2018 ISHR amsterdam

International Society for Heart Research

35th meeting of the International Society of Heart Research – European Section

July 16 – 19

Monday-Thursday

https://ishr2018.amsterdam/

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Welcome

to the 35th meeting of the International Society of Heart Research – European Section in Amsterdam.

During the coming 4 days we hope you will enjoy excellent basic and translational research and actively participate in discussions during oral and poster presentations. The ISHR-ES council members made a selection of oral and poster sessions from all submitted proposals and abstracts. ISHR-ES council members and early career investigators will be judging the Young Investigator session and poster sessions. Awards will be given during the final session on Thursday 19th of July.

Monday (this) evening you are invited to the 'get together' to meet all conference participants.

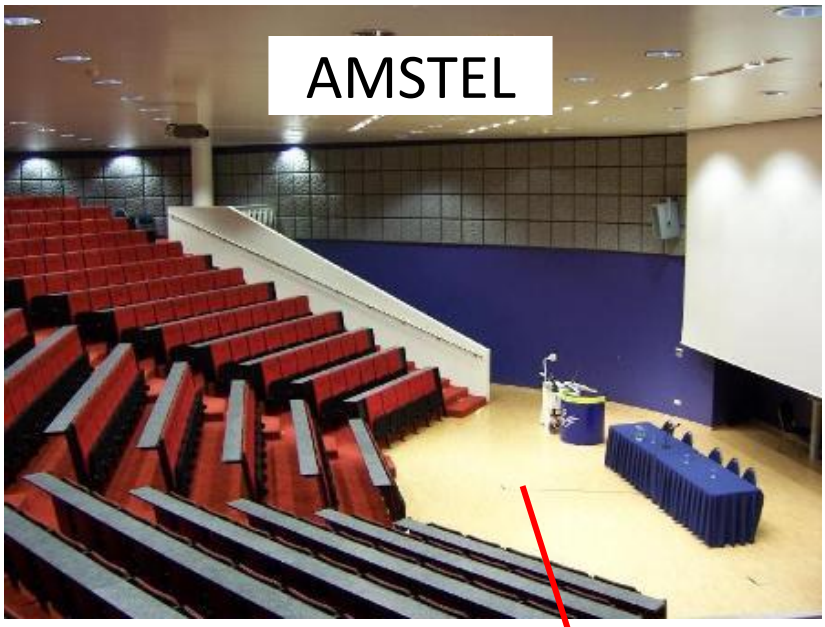
Enjoy the meeting & Amsterdam!

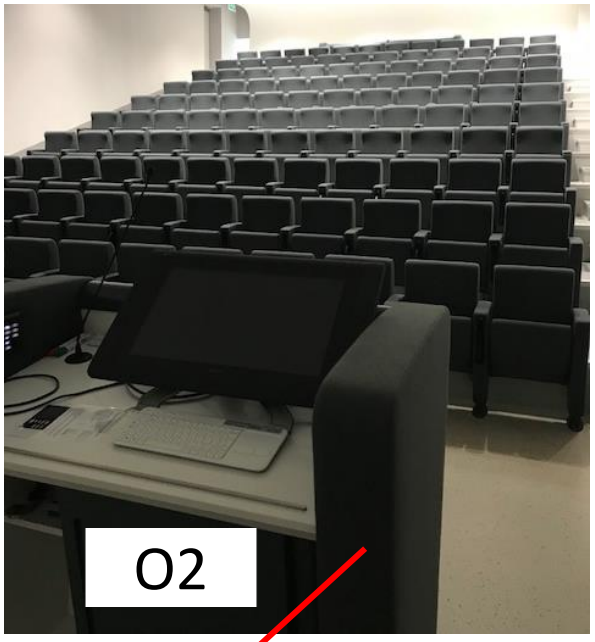
On behalf of all ISHR-ES council members,

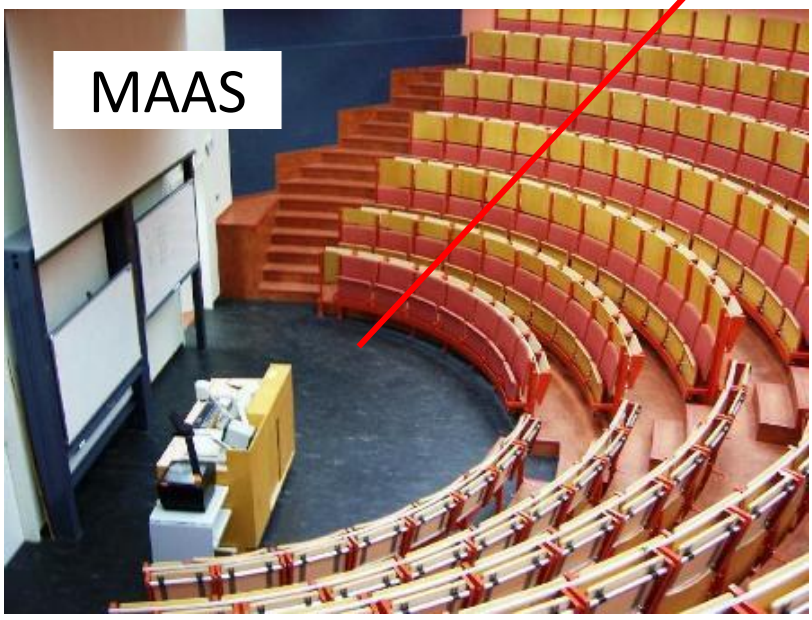
Rodolphe Fischmeister — President ISHR-ES

Jolanda van der Velden — Chair Organizing Committee

MAP – WHERE TO GO







PROGRAM AT ONE GLANCE - AMSTEL

AMSTEL & AMSTEL FOYER

MONDAY 16 JULY	TUESDAY 17 JULY	WEDNESDAY 18 JULY	THURSDAY 19 JULY
9.00-12.30 Early Career Investigator pre-meeting	**9.00-10.00** Plenary session 2 - Outstanding Investigator award 2018	**9.00-10.00** Plenary session 3 - ISHR-ES Ketty Schwartz award	**9.00-10.00** Plenary session 4: Meet the editors
13.30-14.50 Opening & planary lecture	**10.30-12.00** Novel regulatory mechanisms affecting cardiomyocyte function in the heart	**10.00-10.30** ISHR-ES General assembly	**10.00-11.30** Poster session 5
15.00-16.30 Mitochondria as a signalling organelle in cardiac disease	**12.00-13.30** Poster session 2	**11.00-12.30** The renaissance of nitric oxide	**11.30-13.00** Understanding cardiac cell-to-cell communication to develop new therapeutic strategies in heart failure
16.-30-18.00 Poster session 1	**13.30-15.00** Phenotyping and Mechanisms of Heart Failure with Preserved Ejection Fraction	**12.30-14.00** Poster session 4	**13.30-15.00** Plenary session 5 - Medal of Merit, Servier Award - Poster and YI awards, travel grant awardees
18.00-19.30 Protein trafficking in health and cardiac disease	**15.00-16.30** Poster session 3	**14.00-15.30** Microdomains in cellular signaling	
	16.30-18.00 Young Investigators award session	**15.30-23.00** Event & dinner party	

PROGRAM AT ONE GLANCE - MAAS

MAAS

MONDAY 16 JULY	TUESDAY 17 JULY	WEDNESDAY 18 JULY	THURSDAY 19 JULY
	10.30-12.00 Tweaking beta3-adrenergic receptors for cardiovascular protection		
15.00-16.30 Cardiac gene therapy		**11.00-12.30** cGMP/PKG pathway: a therapeutic target in HFpEF?	**11.30-13.00** Uncovering novel mechanisms of atrial function in health and disease
	13.30-15.00 Pathomechanisms in HCM		
18.00-19.30 Molecular switches to progress from hypertrophy to heart failure		**14.00-15.30** Pathomechanisms in cardiomyopathies	

PROGRAM AT ONE GLANCE – O2

O2

MONDAY 16 JULY	TUESDAY 17 JULY	WEDNESDAY 18 JULY	THURSDAY 19 JULY
	10.30-12.00 Cardiovascular signalling in diabetes		
15.00-16.30 What makes the heart beat?		**11.00-12.30** New mediators of inter-organ crosstalk in cardiovascular diseases	**11.30-13.00** Molecular mechanisms underlying ARVC
	13.30-15.00 Metabolic aspects of cancer-related heart disease		
18.00-19.30 Emerging role of O-GlcNAcylation in cardiovascular disease		**14.00-15.30** Coding and non-coding RNA in heart disease	
19.30-21.00 Get together			

POSTER SESSIONS

The poster sessions are organized in the Amstel foyer. Each session (~30 posters) are on view for interactive discussions. We hope everyone actively participates during the poster sessions.

