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1st Annual Scientific Meeting of the International Society of Heart Research Southeast Asia Section (ISHR-SEA)

Frontiers in Cardiovascular Research

October 3rd & 4th 2024, Singapore

Meeting venue:
NUSS Kent Ridge Guild House
9 Kent Ridge Dr, Singapore 119241

Organising committee
ISHR-SEA Section Council
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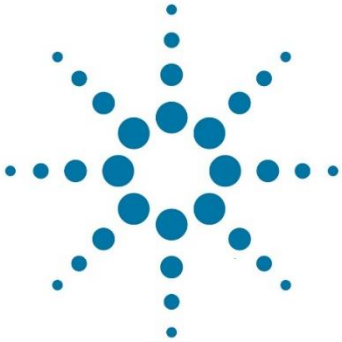

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Day 1
Thursday October 3rd 2024

07:00-08:00 Registration and poster set-up

08:00-08:05 **Welcome and introductions**
Roger FOO (President ISHR-SEA)
Derek HAUSENLOY (Secretary ISHR-SEA)
Haojie YU (Treasurer ISHR-SEA)

08:05-08:40 **Keynote Lecture 1 (30 min talk, 5 min QA)**

Chair: Roger FOO (NUS Medicine, Singapore)

Borja IBÁÑEZ (CNIC, Spain)
New precision medicine paradigm for primary prevention of ASCVD: a disease-centric approach

08:40-10:00 **Scientific Session 1: Ischemic heart disease/acute myocardial infarction**
Chairs: Jiong Wei WANG (NUS Medicine, Singapore), Mark CHAN (NUS Medicine, Singapore)

1. ***Yin Hua ZHANG (Seoul National University, South Korea) (15 min talk)***
   Mitochondria transplantation for ischemic cardiovascular diseases
2. ***Sarawut KUMPHUNE (Chiang Mai University, Thailand) (15 min talk)***
   Applications of anti-serine protease inhibitory protein as a therapeutic agent against myocardial ischemia/reperfusion injury
3. ***Lena HO (Duke-NUS, Singapore) (15 min talk)***
   Cardiac Metabolic Regulation by Microproteins
4. ***Satirah ZAINALABIDIN (Universiti Kebangsaan, Malaysia) (10 min talk)***
   S-allylcysteine attenuates regional ischemia/reperfusion injury in estrogen-deficient model
5. ***Sauri HERNANDEZ (Duke-NUS, Singapore) (10 min talk)***
   DJ-1 mimic as novel treatment for acute myocardial infarction

QA session (15 min)

10:00-10:20 **Coffee Break and Poster Viewing**

10:20-12:00 **Young Investigator Award Session *(4 x 10 min talk + 5 min QA)***
Judging panel - *Yibin WANG (Chair) (Duke-NUS, Singapore), Nipon CHATTIPAKORN (Chiang Mai University, Thailand), Kamisah YUSOF (Universiti Kebangsaan Malaysia), Yin Hua ZHANG (Seoul National University, South Korea), Yuan CHENG (Taipei Medical University, Taiwan).*

1. ***Yifan WANG (NUS Medicine, Singapore)***
   SREBP2 Depletion Protects against Hyperlipidemia and Atherosclerosis by Regulating ANGPTL3-LPL Axis
2. ***Shuo CONG (Duke-NUS, Singapore)***
   Empagliflozin ameliorates the pathological phenotype in human induced pluripotent stem cell-derived cardiomyocytes generated from patients with diabetic heart failure
3. ***Francesco Paolo RUBERTO (NUS Medicine, Singapore)***
   Mitochondrial cristae instability drives ageing-related inflammation and heart failure
4. ***Fan YU (Duke-NUS, Singapore)***
   Cardiometabolic Adaptations in the Cave Nectar Bat Eonycteris spelaea

Sponsor talk 1 – **JeySern TAN (Vazyme) (5min)**
Introduction to Vazyme

Sponsor talk 2 - **Jia Kai LIM (Olink) (5min)**
Revealing the truth of human diseases. Protein by Protein

Sponsor talk 3 - **Aarte GOKHALE (IDT) (15min)**
Overcoming challenges in Genetic Disease Research using NGS solutions.

Speaker talk 4 - **Federica TOMAY (Agilent) (10 min)**
Multimodal Connected Workflow for Cardiotoxicity Assessment Using Human iPSC-Derived Cardiomyocytes

MOU Signing between NUS Yong Loo Lin School of Medicine, CVMD TRP and Agilent Technologies (5 min) **Roger FOO (NUS YLLSoM) and Chow Woai Sheng (Agilent)**

12:00-13:15 **Scientific Session 2: Heart failure**
Chairs: Manvendra SINGH (Duke-NUS, Singapore), Matthew ACKERS-JOHNSON (NUS Medicine, Singapore)

1. ***Sung Joon KIM (Seoul National University, South Korea) (15 min talk)***
   Protective role of cardiac nitric oxide synthase in pulmonary hypertension-induced right ventricular failure
2. ***Nipon CHATTIPAKORN (Chiang Mai University, Thailand) (15 min talk)***
   Potential novel interventions against chemotherapy-induced cardiotoxicity
3. ***Han XIAO (Peking University, China) (15 min talk)***
   Cardiac adrenergic signalling and inflammatory injury
4. ***Kamisah Binti YUSOF (Universiti Kebangsaan Malaysia) (10 min talk)***
   Antihypertrophic effects of Parkia speciosa pod extract in angiotensin II-exposed H9C2 cardiomyocytes
5. ***Bambang WIDYANTORO (University of Indonesia, Indonesia) (10 min talk)***
   Endothelial to mesenchymal transition responsible for myocardial changes in diabetic cardiomyopathy

QA session (15 min)

13:15-14:00 **Lunch and poster viewing**
Shaw Foundation Alumni House

14:00-15:20 **Scientific Session 3: Regenerative medicine**

Supported by 

Chairs: Lynn YAP (LKC, Singapore), Yibin WANG (Duke-NUS, Singapore)

1. ***Yen-Wen LIU (National Cheng Kung University, Taiwan) (15 min talk)***
   Hypoimmunogenic human pluripotent stem cells for cardiac regeneration
2. ***Chrishan RAMACHANDRA (NHCS, Singapore) (15 min talk)***
   Human models of HFpEF for novel target discovery
3. ***Boon Seng SOH (A*STAR IMCB, Singapore) (15 min talk)***
   Mitochondria: A potential rejuvenation tool against cardiovascular aging
4. ***Osvaldo CONTRERAS (Victor Chang Cardiac Research Institute, Australia) (10 min talk)***
   Modelling Perturbations in the Human Cardiomyocyte Cell Cycle and DNA Replication Mechanisms.
5. ***Woan Ting TAY (Duke-NUS, Singapore) (10 min talk)***
   RNA Splicing Regulation in Cardiomyocyte Maturation

QA session (15 min)

15:20-15:45 **Coffee Break and Poster Viewing**

15:45-16:55 **ISHR-SEA Early Career Investigator Rapid Fire Session *(3 min talk + 2 min QA)***

Chairs: Mick LEE (ISHR-SEA ECI rep, Singapore), Yuan Yuan CHENG (ISHR-SEA ECI rep, Taiwan)

1. ***Syaifuzah SAPIAN (Universiti Kebangsaan Malaysia)***
   Ameliorative potentials of polyphenol-rich extract of roselle calyx against diabetes-induced cardiac dysfunction and structure deterioration via regulation of oxidative stress and apoptosis pathways
2. ***Yu-Ru LEE (National Taiwan University, Taiwan)***
   Deciphering the Role of RNA-Binding Proteins in Cardiomyocyte Maturation
3. ***Fitri KUSUMASTUTI (Universitas Gadjah Mada, Indonesia)***
   Predicting the Future of Adult Patients with Atrial Septal Defect and Pulmonary Hypertension: The Role of Emerging Biomarker Bioactive Adrenomedullin
4. ***Michelle MAK (NUS Medicine, Singapore)***
   Identification of a novel enhancer to drive robust cardiac specific gene expression
5. ***Iman Nabilah Abd RAHIM (Universiti Teknologi MARA, Malaysia)***
   Unlocking the Potential of Saffron: A Novel Alternative for Statin Intolerance
6. ***Liyuan JIN (Seoul National University, South Korea)***
   Effects of Mesenchymal Stem Cell-Derived Mitochondrial Transplantation on Donor Hearts
7. ***Dan LIAO (NUS Medicine, Singapore)***
   Prevalence of hypercoagulation in post-acute COVID-19 patients and efficacy of novel anticoagulants as therapeutics in a human ex vivo thrombosis model
8. ***Usana CHATTURONG (Naresuan University, Thailand)***
   Quinazoline-based human phosphodiesterase 5 inhibitors exhibited a selective vasorelaxant effect on rat isolated pulmonary arteries

16:55-17:30 **Keynote Lecture 2 (30 min talk, 5 min QA)**

Chair: Yin Hua ZHANG (Seoul National University, South Korea)

Eun Bo SHIM (Kangwon National University, South Korea)
AI for precision medicine of coronary artery diseases

Shaw Foundation Alumni House
11 Kent Ridge Dr, Singapore 119244

17:30-19:30 **Poster moderator session**
Moderators - Alvin LIN (Duke-NUS, Singapore), Pingjin GAO (Shanghai, China), Elisa LIEHN (NHCS, Singapore), Matthew ACKERS-JOHNSON (NUS Medicine , Singapore), Elena Aisha Binti AZIZAN (National University of Malaysia, Malaysia), Chrishan RAMACHANDRA (NHCS, Singapore), Haojie YU (NUS Medicine, Singapore), Nipon CHATTIPAKORN (Chiang Mai University, Thailand), Kamisah YUSOF (Universiti Kebangsaan Malaysia), Yin Hua ZHANG (Seoul National University, South Korea), Yuan CHENG (Taipei Medical University, Taiwan), Dyah Wulan ANGGRAHINI (Universitas Gadjah Mada, Indonesia), Lynn YAP (LKC, Singapore), Sauri HERNANDEZ (Duke-NUS, Singapore)

19:30-20:30 **Meeting dinner buffet**

Day 2
Friday 4th October 2024

08:00-09:20 **Scientific Session 4: Innovative technologies**

Supported by  

Chairs: Chester DRUM (NUS Medicine, Singapore), Roger FOO (NUS Medicine, Singapore)

1. ***Patrick HSIEH (Academia Sinica, Taiwan) (15 min talk)***
   Gut Bacteria and Heart Healing: The Hidden Players in Post-Infarction Resilience
2. ***Han Wei HOU (LKC, Singapore) (15 min talk)***
   Microfluidic chips for modelling atherosclerosis
3. ***Su-Yi TSAI (National Taiwan University, Taiwan) (15 min talk)***
   Unraveling the Role of RNA-Binding Proteins in Human Cardiac Development and Diseases
4. ***Shengjie LU (NHCS, Singapore) (10 min talk)***
   Nitric oxide-releasing nanoparticles for multiple-targeting cardioprotection
5. ***Wei Wen LIM (NHCS, Singapore) (10 min talk)***
   Interleukin-11 causes acute cardiac electrophysiological dysfunction and predisposes the heart to arrhythmia

QA session (15 min)

09:20-09:55 **Keynote Lecture 3 (30 min talk, 5 min QA)**

Chair: Jean-Paul KOVALIK (Duke-NUS, Singapore)

Christopher NEWGARD (Duke University, USA)
Sexual dimorphism of branched-chain amino acid metabolism and cardiometabolic disease risk

09:55-10:15 **Coffee Break and Poster Viewing**

10:15-11:30 **Scientific Session 5: Joint ISHR Asia-Pacific Sections**
Chairs: Roger FOO (NUS Medicine, Singapore), Derek HAUSENLOY (NHCS, Singapore)

1. ***Ajay BAHL (Vice President of ISHR-Indian section) (15 min talk)***
   Genetics of Indian cardiomyopathy patients
2. ***Huang-Tian YANG (Vice President of ISHR-Chinese section) (15 min talk)***
   Cell and cell products for cardiac repair
3. ***Max Shiang Yong LIM (Council member of ISHR-Australasia section) (15 min talk)***
   Sustained delivery of stem cell secretome for cardiac repair
4. ***Seitaro NOMURA (Council member of ISHR-Japanese Section) (15 min talk)***
   Single-cell and spatial omics analysis to develop cardiovascular precision medicine

QA session (15 min)

11:30-11:50 **JMCC Editors Session**
Panel: Yibin WANG (JMCC Associate Editor), Huang-Tian YANG (JMCC Associate Editor), Roger FOO (JMCC Editor), Yu HUANG (JMCC Editor)

Introduction to JMCC journal and JMCC Plus
How to publish in JMCC
Discussion

11:50-12:25 **Keynote Lecture 4 (30 min talk, 5 min QA)**

Chair: David SILVER (Duke-NUS, Singapore)

Howard ROCKMAN (Duke University, USA)
Allosteric modulators for the beta1-adrenergic receptor

12:25-13:00 **Lunch and poster viewing**
Shaw Foundation Alumni House

13:00-13:35 **Keynote Lecture 5 (30 min talk, 5 min QA)**

Chair: Anissa WIDJAJA (Duke-NUS, Singapore)

Stuart COOK (NHCS, Singapore)
Understanding IL11 as a therapeutic target.

