Cincinnati, Cincinnati, USA

P099

Hydrogel-Based Intra-Pericardial Delivery of Endothelial Colony-Forming Cell-Derived Extracellular Vesicles Promotes Cardiac Repair Post-Myocardial Infarction.

Maia Ross[1,2], Anshul Jadli[1,2], Karina Gomes[1,2], Nadia DiMarzo[1,2], Darrel Belke[2,3], Paul Fedak[2,3], Vaibhav Patel[1,2]
[1]Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Canada. [2]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Canada. [3]Department of Cardiac Sciences, University of Calgary, Calgary, Canada

P100

Pharmacological targeting of circadian mechanism factor ROR improves cardiac repair and prevents heart failure.

Janan Shoja Doost, Mina Rasouli, Tarak Khatua, Reza Fatemi, Ifene David Festus, Tami A. Martino
University of Guelph, Guelph, Canada

P101

SMYD1a Protects Heart from Ischemic Injury by Regulating OPA1-Mediated Cristae Remodeling and Supercomplex Formation.

Marta Szulik[1], Steven Valdez[1], Maureen Walsh[1], Kathryn Davis[2], Ryan Bia[1], Emilee Horiuchi[3], Sean O'Very[1], Anil Laxman[1], Linda Sandaklie-Nicolova[1], Hanin Sheikh[1], Samuel Hickenlooper[1], Magnus Creed[1], Mickey Miller[1], Li Wang[1], June Gacia-Llana[1], Christopher Tracy[1], Stavros Drakos[1], Katsuhiko Funai[1], Dipayan Chaudhuri[1], Sihem Boudina[1], Sarah Franklin[1]
[1]University of Utah, Salt Lake City, USA. [2]University of Uttah, Salt Lake City, USA. [3]niversity of Utah, Salt Lake City, USA

P102

Sirtuin 3 (SIRT3) Prevents Doxorubicin Induced Dilated Cardiomyopathy: Investigating Mitochondrial Protein Acetylation, Cardiac Lipids and Metabolic Dysfunction.

Mateusz Tomczyk[1,2], Arun Surendran[3,2], Bo Xiang[1,2], Evan Abram[1,2], Prasoon Agarwal[1,2], Kyle Cheung[1,2], Stephanie Kereliuk[1,2], Qiang Tong[4,5], Amir Ravandi[3,2], Vernon Dolinsky[1,2]
[1]Children's Hospital Research Institute of Manitoba, Winnipeg, Canada. [2]University of Manitoba, Winnipeg, Canada. [3]St. Boniface Hospital Albrechtsen Research Center, Winnipeg, Canada. [4]Childrens Nutrition Research Center, Houston, USA. [5]Baylor College of Medicine, Houston, USA

P103

MAP kinase-activated protein kinase-2 (MK2) deficiency is cardioprotective in male and female mice following myocardial infarction.

Joëlle Trépanier[1,2], Fatiha Sahmi[2], Sophie Neblai[2], Marie-Ève Higgins[2], Colombe Roy[2], Joanne Vincent[2], Yanfen Shi[2], Billie Chouinard[2], Marie-Élaine Clavet-Lanthier[2], Martin Sirois[1,1], Matthias Gaestel[3], Jean-Claude Tardif[1,2], Bruce G. Allen[1,2]
[1]Université de Montréal, Montreal, Canada. [2]Montreal Heart Institute, Montreal, Canada. [3]Hannover Medical School, Hannover, Germany

P104

Variable ventricular cardiomyocyte expression of PAM is increased in dilated cardiomyopathy.

Elise Walsh[1], Dongwon Lee[2], Arun Patil[1], Tim Nieuwenhuis[1], Dan Arking[1], Marc Halushka[1]
[1]Johns Hopkins University School of Medicine, Baltimore, USA. [2]Boston Children's Hospital, Boston, USA

P105

Lack of endogenous high molecular weight FGF2 causes changes in gene expression associated with prevention of pressure overload-induced cardiac systolic dysfunction.

Navid Koleini, Barbara E Nickel, Raghu S Nagalingam, Natalie M Landry, Robert R Fandrich, Ian M Dixon, Michael Czubryt, Davinder Jassal, Peter A Cattini, Elissavet Kardami
Departments of Physiology and Pathophysiology and Human Anatomy and Cell Sciences, University of Manitoba, and Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, Canada

P106

FGF-2 exerts isoform-specific effects on cardiac mitochondrial permeability transition, mediated by a mitochondrial receptor and intra-mitochondrial signal transduction.

Wattamon Srisakuldee, Barbara E.Nickel, Robert R. Fandrich, Elissavet Kardami.
Departments of Physiology and Pathophysiology and Human Anatomy and Cell Sciences, University of Manitoba, and Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, Canada

P107

Examining the independent and combined effects of muscle strength and cardiorespiratory fitness on cardiovascular risk factors in older females: A secondary analysis of observational data.

Daniel Schwade[1,2], Kevin F. Boreskie[1,2], Jacqueline L. Hay[1,2], Kaitlin M Reilly[1,2], Marcyo Câmara[4], Eduardo C. Costa[3,4], Todd A. Duhamel[1,2]
[1]Faculty of Kinesiology and Recreation Management, University of Manitoba; [2]Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre. Winnipeg, Manitoba, Canada; [3]Graduate Program in Physical Education, Department of Physical Education; [4]Graduate Program in Health Sciences, Federal University of Rio Grande do Norte, Brazil

POSTER ABSTRACTS

Sex-dependent survivorship in periostin knockout mice following post-myocardial infarction.

Besher Abual'anaz[1,2,3], Sunil Rattan[1,2,3], Ian Dixon[1,2,3]
[1]Institute of Cardiovascular Sciences, Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [3]Rady Faculty of Health Sciences, Max Rady College of Medicine, Winnipeg, Canada

A major etiology of heart failure (HF) is ischemic heart disease with attendant myocardial infarction (MI) (1). HF is characterized by remodeling of the extracellular matrix (ECM) (2), and periostin (POSTN) is secreted by myofibroblasts, is a profibrotic matricellular protein which is known to be reexpressed in the adult heart after pathological insult as a secreted protein (3). Following MI, POSTN is secreted by the infarcted adult heart between days 3 and 4 in normal myocardium (4). POSTN is secreted from activated fibroblasts to support wound healing but also contributes to pathologic cardiac hypertrophy, interstitial fibrosis, and ventricular remodeling after HF (5). While it is known that male mice lacking the Postn gene have a low survival rate after MI as a result of ventricular rupture (4), the relative survivorship for female mice lacking POSTN has not been addressed. POSTN knockout (KO) mice were generated by homozygous knock-in of MerCreMer cDNA cassette (PostnMCM/MCM) to delete exon number 1 which encodes the signal peptide that promotes periostin synthesis (6). The deletion was confirmed by western blotting (WB), immunohistochemistry (IHC) and quantitative polymerase chain reaction (qPCR). Following the surgical induction of MI, the survivorship of female mice was 88% (+/- 6.5%) at 3 days post-MI compared to 22.2% (+/- 9.8%) in the male mice age-matched group (***P<0.001) by log-rank test, and the deaths of these mice were associated with left ventricular rupture. Furthermore, female survivorship was 68% (+/- 9.3%) at 7 days post-MI compared to 22.2% (+/- 0.0%) in males (***P<0.001). We extended the observation of groups to 14 days (for females only) and the survivorship remained unchanged at 68% (+/- 0.0%). For the first time, we show that female mice with POSTN KO experience significantly higher survivorship after MI vs male mice. We conclude that POSTN release in myocardium is required for acute cardiac wound healing and maintenance of the integrity of the left ventricular wall after MI, with a significantly higher dependency of POSTN expression in males vs females. Further investigation is required to shed light on the mechanism of the sex-dependency of POSTN KO and differential survivorship among the female and male mice.

Scleraxis' Role in Arterial Stiffness in a Mouse Model of Hypertension.

Danah Alhattab[1,2], Teri Moffat[1], Allison Ledingham[1], Michael Czubryt[1,2]
[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada

Background: Arterial stiffness is one of the most significant pathologies related to blood vessel dysfunction, and is considered an independent risk factor for cardiovascular mortality and morbidity in hypertension. It results in an impairment of vascular tone due to an increase in extracellular matrix proteins (ECM) and vascular smooth muscle proliferation within the vessel wall, which increase vascular stiffness and reduce lumen diameter. Scleraxis is a novel master regulator of cellular phenotype conversion. It induces fibroblast to myofibroblast phenotype conversion, resulting in fibrosis in the heart, and induces Epithelial-to-Mesenchymal Transition in development (1, 2). Our preliminary data has revealed that scleraxis is detectable in the arterial wall, and scleraxis expression is elevated in high pressure versus low pressure regions of vessels. Angiotensin II (AngII) induces high blood pressure and exerts critical roles affecting vascular function. It was reported to induce vascular fibrosis via activation of the transcription factor Smad3 in aortic vascular smooth muscle cells (3). Our lab has shown that Smad3 physically interacts with scleraxis, and critically requires scleraxis to drive TGFβ/Smad fibrotic signaling in cardiac fibroblasts (4). We thus hypothesized that scleraxis overexpression would be sufficient to exacerbate arterial stiffness in AngII-induced vessels.

Methods: Our model is smooth muscle-specific scleraxis overexpression mice, implanted with AngII or saline infusion pumps. Pressure myography to assess vascular geometry and the mechanical and functional responses of 3rd order mesenteric arteries. Gene expression and immunocytochemistry in aortas.

Results: Our data reveals that vascular stiffness is significantly increased in AngII-scleraxis mesenteric arteries through impairment of smooth muscle function and attenuated mechanical compliance. This increase in stiffness is relative to the increase in telemetry blood pressure measurements. Histological sections suggest a reduction of translamellar ECM accumulation and increased cellularity within the vessel wall of AngII-induced scleraxis overexpression aortas. In addition, contractile markers and ECM gene expression are both reduced in AngII-scleraxis aortas. In summary, scleraxis contributes to vascular stiffness by inducing vascular smooth muscle proliferation.

Conclusion: Our findings indicate that scleraxis overexpression exacerbate vascular stiffness of blood vessels in the AngII-induced hypertension model by stimulating VSMC plasticity, reducing ECM accumulation and altering blood pressure.

Nocturnal arterial hypotension and non-arteritic ischemic optic neuropathy: a Meta-Analysis study.

Antoinette Blackman[1,2], Nubia Faria[3], Matheus Moreira[4], Isabella Domingos[5], Marcelo Lopes[6], Natalia Barros[5]

[1]Centro Univeritário de Brasilia CEUB, Brasilia, Brazil. [2]Instituto Cardiovascular São Franciso de Assis, Belo Horizonte, Brazil. [3]Centro Universitário de Brasilia -CEUB, Brasilia, Brazil. [4]Universidade Federal do Rio Grande do Norte - UFRN, Natal, Brazil. [5]Centro Universitário de Brasilia - CEUB, Brasilia, Brazil. [6]Centro Universitário de Brasilia, Brasilia, Brazil

Background: Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic nerve injury and circulatory insufficiency has been considered related to nocturnal systemic hypotension (1). The main clinical feature is sudden, painless loss of vision on awaking from sleep. (1,2). The factors influencing the ocular blood flow are implicated in pathogenesis (4). It continues to be a debate, particularly in patients with sudden visual loss. Hence, the main objective of this systematic review and meta-analysis study was to evaluate the level of hypotension in NAION.

Methods: We performed a systematic review and meta-analysis to identify the level of diastolic blood pressure-related NAION in patients without previous ocular disease. PubMed, EMBASE, and Cochrane databases were searched.

Results: Three studies comprising 319 patients undergoing ambulatory blood pressure were included. Of the AION participants, 159 were compared to a control group. Overall, we found no statistically significant difference in diastolic blood pressure in NAION patients (RR 1,17 [-3.03, 3.37]; p = 0.59) and minimal mean nighttime diastolic blood pressure. There was a significant difference in minimal mean nighttime systolic blood pressure (RR -4.40 [-7.33, -1.47]; p = 0.003).

Conclusion: This meta-analysis suggests that, on ambulatory blood pressure measurement, patients with NAION did not have lower diastolic pressure. It represents the best current evidence. However, more RCTs are needed to consolidate these findings.

Scleraxis is Required for Induction of GLS1 Expression in Cardiac Myofibroblasts.

Sikta Chattopadhyaya[1,2], Raghu S. Nagalingam[1,2], D. Allison Ledingham[1], Teri L. Moffatt[1], Danah S. Al-Hattab[1,2], Pavit Narhan[1], Matthew T. Stecy[1], Kimberley A. O'Hara[1], Michael P. Czubryt[1,2]
[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Canada. [2]Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

Cardiac fibrosis is an aberrant wound healing process involving activation and conversion of fibroblasts to myofibroblasts and excessive deposition of extracellular matrix proteins which interfere with the systolic and diastolic function of the heart, leading to heart failure and death (1). Fibrosis is a very energy intensive process, and in liver and lung fibrosis, glutaminolysis has been reported to supply these increased energy demands (2-3). In contrast, little is known about how the metabolic requirements are met in cardiac fibrosis. The rate-limiting enzyme of the glutaminolysis pathway is glutaminase (GLS1), which catalyzes the conversion of glutamine to glutamate which then is converted to α-ketoglutarate to enter the TCA cycle to generate cellular energy. Here we examined if GLS1 plays a role in the activation of fibroblasts to myofibroblasts, and how its expression is regulated. Fibroblasts are activated by pro-fibrotic growth factors such as TGFβ and our results showed GLS1 expression, myofibroblast marker periostin expression as well as stress fiber formation were highly induced in myofibroblasts compared to fibroblasts and were significantly attenuated upon addition of GLS1 inhibitor CB-839. Our lab has previously shown that scleraxis is required for the transition of fibroblasts to myofibroblasts through transactivation of various profibrotic genes, thus we explored if scleraxis regulates GLS1 expression as well (4). While over-expression of scleraxis induced GLS1 expression by about 20 fold, downregulation or knockout of scleraxis attenuated GLS1 expression by 76% and 70% respectively, and TGFβ could not induce GLS1 expression in the absence of scleraxis. Further, both glutamine and glutamate cellular levels from wild type and scleraxis knockout fibroblasts treated with or without TGFβ also showed results that are consistent with elevated glutaminolysis after TGFβ treatment, and attenuation by scleraxis loss. Using luciferase assay, scleraxis was found to transactivate the human GLS1 promoter primarily by binding to an E-box (scleraxis putative binding site) and this was further validated by chromatin immunoprecipitation assay. These results suggest that scleraxis plays a major role in regulating GLS1 expression to in turn regulate energy production required for the conversion of fibroblasts to myofibroblasts, potentially contributing to cardiac fibrosis.

Understanding the role of Adenosine 2B receptor in macrophages.

Fatima Deuna, Peisan Lew, Robin da Silva
University of Manitoba, Winnipeg, Canada

Macrophages play a central role in atherosclerosis and heart disease. Infiltrating macrophages in the endothelium form foam cells which accumulate lipid, eventually leading to plaque formation known as atherosclerosis. Atherosclerosis is a chronic inflammatory condition exacerbated by the adhesion of activated monocytes that release proinflammatory molecules and lipoprotein binding proteoglycans, contributing to increased inflammation and lipid accumulation (1). A highly inflamed plaque is unstable and is prone to rupturing, which can promote obstructive clot formation. Inhibiting inflammation can decrease the instability of plaques to prevent adverse outcomes in cardiovascular disease (CVD). In a recent study, an inhibitor of the Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome, MCC950, has been used as a therapeutic in animal models of inflammatory diseases including CVD (2). NLRP3 inflammasomes are linked to induction of pyroptotic cell death which stimulates a greater immune response and inflammation. Adenosine receptors (ARs) have also been identified as potential targets for therapies in CVD. There are four G-protein coupled ARs that have been implicated in the regulation of various biological processes. In the cardiovascular system, adenosine is known to regulate vasoconstriction and vasodilation, as well as stimulate T-cell proliferation; but in macrophages, ARs are known to stimulate resolution of inflammation via IL-10 secretion (3). Despite what is known, the details of AR function are still unclear at this time. Recently my lab has found that knocking down the Adenosine 2B (A2B) receptor renders macrophages susceptible to pyroptosis, linking the A2B receptor to NLRP3 inflammasome activity and cell survival (4). This provides a novel target for the regulation of plaques in atherosclerosis, through the decrease of inflammation. In this research, we will determine the role that A2B receptors play in regulating the NLRP3 inflammasome in macrophages, promoting cell survival. Through manipulation of gene expression, knockdown, and overexpression, coimmunoprecipitation and proteomics, we aim to better understand how A2B receptors regulate macrophage function.

Sarco(endo)plasmic reticulum membrane protein REEP5 regulates subcellular structure and function in the heart.

Michelle Di Paola[1,2], Uros Kuzmanov[1,2], Cristine J. Reitz[1,2], Allen C.T. Teng[1,2], Anthony O. Gramolini[1,2]

[1]Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada. [2]Translational Biology and Engineering Program, Ted Rogers Centre for Heart Research, Toronto, Canada

Background: The sarco(endo)plasmic reticulum (SR/ER) is an essential regulator of many key cellular processes, especially those that play a role in the development and progression of cardiac disease. However, many aspects of its structural organization remain poorly defined. Receptor Expression Enhancing Protein 5 (REEP5) is a cardiac enriched SR/ER membrane protein, which regulates organization of the highly differentiated SR/ER network and responses to stress (1,2). Within the cardiomyocyte, depletion of Reep5 in vitro results in decreased muscle cell contraction, disrupted Ca2+ signaling and SR/ER luminal vacuolization. In zebrafish models, genetic knock-out of reep5 results in cardiac functional defects and reduced heart rate. These data show that REEP5 is essential for proper stabilization and maintenance of the SR/ER network (2,3).

Methods and Results: In vivo cardiac knock-down of Reep5 was achieved using recombinant adeno-associated virus serotype 9 (rAAV9)-mediated gene delivery into neonatal CD1 mice. Following knock-down, cardiac tissues or isolated adult cardiomyocytes were harvested, from 1 through to 4 weeks, for biochemical and functional assessments. We observed that the largest significant change in REEP5 expression occurred 4 weeks post-rAAV9 injection, correlating to a 78% knock-down, observed by immunoblotting (one-way ANOVA with Sidak's multiple comparison test, $p<0.0001$, $n=6$-8). 4 weeks following knock-down, mice developed lethal cardiac dysfunction. To assess the importance of REEP5 as a regulator of ER stress, apoptosis, and organelle structure, we have established an organelle-specific cardiac proteomic profile, using subcellular fractionation and mass spectrometry (nLC-ESI-MS-HCD-MS). Coupled with high resolution confocal microscopy and 3D mapping techniques, we have examined localization and expression patterns of key SR/ER and mitochondrial proteins, that have altered expression following knock-down of Reep5 at the myocyte-level. These results will be presented (3,4).

Conclusions and Significance: These findings will provide a detailed understanding of the role that REEP5 plays in maintaining ER homeostasis, SR/ER structure, and general organelle integrity. By identifying the mechanistic significance of REEP5 expression in the heart, we can work to delineate underappreciated pathways in cardiac muscle development.

Cardiac remodeling induced by early postnatal abdominal aorta constriction in rats: sex differences in heart function and geometry.

Jaroslav Hrdlicka[1], Veronika Olejnickova[2,3], Frantisek Papousek[2], Milana Peskova[2], Eva Zabrodska[4], Jan Neckar[2]

[1]Laboratory of Developmental Cardiology, Institute of Physiology, Prague, Czech Republic. [2]Laboratory of Developmental Cardiology, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic. [3]Institute of Anatomy, First Faculty of Medicine, Charles University, Prague, Czech Republic. [4]nstitute of Anatomy, First Faculty of Medicine, Charles University, Prague, Czech Republic

Cardiac remodeling induced by pressure overload leads to changes in myocardial structure and function and it can result in life-threatening arrhythmias (1) and progression of heart failure (2). Early postnatal abdominal aorta constriction (AAC) (3) is a unique experimental model of gradual pressure overload that can be used for understanding the role of neonatal cardiac plasticity in cardiac remodeling (4). Here we investigated the impact of increased pressure load applied in early postnatal period on the development of left ventricle (LV) function and geometry in male and female Wistar rats ju7uuuz6rlpzg.

Newborn pups were subjected to the surgical induction of AAC or sham operation at postnatal day 2 under light ether anesthesia. A silk ligature (0.25 mm in outer diameter) was tied around the aorta in the subdiaphragmatic, suprarenal region. In sham-operated animals, the aorta was exposed, but not constricted. Cardiac function and geometry were assessed at postnatal days 21 and 90 using echocardiography and the hearts were harvested for further analysis.

At postnatal day 90, the relative heart weight was higher in females than in males compared to corresponding sham-operated animals (5.23 ± 0.50 vs. 3.61 ± 0.11 mg/g and 4.35 ± 0.40 vs. 2.71 ± 0.06 mg/g, respectively). AAC led to a gradual increase in LV diastolic diameter by 7% in females and 12% in males compared to sham-operated controls. Diastolic LV wall thicknesses were increased by 11 % in females and by 32 % in males. LV systolic function (expressed as fractional shortening) at postnatal day 90 was decreased in both males (to 35.2 ± 2.9 vs. 45.9 ± 2.5) and females (to 34.9 ± 3.2 vs. 45.1 ± 1.4) with AAC.

Our data suggested that male Wistar rats are more susceptible to AAC-induced cardiomegaly than female rats. This can be partially explained by sexual differences in body growth. However, further investigation should focus on potential sex differences in myocardial structure, conduction system, and metabolic changes.

Supported by the Ministry of Health of the Czech Republic (grant no. NU21J-02-00039) and Czech Science Foundation (grant no. GJ19-04790Y).

Angiogenic and cardiac reparative effects of endothelial colony forming cells derived exosomes in myocardial infarction.

Anshul Jadli, Karina Gomes, Ananya Parasor, Noura Ballasy, Monica Surti, Darrell Belke, Methsala Wijesuriya, Paul Fedak, Vaibhav Patel
University of Calgary, Calgary, Canada

Background: Despite improvements in medical and surgical therapies, ischemic heart disease contributes significantly to the mortality rate in North America (1). Post-myocardial heart exhibits progressive loss of function, majorly attributed to adverse cardiac remodeling. The adverse cardiac remodeling is characterized by loss of cardiomyocyte and coronary vasculature and results in heart failure (2). Though pharmacological, and surgical interventions improve patient survival but fail to address the acute loss of cardiomyocytes and excessive cardiac remodeling, thus offering limited benefits (3). Paracrine effects mediated by exosomes secreted by endothelial colony-forming cell-derived exosomes implicated in angiogenesis and vascular repair (4), the mechanism underlying angiogenesis and functional recovery post-myocardial infarction remain undefined.
Methods and Results: The endothelial colony-forming cells (ECFCs) were characterized using flow cytometry (CD34+/CD31+/CD309+/CD14-/CD45- cells). The administration of ECFCs in a murine model of experimental end-organ ischemia demonstrated an ECFC-exosome-dependent increase in angiogenesis. The ECFC-exosomes were characterized using nanoparticle tracking analysis and western blot for exosome-specific markers (CD63, CD81, TSG101). Using wound healing, tube formation, and aortic ring assays, we identified the angiogenic and vasculoreparative abilities of ECFC-derived exosomes. Intramyocardial administration of ECFCs-exosomes to a murine model of myocardial infarction exhibited improved structural and functional properties of the heart with reduced cardiac remodeling. The Next-generation sequencing for the identification of exosome cargo identified 136 miRNAs associated with ECFC-exosomes. The Ingenuity pathway analysis (IPA) showed the association of ECFC-exosomes miRNAs with angiogenesis-related mRNAs specifically targeting anti-angiogenic genes such as ATF4 and HMGA2, suggesting the angiogenic potential of ECFC-Exosomes via inhibition of anti-angiogenic pathways.
Conclusion: The study provided strong scientific evidence for angiogenic and cardiac reparative properties of ECFCs mediated by exosomes in post-myocardial infarction hearts.

Defining the role of DHHC3 and DHHC7 in cardiac stress signaling.

Tanya Baldwin[1], Matthew Brody[2], Yasuhide Kuwabara[1], Weiqi Zhang[3], Jeffery Molkentin[1]
[1]Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [2]University of Michigan, Ann Arbor, USA. [3]University of Munster, Munster, Germany

Lipid modifications provide a layer of control over cardiac signaling molecules, including small GTPases and heterotrimeric G-proteins. Lipidation of signaling factors often permits their preferential localization to intracellular membranes and organelles where they then activate downstream effectors. S-palmitoylation is a reversible lipid modification catalyzed by a family of 23 palmitoyl acyltransferases, which are characterized by a conserved zinc finger-like aspartate-histidine-histidine-cystine (zDHHC) domain. Although the importance of GTPase palmitoylation is appreciated, our understanding of enzyme-substrate specificity remains uncertain and how these enzymes regulates cardiac stress signaling and hypertrophy is unknown. To examine the roles of the cardiac-expressed zDHHCs, we overexpressed zDHHC3, 5, 6, 7 and 13 using adeno-associated viruses. Overexpression of membrane-localized zDHHC5, ER-localized zDHHC6 or Golgi-localized zDHHC13 had no effect on cardiac function, while overexpression of zDHHC3 or zDHHC7 (both Golgi-localized) caused dilated hypertrophic cardiomyopathy. zDHHC3 and zDHHC7 expression were also upregulated in the heart in response to transverse aortic constriction. To gain a better understanding of the physiological role of zDHHC3 and zDHHC7 in the heart we utilized gene-deleted mice subjected to models of pathological and physiological hypertrophy. Neither single (zDHHC3 and zDHHC7) or double (zDHHC3/7) knockout mice exhibit alterations in cardiac function at baseline. We observe no alterations in hypertrophic progression (pathological and physiological) or endpoint phenotypes compared to controls. Interestingly, both single and double knockout mice have reduced palmitoylation of signaling proteins including Gαs and Rac1. We show that although overexpression of zDHHC3 and 7 contribute to pathological disease, they are not key regulators of hypertrophic signaling.

ATF6 Regulates ANP Secretion and Endocrine Function of Atrial Myocytes.

Erik A Blackwood[1], Alina S Bilal[1], Donna J Thuerauf[2], Alice Zemljic-Harpf[3], Scott A Hahn[1], Sean N Noudali[1], Hemal H Patel[3], Christopher C Glembotski[1]
[1]University of Arizona College of Medicine – Phoenix, Phoenix, USA. [2]San Diego State University, San Diego, USA. [3]University of California San Diego, San Diego, USA

Introduction: Atrial natriuretic peptide (ANP) is stored in secretory granules of atrial myocytes and secreted to adaptively decrease ventricular hypertrophy and increase renal natriuresis. We've recently demonstrated an integral role for the ER stress responsive transcription factor, ATF6, in modulating ventricular myocyte hypertrophy in the setting of pressure-overload via inducing an adaptive gene program. However, it is not known whether ATF6 affects ANP secretion from atrial myocytes in response to hypertensive stress.

Methods: Acute phenylephrine (PE) treatment was used to stimulate ANP secretion from isolated primary neonatal rat atrial myocytes (NRAMs) in culture or mice, in vivo. Separately, a high salt diet was used to model hypertensive stress in control, cardiomyocyte specific ATF6 knockout (ATF6cKO) or atrial myocyte specific ATF6 knockout (ATF6aKO) mice.

Results: Both NRAMs treated with siAtf6 and ATF6cKO mice exhibited a marked decrease in ANP secretion in response to 0.5h PE without affecting ANP gene or protein expression. Furthermore, NRAMs or mice treated with an ATF6-specific activator dramatically increased ANP secretion in response to PE. Both ATF6cKO and ATF6aKO mice displayed increased blood pressure, diastolic dysfunction, and atrial decompensation on a chronic high salt diet with decreased plasma ANP. Transmission electron microscopy showed granule docking at the sarcolemma and membrane fusion was noticeably impaired in ATF6cKO mice. Mechanistically, transcriptomic analysis and ChIP identified the t-SNARE protein, SNAP23, as an ATF6 target. Finally, AAV9-FLAG-SNAP23 treatment rescued ANP secretion in ATF6cKO mice.

Conclusion: ATF6 regulates ANP secretion by transcriptionally regulating Snap23 to facilitate secretory granule docking and exocytosis.

Myocardial protein citrullination as a novel mechanism of sex-specific cardiac aging.

Aykhan Yusifov[1], Kathleen Woulfe[2], Brian Cherrington[1], Danielle Bruns[1]
[1]University of Wyoming, Laramie, USA. [2]University Colorado-Anschutz Medical Campus, Aurora, USA

The heart ages differently between men and women, resulting in sex-specific cardiac aging phenotypes. Testosterone and estrogen regulate cardiac function through distinct mechanisms, the effects of which likely diverge as a result of age-related changes in sex hormones. However, despite the decades-old observation that men and women undergo distinct cardiac aging, the molecular mechanisms underlying these differences remain unclear. Post-translational modification of myocardial proteins regulates cardiac function. Citrullination, an understudied modification, is the conversion of arginine amino acids in target proteins to citrulline and is catalyzed by peptidylarginine deiminase (PAD) enzymes. Widely studied in reproduction, PADs were recently shown to catalyze myocardial protein citrullination. Here, we tested the hypothesis that PAD and citrullination contribute to sex differences in cardiac aging. We quantified PAD expression and myocardial citrullination in adult (4-month) and aged (18-month) male and female C57Bl6 mice. Myocardial PAD expression declined with age in females but was upregulated with aging in males, suggesting a positive regulation of PAD by estrogen and a repression by testosterone. Consistent with changes in PAD, myocardial protein citrullination increased with age in males and decreased in female hearts. Importantly, these changes in PAD expression and citrullination coincide with the sex-specific cardiac aging phenotype. Ongoing work will identify specific sex- and age-regulated citrullinated proteins and directly test the role of PAD expression in the heart in an effort to advance mechanistic understanding of cardiac aging in men and women and lay the foundation for sex-specific therapies for age-related heart disease.

p38 MAPK signaling in mononucleated ventricular cardiomyocytes translates to the acquisition of an inflammasome phenotype and concomitant inhibition of cell cycle re-entry.