Posters from the Young Investigators will be judged by members from the ISHR-ES and ISHR-International councils, and Early career investigators who are not part of the poster award competition, and are lead by Prof. Derek Hausenloy. When the judges come to your poster, you will have ~3 minutes to present your poster, after which questions will be asked for ~3 minutes. Please be present at your poster during your session.

Poster awards will be given during the final award session on Thursday afternoon.

Session 1: Monday 16 July	**16.30-18.00**
Session 2: Tuesday 17 July	**12.00-13.30**
Session 3: Tuesday 17 July	**15.00-16.30**
Session 4: Wednesday 18 July	**12.30-14.00**
Session 5: Thursday 19 July	**10.00-11.30**

PLEASE NOTE THAT ABSTRACTS CAN BE FOUND IN THE SPECIAL ISSUE OF JMCC AND AT THE END OF THIS BOOKLET (PAGES 63-84).

AMSTEL – MONDAY JULY 16

Early Career Investigator pre-meeting Symposium

(sponsored by ISHR-International)

9.00-10.30 Early career investigators - Session I

Chairs: Alessandra GHIGO & Diederik KUSTER

Valentina Sala, Doxorubicin-induced mitochondrial damage activates PI3Kgamma and inhibits protective cardiac autophagy
Upasna Varma, Diabetes-induced diastolic dysfunction is associated with myocardial glycogen accumulation and disrupted autophagy signalling.
Kirstie Anne De Jong, Maternal high fat diet induces early cardiac hypertrophy and alters cardiac metabolism in Sprague Dawley rat offspring
Maximin Détrait, Mechanisms involved in the deleterious impact of intermittent hypoxia on ischemic cardiomyopathy
Azrul Abdul Kadir, Ketone body oxidation rate depends on glycogen content in the isolated rat heart
Justine Dontaine, Inhibiting O-GlcNAcylation by AMP-activated protein kinase, a new way to reverse cardiac hypertrophy development?

10.30-11.00 – Coffee break

11.00-12.30 Early career investigators - Session II

Chairs: Delphine MIKA & Paul WIJNKER

Aurélia Bourcier, Gene therapy of heart failure with phosphodiesterase 4B in two mouse models
Larissa Dorsch, Cardiomyopathy-related Tropomyosin mutations impair calcium handling: the influence of mutation location
Marit Wiersma, Cardiomyocyte mitochondrial stress and dysfunction in experimental and clinical Atrial Fibrillation: potential therapeutic targets
Roman Medvedev, Right ventricular myocytes have less organised membrane structures and different localisation of L-type calcium channels as compared to the left ventricle
Attila Oláh, Sex-specific electrophysiological differences of exercise-induced cardiac hypertrophy in a rodent model of athlete's heart
Friedrich Baark, Non-invasive imaging of mitochondrial dysfunction and anthracycline cardiotoxicity by repurposing 99mTc Sestamibi SPECT imaging

For Early Career Investigators

12.30-13.30 (AMSTEL foyer)

Lunch with Senior Investigators: ECIs meet ISHR-ES and ISHR-Intl Council Members at lunch

LUNCH & Registration 12.30-13.30 (AMSTEL foyer)

AMSTEL Lecture hall

13.30 – 14.00 Opening & welcome

Jolanda van der Velden – Chair Organizing committee

Wouter Bos – Chair Board of Directors Amsterdam UMC (VU)

Rodolphe Fischmeister – ISHR-ES president

14.00-14.50 Plenary Lecture 1 - Christine Mummery

Human heart and blood vessels from human pluripotent stem cells: from disease modelling to drug discovery.

Professor Christine Mummery, Ph.D.

Christine Mummery studied physics at the University of Nottingham, UK and has a PhD in Biophysics from the University of London. After positions as postdoc and tenured group leader at the Hubrecht Institute, she became professor at the University Medical Centre Utrecht in 2002. After a sabbatical at the Harvard Stem Cell Institute in 2007, she introduced human iPS cells to the Netherlands. In 2008, she became Professor of Developmental Biology at Leiden University Medical Centre in the Netherlands and head of the Department of Anatomy and Embryology. Her research concerns heart development and the differentiation of pluripotent human stem cells into the cardiac and vascular lineages and using these cells as disease models, for safety pharmacology and drug discovery. Immediate interests are on developing biophysical techniques for characterization and functional analysis of cardiovascular cells from hPSC. In 2015 she became guest professor at the Technical University of Twente to develop organ-on-chip models. She was recently awarded a multimillion grant for this purpose and is awardee of a prestigious European Research Council Advanced Grant.

She is a member of the Royal Netherlands Academy of Science (KNAW), and former board member of the International Society of Stem Cell research (ISSCR), the KNAW and the Netherlands Medical Research Council (ZonMW). She was recently awarded the Hugo van de Poelgeest Prize for Animal Alternatives in research. She co-authored a popular book on stem cells “Stem Cells: scientific facts and Fiction” (2nd edition 2014) and is editor in chief of the ISSCR journal Stem Cell Reports. She is also on the editorial boards of Cell Stem Cell, Cardiovascular Research and Stem Cells.

Poster awards presented during meeting

Kerstin Timm (session 12) is a British Heart Foundation Immediate Postdoctoral Basic Science Research Fellow at the University of Oxford. She holds a Fulford Junior Research Fellowship and a stipendiary lectureship in medicine, both at Somerville College, Oxford. After her undergraduate in veterinary medicine in Berlin, Germany she went to the Univ. of Cambridge to undertake her MRes and PhD in Professor Kevin Brindle's laboratory. She studied metabolic fluxes in different models of cancer using hyperpolarized magnetic resonance imaging. She completed her PhD in 2016 and subsequently secured her BHF fellowship to work with Prof Damian Tyler at the Department of Physiology Anatomy and Genetics in Oxford. She uses hyperpolarized MRI to study metabolic fluxes in a model of doxorubicin-induced cardiotoxicity.

Saveria Femminò (session 15) is a Ph. D. student in "Experimental Medicine and Therapy" at the Department of Clinical and Biological Sciences of the University of Turin. The main objectives of her studies are to find new targets and new cardioprotective strategies. As new targets, she is studying NLRP3 inflammasome and Sphingosine-1-phosphate. As new strategies, she is testing the cardioprotective effects of platelets. In the past, she studied the effects of endogenous cardioprotective factors involved in metabolic regulation, such as catestatin, obestatin, CGRP, in ex-vivo and in vitro models. She also used co-morbidities and co-medications models to compare the effects of cardioprotective effects in normal and diabetic conditions. Lately, she is also studying the protective effects of controlled delivery of oxygen with Cyclodextrin Nanosponges and Pharmacologically Active Microcarriers in in-vitro models.

Solenne Paiva (session 18) is a third-year Ph.D student at University Pierre and Marie Curie (UPMC) in Paris, receiver of an ISHR-ES prize at Printemps de la Cardiologie 2018. She started in the field of organic chemistry at the Faculty of Sciences of the University of Porto (FCUP) in Portugal designing lipid vectors for gene therapy and fluorescent molecular probes. In terms of biology, she pursued her training in France investigating on Duchenne Muscular Dystrophy, among others. Ranked 1st, she obtained a Ph.D scholarship for a three year period. Her current Ph.D research focuses on unravelling the role of a family of microRNAs called lethal-7 (let-7) throughout cardiogenesis. Differentiation of human pluripotent stem cells into cardiomyocytes provided a good model to mimic human embryonic heart development and carry out her multiple let-7 modulation studies. Moreover, she is already author of a review entitled "MiRroring the Multiple Potentials of MicroRNAs in Acute Myocardial Infarction".

SESSION 1. AMSTEL.