13:35-14:55 **Scientific Session 6: Vascular biology**
Chairs: Christine CHEUNG (LKC, Singapore), Shu YE (NUS Medicine, Singapore)

1. ***Kai-Chien YANG (National Taiwan University, Taiwan) (15 min talk)***
   Targeting Mechanosensitive Endothelial TXNDC5 to Stabilize eNOS and Reduce Atherosclerosis In Vivo
2. ***Yu HUANG (University of Hongkong, China) (15 min talk)***
   Laminar flow inhibits vascular calcification
3. ***Roshni SINGARAJA (NUS Medicine, Singapore) (15 min talk)***
   Semaphorin 3F in the vascular wall
4. ***Elena Aisha AZIZAN (National University of Malaysia, Malaysia) (10 min talk)***
   Primary aldosteronism: molecular medicine meets public health
5. ***Dyah Wulan ANGGRAHINI (Universitas Gadjah Mada, Indonesia) (10 min talk)***
   Risk stratification and prognosis of Pulmonary Arterial Hypertension: the use of biomarkers.

QA session (15 min)

14:55-15:05 **ISHR-SEA Annual General Meeting**
Roger FOO (President ISHR-SEA)
Derek HAUSENLOY (Secretary ISHR-SEA)
Haojie YU (Treasurer ISHR-SEA)

15:05-15:25 **Coffee Break and Poster Viewing**

15:25-16:55 **Scientific Session 7: Metabolism and Aging**
Chairs: Rijan GURUNG (NUS Medicine, Singapore), Paul YEN (Duke-NUS, Singapore)

1. ***Walter KOCH (Duke University, USA) (15 min talk)***
   Heart Failure and Heart-to-Fat Communication- a Role for GRK2
2. ***Phillip WHITE (Duke University, USA) (15 min talk)***

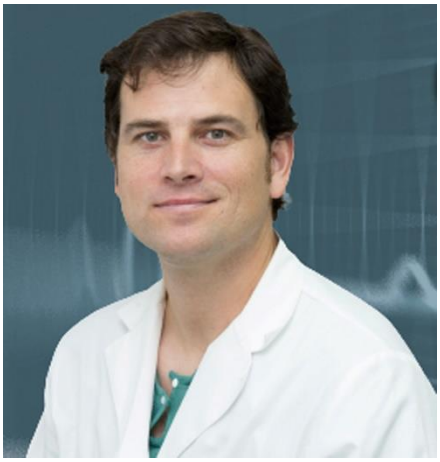
BCAA biology in cardiometabolic diseases

3. ***Rana GUPTA (Duke University, USA) (15 min talk)***
   Adipose Tissue Remodeling in Health and Disease
4. ***Anissa WIDJAJA (Duke-NUS, Singapore) (15 min talk)***
   Inhibition of IL11 signalling extends mammalian healthspan and lifespan
5. ***Haojie YU (NUS Medicine ,Singapore) (15 min talk)***
   Genome-scale CRISPR screening for novel pathways regulating LDL uptake

QA session (15 min)

16:55-17:15 Meeting close
Travel grant awardees and prize giving for YIA, ECI Rapid Fire presenter, and best posters (3 prizes).

Keynote speakers



Borja IBÁÑEZ (Spanish National Centre for Cardiovascular Research, Spain)

Borja IBÁÑEZ is Scientific Director of the Spanish National Center for Cardiovascular Research (CNIC) and interventional cardiologist at University Hospital Fundación Jiménez Díaz. His research has been focused for several years in the clinical stages of ASCVD, making important contributions in the field of cardioprotection during acute myocardial infarction. In recent years he has been interested in the subclinical stages of ASCVD, with a main focus on the early identification of silent atherosclerosis by non-invasive imaging. He is PI of several European Commission H2020 grants, and published more than 350 articles, with an H-index of 82 (scholar). He has received numerous awards for his scientific merits. He served as the Chairperson of the 2023 ESC Guidelines for the management of ACS and of the 2017 ESC STEMI Guidelines.

New precision medicine paradigm for primary prevention of ASCVD: a disease-centric approach

Cardiovascular disease (CVD) remains a major health threat and is the leading cause of morbidity and mortality worldwide. Atherosclerosis is the basis for most CVD. Current primary prevention strategies are based on the burden of classical risk factors. Current risk equations are based on the calculation of the chances for a major adverse event in the next 10 years. Therefore, they are very age-biased (eg young subjects rarely qualify for initiating interventions to control lipid or blood pressure levels. This is paradoxical, since young individuals are more vulnerable to deleterious effects of modifiable risk factors in terms of subclinical disease presence and progression (i.e. cholesterol and blood pressure levels and silent atherosclerosis progression is stronger in young than in older individuals). Silent atherosclerosis can be halted or even completely regressed ("cured") if tackled in its very early stages. The identification of early (silent) atherosclerosis requires the use of imaging. In fact, the identification of silent atherosclerosis by non-invasive imaging has been shown to improve risk stratification provided by classical risk factors alone. We propose a new paradigm of primary prevention where a wide screening for silent atherosclerosis since early ages identify subjects developing the disease. Aggressive risk factors control (mainly lipids and blood pressure) in these early stages of atherosclerosis development can completely stop the process and delay decades the transition from subclinical to clinical disease (infarction, stroke, dementia,..) and have a massive impact in society and healthcare systems in the long term in a cost-effective manner

Eun Bo SHIM (Chuncheon, South Korea)

Eun Bo SHIM, PhD, is a Professor of Mechanical and Biomedical Engineering at Kangwon National University, where he has served since 2003. He earned his Bachelor's degree in Mechanical Engineering from Seoul National University, followed by a PhD in Mechanical Engineering from the Korea Advanced Institute of Science and Technology (KAIST) and a second PhD in Physiology from Kyoto University. Dr. Shim has extensive research experience, including postdoctoral work at MIT and a research position at Harvard-MIT Health Science & Technology. He is also the CEO and Founder of AI Medic Inc., focusing on AI-driven healthcare innovations.

AI for precision medicine of coronary artery diseases

The integration of artificial intelligence (AI) into precision medicine has revolutionized the diagnosis and management of coronary artery diseases (CAD). This paper presents a comprehensive overview of AI technologies applied to medical imaging, particularly focusing on coronary artery analysis. Initially, I introduce AI algorithms developed for plaque analysis using CT images, highlighting their potential to enhance diagnostic accuracy and facilitate personalized treatment strategies for CAD patients. Although these tools have shown promise, they are still in the developmental stage and have not yet been widely implemented in clinical settings or undergone comprehensive clinical trials.

Following this, I explain CT-derived fractional flow reserve (CT-FFR) as a case study in personalized diagnosis. My research includes the presentation of last year's clinical trial results, which demonstrate the clinical utility of our on-site, fully automated CT-FFR technology. This innovative, non-invasive method for assessing the physiological impact of coronary artery stenosis operates within hospital settings with minimal human involvement, streamlining the diagnostic process. The clinical trials revealed significant findings that underscore the practical benefits and reliability of CT-FFR in clinical use.

Moreover, I will discuss the current limitations of CT-FFR technology, including challenges related to accuracy in certain clinical scenarios and the need for further validation in diverse patient populations. I will also explore potential directions for future development, aiming to enhance the technology's precision and expand its applicability in CAD management.

Finally, I discuss the broader clinical outcomes and the current adoption of CT-FFR within the Korean healthcare system, while acknowledging the ongoing development of plaque analysis technologies. Our findings emphasize the potential of these AI-driven tools to offer more precise and patient-specific approaches to CAD management, showcasing the importance of fully automated, AI-integrated solutions in advancing clinical practice and improving patient outcomes.

Christopher NEWGARD (Duke-University, USA)

Christopher B. NEWGARD, Ph.D. is Director of the Sarah W. Stedman Nutrition and Metabolism Center, founding Director of the Duke Molecular Physiology Institute, and the W. David and Sarah W. Stedman Distinguished Professor at the Duke University Medical Center. Prior to coming to Duke in 2002, Dr. Newgard was the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Professor, Department of Biochemistry, and Co-Director of the Touchstone Center for Diabetes Research, University of Texas Southwestern Medical Center, Dallas. Dr. Newgard's research applies interdisciplinary tools for understanding of cardiometabolic disease mechanisms including gene discovery, metabolic engineering, and comprehensive metabolic analysis. Dr. Newgard has authored >425 peer-reviewed and review articles (Clarivate h-index, 111), and has been the recipient of several awards, including the Outstanding Scientific Achievement (Lilly) Award from the American Diabetes Association (2001), a Merit Award from the NIH (2001), a Bristol Meyers-Squibb "Freedom to Discover" Award (2006), a Duke Medical Alumni Association Distinguished Professorship (2016), and an Outstanding Innovator Laureate Award from the Endocrine Society (2020). Over his 37 years as an independent faculty member, >50 graduate student, postdoctoral fellow and junior faculty (K awardees) have been mentored in his laboratory.

Role of branched-chain amino acids in cardiometabolic diseases

Research by our group and others over the past two decades has demonstrated a strong association of BCAA and their metabolic byproducts with cardiometabolic disease phenotypes. Causal links have also been described, for example an effect of lowering of BCAA levels to enhance insulin sensitivity in pre-clinical models of obesity and to shift the isolated working heart from reliance on glucose metabolism to more healthful and energetically efficient use of fatty acids. Moreover, direct exposure of the working heart to levels of BCAA-derived metabolites found in obesity is sufficient to activate a program of chronic protein synthesis, potentially contributing to unhealthy cardiac hypertrophy. More recently, we have discovered new BCAA-derived metabolic intermediates that contribute to muscle-liver trafficking of BCAA carbon skeletons and sexual dimorphism in their catabolism. These processes may contribute to the elevated levels of BCAA and their metabolites and higher risk of development of cardiometabolic disease phenotypes in obese males compared to females. Current studies are focused on manipulation of the newly discovered BCAA-related metabolic circuit(s) and assessment of the impact of such manoeuvres on cardiometabolic disease phenotypes.