Mariana Kebbe[1,2], Patrice Naud[1], Angelo Calderone[1,2]
[1]Montreal Heart Institute, Montreal, Canada. [2]Department of Pharmacology and Physiology, Universite de Montreal, Montreal, Canada

The present study tested the hypothesis that the cardiac regenerative response of the apex-resected neonatal rat heart following administration of the p38 MAPK inhibitor SB203580 was attributed in part to the suppression of a panel of inflammatory cytokines expressed by ventricular cardiomyocytes. The exposure of mononucleated neonatal rat ventricular cardiomyocytes (NNVMs) to the protein kinase C activator phorbol 12,13-dibutyrate (PDBu) for 3-days translated to a significant hypertrophic response but failed to initiate cell cycle re-entry. PDBu treatment of NNVMs increased Reg3ß, CCL2, CCL3, CCL12, CCL22, IL-1α, IL-1ß, IL-6 and TNF-α mRNA levels and protein expression of Reg3ß. In the presence of SB203580 (10 μM), PDBu treatment led to cell cycle re-entry as the density of NNVMs that incorporated bromodeoxyuridine and expressed nuclear phosphohistone-3 were significantly increased as compared to PDBu alone. Furthermore, a subpopulation of cycling NNVMs treated with PDBu/SB203580 was associated with the de novo expression of the intermediate filament protein nestin. SB203580 co-treatment failed to inhibit PDBu-mediated NNVM hypertrophy. However, the increased expression of inflammatory cytokine mRNAs and upregulated Reg3ß protein levels in response to PDBu were suppressed in PDBu/SB203580 treated NNVMs. Lastly, IL-1ß (5 ng/ml) treatment of NNVMs for 24 hours significantly attenuated cell cycle re-entry and the response was reversed following SB203580 co-treatment. Collectively, these data support the novel premise that p38 MAPK signaling in ventricular cardiomyocytes translates to the acquisition of an inflammasome phenotype and the release of inflammatory cytokines may act in an autocrine fashion to suppress cell cycle re-entry.

Early Renal Denervation Protects Against Diastolic Dysfunction in Rodent Model of Heart Failure with Preserved Ejection Fraction.

Jake Doiron[1,2], Zhen Li[1,2], Kyle LaPenna[1,2], Daniel Kapusta[1,2], Traci Goodchild[1,2], David Lefer[1,2]
[1]Louisiana State University Health Sciences Center New Orleans, New Orleans, USA. [2]Cardiovascular Center of Excellence, New Orleans, USA

Background: Prolonged pathological activation of the sympathetic nervous system (SNS) contributes to resistant hypertension and heart failure with reduced ejection fraction. The potential role of SNS overactivation in heart failure with preserved ejection fraction (HFpEF) has yet to be evaluated. We investigated the effects of renal sympathetic denervation on the pathogenesis of cardiometabolic HFpEF in a preclinical model.

Methods: Male ZSF-1 obese rats were subjected to either radiofrequency renal denervation (RF-RDN) or sham renal denervation (Sham-RDN) at 8-weeks of age and were then studied for a period of 20 weeks. Left ventricular (LV) systolic and diastolic function was assessed through echocardiography and invasive hemodynamics. Exercise capacity was similarly measured throughout progression of HFpEF. Vascular reactivity responses to acetylcholine and sodium nitroprusside were evaluated in isolated, thoracic aortic rings.

Results: Radiofrequency renal denervation at an early stage of HFpEF significantly reduced LV pathologic diastolic dysfunction as measured by E/a, E/e' and left ventricular end diastolic pressure (LVEDP). Similarly, early renal denervation increased aortic vascular responses to acetylcholine indicating improved vascular health. We did not observe any significant improvements in exercise performance following RF-RDN therapy.

Conclusion: Our data demonstrate that renal denervation as an early treatment intervention attenuates cardiovascular dysfunction in a rodent model of HFpEF. These results further suggest that the SNS contributes to the pathology seen in HFpEF. Additional studies are currently underway to determine if renal sympathetic denervation could be a viable treatment option for HFpEF patients.

Angiotensin II-induced cardiac hypertrophic remodeling is attenuated by inhibition of Peptidyl arginine deiminases (PADs) activity.

Takeshi Ijichi[1], Rakhi Pandey[2], Niveda Sundararaman[2], Martin Thomas[3], Etai Koronyo[4], Jonathan Kirk[3], Eduardo Marbán[2], Jennifer Van Eyk[2], Justyna Fert-Bober[2]
[1]Tokai University School of Medicine, Tokai, Japan. [2]Cedars Sinai, Los Angeles, USA. [3]Loyola University, Chicago, USA. [4]UC Berkeley, Berkeley, USA

Recently, peptidyl arginine deiminase-4 (PAD4) has been shown to contributes to cardiac ischemic injury by exacerbating the inflammatory response. However, the role of PAD4 and downstream citrullinated proteins during cardiac nonischemic disease is unknown. Here, we tested the hypothesis that pharmacological inhibition of PAD4 can reverse cardiac hypertrophy and reduced cardiac inflammation and fibrosis in angiotensin (Ang) II induced cardiac mouse model. Cardiac hypertrophy was induced in male C57Bl/6 mice by AngII (1.4 mg/kg/min) infusion via mini osmotic pumps for up to 28 days. After 14 days of AngII, multiple doses of PAD4 inhibitor, or saline, were delivered via intraperitoneal injections. AngII infusion after 28 days increased heart/body weight ratio (AngII:6.51±0.8mg/g vs control:5.22±0.6mg/g), interventricular septum thickness (IVSd) (AngII:1.13±0.04mm vs control:0.73±0.02 mm), left ventricular filling pressure (E/A) ratio (AngII:1.6±0.05 vs control:1.3±0.08) and cardiomyocyte fibrosis (AngII: 6.8±0.02% vs control: 4.03±0.01%) compared with control animals. The reverse hypertrophy effect was seen in PAD inhibitor treated mice by significant reduction of heart/body ratio (5.27±0.6mg/g), IVSd (0.79±0.03mm), E/A (1.2±0.02) and cardiac fibrosis (4.58±0.02%). The beneficial effects of PAD inhibitor were associated with changes in heart proteome, with normalization of the proteins involved in contractile pathway (e.g., myosin light chain), remodeling (e.g., TMP4) and lipogenesis (e.g., Fatty acid synthesis). In addition, PAD inhibition normalized level of circulation cytokines, anti-inflammatory interleukin-10 and pro-inflammatory interleukin-6. These suggest that inhibiting PAD4 is one of the potential mechanisms to reverse myocardial remodeling.

The Effects of Daily Swim Exercise Duration on Cardiac Responses and Atrial Fibrillation.

Renée Gorman, Nazary Polidovitch, Robert Lakin, Ryan Debi, Jhonny Mendoza, Peter Backx
York University, Toronto, Canada

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia worldwide, characterized by disorganized atrial activity and is associated with embolization, stroke and mortality. Despite the benefits of moderate exercise, recent studies documented comparable AF risk between professional endurance athletes and cardiovascular disease patients. We previously reported that swim-trained mice recapitulate cardiac adaptations observed in human endurance athletes (increased ventricular dilation, parasympathetic tone, contractile reserve) along with atrial changes promoting AF (fibrosis, inflammation, hypertrophy, arrhythmia susceptibility). To explore the relationship between daily exercise dose and AF vulnerability, we investigated the effects of varying daily swim duration (120-, 180- or 240-minutes/day divided into 2 sessions) at the same total exercise dose (estimated from O2 consumption during swims). Despite similar training intensities, increasing daily swim duration caused progressively greater ($p<0.03$) left ventricular (LV) dilation (LVDdsed:4.26±0.06mm, LVDd120:4.49±0.08mm, LVDd180:4.55±0.09mm, LVDd240:4.66±0.07mm) and enhanced ($p<0.01$) bradycardia (HRsed:534±8bpm, HR120:445±12bpm, HR180:427±14bpm, HR240:408±15bpm) without ventricular arrhythmia inducibility. Contrastingly, AF inducibility increased ($p<0.04$) in the 120-min (2/6) and 180-min (5/15) groups but not in the 240-min group (0/10). Furthermore, atrial refractoriness exhibited trends toward prolongation ($p=0.11$) in the 240-min group (27.15±0.82ms) but not ($p>0.80$) in the 120-min (23.3±1.7ms) or 180-min (25.8±0.7ms) groups compared to sedentary mice (24.4±0.6ms). Preliminary findings also revealed trends ($p=0.06$) toward increased atrial fibrosis with increasing daily training duration. Together, our study suggests that the impact of daily exercise dose on atrial arrhythmia susceptibility involves a complex interplay of atrial responses with compensatory electrophysiological adaptations.

Exploring sarcoplasmic reticulum calcium cycling as a thermogenic mechanism in brown adipose tissue.

Adrienne R. Guarnieri, Sarah R. Anthony, Michael Tranter
University of Cincinnati, Cincinnati, USA

Obesity is associated with decreased life expectancy due to increased risk of associated comorbidities including cardiovascular disease, type II diabetes, and cancer. With a demand for therapies to sustainably increase energy expenditure, the activation of brown adipose tissue (BAT) adaptive non-shivering thermogenesis (NST) has been highlighted as an advantageous target. Canonical thermogenesis in BAT occurs through uncoupling protein 1 (UCP1) which produces heat by dissociating the electrochemical gradient in oxidative phosphorylation. In recent years, additional UCP1-independent processes have also been identified to function through the futile cycling of substrates including creatine, leptin, and calcium. Our lab has previously shown that the RNA-binding protein HuR (Human antigen R) plays a functional role in thermogenic metabolism independent of UCP1, and RNA sequencing analysis from mice with an adipocyte-specific deletion of HuR (Adipo-HuR-/-) revealed a BAT-specific decrease in the expression of many genes responsible for sarcoplasmic reticulum (SR) calcium cycling.

New evidence from our lab shows decreased intracellular calcium levels in BAT isolated from Adipo-HuR-/- mice, and that the deletion of HuR blunts adrenergic-induced increases in intracellular calcium, suggesting HuR-dependent regulation of SER calcium transport in brown adipocytes. Assessing the tissue specificity of this response in brown adipocytes, we generated BAT-specific HuR-/- mice which exhibited impaired thermogenic capacity. Taken together this work suggests an important role of SR calcium cycling as a thermogenic mechanism alongside of traditional UCP1 driven thermogenesis in brown adipose tissue, and that the distinct regulation of HuR in brown adipocytes is sufficient to yield a phenotypic thermal response.

Next-generation α-1-adrenergic receptor antagonists without cardiotoxic side-effects for the treatment of hypertension.

Chastity L. Healy, Ingrid Rodriguez Aragon, Yuk Y. Sham, Timothy D. O'Connell
University of Minnesota, Minneapolis, USA

In the US, hypertension (HTN) prevalence is 47%, with 121M adults diagnosed with HTN. Despite numerous drug options and defined practice guidelines, of those with HTN, only 54% had their HTN controlled suggesting the need for new and better pharmacologic options. Although α1-adrenergic receptor (α1-AR) antagonists (α1-blockers) were once used for HTN, ALLHAT found that the α1-blocker doxazosin increased cardiovascular events by 25% and doubled the risk of heart failure, thus α1-blockers are no longer a first-line option in HTN. The α1-blocker cardiotoxicity identified in ALLHAT is based on our finding that cardiac myocyte (CM) α1-ARs are protective. We also found that atypical of most receptors, α1-ARs localize to and signal at the nucleus in CMs, whereas in smooth muscle (SM), α1-ARs localize to the sarcolemma. Based on this differential receptor localization, we report the development of novel membrane-impermeant α1-blockers without cardiotoxic side-effects. Using a novel α1-blocker-bound α1A-AR homology model, we designed and synthesized a series of novel α1-blockers. Subsequently, we identified two prototypical compounds that were validated as high-affinity α1-ligands in competition binding assays, as antagonists by inhibition of α1-Ca2+ signaling in HEK293 cells expressing the α1A-AR at the plasma membrane, and as membrane-impermeant in uptake assays in adult cardiac myocytes. Further, we demonstrated that in adult cardiac myocytes, these novel α1-blockers do not attenuate α1-ERK cardioprotective signaling or inhibit α1-prevention of cardiac myocyte cell death. Finally, we demonstrated that these novel blockers reduce arterial pressure in vivo in a mouse model of HTN.

Lichen *Xanthoparmelia stenophylla* ameliorates doxorubicin-induced cardiotoxicity in rats.

Jovana Jeremic[1], Aleksandar Kocovic[1], Slobodanka Mitrovic[1], Jasmina Sretenovic[1], Nedeljko Manojlovic[1], Perica Vasiljevic[2], Marijana Andjic[1], Nevena Draginic[1,3], Dejan Baskic[1], Vladimir Zivkovic[1], Vladimir Jakovljevic[1,3]

[1]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]Faculty of Sciences and Mathematics, University of Niš, Nis, Serbia. [3]1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation

Background/Aim. Since ancient times, lichens have had a very important role in traditional medicine and the pharmaceutical industry (1). Xanthoparmelia stenophylla (XS), is a cosmopolitan lichen which contains salazic and usnic acids that have been proven to possess antioxidant, antibacterial, antifungal, and antitumor effects (2). Keeping that in mind, the aim of the study was to examine the biological activity of acetone, methanol and hexane XS extracts and thereafter to examine the best XS extract against doxorubicin (DOX)-induced cardiotoxicity in rats.

Methods. Extracts were prepared using a multiple maceration procedure and acetone, methanol, and n-hexane as solvents. Extracts were characterized and analyzed by HPLC, spectrophotometric techniques, scavenging DPPH, hydroxyl, and superoxide anion radicals, and MTT testing. The acetone extract was chosen as the best for animal testing which included 32 Wistar albino rats divided into four groups: healthy non-treated rats, healthy rats treated with XS extract (125mg/kg/day per os by gavage for 28 days), DOX (15mg/kg, on the 25th day as a single i.p. injection) rats without treatment and DOX rats treated with XS extract (3, 4). When the study was completed, in vivo hemodynamic and ex vivo cardiodynamic parameters were monitored. Systemic oxidative stress parameters were determined and a histopathological examination of the heart was performed.

Results. Our results suggested that acetonic extract of lichen contains the highest amount of total phenols and flavonoids, exhibits the best antioxidant effect according to all analyzed parameters, exhibits intense antibiofilm activity against S. aureus, and has the strongest cytotoxic effect of the tested extracts. In the animal testing, the treatment led to a minor increase in the ejection fraction in the DOX group, while the levels of free radicals were significantly decreased. In the DOX rats treated with XS extract, significantly fewer histopathological changes, reduction of cardiomyocyte apoptosis, as well as improved heart function were observed.

Conclusion. Our study demonstrated the promising antioxidant, antimicrobial and cytotoxic effects of XS extract, as well as significant protective effects against DOX-induced cardiotoxicity through modulation of oxidative stress, suppression of apoptosis, and the possibility to improve myocardial performance and morphometric structure of rats` hearts.

Protective effect of molecular hydrogen on the heart and the whole body in simulated heart transplantation.

Branislav Kura[1], Barbora Kalocayova[1], Vladan Hudec[2], Matej Ondrusek[2], Ivo Gasparovic[2], Rastislav Sramaty[2], Jaroslav Luptak[2], Michal Hulman[2], Jan Slezak[1]
[1]Centre of Experimental Medicine, Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovakia. [2]Department of Cardiac Surgery, Faculty of Medicine, National Institute of Cardiovascular Diseases, Comenius University, Bratislava, Slovakia

Heart transplantation (HT) is usually the last option for patients with heart failure (1). Although it becomes a routine method of treatment, ischemic reperfusion damage to the heart after cold ischemic storage is the most critical part in restoring physiological heart function as a pump (2). During this, mostly mitochondrial dysfunction, inflammation, and overproduction of reactive oxygen species could have a significant impact on the overall success of HT (3). Molecular hydrogen (H2), a selective antioxidative substance, is widely used in many pathologies including ischemia/reperfusion-related diseases with positive results (4). Based on this, we hypothesize that H2 could protect heart against a negative effect of reperfusion damage.

The aim of this study was to examine the effect of H2 on the heart allograft of pigs (female, 4 months old) who underwent a simulated HT. The simulation of HT consisted of occluding venae cavae and pulmonary veins, cross-clamping of ascending aorta, and connection to ECC. Cold crystalloid cardioplegia was administered for 3 hours. After the time of cold arrest, the coronary arteries were flushed, and the aortic clamp was released. This was followed by rewarming the heart. After 60 minutes of spontaneous reperfusion the experiment was terminated. H2 was administered as gas during blood oxygenation (50% O2, 3% H2). In this study, levels and activities of oxidative disbalance markers, markers of heart damage, and expression of miRNAs were measured from blood plasma and left ventricle tissues.

Simulated HT significantly increases activities and amounts of endogenic antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), molecules of oxidative stress damage (uric acid, malondialdehyde, lactate dehydrogenase, 8-hydroxy-2-deoxyguanosine), and heart damage (troponin T, creatine kinase, myoglobin). The application of H2 significantly modulates all selected parameters almost up to control levels. The transplantation causes significant changes also in the levels of selected miRNAs where the H2 treatment had normalization effects either.

We can conclude that the addition of H2 during HT could be a new potential therapeutic strategy for minimalizing the negative effect of ischemia/reperfusion injury, leading to better recovery of patients.

Activation of ATF6α signaling pathway in doxorubicin associated cardiomyopathy and its attenuation by IL-10.

Akshi Malik[1], Ashim K Bagchi[2], Davinder S Jassal[3], Pawan K Singal[1]
[1]Institute of Cardiovascular Sciences, department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, USA. [3]Institute of Cardiovascular Sciences, department of Internal Medicine, University of Manitoba, Winnipeg, USA

Background: The use of anticancer drug, doxorubicin (Dox) has been limited due to the risk of cardiotoxicity (1) via an increase in oxidative stress, mitochondrial dysfunction and disturbed endoplasmic reticulum (ER) homeostasis in cardiomyocytes (2). The latter results in the accumulation of unfolded and/or misfolded proteins referred to as ER stress, that activates certain signaling pathways (3). This study explores which of the ER transmembrane sensor is involved in Dox-induced cardiomyopathy and whether interleukin-10 (IL-10) has any mitigating effect.
Methods: Adult male Sprague dawley rat cardiomyocytes were treated with Dox (10μM) in the presence or absence of IL-10 (10ng/ml) for 24hrs. For the combination group of Dox+IL-10, cells were treated with IL-10 for 1hr before the addition of Dox (4). Treatment groups were compared by one-way analysis of variance (ANOVA), and Tukey-Kramer's test was performed to identify differences between the groups, $P \leq 0.05$ was considered to be significant.
Results: The dox induced unfolded protein response lead to the activation of activating transcription factor 6 α (ATF6α) through the dissociation of glucose regulated proteins 78 (GRP78), followed by its cleavage in the Golgi body. Activated ATF6α increased splicing of X-box binding protein 1 (XBP1s) and inhibited unspliced XBP1 (XBP1u). An increase in XBP1s, subsequently upregulated ER stress markers such as GRP78, GRP94, and protein-disulphide isomerase. Dox also initiates an activation of procaspase-12, which is known to activate caspase-3, BAX and apoptosis through mitochondria. IL-10 treatment reduced the activation of ER-stress, marked by reduction in ER-stress markers. Additionally, IL-10 downregulated procaspase-12, phosphorylation of c-JUN NH2-terminal kinase, Bax activation and thereby promoting cardiomyocyte survival.
Conclusion: The exogenous administration of IL-10, one hour prior to the exposure of cardiomyocytes to Dox for 24hrs, was found to be effective in suppressing the expressions of ER-stress markers via inhibiting the cleavage of ATF6α. The beneficial effects of IL-10 in modulating ER-stress and ER-initiated apoptosis may prove to be a significant advance in restricting cardiac damage during stress or inflammation.

Potential of cyanidin 3-glucoside in the prevention of cardiovascular disease.

Basma Aloud[1], Pema Raj[1], Jason McCallum[2], Chris Kirby[2], Heather Blewett[1], Jeffrey Wigle[3], Thomas Netticadan[1]

[1]Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, Canada. [2]Charlottetown Research and Development Centre, Charlottetown, Canada. [3]Institute of Cardiovascular Sciences, Winnipeg, Canada

Introduction: Polyphenols are an important family of bioactive molecules which have gained a lot of interest in recent years for their potential in the prevention, as well as, the management of disease (1,2). In this regard, we have studied stilbenes, a class of polyphenols, for more than a decade and reported that the polyphenol, resveratrol, has strong cardioprotective properties (3,4). However, resveratrol is not found in large amounts in food sources. Flavonoids are another class of polyphenols, with anthocyanins being a subclass. Anthocyanins are pigment molecules found in coloured grains, fruits, and vegetables. In addition to imparting color, these molecules may help to protect photosynthetic tissues from stressful conditions. Besides, anthocyanins are abundant in darkly colored foods, we therefore examined the therapeutic potential of one such anthocyanin, cyanidin 3-glucoside (C3G).

Methods: We investigated the cardioprotective potential of C3G. For this purpose, we conducted *in vitro* studies utilizing adult rat cardiomyocytes exposed to endothelin 1 (ET1), and *in vivo* studies using two animal models of cardiovascular disease (a) the spontaneously hypertensive rat (SHR), an animal model of hypertension and hypertensive heart disease, and (b) the coronary artery ligated rat, an animal model of ischemic heart disease. In both studies C3G was administered by oral gavage at a dose of 10mg/kg body weight/day, prior to disease development. Echocardiography was performed in all animals to assess cardiac structure and function. Biochemical analysis was performed in blood and heart tissue to assess potential mechanisms of C3G action.

Results: Our *in vitro* studies showed that C3G prevented ET1-induced alterations in cardiomyocyte morphology. The *in vivo* studies showed a reduction in cardiac hypertrophy and improved diastolic heart function in C3G administered SHR, however C3G did not prevent abnormalities in heart structure and function in the coronary artery ligated rat.

Conclusions: C3G may have therapeutic potential in the prevention of hypertensive heart disease, but not ischemic heart disease.

Alternative Splicing Targets Death Gene Bnip3 to Endoplasmic Reticulum for Cell Survival.

Inna Rabinovich-Nikitin, Hongying Gang, Rimpy Dhingra, Vicky Margulets, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

Background/Aim: The signaling networks that coordinate cell survival and cell death in the heart are poorly defined (1). Alternative splicing provides a mechanism by which cells generate proteins with different or even antagonistic properties (2, 3). Herein we describe a novel splice variant of the hypoxia-inducible death gene Bnip3 that we designated NIPLET for (Nip-Like ER Target).

Methods/Results: In contrast to Bnip3 which provoked mitochondrial perturbations and necrotic cell death of cardiac myocytes, NIPLET which contains a C-Terminal (CT) ER retention motif suppressed mitochondrial PTP opening, loss of ΔYm and cell death induced by Bnip3 and hypoxia. Interestingly, ER- targeting of NIPLET was contingent on mitofusin 2 (Mfn2) since deletion or point mutations of critical CT domain of NIPLET impaired ER- targeting. Moreover, loss of function of NIPLET sensitized cardiac myocytes to mitochondrial calcium over-load, mitochondrial PTP and necrosis. (3)

Discussion: To our knowledge our data provide the first evidence for a novel intrinsic survival mechanism that is linked to alternative Bnip3 splicing and Mnf2 regulated ER-mitochondrial pathway (4).

Dual Role of Embryonic Stem Cell Derived Exosomes in Treatment of Triple Negative Breast Cancer and Improvement of Cardiac Function.

Arun Samidurai[1], Anindita Das[1], Donatas Kraskauskas[1], Karthikeya Bhoopathi[1], Bei Zhang[1], Amy Olex[1], Jinze Liu[1], Bin Hu[1], Jennifer Koblinski[1], Dinender Singla[2], Rakesh Kukreja[1]
[1]Virginia Commonwealth University, Richmond, USA. [2]University of Central Florida, Orlando, USA

Background: Triple Negative Breast Cancer (TNBC) is an aggressive form of cancer and is widely treated with doxorubicin (Dox) (1). Dox treatment causes unintended side effects including cardiac dysfunction and skeletal muscle weakness (2). We investigated the effect of embryonic stem cell derived exosomes (Es-Exos) as adjuvant therapy with Dox in improving anti-tumor efficacy and protection against Dox induced side effects.

Methods and Results: Orthotopic xenograft model of TNBC was generated by injecting human MDA-MB-231-Tom-Luc cells in mammary intraductal T4 region of nude mice. Non-tumor bearing female mice were used as control (NT-Con;n=6). Animals (n=10/group) were randomized to receive Saline (Tum-Con); Dox (5 mg/kg/week); Es-Exos (50 µg/animal twice a week; Dox+Es-Exos; Es-Exos alone and MEF-Exos (mouse embryonic fibroblast cell derived exosomes 50 µg/animal twice a week) for up to 4 weeks. Cardiac function measured by echocardiography showed decline in ejection fraction (EF) in tumor bearing Tum-Con and in Dox group, when compared to NT-Con. Treatment with Dox+Es-Exos and Es-Exos improved EF as compared to animals in Tum-Con and Dox cohort. The tumor size was reduced in Dox+Es-Exos treated group as compared to Dox and Tum-Con groups (Tum-Con Vs Dox and Dox+Es-Exos; p-value <0.05). Skeletal muscle grip strength declined in Tum-Con and Dox- tumor bearing mice as compared to NT-Con, which was restored with Es-Exos. Picro Sirius red staining showed increased collagen deposition in Tum-Con, which was reduced in Dox+Es-Exos and Es-Exos groups. RNA seq analysis of Es-Exos identified several anti-proliferative genes including a 6-fold expression of Transcription Factor 7 and 6.5-fold higher expression of E-Cadherin (CDH1). Cytokine array data showed increased levels of serum inflammatory markers in Tum-Con, which was decreased upon Es-Exos treatment. Immunohistochemistry of tumor tissue showed abundant expression of Ki-67, VEGF and CD206 (marker for M2 macrophage) in untreated Tum-Con, which was reduced by treatment with Es-Exos and Dox. However, CD206 staining was enhanced upon Es-Exos treatment in heart tissue.

Conclusion: The anti-proliferative and anti-inflammatory molecules in Es-Exos potentially contribute to the anti-tumor effect in TNBC xenograft model while improving cardiac function and skeletal muscle grip force.

Reduced cyclooxygenase 2 levels result in the loss of immunoprivilege of allogeneic mesenchymal stem cells following hypoxia.

Niketa Sareen[1], Ejlal Abu-El-Rub[1], Hania I. Ammar[2], Weiang Yan[1], Glen Lester Sequiera[1], Meenal Moudgil[1], Elika Verma[1], Sanjiv Dhingra[1]
[1]University of Manitoba, Winnipeg, Canada. [2]Cairo University, Cairo, Egypt

Mesenchymal stem cells (MSCs) from young and healthy, allogeneic sources have the potential to treat multiple immunological and degenerative disorders. However, recent animal studies and clinical trials demonstrate that immunogenicity and poor survival of transplanted MSCs impairs the efficacy of cells for regenerative applications (1). It is reported that initially immunoprivileged under in vitro conditions, MSCs are targeted by the host immune system after transplantation in the ischemic tissues in vivo (2,3). We performed in vitro and in vivo (in rat model of myocardial infarction [MI]) studies to elucidate the mechanisms responsible for the change in the immunophenotype of MSCs from immunoprivileged to immunogenic under ischemic conditions. In our study, we found that PGE2 levels, decreased in MSCs following exposure to hypoxia compared to normoxic controls. Further, we found that proteasome-mediated degradation of cyclooxygenase-2 (COX2, rate-limiting enzyme in PGE2 biosynthesis) in hypoxic MSCs is responsible for PGE2 decrease and loss of immunoprivilege of MSCs (4). While investigating the mechanisms responsible for COX2 degradation in hypoxic MSCs, we found that in normoxic MSCs, COP9 signalosome subunit 5 (CSN5) binds to COX2 and prevents its degradation by the proteasome. However, exposure to hypoxia leads to a decrease in CSN5 levels and its binding to COX2, rendering COX2 protein susceptible to proteasome-mediated degradation. This subsequently causes PGE2 downregulation and loss of immunoprivilege of MSCs. Maintaining COX2 levels in MSCs preserves immunoprivilege in vitro and improves the survival of transplanted MSCs in a rat model of MI. This data provides novel mechanistic evidence that PGE2 is downregulated in hypoxic MSCs which is responsible for the post-transplantation rejection of allogeneic MSCs; suggesting that new strategies that target CSN5-COX2 signaling may improve survival and utility of transplanted allogeneic MSCs in the ischemic heart.

The effects of Amiodarone and Dronedarone on heart function and redox balance of isolated hypertensive rat hearts.

Ivan Srejovic[1,2], Stefan Simovic[3], Jovana Jeremic[4], Vladimir Zivkovic[1,2], Maja Nikolic[1], Slobodanka Mitrovic[5], Vladimir Jakovljevic[1,6]

[1]University of Kragujevac, Faculty of Medical Sciences, Department of Physiology, Kragujevac, Serbia. [2]I.M. Sechenov First Moscow State Medical University, Department of Pharmacology of the Institute of Biodesign and Complex System Modelling, Moscow, Russian Federation. [3]University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia. [4]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia. [5]University of Kragujevac, Faculty of Medical Sciences, Department of Pathology, Kragujevac, Serbia. [6]I.M. Sechenov First Moscow State Medical University, Department of Human Pathology, Moscow, Russian Federation

Background/Aim: Arrhythmia in hypertensive patients is attracting increasing scientific interest. Amiodarone is one of the most widely used antiarrhythmic drug that blocks ion channels to treat atrial fibrillation and prevent sudden cardiac death (1). Dronedarone is a newer generation antiarrhythmic that is used in reduction of risk of atrial fibrillation (2). The aim of this study was to assess th chronic, dose-dependent effects of Dronedarone and Amiodarone on cardiodynamic parameters and oxidative stress of spontaneously hypertensive rat (SHR) heart.

Methods: The experiment was conducted on 42 SHR and normotensive Wistar Kyoto male rats (6 rats per each group): normotensive control group, and 6 experimental groups treated by oral gavage for 4 weeks: 3 groups treated with Amiodarone in dose of 100 mg/kg, 50 mg/kg and 10 mg/kg, respectively, and 3 groups treated with Dronedarone in dose of 50 mg/kg, 10 mg/kg and 5 mg/kg, respectively. Isolated rat hearts were retrogradely perfused by according to the Langendorff technique. Parameters of oxidative stress were determined spectrophotometrically (3).