MITOCHONDRIA AS A SIGNALLING ORGANELLE IN CARDIAC DISEASE

CHAIRS: Derek Hausenloy & Peter Ferdinandy

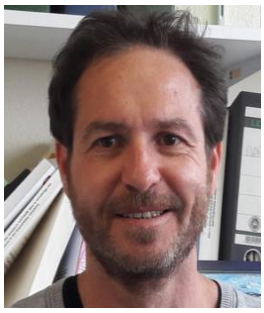
15.00-15.22 Frank Lezoualch - Mitochondrial Epac and myocardial cell death

15.22-15.44 Fabio di Lisa - Mitochondrial reactive oxygen species and calcium homeostasis

15.44-16.06 Sang-Bing Ong - Mitochondrial dynamics in cardiac disease

16.06-16.18 Xiaoqing Sun - The effect of Monoamine oxidase A inhibition on experimentally induced pulmonary arterial hypertension (abstract 10)

16.18-16.30 Maria Luisa Barcena de Arellano - Sex differences in age-related AMPK-Sirt1 axis alteration in human heart (abstract 140)

Frank Lezoualch	**Toulouse, France**
	Frank Lezoualc'h obtained a PhD in molecular endocrinology from the University Pierre & Marie Curie, Paris in 1995. He is Director of Research at Inserm and is heading the dept "Cardiac and Kidney remodeling" and the laboratory "Signaling and Pathophysiology of Heart failure" at the Institute of Metabolic and Cardiovascular diseases", Inserm UMR-1048, Toulouse, France. His major goal is to better understand the molecular and cellular mechanisms by which pathological stimuli act on cardiac function. The long-term objective is to obtain a comprehensive knowledge of signaling alterations in the failing myocardium in order to identify relevant targets for the treatment of HF. His research programs were successful to identify novel therapeutic targets (e.g EPAC, Carabin) and drug candidates (EPAC pharmacological inhibitors).
Fabio di Lisa	**Padova, Italy**
	Fabio Di Lisa has provided significant contributions elucidating the role of mitochondrial dysfunction in cardiac diseases. By developing methods to study the PTP in isolated cells and intact hearts Prof. Di Lisa characterized the occurrence of transient and prolonged openings demonstrating that the latter modality is involved in cell death. In addition, PTP opening was causally related to NAD depletion and loss of viability induced by reperfusion. Regarding oxidative alterations, Prof. Di Lisa demonstrated that the oxidation of myofibrillar proteins correlates linearly with contractile impairment. This relationship has been extended to muscular dystrophy. Concomitantly, he demonstrated the relevance of monoamine oxidases (MAO) as a relevant source of reactive species in cardiac and muscular diseases.
Sang-Bing Ong	**Duke-NUS Medical School, Singapore**
	Sang-Bing Ong received his PhD in 2010 from University College London (UCL), UK whilst working with Derek Hausenloy and Derek Yellon at the Hatter Cardiovascular Institute as a Dorothy Hodgkin Scholar. He then went on to pursue postdoctoral research at the University of California San Diego (UCSD), USA with Åsa Gustafsson and subsequently, Duke-NUS Medical School, Singapore under a Khoo Postdoctoral Fellowship. He is currently a Singapore Ministry of Health National Medical Research Council (NMRC)-funded Assistant Professor at Duke-NUS Medical School in Singapore. His research interest lies in modulating cardiac mitochondrial dynamics to combat cardiovascular disorders.

NOTES

THIS SESSION IS CO-SPONSORED BY THE NETHERLANDS HEART FOUNDATION Hartstichting

SESSION 2. MAAS. CARDIAC GENE THERAPY

CHAIRS: Lucie Carrier & Maksymilian Prondzynski

15.00-15.22 Silvia Priori (NHS Lecture) - Allele-specific RNA interference to treat CPVT

15.22-15.44 Giulia Mearini - Gene replacement to treat severe sarcomeric cardiomyopathies

15.44-16.06 Mauro Giacca - Small RNAs for cardiac gene editing and regeneration

16.06-16.18 Anca Remes - AAV9-mediated delivery of a NFAT decoy oligonucleotide prevents pathological myocardial hypertrophy and heart failure in mice (abstract 16)

16.18-16.30 Anke Tijsen - Abnormally persisting KCNQ1 imprinting interferes with disease modeling of hiPSC-derived cardiomyocytes (abstract 26)

Silvia Priori	**Pavia, Italy**
 **NHS Lecture**	Prof. Priori is Global Scientific Director of Istituti Clinici Scientifici Maugeri SpA SB, Full Prof. of Cardiology in the Dept. of Molecular Medicine at the Univ. of Pavia, Director of Molecular Cardiology at the Centro National de Investigaciones Cardiovasculares Carlos III Madrid and at the ICS MAUGERI in Pavia. She is best known for her work on genetics and pathophysiology of genetic cardiac arrhythmias. The translational research conducted in her laboratories ranges from molecular studies in induced-pluripotent stem cells derived myocytes used as a disease model to functional investigations in transgenic animals and to the development of gene therapies. Several landmark studies in the field of inherited arrhythmias have identified novel therapies, developed risk stratification schemes and contributed to the definition of clinical management for patients with inherited cardiomyopathy.
Giulia Mearini	**Hamburg, Germany**
	Giulia Mearini obtained her PhD (2004) at the Univ. of Hamburg, exploring the nuclear matrix and its binding to viral and non-viral DNA. Since then, she is scientist in the Dept. of Experimental Pharmacology and Toxicology, Cardiovascular Research Center at the UMC Hamburg-Eppendorf, in the group of Prof. Lucie Carrier. She investigated pathophysiological mechanisms of hypertrophic cardiomyopathy and particularly the regulation by the nonsense-mediated mRNA decay and the ubiquitin proteasome system of mutations in Mybpc3, encoding cardiac myosin-binding protein C, in a mouse model. After proof-of-concept studies of MYBPC3 gene therapy (by exon skipping, trans-splicing, gene replacement, CRISPR/Cas9) in a mouse model and iPSC-cardiomyocytes, she is currently interested in the translation of the therapeutic approach in a large animal model of severe forms of pediatric cardiomyopathy.
Mauro Giacca	**Trieste, Italy**
	Mauro Giacca is the Director-General of the International Centre for Genetic Engineering and Biotechnology, an international organization in the United Nations system for advanced research and education, with laboratories in Trieste, New Delhi and Cape Town (www.icgeb.org). He is Full Prof. of Molecular Biology at the Univ. of Trieste. He is serving on the Boards of numerous scientific organizations and scientific journals internationally. His research interests focus on the development of novel biotherapeutics for cardiovascular disorders, in particular on the identification of growth factors and microRNAs able to stimulate new blood vessel formation and cardiac regeneration in patients with myocardial infarction and heart failure. He is an expert in the use of adeno-associated virus vectors for cardiovascular applications and also maintains a strong interest in the molecular biology of HIV-1 infection. Further information: http://www.icgeb.org/mauro-giacca.html

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SESSION 3. O2. WHAT MAKES THE HEART BEAT?

CHAIRS: David Eisner & Livia Hool

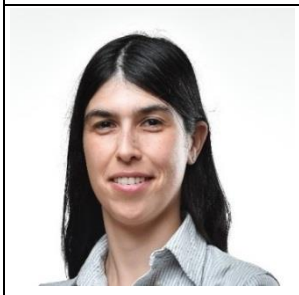
15.00-15.22 Ana-Maria Gomez - Pacemaker function in CPVT

15.22-15.44 Yael Yaniv - Schrödinger's dog: Non-invasive in-vivo analysis of intrinsic clock-like pacemaker mechanisms

15.44-16.06 Matteo Mangoni - Functional role of voltage gated Ca^{2+} channels in heart automaticity

16.06-16.18 Claire Hopton - Using human induced pluripotent stem cells to model a novel nonsense mutation of RYR2 and identify potential therapeutic agents for patients with CPVT (abstract 23)

16.18-16.30 Árpád Kovács – Omecamtiv mecarbil evokes electromechanical alternans in control rat hearts (abstract 27)

Ana-Maria Gomez	**Paris, France**
	Ana M Gómez received her PhD in 1994 at Universidad Complutense de Madrid (Spain) and her Habilitation (HDR) in 2001 at Université Montpellier 1 (France). She is Director of Research Inserm since 2008. She is best known for her work on cardiac excitation contraction coupling and its modulation in cardiac pathophysiology, notably heart failure, focusing in intracellular calcium signaling and calcium sparks. Her recent interest is the role of the cardiac calcium release channel in rhythmic disorders, genetic or acquired, in ventricular cardiomyocytes but also in pacemaker cells.
Yael Yaniv	**Haifa, Israel**
	Yael Yaniv received her PhD in 2007 at Technion-IIT. She is the head of Bioelectrical and Bioenergetic system lab since 2014 in Biomedical Engenering Faculty, Technion-IIT. She is best known for her work in pacemaker field, including characterization of pacemaker biochemical and bioenergetic properties. Her recent interest is the contribution of pacemaker cell to heart rate variability during normal and abnormal rhythm.
Matteo Mangoni	**Montpellier, France**
	Matteo Mangoni (PhD in 1995 at the University of Milan) is currently senior CNRS Research Director at the Institute of Functional Genomics in Montpellier. He has been interested in the ionic mechanisms underlying heart automaticity since his very early career stage. As a Ph.D. student he contributed to the description of the action of cAMP on "pacemaker" f-channels with Dario DiFrancesco. During his postdoctoral training in Montpellier, he described new physiological roles of L-type Ca^{2+} channels in automaticity. He has been the first scientist to characterize mouse pacemaker cells. As a tenured CNRS researcher, he demonstrated that L-type Cav1.3, T-type Cav3.1 and G-protein activated GIRK4 channels play important roles in pacemaking. His team contributed also to define the role of f-HCN4 channels in basal heart rate and atrioventricular conduction. He recently proposed the concept of "compensatory" ion channel targeting for the development of an innovative pharmacologic therapy to improve heart rate in sino-atrial dysfunction.