Howard ROCKMAN (Duke University, USA)

Howard ROCKMAN is a physician-scientist whose research is focused on the molecular mechanisms of cardiac hypertrophy and heart failure with emphasis on the role of G protein-coupled receptors. He received his MD from McGill University in 1983, completed medical residency at the Montreal General Hospital in 1987 and in 1991, Cardiology Fellowship at the University of California, San Diego. Work in his laboratory has led to a new understanding for the role of G protein-coupled receptor (GPCR) signaling in the pathogenesis of the failing heart as it relates to the concept known as biased GPCR signaling. He pioneered the development of mouse models to study the molecular underpinnings of cardiac hypertrophy and was the first to develop a noninvasive means to measure cardiac function in Drosophila. His work has led to the development of new drug therapies to treat heart disease.

He has received a number of awards and honors, including the Burroughs-Wellcome Fund Award for translational medicine and the Distinguished Achievement Award from the American Heart Association. In 2015, he received the distinction of being named a Distinguished Scientist by the American Heart Association. In 2016, he received the Distinguished Faculty Award from the Duke Medical Alumni Association. He has been elected to both the Association of American Physicians and the American Society for Clinical Investigation. He has authored over 230 journal articles and is the former editor-in-chief of the Journal of Clinical Investigation, and founding editor of JCI Insight.

Dr. Rockman has trained more than 75 scientists and actively involved in the teaching of medical students and residents and is recognized for his passion in mentoring young scientists and physicians. He is a recipient of both the Duke School of Medicine Research Mentoring Award and the prestigious Master Teaching Award.

Allosteric Modulators for the β1-Adrenergic Receptor

While traditional β-blockers (i.e. competitive orthosteric antagonists of β-adrenergic receptors; βARs) are widely used as cardiovascular therapeutics, adverse effects such as fatigue and the nonselective inhibition of multiple receptor subtypes often limit maximal effectiveness. An emerging approach to enhance therapeutic targeting is to identify allosteric modulators that act cooperatively with orthosteric ligands. In contrast to orthosteric ligands which bind the endogenous ligand binding site, allosteric modulators bind to regions that are topographically distinct from the orthosteric pocket and can enhance (positive allosteric modulator; PAM) or reduce (negative allosteric modulator; NAM) the activities of orthosteric agonists/antagonists. Since allosteric regions exhibit greater sequence and structural diversity among receptor subtypes relative to the more highly conserved orthosteric pocket, allosteric modulators are more likely to be subtype specific and/or generate less adverse effects. We embarked on a DNA-encoded small molecule library (DEL) screen to identify novel allosteric modulators of the β1AR. Following multiple rounds of affinity selection using purified, functional, β1ARs reconstituted in lipid nanodiscs and a DEL containing more than 1 billion unique compounds, we identified Compound 11 (C11) as an allosteric modulator with unique pharmacological properties. Notably, C11 binds to the β1AR with micromolar affinity and enhances the binding affinity of orthosteric agonists and certain antagonists to the β1AR. In contrast to its positive cooperative effect on ligand binding, cell signaling assays showed C11 potently inhibits G protein and β-arrestin signaling downstream of the β1AR. Importantly, C11 showed high β1AR specificity with no effect on β2AR or AT1R signaling. These results suggest that C11 is a β1AR-specific PAM in terms of ligand binding but a NAM in terms of agonist efficacy, belonging to a largely under-characterized class of allosteric modulators termed PAM-antagonists. With a unique pharmacological profile, C11 is a promising potential therapeutic for conditions of enhanced sympathetic nervous activation.

Stuart COOK (NHCS, Singapore)
Dr Cook grew up in Kenya and studied medicine at St Bartholomew's in London. He did a PhD at the National Heart and Lung Institute, UK and a Postdoctoral Fellowship at Harvard. He is a Group Head at the MRC London Institute of Medical Sciences and Professor at Imperial College, London and Duke-National University of Singapore (Duke-NUS). He was the founding Director of the National Heart Research Institute Singapore and Director of the CVMD program at Duke-NUS. His work on genetic heart muscle disease led to a new diagnostic test for inherited cardiac conditions that was commercialised by Illumina and resulted in new clinical genetics services in both the UK and Singapore. His group identified IL11 as a pro-fibrotic factor in 2017 and went on to define a key role for IL11 in a range of fibroinflammatory diseases. He is a co-founder of Enleofen Bio, a biotechnology company developing anti-fibrotic therapies that partnered with Boehringer Ingelheim in 2019, and of VVB Bio. The current focus of his research groups is on identifying new biology and targets for healthspan, genetic diseases, sepsis and cardiorenal conditions.

Understanding IL11 as a therapeutic target.

Scientific Session 1: Ischemic heart disease/acute myocardial infarction

Yin Hua ZHANG (Seoul National University, South Korea)

Yin Hua ZHANG, MD PhD, Professor of Department of Physiology & Biomedical Sciences, Seoul National University, College of Medicine, Korea. Dr Zhang was awarded MD degree in Yanbian University College of Medicine and Master's degree and PhD in Seoul National University, College of Medicine. She gained extensive research experience in the University of Bristol and Oxford University in the UK. Current research focuses on mitochondria and translational studies for Cardiovascular diseases using techniques combining electrophysiology, cell shortening, Ca handling of Cardiomyocytes and biochemical assays. Dr Zhang's research team also conducts clinical studies for myocardial infarction and hypertensive patients.

Mitochondria transplantation for ischemic cardiovascular diseases

Recently, mitochondria transplantation (MT) is emerged as a novel therapeutic strategy targeting ischemic cardiovascular diseases, but the roles of MT in the donor hearts for transplantation remain unidentified. Here, we tested the efficacy of human platelet derived mitochondria (pl MT) and mesenchymal stem cell derived mitochondria (MSC MT) on mitochondrial and cardiac function of the donor hearts for heart transplantation. Incubation of donor rat hearts with pl MT ex vivo for 9 hrs resulted in the internalization of pl MT in cardiomyocytes and the enhancement of cardiac mitochondrial activity and ATP production without increasing reactive oxygen species production. Contractility and coronary arterial perfusion w ere improved with pl MT. MSC MT incubation of mice hearts for 9 hrs showed increased mitochondrial activity reduced apoptosis and improved conduction velocity of the hearts. MSC MT reversed pathological phenotypes of the hearts by improving structure and fusion process of the mitochondria. Similar improvement was observed in aged mice hearts. Taken together, the study provides the proof of principle for exogenous mitochondria transplantation as an enhancer of the donor heart.

Sarawut KUMPHUNE (Chiang Mai University, Thailand)
Associate Professor Dr. Sarawut KUMPHUNE obtained a bachelor's degree in medical technology and a master's degree in biochemistry from Mahidol University, Thailand. In 2009, he received a PhD in Medicine—Cardiovascular Research from King's College London, University of London, UK. Prior to his current position at the Biomedical Engineering Institute at Chiang Mai University, he was head of the Biomedical Research Unit in Cardiovascular Science at Naresuan University. His research focuses on cell and molecular biology, cardiovascular sciences, biochemistry, pharmaceutical sciences, clinical biochemistry, drug delivery, and nanomedicine.

Applications of anti-serine protease inhibitory protein as a therapeutic agent against myocardial ischemia/reperfusion injury
Protease enzymes are responsible for extensive damage to the heart tissue during and after myocardial ischemia/reperfusion (I/R) injury. They also play a role in the process of myocardial remodeling and hypertrophy. Suppressing the activity of proteases can be regarded as a potent approach to hinder the growth of damaged tissue and the advancement of cardiac remodeling and hypertrophy. While numerous small-molecule protease inhibitors have been under development, the significant issue lies in the "off-target effect" exhibited by these therapeutic candidates. Alternatively, utilizing a wide-ranging endogenous anti-protease peptide could yield more dependable outcomes and ensure safety.
Secretory leukocyte protease inhibitor (SLPI) is an 11.7 kDa positively charged protein that is released into the environment and has been proven to prevent several inflammatory serine proteases from functioning. The initial data regarding the cardioprotective impact of SLPI was established in 2002. Our previous study demonstrated that giving recombinant human secretory leukocyte protease inhibitor (rhSLPI) by mean of overexpression of rhSLPI gene [4] or treatment with recombinant protein of human SLPI provided cytoprotective effect against I/R injury both in an in vitro, ex vivo, and in vivo study model. Interestingly, our recent unpublished data showed that recombinant protein of anti-protease deficient mutant SLPI (L72K, M73G, L74G) (mt-SLPI) also provided cardioprotection against I/R injury. Therefore, the therapeutic potential of SLPI is believed to be in part by direct effect of SLPI. Further investigation is required to fully understand the roles of SLPI in post-ischemic cardiac remodeling, as well as the potential of nanomedicine to facilitate targeted delivery of SLPI to the heart, and the uses of tiny therapeutic peptides produced from SLPI.

Lena HO (Duke-NUS, Singapore)
Lena obtained her PhD at Stanford (mentor: Gerald Crabree) and completed postdoctoral training at IMB-A*STAR (mentor: Bruno Reversade), where she discovered the paradigm that non-coding RNAs can in fact encode peptides from small open reading frames (sORFs). In 2017, Lena established the Endogenous Peptides Lab in Duke-NUS Medical School, which utilizes a combinatorial platform to discover and functionalize novel sORF-encoded peptides (SEPs) in the human genome. Her goal is to uncover programmatic functions that SEPs might play, afforded by their special size, biochemical and genomic properties, as well as detailed molecular mechanisms employed by individual SEPs where they operate. The Ho lab focuses on SEPs that function in the mitochondria to regulate metabolism, especially those that are required for cardiac bioenergetics and physiology.

Targeting mitochondrial function for cardioprotection
The emergence of microproteins encoded by cryptic open reading frame in regions of the genome previously thought to be non-coding, is rapidly expanding the known proteome at the lower end of the size distribution. Our lab has demonstrated that the mitochondrial proteome, particularly the electron transport chain (ETC), is enriched for such small ORF-encoded proteins (mito-SEPs). Here, they perform a variety of functions ranging from assembling the electron transport chain (ETC), to regulating metabolite transport and cellular signalling. The failing heart is characterized by chronic energy deficiency, mitochondrial dysfunction and oxidative stress. In this talk, I will discuss our efforts to find novel targets within the mitochondrial microproteome for improving cardiac bioenergetics during heart failure

Satirah ZAINALABIDIN (Universiti Kebangsaan, Malaysia)

Dr. Satirah ZAINALABIDIN is an academic and researcher in the field of cardiovascular science at the Biomedical Science Department, Universiti Kebangsaan Malaysia (UKM). She earned her PhD from the University of Strathclyde, Glasgow, in 2011. Her research focuses on exploring the therapeutic potential of natural compounds for treating cardiovascular diseases, utilizing various animal models. She is dedicated to developing new strategies for the prevention and treatment of cardiovascular conditions. In addition to her research, she teaches Physiology and Pharmacology subjects. Currently, she serves as the Deputy Dean of Research and Innovation at the Faculty of Health Sciences, UKM.

S-allylcysteine attenuates regional ischemia/reperfusion injury in estrogen-deficient model

Menopausal women are predisposed to developing ischemic heart disease compared to men due to a lack of estrogen. S-Allyl-L-cysteine (SAC), abundant in aged garlic, is believed to protect against myocardial ischemia-reperfusion injury (IRI) by stimulating the production of hydrogen sulfide (H2S). However, the impact of SAC treatment in myocardial IRI models in ovariectomized rats remains unclear. Female Wistar ovariectomized rats were used in this study. Isolated rat hearts were Langendorff-perfused and induced 45 mins of regional ischemia and 120 mins of reperfusion. SAC (1 mM) was perfused as the treatment after the IRI induction. Ischemia impaired the left ventricle developed pressure (LVDP), which was improved with SAC treatment. SAC significantly reduced the total LDH release and the percentage of infarct size. The co-administration of SAC and PAG showed no significant improvement in the heart function and infarct size. Overall, SAC showed cardioprotective potential in preventing detrimental effects after myocardial IRI in ovariectomized rats.