Results: Amiodarone in the lowest dose significantly improved cardiac contractility, while Amiodarone in the highest dose significantly decreased all parameters of cardiac function. Surprisingly, the lowest dose of Amiodarone increased levels of oxidative stress biomarkers, compared to higher doses. Dronedarone, in all applied doses, induced reduction of heart function, in dose dependent manner. Comparison between groups treated with Amiodarone and Dronedarone revealed that Amiodarone had more pronounced protective effects on cardiac function, while Dronedarone exerted antioxidative property (4). When compared to Amiodarone, Dronedarone lowered all oxidative stress parameters in high, middle and low-dose.

Conclusion: Dose-dependent, chronic administration of Dronedarone severely depressed SHR cardiac function. Amiodarone showed less pronounced effects in high and middle dose, while low dose increased cardiac function. By comparing the effects of Amiodarone and Dronedarone, Amiodarone showed better effects on SHR cardiac function in all doses, while Dronedarone significantly reduced parameters of oxidative stress.

Cardiac-specific branched-chain aminotransferase ($BCATm^{Cardiac-/-}$) deletion exacerbates adverse cardiac hypertrophy in heart failure.

Qutuba Karwi[1], Liyan Zhang[1], Cory Wagg[1], Keshav Gopal[2], Kim Ho[1], Jody Levasseur[1], Qiuyu Sun[1], Sai Panidarapu[1], John Ussher[2], Jason Dyck[1], Gary Lopaschuk[1]

[1]Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada. [2]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

Recent studies have shown that cardiac-specific branched-chain aminotransferase (BCATmCardiac-/-), which is a maneuver to increase cardiac branched-chain amino acids and lower cardiac branched-chain keto acids (BCKA), enhances insulin-stimulated cardiac glucose oxidation rates while increasing left ventricular (LV) mass. Since stimulating cardiac glucose oxidation is shown to be a cardioprotective approach in heart failure, we hypothesized that lowering BCKAs via BCATm deletion will have a beneficial effect on cardiac function and energy metabolism in the failing heart. BCATmCardiac-/- male mice underwent a sham or transverse aortic constriction (TAC) surgery to induce heart failure. Changes in cardiac function and structure were monitored pre-and post-TAC using echocardiography. Five weeks post-TAC, hearts were collected and perfused as isolated working hearts to assess cardiac energy metabolism. BCATm deletion did not improve cardiac function in the failing hearts compared to the WTCre+ failing hearts in vivo or ex vivo. However, BCATm deletion exacerbated adverse cardiac hypertrophy, as evidenced by an increase in left ventricular mass in BCATmCardiac-/- failing hearts, and triggered the mTOR/P70S6K/4E-BP1 signalling pathway. Despite the lack of functional protection, BCATm deletion did increase insulin-stimulated glucose oxidation rates and cardiac efficiency in the failing hearts, which was associated with enhanced mitochondrial Akt activity. Lowering BCKA levels enhances cardiac efficiency in the failing heart via enhancing insulin-stimulated glucose oxidation. However, BCAA accumulation in the failing heart due to BCATm deletion worsens adverse remodelling and offsets any potential beneficial effects of lowering BCKA and improving insulin sensitivity in the failing heart.

CD38 inhibition decreases myocardial glucose utilization and impairs post-ischemic recovery without altering protein acetylation status.

Ezra Ketema, Qutuba G. Karwi, Liyan Zhang, Gary D. Lopaschuk
Cardiovascular Research Centre, Department of Pediatrics, University of Alberta, Edmonton, Canada

INTRODUCTION: Myocardial ischemia and reperfusion are associated with deleterious cardiac energy metabolic changes which impair post-ischemic recovery. A decrease in NAD+ levels partly due to an upregulation of CD38 may contribute to the dysregulation of acetylation, which could, in turn, affect metabolic shifts in energy metabolism, by influencing the activity of sirtuins (deacetylases) in the post-ischemic heart. However, it is not known whether decreasing acetylation by CD38 inhibition can restore metabolic flexibility and improve cardiac function in the post-ischemic heart.

METHOD: Hearts from Sprague Dawley rats were isolated and perfused in the ex vivo working mode or subjected to 30 minutes of ischemia followed by 40 minutes of reperfusion in the presence or absence of a CD38 inhibitor (50 μM compound 78c). Changes in acetylation status, as well as metabolic rates and functional recovery, were compared between treatments versus control groups.

RESULTS: Inhibition of CD38 has no significant effect on ex-vivo cardiac function in non-ischemic hearts. However, the CD38 inhibitor decreased post-ischemic recovery of heart function. While glucose oxidation rates were significantly decreased following ischemia and reperfusion, fatty acid oxidation rates were increased. CD38 inhibition significantly decreased glucose utilization but did not affect fatty acid oxidation rates in non-ischemic hearts. NAD+ levels were significantly decreased in post-ischemic hearts while NADH levels remained unchanged. There were no significant differences in total acetylation status in both non-ischemic versus ischemic and CD38 inhibitor-treated vs control groups.

CONCLUSION: CD38 inhibition may actually have deleterious effects in postischemic hearts partly by impairing glucose utilization.

Transcriptional Blueprint of the Postnatal Atrioventricular Conduction system.

Yena Oh[1,2], Rimshah Abid[1,2], David Cook[2,3], Jin G. Park[4], Barbara Vanderhyden[2,3], Nikhil Munshi[5], Kyoung-Han Kim[1,2]

[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada. [3]Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, Canada. [4]Virginia G. Piper Center for Personalized Diagnostics, Biodesign Institute, Arizona State University, Tempe, USA. [5]Center for Regenerative Science and Medicine, UT Southwestern Medical Center, Dallas, USA

The atrioventricular conduction system (AVCS), making up <0.05% of the heart, is a network of specialized cardiomyocytes responsible for coordinated spreading of electrical impulses throughout the heart for synchronized contractions. The AVCS is composed of the AV node (AVN), which controls electrical pathway between atria and ventricles, and the ventricular conduction system (VCS), which rapidly propagates the signal throughout the ventricles. Although these structures were anatomically discovered >100 years ago, their molecular constituents largely remain undefined. Previous studies have shown overlapping and nonoverlapping expression patterns of key developmental transcription factors, including Irx3 and Tbx3, within the AVCS, suggesting that the AVCS consists of heterogeneous cell populations with unique molecular profiles. To test our hypothesis, ~7000 AVCS cells were isolated and purified from early postnatal fluorescent reporter mouse hearts (Cntn2-Cre; Rosa26TdTomato) and were subjected to single-cell RNA-sequencing. Unbiased cluster analysis showed distinct transcriptomic profiles in the AVN, proximal-VCS (His-bundle and bundle branches), distal-VCS (Purkinje fibers) as well as a novel cluster of proliferating cells. Using established markers, such as Irx3 in the VCS and Tbx3 in the proximal-AVCS, we identified novel markers of the AVN (Sln), proximal-VCS (Lyz2, S100a6, Nppa) and distal-VCS (Psd3). Moreover, we revealed a region-specific gene regulatory interaction between transcription factors, Irx3 and Tbx3, mediating their downstream targets, Gja1 and Gja5. Importantly, this regional regulation was recapitulated in cultured neonatal mouse atrial and ventricular myocytes overexpressing Irx3 and/or Tbx3. Overall, our study provides a comprehensive and high-resolution map of the molecular heterogeneity within the postnatal AVCS in mice.

Chamber-specific atrial and ventricular structural and arrhythmogenic remodeling in response to chronic volume overload in a mouse model of aortic regurgitation.

Robert Lakin[1], Nazari Polidovitch[1], Xueyan Liu[1,2], Ryan Debi[1], Parashar Bhatt[1], Simona Yakobov[1], Peter Backx[1]

[1]York University, Toronto, Canada. [2]China-Japan Union Hospital of Jilin University, Changchun, China

Valvular heart disease (VHD) predisposes to cardiovascular as well as arrhythmias, particularly atrial fibrillation (AF), suggesting unique chamber-specific arrhythmogenic remodeling. To determine the mechanisms underlying chamber-specific arrhythmogenic remodeling in VHD, we developed a mouse model of aortic regurgitation (AR). Telemetry-hemodynamics revealed that following AR, left ventricular end-diastolic pressures (LVEDPs) markedly elevate ($P<0.05$) in the first 48hrs (20-45mmHg) and then decline at 1-week to levels similar to ($P=0.09$) baseline, rising ($P<0.05$) progressively thereafter (2Wks: 14±3mmHg; 4Wks: 21±3mmHg) in association with progressive LV dilatation (LVDd: 5.40±0.25mm vs. 4.36±0.13mm) and functional impairment (FS: 28.2±3.8% vs. 34.9±1.9%) at 4-weeks. After 4-weeks of AR, LVs underwent marked hypertrophy (27.4% increase) which was not accompanied by measurable ($P>0.113$) changes in either macrophage infiltration (F4/80+: 24±7 vs. 12±6 cells/mm2) or fibrosis (6.3±0.8% vs 5.2±0.6%) compared to SHAM. By contrast, atria showed pronounced ($p<0.05$) atrial hypertrophy (27.2% increase), fibrosis (14.0±2.6% vs. 5.3±1.6%) and macrophage infiltration (143±19 vs. 39±11 cells/mm2) compared to SHAM mice. Compared to the ventricles, fibrosis (2.3-fold) and macrophage infiltration (6-fold) was more pronounced in the atria. Moreover, atrial conduction velocities were reduced and both atrial effective refractory periods (ERPs) and action potential durations were increased in AR mice, with no differences ($P=0.59$) in ventricular ERPs. Importantly, AR increased ($P<0.05$) both in vivo and ex vivo AF inducibility, with no evidence of ventricular arrhythmias. Our results establish unique chamber-specific structural, electrical and arrhythmogenic remodeling in response to chronic volume overload in VHD.

Nitrosothiol Signaling Dysfunction is Driven by GSNOR in the Pathogenesis of Heart Failure with Preserved Ejection Fraction.

Kyle LaPenna[1], Zhen Li[1], Jake Doiron[1], Thomas Sharp[1], Huijing Xia[1], Karl Moles[1], Amelia Haydel[1], Timothy Allerton[2], Ravi Patel[3], Sanjiv Shah[3], Traci Goodchild[1], David Lefer[1]
[1]LSU Health Sciences Center, New Orleans, USA. [2]Pennington Biomedical Research Center, Baton Rouge, USA. [3]Northwestern University Feinberg School of Medicine, Chicago, USA

Background: Heart Failure with Preserved Ejection Fraction (HFpEF) is a systemic inflammatory condition driven by diabetes, obesity, aging and hypertension that culminate in pathological cardiac remodeling. We sought to further elucidate the role of dysregulated nitric oxide (NO) signaling in HFpEF utilizing the ZSF1 obese rat, a clinically relevant animal model of cardiometabolic HFpEF.

Methods: Male ZSF1 obese and normotensive, lean control Wistar Kyoto (WKY) rats (n=6-7 per group) were studied at 14, 18, and 26 weeks of age. At each time point circulating and tissue nitric oxide metabolites (i.e., nitrite and nitrosothiols) were measured. We also quantified the activity of the denitrosylase, s-nitrosoglutathione reductase (GSNOR), using a well-established biochemical assay.

Results: We observed reductions in both plasma and cardiac nitrite in the ZSF1 group vs. WKY indicating dysfunction in the production of nitric oxide via eNOS. Despite the reduction in NO bioavailabilty and lack of iNOS upregulation we observed increased myocardial nitrosothiol (RxNO) levels in the ZSF1 rat. Furthermore, the activity a key enzyme that regulates nitrosothiol levels, GSNOR, was shown to be impaired following the establishment of HFpEF.

Conclusion: Our data provides insight into pathological alterations in NO bioavailability and signaling in HFpEF. Despite reductions in the pool of NO available for normal physiological function and the lack of iNOS upregulation, we observed elevated nitrosylated proteins in the myocardium which was accompanied by reduced GSNOR activity. These data suggest that myocardial nitrosative stress in HFpEF is a result of impaired regulation of nitrosothiol levels and not iNOS upregulation.

PSAT1 Promotes Serine Synthesis Pathway and Cardiac Regeneration Post-Myocardial Infarction.

Ajit Magadum[1], Vandana Mallaredy[1], Rajika Roy[1], Zhongjian Cheng[1], Vagner O C Rigaud[1], Celio X.C. Santos[2], Chunlin Wang[1], Mohsin Khan[3], Ajay Shah[2], Walter Koch[3], Raj Kishore[3]
[1]Center for Translational Medicine, Lewis Katz School of Medicine, Temple University., Philadelphia, USA. [2]King's College London British Heart Foundation Centre, School of Cardiovascular Medicine & Sciences, London, USA. [3]Center for Translational Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, USA

Permanent loss of cardiomyocytes (CM) after myocardial infarction (MI) and limited cardiac regenerative capacity lead to heart failure. The hiPSC-derived extracellular vesicles (EV) have been shown to improve cardiac protection and function. However, the hiPSC-EVs-mediated cardiac function improvement mechanism remains unclear and largely pertains to microRNAs and other RNAs, but not proteins. Here we show that hiPSC-EVs treatment augmented cardiac functions and induced significant CM cell cycle in mice post-MI. Proteomic analysis of hiPSC-EV identified PSAT1 (phosphoserine aminotransferase 1) as a protein expressed exclusively in hiPSC-EVs. The role of PSAT1 in CM proliferation and cardiac regeneration is not studied. Cardiac delivery of PSAT1 modified mRNA (modRNA) induced a significant CM proliferation post-MI. This increase in the CMs proliferation by the PSAT1 modRNA was associated with reduced scar size, CM survival, reduced oxidative stress, CM apoptosis, and improved cardiac function, post-MI. Additionally, PSAT1 modRNA inhibited the CM apoptosis by reducing oxidative stress and DNA damage response post-MI. Moreover, we show that the YAP1, a master regulator of cardiac regeneration, binds to the promoter of PSAT1 and induces its expression. Finally, PSAT1 modRNA induced the serine biosynthesis pathway in CMs, resulting in increased nucleotide synthesis and reduced oxidative stress, thereby supporting CM proliferation. Our studies uncover a novel role of hiPSC-EV specific protein PSAT1, and serine synthesis pathway activation leads to post-MI CM proliferation, inhibition of oxidative stress, and improved cardiac function. Furthermore, this work emphasizes the therapeutic prospect of using PSAT1 modRNA as a gene delivery approach for ischemic heart Diseases.

Transforming growth factor β-dependent regulation of cardiomyocyte maturation.

Rachel Minerath[1], Kelly Grimes[1], Michelle Sargent[1], Allen York[1], Yasuhide Kuwabara[1], Anthony Saviola[2], Christina Alfieri[1], Kirk Hansen[2], Katherine Yutzey[1], Jeffery Molkentin[1]
[1]CCHMC, Cincinnati, USA. [2]UC Denver, Aurora, USA

Transforming growth factor β (TGFβ) is a secreted growth factor that is sequestered to the ECM as a latent complex and released in response to cardiac stress. Once released, TGFβ is required for conversion of quiescent fibroblasts to myofibroblasts that support cardiac repair and fibrosis through production of ECM components. While these functional features of TGFβ are well known, the greater effector function of TGFβ in the heart is unknown. We hypothesized that TGFβ is the critical ECM-cell cross talk mediator in the heart whereby cardiomyocyte (CM)-generated TGFβ communicates with fibroblasts to program stability and composition of the ECM in a reinforcing feedback network. We found that deletion of TGFβ ligands (Tgfb1, Tgfb2, and Tgfb3) from cardiomyocytes (Tgfb123fl/fl-αMHC-Cre), but not fibroblasts (Tgfb123fl/fl-Tcf21-MCM), results in cardiac dysfunction suggesting that CMs are the predominant source of TGFβ in the heart. Paradoxically, ECM deposition is increased in Tgfb123fl/fl-αMHC-Cre hearts. However, in response to injury, Tgfb123fl/fl-αMHC-Cre hearts produce shorter, disorganized collagen fibers suggesting that while Tgfb123fl/fl-αMHC-Cre mice are producing more ECM, the ECM organization is impaired. Gene expression profiling of Tgfb123fl/fl-αMHC-Cre hearts demonstrates improper CM maturation. Additionally, Tgfb123fl/fl-αMHC-Cre CMs remain in cell cycle for a longer duration and exhibit increased mononucleation. However, deleting TGFβ receptors I/II or Smad2/3 from CMs does not recapitulate this phenotype suggesting that TGFβ is not driving CM maturation in an autocrine manner. Instead, these findings indicate that TGFβ functions as a critical cross-talk mediator to fibroblasts to establish proper ECM organization and content that drives CM maturation.

Enalapril reduces frailty and increases MAPK expression in heart and muscle in aging male mice, even when drug is deprescribed.

Manish Mishra[1], Alice E Kane[2], Susan E. Howlett[1]
[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA

Chronic treatment with an angiotensin converting enzyme inhibitor reduces frailty in aging mice. Here we investigated underlying mechanisms. Frailty was assessed in C57Bl/6 mice (both sexes) with a frailty index (FI). Mice were treated with enalapril (30 mg/kg/day, chow) or control from 16 mos of age, then deprescribed. Enalapril reduced frailty scores in both sexes (FI=0.27±0.01 vs 0.21±0.01, 23 mos, n=10/group; 0.35±0.02 vs 0.22±0.01, 21 mos; n=6/group), although frailty increased earlier and was higher in females than males. Beneficial effects of enalapril persisted after drug was discontinued (FI=0.20±0.03 vs 0.19±0.02; 25 mos; n=4,3). We used qPCR to investigate whether enalapril affected markers of senescence, cellular repair and apoptosis in heart and skeletal muscle. Drug treatment had no effect on P21 or P16 in either tissue, regardless of sex. However, cardiac (but not skeletal muscle) MAPK12 expression was higher in drug-treated males than females (1.2±0.3 vs. 0.6±0.1; $p<0.05$; n=6,5) even after enalapril was deprescribed (1.3±0.2 vs. 0.6±0.2; $p<0.05$). Interestingly, cardiac, and skeletal muscle MAPK11 expression was higher in males than females even when enalapril was deprescribed (heart: 1.4±0.2 vs. 0.7±0.2, n=5,6; skeletal muscle: 1.7±0.4 vs. 0.7±0.1, n=5,5; $p<0.05$). Higher levels of MAPK11 and MAPK12 are thought to reduce apoptosis and resist damage in heart, while increased MAPK11 promote myogenesis in skeletal muscle. These effects may contribute to beneficial effects of enalapril on cardiac and skeletal muscle health as well as frailty, especially in older males.

Exploring the role of metformin on cardiac function in PAI-1 deficient mice.

Serena Pulente[1,2], Sweta Gupta[3], Magdalena Lewandowski[3], Amy Shapiro[3], Kyoung-Han Han[1,1], Erin Mulvihill[2,4]
[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]University of Ottawa, Ottawa, Canada. [3]Indiana Hemophilia & Thrombosis Center, Indianapolis, USA. [4]Univeristy of Ottawa Heart Institute, Ottawa, Canada

Plasminogen activator inhibitor-1 (PAI-1/SERPINE1) is a circulating, protease inhibitor that prevents fibrinolysis activation. Interestingly, histological analysis of PAI-1 deficient mice has determined spontaneous cardiac fibrosis in response to aging. These results are consistent with an increased cardiac fibrosis burden in individuals carrying a loss-of-function mutation in SERPINE1. As fibrosis can be pathologically exacerbated under cardiac stress, impairing cardiac healing, effective care of the pro-fibrotic condition is essential.

Metformin is a first line anti-diabetes drug which has a strong safety record and glucose-lowering efficacy. Metformin treatment improves cardiac dysfunction and reduces cardiac fibrosis in a pre-clinical heart failure model induced by transverse-aortic constriction (TAC) surgery. Thus, we hypothesize that the treatment of mice lacking Serpine1 with metformin will reduce cardiac fibrosis and improve cardiac function.

To investigate this, PAI-1 deficient mice were subjected to TAC surgery with/without metformin treatment, and their cardiac function was assessed using echocardiography. Our data demonstrate that the untreated mice at 5-, 8- and 12-weeks post-TAC exhibited continuous worsening of ejection fraction (EF), indicative of deterioration of left ventricular systolic function. On the other hand, metformin treatment trended to stabilize EF, preventing further decline at 8- and 12-weeks post-TAC surgery in PAI-1 deficient mice. The findings will aid in discerning the potential of metformin for preserving cardiac function in the setting of PAI-1 deficiency.

Determining the Role of Zeb1 and Zeb2 in Cardiac Fibroblast Activation.

Rohini Suresh[1,2], Jessica McBride[1,2], Nicolas Leclerc[1,2], Jeffrey Wigle[1,2]
[1]Department of Biochemistry and Medical Genetics, Winnipeg, Canada. [2]Institute of Cardiovascular Sciences, St. Boniface Hosp. Albrechtsen Res Centre, Winnipeg, Canada

Resident cardiac fibroblasts become activated by different pathological stimuli and produce and remodel the extracellular matrix leading to cardiac fibrosis and eventual cardiac dsyfunction. ZEB1 and ZEB2, members of the Zinc finger transcription factor family, have crucial roles in embryonic development, angiogenesis, Epithelial-Mesenchymal transition (EMT), and Endothelial-Mesenchymal transition (EndoMT).[1,2] Previous studies in our lab have shown that Zeb2 is expressed in activated cardiac fibroblasts and that its' expression can be downregulated by Ski, an inhibitor of TGFβ/SMAD signaling.[3] We showed that ZEB2 was sufficient to induce cardiac fibroblast activation but was not required for this process.[4] This could be a result of ZEB1 also being expressed in cardiac fibroblasts compensating for the loss of ZEB2.

We hypothesize that:

1) ZEB1 and ZEB2 initiate and maintain the activated cardiac fibroblast phenotype and 2) ZEB1 and ZEB2 may form a negative feedback loop to maintain an optimal level of expression in cardiac fibroblasts.

We compared the protein levels of ZEB1 and ZEB2 in primary adult male and female rat cardiac fibroblast cells during the process of fibroblast activation in vitro by western blotting. The effect of knockdown of Zeb1 and Zeb2 both in mouse NIH 3T3 fibroblast cell line as well as in primary rat cardiac fibroblast cells was also examined. Our results showed that both ZEB1 and ZEB2 are expressed in the activated fibroblasts with ZEB1 expression being highest at 48 hours (an intermediate state of activation) and then decreasing. In contrast, ZEB2 expression is constant from 48 hours to 96 hours. We observed that ectopic expression of Zeb2 in both NIH 3T3 fibroblast cell line and rat primary cardiac fibroblasts resulted in a corresponding decrease in endogenous ZEB1 expression at the protein level. Furthermore, siRNA-mediated knockdown of Zeb2 resulted in increased ZEB1 expression in cardiac fibroblasts. Similarly, Zeb1 knockdown resulted in increased ZEB2 expression.

ZEB1 is expressed during primary rat cardiac fibroblast activation and ZEB1 and ZEB2 negatively regulate their expression. Therefore, the loss of one ZEB family member may be functionally compensated for by increased expression of the other family member.

Curcumin mitigates heart function, oxidative stress and proinflammatory cytokine levels in rats with rheumatoid arthritis.

Tamara Nikolic Turnic[1,2], Andjela Milojevic-Samanovic[1], Katarina Djordjevic[1], Igor Ilic[3], Marko Folic[1], Vladimir Zivkovic[1], Ivan Srejovic[1], Jovana Jeremic[1], Nevena Jeremic[1], Vladimir Jakovljevic[1,2]

[1]University of Kragujevac, Kragujevac, Serbia. [2]IM Sechenov University, Moscow, Russian Federation. [3]Clinical Center Kragujevac, Kragujevac, Serbia

BACKGROUND/AIM: Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by aggressive and symmetric polyarthritis (1). Curcumin is a chemical composition extracted from the roots of Zingiberaceae and Araceae. Because curcumin has extensive pharmacological actions, a low rate of side effects is easily sourced and relatively cheap, and it has attracted great interest. Previous studies have shown that curcumin has defensive and therapeutic effects on the occurrence and development of RA (2, 3). In this study, we analyzed whether curcumin modulates RA-induced inflammation and synovial hyperplasia and investigated the associated mechanism.

METHODS: Complete Freud's Adjuvant-induced arthritis (CFA) (4) was developed in Wistar rats and used as a model resembling RA in humans. Rats were treated with curcumin (200 mg/kg three times per week per os) and/or the methotrexate (MTX) (0.75 mg/kg twice per week i.p.) for 4 weeks. Effects of the treatment on heart function, local joint (paw thickness, articular score, X ray imaging), peripheral blood (inflammatory markers and oxidative stress), and synovial hyperplasia, in the pathogenesis of CFA were analyzed.

RESULTS: Curcumin and MTX treatment inhibited the increased levels of proinflammatory cytokines including CRP, RF, IL-6, TNF-α, MMP-1, and MMP-3 in CFA rats.

CONCLUSION: Our findings show that curcumin alleviates CFA-induced inflammation, synovial hyperplasia, and the other main features involved in the pathogenesis of CFA. These results provide evidence for the anti-arthritic properties of curcumin and promote its potential use for the treatment of RA.

Identification of Fkbp8 as a Novel Interacting Partner to PLN in Mouse Hearts.

Ava Vandenbelt[1,2], Allen Teng[1,3], Marjan Tavassoli[1,3], Anthony Gramolini[1,3]
[1]Translational Biology and Engineering Program, Ted Rogers Centre for Heart Research, Toronto, Canada. [2]Faculty of Kinesiology & Physical Education, University of Toronto, Toronto, Canada. [3]Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada

Phospholamban (PLN) is critical for modulating Ca2+ uptake into the sarcoplasmic reticulum via sarco(endo)plasmic reticulum Ca2+ ATPase in mammalian hearts[1]. Impaired Ca2+ cycles in myocytes are often associated with the activation of cellular mechanisms, including unfolded protein response[2], mitochondria dysfunction[3], and apoptosis[4], but detailed mechanisms remain largely unknown. Here, we identified the mitochondrial FK506-binding protein subtype 8 (Fkbp8) as a novel PLN-interacting protein via bioinformatic analyses. While fluorescent microscopy showed PLN/Fkbp8 co-localization in both mouse ventricles and isolated adult cardiomyocytes, co-immunoprecipitation (Co-IP) assays confirmed PLN/Fkbp8 interactions in mouse ventricles and transfected HEK293 cells. Interestingly, the interaction is independent of Ca2+ concentration (1 mM Ca2+ ion or 0.5 mM EDTA), despite the presence of calmodulin-binding domain in Fkbp8. Subsequent Co-IP assays mapped the PLN-interacting domain to the N-terminus of Fkbp8, where microtubule-associated protein light chain 3 (LC3) interacting domain was located. Together, these results have established Fkbp8 as a new interacting partner for PLN in vivo and in vitro.

Lipidomic predictors of coronary no reflow.

Arun Surendran[1,2,3], Umar Ismail[4], Negar Atefi[1], Ashim K Bagchi[4], Pawan K Singal[4] Ashish Shah[4,5], Michel Aliani[2], and Amir Ravandi[1,4,5]

[1]Cardiovascular Lipidomics Laboratory, St. Boniface Hospital, Albrechtsen Research Centre, Winnipeg, Canada, [2]Faculty of Agricultural and Food Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada, [3]Mass Spectrometry and Proteomics Core Facility, Rajiv Gandhi Centre for Biotechnology, Kerala, India, [4]Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada, [5]Section of Cardiology, Department of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

Background: The 'no-/slow-reflow' phenomenon (NRP), after primary percutaneous coronary intervention (PCI), is associated with worse outcomes including poor prognosis. The pathophysiology of NRP is not well understood, and effective treatments are lacking. We have performed an untargeted lipidomics analysis to find NRP lipid signatures and to better understand the lipid pathways involved in the pathophysiology of NRP.

Methods: A targeted lipidomic approach was used to identify 322 lipids in plasma from 126 STEMI patients before and after primary PCI. The patients were grouped into normal flow and slow flow based on corrected TIMI frame count.

Results: The lipids (n=31) that were significantly elevated ($p<0.05$) in slow flow patients belong to three classes: phosphatidylcholine (PC), alkylphosphatidylcholine (PC(O)), and sphingomyelin (SM). Strikingly, fatty acids, including 18:2, 18:3, 20:4, 20:5, and 22:6, as well as total fatty acid levels, were also significantly decreased in slow flow subjects ($p<0.05$). While the levels of PC, PC(O), and SM were significantly higher in slow flow patients after PCI, the levels of fatty acids were significantly lower in slow flow patients. Time-series analysis showed that, except for fatty acids, the levels of PC, PC(O), and SM were significantly different ($p<0.05$) across time (before and after PCI). Of these, five lipids, including PC 35:4, PC 37:5, PC(O-36:4), PC(O-36:5), and PC(O-38:5), were also associated with in-hospital cardiovascular events. The correlation analysis revealed a significant negative correlation of these five lipid species with Stromal Cell-Derived Factor 1 (SDF-1), a known biomarker of heart failure and mortality risk, indicating the potential of these lipid species to serve as markers of NRP.

Conclusions: We have identified novel plasma lipidomic profiles that distinguish individuals at risk of NRP during primary PCI. Given the difficulty identifying patients at risk of NRP our data provide valuable insight into the pathophysiological role of lipids in NRP.

One-year outcomes in patients who underwent coronary intravascular shockwave lithotripsy for highly-calcified coronary lesions.

Evan J Wiens[1,2], Sarah Gibbs[1], Kunal Minhas[1,2]
[1]Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, [2]Section of Cardiology, University of Manitoba, Winnipeg, Manitoba

Introduction: Intravascular lithotripsy (IVL) has been shown to have excellent angiographic and short-term clinical results in patients with heavily calcified lesions who require percutaneous coronary intervention in both randomized and observational studies. However, there is limited data regarding the long-term outcomes in real-world patients. We conducted a follow up of a high-risk IVL cohort at a tertiary care center to help better define outcomes over a 1-year period post IVL.