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MONDAY 16 JULY
16.30-18.00 POSTER SESSION 1

	Abstract #	Name
1	1	Nikolaou Panagiota Efstathia
2	2	Yohan Santin
3	6	Duvaraka Kulaveerasingam
4	7	Moises di Sante
5	10	Xiaoqing Sun
6	15	Josine Marieke de Winter
7	17	Maksymilian Prondzynski
8	19	Attila Oláh
9	20	Marine Gandon-Renard
10	21	XUE Jianbin
11	22	Semir Ozdemir
12	24	Violeta Trendafilova
13	25	Savyon Mazgaoker
14	28	Larissa M. Dorsch
15	29	Roy Kalfon
16	30	Jessica Sabourin
17	31	Tamás Radovits
18	32	Mihály Ruppert
19	33	Marta Vigil-Garcia
20	36	Victoria Pell
21	38	Mona Malek Mohammadi
22	39	Lize Evens
23	40	Emilie Dubois-Deruy
24	141	Moulin Sophie
25	144	Umber Saleem
26	146	Roberto Pane
27	147	Loubna Laib
28	148	Luc Bertrand
29	149	Justine Dontaine
30	159	Vladislava Zohdi

SESSION 4. AMSTEL. PROTEIN TRAFFICKING IN HEALTH AND CARDIAC DISEASE

CHAIRS: Tish Murphy & Marit Wiersma

18.00-18.22 Luca Scorrano - Crosstalk between mitochondrial dynamics and autophagy in the cardiac progenitor cells

18.22-18.44 Kinya Otsu - Receptor-mediated mitophagy

18.44-19.06 Riekelt Houtkooper - Improving metabolism to combat aging and cardiometabolic disease

19.06-19.18 Larissa Dorsch - Altered protein quality control in heart tissue of patients with hypertrophic cardiomyopathy (abstract 28)

19.18-19.30 Nikolaou Panagiota Efstathia - Investigation of the glycogen synthase kinase 3 beta-mPTP interaction in cardioprotection with novel GSK3β inhibitors (abstract 01)

Luca Scorrano	**Padova, Italy**
	Luca Scorrano's work has changed classical tenets in the field of apoptosis and mitochondrial pathophysiology. During his postdoc with Stan Korsmeyer, he discovered the process of mitochondrial cristae remodeling that allows complete cytochrome c release and apoptosis. His lab discovered a molecular staple holding cristae junctions tight and exploited it in vivo to correct muscular atrophy, mitochondrial diseases and ischemia-reperfusion damage; discovered the first molecular bridge between ER and mitochondria, how mitochondria control autophagy, the molecular link between mitochondrial respiration and cristae shape, and the paradigm-shifting notion that heart development is controlled by mitochondrial fusion via Notch1 signaling. After 7 years as Prof. at the Univ. of Geneva, since 2013 he is Chair of Biochemistry and Director of the Venetian Institute of Molecular Medicine at the University of Padova.
Kinya Otsu	**London, United Kingdom**
	Kinya Otsu received his MD in 1983 and PhD in 1992 at Osaka University. He is Professor and BHF Chair of Cardiology since 2012 in the School of Cardiovascular Medicine and Sciences at King's College London, UK. His research focuses on mechanisms underlying the development of heart failure, with particular emphasis on cardiomyocyte death, including apoptosis, necrosis and autophagy. His recent interest is to elucidate pathophysiological roles of degradation systems of macromolecules and organelles and inflammation.
Riekelt Houtkooper	**Amsterdam, The Netherlands**
	Houtkooper received his PhD in the lab. of Genetic Metabolic Diseases of the Academic Medical Center Amsterdam. His research centered on cardiolipin metabolism, particularly in relation to the rare mitochondrial disorder Barth syndrome. In 2009, Riekelt joined the lab of prof. Auwerx at EPFL Lausanne for a postdoctoral project geared towards understanding and treating more common metabolic diseases. In 2012 Riekelt started his own group within the laboratory Genetic Metabolic Diseases in Amsterdam, funded by VENI & VIDI grants (Netherlands Organization for Scientific Research) and an ERC Starting grant. For his contribution to the metabolic field, Dr. Houtkooper received the 2014 NVBMB Prize from the Dutch Society for Biochemistry and Molecular Biology. Current research in the group focuses on molecular and translational metabolism, both in the context of inborn errors of metabolism and aging.

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SESSION 5. MAAS. MOLECULAR SWITCHES TO PROGRESS FROM HYPERTROPHY TO HEART FAILURE

CHAIRS: Rainer Schulz & Charles Steenbergen

18.00-18.22 Jacqueline Heger - ANT1 and beyond – Mitochondrial transporters as modulators of heart failure progression

18.22-18.44 Blanche Schroen - MicroRNA Involvement in Heart Failure

18.44-19.06 Guiseppe Rengo - Adrenal adrenoceptors in heart failure

19.06-19.18 David Aluja González - Oral pharmacological inhibition of calpains attenuates isoproterenol-induced myocardial hypertrophy and fibrosis (abstract 34)

19.18-19.30 Roberto Pane - The histone methyltransferase MLL3 controls the development of cardiomyocyte hypertrophy (abstract 146)

Jacqueline Heger	**Gießen, Germany**
	Jacqueline Heger received her PhD in 1999 at Heinrich-Heine-University in Düsseldorf and her Habilitation in 2013 at Justus-Liebig-University in Gießen. Since then she is research associate and project leader in the Institute of Physiology in Gießen, Germany. In 2015 she became Physiological Consultant. Her research priorities are cardiac growth signals, remodeling processes and apoptosis. She analyzed signaling pathways in cardiomyocytes affecting heart failure progression with focus on TGFβ pathway and intermingling signaling molecules like NO, YB-1 or PI3K. Her recent interest is myocardial infarction and protection with emphasis on mitochondrial function. In this context she investigates the contribution of mitochondrial proteins like ANT1 to cardio protection.
Blanche Schroen	**Maastricht, The Netherlands**
	Blanche Schroen is professor of Experimental Cardiology at the Cardiology department within the Cardiovascular Research Institute Maastricht of Maastricht University. Her PhD (2006) at Maastricht University under supervision of Prof Yigal Pinto aimed at finding molecular determinants of heart failure susceptibility. After a post-doc on cardiac genetical genomics at Imperial College London, she returned in 2008 to Maastricht University and started her current research on the role of non-coding RNAs as susceptibility factors for the development of heart failure.
Guiseppe Rengo	**Naples, Italy**
	Dr. Rengo obtained his Medicine degree (2002), the PhD in "Clinical Physiopathology and Exp. Medicine" (2010) and Cardiology degree (2015) at the Univ. of Naples "Federico II". From 2006 to 2009 he was post-doctorate fellow at the Dept. of Medicine, Center for Translational Medicine, Thomas Jefferson Univ. of Philadelphia. During this period, Dr. Rengo won the AHA award (Postdoc Fellowship) and he has collaborated with Dr. Koch in developing new tools for AAV-mediated cardiac gene therapy as therapeutic approach for heart failure. From 2015, Dr. Rengo is Assist. Prof. of Internal Medicine and Geriatrics at the Univ. of Naples. His work is based around heart failure and the molecular mechanisms involved in the regulation of signalling through cardiovascular G protein-coupled receptors, including beta-adrenergic receptor function and signalling. He is also studying new molecular mechanisms responsible of neurohormonal overdrive observed in heart failure.

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THIS SESSION IS SPONSORED BY JMCC

SESSION 6. O2. EMERGING ROLE OF O-GLCNACYLATION IN CARDIOVASCULAR DISEASE

CHAIRS: Metin Avkiran & Friederike Cuello

18.00-18.22 John Chatham - Is O-GlcNAcylation the new phosphorylation?