Sauri HERNANDEZ (Duke-NUS, Singapore)
Dr. Hernandez is a Senior Research Fellow at Duke-NUS Medical School and an Affiliate Investigator at the National Heart Centre, Singapore. Her research focuses on elucidating the molecular mechanisms underlying heart failure (HF) after myocardial infarction (MI). Dr. Hernandez aims to develop strategies that protect the heart from ischemic injury, reduce myocardial infarct size, and prevent the progression to heart failure post-acute myocardial infarction.

DJ-1 mimic as novel treatment for acute myocardial infarction
Despite advances in medical treatments and coronary interventions, heart failure (HF) after myocardial infarction (MI) continues to be a major cause of morbidity and mortality. New therapies are urgently needed. This study explored ND-13, a peptide derived from the protein DJ-1, for its potential to reduce the harmful effects of MI. In isolated cardiomyocytes, ND-13 lowered cell death by 42%, blocked mitochondrial fission, and maintained ATP levels. Both ex vivo and in vivo models demonstrated that ND-13 significantly reduced infarct size, preserved cardiac function, and enhanced mitochondrial bioenergetics.

Scientific Session 2: Heart failure

Sung Joon KIM (Seoul National University, South Korea)
Dr. Sung Joon KIM earned his MD (1991) and PhD (1997) from Seoul National University College of Medicine (SNUCM). He completed postdoctoral research at Freiburg University, Germany, in 2000, and served as professor at SNUCM since 2004. His research focuses on cardiovascular physiology, particularly pulmonary arterial hypertension and right heart disease, as well as ion channels in immune cells. Dr. Kim has published 192 peer-reviewed papers and served as Director of the Division of Medical Sciences at the National Research Foundation of Korea.

Protective role of cardiac nitric oxide synthase in pulmonary hypertension-induced right ventricular failure
The physiological and pathophysiological properties of right ventricular cardiac myocytes (RVCMs) are less understood compared to left ventricular myocytes (LVCMs). We previously reported key differences in electrophysiological parameters, Ca2+ transients, and sarcomere function between RVCMs and LVCMs. Notably, neuronal nitric oxide synthase (nNOS) played a distinct role in E-C coupling in RVCMs, leading to Ca2+ desensitization of myofilaments via cTnI targeting. Higher phosphorylation of the nNOSβ isoform was observed in RVCMs. In monocrotaline-induced pulmonary arterial hypertensive rats, nNOS inhibition caused significant functional disturbances, including arrhythmogenesis due to abnormal Ca2+ waves.

Nipon CHATTIPAKORN (Chiang Mai University, Thailand)

Professor Dr. Nipon CHATTIPAKORN received his M.D. from the Faculty of Medicine, Chiang Mai University, Thailand, and Ph.D. in Physiology and Biophysics from the University of Alabama at Birmingham (UAB), USA, and had his Postdoctoral Fellow training in the Division of Cardiovascular Diseases, Department of Medicine, at UAB. He is currently the Director of the Cardiac Electrophysiology Research and Training (CERT) Center, Faculty of Medicine, Chiang Mai University. His research interest is in the field of cardiac electrophysiology and pathophysiology of the heart, including ischemia-reperfusion injury, heart failure and cardio-oncology, using models ranging from cardiac mitochondria to the bedside studies.

Potential novel interventions against chemotherapy-induced cardiotoxicity

Cardiac mitochondrial dynamic alterations have been recognized as contributors to cardiotoxicity following doxorubicin treatment. Both mitochondrial fission inhibitor-1 and fusion promoter were shown to exert cardioprotection in several cardiovascular pathologies including cardiac ischemia. However, their effects in doxorubicin-induced cardiotoxicity are unclear. We demonstrated that both mitochondrial fission inhibitor and mitochondrial fusion promotor provided cardioprotective effects against cardiotoxicity induced by doxorubicin as indicated by an attenuation in mitochondrial dysfunction, oxidative stress, inflammation, and mitochondrial dynamic imbalance. All of these led to improved left ventricular function. These findings suggested that either inhibiting mitochondrial fission or promoting mitochondrial fusion could be new strategies in fighting against doxorubicin-induced cardiotoxicity.

Han XIAO (Peking University, China)

Dr. Han XIAO received her M.D. & Ph.D. from Peking University in 2008 and continued her postdoctoral work at the University of California, Riverside, USA, from 2010-2012. Her research mainly focuses on the inflammatory mechanisms of cardiac remodeling and the potential therapeutic strategy. Recently, she mainly focused on adrenergic signaling and cardiac remodeling.

As the first or corresponding author, she has published 40 papers in famous journals, including Circulation Research, European Heart Journal, Circulation, and the British Journal of Pharmacology. As the chief principal investigator, she has acquired foundations from the National Science Fund for Outstanding Young Scholars, the National Natural Science Foundation of China Key program, and the National Key R & D program. She obtained the CNPHARS-SERVIER Young Investigator Award in Pharmacology (2017), the Chiang Pi-ning award-outstanding Young Investigator Award (2020), and the VCANBIO Award for Innovations and Breakthroughs in Life Sciences and Medicine (2021). She is currently the Deputy Secretary-General of the Chinese Committee of the International Society for Heart Research (ISHR).

Cardiac adrenergic signalling and inflammatory injury

β-adrenergic receptor (β-AR) overactivation is a major pathological cue associated with cardiac injury and diseases. Previously, we discovered that inflammasome-dependent activation of interleukin-18 within the myocardium upon acute β-AR overactivation triggers cytokine cascades, macrophage infiltration, and pathological cardiac remodeling. Furthermore, we demonstrated that exercise training can alleviate cardiac inflammation induced by β-AR overactivation by inhibiting the NLRP3 inflammasome pathway through an AMP-activated protein kinase (AMPK)-dependent mechanism. AMPK, a highly conserved energy sensor, regulates energy metabolism and confers cardioprotective effects. In the present study, we identified a novel substrate for AMPK, namely β-arrestin-1. The phosphorylation of β-arrestin-1 at serine 330 by AMPK enhances the expression and activity of phosphodiesterase 4, thereby inhibiting the activation of the β-AR/cyclic AMP/protein kinase A signaling pathway. As a result, the phosphorylation of β-arrestin-1 at serine 330 effectively suppresses β-AR-induced activation of the cardiac inflammasome and subsequent remodeling.

Kamisah Binti YUSOF (Universiti Kebangsaan Malaysia)

Dr. Kamisah YUSOF serves as an associate professor within the Department of Pharmacology at the Faculty of Medicine, Universiti Kebangsaan Malaysia. Previously, she held the positions of Head of Department of Pharmacology at the Faculty of Medicine and Chairperson of the university's Animal Ethics Committee. Presently, she leads as the Head of the Cardiovascular and Pulmonary Research Group. Her primary research focus lies in cardiovascular ethnopharmacology, particularly exploring cardiomyocyte hypertrophy and investigating the potential protective effects of medicinal plants, notably Parkia speciosa. Additionally, she contributes her expertise as an Associate Editor for Frontiers in Pharmacology, specifically within the Ethnopharmacology section.

Antihypertrophic effects of Parkia speciosa pod extract in angiotensin II-exposed H9C2 cardiomyocytes

Cardiac hypertrophy, a key feature of heart failure, presents a significant therapeutic challenge. This study investigated the antihypertrophic effects of the ethyl acetate (EA) fraction from Parkia speciosa Hassk. empty pod extract, a plant native to Southeast Asia, on angiotensin II-induced hypertrophied cardiomyocytes. The EA fraction significantly reduced cardiomyocyte size, protein content, reactive oxygen species, and levels of B-type and atrial natriuretic peptides. It also downregulated the mitogen-activated protein kinase (MAPK) and calcineurin-nuclear factor of activated T-cells C3 (NFATC3) signaling pathways. These results suggest that the EA fraction can mitigate cardiomyocyte hypertrophy by modulating the calcineurin-NFAT/MAPK pathways

Bambang WIDYANTORO (University of Indonesia, Indonesia)
Dr. Bambang WIDYANTORO completed cardiology training at Universitas Indonesia and further specialized in critical care and interventional cardiology through fellowship at the National Cardiovascular Center (NCVC) Harapan Kita, Jakarta. He earned his PhD in Cardiovascular Science from Kobe University, Japan. Currently, he serves as the Chair of the Department of Cardiology and Vascular Medicine at Universitas Indonesia and heads Research Division at NCVC Harapan Kita. Working as critical care cardiologist in the Intensive and Cardiovascular Care Unit (ICVCU) at NCVC Harapan Kita, his clinical and research areas of interest include acute cardiovascular care, advanced heart failure, hypertension, and diabetic heart disease. Additionally, he is Deputy Editor for Indonesian Journal of Cardiology and Associate Editor for Korean Circulation Journal.

Endothelial to mesenchymal transition responsible for myocardial changes in diabetic cardiomyopathy

Scientific Session 3: Regenerative medicine

Yen-Wen LIU (National Cheng Kung University, Taiwan)

Dr. Yen-wen LIU is an associate professor of clinical medicine in the Department of Internal Medicine at National Cheng Kung University's College of Medicine. Dr. Liu was formerly one of the researchers at Professor Charles Murry's lab in the University of Washington's Institute for Stem Cell and Regenerative Medicine. Dr. Liu worked together with a team of researchers in Murry's lab to unlock the process of regeneration of cardiac muscle tissue in non-human primates. Following the induction of myocardial infarction (i.e., heart attack), the team implanted cardiac muscle cells derived from human embryonic stem cells into primates which successfully regenerated the damaged cardiac muscle tissue. This procedure restored severely damaged cardiac tissue and cardiac function. Their research was published in the internationally renowned scientific journal Nature Biotechnology.

Hypoimmunogenic human pluripotent stem cells for cardiac regeneration

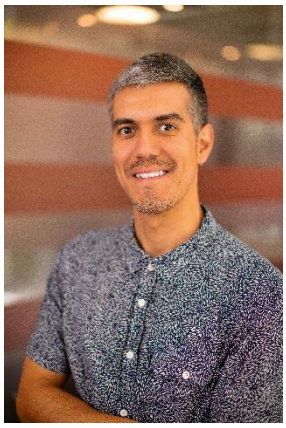
Human pluripotent stem cell (hPSC)-derived cardiomyocytes (hPSC-CMs) are proved to remuscularize infarcted hearts and to restore post-infarct cardiac function. However, post-transplant rejection resulting from human leukocyte antigen (HLA) mismatch is an enormous obstacle of allogeneic cell therapy. Here, we demonstrated the feasibility of hypoimmunogenic hPSCs for cardiac regeneration. Using an infarcted swine model, we proved the therapeutic effect of hypoimmunogenic hPSC-CM transplantation under the treatment of low dose immunosuppressive agents. We tried to identify the recommended dose of immunosuppressive drugs in the infarcted swine model receiving hypoimmunogenic hPSC-CM intramyocardial transplantation. Therefore, the hypoimmunogenic hPSC may serve as a universal cell source for regeneration medicine.