Objective: To determine 1-year outcomes in a cohort of high-risk patients who received IVL at a single provincial cardiac referral center.

Methods: We conducted a retrospective cohort study of 50 consecutive patients who underwent IVL between September 1, 2019 and January 31, 2020. 1-year outcomes were available for 47/50 patients; 3 patients who did not survive their index hospitalization (for reasons unrelated to IVL) were excluded. The primary outcome was need for target vessel revascularization (TVR) at 1 year from index procedure. Secondary outcomes included cardiovascular mortality, myocardial infarction (MI), and freedom from angina.

Results: The mean age of the cohort was 71.5 years and 38% of patients were female. 53% of patients presented with non-ST elevation ACS as the indication for initial IVL. 26% of patients underwent IVL for lesions of the left main coronary artery, and 26% underwent IVL for in-stent restenosis (ISR). Of a total of 47 patients (61 lesions), 4% of patients (3% of lesions) required TVR within 1 year; 96% of patients who underwent IVL remained free from repeat intervention on the same vessel. 2 (4%) suffered mortality at one year from non-cardiovascular causes. 85% of patients remained free from angina at 1 year. 1 patient suffered an MI within 1 year; the culprit vessel had not previously been treated with IVL.

Conclusion: IVL is associated with favorable results out to 1 year with very low rates of TVR. This suggests that IVL is an effective and durable modality for treatment of highly calcified coronary lesions in high-risk patients, including those requiring IVL for the indication of ACS or ISR.

Resting and exercise-augmented hemodynamic evaluation in heart failure patients with preserved ejection fraction.

Olivia Pieroni, Emelissa Valcourt, Karen Alvarez, Mohammad Zahurul Islam, Amir Ravandi, Shelly Zieroth, Ashish H Shah
St. Boniface Hospital; University of Manitoba, Winnipeg, MB, Canada

Background: Heart failure (HF) affects over 600,000 Canadians and causes over 45,000 hospitalizations annually; majority of whom have reduced ejection fraction (HFrEF), defined as LVEF<40%. Despite optimum management, nearly 32% and 64% of patients die by 1 year and 5 years, respectively. These patients are managed in specialized HF clinics, where their evaluation is heavily depended on subjective description of symptoms. As HFrEF patients are likely to have impaired resting and/or exercise-augmented hemodynamic, monitoring of such parameters are likely to identify patients at-risk for adverse outcomes.

Material & methods: Clinically stable HFrEF patients from the HF clinic, St. Boniface Hospital were recruited. Resting and exercise-augmented (25 watts, for up to 12 minutes on a mounted bike) hemodynamic parameters were obtained using a Non-Invasive Cardiac System (NICaS), a whole-body impedance cardiography-based validated technology that is approved by the FDA (USA).

Results: A cohort of 65 HFrEF patients [64.5 ± 15.0 years, 10 (17.5%) female and mean BMI 31.1 ± 7.0 kg/m2] was recruited. At 6-month follow-up, subjects experiencing poor outcomes [unplanned HF hospitalizations and all-cause death], demonstrated lower resting stroke index [32.1 ± 8.4 vs. 37.3 ± 8.3 ml/m2; p=0.03), and cardiac power index (CPI) [0.5 ± 0.2 vs. 0.6 ± 0.2 W/m2; p=0.04]. Moreover, patients with poor outcomes demonstrated exaggerated exercise-augmented Granov-Goor Index (GGI), a surrogate marker of ejection systolic time.

Conclusion: NICaS-derived resting hemodynamic parameters demonstrate potential to identify high-risk HFrEF patients in an outpatient clinic setting. Early identification, and timely management may potentially improve outcomes.

Single nucleus transcriptomics: Apical resection prolonged cardiomyocyte regenerative window in neonatal swine hearts.

Yuji Nakada
The University of Alabama, Birmingham, USA

We have shown that when permanent occlusion of left anterior descending coronary artery surgery is performed in newborn pigs on postnatal day 1 (P1), the animals can completely recover from a myocardial infarction (MI) that occurs on postnatal day 28 (P28) with no evidence of scarring or decline in contractile performance. Our results also suggested that cardiac apical resection (AR) on P1 preserved cardiomyocyte (CM) cell cycle activity as the animals aged; thus, we analyzed single-nucleus RNA-sequencing datasets to compare the transcriptomes of cardiomyocytes from double injury (ARP1MIP28), MI only, and control (CTL) groups.

Louvain clustering identified that cardiomyocytes were distributed among six clusters: CM1-CM6. Three of the clusters were almost entirely composed of cardiomyocytes from a single experimental group: CM2 (96.2% CTL-P56), CM3 (95.7% CTL-P1), and CM6 (92.4% fetal); while clusters CM4 and CM5 contained primarily ARP1MIP28-P35 cardiomyocytes (68.6% and 97.8%, respectively). The CM1 cluster included cardiomyocytes from all other animal groups and time points. Sparse modeling analysis revealed that AR and MI injury, both alone and in combination, appeared to extend the regenerative capacity of cardiomyocytes and perturb cardiomyocyte maturation.

Interestingly, the CM5 cluster was characterized by a highly expressed isoenzyme of the glycolytic enzyme pyruvate kinase M2 (Pkm2) and was activated G2M score and Glycolysis gene expression at almost neonatal levels. These results indicated that transient expression of the CM5 cluster induced by the AR might contribute to sustained remuscularization and myocardial function recovery following an acute MI in large mammals.

HuR-dependent expression of Wisp1 is necessary for TGFβ-induced cardiac myofibroblast activity.

Sharon Parkins[1], Lisa Green[1], Sarah R Anthony[1], Adrienne Guarnieri[1], subhan Khalid[2], Onur Kanisicak[1], Mike Tranter[1]
[1]University of Cincinnati collage of medicine, Cincinnati, USA. [2]University of Cincinnati, Cincinnati, USA

The development and regulation of cardiac fibrosis is influenced by the phenotypic activation of quiescent cardiac fibroblasts (CFs) to active myofibroblasts (MFs). These two distinct cell types play key roles in maintaining the homeostasis of extracellular matrix (ECM) remodeling and contractile functions of the heart.

Previous studies from our lab have shown that the RNA binding protein Human antigen R (HuR) is a key component of the development and regulation of cardiac fibrosis by directly mediating the hypertrophic signaling in cardiac myocytes (CMs). Pathological remodeling and declining cardiac function is also reduced following pressure overload upon HuR inhibition (pharmacological or CM-specific genetic deletion).

In this work, we aimed to determine the specific role of HuR in CF-to-MF activation and the benefits of HuR deletion in cardiac fibroblast during pathological cardiac remodeling. We used primary adult mouse cardiac fibroblasts to show that HuR expression in cardiac fibroblasts is necessary for the TGFβ-dependent expression of MF-associated genes (postn, αSMA, CTGF). Furthermore, we show HuR to be essential for the MF functions of collagen secretion, wound healing/migration, and collagen gel contraction in vitro. Critically, we have identified Wisp1 (Ccn4) as a downstream HuR-dependent mediator of MF activation. HuR directly binds and regulates expression of Wisp1, a previously identified MF marker gene, following TGFβ stimulation. Importantly, exogenous addition of recombinant Wisp1 partially restores MF function following HuR inhibition, demonstrating that HuR is necessary for TGFβ-dependent MF activation in part through regulation of Wisp1 expression.

Study of L-glutamine supplementation on function and metabolism of the diabetic heart and muscle in mice.

Anna Pfister[1,2], Michelle Wintzinger[2], Karen Miz[2], Manoj Panta[2], Mattia Quattrocelli[2,3]
[1]North Carolina State University, Raleigh, USA. [2]Division of Molecular Cardiovascular Biology, Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, USA

Diabetes mellitus increases the risk of developing cardiovascular disease and skeletal muscle dysfunction. Considering the global pandemic scale of diabetes mellitus, the potential benefits of affordable and widely available supplements could support disease management. L-glutamine is a conditionally essential amino acid and a critical substrate for important physiological and metabolic processes. Supplementation of L-glutamine improved muscle function and cardiac metabolism, but the extent to which this applies to type-2 diabetic conditions is still unknown. On the other hand, L-glutamine supplementation lowered plasma glucose and body weight in diabetic rats, but the specific effects on diabetic heart and muscle function are still unknown. Here, we investigate the extent to which L-glutamine supplementation improves heart and muscle metabolism in type-2 diabetic conditions. We address this question comparing L-glutamine (1g/kg) to vehicle with once-daily, four-week-long regimens in lean control mice versus two mice models of type-2 diabetes, i.e. i) mice exposed to streptozocin with high-fat diet and ii) db/db mutant mice. Body-wide metabolism is monitored through echoMRIs and glucose/insulin tolerance tests. Heart function is assessed over time through echocardiography, while muscle function is assessed through grip strength, treadmill and in situ force analyses. Effects on heart and muscle mitochondrial health are quantitated through Seahorse respirometry and NMR metabolomics, as well as analysis of mitochondrial abundance and reactive oxygen species. In summary, our study evaluates the extent to which supplementation of L-glutamine improves function and metabolism of the diabetic heart and muscle.

Perinuclear Ryanodine Receptors Modulate Calcineurin Mediated Gene Expression.

Sofia Possidento[1], Moriah Turcotte, Ph.D.[1], Hrishikesh Thakur, MS, M.Sc.[2], Michael Kapiloff, M.D., Ph.D.[2], Kimberly Dodge-Kafka, Ph.D.[1]
[1]University of Connecticut Health Center, Farmington, USA. [2]Stanford University, Stanford, USA

Extensive research has demonstrated the Ca2+/calmodulin dependent phosphatase calcineurin (CaN) promotes cardiac hypertrophy through dephosphorylation of hypertrophic transcription factor NFAT. However, therapeutic targeting of CaN has proven difficult due in part to a lack of knowledge concerning CaN activation under sympathetic stimulation. Data from our lab demonstrates following sympathetic stimulation, CaN associates with scaffold muscle-specific A-Kinase-Anchoring Protein β (mAKAPβ), located at the nuclear envelope in cardiomyocytes. Notably, this interaction requires a Ca2+ release, ostensibly not obtained through cycled Ca2+ during contraction, and does not decrease CaN activity. We have previously shown mAKAPβ expression is required for the development of cardiac hypertrophy and dephosphorylation of NFAT; achieved via regulation of PKA-modulated perinuclear Ca2+ transients from local ryanodine receptors (RyRs). By using novel nesprin-1α tools specific for RyR, we now show activity of perinuclear RyRs localized to the mAKAPβ complex are necessary and sufficient for CaN-modulated NFAT activation and hypertrophic gene expression in primary cardiomyocytes. Additionally, we have previously demonstrated mAKAPβ association with CaN regulates gene transcription in skeletal muscle. As other labs have demonstrated RyR sourced perinuclear Ca2+ transients in skeletal muscle results in NFAT activation, we hypothesized CaN activity in skeletal muscle may be supported by perinuclear RyRs. We now show mAKAP-associated RyRs are necessary and sufficient to promote NFAT activation and myogenic differentiation in murine skeletal muscle. As CaN remains a key target in cardiac disease prevention, our research suggests avenues for new therapies focused on CaN regulation.

Crossing a Fine Line: Disrupted intracellular calcium handling in the myocardium of a mouse model of perimenopause.

Ciara Barry[1], Sarah Rouhana[1], Jessica Braun[2], Mia Geromella[2], Val Fajardo[2], Glen Pyle[1]
[1]University of Guelph, Guelph, Canada. [2]Brock University, St. Catharines, Canada

The risk of heart failure (HF) in women, specifically HF with preserved ejection fraction (HFpEF), increases with menopause. Estrogens are understood to provide protection against cardiovascular disease (CVD), but how the reduction in ovarian estrogen production with menopause increases the risk of HFpEF on a molecular level is not fully understood. Calcium plays a key role in setting cardiac function and the disruption of calcium handling is one of the main factors that contribute to the negative molecular remodeling in HF. To determine if calcium handling is disrupted during the menopause transitional phase of perimenopause, we used the 4-Vinylcyclohexene-diepoxide (VCD) mouse model. VCD induces gradual ovarian follicular failure, which recapitulates the hormonal changes of perimenopause. We injected female mice with VCD (160 mg/kg/d IP) to induce menopause over 120 days (VCD 120). Day 60 (VCD 60) was chosen to represent the perimenopausal phase. We investigated calcium removal by SERCA using an enzyme-linked spectrophotometric ATPase assay and an Indo-1 based fluorometric calcium uptake assay, along with the expression and post-translational modification of key calcium handling proteins by immunoblotting. Calcium uptake by SERCA was decreased at VCD 60 and 120. Maximum SERCA activity was decreased at VCD 60 but not 120. NCX expression was transiently upregulated at VCD 60 and normalized by VCD 120. These data represent the first investigation of calcium handling in a mouse model of menopause and show that calcium handling disruption occurs early in the perimenopausal transition, coinciding with the altered expression of key cardiomyocyte proteins.

Integrative proteomic and phosphoproteomic analysis identifies etiology-specific phosphorylation patterns in the failing human heart.

Cristine Reitz[1], Marjan Tavassoli[1], Da Hye Kim[1], Sina Hadipour-Lakmehsari[1], Saumya Shah[2], Allen Teng[1], Andrew Emili[3], Gavin Oudit[2], Uros Kuzmanov[1], Anthony Gramolini[1]
[1]University of Toronto, Department of Physiology, Ted Rogers Centre for Heart Research, Toronto, Canada. [2]University of Alberta, Department of Medicine, Edmonton, Canada. [3]Boston University, Department of Biology and Biochemistry, Boston, USA

The prognosis and treatment outcomes of heart failure patients rely heavily on patient etiology, yet the underlying signaling mechanisms are not fully elucidated. Protein phosphorylation is a key regulatory element influencing the activity and function of signaling networks; however, there is a lack of comprehensive phosphoproteomic studies in human heart failure. We assessed the hypothesis that an integrative phosphoproteomic analysis of human ischemic (ICM) and dilated (DCM) cardiomyopathy would reveal etiology-specific disease pathways. Combined proteomic and phosphoproteomic analysis of left ventricular tissue explants from DCM patients (n=4) vs. non-failing controls (n=4), and left ventricular infarct vs. non-infarct, and peri-infarct vs. non-infarct regions of ICM patients (n=4) identified 5,570 unique proteins with 13,624 corresponding phosphorylation sites. We identified αT-catenin as a cardiac-enriched intercalated disc phosphoprotein with a cluster of 4 hyper-phosphorylated sites, within a conserved "phospho-linker" domain, specifically in DCM hearts ($P<0.0001$). High-resolution imaging showed elongated intercalated disc morphology in DCM hearts (10.07±0.76μm control vs. 17.20±1.87μm DCM, $P<0.05$, n=3/group), with significantly increased colocalization of αT-catenin with the intercalated disc protein N-cadherin (Pearson's coefficient 0.55±0.04 control vs. 0.71±0.02 DCM, $P<0.05$, n=3/group). To investigate the functional role of αT-catenin phosphorylation, we overexpressed WT protein vs. non-phosphorylatable vs. phospho-mimetic forms in adult mouse cardiomyocytes using lentiviral transduction. Confocal imaging revealed significant internalization of the phospho-null protein, reduced interaction with N-cadherin, and impaired cell-cell adhesion, with rescue by the phospho-mimetic. Together, these findings demonstrate a role for αT-catenin phosphorylation in cardiomyocyte intercalated disc organization and cell-cell adhesion in human DCM.

The Pause Before the Storm: Identifying Cardiac Molecular Changes in a Mouse Model of Menopause.

Sarah Rouhana[1], Ciara Barry[1], Jessica Braun[2], Mia Geromella[2], Val Fajardo[2], W Glen Pyle[1]
[1]Laboratory of Molecular Cardiology, Department of Biomedical Sciences, University of Guelph, Guelph, Canada. [2]Department of Kinesiology and Centre for Bone and Muscle Health, Brock University, St. Catharines, Canada

Women are protected against cardiovascular disease (CVD) until the onset of menopause. This protection, attributed to circulating estrogens, is lost with deceased ovarian estrogen production. Not only is the risk of CVD elevated in post-menopausal women when compared to age-matched men, the rates of adverse cardiovascular events and mortality are higher. Although the female heart doesn't exhibit pronounced clinical changes in function or gross structural remodeling with menopause, subclinical changes driven by molecular remodeling as early as the perimenopausal transition may set the stage for increased risk of CVD mortality. To identify the mechanisms underlying the increased risk of adverse CVD outcomes in menopause, we injected female mice with 4-vinylcyclohexene diepoxide (VCD, 160 mg/kg/d IP) to induce menopause over 120 days (VCD 120). This model recapitulates the natural, physiological transition through perimenopause and allows for an investigation of functional and molecular changes during a perimenopausal phase (VCD 60). Echocardiography found no significant structural or functional changes in mice up to 120 days after VCD injection. Extracellular matrix remodeling was evident by changes in MMP activity and a significant increase in periostin expression. Masson's trichrome staining demonstrated a significant increase in fibrosis in the VCD 60 group vs intact and VCD 120 group. Abnormal calcium handling was observed in both VCD 60 and VCD 120 mice. These data represent the first investigation of cardiac molecular changes that predispose the heart to diastolic dysfunction and may provide a mechanistic basis for the increased risk of HFpEF in postmenopausal women.

Cardiac glucose oxidation is impaired in heart failure with preserved ejection fraction (HFpEF).

Qiuyu Sun, Berna Güven, Cory Wagg, Amanda Oliveira, Heidi Silver, Ander Arana, Brandon Chen, Qutuba Karwi, Faqi Wang, Liyan Zhang, Jason Dyck, Gavin Oudit, Gary Lopaschuk
Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

Heart failure with preserved ejection fraction (HFpEF) is a debilitating disease that is prevalent in our society. Despite continued efforts, few reliable therapies have proven to be effective in treating HFpEF. While it is well-accepted that HF involves changes in myocardial energetics, it remains unclear whether alterations in cardiac energetics contribute to HFpEF severity. Therefore, the objectives of this study were to define the cardiac energy metabolic profile in HFpEF and then attempt to lessen the severity of HFpEF by improving cardiac energetics. Mice were subjected to a 2-hit HFpEF protocol (obesity and hypertension) over a 10-week period resulting in HFpEF development. Hearts from these mice were perfused with radiolabeled energy substrates to directly measure rates of glucose oxidation and fatty acid oxidation. In HFpEF mice hearts, glucose oxidation was significantly suppressed, with a parallel increase in fatty acid oxidation. We then established a '4-hit' mouse model of HFpEF (obesity, hypertension, aging and female), to assess whether stimulation of glucose oxidation using a pyruvate dehydrogenase kinase inhibitor (PDKi, 40 mg/kg/day MMR0209-13) can protect the heart from HFpEF. PDKi treated mice had improved systolic and diastolic function compared to vehicle treated mice, in addition to improved survival rates. Consistent with the '2-hit' HFpEF mice, the '4-hit' HFpEF mice also had significantly decreased glucose oxidation rates, which was increased with PDKi treatment. In conclusion, hearts become metabolically inflexible in HFpEF due to a prominent decrease in glucose oxidation, and stimulation of glucose oxidation can improve cardiac function in these mice.

Tmem65 is critical for the structure and function of the intercalated discs in mouse hearts.

Allen Teng[1], Liyang Gu[1], Michelle Di Paola[1], Robert Lakin[2], Zachary Williams[3], Aaron Au[1], Wenliang Chen[2], Neal Callaghan[1], Farigol Hakem-Zadeh[1], Yu-Qing Zhou[1], Meena Fatah[4], Diptendu Chatterjee[4], Jane Jourdan[3], Jake Liu[1], Craig Simmons[1], Thomas Kislinger[1], Christopher Yip[1], Peter Backx[2], Robert Gourdie[3], Robert Hamilton[4], Anthony Gramolini[1]

[1]University of Toronto, Toronto, Canada. [2]York University, Toronto, Canada. [3]Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, USA. [4]Hospital for Sick Children, Toronto, Canada

The intercalated disc (ICD) is unique membrane structure that is indispensable to normal heart function, yet its structural organization is not completely understood. Previously, we showed that the ICD-bound transmembrane protein 65 (Tmem65) was required for connexin 43 (Cx43) localization and function in cultured mouse neonatal cardiomyocytes. Here, we investigated the role of Tmem65 in ICD organization in vivo. A mouse model was established by injecting CD1 mouse pups (3-7 days after birth) with recombinant adeno-associated virus 9 (rAAV9) harboring Tmem65 shRNA which resulted in a 90% reduction of Tmem65 expression in mouse ventricles compared to mice injected with scrambled shRNA. Tmem65 knockdown (KD) resulted in increased mortality which was accompanied by eccentric hypertrophic cardiomyopathy within 3 weeks of injection, progressing to dilated cardiomyopathy with severe cardiac fibrosis by 7 weeks post-injection. Tmem65 KD hearts displayed depressed hemodynamics, measured echocardiographically, accompanied by electrocardiogram changes (prolonged PR intervals and QRS duration) consistent with impaired conduction, which was confirmed with optical mapping of isolated hearts. Immunoprecipitation and super-resolution microscopy demonstrated a physical interaction between Tmem65 and sodium channel β subunit (β1) in mouse hearts and this interaction appeared to be required for the establishment of perinexal nanodomain and the localization of both voltage-gated sodium channel 1.5 (NaV1.5) and Cx43 to ICDs. Whole-cell patch clamp electrophysiology revealed reductions in Ca2+ and K+ currents in Tmem65 KD cardiomyocytes in comparison to control cells. We conclude that disrupting Tmem65 function results in impaired ICD structure, abnormal cardiac electrophysiology, and ultimately cardiomyopathy.

Elucidating the molecular mechanisms and cellular specificity of HDAC inhibitor efficacy in diastolic dysfunction.

Joshua Travers[1], Sara Wennersten[1], Marcello Rubino[1], Jessica Schwisow[1], Eric Jonas[1], Rui Fu[1], Ryan Sheridan[1], Harrison Smith[2], Rachel Hirsch[2], Lauren Vanderlinden[3], Ying-Hsi Lin[1], Ilaria Ferrari[1], Doron Regev[1], Kimberly Demos-Davies[1], Rushita Bagchi[1], Evgenia Dobrinskikh[1], Maria Cavasin[1], Luisa Mestroni[1], Christian Steinkuhler[4], Charles Lin[5], Steven Houser[6], Amrut Ambardekar[1], Brisa Pena[1], Kathleen Woulfe[1], Maggie Lam[1], Ronald Vagnozzi[1], Michael Bristow[1], Timothy McKinsey[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, USA. [2]Baylor College of Medicine, Houston, USA. [3]Colorado School of Public Health, Aurora, USA. [4]Italfarmaco SpA, Milan, Italy. [5]Kronos Bio, San Mateo, USA. [6]Temple University, Philadelphia, USA

Impaired left ventricular relaxation or compliance is associated with the progression to HFpEF, a devastating syndrome with poor prognosis for which limited therapeutic strategies currently exist. Pharmacological inhibition of histone deacetylases (HDACs), epigenetic enzymes that regulate chromatin-dependent signal transduction, has shown promise pre-clinically in the setting of diastolic dysfunction. We evaluated the therapeutic efficacy, cellular specificity and molecular mechanisms of ITF2357/Givinostat, a clinical-stage inhibitor of HDAC catalytic activity, in a murine model of diastolic dysfunction with preserved ejection fraction and in primary failing human cardiac fibroblasts. Administration of ITF2357/Givinostat in the setting of preexisting diastolic dysfunction led to a nearly complete restoration of physiological diastolic function as measured by echocardiography. While no appreciable collagen deposition could be detected by conventional techniques, quantitative mass spectrometry revealed induction in the expression of >100 extracellular matrix proteins, which correlated with profound tissue stiffening based on atomic force microscopy. Remarkably, ITF2357/Givinostat treatment entirely blocked extracellular matrix expansion and LV stiffening. The HDAC inhibitor was subsequently shown to suppress myofibroblast activation in failing human cardiac fibroblasts. The recent implementation of single-cell RNA sequencing technologies is now shedding light on the effect of diverse cell populations in the pathogenesis of diastolic dysfunction, including cardiac fibroblasts and macrophages, and the mechanisms by which HDAC inhibition triggers reversal. These findings demonstrate the potential of HDAC inhibition as a therapeutic intervention to reverse existing diastolic dysfunction, and establish blockade of covert extracellular matrix remodeling by cardiac fibroblasts as a mechanism by which HDAC inhibitors improve ventricular filling.

Perinuclear β-Adrenergic Receptors are Necessary and Sufficient to Promote Cardiac Hypertrophy.

Moriah Turcotte, Ph.D[1], Hrishikesh Thakur, MS, M.Sc.[2], Michael Kapiloff, M.D., Ph.D[2], Kimberly Dodge-Kafka, Ph.D[1]
[1]University of Connecticut Health Center, Farmington, USA. [2]Stanford University, Stanford, USA

Cardiac β-adrenergic receptor (β-AR) signaling dogma posits that binding of extracellular agonists to plasma membrane receptors triggers an intracellular signaling cascade which facilitates chronotropic and inotropic responses. While it is documented that β1 and β2-ARs on the plasma membrane will reorganize and internalize during disease, more recent research suggests the hypothesis that β-AR subcellular localization and activation may be critical to regulation of deleterious phenotypes. In particular, functional β1 and β3-ARs are expressed on the nuclear membrane of the cardiomyocyte, although their contribution to cardiomyocyte physiology is still not understood. Cardiac hypertrophy, or the non-mitotic growth of cardiomyocytes in response to stress, is dependent upon upregulation of key hypertrophic genes in response to chronic sympathetic stimulation. We hypothesize that sympathetic stimulation via catecholamine norepinephrine (NE) binds to nuclear β-ARs leading to localized cAMP production and PKA-mediated phosphorylation of downstream substrates leading to increased hypertrophic gene expression. Critical to hypertrophic gene regulation is muscle-specific A-Kinase-Anchoring protein β (mAKAPβ), expressed exclusively on the nuclear envelope via membrane protein nesprin-1α. We have extensively demonstrated in both cellular knockdown studies and cardiac-specific gene deletion that mAKAPβ expression is required for cardiac hypertrophy induction. We now demonstrate in neonatal and adult rat cardiomyocytes using novel nesprin-1α targeted tools that β-ARs local to the mAKAPβ “signalosome” are both necessary and sufficient to promote PKA-mediated cardiac hypertrophy, and furthermore, this process occurs independent to cytosolic PKA activity. As β-blockers are currently a standard in high blood pressure treatment, our research is vital to new therapy development.

Loss of free fatty acid receptor 4 impairs left ventricular functional recovery after ischemia reperfusion.

Michael Zhang[1], Sergey Karachenets[2], Chastity Healcy[2], Timothy O'Connell[2]
[1]University of Minnesota, Minneapolis, USA. [2]University of Minnesota, Minneapolis, USA

Omega-3 fatty acid treatment can reduce incident coronary heart disease, and free fatty acid receptor 4 (Ffar4) is a G-protein coupled receptor for medium and long chain fatty acids that is activated by omega-3 fatty acids. Using a mouse model of ischemia (60 min)-reperfusion (I/R), we found that in mice with systemic deletion of Ffar4 (Ffar4KO), loss of Ffar4 in males and females had no effect on area-at-risk or infarct size 24 hr post-I/R, but significantly impaired recovery of LV systolic function through 28 days post-I/R. To examine the molecular basis for the worsened functional recovery in Ffar4 KO hearts, we performed an unbiased transcriptomics analysis comparing sham to the infarct and non-infarct regions of hearts from wildtype and Ffar4KO mice 3-days post-I/R. After sequence alignment and read counting, the limma R package was used to analyze differential gene expression. To define differences in gene expression patterns, we performed a principal component analysis. Principle component 1 (PC1) separated infarct from non-infarct and sham for both WT and Ffar4KO, whereas PC2 separated the infarct region between WT and Ffar4KO. Pathway analysis revealed enrichment of metabolic pathways (e.g.: Glycolysis, amino acid biosynthesis, carbohydrate metabolism), signaling pathways (e.g.: Focal adhesion, EGFR1 signaling) and extracellular matrix (e.g. Collagen synthesis, collagen formation). Interestingly, we found that phosphodiesterase 6c expression was increased 5.6-fold in Ffar4KO hearts, which was subsequently confirmed by immunoblotting. Ongoing studies are establishing the link between high levels of phosphodiesterase 6c and impaired LV systolic function post-I/R.

GENE THERAPY ENCODING CELL CYCLE FACTORS IMPROVES CARDIAC FUNCTION IN A CHRONIC HEART FAILURE RAT MODEL.

Riham Abouleisa[1], Abou-Bakr Salama[1], Qinghui Ou[1], Xian-Liang Tang[1], Hania Abdelhafez[1], Amie Woolard[2], Dana Hammouri[1], Sarah Cayton[3], Roberto Bolli[1], Tamer Mohamed[1]
[1]University of Louisville, Louisville, USA. [2]Georgetown college, Georgetown, USA. [3]Transylvania University, Lexington, USA

Background: Treatment of heart failure (HF) is limited due to the limited regenerative capacity of cardiomyocytes (1, 2). Ectopic expression of Cdk1/CyclinB1 and Cdk4/CyclinD1 (named 4F) via adenovirus vector promotes cardiomyocyte proliferation in 20% of infected cardiomyocytes in vitro and in vivo and improves cardiac function after myocardial infarction (3). Recently, we demonstrated that a polycistronic non-integrating lentivirus encoding 4F, each driven by a TNNT2 promoter (TNNT2-4F-NIL), promotes cardiomyocyte proliferation on a single-cell transcriptomics level as well as in vitro and in vivo. Furthermore, when TNNT2-4F-NIL was administered one week after ischemic reperfusion (subacute ischemic heart failure (subacute-IHF)), TNNT2-4F NIL treatment significantly improved cardiac function (4). Furthermore, TNNT2-4F-NIL improved the HF-induced congestion in the lung, as evidenced by the improvement of lung weight/body weight (4).

Aim: To test the efficacy of TNNT2-4F-NIL in a chronic ischemic heart failure model (Chronic-IHF).