18.22-18.44 Ajay Shah - Redox modulation of O-GlcNAcylation promotes cardiac adaptation to stress

18.44-19.06 Johannes Backs - HDAC-dependent detrimental role of O-GlNAcylation

19.06-19.18 Lize Evens - Impact of glycated proteins on cardiomyocyte function (abstract 39)

19.18-19.30 Luc Bertrand - O-GlcNAcylation inhibition by the AMP-activated protein kinase (AMPK), a new duet to prevent cardiac hypertrophy development (abstract 148)

John Chatham	**Birmingham, USA**
	John Chatham received his D.Phil. (1987) from the Department of Biochemistry at the Univ. of Oxford. He is currently Professor of Pathology in the Division of Molecular and Cellular Pathology at the University of Alabama at Birmingham. His recent work has focused on the role of the glucose-dependent, post-translational modifications of proteins by O-linked beta-N-acetylglucosamine moiety (O-GlcNAc) in mediating cardiomyocyte stress responses. Work from his laboratory has demonstrated that acute increases of O-GlcNAc levels are cardioprotective; conversely, in the setting of diabetes where O-GlcNAc levels are chronically elevated cardiomyocytes cell survival pathways such as autophagy are impaired in an O-GlcNAc dependent manner. Additional interests include the role of store-operated calcium entry in cardiomyocytes and how this is regulated by O-GlcNAc.
Ajay Shah	**London, United Kingdom**
	Ajay Shah is British Heart Foundation Professor of Cardiology and Head of the School of Cardiovascular Medicine and Sciences at King's College London; James Black Professor of Medicine; Director of the King's BHF Centre of Research Excellence; and Hon. Consultant Cardiologist at King's College Hospital. His main research interests are in the pathophysiology of heart failure, with a focus on redox signalling pathways. His group has undertaken seminal studies on the role of NADPH oxidases in the heart. He has a long-standing interest in the actions of NO in the heart and more recently has pursued first-in-man studies investigating the roles of nNOS in the human cardiovascular system. Ajay is a Fellow of the UK Academy of Medical Sciences, ISHR, ESC, and AHA. He is Associate Editor of the American Journal of Physiology (Heart & Circulation), Consulting Editor for Cardiovasc Res, and on the Editorial Boards of Circulation and the Eur Heart Journal.
Johannes Backs	**Heidelberg, Germany**
	Johannes received the MD degree from Heidelberg Univ. in 2002. He conducted his postdoctoral studies on transcriptional control mechanisms in the heart in Dallas from 2003-2007 under the supervision of Eric Olson. After leading an Emmy Noether Junior Research Group in Heidelberg, he was in 2013 appointed as a W3 and DZHK professor (Dept. of Cardiology, Hugo A.Katus), and in 2015 he was promoted to the Director of the Department of Molecular Cardiology & Epigenetics (Center of Internal Medicine of the University Hospital Heidelberg). He is board member of the Heart Failure Association of the ESC and the ISHR. He is interested in the regulation of chromatin-modifying enzymes by environmental signals. In particular, he could link kinases (CaMKII, PKA) that are sensitive to beta-adrenergic receptors to one histone deacetylase (HDAC4). He is currently investigating the impact of these regulatory pathways on cardiac function in the context of metabolic alterations.

NOTES

19.30
DRINKS – GET TOGETHER
O2 BUILDING

AMSTEL Lecture hall

9.00-10.00 Plenary Lecture 2 - Outstanding Investigator award Steven Jones

Non-catabolic Fates of

Glucose in the Heart

Session chaired by: Tish Murphy

President ISHR International

THIS SESSION IS SPONSORED BY JMCC

SESSION 7. AMSTEL. NOVEL REGULATORY MECHANISMS AFFECTING CARDIOMYOCYTE FUNCTION IN THE HEART

CHAIRS: Wolfgang Linke & Josine de Winter

10.30-10.52 Ether Creemers - RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling

10.52-11.14 Izhak Kehat - Localized translation in the sarcomere

11.14-11.36 John Solaro - Signaling to Cardiac Sarcomeres Via β-Arrestin

11.38-11.48 Monika Gladka - Zeb2 protects the heart from ischemic damage by enhancing the release of cardioprotective factors (abstract 45)

11.48-12.00 Bernadin Ndongson Dongmo - Characterization of early cardiotoxicity action of calcineurin inhibitors (abstract 64)

Esther Creemers	**Amsterdam, The Netherlands**
	Esther Creemers is appointed as an Assistant Professor at the department of Experimental Cardiology of the Academic Medical Center (AMC) in Amsterdam. She has received her PhD in life sciences in 2000 at the University of Maastricht and was a postdoctoral fellow at the UT Southwestern Medical Center in Dallas, in the lab of Prof. Eric Olson from 2002-2006. In her current position at the AMC her research aims at understanding why an overloaded heart ultimately fails. Her current focus is on RNA regulatory molecules like microRNAs, lincRNAs and the recently discovered circular RNAs, but also on RNA splicing as a key regulator of maladaptive changes in the failing heart.
Izhak Kehat	**Haifa, Israel**
	Izhak kehat received his PhD (2005) at the Faculty of Medicine at the Technion under the supervision of Prof. Lior Gepstein. His post-doctoral studies were done under the supervision of Jeffery Molkentin at Cincinnati (2006-2010) where he studied the signalling and epigenetic control of cardiac hypertrophy. Since 2012 he is a principal investigator at the Dept. of Physiology, biophysics, and system biology, at the Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, and a senior cardiologist at the Rambam Medical canter echocardiography unit. The Kehat lab is focused on the systemic identification of the transcriptional, translational, and epigenetic control of the cardiovascular system, particularly in cardiac hypertrophy, heart failure, and in the process of vascular and valve calcification. Izhak is the treasurer of the Israeli sub-section of the ISHR.
John Solaro	**Chicago, USA**
	R. John Solaro received his PhD (1971) from University of Pittsburgh, College of Medicine. He is Distinguished University Professor in the University of Illinois System, Director of the Center for Cardiovascular Research at the University of Illinois at Chicago, and Editor in Chief of J Mol Cell Cardiol. His work has elucidated mechanisms important in controlling cardiac contractility by signaling to and from the sarcomeres. Early work demonstrated the significance of sarcomere protein phosphorylation signaled by adrenergic signaling. Later studies investigated mechano-signaling at the Z-disk. These studies led to the concept of sarcomeric proteins as targets for inotropic drugs useful in acquired and familial cardiac disorders. Recent work has focused on biased ligands promoting beta-arrestin signaling while blocking the AT1-R and signaling to sarcomeres as therapy in genetic dilated cardiomyopathies.

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SESSION 8. MAAS. TWEAKING β3-ADRENERGIC RECEPTORS FOR CARDIOVASCULAR PROTECTION

CHAIRS: Sian Harding & Marisol Ruiz-Meana

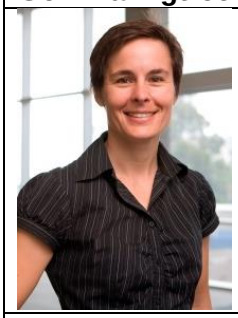
10.30-10.52 Patrick Rensen - Brown fat activation by β3AR stimulation protects from atherosclerosis

10.52-11.14 Gemma Figtree - Remodelling caveolar redox signalling via β3AR stimulation-broad cardiovascular benefits from diabetes to heart failure

11.14-11.36 Jean-Luc Balligand - β3AR protection from myocardial remodeling: NO and beyond

11.36-11.48 Alex Ali Sayour - Comparison of the anti-remodeling effect of pressure unloading and chronic soluble guanylate cyclase activation in rats with left ventricular myocardial hypertrophy (abstract 53)

11.48-12.00 Shigemiki Omiya - Regnase-1, a ribonuclease, in cardiomyocytes regulates immune responses in the heart (abstract 119)