Chrishan RAMACHANDRA (NHCS, Singapore)
Chrishan RAMACHANDRA is Assistant Professor in the SingHealth Duke-NUS Cardiovascular Sciences Academic Clinical (CVS ACP) Programme, and Junior Principal Investigator at National Heart Research Institute Singapore (NHRIS). His research focuses on modelling human cardiac diseases with induced pluripotent stem cells (iPSCs) to discover personalised therapeutics and new treatment targets for heart failure. His group has gained key mechanistic insight into various forms of heart failure and identified new treatments, some of which are undergoing clinical evaluation. He has been the recipient of various awards for his noteworthy contributions in stem cells and drug discovery. He serves on editorial boards of scientific journals and is actively engaged in education.

Human models of HFpEF for novel target discovery
Cardiomyocytes (CMs) derived from induced pluripotent stem cells (iPSCs) generated from patients with cardiac diseases underpinned by genetic mutations have been shown to faithfully recapitulate the clinical phenotype in a dish. Known as disease modelling, this approach provides an unprecedent opportunity to gain insight into human cardiac physiology and disease in order to identify new therapeutic targets. Here, we demonstrate that heart failure with preserved ejection fraction (HFpEF) – a disease widely regarded as heterogenous and with no underpinning genetic mutation, can be disease modelled using HFpEF patient-specific CMs. In addition to displaying structural and functional abnormalities common to various forms of heart failure, we show that HFpEF CMs display unique metabolic signatures similar to human HFpEF myocardial tissue and an inflammatory response consistent with a metainflammation phenotype. Furthermore, we validated the effects of two new therapies for ameliorating the pathological phenotype in HFpEF CMs. Human models that faithfully recapitulate the cardiac features of HFpEF could serve as an indispensable platform to identify novel cardiac-specific targets for improving health outcomes in patients with HFpEF.

Boon Seng SOH (A*STAR IMCB, Singapore)
Dr. Boon Seng SOH is a Principal Investigator at ASTAR's Institute of Molecular and Cell Biology. He earned his PhD from Imperial College London and completed postdoctoral training at Harvard University under Professor Kenneth Chien, focusing on multipotent cardiac stem cells. Notably, Dr. Soh has pioneered a 3D chambered cardiac organoid model and integrated AI into his research platform. His current research work centers on modeling human heart diseases, exploring cardiac aging, and delving into the intricacies of heart metabolism, establishing both in vitro and in vivo platforms for therapeutics development.

Mitochondria: A potential rejuvenation tool against cardiovascular aging
Mitochondrial therapy is an innovative approach in regenerative medicine that focuses on transferring healthy mitochondria into diseased or aged cells to restore cellular function. This method is gaining significant attention due to its potential in combating age-related diseases and enhancing cell-based therapies. In a recent groundbreaking study by Lin et al. (Nature, 2024), the authors demonstrated how mitochondrial transplantation can enhance the efficacy of vascular cell therapies, providing a new avenue for treating cardiovascular conditions. Our research expands on this concept by using SIRT6 knockdown model of induced pluripotent stem cell (iPSC)-derived cardiomyocytes and cardiovascular organoids to simulate aging and assess the therapeutic potential of mitotherapy. Specifically, we evaluated its effects on age-related cardiovascular dysfunctions, a major contributor to heart disease and other systemic ailments. Our preliminary findings reveal that mitochondrial therapy not only slows down cellular aging phenotypes but also significantly enhances the bioenergetic capacity of the cells. Furthermore, it improves cardiovascular contractility, which is critical for maintaining healthy heart function. These promising results suggest that mitochondrial therapy could play a pivotal role in addressing age-related metabolic decline, providing a novel and powerful tool for advancing the field of regenerative medicine



Osvaldo CONTRERAS (Victor Chang Cardiac Research Institute, Australia)
Postdoctoral Fellow Osvaldo CONTRERAS is a cell biologist and a biomedical researcher studying tissue regeneration and homeostasis loss in mammals with a focus on the stromal and stem cell compartments. After completing his MSc degree, he received his PhD in cell and molecular biology in 2019. His PhD focused on tissue-resident fibro-adipogenic progenitor cell fate, plasticity, and heterogeneity in muscle regeneration and heart repair in Prof. Enrique Brandan's Lab at Pontificia Universidad Católica de Chile with the co-supervision of Prof. Fabio Rossi at the University of British Columbia, Vancouver, Canada. Since his PhD, Osvaldo has focused on comprehending myopathies and myogenic and fibroblast fate determination and differentiation in the context of fibro-fatty deposition, centering on three major signalling pathways: PDGF, TGF-B, and Wnt signalling, and their cross-talk. As a Postdoctoral Scientist, Dr Contreras works on stem cell-based strategies for improving our understanding of heart development and repair under the supervision of Prof. Richard Harvey at the Victor Chang Cardiac Research Institute and holds a Conjoint Lecturer position at UNSW Sydney, Faculty of Medicine and Health.

Modelling Perturbations in the Human Cardiomyocyte Cell Cycle and DNA Replication Mechanisms
The cell cycle is a fundamental biological process that controls organisms' growth, development, and reproduction. Disruptions to this process can cause various diseases, including cancer and congenital disorders. Severe congenital heart disease (CHD) is a rare condition that results in altered heart tissue architecture and the loss of cardiomyocytes (CMs), indicating an abnormal cell cycle as a cornerstone of paediatric CHD. However, investigating human cardiomyocyte cell division is challenging, and the foetal and paediatric cell cycle remains largely unknown.

This study investigates the dynamics of core cell cycle proteins and cell division by differentiating patient- derived induced pluripotent stem cells (iPSCs) into ventricular and atrial CM lineages at multiple stages. Using single-cell flow cytometry and high-resolution imaging, we developed multiplex analyses to map the CM cell cycle. Our results showed that most ventricular and atrial CMs were in the G0/G1 phase and cell cycle arrest. At the same time, a significant fraction was positive for Ki67, a proliferation marker, with high levels in G2/M stages. Additionally, we successfully optimized a new non-toxic thymidine analogue, F-ara-EdU, to label S-phase replicating CMs and study CM cell cycle progression using pulse-chase experiments. Our study found atrial CMs proliferate faster than ventricular CMs, suggesting unique cell cycle fine-tuning mechanisms. Moreover, mRNA-seq and untargeted proteomic data show distinct cell cycle stressors impair cardiomyocyte cell indentity via DNA replication stress mechanisms, linking cell cycle progression with genome integrity and DNA repair.

Through our approach to reveal the human cardiomyocyte cell cycle, we can gain insights into defective organ morphogenesis caused by environmental and cell cycle perturbations and disease, thereby accelerating our knowledge of heart development and disease. This research has the potential to identify therapeutic targets by improving our understanding of the human cell cycle.

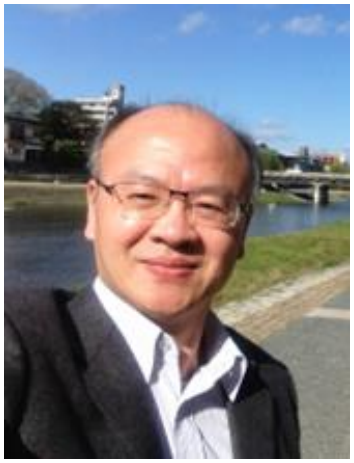
Woan Ting TAY (Duke-NUS, Singapore)

Ms. Woan Ting TAY is a Ph.D. candidate at Duke-NUS Medical School, focusing on the molecular regulation of cardiomyocyte maturation. Her work investigates the role of RNA-binding proteins and isoform-switching events in heart maturation and heart diseases, aiming to uncover new insights into cardiac biology. Although early in her research career, Ms. Tay is dedicated to advancing the field through rigorous exploration, and she believes that collaboration among researchers with varied expertise is key to driving innovation and expanding knowledge in cardiovascular research. She is passionate about translating her findings into potential therapeutic applications.

RNA Splicing Regulation in Cardiomyocyte Maturation

Heart maturation involves extensive metabolic, structural, and molecular changes in cardiomyocytes to sustain the postnatal systemic circulation and accommodate the increased hemodynamic load. Through comparative transcriptome analysis of neonatal and adult rat hearts, our study identified mRNA splicing as a key regulatory pathway, with RNA Binding Fox-1 Homolog 1 (Rbfox1) emerging as a significant splicing regulator. We characterized the alternative splicing events that define the transition from fetal to adult cardiomyocytes by utilizing full-length isoform sequencing. In addition to providing insights into the isoform dynamics that underlie cardiomyocyte maturation, this study may offer perspectives for understanding the molecular mechanisms of heart diseases and offer a basis for exploring future therapeutic approaches.

Scientific Session 4: Innovative technologies



Patrick HSIEH (Academia Sinica, Taiwan)

After completing his clinical training and becoming a certified cardiovascular surgeon in Taiwan, Dr. Hsieh went to the US for his PhD degree in bioengineering and postdoctoral training in cardiac stem cell therapy and nanomedicine. Since back to Taiwan in 2006, Dr. Hsieh focuses his research on cardiovascular regeneration, cancer nanomedicine, microbiota and metabolism, iPSC technologies and translational research. He is the principle investigator of several flagship projects in Taiwan, and leads the Taiwan iPSC Consortium (2015~), the Taiwan Tissue Chip Project (2016-2020) and the Taiwan Precision Regenerative Medicine project (2022~), working on establishing Taiwan's superdonor iPS cell bank for clinical cell therapy. Dr. Hsieh has received many awards and honors, including National Innovation Award (twice), Ministry of Science and Technology Outstanding Research Award (twice), Teco Award, Taiwan Bio-developmental Foundation Chair Award, Outstanding Alumnus Award of Kaohsiung Medical University and National Heath Research Institutes Merit Award. He was elected to International Fellow of American Heart Association, and was recognized as a top translational researcher by Nature Biotechnology. Dr. Hsieh has published 112 scientific papers including those in Nature Medicine, Science Translational Medicine, Journal of Clinical Investigation, Circulation, Circulation Research, PNAS, Science Advances, Nature Communications and ACS Nano. He has filed more than 40 international patents, tech-transferred to two domestic companies, collaborated with global big pharma/biotech companies (Gilead, AZ, Celgene, Takeda & Moderna) and has applied his research results into clinical therapy for cardiovascular regenerative medicine.

Gut Bacteria and Heart Healing: The Hidden Players in Post-Infarction Resilience

Embark on a journey that uncovers the intricate interplay between our gut microbiota and the remarkable process of heart repair. This presentation delves into the captivating realm where gut microbes wield profound influence over the recovery following a heart attack. Explore how these microscopic inhabitants orchestrate a symphony of effects on immune cell composition and essential short-chain fatty acids, intricately weaving into the tapestry of post-infarction cardiac healing.

Navigate through the world of specialized gut bacteria, with a spotlight on the remarkable butyrate-producers, whose presence has been linked to a heightened capacity for cardiac protection post-heart attack. Venture into both human and animal studies that shed light on the enrichment of these beneficial bacteria in the aftermath of myocardial infarction. Delve deeper to understand how the introduction of these microbes ignites the production of beta-hydroxybutyrate, a powerful ketone associated with enhanced cardiac function in the wake of heart injury.

This multidimensional exploration uncovers the nexus between microbial metabolites, immune dynamics, and the intricacies of heart repair. As we decipher these mechanisms, novel avenues emerge for potential therapeutic interventions that could reshape the landscape of post-infarction outcomes. These studies not only highlight the captivating connection between our gut and heart but also emphasize the promising potential of harnessing this relationship to usher in a new direction of cardiovascular health enhancement.

Han Wei HOU (LKC, Singapore)

Dr. Han Wei HOU is an Associate Professor at the School of Mechanical and Aerospace Engineering, Nanyang Technological University. He received his BEng (2008) and PhD (2012) in Biomedical Engineering at National University of Singapore, and did his postdoctoral training at MIT (USA) and LKCMedicine/NTU. He has authored over 60 peer-reviewed journal publications and filed 12 patents/patent applications on microfluidics cell sorting and vascular chip models. His recent research accolades include World's Top 2% Scientists (By Stanford University) (2023), International Academy of Medical and Biological Engineering (IAMBE) Early Career Award (2022), and International Society for Advancement of Cytometry Innovators (2021).