Methods and Results: To assess the efficacy of TNNT2-4F-NIL on the chronic-IHF model, rats were subjected to ischemic reperfusion; four weeks later, animals were injected (intramyocardially) with either TNNT2-4F-NIL or control-NIL. Four weeks after injection, TNNT2-4F-NIL treated rats showed a significant improvement in left ventricular ejection fraction (EF) and fractional shortening (FS) compared to controls as assessed by echocardiography (EF: TNNT2-4F-NIL 60.7±2.8% vs. control-NIL 44.8±2.8%; FS: TNNT2-4F-NIL 18.9±2.7% vs. control-NIL 8.3±0.8%; $p<0.01$ n=6/group). TNNT2-4F-NIL reduced the cardiac dilatation associated with chronic IHF as indicated by end-diastolic (EDV) and end-systolic volumes (ESV) (EDV and ESV: TNNT2-4F-NIL 245.4±18.8 and 97.3±11.8µl vs. control-NIL 316±20.8 and 174.0±13.9µl, respectively, $p<0.01$ n=6/group). The left ventricular area was also significantly reduced in TNNT2-4F-NIL treated rats compared to controls. TNNT2-4F-NIL treated rats showed a significant 30% reduction in scar size compared to controls n=6/group, $p<0.01$). However, TNNT2-4F-NIL treated rats did not improve lung weight per body weight.

Conclusion: This study provides a proof of concept that TNNT2-4F-NIL could be efficient in improving cardiac function in a chronic heart failure model. Further studies are needed to validate this efficacy in large animal models and assess the sustainability of the beneficial effects of TNNT2-4F-NIL for several months post-treatment.

MXene quantum dots promote maturation of induced pluripotent stem cells derived cardiomyocytes.

Keshav Narayan Alagarsamy, Leena Regi Saleth, Alireza Rafieerad, Abhay Srivastava, Weiang Yan, Niketa Sareen, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

Induced pluripotent stem cells derived cardiomyocytes (iPSC-CMs) provide a powerful platform for understanding disease mechanisms, drug screening and its application in cellular regenerative therapies (1). However, the current differentiation protocols produce immature iPSC-CMs resembling fetal cardiomyocytes rather than its adult counterpart. Various tissue engineering strategies are currently being tested to develop strategies to produce mature cardiomyocytes from iPSCs. One of the approaches is to employ electroconductive nanomaterials to mimic the mechanical and electrical microenvironment of the native myocardium (2). In this regard, MXene, an emerging class of electroconductive nanomaterial with its unique electrical and physiochemical properties has found its way in a wide variety of biomedical applications such as bioimaging, biosensing and drug delivery (3-4). Here, we fabricated a novel MXene matrix with excellent electroconductivity and biocompatibility for iPSC-CMs maturation. In comparison with cells grown on matrix without MXene, iPSC-CMs grown on MXene matrix beat at a faster pace and display better calcium kinetics and action potential. Additionally, iPSC-CMs grown on MXene matrix showed mature metabolic phenotype, as measured by mitochondrial membrane potential and respiratory capacity, resulting in an overall improvement in metabolism. As a result, MXene provides a superior electroconductive matrix for maturing iPSC-CMs for cardiovascular theranostics applications.

CANFLAX: Can flaxseed “milk” prevent broken hearts in women with breast cancer?

Vibhuti Arya[1], Lana Mackic[1], Sara Telles-Langdon[1], David Y.C. Cheung[1], Paris R. Haasbeek[2], Danielle Desautles[3], Vallerie Gordon[3], Jeffrey Graham[3], Susan Green[3], Debjani Grenier[3], Christina Kim[3], Saroj Niraula[3], Maclean Thiessen[3], Marshall Pitz[3], Davinder S. Jassal[1,3,4]

[1]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Faculty of Science, University of Manitoba, Winnipeg, Canada. [3]Section of Oncology, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada. [4]Section of Cardiology, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

Introduction: Cardiovascular disease and cancer are major public health concerns worldwide. Despite the beneficial effects of the anthracycline based anti-cancer agents Doxorubicin (DOX) for improving overall survival in women with breast cancer, cardiotoxicity remains a serious challenge for these drugs (1,2). Although recent basic sciences studies have demonstrated the cardioprotective role of flaxseed (FLX) in the prevention of DOX mediated cardiotoxicity, little is known about the effects of this nutraceutical in the clinical setting (3,4).

Objective: The aim of the CANFLAX study is to investigate whether consumption of FLX “milk” can prevent heart failure in women with breast cancer treated with anthracyclines.

Methods: In this double-blind prospective randomized controlled clinical trial, prior to initiation of DOX-based chemotherapy, women with breast cancer will be randomized to either placebo oat fiber “milk” or FLX “milk” for a total of 4 months. Serial demographic data, echocardiography, and blood work will be measured at baseline, 4-months, 6-months and 12-months post-intervention.

Results: Of a total 17 women (mean age 45±2 years with an average body mass index (BMI) of 28±1 kg/m2) enrolled between June 2021 and June 2022, 10 were randomized to group A and 7 were randomized to group B; the identity of the oat fiber “milk” or FLX “milk” is blinded. The prevalence of underlying cardiovascular risk factors was low in both groups. In total, 1 (6%) participant had hypertension, 2 (12%) participants had hyperlipidemia and past smoking history, and 3 (17%) participants had a family history of premature coronary artery disease (CAD). Additionally, there was no difference in the location and size of breast cancer, axillary lymph node involvement, or radiation use between the two groups. The majority of the patients 15 (88%) received 4 cycles of adriamycin and cyclophosphamide (AC). The baseline left ventricular ejection fraction (LVEF) values were 62±5% and 60±6%, for groups A and B, respectively

Conclusion: The baseline demographics are comparable between the two study groups. Whether the prophylactic administration of FLX “milk” is cardioprotective in the setting of anthracycline-mediated cardiotoxicity in the breast cancer setting remains to be determined.

Lady's bedstraw extract as a novel cytoprotective agent against doxorubicin-induced cardiotoxicity in rats.

Jovana Bradic[1], Jovana Jeremic[1], Vladimir Jakovljevic[2,3], Marijana Andjic[1], Marina Tomovic[1], Marina Nikolic[1]

[1]Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [3]Department of Human Pathology, 1st Moscow State Medical, University IM Sechenov, Moscow, Russian Federation

Background/Aim: Although previous data confirmed the strong antioxidant capacity and cardioprotective potential of lady's bedstraw herb extract (Galium verum L, GVE), there are no information referring to the role of this plant species in DOX-induced cardiac damage (1, 2). Since natural antioxidant represent a worthwhile tool for reduction of heart damage associated with DOX therapy, we hypothesized that lady's bedstraw extract would alleviate DOX- induced heart damage (3). Therefore, this study was conducted to assess the influence of two-week GVE intake on doxorubicin-induced cardiotoxicity in rat model.

Methods: 24 male Wistar albino rats were randomly divided into the following groups: healthy control (CTRL), doxorubicin (DOX), and DOX+GVE. GVE was applied per os (50 mg/kg/day for 2 weeks). In order to establish doxorubicin-induced cardiotoxicity, doxorubicin was injected as a single dose of 15 mg/kg. Three days after DOX application, all animals were sacrificed, blood samples were collected and hearts were isolated for performing ex vivo measurements. Concentration of pro-oxidants and antioxidants was determined spectrophotometrically in blood samples in order to assess the influence of GVE on systemic redox status. Functional cardiac parameters were monitored during the autoregulation protocol (40-120 mmHg) on the Langendorff apparatus. Cardiac redox status was assessed spectrophotometrically in heart tissue homogenates, while histological examinations in heart tissue samples were performed to verify morphological changes (4).

Results: Our results demonstrated that GVE consumption effectively suppressed disturbed cardiac response induced by DOX. GVE treatment was able to diminish most of the measured pro-oxidant parameters, as well as to increase the activity of the antioxidant enzymes compared to the DOX group. Histological data showed that GVE consumption alleviated the pathological injuries caused by DOX injection such as myofibres degeneration, myocardial edema, and congestion.

Conclusion: Our findings suggest that two-week GVE intake could relieve DOX-induced cardiotoxicity, via improvement in heart contractility, attenuation of oxidative stress and prevention or alleviation of structural heart damage. Therefore, this plant species extract could be a promising cytoprotective therapeutic approach against DOX-induced cardiotoxicity.

Mitochondrial Autophagy and Cell Survival is Regulated by the Circadian Clock Gene in Cardiac Myocytes during Ischemic Stress.

Molly Crandall[1], Inna Rabinovich-Nikitin[1], Tami Martino[2], Lorrie Kirshenbaum[1]
[1]University of Manitoba, Winnipeg, Canada. [2]University of Guelph, Guelph, Canada

Background/Aim: Cardiac function is highly reliant on mitochondrial oxidative metabolism and quality control (1). The circadian Clock gene is critically linked to vital physiological processes including mitochondrial fission, fusion and bioenergetics; however, little is known of how the Clock gene regulates these vital processes in the heart (2).

Methods/Results: We identified a putative circadian CLOCK-mitochondrial interactome that gates an adaptive survival response during myocardial ischemia. We show by transcriptome and gene ontology mapping in CLOCK D19/D19 mouse that Clock transcriptionally coordinates the efficient removal of damaged mitochondria during myocardial ischemia by directly controlling transcription of genes required for mitochondrial fission, fusion and macroautophagy/autophagy. Loss of Clock gene activity impaired mitochondrial turnover resulting in the accumulation of damaged reactive oxygen species (ROS)-producing mitochondria from impaired mitophagy. This coincided with ultrastructural defects to mitochondria and impaired cardiac function. Interestingly, wild type CLOCK but not mutations of CLOCK defective for E-Box binding or interaction with its cognate partner ARNTL/BMAL-1 suppressed mitochondrial damage and cell death during acute hypoxia. Additionally, the autophagy defect and accumulation of damaged mitochondria in CLOCK-deficient cardiac myocytes were abrogated by restoring autophagy/mitophagy. Inhibition of autophagy by ATG7 knockdown abrogated the cytoprotective effects of CLOCK.

Discussion: Collectively, our results demonstrate that CLOCK regulates an adaptive stress response critical for cell survival by transcriptionally coordinating mitochondrial quality control mechanisms in cardiac myocytes (3). Interdictions that restore CLOCK activity may prove beneficial in reducing cardiac injury in individuals with disrupted circadian CLOCK (4).

NF-κB Signaling Regulates Mitochondrial Permeability Transition Pore Opening of Cardiac Myocytes via Cyclophilin D (CypD) Modulation.

Rimpy Dhingra, Matthew Guberman, Victoria Margulets, Floribeth Aguilar, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

Background: Nuclear Factor-κB (NF-κB) is ubiquitously present transcription factor that regulates a variety of cellular functions including cell survival (1). Herein, we show a critical role for NF-κB signaling in regulation of mitochondrial permeability transition pore opening (mPTP) that involves cyclophilin D (CypD).

Methods: Using a combination of in vivo (C57Bl/J mice) and in vitro approaches, we monitored cardiac ultrastructure, mitochondrial calcium, mitochondrial bioenergetics, LDH and cardiac cell viability.

Results: Cardiac myocytes expressing a kinase defective form of IKKβ (IKKK-M), the principle IKK required for NF-κB activation, displayed impaired NF-κB gene activity (2). Defects in NF-κB signaling coincided with an increase in mPTP opening and cell death. Interestingly, mPTP opening and cell death observed in the NF-κB defective cardiomyocytes was supressed by inhibition of mPTP modulator CyclophilinD (CypD), with cyclosporin A (CSA) or by siRNA knock down (CypDsiRNA), suggesting a link between mPTP regulation and NF-κB signaling. Earlier, we reported that chemotherapy drug doxorubicin (Dox) treatment resulted in severe ultra-structural defects including disrupted mitochondrial cristae and impaired respiration (in vitro and in vivo), increased mitochondrial calcium overload, mPTP opening and a widespread cell death (3)(4). Interestingly, we observed a dramatic reduction in NF-κB signaling in cardiac myocytes treated with doxorubicin (18 Hrs), coupled with impaired respiration and increased protein complexes between mitochondrial death gene Bnip3 and CypD. Inhibition of CypD suppressed doxorubicin induced cell death of cardiac myocytes. Finally, restoration of NF-κB signaling in cardiac myocytes treated with doxorubicin by IKKβ, active kinase, suppressed Bnip3-CypD complex, mitochondrial calcium overload, respiration defects and cell death.

Conclusion: The data herein, provides the first direct evidence that impaired NF-κB signaling predispose Dox treated cardiac myocytes to mitochondrial injury and cell death. Hence, interventions that preserve NF-κB survival signaling pathways in the heart may prove beneficial in reducing cardiac dysfunction and heart failure in cancer patients undergoing doxorubicin chemotherapy.

Dual Mitophagy and Necrosis Dependent Pathways Functionally Couple Mitochondrial Death protein Bnip3 to Doxorubicin Cardiomyopathy.

Matthew Guberman, Rimpy Dhingra, Victoria Margulets, Floribeth Aguilar, Lorrie Kirshenbaum
University of Manitoba, Winnipeg, Canada

Background/Aim: Autophagy is a homeostatic process by which damaged organelles such as mitochondria are degraded by an autophagosomal regulated pathway (1). Accordingly, excessive autophagy can be detrimental and promote cell death (2). Herein, we provide new compelling evidence that mitophagy and necrotic cell death induced by the chemotherapy drug doxorubicin are obligatorily linked to and mutually dependent upon the Bcl-2 protein Bnip3.

Methods/Results: In contrast to saline treated mice, a marked increase in mitochondrial targeting of Bnip3 was observed in hearts of mice treated with DOX. This coincided with severe morphological defects, including recruitment of Parkin to mitochondria, increased co-localization of Bnip3 and LC3II and numerous cytoplasmic vesicles containing mitochondria - indicative of increased mitophagy. Interestingly, mitophagy was accompanied by an increase of the necrosis markers Lactate Dehydrogenase (LDH), Troponin T (cTnT) and loss of nuclear High Mobility Group Box 1 (HMGB1). Further, while mitochondria of wild type mouse embryonic fibroblasts (MEFs) treated with DOX, were severely damaged, resulting in mitophagy and necrotic cell death, Bnip3 - /- MEFs were resistant to the cytotoxic effects of doxorubicin. Conversely, inhibition of autophagy with 3-Methyl Adenine (3-MA), knock-down of Atg 7 or Bnip3 suppressed mitophagy and necrotic cell death of cardiac myocytes treated with DOX. Concordantly, mice deficient for Bnip3 were resistant to mitochondrial injury and mitophagy induced by DOX and exhibited lower mortality than corresponding wild type mice treated with doxorubicin.

Discussion: To our knowledge our data provide the first direct evidence that mitophagy induced by DOX is maladaptive and leads to necrotic cell death by a mechanism that is mutually dependent upon and obligatorily linked to Bnip3 (3). Interventions that mitigate abnormal mitophagy may provide beneficial in suppressing necrotic cell death and cardiac dysfunction in cancer patients treated with doxorubicin (4).

Is DHA beneficial or not for your blood vessels: Concentration and growth state dependent effects of DHA on endothelial cells.

Shiqi Huang[1,2], Carla Taylor[1,2], Peter Zahradka[1,2]
[1]University of Manitoba, Winnipeg, Canada. [2]Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, Canada

Background: Docosahexaenoic acid (DHA) is widely assumed to be atheroprotective [1]. Yet, recent clinical trials have yielded divergent findings regarding the benefits of DHA on cardiovascular disease (CVD) [2,3]. Our laboratory previously reported that DHA differentially affected growing and quiescent human endothelial cells [4], which represent the atherogenic and healthy states *in vivo*, respectively. Therefore, we hypothesized that the atheroprotective effects of DHA may be growth-state dependent. Methods: Human EA. hy926 cells were cultured on Matrigel-coated plates to growing and quiescent states, and then treated with DHA. The activation states and/or total levels of endothelial nitric oxide synthase (eNOS), nuclear factor κB (NF-κB), and cAMP-response-element binding protein (CREB) were determined by Western blotting. Cell cycle profiles were assessed by flow cytometry. Results: Treatment with 20 μM DHA activated eNOS, downregulated the activity of NF-κB, and decreased the number of cells in the sub G0/G1 and S phases in quiescent cells only, while CREB activation was suppressed by 20 μM DHA in growing cells. In contrast, 125 μM DHA reduced total eNOS levels and activated CREB in both growth states. Also, the activity of NF-κB was upregulated by 125 μM DHA in quiescent cells only, while the percentage of cells in the sub G0/G1 phase were increased in growing cells only. In general, quiescent cells were more responsive to the potential beneficial effects of 20 μM DHA compared to growing cells, while the effects of 125 μM DHA were similar in both growing and quiescent cells, and may be deleterious. Conclusion: Overall, the effect of DHA on endothelial cells was growth-state-dependent, implying that DHA might be more effective in primary prevention of CVD for healthy individuals compared to patients with impaired endothelial function. In addition, the contradictory effects of DHA at different concentrations indicate that further research is needed to better define DHA intakes and supplementation strategies as a means of achieving optimal plasma DHA levels with respect to an individual's health status.

Adipose tissue expression of HuR modulates cardiac pathology via adipose tissue-derived extracellular vesicles.

Sarah Anthony, Adrienne Guarnieri, Lisa Green, Sam Slone, Rohan Desarapu, A. Phillip Owens, Onur Kanisicak, Michael Tranter
University of Cincinnati, Cincinnati, USA

Adipose tissue serves a broad role as an endocrine organ and has been shown to have a multitude of effects on cardiac physiology depending on metabolic state, adipose depot location, and primary cell type. We have previously shown that adipocyte-specific deletion of HuR (Adipo-HuR-/-) in mice is sufficient to induce the spontaneous development of cardiac hypertrophy and fibrosis. We also previously showed that the primary adipose tissue phenotype of the Adipo-HuR-/- mouse is an impairment of acute thermogenesis, a canonically brown adipose tissue (BAT)-driven function, but this model induces HuR knockdown in both brown and white adipocytes.

The goal of this work is to identify the adipose depot(s) responsible for the cardiac endocrine effects observed in our model and begin to decipher the underlying mechanisms. Here, we show that mice with HuR deletion specifically in brown and beige adipocytes (using a UCP1-driven cre model) maintain normal cardiac function compared to Adipo-HuR-/- mice. This result suggests a white adipose tissue (WAT)-specific mechanism, consistent with our previously published bioinformatic analysis suggesting HuR-dependent adipose tissue-derived extracellular vesicles (Ad-EVs) from subcutaneous WAT (scWAT) as the mediator of cardiac pathology. Accordingly, our results show that EVs isolated from both the plasma or extracted scWAT of Adipo-HuR-/- mice, but not wild-type littermate controls, induce a significant increase in hypertrophic gene expression in cultured cardiomyocytes.

In conclusion, our results demonstrate that loss of HuR expression in adipose tissue is sufficient to induce cardiac hypertrophy and fibrosis, in part through endocrine-mediated Ad-EV signaling.

Chronic Testosterone Deficiency Increases Late Inward Sodium Current and Promotes Triggered Activity in Ventricular Myocytes from Aging Male Mice.

Shubham Banga[1], Manish Mishra[1], Susan Howlett[1,2]
[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Medicine (Geriatric Medicine), Dalhousie University, Halifax, Canada

Clinical studies show low testosterone is associated with increased arrhythmias and prolonged QT. We investigated whether chronic low circulating testosterone promotes electrical remodeling in aging mouse hearts and determined the role of late inward sodium current (INa-L). Male C57BL/6 mice had either a gonadectomy (GDX) or sham surgery (1 month) and then aged to 23-28 months. Ventricular myocytes were isolated and transmembrane voltage and currents were recorded (20-25 MΩ; current, discontinuous single electrode voltage clamp; 37°C). We observed that action potential duration at 90% repolarization (APD90) was prolonged in GDX cells (55.4 ± 2.0 vs 96.9 ± 3.2 ms; p<0.001). INa-L was also larger in GDX compared to sham myocytes (-0.62 ± 0.08 vs -1.17 ± 0.18 pA/pF; p=0.007). When myocytes were superfused with the INa-L antagonist ranolazine (10 μM), INa-L declined in GDX cells (-1.53 ± 0.27 vs -0.36 ± 0.08 pA/pF; p=0.003) and APD90 was reduced. GDX cells exhibited increased triggered activity (early/delayed afterdepolarizations, EADs/DADs) compared to sham, and this was inhibited by ranolazine. To investigate underlying mechanisms, cells were superfused with A-803467 (30 nM), a selective NaV1.8 blocker. A-803467 reduced and normalized INa-L and APD90 in GDX cells and abolished triggered EADs and DADs. Molecular studies showed increased expression of SCN5A (NaV1.5) and SCN10A (NaV1.8) mRNA in GDX ventricles compared to sham controls. Our findings demonstrate that long-term testosterone deficiency increases triggered cellular arrhythmias in older male mice via prolonged APD90 arising from larger INa-L. These effects may be attributable to increased NaV1.8-associated currents in testosterone-deficient hearts.

The Selenoprotein, VIMP, Selectively Regulates a Newly Defined Non-Canonical Form of Proteasomal Degradation at the ER to Modulate Cardiac Hypertrophy.

Erik Blackwood[1], Lauren MacDonnell[1], Donna Thuerauf[2], Alina Bilal[1], Christopher Glembotski[1]
[1]University of Arizona College of Medicine, Phoenix, USA. [2]San Diego State University, San Diego, USA

Rationale: Perturbations in protein folding in the ER via increases in protein folding demands are alleviated, in part, via the adaptive retrotranslocation, polyubiquitylation, and a proteasomal degradation process referred to as ER-associated degradation (ERAD). To investigate a role for ERAD in a mammalian pathophysiological model, we examined a functional component of ERAD, VCP-interacting membrane protein (VIMP), positing that decreasing VIMP would decrease ERAD, which would be maladaptive in a mouse model of pathological cardiac hypertrophy. To this end, Mice were injected with adeno-associated virus (AAV) to transduce cardiomyocytes with either a shRNA targeting VIMP (shVIMP), or ectopic wild-type or an ERAD-deficient AAV-FLAG-VIMP and subjected to pressure overload-induced cardiac hypertrophy. Mice were also injected with a novel AAV expressing a canonical ERAD substrate to monitor the rate of ERAD, in vivo, for the first time in any organ system.

Results: Unexpectedly, while required for canonical ERAD in model cell systems, in the heart, VIMP impeded a non-canonical role for ERAD in the degradation of the pro-hypertrophic kinase, SGK1. Despite never being in the ER, SGK1 is recognized as an ERAD substrate by DERLIN1, which is displaced from recruiting the AAATPase, VCP, to the ER by VIMP.

Conclusion: Thus, the relative levels of VIMP and DERLIN1 comprise a molecular switch mechanism that regulates a newly defined non-canonical ERAD-mediated degradation of SGK1, a critical signaling kinase contributing to pathological cardiac hypertrophy. Our results suggest that this newly defined class “ERAD-Out” is prioritized in the heart to abate pathological stimuli and preserve cellular integrity.

Rapamycin treatment reveals a sexually dimorphic pattern of scar expansion of the infarcted adult rat heart; potential relationship between mTOR and K_{ATP} channels.

Aya Al-Katat[1], Lucie Parent[1,2], Maxime Lorenzini[1], Celine Fiset[1,3], Angelo Calderone[1,2]
[1]Montreal Heart Institute, Montreal, Canada. [2]Department of Pharmacology and Physiology, Universite de Montreal, Montreal, Canada. [3]Faculty of Pharmacy, Universite de Montreal, Montreal, Canada

Pharmacological inhibition of mammalian target of rapamycin (mTOR) or KATP channels translated to scar expansion of the infarcted adult female rodent heart. The present study tested the hypothesis that rapamycin-mediated scar expansion was sex-specific and mTOR signaling influenced KATP channel subunit expression/activity. One week following complete coronary artery ligation of the adult rat heart, scar surface area and scar weight were significantly smaller in females versus males. Rapamycin treatment of myocardial infarcted female rats led to significant scar expansion whereas no effect was observed in myocardial infarcted male rats. Phosphorylation of the serine2448 residue of mTOR was significantly higher in normal adult female rat hearts and associated with a greater inactivation of the upstream inhibitor GTPase tuberin. Protein levels of KATP channel subunits Kir6.2 and SUR2A were similar in normal adult male and female rat hearts. Neonatal rat ventricular cardiomyocytes (NNVMs) treated with the protein kinase C activator phorbol 12,13-dibutyrate (PDBu) induced hypertrophy, increased p70S6K phosphorylation and concomitantly upregulated SUR2A protein levels. Rapamycin attenuated PDBu-mediated hypertrophy, suppressed mTOR signaling and inhibited SUR2A protein upregulation. In low ATP levels, a rapamycin-independent pathway significantly reduced KATP channel activity in PDBu-induced hypertrophic NNVMs. Thus, rapamycin-mediated sex-specific effect on scar expansion was associated with greater mTOR phosphorylation in female rat hearts and PDBu recruitment of mTOR signaling in NNVMs increased SUR2A protein levels. However, mTOR-independent signaling events reduced KATP channel activity of PDBu-induced hypertrophic NNVMs thereby overriding the potential beneficial impact associated with SUR2A upregulation in cardiomyocytes with compromised ATP levels.

Characterizing the effects of βARKct-S670A mutation in mitochondrial mechanisms of heart failure pathophysiology.

Heidi Cho, Kimberly Ferrero, J. Kurt Chuprun, Erhe Gao, Walter Koch
Lewis Katz School of Medicine at Temple University, Philadelphia, USA

Heart failure (HF) is characterized by aberrant cardiac beta-adrenergic receptor (β-AR) signaling, leading to upregulation of GPCR kinase 2 (GRK2) and subsequent phosphorylation and desensitization of β-ARs. A peptide inhibitor of GRK2, comprised of the last 194 carboxyl-terminal amino acids of GRK2 (βARKct), has been shown to bind to the G protein beta-gamma subunits, preventing GRK2 binding and β-AR desensitization. Overexpression of βARKct attenuates HF and improves outcomes in animal models. Emerging evidence indicates that following oxidative stress, mitogen-activated protein kinases (MAPKs) phosphorylate the Ser670 (S670) residue of GRK2, which induces GRK2 binding to Hsp90 and localization to mitochondria, where pro-death pathways are initiated. As S670 is also found in βARKct it may prevent endogenous GRK2 accumulation in the mitochondria. We hypothesize that βARKct-mediated cardioprotection in HF is due to mitochondrial GRK2 blockade by βARKct. Our lab has generated a cardiac-specific mutant βARKct-S670A transgenic mouse harboring a Ser-to-Ala mutation at the S670 residue that prevents Hsp90 binding and allows for endogenous GRK2 to continue to translocate to the mitochondria upon ischemic injury, while retaining βARKct in the cytosol to act on β-AR signaling pathways. Hemodynamic analysis of βARKct-S670A mice demonstrates increased baseline contractility compared to normal littermate controls, indicating similar cardioprotective effects of βARKct mice lacking the Ser-to-Ala mutation. Studies characterizing the mitochondrial pathways involved in HF rescue following ischemic injury are ongoing. These findings identify new mechanistic insight on GRK2 inhibition in HF, and elucidate a new method for attenuating mitochondrial dysfunction during HF.

Deficiency of 3-Mercaptopyruvate Sulfurtransferase Exacerbates Heart Failure with Preserved Ejection Fraction.

Jake Doiron[1,2], Zhen Li[1,2], Kyle LaPenna[1,2], David Lefer[1,2]
[1]Louisiana State University Health Sciences Center New Orleans, Department of Pharmacology, New Orleans, USA. [2]Cardiovascular Center of Excellence, New Orleans, USA

Background: Dysregulation of hydrogen sulfide (H2S) bioavailability and signaling has been implicated in a number of cardiovascular diseases. 3-mercaptopyruvate sulfurtransferase (3-MST) is a mitochondrial-localized H2S-producing enzyme that is a key regulator of mitochondrial respiration. However, little is known regarding the role of H2S and 3-MST in heart failure with preserved ejection fraction (HFpEF), a condition characterized by mitochondrial and metabolic dysfunction. Herein, we describe the influence of 3-MST genetic knockout on the development of HFpEF pathology in a two-hit murine model of cardiometabolic HFpEF.

Methods: We studied 9-week-old male 3-MST global KO and C57/BL6J littermate control (WT) mice that were fed a high fat, Western diet (HFD) and received L-NG-Nitro arginine methyl ester (L-NAME) in the drinking water (0.5g/L) for 10 weeks to induce HFpEF. Echocardiography, left ventricular invasive hemodynamics, exercise capacity, and vascular reactivity were performed to assess cardiovascular and overall disease severity.

Results: Mitochondrial H2S production was significantly reduced in the 3-MST KO as compared to WT mice at baseline conditions. Genetic knockout of 3-MST failed to alter LV E/e', but did result in a significant increase in diastolic dysfunction as measured by LV end-diastolic pressure (LVEDP). Similarly, total work during exercise and endothelium-dependent aortic relaxation in response to acetylcholine were significantly impaired in 3-MST KO mice.

Conclusion: These data indicate that genetic deficiency of 3-MST exacerbates key parameters of HFpEF pathology. This further implicates the vital role of mitochondria in HFpEF and suggests that mitochondrial H2S dysregulation could be a contributing factor to HFpEF disease progression.

Unique Mitochondrial Gene Profiles in Activated Cardiac Fibroblasts.