Patrick Rensen	**Leiden, The Netherlands**
	Patrick Rensen received his PhD (1992) at Leiden University and is professor of "Metabolic Aspects of Vascular Disease" at the Leiden UMC since 2012. He is Established Investigator of the Heart Foundation and chairman of the European Lipoprotein Club. His research focuses on brown adipose tissue (BAT) activation as a novel strategy to combat obesity, type 2 diabetes and cardiovascular disease (Nat Comm 2015; PNAS 2015; Circ Res 2016; Sci Transl Med 2016; Nat Comm 2017). He currently investigates novel targets that modulate BAT activity including the biological clock, and searches for novel non-invasive techniques and biomarkers to quantify BAT activity, by combining BAT-targeted intervention studies in preclinical models and humans with the Netherlands Epidemiology of Obesity cohort.
Gemma Figtree	**Sydney, Australia**
	Gemma Figtree is a Professor in Medicine at the University of Sydney, and Research Lead for Cardiothoracic and Vascular Health at the Kolling Institute, and co-leads the Cardiovascular Theme for Sydney Health Partners, a NHMRC Advanced Health Research and Translation She is committed to improving the care for heart attack patients- using her knowledge of redox signalling and molecular biology to develop methods of identifying those at highest risk of adverse outcome, and discovering novel therapies to prevent and treat events, inspired by her clinical work as an interventional cardiologist. Her research and clinical perspective and leadership are recognised by her appointment to the Expert Advisory Panel for NHMRC Structural Review of Grants Program.
Jean-Luc Balligand	**Brussels, Belgium**
	Balligand developed the core of his research projects in the biochemistry and cellular biology of nitric oxide synthases (NOS) including their regulation in cardiovascular tissues. He initiated the research on the role of NOS in cardiomyocyte contractility which is being extended in the context of myocardial remodelling and regeneration (in response to catecholamines and beta-adrenoceptors). His group provided seminal observations on the mechanism of endothelial dysfunction by LDL-cholesterol and pleiotropic effects of hypolipemiant drugs (e.g. statins) on the endothelium. He is Head of the Pole of Pharmacology and Therapeutics and President of the Institut de Recherche Expérimentale et Clinique, Faculty of Medicine, UC Louvain. He also is practicing Physician at the Cliniques Univ. Saint-Luc and teaches cardiovascular physiology and pharmacology at the Fac. of Medicine. He is member of the Royal Academy of Medicine of Belgium and Board member of the Health competitiveness cluster of the Wallonia Region, BioWin.

NOTES

SESSION 9. O2. CARDIOVASCULAR SIGNALLING IN DIABETES

CHAIR: Sandrine Lecour & Coert Zuurbier

10.30-10.52 Rebecca Ritchie - Therapeutic targetting of ROS signalling in diabetes

10.52-11.14 Mark Kearney - IGF receptor signalling in diabetes and insulin resistance

11.14-11.36 David Grieve - GLP-1 sigalling in the diabetic heart

11.36-11.48 Min Park - MitoGamide ameliorates diabetic cardiomyopathy by scavenging mitochondrial dicarbonyls in type 1 diabetic Akita mice (abstract 72)

11.48-12.00 Luween Uthman - Empagliflozin effects on ischemic contracture and I/R injury in isolated mouse hearts perfused with or without insulin (abstract 51)

Rebecca Ritchie	**Melbourne, Australia**
	Rebecca Ritchie is Head of Heart Failure Pharmacology and Chair of Science Faculty at the Baker Heart and Diabetes Institute. She holds an NHMRC Senior Research Fellowship, holds an adjunct Prof appointment at the Dept of Diabetes at Monash University and is the Membership Secretary for the ISHR Australasian Section. Prof Ritchie is internationally-recognised for her contributions to cardiac pharmacology. Her research achievements to date have enabled her to identify potential new treatment strategies, both pharmacological and gene delivery-based, for arresting the progression of heart failure, particularly in the context of diabetes and myocardial infarction, maintaining a translational focus to this fundamental research. Several of these target inappropriate cardiac ROS generation and its consequences. Her efforts have been recognised by the 2012 Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists Achievement Award, the 2013 Diabetes Australia Millenium-Type 1 Diabetes Award, and election as a Fellow of the AHA in 2013.
Mark Kearney	**Leeds, United Kingdom**
	Professor Kearney is Professor of Cardiovascular and Diabetes Research at the British Heart Foundation, and in the Leeds Institute for Cardiovascular and Metabolic Medicine: a multidisciplinary research centre focused around cardiovascular disease and diabetes. His interest is in the role of insulin resistance at the level of the endothelium and nitric oxide biology and atherosclerosis. Previously a member of the British Heart Foundation Project Grants and Fellowships Committees, Professor Kearney leads a research group of over 20 researchers. He is also a practicing clinician with an interest in chronic heart failure.
David Grieve	**Belfast, United Kingdom**
	David Grieve received his PhD from the Royal Veterinary College (University of London) in 1998 before joining the laboratory of Ajay Shah at King's College London. In 2005, he took up an academic position at the School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast where he is now a Reader with an independent research programme focused on investigating mechanisms underlying cardiovascular remodelling and dysfunction. His group has a particular interest in the role of oxidative stress, novel peptide hormones, endothelial progenitor cells, and the influence of diabetes on the adaptive, but ultimately detrimental changes that occur during cardiovascular disease and how these may be modulated for potential therapeutic benefit. He is currently a member of the British Heart Foundation Projects Grants Committee and NC3Rs Grant Assessment Panel and serves as Honorary Secretary of the British Society for Cardiovascular Research.

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TUESDAY 17 JULY

12.00-13.30 POSTER SESSION 2

	Abstract #	Name
1	41	Marine Gandon-Renard
2	42	Bas Molenaar
3	43	Manuela Zaccolo
4	44	Vasco Miguel Sampaio Pinto
5	45	Monika Gladka
6	46	Liad Segal
7	47	Maximin Détrait
8	48	Solenne Paiva
9	49	Yair E. Lewis
10	51	Laween Uthman
11	52	Zeina Harhous
12	53	Alex Ali Sayour
13	54	Natalie Savage
14	55	Monika Bartekova
15	56	Alexandra Riddell
16	57	Nataliya Shtefan
17	58	Ashley Bradley
18	59	Azrul Abdul Kadir
19	60	Tanju Mercan
20	61	Daniel Benak
21	62	Veronika Tibenská
22	63	Jaroslav Hrdlicka
23	64	Bernadin Ndongson Dongmo
24	65	Tanya Ravingerova
25	66	Sevil KORKMAZ-ICÖZ
26	68	Kevin Edgar
27	69	Upasna Varma
28	70	Jens van de Wouw
29	71	Cher-Rin Chong
30	72	Min Park
31	73	Ven Gee LIM
32	150	Laudette Marion
33	162	Torkia Lalem

SESSION 10. AMSTEL. PHENOTYPING AND MECHANISMS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

CHAIRS: Ajay Shah & Gabriele Schiattarella

13.30-13.52 Wolfgang Linke - Oxidation of titin as a novel regulator of the mechanical properties of cardiac sarcomeres

13.52-14.14 Javier Diez - The Stiff Heart: Extra-Cardiomyocytes Mechanisms in HFpEF

14.14-14.36 Gabriele Schiattarella - The Fat Heart: Lipid metabolism in HFpEF

14.36-14.48 Louise Nijenkamp - Sex-differences in diastolic dysfunction in hypertrophic cardiomyopathy (abstract 77)

14.48-15.00 Rio Putra Juni - Empagliflozin for heart failure with preserved ejection fraction: targeting cardiac endothelial cell-cardiomyocyte interaction (abstract 74)

Wolfgang Linke	**Muenster, Germany**
	Wolfgang Linke received postdoctoral training at the University of Washington in Seattle for 3 years. In 1994 he became Research Assistant Prof. at the Institute of Physiology, University of Heidelberg, where he stayed until 2003, interrupted by sabbaticals at the Mayo Clinic Rochester and Columbia Univ. New York. He was appointed Full Professor and Head of the Physiology & Biophysics Group at the University of Muenster from 2003-2009. From 2009-2017 he was Department Chair and Prof. for Cardiovascular Physiology at Ruhr Univ. Bochum. Since 2017, he is Prof. of Physiology and Director of the Institute of Physiology II at the Univ. of Muenster. He also holds a Professorship in Cardiac Mechanotransduction at the Heart Center in Goettingen. His main research interests include basic and translational aspects of heart failure development, cardiac myocyte mechanical function, mechanosensitivity, and protein quality control.
Javier Diez	**Navarra, Spain**
	Prof. Díez, male, was born in Logroño (La Rioja, Spain). He was graduated in Medicine at the Medical School of the Autónoma University of Madrid, in 1976. He became a research fellow at the Necker Hospital, Paris, from 1982 to 1984, and at the Brigham and Women's Hospital, Boston, in 1985, where he trained in cardiovascular biology. In 2009 he was appointed as Full Prof. of Medicine of the Univ. of Navarra. At present, he is the Director of the Program of Cardiovascular Diseases in the same Center, and Consultant and Head of Cardiovascular Research in the Dept. of Cardiology and Cardiac Surgery at the Univ. Clinic of the University of Navarra. His main research interest focused on the mechanisms of myocardial fibrosis involved in non-ischemic heart diseases and heart failure. In addition, his work aimed to identify circulating biomarkers of myocardial fibrosis potentially useful in the cardiac assessment and handling of cardiac patients.
G Schiattarella	**Dallas, USA**
	Gabriele Schiattarella received his MD from the Univ. Federico II of Naples in 2009. After completing the Fellowship in Cardiology and starting a PhD program in Experimental Medicine, he moved to the UT Southwestern Medical Center (Dallas, Texas) under the supervision of Joseph A. Hill. Gabriele's background is in medicine, experimental cardiology and cellular/molecular biology, with specific training and expertise in murine models of cardiovascular diseases and preclinical assessment of cardiovascular function. His research interests include metabolic regulation of cardiac remodeling and failure, mitochondrial dysfunction and autophagy. He is currently active in several clinical and research projects. His research awards include the travel award of the ESC, the Research Award for Young Investigator of the Italian Society of Cardiology and the STAR Award, Young Researcher Mobility of the University Federico II of Naples.