Microfluidic chips for modelling atherosclerosis

In this talk, I will present a microfluidic stenosis model which is capable of mimicking atherogenic flow environment to enhance leukocyte and platelet adhesion to endothelium. By perfusing patient's whole blood through the inflamed circular channel and analyzing the immune cell adhesion at the stenosis and post-stenosis regions through on-chip immunostaining, we were able to assess cardiovascular risk and immune inflammation in a cohort of convalescent COVID-19 patients with different metabolic conditions (T2DM, hyperlipidaemia and hypertension). Our results suggest platelet adherence as a novel functional biomarker for rapid vascular risk stratification in cardiometabolic diseases.

Su-Yi TSAI (National Taiwan University, Taiwan)
She is a Professor at National Taiwan University, Department of Life Science, Genome and Systems Biology Program. She received her PhD at Mount Sinai School of Medicine in the Program in Developmental and stem cell biology. My laboratory's primary focus is on utilizing Human pluripotent stem cells (hPSCs) as a model to investigate human cardiac development and heart diseases. Currently, we are engaged in two key research areas: (1). We employ patient-specific induced pluripotent stem cells (iPSCs) or CRISPR/Cas9 techniques to generate isogenic cell lines. These cell lines serve as invaluable tools for studying cardiac cell development and modeling diseases such as dilated cardiomyopathy (DCM) and glycogen storage disease (GSD). (2). Our research extends to exploring the pivotal role of non-coding RNA, including Long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNA, in the context of cardiac development and diseases.

Unraveling the Role of RNA-Binding Proteins in Human Cardiac Development and Diseases
Sarcomeres are fundamental to cardiac muscle contraction. Their impairment can elicit cardiomyopathies, leading causes of death worldwide. However, the molecular mechanism underlying sarcomere assembly remains obscure.
Apart from the scaffold proteins that assemble into the building blocks of sarcomeres, the sarcomere assembly process is modulated by multiple regulatory factors, such as RNA-binding proteins (RBPs) and molecular chaperones. Our previous study demonstrated that the RBP RBM24 mediates alternative splicing of core myofibrillogenesis genes in a stage-specific manner and that ACTN2 interacts with the N-terminus of TTN (TTN-N), allowing MYH6 to bind the C-terminus of TTN (TTN-C). Notably, our unpublished data suggests that RBM24 might play a role in cardiomyocyte maturation by regulating the expression of a novel long non-coding RNA, LINC C.
In summary, our research leveraged human pluripotent stem cell (hPSC)-derived cardiomyocytes (CMs) to unveil the stepwise spatiotemporal regulation of core cardiac myofibrillogenesis-associated proteins. Furthermore, we discovered a novel regulator, LINC C, which potentially participates in cardiac maturation. Our next focus is to delve deeper into the molecular mechanisms governing how LINC C mediates cardiomyocyte maturation. This investigation holds the promise of shedding light on the potential applications of hPSC-CMs in cell therapeutics.

Shengjie Lu (NHCS, Singapore)

Dr Lu is Junior Principal Investigator (PI) at National Heart Research Institute Singapore (NHRIS) and Assistant Professor at Duke-NUS Medical School. His research interest is focusing on biomaterial-based therapeutic solution and innovation for cardiovascular diseases, as well as bench-to-beside medical technologies on medical devices.

Dr Lu obtained PhD degree at National University of Singapore (NUS), where he received intensive research trainings in polymer chemistry and nanomaterial-based drug delivery. As Research Fellow, he joins NHCS starting with medical device innovation, and then setting up a biomaterial platform at NHCS, so as to extend his research into diverse heart disease therapy and imaging. He has authored 20+ publications, editorials, and book chapters, and established local and oversea collaborations funded by couples of national grants as PI.

Nitric oxide-releasing nanoparticles for multiple-targeting cardioprotection

The clinical need to discover novel therapies for myocardial infarction (MI) in order to improve survival in MI patients remains unmet. Although some targeting drugs have been studied on reducing MI size in animal model, superior therapeutics into diseased heart is still challenging. Microvascular obstruction (MVO), due to damage to the coronary microvasculature is a key determinant of infarct size, heart failure and poor outcomes following acute MI. In this study, we have developed a novel nitric oxide (NO)-releasing nanoparticle (NONP) to deliver Cyclosporine (CsA), a well-known inhibitor of the mitochondrial permeability transition pore (mPTP), to the ischaemia heart. As a multi-targeting strategy, we target vasodilation with NO treatment to prevent MVO and improve drug penetration, and mPTP inhibition with CsA to rescue cell death. When formulated into nanomedicine, we have shown that his strategy can confer a superior cardioprotective effect on reducing infarct size by 60% comparing with vehicle treatment in mice following with IRI.

Lim Wei Wen (NHCS, Singapore)
Dr Lim completed his PhD studies at the University of Adelaide, South Australia, mentored by Professors David Saint and Prash Sanders. There, he studied cardiac tissue remodelling in preclinical mouse models of diabesity and hypertrophic cardiomyopathy and identified structural and electrical substrates that predispose to arrhythmias. He is a current Research Fellow in the Stuart Cook Laboratory at the National Heart Research Institute of Singapore (NHRIS) and Duke-National University of Singapore where he studies the roles of interleukin-11 in fibrosis and inflammation contributing to cardiac arrhythmias, cardiomyopathies and aortopathies.

Interleukin-11 causes acute cardiac electrophysiological dysfunction and predisposes the heart to arrhythmia
Interleukin-11 (IL11) is used to treat chemotherapy-induced thrombocytopenia since 1998. At the approved dosage of 50 µg/kg/day up to 21 days, ~17% of treated patients develop cardiac arrhythmias and transient BNP elevations comparable to acute heart failure diagnosis. Here, we investigated the electrophysiological impact of clinically-relevant doses of IL11 in the mouse. Repeated IL11 dosing prolonged atrial and ventricular repolarization on ECG, coinciding with increased arrhythmia propensity with caffeine-epinephrine challenge. Aged mice subjected to a single dose of IL11 trended increased risk of pacing-induced atrial fibrillation. We show for the first time that IL11 causes direct electrophysiological changes predisposing to arrhythmias.

Scientific Session 5: Joint ISHR Asia-Pacific Sections

Ajay BAHL (Vice President of ISHR-Indian section)
Ajay BAHL, MD, DNB, FRCP, DM, Professor, Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
Areas of interest: Cardiomyopathies, genetics.

Genetics of Indian cardiomyopathy patients
The first Indian report identifying a mutation in an Indian cardiomyopathy patient was published in 2000. Despite genotyping being widely available, there were only 63 publications on genetics of Indian cardiomyopathy between 2000-2020. Like all populations, Indians also have a unique genetic makeup. In addition, India is a large and diverse country with regional differences. Due to the founder effect, individual sequence variations would accumulate over generations in different populations. The most notable example in Indians is a 25 basepair deletion in intron 32 of MYBPC3 that causes skipping of exon 33. This variation is seen in 4% of the Indian population and is more common in cardiomyopathy patients. The role of this variation in the pathogenesis of cardiomyopathies is still not clear. It is possible that another common variation -MyBPC3 p.Asp389Val is found in around 10% individuals in a specific western Indian population along with the 32 basepair deletion and is linked to the deletion. This variation was associated with abnormal cardiac contractility and may be responsible for the increased risk of cardiomyopathies associated with the 32 basepair deletion. 35% of all published variants in Indians were described to be novel.
There is an urgent need to build Indian database of sequence variations in cardiomyopathies. These databases should have strong phenotypic and outcome data and are essential applying the genotyping information to an individual patient. Genotyping is currently useful in confirm a diagnosis and predicting risk of disease in relatives of cardiomyopathy patients. Clinical decisions often have to made on limited information since most variations have been reported in only a few patients. Creation of a large and comprehensive database will expand the information base on which clinical decisions are made. The department of biotechnology is supporting the creation of different genetic databases in Indians including on cardiomyopathies. These would help in individual patient management.

Huang-Tian YANG (Vice President of ISHR-Chinese section)

Huang-Tian YANG, M.D., Ph.D., Fellow of the ISHR Principal Investigator and head of Laboratory of Molecular Cardiology, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences. She received M.D. from Yamagata University School of Medicine in 1994, served as an instructor/associate professor at the Dept of Pharmacology in Nantong Medical College and Yamagata University School of Medicine, then moved to NIH/NIA in 1997, and took the current position since 2000.

Research Interests: Elucidation of molecular mechanisms underlying the cell death in infarcted hearts and formation of cardiomyocytes, and exploration of new reparative therapies for infarcted hearts offered by hPSC- and non-cell-based approaches as well as exploring their translational potential.

Professional Activities: Vice President of the ISHR-China Section; Council members of Chinese Association of Pathophysiology in Cardiovascular Sciences, Chinese Pharmacological Society for Cardiovascular Pharmacology, Chinese Medical Association for Tissue Repair and Regeneration of Hearts, and Professional Membership of AHA/American Stroke Association, etc.; Associate Editor of JMCC, Executive Editors of Pflügers Archiv, Receiving Editor of Cell Death & Disease, editorial board members of Acta Pharmacol Sinica, Cardiovascular Drugs and Therapy, Current Opinion in Physiology, etc.

Cell and cell products for cardiac repair

Acute myocardial infarction (MI) causes excessive myocardium damage, including cardiomyocytes, vessels and epicardium. Current treatments improve the symptoms and survival but cannot compensate for MI-caused irreversible loss of contractile myocardial tissue due to extensive cardiomyocyte loss and massive vascular disruption. Cell-based reparative therapies by implantation of human pluripotent stem cell (hPSC)-derived cardiovascular cells offer an opportunity for repair of infarcted hearts. By using mouse, porcine, and nonhuman primate models of MI, we evaluated the cell types suitable for the therapy and the mechanisms underlying. Our studies demonstrated that intramyocardial injection of hPSC-derived cardiovascular progenitor cells, cardiomyocytes, and epicardial cells at the acute phase of MI ameliorated functional worsening and scar formation. Concomitantly, the cardiomyocyte survival, angiogenesis and lymphangiogenesis were enhanced in the infarcted hearts. The mechanistical analysis showed that these cells secreted extracellular vesicles and proteins, which modulated inflammatory microenvironment, inhibited cell death pathways, and promoted regeneration of vasculature and cardiomyocytes. Further, the reparative efficacy was enhanced by cardiac patches made by a combination of these cells with the extracellular matrix. These findings provide new knowledges for the functions and mechanisms of hPSC-derived cardiovascular cells for cardiac repair and suggest therapeutic options of these cells and cell products for ischemic myocardial repair (Grants: National Key R&D Program of China (2017YFA 0103700, 2022YFA1104500, 2022YFA1105100; NSFC (81520108004)).

Max Shiang Yong LIM (Council member of ISHR-Australasia section)

Associate Professor Lim is a Principal Research Fellow and Head of the Cardiac Regeneration group at St Vincent's Institute of Medical Research (SVI) in Australia. He is currently serves as an Associate Editor of Frontiers in Physiology, is a Council member of the ISHR (Australasian section), and is an active member of both the Australasian Society for Stem Cell Research (ASSCR) and the Australian Cardiovascular Alliance. Lim earned his Ph.D. from University of Strathclyde (UK) in 2005 and completed a four-year post-doctoral fellowship at The Hatter Cardiovascular Institute, University College London.