Alexandra Garvin[1], Joshua Talboom[2], Matthew De Both[2], Matthew Huentelman[2], Merry Lindsey[3], Taben Hale[1]

[1]University of Arizona College of Medicine, Phoenix, USA. [2]The Translational Genomics Research Institute, Phoenix, USA. [3]Meharry Medical College, Nashville, USA

Conflicting reports of altered bioenergetic signatures of activated fibroblasts indicate dynamic metabolic phenotypes that mediate cardiac fibrosis. We previously identified 9 subpopulations of fibroblasts in the left ventricle of hypertensive rats using single cell RNA-sequencing. Three clusters characterized by various states of activation – Fibrogenic/Inflammatory (Fib/Inf), proliferative (Prolif), and moderately fibrogenic (ModFib) – were re-analyzed for differentially expressed genes (DEGs) that influence mitochondrial metabolism and morphology. The Fib/Inf cluster exhibited a unique expression pattern of mitochondrial (mt) and nuclear-encoded respiratory complex subunits compared to either the Prolif or ModFib clusters. DEGs for mitochondrial respiratory complex subunits that are mitochondrial-encoded (e.g., mt-ND4; $p<1x10-46$) were downregulated, while those nuclear-encoded (e.g., Ndufs3, Cox4; $p<3x10-18$) were upregulated in the Fib/Inf cluster. Coordination of respiratory complex protein abundance is regulated by acute changes in translation. Analysis of ribosomal DEGs revealed downregulation of genes that encode mito-ribosome subunits in the Fib/Inf cluster. Though cytosolic ribosome gene expression is increased in the Fib/Inf cluster, components of the mitochondrial translocase of the inner membrane complex were downregulated (e.g., TIMM23; $p<1x10-5$). Additional DEGs in the Fib/Inf cluster suggest suppression of mitochondrial fusion (e.g., Stoml2, Vat1; $p<5x10-5$), glycolysis (e.g, Pgam1, Eno1; $p<3x10-11$), non-oxidative pentose phosphate pathway shunt (e.g., Rpia, Tkt; $p<9x10-13$), and TCA cycle (e.g., Pdha1, Mdh1; $p<.002$). These findings reveal that Fib/Inf cardiac fibroblasts exhibit altered expression of mitochondrial- and nuclear-encoded genes that regulate mitochondrial function and metabolism, potentially representing novel therapeutic approaches for targeting activated fibroblasts.

Identification of nuclear localization signal (NLS) in Rbm20 and its role in Rbm20 nucleocytoplasmic transport and the development of dilated cardiomyopathy (DCM).

Zachery Gregorich[1], Yanghai Zhang[1], Kavish Khinsar[1], Mohammad Abdullah Khan[1], Camila Urbano Braz[1], Yang Liu[1], Timothy Hacker[1], Henk Granzier[2], Wei Guo[1]
[1]University of Wisconsin-Madison, Madison, USA. [2]University of Arizona, Tucson, USA

Background: Knockout or mutations in the splicing factor Rbm20 result in DCM. Rbm20 has two primary domains, an RNA recognition motif (RRM) that binds RNA and an arginine/serine-rich (RS) domain that mediates spliceosome assembly and nuclear localization. Loss of the RRM domain disrupts splicing but does not cause DCM. The objective of this study was to determine the function of the RS domain in DCM.

Methods: Mice expressing Rbm20 lacking the RS domain (Rbm20ΔRS) were generated using CRISPR/Cas9. Cardiac structure and function were assessed by histology and echocardiography. Rbm20 localization was assessed using immunohistochemistry and splicing of target transcripts was evaluated by gel electrophoresis and RNA-seq. In silico analysis was used to identify putative NLSs in the RS domain. In vitro experiments in H9c2 cells were used to define the Rbm20 core NLS and establish the role of NLS phosphorylation in nuclear localization.

Results: Rbm20ΔRS mice developed DCM. Splicing of Rbm20 targets was disrupted in both Rbm20ΔRS and Rbm20ΔRRM mice, yet Rbm20 was mis-localized only in Rbm20ΔRS mice. In silico analysis identified two putative NLSs within the RS domain of Rbm20, termed D1 and D2. In vitro experiments revealed that only D1 is essential for Rbm20 nuclear localization. Phosphorylation of D1 does not affect Rbm20 localization, however, the amino acid composition of D1 is key for nuclear localization.

Conclusions: Loss of Rbm20 nuclear localization is causative in DCM. D1 constitutes the core NLS for Rbm20 and the amino acid composition, not phosphorylation, of D1 is indispensable for Rbm20 nuclear localization.

Histone Demethylase KDM5 Regulates Maturation of iPSC-Cardiac Myocytes.

Manisha Deogharia, Ali J Marian, Priyatansh Gurha
University of Texas Health Sciences Center at Houston, Houston, USA

Human pluripotent stem cell-cardiac myocytes (hiPSC-CMs) are a valuable tool for gaining insights into the molecular mechanisms of diseases and regenerative therapies. The hiPSC-CMs have properties like those of immature fetal CMs, which limit their utilities. Our published data implicate histone lysine demethylases 5 A and B (KDM5A and B) in the regulation of OXPHOS and cell cycle genes, two important CM maturation characteristics. To determine the role of KDM5 in the maturation of Cardiac Myocytes the hiPSC were differentiated to CM by a conventional chemically defined method and were then treated for 2 weeks with the pan KDM5 inhibitor KDM5-C70. RNA-Seq analysis showed that inhibition of KDM5s led to differential expression of 1600 genes, representing an expression profile resembling that of adult CMs. Specifically, KDM5 inhibition induced expression of genes involved in OXPHOS and sarcomeric assembly, while those involved in EMT were suppressed. Accordingly, levels of TNNI3 and MYL2 proteins, markers of adult CMs, were induced in the treated cells. Inhibition of KDM5s also induced expression of genes involved in fatty acid oxidation. In addition, inhibition of KDM5s was associated with increased mitochondrial oxidative capacity, as evidenced by a 3.2±0.8-fold higher basal respiration, 4.6±1.5-fold higher maximal respiration, and 5.3±1.7-fold greater spare respiratory capacity. Mechanistically, expression of ESRRA, PPARA, and MEF2A transcription factors, which are implicated in OXPHOS, Fatty Acid Oxidation, sarcomeric gene expression, and CM maturation was induced upon treatment. Thus, the results indicate a potential role for the KDM5 family of proteins in CM maturation.

Therapeutic tools to increase energy expenditure and activate browning of white adipose tissue.

Nevena Jeremic[1,2], Marina Rankovic[3], Jovana Jeremic[3], Jovana Bradic[3], Ivan Srejovic[3], Slobodanka Mitrovic[3], Vladimir Jakovljevic[3,4]

[1]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. [2]1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation. [3]Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia. [4]Department of Human Pathology, 1st Moscow State Medical University IM Sechenov, Moscow, Russian Federation

BACKGROUND/AIM: The conversion of white adipose tissue (WAT) into brown adipose tissue (BAT) appears to be a potential therapeutic strategy to tackle with obesity and metabolic related diseases (1, 2). Experimental and clinical studies promote the attitudes that diabetes type 2, obesity and metabolic syndrome are diseases characterized by NPs deficiency, recognized as NPs handicap when adipose tissues are insensitive to circulating NP leves. This statement formed on majority of evidence indicating that increase in NPs may lead to treatment of metabolic disturbance (3). Sacubitril/valsartan as an angiotensin receptor-neprilysin inhibitor is primarily regarded as antihypertensive drug, but it also possesses ability to stimulate adipocyte browning and improve insulin tissue sensitivity (4).

METHOD: We investigated the effects of sacubitril/valsartan treatment on beige adipocytes formation in rats with metabolic syndrome. This experimental study was conducted on 24 male Wistar albino rats (12 per group, 8 weeks old, bw: 200-250 g) divided into two groups as follows: rats with metabolic syndrome (MetS) and MetS rats treated with sacubitril/valsartan (MetS + sacubitril/valsartan). The treatment phase with sacubitril/valsartan lasted 4 weeks and animals from those groups received sacubitril/valsartan oral suspension every day in dosage of 68 mg/kg. At the end of experimental protocol, animals were sacrificed and inguinal and epididimal adipose tissues were dissected for further analyses. We measured oxidative stress markers, enzymes of antioxidative protection, uncoupling protein 1 (UCP-1) expressed in white tissue, cardiodynamic parameters.

RESULTS: The results of our study demonstrated enlarged lipid droplets of both adipose tissues in rats with MetS that were reduced with sacubitril/valsartan treatment. However, the most prominent are expected in MetS + sacubitril/valsartan group of rats that expressed the highest level of UCP-1 in both WAT tissues.

CONCLUSION: Taken together, the data implicate that administration of sacubitril/valsartan probably can effectively increase tissue levels of browning markers making these therapeutical approaches as a potential strategy to combat with obesity and its related disorders.

IDENTIFYING SOCIAL FACTORS THAT MAY LIMIT EARLY DISCHARGE IN LOW-RISK ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION.

Sandeep Krishnan[1], Gabriella Niemcyzk[1], Christopher Parr[1], Yixiu Liu[2], Thang Nguyen[1], Lorraine Avery[3], John Ducas[1], Shuangbo Liu[1]

[1]Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada. [2]Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada. [3]Cardiac Sciences Manitoba, St. Boniface Hospital, Winnipeg, Canada

Through the utilization the Zwolle Risk Score (ZRS) in identifying low risk STEMI and early discharge pathways, patients have been safely discharged within 48 hours (1-4). Our study aimed to determine the proportions of low-risk STEMI patients with favorable and unfavorable social parameters for early discharge.

From an existing provincial cardiac catheterization laboratory database, all patients who presented with STEMI over a 9-month period from November 2019 to July 2020 were reviewed (n=452). Approximately 59% of patients were low-risk STEMI, defined as ZRS ≤3, and included for analysis.

From review of individual social variables, patients were analyzed in 2 groups: favorable (n=111, 55%) and unfavorable (n=92, 45%) for potential early discharge. We defined favorable factors as urban location, employed or retired, lives alone or with family/friend, independent mobility or using gait aid, no communication barriers, no homecare or existing client with housekeeping or hygiene assistance, no financial aid or community resources, no concerns at discharge, and demonstrated knowledge, understanding, and adherence to prescribed medications. Of the patients that were unfavorable for early discharge, the most common reason was rural location (n=66, 72%). Additionally, 41% of patients had more than 1 unfavorable factor. Approximately 7.9% of patients were unemployed and 36 (18%) lived alone, in a group home, or assisted living. No patients were wheelchair or bedbound and barriers to effective communication were identified in 4.5%. Homecare services were required in eight patients (3.9%), with four patients requiring daily homecare for medication administration and the other four requiring weekly homecare for hygiene and housekeeping. Seven patients (3.4%) received financial assistance. On admission, 8.4% of patients self-identified concerns regarding discharge and 9.0% of patients did not demonstrate a good understanding of their condition and medications. The composite outcome of 30-day mortality, recurrent MI, unplanned PCI, stroke, and hospitalization occurred in 5 (2.5%) with unfavorable characteristics for early discharge and 6 patients (3.0%) with favorable characteristics for early discharge.

In low-risk STEMI, implementation of an early discharge protocol may be safe with carefully selected social parameters. Additionally, intensified outpatient resources may be directed to support patients without favorable conditions in discharge planning.

Influence of oxime K870 and obidoxime on survival and cardiorespiratory parameters in rats poisoned with paraoxon.

Žana M. Maksimović[1], Ranko Škrbić[2], Miloš P. Stojiljković[2]
[1]Centre for Biomedical Research, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina. [2]Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegovina

Background/Aim. Paraoxon, an organophosphorus compound is an irreversible inhibitor of acetylcholinesterase. The aim of the study was to examine the effect of antidotes (obidoxime and oxime K870) on survival and cardiorespiratory parameters in rats poisoned with paraoxon.

Methods. Paraoxon (0.25 mg/kg subcutaneously) (1) was administered to Wistar albino rats, then 1 minute later N-butyl scopolamine (63.36 mg/kg intramuscularly) and in 0.9% NaCl, obidoxime (22 mg/kg) or oxime K870 (35 mg/kg) were injected intramuscularly (2). The rat's blood pressure was measured non-invasively and the ECG was recorded. The transducer measured spontaneous contractions of the diaphragm. Arterial blood from the femoral artery was taken for gas analyses.

Results. An average survival time for rats treated with saline (unprotected rats) was 55.8 min. Rats treated with obidoxime lived significantly longer (144.2 min) and with oxime K870 217.6 min, significantly longer compared to both saline and obidoxime. In unprotected rats heart rate increased from the average 285 bpm baseline value to average 480 bpm 10 minutes after paraoxon administration (3). Significantly lower increase in heart rate was noted in obidoxime and oxime K870 protected rats (420 and 395 bpm, respectively). Ventricular tachycardia was noticed in 90% of rats prior to arrest. Transitory bradycardia was noticed in 15% of oxime-protected rats during first hour after paraoxon administration. In unprotected rats, blood pressure (BP) increased 10 minutes after paraoxon administration (from mean BP: 83 mmHg up to 159 mmHg), hypertension lasted for 15 minutes, then slowly decreased to baseline values, hypotension (39 mmHg) and immeasurable values. Significantly lower increase in blood pressure was noted in obidoxime and oxime K870 protected rats (129 mmHg and 121 mmHg, respectively). Respiratory rate in unprotected rats showed bradypnoea (30-40% of baseline values) 15 minutes after paraoxon administration while rats treated with oximes showed slight oscillations in respiratory rate (10-20% of baseline values) (4). Severe acidosis in unprotected rats occurred as early as 15 min compared to 45 min in protected rats.

Conclusion. Oximes significantly prolonged survival and improved cardiorespiratory parameters in rats poisoned with paraoxon, with better antidotal potential of oxime K870 compared to obidoxime.

Early success and cost-effectiveness of a social media campaign to reduce pre-hospital delays in patients with possible acute coronary syndrome.

Harram Memon, Kirsten Marshall, Emily Czaplinski, Rob Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
St. Boniface Hospital, Winnipeg, Canada

Background: Despite improvements in percutaneous coronary intervention (PCI) and hospital systems of care, prehospital delay remains a significant barrier to timely reperfusion in acute coronary syndromes (ACS). Prolonged delays to reperfusion results in poor patient outcomes (1). There is data to support the efficacy of educational interventions to reduce patient-related prehospital delay in ACS (2-4). Traditional media are highly dependent on a ratings system: that is, how many people in an audience can be reached. Given the recent decline of television viewership and radio audiences, these are less reliable forms of message transmission. In addition, cost remains high, further lowering cost-effectiveness when funding a campaign. Hence, we have launched a novel low-cost social media-based education campaign targeting patients with chest pain to reduce pre-hospital delays.

Methods and results: The primary campaign messages are to have patients recognize the most common signs of a heart attack, to call 911 to seek medical care quickly, and not to drive themselves to the hospital. Our motto is: “Dial, Don’t Drive”.
In the first 8 weeks of our campaign, we created 17 posts on Facebook and Instagram. We utilized popular and interactive tools such as Instagram reels and hashtags to reach our target audience. We posted information regarding symptoms, patient stories, and introduced Team Heart Attack (Fig 1).
We reached 62,700 people through Facebook, and a further 19,100 via Instagram. We had 102,748 and 33,059 content displays on Facebook and Instagram, respectively. Currently, we have 206 followers on Facebook and 155 on Instagram. The total cost of this campaign was $903.71 ($737.99 for software and $165.72 for advertisement). In comparison, tradition media for a billboard in our community is $12,150.00 for 1 month, a weekend newspaper ad is $5880.00 and interior bus post is $8886.08 for 2 months.

Conclusion: In the first 8 weeks of our novel social media-based education campaign, there is evidence of our content reaching our target audience and producing engagement within our community. Cost-effectiveness appears to be promising at this early time point.

Delayed Symptom Onset-to-first Medical Contact in ST-segment Elevation Myocardial Infarction is Associated with Mortality.

David Nelson, Kirsten Marshall, Yixiu Liu, Robert Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
University of Manitoba, Winnipeg, Canada

Background/Aim: Early reperfusion in ST-segment elevation myocardial infarction (STEMI) improves outcomes (1). Prior studies have focused on reducing the time from first medical contact (FMC) to coronary intervention (FMC-Device) (2,3). However, the time from symptom-onset to FMC (Sx-FMC) represents a large component of the total ischemic time, and is an important contributor to morbidity and mortality (4). The objective of this study was to analyze how Sx-FMC and FMC-Device times impact 1-year mortality and the need for repeat PCI within one year.

Methods and Results: Data for 616 STEMI patients between January 2013 and December 2014 was collected. Patient demographics were recorded via chart review (Table 1). The median age was 61 years (IQR 53-70), and 22% of patients were female. Of the total patients, 40% of STEMIs were anterior, 78% of patients presented for primary PCI, while 22% of patients received Tenecteplase (TNK). Median Sx-FMC, FMC-Device, and total ischemic times were 120 minutes (IQR 55-262), 97 minutes (IQR 67-176), and 269 minutes (IQR 146-472), respectively. Shorter total ischemic times (< median) were associated with a reduced 1-year mortality (1% vs 5%, $p<0.01$). Further, lower odds of 1-year mortality (OR 1.06, 95% CI 1.01-1.10, $p<0.01$) was associated with a shorter Sx-FMC time, but was not associated with a shorter FMC-Device time (OR 1.02, 95% CI 0.96-1.09, $p=0.45$).

Conclusions: In this analysis, shorter Sx-FMC times were associated with a reduced 1-year mortality. The Sx-FMC time period should be a key area of focus in order to reduce mortality in STEMI. Educational efforts need to be made to increase public awareness about STEMI symptoms and allow them to promptly seek medical care.

Factors Associated with Delay in STEMI Patients Seeking Medical Attention.

David Nelson, Kirsten Marshall, Yixiu Liu, Ashish Shah, Robert Grierson, Lorraine Avery, John Ducas, Shuangbo Liu
University of Manitoba, Winnipeg, Canada

Background/Aim: In STEMI, shorter reperfusion time is critical for best outcomes (1). Advances in systems of care focused after first medical contact (FMC) have reduced reperfusion time and improved outcomes (2). Unfortunately, symptom to FMC (Sx-FMC) delays remain a significant component of total ischemic time and an important contributor to morbidity and mortality in STEMI (3). Older age, female sex, lower socioeconomic status or education level, and the presence of atypical symptoms are associated with longer delays in seeking medical attention (4). Our objective was to examine the Sx-FMC times in a provincial tertiary care centre and determine characteristics of patients presenting late with STEMI.

Methods and Results: Data for 616 STEMI patients between January 2013 and December 2014 was collected via chart review. The median age was 61 (IQR 53-70) and 21% were female. Approximately 78% of patients presented for primary PCI (22% via emergency medical services and 56% via emergency department (ED)). 22% of patients received Tenecteplase (TNK), almost exclusively rural patients >100 minutes transfer time to a PCI-capable centre.

The median Sx-FMC for the cohort was 120 minutes (IQR 55-262 minutes), but 28% of patients had very prolonged Sx-FMC of >240 minutes. Factors associated with longer than median Sx-FMC included self-presentation to ED ($p< 0.001$), female sex ($p< 0.01$), and use of TNK ($p< 0.05$). Factors without effect on Sx-FMC (i.e., not associated with shorter times) included previous diagnosis of acute coronary syndrome, older age, or time of day of presentation. Neither traditional risk factors for coronary artery disease or previous diagnosis of cardiac disease were associated with shorter Sx-FMC. Importantly, shorter Sx-FMC times (less than median) were associated with decreased 1-year mortality compared to longer Sx-FMC times (1% vs 5%, $p< 0.05$).

Conclusion: There is a need to increase public awareness with regards to STEMI symptoms and the need to promptly seek medical care. Special concern should be taken to address shorter Sx-FMC in patients with known cardiac disease. We intend to use this data to target future educational interventions to reduce patient delays to medical care in STEMI and improve outcomes.

Renal mechanism of preserved ejection fraction.

Sathnur Pushpakumar, Subir Kumar Juin, Irina Smolenkova, Suresh Tyagi
University of Louisville, Louisville, USA

Although during hypertension, diabetes, aging, and chronic kidney disease, the kidney initially compensates by increasing glomerular filtration rate (GFR) and modulation of renal sympathetic nerve activity, whether a similar process occurs during heart failure with preserved ejection fraction (HFpEF) is unknown. Volume overload and anemia coexist in HFpEF. The kidney is an important regulator of central nervous system outflow to the heart and vasculature, and SNS activity is critical to cardiac function. Current evidence suggests that SNS overactivation is associated with HFpEF, however, whether it is a cause or effect of HFpEF is unknown. Further, the renal response to anemia involves releasing erythropoietin (EPO) that in addition to erythropoiesis, mobilizes hematopoietic stem and progenitor cells (HSPCs) from the bone marrow. Although several preclinical and clinical studies investigated HSPCs in HF, the results are inconclusive. Therefore, the purpose of the study was to investigate whether renal denervation (RDN) in HFpEF modulates SNS activity thus RAS to reduce ACE1 (but parallel increase in ACE2 and GFR) and EPO recruits HSPCs to reduce stress and apoptosis. C57BL/6J (WT, 50-52 wks) mice w/o and with HFpEF, and w/o and with RDN were used in the study. Aorto-vena cava fistula (AVF) was created as a model of diastolic dysfunction and serial ECHO was done to denote HFpEF (ejection fraction, EF > 50%). Exosomal EPO was increased in AVF and AVF+RDN. CD117+/Sca1+ cells were increased in AVF+RDN compared to AVF and WT groups. RDN attenuated abnormal cardiac indices (EF, FS, E/A ratio, E/e' ratio) and SNS activity following AVF. GFR was increased and renal resistive index (RI) decreased in AVF+RDN mice. In AVF mice, cardiac and renal vasculature showed rarefaction and reduction of septal branches, and segmental and arcuate arteries resp. and improved following RDN. AVF mice showed increased ACE1 expression, reduction of eNOS in the kidney, and RDN increased ACE2. AVF mice demonstrated increased stress and apoptosis and was abrogated with RDN. Taken together, our results suggest that RDN and EPO enhance cardiac regeneration by modulating SNS activity, improving renal function, and via paracrine effects of EPO.

Immunoengineered Tantalum Carbide MXene Quantum Dots for Prevention of Transplant Vasculopathy.

Weiang Yan, Alireza Rafieerad, Keshav Narayan Alagarsamy, Abhay Srivastava, Niketa Sareen, Rakesh Arora, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

Background: Transplant vasculopathy is an aggressive form of atherosclerosis that manifests uniquely in transplanted hearts, lungs, and kidneys (1). Recently, immunoengineered transition metal carbides, or MXenes, have demonstrated unique immunomodulatory properties (2)(3). We postulated that these features can potentially be leveraged to prevent transplant vasculopathy.

Methods and Results: Here, we present the synthesis, characterization and application of novel zero-dimensional tantalum carbide ($Ta_4C_3T_x$) MXene quantum dots (MQDs) for immunomodulation. A facile hydrofluoric acid-free etching protocol was developed to synthesize zero-dimensional $Ta_4C_3T_x$ MQDs from Ta_4AlC_3 MAX phase. The resultant MQDs are 3 to 7 nm in diameter and are surface modified with carboxyl, hydroxyl, and amine functional groups for biological interactions. Immunomodulation was assessed *in vitro* through co-cultures of human umbilical vein endothelial cells (ECs) and peripheral blood mononuclear cells. We found that MQDs interact with activated human ECs *in vitro* to reduce activation and pro-inflammatory T_H1 polarization of allogeneic $CD4^+$ lymphocytes (4). Mechanistically, we showed using quantitative PCR that treatment with MQDs significantly increased endothelial surface expression of the T-cell co-inhibitory molecule PD-L1 and decreased the co-stimulatory molecule CD86. Furthermore, exploratory bulk RNA-sequencing of co-cultured lymphocytes showed decreases in the immunologic signatures of naïve T-cells and increases in the immunologic signatures of $CD25^+$ regulatory T-cells, suggesting activation of this suppressive T-cell population. Finally, when applied in an *in vivo* rat model of transplant vasculopathy, treatment with MQDs reduced lymphocyte infiltration and preserved medial smooth muscle cell integrity within transplanted aortic segments.

Conclusion: These findings suggest that these novel MQDs have potential as an effective treatment to ameliorate transplant vasculopathy.

Caloric restriction attenuates sinoatrial node dysfunction and atrial arrhythmogenesis in aged and frail female mice.

Lockhart Jamieson[1], Megan McRae[1], Robert Rose[2]
[1]Libin Cardiovascular Institute, Calgary, Canada. [2]Libin Cardiovascular Institute, Calgary, Canada

Background: Sinoatrial node (SAN) dysfunction and atrial fibrillation (AF) are serious and often co-occurring cardiac arrhythmias highly prevalent in elderly individuals. The natural heterogeneity of aging has led to the concept of 'frailty', a state of increased vulnerability to adverse health outcomes in aging. Our lab has developed the mouse clinical 'frailty index (FI)' to quantify frailty in aging mice, based on similar methods used in clinical gerontology. We have previously demonstrated in aged mice that arrhythmogenesis and changes in fibrosis are better described by frailty status than chronological age.

Mild caloric restriction (CR), reducing caloric intake without malnutrition, is a well-characterized longevity model that can preserve cardiac function and improve healthspan. Yet whether CR alters frailty associated with changes in atrial/SAN structure, function, and fibrosis is unknown.

Methods: At 52-56 weeks of age, C57BL6 mice were placed on 25% CR or control diet ad libitum (AL). Frailty scoring was performed monthly for 24 weeks, where after mice underwent comprehensive assessment of atrial/SAN function using in vivo intracardiac electrophysiology and high-resolution optical mapping.

Results: 16 weeks of 25% CR significantly reduces frailty in aged female mice associated with preserved SAN function, reduced arrhythmia susceptibility, and improved conduction.

Summary: These data demonstrate 25% CR attenuates frailty and arrhythmogenesis in aging animals, giving insight into the etiology and potential drug targets for age-related arrhythmia.

Cardiomyocyte-derived signaling factors are responsible for heart-fat communication and mediate the development of cardiometabolic disease.

Stephanie Kereliuk, Kenneth Gresham, Walter Koch
Center for Translational Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, USA

Cardiomyocytes are known to secrete signaling factors that can communicate with other organ systems, particularly in response to cardiometabolic stressors such as obesity. Under conditions of cardiometabolic stress, the expression and activity of cardiac GPCR kinase 2 (GRK2), which regulates β-adrenergic receptors in the heart, is upregulated. Previously we have shown that cardiac signaling factors alter adiposity in mice fed a high fat diet, and specific metabolic responses in adipose tissue are dependent on cardiac GRK2 levels and activity. However, the mechanisms responsible for this are unknown. We hypothesize that signaling factors secreted from the heart mediate adiposity and the development of cardiometabolic disease and are regulated by GRK2. To test this, conditioned media from control and GRK2 overexpressing neonatal rat ventricular myocytes (NRVM) was collected and applied to 3T3-L1 adipocytes. 3T3-L1 cells were then assessed by BODIPY fluorescent imaging, protein immunoblotting and qPCR. NRVM conditioned media was also analyzed by mass spectrometry to identify potential signaling factors. Conditioned media treated 3T3-L1 adipocytes demonstrated reduced lipid accumulation and adipogenic marker expression. Conditioned media from GRK2 overexpressing NRVMs further decreased lipid accumulation and differentiation in 3T3-L1 adipocytes. Proteomic analysis of conditioned media revealed several proteins with adipocyte regulatory roles. These findings indicate that cardiomyocyte-released signaling factors influence adipocyte differentiation that is further enhanced by GRK2 overexpression. Future work aims to identify the specific factors responsible and whether these may be from cardiac secreted exosomes. These findings will be used to elucidate novel mechanisms involved in heart-fat communication and cardiometabolic disease development.

IRX5 is the major regulator of ventricular transmural heterogeneity in the healthy and diseased heart.

Saif Dababneh[1,2], Yena Oh[1,3], Julie Pan[1,3], Gavin Oudit[4,5,6], Peter Backx[7,8], Kyoung-Han Kim[1,3]
[1]University of Ottawa Heart Institute, Ottawa, Canada. [2]MD/PhD Program, Faculty of Medicine, University of British Columbia, Vancouver, Canada. [3]Department of Cellular and Molecular Medicine, Facultu of Medicine, University of Ottawa, Ottawa, Canada. [4]Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada, Edmonton, Canada. [5]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada. [6]Department of Physiology, University of Alberta, Edmonton, Canada. [7]Department of Biology, Faculty of Science, York University, Toronto, Canada. [8]Toronto General Research Institute, University Health Network, Toronto, Canada

Transmural heterogeneities in electrophysiology, contractility, and metabolism across the ventricular wall are essential for normal heart function. Disruption of these regional differences is one of the pathological hallmarks observed in cardiomyopathy and heart failure. However, molecular insights into the establishment and regulation of the ventricular transmural heterogeneities in the normal and diseased heart remain elusive. Transcriptomic profiling using RNA-sequencing on left ventricular (LV) endo-myocardial (ENDO), mid-myocardial, and epi-myocardial (EPI) tissues from non-failing donor hearts revealed over 1400 differentially expressed genes with ENDO-to-EPI gradients. Pathway analysis showed the EPI to be enriched with genes underlying fatty acid metabolism and amide transport, whereas the ENDO was enriched with genes underlying collagen-containing extracellular matrix (ECM) and sarcomeric contraction. Comparison of human data with the transcriptome of mouse LV ENDO and EPI demonstrated a strong correlation in the enriched pathways between humans and mice, including ECM and sarcomeres, suggesting evolutionarily conserved transmural heterogeneities. Notably, IRX5 was the top transcription factor expressed in both human and mouse ENDO, and absence of Irx5 in mice largely disturbed transcriptomic transmural gradients. We further examined the role of Irx5 in transmural ventricular gradients in the pressure overload-induced cardiac hypertrophy caused by transverse aortic constriction. This study showed that Irx5 transmurally modulates the compensatory hypertrophic response, with greater enlargement in ENDO myocytes, as Irx5 knockout hearts displayed early decompensation with impaired cardiac hypertrophy but increased fibrosis. Together, our results posit that IRX5 is the major transcriptional regulator of transmural ventricular heterogeneity in the healthy and diseased heart.

Novel Synthetic Analogs of Omega-3 Fatty Acids Demonstrate Cardioprotective Properties.