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SESSION 11. MAAS. PATHOMECHANISMS IN HCM

CHAIRs: Pieter de Tombe & Vasco Sequeira

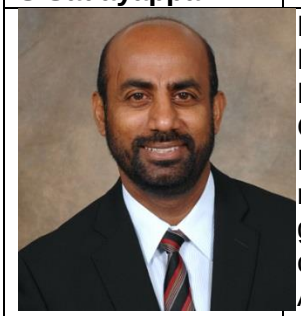
13.30-13.52 Judith Montag - Imbalanced expression of MYH7-alleles in the myocardium as a trigger for HCM-development

13.52-14.14 Sakthivel Sadayappan - Molecular mechanism of HCM in populations of South Asian descendants

14.14-14.36 Christoph Maack - Mitochondrial dysfunction in HCM

14.36-14.48 Paul Wijnker – Empagliflozin partly restores impaired relaxation in human engineered heart tissue carrying a MYH7 mutation (abstract 84)

14.48-15.00 Frederik Flenner - Ventricular arrhythmias and remodeling in a mouse model of hypertrophic cardiomyopathy (abstract 82)

Judith Montag	**Hannover, Germany**
	Judith Montag received her PhD (2007) at the Univ. of Göttingen. She started her scientific career at the German Primate Centre in Göttingen. Since 2011 she is a junior group leader in the dept. of Molecular- and Cell Physiology at the Hannover Medical School. As a microbiologist, she works on the molecular pathomechanisms of diseases, ranging from infectious to genetically inherited disorders. Her work covered prion diseases, herpesviruses and inherited HCM. Her special interest always lay on the mRNA-expression alteration caused by the different diseases. Her recent research focuses on the molecular mechanisms underlying the hypertrophic cardiomyopathy with a special interest on the allele-specific expression of the heterozygously mutated genes – both in the whole tissue and in individual cells. In addition, she works on the establishment of a large animal model for HCM by specific genome editing in pigs.
S Sadayappan	**Cincinnati, USA**
	Dr. Sakthivel Sadayappan received his PhD (1999) in Biochemsistery at Madurai Kamaraj University, India. For his postdoctoral training, he attended the Max-Planck- Institute in Bad Nauheim, Germany, and Cincinnati Children's Hospital in Cincinnati. He is currently Professor of Internal Medicine and Director of the Heart Branch, Heart, Lung and Vascular Institute, at the Univ. of Cincinnati. His research is driven by the desire to improve cardiac health with the long-range goal of preventing the development of heart failure that results from hypertrophic cardiomyopathy and coronary heart disease. He is also actively involved in the AHA, American Physiological Society and ISHR organizing committees. Dr. Sadayappan has received funding from the National Heart, Lung, and Blood Institute, the American Heart Association, and pharmaceutical industries.
Christoph Maack	**Würzburg, Germany**
	Christoph Maack received his MD (2000) at the Univ. of Cologne. From 2000-2017, he worked at the Cardiology Dept. of the Univ. of Saarland in Homburg, and from 2002-2005 as a post-doc in the lab of Brian O'Rourke at the Cardiology Dept. at Johns Hopkins Univ. in Baltimore. In 2017, he became Director of the Comprehensive Heart Failure Center at the Univ. Clinic in Würzburg, where he also chairs the Dept. of Translational Science. His work focuses on cellular defects in chronic heart failure, with a special emphasis on the mechanisms of contractile, mitochondrial and metabolic dysfunction in heart failure. Other research areas are epigenetic regulation and adrenergic signaling in heart failure.

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SESSION 12. O2. METABOLIC ASPECTS OF CANCER-RELATED HEART DISEASE

CHAIRS: Thomas Eschenhagen & Alessandra Ghigo

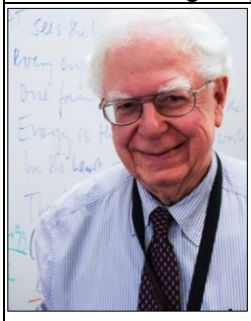
13.30-13.52 Heinrich Taegtmeyer - Oncometabolic Tracks in the Heart

13.52-14.14 Denise Hilfiker - Insulin as key regulator of cancer and cancer therapy induced cardiomyopathy

14.14-14.36 Pietro Ameri - Cardiac fibroblasts in doxorubicin cardiotoxicity: just bystanders?

14.36-14.48 Kerstin Timm - Hyperpolarized 13C magnetic resonance spectroscopy identifies changes to myocardial metabolic fluxes in a rat model of doxorubicin-induced cardiotoxicity (abstract 91)

14.48-15.00 Lorrie Kirshenbaum - Dual mitophagy and necrosis dependent pathways functionally couple mitochondrial death protein bnip3 to doxorubicin cardiomyopathy (abstract 14)

Heinrich Taegtmeyer	Houston, USA
	Heinrich Taegtmeyer received his medical degree summa cum laude from the Albert Ludwigs University of Freiburg im Breisgau, Germany, and a D.Phil. (Ph.D.) in metabolism from the University of Oxford, England. Following training in Internal Medicine at the Boston City Hospital (Harvard Service) and in Cardiology at the Peter Bent Brigham Hospital (Harvard Medical School), he moved to the medical school at The University of Texas Health Science Center at Houston in 1982. Moving through the ranks, he is now the oldest board-certified cardiologist at McGovern Medical School. Dr. Taegtmeyer continues to care for patients while leading a productive lab, which has been supported by the NIH for over 40 years. He has published widely on metabolism of the stressed and the failing heart, as well as on diabetes and the heart.
Denise Hilfiker	**Hannover, Germany**
	Prof. Hilfiker-Kleiner received her PhD (1994) at the Univ. of Zurich and Emory University, Atlanta. She is dean of research of the MHH and leads the Dept. of Molecular Cardiology. She has a longstanding experience in analyzing signaling pathways in cardiac cells relevant for physiological and pathophysiological processes as well as for endogenous regeneration abilities of the heart especially after pregnancy or treatment with cardiotoxic agents. She is member of a commission of the German Council of Science & Humanities of the Federal Government and the State. She is a member of the German Cardiac Society and the ESC Program Committee, a founding member of the study group on PPCM and the translational research group of the Heart Failure Ass of the ESC. She is a core PI of the REBIRTH Excellence Cluster at the MHH and the lead scientist and organizer of the multicenter clinical trial on the efficacy of Bromocriptin in PPCM funded by the German Federal Ministry of Education and Research.
Pietro Ameri	**Genova, Italy**
	After graduating in Medicine in 2006, Pietro Ameri completed the residency and received his PhD in 2014 at the University of Genova, Italy. He is now Assistant Professor in Cardiology in Genova, where he directs a heart failure clinical program and runs a laboratory of cardiovascular biology. He is involved with the Cardio-Oncology Committee of the European Society of Cardiology and is chair of the Cardio-Oncology Committee of the Italian Research Hospital Network. Dr. Ameri is currently pursuing two main lines of research: the pathogenesis of the cardiotoxicity of anticancer treatments; and the interaction between cardiomyocytes and stromal cells in cardiac hypertrophy and heart failure, with particular attention to paracrine and juxtacrine signals modulating cardiomyocyte metabolism, function and survival.