Lim joined the then O'Brien Institute in 2010, which later merged with SVI in 2015. As a translational research scientist, his work focuses on cardiometabolic diseases. His multidisciplinary research programme integrates stem cell biology, bioengineering, and pharmacology to develop innovative and translatable therapies for cardiometabolic diseases. Notably, Lim pioneered a method for the sustained delivery of stem cell secretome for heart disease and developed the multicellular cardiac organoid model, advancing the functional validation and clinical translation of his research findings.

Sustained delivery of stem cell secretome for cardiac repair

Therapeutic strategies for protecting the ischemic heart remain a critical unmet medical need, and stem cell therapy holds significant promise for cardiac repair. The beneficial effects of stem cells in ischemic heart disease are largely attributed to their secretome, which modulates the local microenvironment to promote a regenerative phenotype, thereby triggering cardiac repair. However, safe, effective and affordable method to deliver stem cells for cardiac repair following ischemic heart disease are not yet available.

In this study, we present an innovative and minimally invasive methodology for sustained deliver of the secretome from Cymerus (clinical grade human mesenchymal stem cells derived from induced pluripotent stem cells (iPSCs)). This is achieved using a clinical grand retrievable immunoisolation cell encapsulation device (Procyon) implanted subcutaneously, designed to provide a long-term cardioreparative effect.

In a rat model of reperfused myocardial infarction, subcutaneous transplantation of Cymerus within the Procyon device significantly improved cardiac function, reduced maladaptive remodeling of the left ventricle, and reduced fibrotic scar tissue at 12 weeks following myocardial infarction in both young (14-week-old) and middle aged (52-week-old) male and female immunocompetent rats. Encapsulated mesenchymal stem cells remained viable and continued to release secretome after implantation. Additionally, the secretome (conditioned media) of Cymerus exhibited protective effects on human iPSC-derived cardiac organoids subjected to simulated ischaemia-reperfusion injury. Proteomic analysis identified 3,851 proteins in the secretome, with functional enrichment analysis revealing their involvement in various cardiac repair processes, including extracellular matrix organization, inflammatory response, regulation of apoptosis, PI3K-Akt signalling pathway, antioxidant activity, wound healing, angiogenesis, tissue remodelling, positive regulation of mitochondrial proteins and function, and cholesterol metabolism.

Our proof-of-concept translational studies demonstrate a novel, safe and minimally invasive approach to harnessing the cardioreparative potential of stem cell secretome for effective ischemic cardiac repair.

Seitaro NOMURA (Council member of ISHR-Japanese Section)

I am a Council member of ISHR-Japanese section and Associate Professor of Department of Cardiovascular Medicine at the University of Tokyo. After graduating from Chiba University School of Medicine and obtaining MD in 2005, I completed my clinical training at St. Luke's International Hospital with the honor of receiving the Best Resident Award. Subsequently, I started basic research in my laboratory at Chiba University (Issei Komuro's Laboratory). After I received PhD in 2013 from Chiba University Graduate School of Medicine, I was promoted to Assistant Professor at the University of Tokyo in 2016 and started my laboratory to advance genome and omics analysis research in cardiovascular medicine. Our laboratory has reported a succession of essential findings on system structures and molecular mechanisms in cardiovascular diseases through genome and omics analysis research. I became an associate professor in 2023 and founded a new laboratory, the Department of Frontier Cardiovascular Science.

Single-cell and spatial omics analysis to develop cardiovascular precision medicine

By integrating single-cell and spatial omics analyses, we have identified cell types and molecular mechanisms characteristic of specific phenotypes and genotypes of heart failure, including DNA damage-positive metabolically dysfunctional cardiomyocytes (Nat Commun. 2018), Csrp3-positive mechanosensitive cardiomyocytes (Nat Cardiovasc Res. 2022), LMNA mutation-induced TEAD1 dysfunctional cardiomyocytes (Science Adv. 2023), dopamine D1-positive cardiomyocytes in patients with ventricular arrhythmias (Nat Commun. 2020), HTRA3-positive fibroblasts suppressing excessive TGF-β signaling (Nat Commun. 2022), macrophage-lymphocyte interactions in cardiac sarcoidosis granulomas, cytotoxic T lymphocytes specific for severe myocarditis, and senescent endothelial cells secreting IGFBP7 (Circulation. 2024). We are further developing gene therapy, vaccine therapy, and chemical compound therapy that target these mechanisms, promoting the development of cardiovascular precision medicine.

Scientific Session 6: Vascular biology

Kai-Chien YANG (National Taiwan University, Taiwan)

As a physician-scientist with extensive training in clinical medicine and basic science research, I'm dedicated to tackling important biological questions linked to human diseases and eager to translate novel experimental findings into clinically useful therapeutics. Since establishing my lab in 2014, my research has centered on cardiovascular diseases, particularly cardiac fibrosis, atherosclerosis, and cardiac regeneration. Using a multidisciplinary approach, we've identified key molecular determinants like long noncoding RNAs and the ER protein TXNDC5, crucial in the development of cardiac fibrosis and cardiomyopathy. Our work extends to non-cardiac fibrotic disorders and has led to promising therapeutic strategies, including nanomedicine for atherosclerosis. We are also exploring cardiac regeneration and RNA modification in cardiovascular diseases.

Targeting Mechanosensitive Endothelial TXNDC5 to Stabilize eNOS and Reduce Atherosclerosis In Vivo

Although atherosclerosis preferentially develops at arterial curvatures and bifurcations where disturbed flow (DF) activates endothelium, therapies targeting flow-dependent mechanosensing pathways in the vasculature are unavailable. Here, we provided experimental evidence demonstrating a previously unidentified causal role of DF-induced endothelial TXNDC5 (thioredoxin domain containing 5) in atherosclerosis. TXNDC5 was increased in human and mouse atherosclerotic lesions and induced in endothelium subjected to DF. Endothelium-specific Txndc5 deletion markedly reduced atherosclerosis in ApoE-/- mice. Mechanistically, DF-induced TXNDC5 increases proteasome-mediated degradation of heat shock factor 1, leading to reduced heat shock protein 90 and accelerated eNOS (endothelial nitric oxide synthase) protein degradation. Moreover, nanoparticles formulated to deliver Txndc5-targeting CRISPR-Cas9 plasmids driven by an endothelium-specific promoter (CDH5) significantly increase eNOS protein and reduce atherosclerosis in ApoE-/- mice. These results delineate a new molecular paradigm that DF-induced endothelial TXNDC5 promotes atherosclerosis and establish a proof of concept of targeting endothelial mechanosensitive pathways in vivo against atherosclerosis.

Yu HUANG (University of Hongkong, China)
Yu HUANG received his PhD from University of Cambridge. He is Jeanie Hu Professor of Biomedical Sciences at City University of Hong Kong. He is Vice President of Chinese Section of International Society for Heart Research (ISHR), elected Fellow of ISHR, International Union for Physiological Sciences Academy of Physiology, and British Pharmacological Society, and Associate Editor of Circulation Research. His team aims to elucidate cellular and molecular events in the initiation and progression of endothelial cell dysfunction in hypertension, diabetes, and atherosclerosis, and to uncover novel biomarkers of vascular pathogenesis.

The aim of Huang's team is to investigate the cellular and molecular processes that cause endothelial cell dysfunction in high blood pressure, obesity and diabetes. They also aim to find new biomarkers for vascular disease and to discover ways to reverse vascular dysfunction in animal models of cardio-metabolic disorders. He has co-authored 507 publications in SCI-indexed journals including Nature, Science, Cell Metabolism, Circulation Research, European Heart Journal, PNAS, Diabetes, Hypertension, ATVB, Stroke, Kidney International, etc. His work has earned him over 33,950 citations on Google Scholar (an h-index of 96).

Laminar flow inhibits vascular calcification

Roshni SINGARAJA (NUS Medicine , Singapore)

Roshni SINGARAJA is an Assistant Professor at the Cardiovascular Research Institute, Yong Loo Lin School of Medicine, National University of Singapore. Her research is focused primarily on genetic diseases, with an emphasis on genetics of cardiometabolic disorders. The scope of her work includes Mendelian and population-based genetics, target identification, and validation utilizing human cohorts, as well as mouse and in vitro models. During her PhD training at the University of Amsterdam, her post-doctoral training at the University of British Columbia, as a Scientist at Xenon Pharmaceuticals in Canada, and as a Principal Investigator at the Agency for Science, Technology and Research in Singapore, she has identified or characterized several genes underlying cardiometabolic diseases, as well as genes contributing to Huntington Disease, familial exudative vitreoretinopathy and amyotrophic lateral sclerosis 2. Roshni has published close to 90 peer reviewed articles in journals such as Nature Genetics, Nature Cell Biology, Nature Neuroscience, Neuron, The Journal of Clinical Investigation and Circulation.

Semaphorin 3F in the vascular wall

We previously identified semaphorin signaling as associating with coronary artery disease in the CARDIoGRAM cohort. Of the semaphorins, human vascular expression profiling suggested SEMA3F as potentially linked to atherogenesis. In hyperlipidemic mice, SEMA3F reduced aortic lesion area, and increased fibrous cap endothelial content, leading to plaque stability. In a disturbed-flow-mediated endothelial dysfunction-driven lesion model, the absence of Sema3f increased plaques, further implicating SEMA3F in endothelial function. Monocyte adhesion to Sema3f-/- vascular endothelial cells (VECs) was elevated, driven by increased PI3K activity, leading to increased NF-κB-mediated elevation in VCAM1 and ICAM1 expression, suggesting that SEMA3F reduces VEC PI3K activity. Increased endothelial permeability led to increased monocyte transmigration through Sema3f-/- VECs, modulated by decreased mTOR phosphorylation, leading to suppression of VE-cadherin expression and cell-cell adherens junction stability. Actomyosin fiber formation was decreased in Sema3f-/- VECs, which was reversed by PI3K inhibition, further implicating SEMA3F in adherens junction stability. In Sema3f-/- vascular smooth muscle cells (VSMCs), active PI3K was also increased. PI3K facilitates VSMC proliferation, migration, and pro-atherogenic phenotype switching, which were reduced by SEMA3F. In agreement, in a model of VSMC proliferation and migration-induced neointima formation, SEMA3F reduced plaques. Semaphorin3F is causally atheroprotective. SEMA3F's suppression of VEC and VSMC PI3K activation may contribute to its atheroprotection.

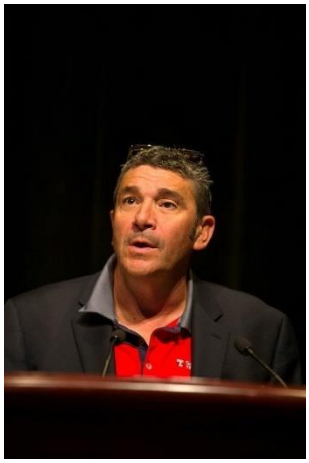
Elena Aisha AZIZAN (National University of Malaysia, Malaysia)
Elena's research career began as a PhD student at the University of Cambridge, focusing on primary aldosteronism, a common curable cause of secondary hypertension. Her PhD on genetics and histology of adenomas earned international recognition, including the prestigious Servier award from the International Society of Hypertension. Now a Principal Investigator at the National University of Malaysia (UKM), her research team focuses on adrenal cell fate with publications in Nature Genetics and New England Journal of Medicine. Elena's research at UKM has been further recognized nationally and internationally, most recently by the 2023 L'Oreal-Unesco FWIS Award and the 2021 ENS@T Award.