Joshua Kranrod[1], Ahmed Darwesh[1], Wesam Bassiouni[1], Liye Fang[1], John Falck[2], John Seubert[1]
[1]University of Alberta, Edmonton, Canada. [2]UT Southwestern Medical Center, Dallas, USA

Evidence suggests that CYP epoxygenase metabolites of docosahexaenoic acid (DHA), called epoxydocosapentaenoic acids (EDPs), limit mitochondrial damage following ischemic cardiac injury. However, the bioavailability of EDPs is limited by several factors including; oxidation of the unsaturated carbon backbone, plasma membrane esterification, and metabolic conversion to less active diol compounds by soluble epoxide hydrolase (sEH). This study investigated our novel synthetic 19,20-EDP analog compounds for protection against cardiac IR injury. Methods: Isolated C57BL/6 mouse hearts were perfused via Langendorff apparatus with vehicle, SA-20 (1μM), SA-22 (1μM), JVKR-20 (1μM), JVKR-24 (1μM), or JVKR-34 (1μM) for 20 min baseline and subjected to 30 min of global ischemia followed by 40 min of reperfusion to assess changes in cardiac function induced by IR injury. Recovery of myocardial function is represented by percentage of left ventricular developed pressure (%LVDP) following 40 minutes of reperfusion (R40). Mitochondria were assessed for sirtuin-3 (SIRT3), manganese superoxide dismutase (MnSOD), and optic atrophy type-1 (OPA-1). Results: Every analog significantly enhanced postischemic functional recovery and treatment was associated with decreased accumulation of short OPA-1 isoforms and increased SIRT3 activity. Conclusion: This data demonstrates the cardioprotective effects of our novel synthetic 19,20-EDP analogs against IR injury. Treatment resulted in improved postischemic cardiac function correlated with evidence of limited mitochondrial degradation and enhanced SIRT3 activity. This pilot data provides the framework for further development of therapeutic agents.

Impaired S-Nitrosoglutathione Reductase (GSNOR) Activity Promotes Nitrosative Stress in Cardiometabolic HFpEF.

Kyle LaPenna[1], Zhen Li[1], Karl Moles[1], Jake Doiron[1], Thomas Sharp[1], Huijing Xia[1], Amelia Haydel[1], Timothy Allerton[2], Sanjiv Shah[3], Ravi Patel[3], Traci Goodchild[1], David Lefer[1]
[1]LSU Health Sciences Center, New Orleans, USA. [2]Pennington Biomedical Research Center, Baton Rouge, USA. [3]Northwestern School of Medicine, Chicago, USA

Background: Heart Failure with Preserved Ejection Fraction (HFpEF) is a systemic inflammatory condition driven by diabetes, obesity, aging and hypertension that culminate in pathological cardiac remodeling. We sought to further elucidate the role of dysregulated nitric oxide (NO) signaling in HFpEF utilizing the ZSF1 obese rat, a clinically relevant animal model of cardiometabolic HFpEF.

Methods: Male ZSF1 obese and normotensive, lean control Wistar Kyoto (WKY) rats (n=6-7 per group) were studied at 14, 18, and 26 weeks of age. At each time point circulating and tissue nitric oxide metabolites (i.e., nitrite and nitrosothiols) were measured. We also quantified the activity of the denitrosylase, s-nitrosoglutathione reductase (GSNOR), using a well-established biochemical assay.

Results: We observed reductions in both plasma and cardiac nitrite in the ZSF1 group vs. WKY indicating dysfunction in the production of nitric oxide via eNOS. Despite the reduction in NO bioavailabilty and lack of iNOS upregulation we observed increased myocardial nitrosothiol (RxNO) levels in the ZSF1 rat. Furthermore, the activity a key enzyme that regulates nitrosothiol levels, GSNOR, was shown to be impaired following the establishment of HFpEF.

Conclusion: Our data provides insight into pathological alterations in NO bioavailability and signaling in HFpEF. Despite reductions in the pool of NO available for normal physiological function and the lack of iNOS upregulation, we observed elevated nitrosylated proteins in the myocardium which was accompanied by reduced GSNOR activity. These data suggest that myocardial nitrosative stress in HFpEF is a result of impaired regulation of nitrosothiol levels and not iNOS upregulation.

Effects of Cardiac Deletion of Essential MCU Regulator (EMRE) in the Short and Long Term.

Hector Chapoy Villanueva, Jae Hwi Sung, Jackie Stevens, Peyton Nelson, Michael Zhang, Timothy O'Connell, DeWayne Townsend, Julia Liu
University of Minnesota, Minneapolis, USA

Transport of Ca2+ into mitochondria is thought to stimulate ATP production to match energy supply to demand, but mitochondrial Ca2+ overload can trigger cell death. The mitochondrial Ca2+ uniporter, the primary route of mitochondrial Ca2+ influx, is a multi-protein complex in which the channel-forming protein MCU and the regulatory protein EMRE are essential. Previous mouse studies revealed that germline (“chronic”) Mcu or Emre deletion differ from tamoxifen-inducible (“acute”) cardiac Mcu deletion (McucKO) in response to adrenergic stimulation and ischemia/reperfusion (I/R) injury, despite equivalent inactivation of rapid mitochondrial Ca2+ uptake. To explore this discrepancy between chronic and acute loss of uniporter activity, we tested whether tamoxifen-inducible Emre deletion in adulthood acutely would recapitulate the McucKO phenotype, but longer time durations post-tamoxifen would be sufficient to induce the chronic Mcu/Emre-deficient phenotype. We generated a novel cardiac-specific, tamoxifen-inducible mouse model of Emre deletion. At 3 weeks (“short-term”) post-tamoxifen, cardiac mitochondria from these EmrecKO mice were unable to take up Ca2+, as expected. EmrecKO cardiac mitochondria displayed lower basal mitochondrial Ca2+ levels and attenuated Ca2+-induced ATP production and mPTP opening. Short-term EMRE loss led to blunted response to adrenergic stimulation and better-maintained cardiac function in a Langendorff ex vivo I/R model. However, at 3 months post-tamoxifen (“long-term deletion”), despite impaired adrenergic response similar to short-term deletion, EmrecKO mice showed no difference from controls in I/R. Hence, protection from I/R is transient, presumably due to time-dependent cellular rewiring upon uniporter loss, which however is insufficient to restore adrenergic response.

The Role of Reactive Oxygen Species Modulator 1 (ROMO1) in the Heart.

Matthew Martens[1,2], Seyed Amirhossein Tabatabaei Dakhili[1], Claudia Holody[1], Heidi Silver[1,2], Mourad Ferdaoussi[1,2], Mihir Parikh[1,2], Helene Lemieux[1], Gavin Oudit[1,2], John Ussher[1], Robert Screaton[3,4], Jason Dyck[1,2]

[1]University of Alberta, Edmonton, Canada. [2]Cardiovascular Research Center, Edmonton, Canada. [3]University of Toronto, Toronto, Canada. [4]Sunnybrook Research Institute, Toronto, Canada

The mitochondrial protein, Reactive Oxygen Species Modulator 1 (ROMO1) plays an important role in the regulation of mitochondrial function. Since very little is known about the role of ROMO1 in the heart, we explored the effect of reduced ROMO1 activity using a novel small molecule inhibitor developed in-house. We show that ROMO1 inhibition in cultured human cardiomyocytes results in diminished succinate pathway flux through complex II, as well as reduced overall ATP production. We also generated inducible, cardiomyocyte-specific ROMO1-knockout (KO) mice. At baseline, no overt cardiac phenotype was observed in the KO mice, but when these mice were challenged with angiotensin-II, they failed to undergo adaptive cardiac remodeling and progressed more rapidly to heart failure (HF) than their wild-type counterparts. As such, we hypothesized that ROMO1 becomes downregulated during HF, which subsequently promotes mitochondrial dysfunction and worsening cardiac function. To test this, we induced HF in mice via transverse aortic constriction. Mice in overt heart failure (i.e. % ejection fraction <45) demonstrated a more than 54% decrease in ROMO1 protein expression; a finding that was also observed in explanted hearts from human patients with HF. Additionally, in mice with recovered HF, a result of debanding surgery following HF-induction via TAC, we observed a robust functional recovery, concurrent with a complete restoration of ROMO1 expression. Together, these findings suggest that ROMO1 maintains mitochondrial function in the stressed heart, and that the loss of ROMO1 may contribute to worsening HF.

Atrial Natriuretic Peptide promotes differentiation of Cx40 expressing cardiomyocytes by targeting cellular metabolic pathways.

Abhishek Mishra, Mahtab Tavasoli, Christopher McMaster, Kishore Pasumarthi
Dalhousie University, Halifax, Canada

Atrial Natriuretic Peptide (ANP) is an important regulator of cardiovascular homeostasis. Mice lacking ANP high-affinity receptor (NPRA) revealed a hypoplastic phenotype in the ventricular conduction system (VCS) formation. However, the mechanism(s) underlying the effects of ANP/NPRA signaling in VCS development are not known. The role of metabolic adaptations in embryonic development is well documented. We hypothesized that ANP regulates metabolic changes in a subset of embryonic ventricular cells to promote VCS cell formation. In this study, cells were isolated from E11.5 cardiac ventricles which are yet to develop a fully functional VCS and cultured with or without exogenous ANP treatment. E11.5 cells revealed a significant increase in lipid accumulation and higher expression of Cx40 in response to the ANP treatment. Seahorse assay confirmed significant increases in glycolytic rate (ECAR) and mitochondrial oxygen consumption rate (OCR) in cells treated with ANP. These results further indicated that ANP treatment promotes a switch in energy metabolism from an anaerobic to a more aerobic state in embryonic ventricular cells. RT-qPCR analyses showed significant increases in PPARγ, PDK4 and LDHA gene expression and reductions in the expression of C/EBPα, PGC1α and β in ANP-treated cultures. ANP-mediated Cx40 expression is downregulated by PPARγ inhibition. Similarly, Cx40 expression is decreased by inhibition of fatty acid oxidation by a CPT1a inhibitor (Etomoxir). Collectively, these results suggest ANP-mediated metabolic changes play a critical role in VCS cell differentiation.

Impact of age and sex on the expression of common reference genes in ventricular muscle from aging C57BL/6 mice.

Manish Mishra[1], Susan E Howlett[2,3]

[1]Department of Pharmacology, Dalhousie University, Halifax, Canada. [2]Department of Pharmacology, Dalhousie University, Halifax, Canada. [3]Department of Medicine (Geriatric Medicine), Dalhousie University, Halifax, Canada

Changes in cardiac gene expression with age are typically normalized to constitutively expressed reference genes (RGs). However, RG expression may be affected by age as well by sex. We investigated impacts of age and sex on common RG expression (Gapdh, Rplp0, Tubb5, Hprt, Rpl4, Ppia, B2m) in ventricles from young (4-mos) and aged (24-26-mos) mice. Standard programs (RefFinder/GeNorm/NormFinder/BestKeeper) identified different orders of optimal RGs without considering age or sex. When Cq values were compared, none of the RGs were stable at both ages in both sexes. However, Rplp0 was similar regardless of sex and B2m was similar at both ages. When qPCR data were normalized to Rplp0, we found that sex greatly affected RG expression and effects differed by age. For example, Gapdh expression was higher in young females than males (1.13±0.07 vs. 0.61±0.06; $p<0.05$; n=4/group) but this difference was abolished by age (0.28±0.07 vs. 0.29±0.05). By contrast, Hprt expression was lower in young females than males (44.9±7.7 vs. 78.5±10.7; $p<0.05$), an effect not seen in old mice (46.6±8.8 vs. 37.2±10.5). When qPCR data were normalized to B2m, age greatly affected RG expression, especially in males where Rplp0, Tubb5, Hprt, Rpl4, and Ppia expression increased with age, but only Rpl4 was higher in females. Thus, common RG expression is substantially modified by both age and sex. Care must be taken in RG selection when hearts from mice of varying ages and sexes are assessed.

Development of induced pluripotent stem cell based clinical trial selection platforms for patients with metabolic disorders.

Abhay Srivastava, Glen Lester Sequiera, Niketa Sareen, Weiang Yan, Keshav Narayan Alagarsamy, Elika Verma, Michel Aliani, Cheryl Rockman-Greenberg, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

Novel and ultrarare mutations make it difficult for patients with inherited disorders to be considered for clinical trials due to non-availability of mutation specific drug response data. Therefore, a “Leap of Faith” approach is used to develop a treatment protocol, often based on empiric observations from patients with overlapping phenotypes but different or more prevalent mutations. This uncertainty reflects the need for development of personalized clinical trial selection platforms to assess drug efficacy to facilitate decision-making process in enrolling such patients in suitable clinical trials. Leigh syndrome is a multisystemic mitochondrial disorder that may result in cardiovascular complications. In this study we report an 18-year-old male patient with Leigh-like syndrome (LS) harboring compound heterozygous variants in the ECHS1 gene (1). This patient had previously participated in 2 clinical trials with unfavorable responses. We established an induced pluripotent stem cell (iPSC)- based platform for this patient and the safety and efficacy of a panel of drugs on patient cardiomyocytes was assessed (2,3). To further demonstrate validity of this platform by observing improved phenotype and function of patient cardiomyocytes in response to drug treatment. Hence, we validated the safety and efficacy of three screened drugs which were administered to the patient (Ubiquinol, α-Lipoic acid and Riboflavin) (4). Additionally, upon administration of these drugs to the patient for a period of 3 years, we observed a significant shift in the metabolic profile of this patient towards that of a healthy control, showing improvement in both energy flux and ROS reduction thereby confirming the validity of iPSC-based drug screening platform. Therefore, this personalized iPSC-based platform can act as a pre-screening tool to help in decision-making with respect to patient's participation in future clinical trials.

Is flaxseed equivalent and/or synergistic with ACE inhibition in the treatment of chemotherapy mediated cardiotoxicity?

Sara M. Telles-Langdon[1], Vibhuti Arya[1], David Y. C. Cheung[1], Paris R. Haasbeek[2], J. Alejandro Austria[1], James Thliveris[3], Pawan K. Singal[1], Davinder S. Jassal[1,4]

[1]Department of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada. [2]Faculty of Science, University of Manitoba, Winnipeg, Canada. [3]Department of Human Anatomy and Cell Sciences, University of Manitoba, Winnipeg, Canada. [4]Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

Background/Aim: Breast cancer is a major public health concern in Canada. Although the current combination of surgery, radiation, and chemotherapy may lead to a cure in the breast cancer setting, the administration of the anti-cancer drugs Doxorubicin and Trastuzumab (DOX+TRZ) is associated with an increased risk of developing heart failure (1-3). Little is known on whether flaxseed (FLX) is equivalent to angiotensin-converting enzyme inhibition (ACEi) in the treatment of DOX+TRZ mediated cardiotoxicity. The specific aim is to evaluate whether FLX is comparable and/or incremental to standard pharmacological therapy using the ACEi perindopril (PER) in the treatment of DOX+TRZ mediated cardiotoxicity.

Methods: In a chronic *in vivo* murine model of chemotherapy mediated cardiotoxicity, DOX+TRZ (8mg/kg and 3mg/kg, respectively) were administered weekly for a total of 3 weeks (4). Following this, the mice were randomized to daily consumption of a 10% FLX supplemented diet, administration of PER (3mg/kg) via oral gavage, or a combination of both FLX+PER for an additional 3 weeks. Serial echocardiography was performed weekly. At the end of week 6, the mice were euthanized and histological analysis was performed on cardiac tissue.

Results: In mice treated with DOX+TRZ, the left ventricular ejection fraction (LVEF) decreased from 72±4% at baseline to 30±2% at week 6. Treatment with either FLX, PER, or FLX+PER improved LVEF to 52±4%, 54±4%, and 55±3%, respectively ($p<0.05$). Histological analyses confirmed significant disruption of myofibrils, vacuolization, and sarcomere integrity in the DOX+TRZ treated mice. Treatment with FLX, PER, or FLX+PER, however, improved myofibril integrity at week 6 in mice receiving DOX+TRZ.

Conclusion: In a chronic *in vivo* murine model of DOX+TRZ induced cardiotoxicity, FLX was equivalent to PER in the treatment of adverse LV remodeling, but the combination of FLX and PER was not synergistic.

Gender and racial differences in stress induced cardiomyopathy- etiology or biology?

Srikanth Vallurupalli
University of Arkansas for Medical Sciences, Little Rock, USA

Introduction: Stress induced cardiomyopathy (also called Takotsubo cardiomyopathy) results in myocardial dysfunction in response to emotional or physical stress. (1,2) Since it affects mostly women and in the setting of emotional distress, current knowledge of pathogenesis is mostly restricted within this paradigm. Pathogenesis and outcomes in the setting of physical or medical stress (which occurs mostly in men) are limited. (3) Similarly, racial differences in long term outcomes are unexplored.(4)

Methods: We created a national database of patients diagnosed with stress induced cardiomyopathy in the US Veteran Healthcare Administration (covering almost 8 million veterans). With inclusion of over 400 men (around 20% are of African American descent), this is the largest known database of men with this condition. Laboratory, imaging and long-term outcomes were collected and analyzed.

Results: We have delineated several differences in phenotypes of presentation, laboratory and imaging measures between genders and races in this condition. There were important differences in coagulation and inflammatory markers despite similar thrombotic outcomes (such as occurrence of left ventricular thrombus). There were significant differences in in-hospital and long-term outcomes.

Conclusion: The current paradigm of the emotional mechanism of stress induced cardiomyopathy is insufficient to explain gender and racial differences in pathogenesis and outcomes. The VA national database provides valuable insight into these differences but highlights the need for prospective evaluation using a translational science approach.

Immunoengineered Tantalum Carbide MXene Quantum Dots for Prevention of Transplant Vasculopathy.

Weiang Yan, Alireza Rafieerad, Keshav Narayan Alagarsamy, Abhay Srivastava, Niketa Sareen, Rakesh Arora, Sanjiv Dhingra
University of Manitoba, Winnipeg, Canada

Background: Transplant vasculopathy is an aggressive form of atherosclerosis that manifests uniquely in transplanted hearts, lungs, and kidneys (1). Recently, immunoengineered transition metal carbides, or MXenes, have demonstrated unique immunomodulatory properties (2)(3). We postulated that these features can potentially be leveraged to prevent transplant vasculopathy.

Methods and Results: Here, we present the synthesis, characterization and application of novel zero-dimensional tantalum carbide ($Ta_4C_3T_x$) MXene quantum dots (MQDs) for immunomodulation. A facile hydrofluoric acid-free etching protocol was developed to synthesize zero-dimensional $Ta_4C_3T_x$ MQDs from Ta_4AlC_3 MAX phase. The resultant MQDs are 3 to 7 nm in diameter and are surface modified with carboxyl, hydroxyl, and amine functional groups for biological interactions. Immunomodulation was assessed *in vitro* through co-cultures of human umbilical vein endothelial cells (ECs) and peripheral blood mononuclear cells. We found that MQDs interact with activated human ECs *in vitro* to reduce activation and pro-inflammatory T_H1 polarization of allogeneic $CD4^+$ lymphocytes (4). Mechanistically, we showed using quantitative PCR that treatment with MQDs significantly increased endothelial surface expression of the T-cell co-inhibitory molecule PD-L1 and decreased the co-stimulatory molecule CD86. Furthermore, exploratory bulk RNA-sequencing of co-cultured lymphocytes showed decreases in the immunologic signatures of naïve T-cells and increases in the immunologic signatures of $CD25^+$ regulatory T-cells, suggesting activation of this suppressive T-cell population. Finally, when applied in an *in vivo* rat model of transplant vasculopathy, treatment with MQDs reduced lymphocyte infiltration and preserved medial smooth muscle cell integrity within transplanted aortic segments.

Conclusion: These findings suggest that these novel MQDs have potential as an effective treatment to ameliorate transplant vasculopathy.

Attenuation of oxidized phospholipid activity decreases infarct size in a porcine model of ischemia/reperfusion injury.

Aleksandra Stamenkovic[1,3], Grant N. Pierce[1,3], Joseph L. Witztum[2], Sotirios Tsimikas[2], Amir Ravandi[1,3]

[1]Institute of Cardiovascular Sciences, St. Boniface Hospital, [2]Division of Cardiovascular Sciences, University of California San Diego, La Jolla, CA, USA. [3]Departments of Physiology and Pathophysiology, University of Manitoba, Winnipeg, Canada

Introduction: Myocardial ischemia/reperfusion injury (IRI) results in additional myocardial cell loss post reperfusion. Oxidized phosphocholine (PC)-containing phospholipids (OxPL) have been shown to result in cardiomyocyte cell death during IRI. E06 is a natural murine monoclonal IgM antibody which binds to the PC headgroup of OxPL. Transgenic mice expressing a single-chain Fv E06 fragment have recently been shown to have smaller infarct sizes post myocardial IRI. The objective of this study was to determine if directly infused E06 IgM reduced IRI in a porcine model of reperfusion injury that more closely reflects human physiology.

Methods: Male pigs, 45 to 50 kg, were randomized equally to IRI in two groups: 1) control with saline coronary infusion (n=7). 2) IgM E06 coronary infusion over 1 hour (n=7). The left anterior descending (LAD) artery was occluded distal to the second diagonal branch for 60 minutes using an angioplasty balloon. Following balloon deflation, saline or IgM E06 was infused over 60 min through a microcatheter. Following 120 min of total reperfusion, the area at risk (AAR) and infarct size (IS) were determined by triphenyltetrazolium chloride staining technique (TTC), and myocardial salvage index (AAR-IS/AAR) determined.

Results: All animals survived post reperfusion and no differences were present in hemodynamics at the baseline and 2 h post reperfusion between groups. A 51.3% reduction in infarct size was noted in animals receiving intracoronary E06 compared to controls (IS/AAR 21.7% ± 3.4 vs 42.3% ± 3.7 $p<0.0005$). IS/LV size (7.7 ± 3.2 vs 11.9 ± 1.2 $p<0.004$) and myocardial salvage index (82.6% vs 57.6% in controls) were significantly improved in animals receiving E06 compared to controls.

Conclusion: Intracoronary delivery of E06 antibody at the time of reperfusion leads to a significant reduction in infarct size, suggesting that generation of OxPL during reperfusion leads to cardiomyocyte cell death. Translation of this approach using humanized anti-OxPL antibodies may allow a novel approach to treat myocardial IRI in humans.

Resting and exercise-augmented hemodynamic evaluation in heart failure patients with reduced ejection fraction: Identification of outcome associated markers.

Emelissa Valcourt, Olivia Pieroni, Karen Alvarez, Mohammad Zahurul Islam, Hilary Bews, Amir Ravandi, Shelly Zieroth, Ashish H Shah
St. Boniface Hospital; University of Manitoba, Winnipeg, MB, Canada

Background: Heart failure (HF) affects over 600,000 Canadians and causes over 45,000 hospitalizations annually; majority of whom have reduced ejection fraction (HFrEF), defined as LVEF<40%. Despite optimum management, nearly 32% and 64% of patients die by 1 year and 5 years, respectively. These patients are managed in specialized HF clinics, where their evaluation is heavily depended on subjective description of symptoms. As HFrEF patients are likely to have impaired resting and/or exercise-augmented hemodynamic, monitoring of such parameters are likely to identify patients at-risk for adverse outcomes.

Material & methods: Clinically stable HFrEF patients from the HF clinic, St. Boniface Hospital were recruited. Resting and exercise-augmented (25 watts, for up to 12 minutes on a mounted bike) hemodynamic parameters were obtained using a Non-Invasive Cardiac System (NICaS), a whole-body impedance cardiography-based validated technology that is approved by the FDA (USA).

Results: A cohort of 65 HFrEF patients [64.5 ± 15.0 years, 10 (17.5%) female and mean BMI 31.1 ± 7.0 kg/m2] was recruited. At 6-month follow-up, subjects experiencing poor outcomes [unplanned HF hospitalizations and all-cause death], demonstrated lower resting stroke index [32.1 ± 8.4 vs. 37.3 ± 8.3 ml/m2; p=0.03), and cardiac power index (CPI) [0.5 ± 0.2 vs. 0.6 ± 0.2 W/m2; p=0.04]. Moreover, patients with poor outcomes demonstrated exaggerated exercise-augmented Granov-Goor Index (GGI), a surrogate marker of ejection systolic time.

Conclusion: NICaS-derived resting hemodynamic parameters demonstrate potential to identify high-risk HFrEF patients in an outpatient clinic setting. Early identification, and timely management may potentially improve outcomes.

Cardiomyocyte Krüppel-Like Factor 5 accounts for myocardial ischemia/reperfusion injury.

Nikolaos Mylonas[1], Effimia Maria Zacharia[2], Christine J. Pol[3], Ioannis D. Kyriazis[3], Matthew Hoffman[3], Alycia Hildebrand[3], Ira J. Goldberg[4], Vincent W. Yang[5], Agnieszka B. Bialkowska[5], Erhe Gao[3], John Elrod[3], Konstantinos Drosatos[1]

[1]Metabolic Biology Laboratory, Department of Pharmacology & Systems Physiology, College of Medicine, University of Cincinnati, Cincinnati, OH, USA. [2]Cardiology Division of the Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. [3]Center for Translational Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA. [4]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA. [5]Department of Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA

Background: Krüppel-like factor 5 (KLF5) is a transcriptional factor, which we have associated with diabetic cardiomyopathy and ischemic heart failure. For this study, we investigated potential involvement of KLF5 in myocardial ischemia/reperfusion (I/R) injury.

Methods: C57BL/6 mice were subjected to either 30' Ischemia (I)/120' reperfusion (R) or SHAM surgery and both myocardial area at risk (AAR) and remote myocardium were collected for assessment of KLF5 mRNA and protein levels. In a second series, KLF5 was inhibited either pharmacologically (ML-264) or genetically (cardiomyocyte (CM)-specific KLF5 knockout; aMHC-KLF5-/-) and we evaluated: i) spatial myocardial function using speckle-tracking echocardiography and ii) infarct size (IS), upon 30' I/24h R.

Results: KLF5 mRNA and protein levels were significantly increased in myocardial AAR of the I/R group, compared to the SHAM group, while no differences were observed in the remote myocardium. Pharmacological, as well as CM-specific KLF5 inhibition significantly increased lateral wall radial strain and lateral wall radial strain rate at 24h post-R, indicating an improved myocardial function. Also, pharmacological inhibition of KLF5 reduced IS, implying that KLF5 is an important mediator of myocardial I/R injury. Finally, CM-specific KLF5 deletion led to IS reduction, indicating that CM-derived KLF5 drives myocardial injury.

Conclusions: CM KLF5 expression is induced upon reperfusion and accounts for myocardial I/R injury. Accordingly, either pharmacological or CM-specific inhibition of KLF5 improve myocardial function and alleviate IS. Thus, KLF5 emerges as a novel therapeutic target for the treatment of myocardial I/R injury.

Expanding the GRK-5 Interactome.

Morgan Pantuck[1], Sudarsan Rajan[1], Eric Barr[1], Jessica Ibetti[1], Joanne Garbincius[1], Ryan Coleman[2], Kurt Chuprun[1], Walter Koch[1]
[1]Temple University, Philadelphia, USA. [2]University of Colorado Denver, Colorado, USA

Heart failure (HF) is a pathological state where the activity of the heart is insufficient to meet the metabolic needs of the body. As HF develops, the body attempts to increase the contractile force of the heart by stimulating cardiac hypertrophy. This compensatory growth is initially helpful but ultimately drives disease progression. G Protein-Coupled Receptor Kinase 5 (GRK-5) plays a key role in driving hypertrophic growth in the heart. Although some pathological mechanisms involving GRK-5 are well understood, the full interactome of GRK-5 has yet to be determined. Therefore, we performed biotin proximity labeling in order to identify novel protein/protein interactions involving GRK-5. In this assay, the protein of interest is fused to BioID2, a promiscuous biotin ligase. When BioID2 comes within ~15 nanometers of another protein, it irreversibly biotinylates the target, which can be subsequently captured on streptavidin beads and analyzed via mass spectrometry (MS). In this way, many potential protein/protein interactions can be identified, including weak or transient ones. To this end, we introduced a GRK-5/BioID2 fusion protein into Neonatal Rat Ventricular Myocytes (NRVMs) using an adenoviral vector. Cells were stimulated +/- phenylephrine to induce hypertrophy. BioID2 expressed by itself served as a negative control. Approximately 4500 proteins were identified via MS, including many that were significantly enriched in the GRK-5/BioID conditions relative to controls. These data will support the discovery of novel mechanisms by which GRK-5 facilitates pathological hypertrophy, which may reveal new therapeutic targets for HF treatment.

The Warburg effect is reduced in matured cardiomyocytes due primarily to a decrease in glycolysis.

Kaya Persad, Donna Andre, Berna Guven, Madeline Houncaren, Liyan Zhang, Jalene Greenwood, Gary Lopaschuk
Cardiovascular Research Center, Department of Pediatrics, University of Alberta, Edmonton, Canada

Proliferating cells, such as neonatal cardiomyocytes, have a high Warburg effect, which is a metabolic state characterized by highs rates of glycolysis uncoupled from glucose oxidation under aerobic conditions. In the newborn period there is a decreased proliferation of cardiomyocytes accompanied by a decrease in glycolysis. Changes in metabolic substrates, such as ketones may influence this metabolic change. Ketones can modify the Warburg effect, either through altering glycolysis or glucose oxidation. Ketones, such as β-hydroxybutyrate (βOHB), may also affect the developing cardiomyocyte through the endogenous inhibition of histone deacetylases (HDACs).

In this study, we directly examined the effects of exogenous βOHB on proliferating and differentiated H9c2 cardiomyocytes. We directly measured metabolic rates of glycolysis, glucose oxidation, ketone oxidation and fatty acid oxidation. We found that the Warburg effect was high in proliferating cardiomyocytes and decreased by 78% ($p<0.05$) with maturation. This was not due to an increase in glucose oxidation, but rather due to a decrease in glycolysis in proliferating versus matured cells (1482 ± 111 vs 329 ± 88 nmol.mg protein-1.hr-1, $p<0.05$). Ketones decreased the Warburg effect by 28% ($p<0.05$). This was due solely to a decrease in glycolysis and not glucose oxidation. Ketone oxidation remained unchanged between groups, and the fatty acid oxidation contribution to ATP production was insignificant.

We conclude that cardiomyocyte maturation is associated with a reduced Warburg effect, due exclusively to a decrease in glycolysis. Ketones contribute to the decrease in the Warburg effect primarily by inhibiting glycolysis.

Ketones provide an extra source of fuel for the failing heart without impairing glucose oxidation.