Primary aldosteronism: molecular medicine meets public health
Primary aldosteronism (PA) is a common yet underdiagnosed cause of secondary hypertension that significantly increases cardiovascular risk. PA can potentially be cured surgically if localized to a unilateral aldosterone-producing adenoma (APA) on one adrenal gland. Molecular research on excised tissue has identified numerous genes and mechanisms linked to APAs, with specific mutations leading to different clinical outcomes. Herein, the presentation will focus on molecular discoveries and associated phenotypes that have the potential to transform the clinical management of patients with PA and culminate in a hypothesis that suggests PA arises as a maladaptive response to the chronic over-ingestion of salt.

Dyah Wulan ANGGRAHINI (Universitas Gadjah Mada, Indonesia)
Current position is academic staff in Department of Cardiology and Vascular Medicine, School of Medicine, Gadjah Mada University; interventional cardiologist and structural heart disease in Sardjito General Hospital, the main teaching hospital for the university. She studied the Endothelin-1 in vascular biology during her doctoral study in Kobe University Japan, where she received International Young Investigator Award of Japanese Circulation Society. Her clinical training in cardiology was in Sardjito Hospital and further advance training in Apollo Hospital New Delhi, India and National Cardiovascular Center Harapan Kita, Jakarta. Her main researches are in the field of pulmonary hypertension, adult congenital heart disease, rheumatic mitral stenosis, and heart disease in pregnancy. She is currently the coordinator for Cardiology research office and the CV Working Group of Translational Research Unit in the Faculty of Medicine; as well as the co-PI for Rare Disease Hubs (for CV section) of Indonesian Biogenomic and Science Initiatives Programme

Risk stratification and prognosis of Pulmonary Arterial Hypertension: the use of biomarkers
Pulmonary arterial hypertension (PAH) is a rare disease with complex mechanism characterized by increased pulmonary vascular resistance leading to high mortality due to right heart failure. A risk stratification at initial presentations and during periodic follow-up determines prognosis in patients with PAH. The current mortality rate among patients with PAH in COHARD-PH registry is still high; the 10-year mortality rate is 31% and 60% in patients with Eisenmenger Syndrome and iPAH, respectively. In those with high-risk stratification the odd of mortality rate is 13,8 higher compare to those with low-risk. Several clinical parameters account for the high-risk predictors for mortality, including NTProBNP level in which the level is increase in those with shunt-related PAH as well as iPAH and significantly associated with higher mortality. In those with acute decompensated PAH, NTproBNP level also predict the in-hospital mortality. Furthermore, in our cohort population, we have found that two emerging bioamarkers; i.e. Activin-A and Bio-adrenomedullin are both increase in PAH and tends to be associated with the poor prognosis. Thus, in patients with shunt-related PAH and iPAH, monitoring biomarkers in addition to clinical parameters could provide a tool for predicting outcomes, allowing more appropriate management strategies.

Scientific Session 7: Metabolism and Aging



Walter KOCH (Duke University, USA)

Dr. Walter J. KOCH recently re-joined the faculty at Duke University School of Medicine in the Departments of Surgery and Medicine at being the Chair of Pharmacology at Temple for 12 years. Dr. Koch received his PhD in Pharmacology and Cell Biophysics in 1990 from the University of Cincinnati College of Medicine in the lab of Dr. Arnold Schwartz. He went to Duke University Medical Center and the Howard Hughes Medical Institute as a postdoctoral fellow (1990-1994) in the lab of Dr. Robert J. Lefkowitz (Nobel Prize in Chemistry, 2012). The Koch lab studies molecular mechanisms for cardiac injury and repair focusing on G protein-coupled receptor kinase (GRK) signaling in the heart and also development of novel molecular strategies to repair the heart.

Heart Failure and Heart-to-Fat Communication- a Role for GRK2

Heart disease in the presence of obesity results in cardiometabolic disease, a condition where there is dysregulation of adipose and cardiac function. Under conditions of cardiometabolic stress, cardiomyocytes secrete signaling factors that communicate with other organ systems, including adipose tissue. Under this metabolic stress, G protein-coupled receptor kinase 2 (GRK2) is elevated in the heart as it also is in heart failure (HF) and previously we showed that in transgenic mice with cardiomyocyte-specific GRK2 overexpression fed a high fat diet, these mice gained less weight than control mice and it appeared to be due to a secreted factor from the heart regulated by GRK2. However, the nature or identity of this factor or the GRK2-rekated mechanisms involved in this heart-fat communication are unknown. Overall, we hypothesize that cardiac secreted signaling factors mediating adiposity, and the development of cardiometabolic disease involve pathways regulated by GRK2. Conditioned media from control and GRK2 overexpressing adult rat cardiomyocytes was collected and applied to 3T3-L1 adipocytes, which reduced lipid accumulation and adipogenic marker expression. In mice, sex-specific alterations in white adipose tissue (WAT) depots following pressure overload-induced HF were observed. Male mice in heart failure demonstrated reduced WAT depots when compared to shams, while female mice showed no alterations in WAT depots. Cardiac GRK2 overexpression further exacerbated WAT reduction in male mice with HF. WAT from male mice in HF was also characterized by adipocyte hyperplasia and reduced lipolytic potential compared to shams. These findings indicate that cardiac released signaling factors alter adiposity and are further enhanced by GRK2 overexpression. Further research is needed to identify the factors responsible for this sex-specific regulation of adiposity in HF that is regulated by cardiac GRK2.

Phillip WHITE (Duke University, USA)

Phillip J WHITE, PhD, is an Associate Professor of Medicine, in the Division of Endocrinology, Metabolism, and Nutrition at Duke University. Phillip co-leads the White-McGarrah lab at the Duke Molecular Physiology Institute with his physician scientist colleague Robert McGarrah. The White-McGarrah Lab conducts both translational and basic research projects with the goal of uncovering innovative approaches for the prevention and treatment of cardiometabolic diseases. The lab is particularly interested in understanding how dysregulation of metabolic regulatory mechanisms and inter-organ metabolic crosstalk contributes to the pathophysiology of diabetes, MASLD, and heart failure.

BCAA biology in cardiometabolic diseases

Dysregulated branched-chain amino acid (BCAA) metabolism is a harbinger of type 2 diabetes and cardiovascular disease. A major focus of our groups work is to define the mechanisms by which alterations in branched-chain amino acid metabolism are connected to the progression of these disorders. Recent studies conducted in our lab have revealed that acute exposure of the heart to a class of BCAA metabolites termed branched-chain a-keto acids or BCKA at levels found in the setting of insulin resistance and fatty liver disease robustly increases protein metabolism. This seminar will discuss our recent work to define the mechanisms controlling systemic BCKA homeostasis and the impact of chronic elevations of BCKA on the heart.

Rana GUPTA (Duke University, USA)

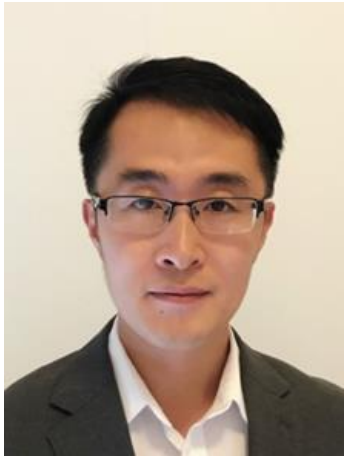
Dr. Gupta is a Professor in the Department of Medicine and Division of Endocrinology and Metabolism. He joined the DMPI in July of 2022, after spending ten years as a faculty member in the Department of Internal Medicine and Touchstone Diabetes Center at UT Southwestern Medical Center. Dr. Gupta is the Section Chair of Basic Sciences at the DMPI. Since 2012, Dr. Gupta's laboratory has remained laser-focused on understanding the mechanisms governing mammalian cell differentiation and tissue remodeling under physiological and pathophysiological conditions. The lab's specific focus is on 1) the mechanisms governing the establishment and maintenance of the adipocyte lineage, and 2) the identity of adipocyte precursors and their importance to healthy adipose tissue expansion in obesity. The long-term goals are to understand how adipose tissue expands in obesity and uncover how maladaptive adipose remodeling can lead to diabetes and other chronic metabolic diseases.

Adipose Tissue Remodeling in Health and Disease

The ability of mammalian adipose tissue to adapt to the physiological and environmental challenges of adulthood is highly dependent on its capacity to undergo extensive "tissue remodeling." *Adaptative* adipose tissue remodeling supports pregnancy, lactation, thermoregulation, and efficient energy storage in the face of overnutrition. *Maladaptive* adipose tissue remodeling, including the acquisition of fibrosis and metabolic inflammation, leads to adipocyte dysfunction and is a hallmark and a driving force behind the development of multiple chronic metabolic disorders including insulin resistance and type 2 diabetes. I will discuss our ongoing studies of functionally diverse subpopulations of mesenchymal stromal cells that reside in adipose tissue, including adipocyte precursor cells, and their multifaceted roles in both adaptative and maladaptive adipose remodeling.

Anissa Anindya WIDJAJA (Duke-NUS, Singapore)
Dr Widjaja grew up in Indonesia and completed her study in molecular biology in NTU, Singapore. She is currently an Assistant Professor at Duke-NUS Medical School, Singapore. Her research in Interleukin-11 biology has initiated the development programs for IL11 inhibition in fibrotic diseases that have been licensed to Boehringer Ingelheim. With extensive expertise in proof-of concept models of human diseases and molecular biology techniques, her team focuses on unravelling the complexities of ageing and kidney diseases to develop new targeted therapies. She also serves as a Faculty-Industry Liaison, facilitating researchers to bridge the gap and translating translation scientific discoveries into practical applications.

Inhibition of IL11 signalling extends mammalian healthspan and lifespan
For healthspan and lifespan, ERK/AMPK/mTORC1 represent critical pathways and inflammation is a centrally important hallmark. Here, we examined the hypothesis that IL11, a pro-inflammatory cytokine, negatively impacts age-associated disease and lifespan. As mice age, IL11 is upregulated across cell types and tissues to regulate an ERK/AMPK/mTORC1 axis to modulate cellular, tissue- and organismal-level ageing pathologies. Administration of anti-IL11 to old mice for 25 weeks improves metabolism and muscle function, and reduces ageing biomarkers and frailty, across sexes. Treatment of mice with anti-IL11 from 75 weeks of age until death extends the median lifespan of males by 22% and females by 25%. This is the first report demonstrating a role for a pro-inflammatory factor in mammalian healthspan and lifespan. We suggest that anti-IL11 therapy, currently in early-stage clinical trials, may provide a translational opportunity to determine the IL11 inhibition effects in elderly humans



Haojie YU (NUS Medicine , Singapore)
Dr. Haojie YU joined National university of Singapore in 2020 and now he is an Assistant Professor in the Department of Biochemistry, Yong Loo Lin School of Medicine. His research aims to discover novel therapeutic strategies to tackle atherosclerotic coronary artery disease (CAD) and non-alcoholic steatohepatitis (NASH). His group combines functional genomics, CRISPR/Cas9-based functional screening, computational science and animal models to understand how alterations in lipid metabolism and trafficking contribute to NASH and atherosclerotic plaque progression and regression.

Genome-scale CRISPR screening for LDLR-independent pathways regulating LDL uptake
LDLR is the primary receptor in hepatocytes for cleaning up LDL particles from circulation. While fibroblasts isolated from HoFH (LDLR negative) patients showed almost completely abolished LDL uptake, the primary hepatocytes from these patients still bind and internalize LDL to a considerable extent, suggesting existence of LDLR-independent pathways in hepatocytes to uptake LDL. In this study, we combined genome-scale CRISPR knockout screen, co-essentiality gene network analysis, and human biobank coding variant burden analysis, to discover the previously uncharacterized pathways in hepatocytes regulating LDLR-independent uptake of LDL. Our unbiased screen has discovered 802 genes whose disruption impacts hepatic LDL uptake.