Simran Pherwani, David Connolly, Qutuba Karwi, Michael Carr, Kim Ho, Cory Wagg, Qiuyu Sun, Liyan Zhang, Jody Levasseur, Heidi Silver, Jason Dyck, Gary Lopaschuk
Cardiovascular Research Centre, University of Alberta, Edmonton, Canada

The failing heart is energy starved due to decreased cardiac glucose oxidation. Increasing ketone oxidation is a potential approach to increasing energy production in heart failure. However, any beneficial effects of this could be countered by detrimental effects on glucose oxidation. Therefore, we determined what effect increasing ketone concentration has on overall energy production in heart failure. Eight-week old male C57BL6/N mice underwent sham or transverse-aortic-constriction (TAC) surgery to induce pressure-overload heart failure over 7 weeks. Some TAC mice were treated with the sodium glucose co-transporter 2 inhibitor (SGLT2i), dapagliflozin, for 4 weeks (raises blood ketones). Cardiac function was assessed by echocardiography. Cardiac energy metabolism was measured in isolated working hearts perfused with 5 mM glucose, 0.8 mM palmitate, and either 0.2 mM or 0.6 mM ß-hydroxybutyrate (ßOHB; ketones). Compared to sham hearts, %EF significantly decreased in TAC hearts, with no effect of dapagliflozin, and at 0.2 mM ßOHB, glucose oxidation rates significantly decreased in TAC hearts. Glucose oxidation did not decrease further in dapagliflozin treated TAC hearts, despite ketone oxidation increasing at 0.6 mM ßOHB compared to TAC untreated hearts. Cardiac ATP production increased at both ßOHB concentrations in dapagliflozin treated TAC mice. Cardiac efficiency was not improved with dapagliflozin or increasing ßOHB in the perfusate. We conclude that increasing ketone concentration can increase energy production in the energy-starved failing heart without further impairing glucose oxidation. Increasing cardiac ketone supply may be a therapeutic approach to treating heart failure.

Homology model of free fatty acids receptor 4 and Gq in complex uncovers the pharmacology of endogenous fatty acid binding and receptor activation.

Sara Puccini, Timothy O'Connell, Yuk Sham
University of Minnesota, Minneapolis, USA

The high prevalence of metabolic syndrome (34.3%) is largely being driven by obesity and type 2 diabetes, induced by poor diet, specifically high-saturated fat, high-carbohydrate diets. Not surprisingly, attendant cardiometabolic diseases like heart failure (HF, particularly heart failure with preserved ejection fraction, HFpEF), coronary heart disease (CHD), myocardial infarction, and stroke are on the rise. Free fatty acid receptor 4 (Ffar4) is a GPCR expressed in multiple cell types pertinent to cardiometabolic diseases such as cardiac myocytes, macrophages and adipocytes. Ffar4 binds to and is activated by endogenous long-chain saturated, monounsaturated, and polyunsaturated fatty acids (SFAs, MUFAs, and PUFAs). Previous studies have suggested that SFAs, like palmitic acid, function as partial agonists, whereas MUFAs and PUFAs, including cardioprotective w3-PUFAs, have similar potency and efficacy at Ffar4. Despite this interesting pharmacology, the impact of altering dietary FAs on Ffar4 signaling to worsen or improve cardiometabolic disease is unclear. Therefore, defining the molecular basis for endogenous FA ligand potency and efficacy at Ffar4 has important implications for cardiometabolic diseases. We hypothesize that Ffar4 adopts a spectrum of dynamic, ligand-bound active-state conformations, allowing for differential activation of Gq, and thus Gq's downstream effectors. Here, we report the development of a novel Ffar4-Gq homology model, created with Schrödinger Software, to define the ligand-bound Ffar4-Gq active-state conformations for endogenous FA ligands. Using this homology model, we performed molecular dynamics, ligand docking, and mutagenesis simulations and identified differences between PUFA- and SFA-Ffar4-Gq active-state conformations that might uncover a novel molecular mechanism to explain Ffar4 pharmacology.

Timing reconverts glucocorticoid pharmacology for heart metabolism through cardiomyocyte-autonomous mechanisms.

Michelle Wintzinger[1], Manoj Panta[1], Karen Miz[1], Ashok Prabakaran[1], Hima Bindu Durumutla[1,2], Mattia Quattrocelli[1,2]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, USA. [2]University of Cincinnati, Cincinnati, USA

Glucocorticoids regulate energy metabolism, but little is known about the cardiomyocyte-autonomous effects of exogenous glucocorticoids in heart. Here we investigate the extent to which two complementary time dimensions impact glucocorticoid pharmacology in heart. In the first dimension, we investigated the impact of circadian time of intake. Glucocorticoid signaling follows circadian oscillations, but the extent to which the circadian clock gates glucocorticoid effects in cardiomyocytes is unknown. In mice with either normal or infarcted hearts, we found that the glucocorticoid prednisone improved cardiac content of NAD+ and ATP with light-phase dosing (ZT0), while the effects were blocked by dark-phase dosing (ZT12). This correlated with time-specific effects on upregulation of Nampt (NAD+ biogenesis) and Pparcg1a (mitochondrial biogenesis). These effects were cardiomyocyte-autonomous and clock-dependent, as shown by inducible cardiomyocyte-restricted inducible ablation of either the glucocorticoid receptor or the clock factor BMAL1. In the second dimension, we investigated the impact of frequency of intake. We recently discovered that once-weekly intermittence reverses the metabolic stress induced by once-daily dosing, but the effects of glucocorticoid intermittence on heart dysmetabolism remain unknown. In diabetic db/db mice, light-phase-restricted intermittent prednisone rescued NAD+ content, glucose-fueled respiration and diastolic function in heart. In aging hearts of male and female 24-month-old mice, glucocorticoid intermittence increased mitochondrial respiration, NAD+ and ATP/phosphocreatine content, correlating with reductions in intramyocardial lipids and heart-to-body weight ratios in both male and female mice. In summary, our study identifies two timing dimensions to leverage glucocorticoid chrono-pharmacology as metabolic booster for the heart.

Hydrogel-Based Intra-Pericardial Delivery of Endothelial Colony-Forming Cell-Derived Extracellular Vesicles Promotes Cardiac Repair Post-Myocardial Infarction.

Maia Ross[1,2], Anshul Jadli[1,2], Karina Gomes[1,2], Nadia DiMarzo[1,2], Darrel Belke[2,3], Paul Fedak[2,3], Vaibhav Patel[1,2]

[1]Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Canada. [2]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Canada. [3]Department of Cardiac Sciences, University of Calgary, Calgary, Canada

Following myocardial infarction (MI), available treatments fail to address the chronic loss of cardiac vasculature and cardiomyocyte death, permitting progressive maladaptive remodeling and subsequent heart failure (HF). Thus, MI remains a leading cause of global mortality. Extracellular vesicles (EVs) derived from endothelial colony-forming cells (ECFCs) facilitate adaptive cardiac remodeling post-MI. ECFC-EVs are attractive as a potential therapeutic as ECFC function is compromised in patients with type-2 diabetes, a common MI risk factor, limiting the applicability of autologous cell-based therapies. As current strategies present difficulties regarding invasiveness, retention, and efficacy, determining an appropriate method of therapeutic administration is an additional challenge.

We hypothesized that the minimally-invasive intra-pericardial (IP) injection of ECFC-EVs within an F-127 hydrogel would facilitate cardiac repair in a murine model of MI by promoting therapeutic retention and sustained release. This repair was anticipated to be greater with the use of ECFC-EVs derived from wildtype mice than from a diabetic mouse model. Accordingly, the impact of wildtype and diabetic ECFC-EVs on angiogenesis and cardiac repair was evaluated using in vitro and in vivo approaches.

Our findings indicate that F-127 hydrogel use facilitates sustained release of ECFC-EVs, the administration of which increased coronary endothelial cell proliferation, migration, and vascularization in vitro, and reduced maladaptive cardiac remodeling, improving cardiac contractility and function in vivo. These beneficial effects appeared more pronounced with the use of wildtype ECFC-EVs. Taken together, our results underscore the therapeutic promise of ECFC-EVs to improve cardiac repair and prevent HF following MI.

Pharmacological targeting of circadian mechanism factor ROR improves cardiac repair and prevents heart failure.

Janan Shoja Doost, Mina Rasouli, Tarak Khatua, Reza Fatemi, Ifene David Festus, Tami A. Martino
University of Guelph, Guelph, Canada

Myocardial infarction (MI) is commonly morbid and mortal worldwide, and its timing of onset, as well as severity of adverse outcomes, have shown circadian rhythm dependency. Therefore, pharmacological targeting of the circadian mechanism post-MI is a promising new approach to benefit outcomes and prevent heart failure (HF).

Here, we aimed to pharmacologically target circadian factor retinoic acid-related orphan-receptor (ROR) at reperfusion-time post-MI to improve outcomes. Murine myocardial ischemia-reperfusion (mI/R) was surgically induced at murine sleep-time, and the ROR inverse agonist SR2211 (20mg/kg) was administered at reperfusion. Compared to vehicle-treated mI/R controls, we found that SR2211-treated mice developed smaller left ventricular diastolic and systolic dimensions (4.43±0.03mm vs. 4.75±0.04mm; 3.10±0.06mm vs. 3.52±0.04mm), as well as better ejection-fraction (64.41±0.58% vs. 57.39±0.33%) on echocardiography at 8-weeks post-mI/R. Hearts were also smaller (132.36±5.62mg vs. 150.29±3.07mg) and had reduced infarct size (2.86±0.20% vs. 7.09±0.78%) 8-weeks post-mI/R. Ongoing studies investigate SR2211's best time-of-day efficacy, sex differences in recovery, and molecular pathways important for cardiac repair.

These studies demonstrate that targeting the circadian factor ROR once at the time of reperfusion improves cardiac repair and is a promising new therapy to prevent HF.

SMYD1a Protects Heart from Ischemic Injury by Regulating OPA1-Mediated Cristae Remodeling and Supercomplex Formation.

Marta Szulik[1], Steven Valdez[1], Maureen Walsh[1], Kathryn Davis[2], Ryan Bia[1], Emilee Horiuchi[3], Sean O'Very[1], Anil Laxman[1], Linda Sandaklie-Nicolova[1], Hanin Sheikh[1], Samuel Hickenlooper[1], Magnus Creed[1], Mickey Miller[1], Li Wang[1], June Gacia-Llana[1], Christopher Tracy[1], Stavros Drakos[1], Katsuhiko Funai[1], Dipayan Chaudhuri[1], Sihem Boudina[1], Sarah Franklin[1]
[1]University of Utah, Salt Lake City, USA. [2]University of Uttah, Salt Lake City, USA. [3]niversity of Utah, Salt Lake City, USA

SMYD1, a striated-muscle specific histone methyltransferase, was originally shown to play significant role in regulating cardiac development. In the adult myocardium, using inducible, cardiomyocyte-specific Smyd1 knockout mice, loss of SMYD1 leads to massive downregulation of mitochondrial bioenergetics fulminating in heart failure. However, the effects of SMYD1 overexpression in the heart and its molecular function in the cardiomyocyte in response to ischemic stress remains unknown. Here we demonstrate that SMYD1a, the mouse ortholog of human SMYD1, positively regulates cardiac energetics and protects heart from ischemic injury. To delineate how SMYD1a controls energy efficiency and metabolism, we generated a novel mouse model capable of inducible cardiomyocyte-specific SMYD1a overexpression. When subjected to ischemic injury these transgenic mice display reduced infarct size and cardiomyocyte death concomitant with enhanced mitochondrial respiratory efficiency. Additionally, our molecular analysis revealed that the cardiac tissue in these animals is protected from ischemic injury through SMYD1a's synergistic regulation of two key mitochondrial pathways. First, through its histone methyltransferase activity, SMYD1a maintains metabolic homeostasis by preserving basal expression of PGC-1α and its downstream targets including electron transport chain subunits. Second, SMYD1a regulates expression of OPA1, a key regulator of cristae morphology and the electron transport chain supercomplex formation by which it enhances mitochondrial respiration and ATP production. This work highlights that SMYD1a is the only known epigenetic regulator of cristae morphology. It provides broad implications for understanding the epigenetic mechanisms driving cardiac energetics and identifies a novel signaling pathway by which cardiomyocytes regulate energy efficiency, protecting them from ischemic injury.

Sirtuin 3 (SIRT3) Prevents Doxorubicin Induced Dilated Cardiomyopathy: Investigating Mitochondrial Protein Acetylation, Cardiac Lipids and Metabolic Dysfunction.

Mateusz Tomczyk[1,2], Arun Surendran[3,2], Bo Xiang[1,2], Evan Abram[1,2], Prasoon Agarwal[1,2], Kyle Cheung[1,2], Stephanie Kereliuk[1,2], Qiang Tong[4,5], Amir Ravandi[3,2], Vernon Dolinsky[1,2]
[1]Children's Hospital Research Institute of Manitoba, Winnipeg, Canada. [2]University of Manitoba, Winnipeg, Canada. [3]St. Boniface Hospital Albrechtsen Research Center, Winnipeg, Canada. [4]Childrens Nutrition Research Center, Houston, USA. [5]Baylor College of Medicine, Houston, USA

Doxorubicin (DOX) is an effective chemotherapeutic, that can lead to dose-dependent dilated cardiomyopathy. Previously, we showed that DOX treatment alters mitochondrial protein acetylation, involving reduced expression of the mitochondrial lysine deacetylase, SIRT3 in wild-type mice. Here, we hypothesize that increased expression of mitochondria localized M1-SIRT3 attenuates DOX-induced cardiac dysfunction by regulating the acetylation of enzymes involved in metabolic processes.

DOX (8mg/kg body weight for 4 weeks) or saline was administered to transgenic mice which have cardiac expression of full length M1-SIRT3 (mitochondrial), short form M3-SIRT3 (lacking mitochondrial localization sequence), or non-transgenic (Non-Tg) littermates. Transthoracic echocardiography revealed that DOX treatment caused cardiac dysfunction in Non-Tg mice, whereas expression of M3-SIRT3 and M1-SIRT3 attenuated cardiac remodeling and reduced cardiac output ($p<0.05$, n=6-13). Mass spectrometry (n=5-6) of cardiac acetylated mitochondrial peptides showed that DOX increased acetylation of proteins involved in cardiac energy production and lipid metabolism, such as acyl-CoA oxidase (ACO2) and hydroxyacyl-CoA dehydrogenase (HADHA). Notably, M1-SIRT3 expression mitigated these effects on acetylation. Global lipidomic analysis of cardiac tissue (n=6) revealed that DOX decreased triglycerides in Non-Tg and M3-SIRT3 DOX treated mice, but not in M1-SIRT3 mice. Using radio-labeled 18F-FDG PET/MRI imaging (n=6), in vivo glucose uptake was increased in Non-Tg, and M3-SIRT3 DOX treated mice ($p<0.05$), but unchanged in M1-SIRT3 mice.

Our data show that DOX altered cardiac structure and function in association with altered cardiac protein acetylation, lipid metabolism and glucose uptake. Importantly, increased expression of mitochondrial M1-SIRT3 in the heart prevented DOX-induced dilated cardiomyopathy and attenuated DOX-induced metabolic dysfunction.

MAP kinase-activated protein kinase-2 (MK2) deficiency is cardioprotective in male and female mice following myocardial infarction.

Joëlle Trépanier[1,2], Fatiha Sahmi[2], Sophie Neblai[2], Marie-Ève Higgins[2], Colombe Roy[2], Joanne Vincent[2], Yanfen Shi[2], Billie Chouinard[2], Marie-Élaine Clavet-Lanthier[2], Martin Sirois[1,1], Matthias Gaestel[3], Jean-Claude Tardif[1,2], Bruce G. Allen[1,2]
[1]Université de Montréal, Montreal, Canada. [2]Montreal Heart Institute, Montreal, Canada. [3]Hannover Medical School, Hannover, Germany

An inflammatory response is the first phase of wound healing following myocardial infarction (MI). Alterations in the magnitude and/or timing of the inflammatory response can be detrimental to repair of the damaged myocardium.

MAPK-activated protein kinase-2 (MK2) is a protein serine/threonine kinase activated by p38α/β MAPK. MK2-/- mice and splenocytes show impaired tumor necrosis factor-α, interleukin-1β, and interleukin-6 production in response to lipopolysaccharide (LPS). Overall, MK2 is thought to be an important regulator of inflammation post-LPS and in inflammation-based cancers. In the context of post-MI wound healing, MK2 deficiency did not impair inflammation. Instead, it reduced mortality and attenuated LV dilation in 12-week-old male mice 5-d post-ligation (permanent) of the left anterior descending coronary artery (LADL, Trépanier et al., In Preparation).

Hence, we sought to determine if scar maturation was altered in 12-week-old male (M) and female (F) MK2+/+ and MK2-/- mice. Echocardiographic assessment of cardiac structure and function was performed prior to and 21-days post-LADL. Hearts then underwent morphometric and histological analysis. F-MK2-/- were smaller than M-MK2-/- littermates in terms of body and heart mass and both M-MK2-/- and F-MK2-/- mice were bradycardic. Twenty-one days post-MI, survival was lowest in M-MK2+/+ and highest in F-MK2-/- mice. LV dilation was observed in all LADL groups except F-MK2-/- mice. However, only mice in the M-MK2+/+ group displayed a decrease in fractional shortening, whereas hypertrophy was greater in the surviving myocardium of M-MK2-/- mice.

Hence, MK2 deficiency did not impair scar formation and improved survival in male and female mice.

Variable ventricular cardiomyocyte expression of PAM is increased in dilated cardiomyopathy.

Elise Walsh[1], Dongwon Lee[2], Arun Patil[1], Tim Nieuwenhuis[1], Dan Arking[1], Marc Halushka[1]
[1]Johns Hopkins University School of Medicine, Baltimore, USA. [2]Boston Children's Hospital, Boston, USA

Recent discoveries have highlighted the fact that cardiomyocytes do not have uniform gene expression within the same regions of the heart. Our laboratory previously identified 143 proteins that exhibited mosaicism, including MYL4 and PAM. Other studies have shown that PAM exhibits greater expression in dilated cardiomyopathy (DCM) compared to control heart tissues, but the reason for this remains unknown. To characterize cell states, a multiplex immunohistochemistry (mIHC) approach was employed on four matched DCM hearts and controls using antibodies for 14 proteins. We also performed standard IHC for PAM on five tissue microarrays across 726 heart samples. Finally, we analyzed ATAC-seq data to begin studying mechanisms of PAM regulation. Of the 14 proteins, PAM was the only one found to have higher expression in DCM cases compared to controls. Across the TMAs, the percentage of PAM positive cells was higher not only in DCM ($p=1.95\times10-15$, Wilcoxon signed-rank test), but also, hypertrophic cardiomyopathy (HCM, $p=1.96\times10-14$), idiopathic heart disease (IHD, $p=2.71\times10-8$), and sudden cardiac death (SCD, $p=6.97\times10-3$). Finally, in six DCM ATAC-seq data sets compared to three controls, there was increased PAM locus chromatin accessibility, consistent with PAM overexpression. Overall, four ventricular cell states were identified by mIHC, but this result is limited by the number of antibodies used. PAM was found to be overexpressed in DCM compared to control heart tissues, suggesting that cardiomyocytes change cell states to adjust to heart failure. Further research should be done to elucidate PAM regulation and potential for therapeutics.

Lack of endogenous high molecular weight FGF2 causes changes in gene expression associated with prevention of pressure overload-induced cardiac systolic dysfunction.

Navid Koleini, Barbara E Nickel, Raghu S Nagalingam, Natalie M Landry, Robert R Fandrich, Ian M Dixon, Michael Czubryt, Davinder Jassal, Peter A Cattini, Elissavet Kardami
Departments of Physiology and Pathophysiology and Human Anatomy and Cell Sciences, University of Manitoba, and Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, Canada

Fibroblast growth factor 2 (FGF2) is multifunctional protein, produced as high (>20 kDa, Hi-) and low molecular weight (18kDa, Lo) isoforms in the heart, at a 7:3 ratio. While administered Lo-FGF2 has been established as a cytoprotective agent in multiple models of tissue and cellular injury, there is limited information about the role of Hi-FGF2 in the heart. To investigate the effect of endogenous Hi-FGF2 on cardiac gene expression we used mice expressing or not Hi-FGF2, and examined their cardiac transcriptome under non-stressed and chronic stress conditions. Chronic stress, leading eventually to heart failure, was induced by pressure overload via transverse aortic constriction surgery.
Our results showed that lack of endogenous Hi-FGF2 in the FGF2(lo) mice protected from pressure overload-induced: myocardiac stress; decline in ejection fraction. Increased cardiac mass post-TAC could be attributed to cardiomyocyte hypertrophy in the FGF2(WT) mice; and to decreased incidence of myocyte cell death in the FGF2(Lo) mice. Endogenous Hi-FGF2 altered global gene expression under baseline (non-stress) as well as stress conditions. Upregulation of HSP70 under baseline conditions is proposed to have contributed to increased resistance from injury and cell death in the FGF2(Lo) hearts, in a pre-conditioning like fashion. Upregulation of the transcriptional regulator nuclear receptor NR1D1 during TAC may also have contributed to cardioprotection in the FGF2(Lo) mice.

FGF-2 exerts isoform-specific effects on cardiac mitochondrial permeability transition, mediated by a mitochondrial receptor and intra-mitochondrial signal transduction.

Wattamon Srisakuldee, Barbara E.Nickel, Robert R. Fandrich, Elissavet Kardami.
Departments of Physiology and Pathophysiology and Human Anatomy and Cell Sciences, University of Manitoba, and Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, Canada

Fibroblast growth factor 2 (FGF-2) is a multifunctional protein, produced as >20 kDa high (Hi) or 18 kDa low (Lo) molecular weight isoforms. Both isoforms are present in the extracellular space but also in the intracellular environment. We showed that intracellular Hi-FGF-2, but not Lo-FGF-2, promotes cardiomyocyte cell death, requiring mitochondrial engagement. We have now examined the hypothesis that FGF-2 isoforms can directly modulate mitochondrial viability and permeability transition (mPTP).

Using rat cardiac subsarcolemmal or interfibrillar mitochondrial suspensions, we found that while recombinant Lo-FGF2 prevented calcium-overload-induced mPTP, recombinant Hi-FGF2 was toxic to cardiac mitochondria by stimulating mPTP. Anti-FGFR1 immunoreactive bands were detected in all mitochondrial preparations by western blotting. A variety of FGFR1 inhibitors prevented both the protective effect of Lo-FGF2, and the toxic effect of Hi-FGF2. In addition, Hi-FGF2 promoted mPTP by activating a mitochondrial PP1-like phosphatase. Lo-FGF-2 protected from calcium overload- or Hi-FGF-2-induced toxicity by activating mitochondrial PKCepsilon. We propose that the relative cytosolic concentrations of FGF-2 isoforms would be expected to regulate cell survival by directly influencing mitochondrial integrity or resistance to damage.

Examining the independent and combined effects of muscle strength and cardiorespiratory fitness on cardiovascular risk factors in older females: A secondary analysis of observational data.

Daniel Schwade[1,2], Kevin F. Boreskie[1,2], Jacqueline L. Hay[1,2], Kaitlin M Reilly[1,2], Marcyo Câmara[4], Eduardo C. Costa[3,4], Todd A. Duhamel[1,2]

[1]Faculty of Kinesiology and Recreation Management, University of Manitoba; [2]Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre. Winnipeg, Manitoba, Canada; [3]Graduate Program in Physical Education, Department of Physical Education; [4]Graduate Program in Health Sciences, Federal University of Rio Grande do Norte, Brazil

Background: Cardiovascular disease (CVD) is the leading cause of death in older adults (1). While it is known that high muscle strength (MS) (2) and cardiorespiratory fitness (CRF) (3) are associated with a lower risk of CVD (4), no studies have addressed the differences in CVD risk profiles between older females with different physical fitness phenotypes, such as high MS but poor CRF and vice-versa. We hypothesized the prevalence of CVD risk factors will differ across physical fitness phenotypes.

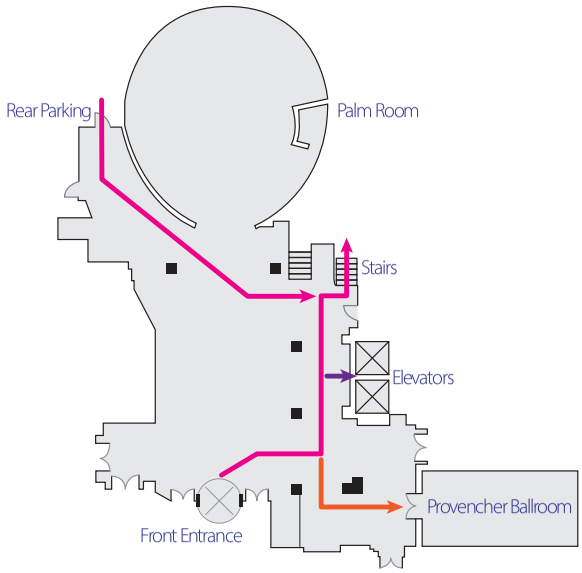
Methods: This study is a secondary analysis of data from a previous trial (NCT02863211), which examined CVD risk factors in 985 females aged 55 and older with no previous history of CVD. Participants were assigned to one of 5 groups based on their performance on the grip strength (GS) and 6-minute walk test (6MWT): 1) High CRF-High MS; 2) High CRF-Low MS; 3) Normal CRF-Normal MS; 4) Low CRF-High MS, and 5) Low CRF-Low MS. A generalized linear regression model adjusted for age and BMI assessed the influence of proxy measures of CRF (6MWT) and MS (GS) on each CVD risk factor.

Results: In our model, differences in the Framingham Risk Score (FRS) were only found between the group with High CRF-Low MS and the group with Low CRF-Low MS (8.5 ± 0.4 vs. 11.2 ± 0.6, $p = 0.011$). Additionally, relationships were found between higher CRF and FRS ($\beta = -0.008$, $p = 0.003$), triglycerides ($\beta = -0.001$, $p = 0.036$), resting SBP ($\beta = -0.018$, $p = 0.036$), pulse pressure ($\beta = -0.016$, $p = 0.009$), and post-exercise SBP ($\beta = -0.029$, $p = 0.017$), and large artery elasticity (LAE) ($\beta = 0.006$, $p = 0.002$). Higher MS was only associated with increased LAE ($\beta = 0.091$, $p < 0.001$) and small artery elasticity (SAE) ($\beta = 0.060$, $p < 0.001$).

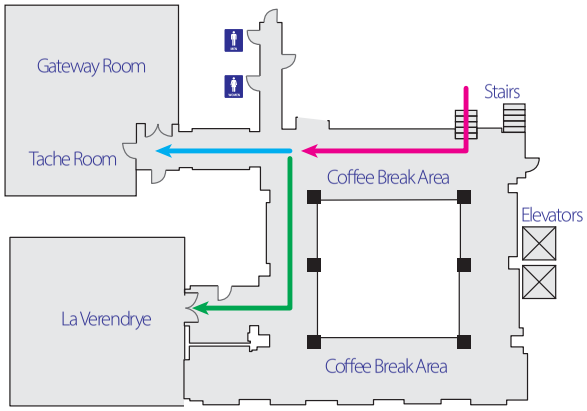
Conclusions: We found that the group with both high CRF and MS had more favorable CVD risk profiles than the group with higher MS alone. Additionally, the presence of high CRF alone was associated with a better CVD risk profile in older females when compared to high MS alone.

Orientation Plan

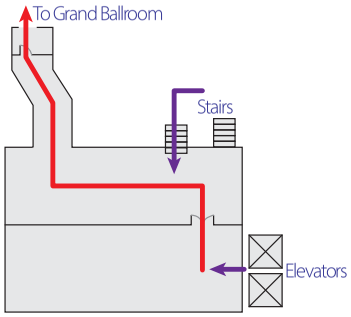
Hotel Lobby



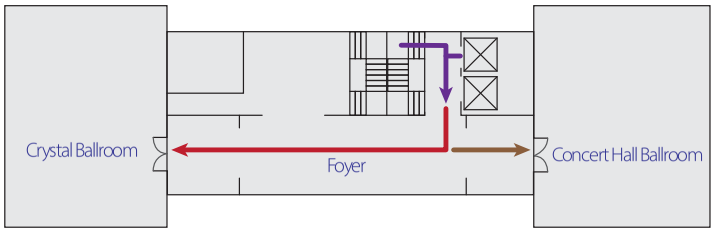
Mezzanine



1st Floor



7th Floor



Room List

Please follow the coloured paths to your destination.

1) Provencher Ballroom - Main Floor

2) Mezzanine - 2nd Floor (MZ)

3) Gateway/Tache Room – Mezzanine Level 2nd floor

4) LaVerendrye Room - Mezzanine Level 2nd floor

5) Crystal Ballroom – 7th floor (Poster sessions)

6) Concert Hall – 7th floor

7) Grand Ballroom

JMCC
JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY

CALL FOR PAPERS

JMCC is seeking submissions from early career investigators on the following topic:

"Mechanisms of Heart Failure: Insights by the Next Generation of Cardiovascular Researchers"

Submission window is now open
Submission deadline: March 31, 2023

Topics of interest include, but are not limited to:
-Technical developments and use of iPSC-derived models of heart failure
-Intercellular and interorganelle crosstalk
-Metabolic perturbations in heart failure
-Small molecule targeting and preclinical development
-Epigenetic and transcriptional regulation in heart failure
-Developments in and use of animal models of heart failure
-Novel technologies and methodologies for cardiovascular physiology monitoring
-Perspectives on current and future needs in cardiovascular medicine

Guidelines:
-Submissions are limited to a review or short communication
-All authors must be of ECI status (no more than 8 years removed from terminal degree) and be members in good standing of the International Society for Heart Research
-It is encouraged that authors be of different sections of the ISHR and have attended the 2022 ISHR World Congress
-Submissions will undergo a standard peer-review process

Guest Editors:
Erik Blackwood, PhD
Evangelia (Litsa) Kranias, PhD
Carmen (Kika) Sucharov, PhD

Abstracts may be submitted to guest editors for pre-submission inquiry
Contact Erik Blackwood (eablackwood@arizona.edu) with questions

Submission guidelines at jmcc-online.com
Select "VSI: Next Generation Researchers" as Article Type upon submission

International Society for Heart Research
North American Section

NAS2023

Madison, WI (6/26-6/30)

Hosted by
University of Wisconsin
Cardiovascular Research Center

Timothy Kamp

Ying Ge

Héctor Valdivia

NAS2024

Los Angeles, CA (5/19-5/24)

Hosted by
UCLA DG School of Medicine
& Cedars-Sinai Medical Center

Peipei Ping

Jenny Van Eyk

Yibin Wang

Tom Vondriska

Reza Ardehali