NOTES

TUESDAY 17 JULY

15.00-16.30 POSTER SESSION 3

	Abstract #	Name
1	16	Anca Remes
2	18	Angelica Roa
3	23	Claire Hopton
4	26	Anke Tijsen
5	27	Árpád Kovács
6	34	David Aluja González
7	35	Bilge Eren YAMASAN
8	67	Laween Uthman
9	74	Rio Putra Juni
10	75	Elisa Dal Canto
11	76	Johannes Petutschnigg
12	77	Louise A.M. Nijenkamp
13	78	Antonia Raaijmakers
14	80	Rahana Y. Parbhudayal
15	81	Ronen Ben Jehuda
16	82	Frederik Flenner
17	83	Maike Schuldt
18	84	Paul J.M. Wijnker
19	85	Huang-Tian Yang
20	86	Friedrich Baark
21	87	Valentina Sala
22	88	Georgios Kremastiotis
23	89	Jessica Gambardella
24	90	Hardip Sandhu
25	91	Kerstin N. Timm
26	92	Edward Clive Thomas Waters
27	142	Aurélia Bourcier
28	145	Annie TURKIEH
29	151	Eric Morel & Gomez
30	161	Andria Priyana
31	163	Inna Rabinovich-Nikitin

YOUNG INVESTIGATORS SESSION AMSTEL

CHAIRS: Zoltan Papp & Sandrine Lecour

Jury: Alessandra Ghigo, Rodolphe Fischmeister, Paula da Costa Martin, Yael Yaniv

16.30-16.48	Diana Bou Teen - Glycation of mitochondrial ATP synthase is involved in the increased vulnerability of senescent cardiomyocytes to mitochondrial permeabilization and death (abstract 3)
16.48-17.06	Mona Malek Mohammadi - Neonatal mice adapt to pressure overload by inducing cardiomyocyte proliferation and angiogenesis (abstract 38)
17.06-17.24	Bas Molenaar - smORF4, a novel cardiac micropeptide involved in cardiac biology (abstract 42)
17.24-17.42	Maksymilian Prondzynski - CRISPR/Cas9 genome editing repairs a novel ACTN2 mutation and prevents the disease phenotype in human iPSC-derived cardiomyocytes and engineered heart tissue (abstract 17)
17.42-18.00	Maike Schuldt - Location-specific effects of Hypertrophic Cardiomyopathy-causing Troponin T mutations (abstract 83)

AMSTEL Lecture hall

9.00-10.00 Plenary Lecture 3

The ISHR-ES Ketty Schwartz award

Session chaired by: Rodolphe Fischmeister

President ISHR - European Section

Ketty Schwartz Award 2018

Ketty Schwartz, Ph.D.
1937-2007

Award Winner

Denise Hilfiker-Kleiner, Ph.D

"Peripartum cardiomyopathy, a heart breaking story with the potential for a happy end "

10.00-10.30 General assembly

10.30-11.00 Coffee break

SESSION 13. AMSTEL. THE RENAISSANCE OF NITRIC OXIDE

CHAIRS: Tomasz Kuzic & Delphine Mika

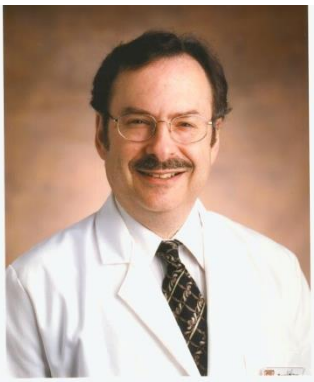
11.00-11.22 Jay Zweier - Cytoglobin regulates blood pressure and vascular tone through nitric oxide metabolism in the vascular wall

11.22-11.44 Matthias Totzeck - Nitrite and cardioprotection

11.44-12.06 Phil Eaton - Mechanisms of thiol-redox signalling in the cardiovascular system

12.06-12.18 Natalie Savage - The role of cardiomyocyte Nox4D, a redox-active splice variant of NADPH oxidase-4 (abstract 54)

12.18-12.30 Michele Ciccarelli - GRK2 regulates the endothelial responsiveness to Bradykinin: role in Human Angioedema (abstract 89)

Jay Zweier	**Ohio State University College of Medicine, USA**
	Dr. Zweier received his baccalaureate degrees in Physics and Mathematics at Brandeis Univ. in 1976. After PhD training in Biophysics at the Albert Einstein College of Medicine, he pursued medical training at the Univ. of Maryland School of Medicine and received his MD in 1980. Subsequently, he completed his residency in internal medicine followed by his cardiology fellowship at Johns Hopkins in 1986. In 1987, he joined the faculty of The Johns Hopkins Univ. School of Medicine. At Hopkins, he established the molecular and cellular biophysics laboratories and the institutional Electron Paramagnetic Resonance Center. In 1998 he was promoted to the rank of Professor, and in 2000 he was appointed as Chief of Cardiology Research, directing cardiovascular research at the Johns Hopkins Bayview Campus. In 2002 Dr. Zweier joined The Ohio State Univ. College of Medicine as Director of the Davis Heart & Lung Research Institute and the John & Mildred Lumley Chair in Medicine.
Matthias Totzeck	**Essen, Germany**
	Dr. Totzeck is an attending and associate professor in the Department of Cardiology and Vascular Medicine, West German Heart an Vascular Center Essen, University Hospital Essen. His main research focus is on acute cardiac injury. An acute myocardial infarction remains one of the leading causes of death world-wide. Both ischemia - induced by arteriosclerotic plaque rupture and coronary artery occlusion - and reperfusion contribute to the final myocardial cell death (I/R injury). The main goals of Dr. Totzeck's group are the elucidation of the underlying cellular mechanisms and the translation of these findings into novel therapeutic strategies.
Phil Eaton	**London, United Kingdom**
	Philip Eaton gained a BSc in Biochemistry from Queen Mary College, University of London in 1989 before completing his PhD at the University of Sussex. He joined the Department of Cardiovascular Research at the Rayne Institute, St Thomas' Hospital in 1995. He remains there still, now based within the King's College London British Heart Foundation Centre of Research Excellence. A major focus of his work is the covalent modification of cardiac proteins by oxidants, with a particular emphasis on thiol-targeted post-translational modifications. By identifying cardiac proteins that undergo these redox reactions and determining the impact these alterations have on protein activity, it is hoped to better understand the biological significance of these modifications during health and disease.

NOTES

SESSION 14. MAAS. cGMP/PKG PATHWAY: A THERAPEUTIC TARGET IN HFpEF?

CHAIRS: Zoltan Papp & Yoshihiko Saito

11.00-11.22 Nazha Hamdani - The metabolic road of co-morbidities to understanding the pathophysiology of heart failure: the role of inflammatory signaling pathways in obesity and diabetes

11.22-11.44 Lise Moltzau - C-type natriuretic peptide and HFpEF

11.44-12.06 Peter Sandner - The cGMP/PKG pathway and the use of sGC stimulators: a new treatment approach in chronic HF and HFpEF

12.06-12.18 David Hutchings - Phosphodiesterase-5 inhibition with sildenafil suppresses triggered ventricular arrhythmias and calcium waves via reduced sarcoplasmic reticulum content in the large mammal (abstract 98)

12.18-12.30 Elisa Dal Canto - Cyclic guanosine monophosphate enhancing therapeutic strategy for HFpEF (cGETS study): effects on cardiac dysfunction and remodeling (abstract 97)

Nazha Hamdani	**Bochum, Germany**
	Nazha Hamdani graduated in Pharmaceutical Science at the Free University of Amsterdam and Medicine at the Free University Brussels, Belgium. She received her PhD in Physiology in 2009 from Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, Amsterdam, The Netherlands. Currently, she is a group leader in the department of Cardiovascular Physiology at the Institute of Physiology at Ruhr University in Bochum, Germany. She is interested in understanding the pathophysiology of heart failure with preserved ejection fraction via resolving the complex structural, functional, molecular, and biological interactions underlying diastolic dysfunction to achieve one goal: providing a novel heart failure therapy.
Lise Román Moltzau	**Oslo, Norway**
	Lise Román Moltzau received her PhD (2012) at the Dept. of Pharmacology, University of Oslo in the group of Prof. Finn Olav Levy. She now holds a researcher position at the Dept. of Pharmacology, leading her own sub-group. Moltzau is at the board of Norwegian Society for Pharmacology and Toxicology and is the chair of the 2018 Gordon Research Seminar on Cyclic Nucleotide Phosphodiesterases. She has been working with cyclic nucleotides and phosphodiesterases in the heart for several years. In the recent years her focus has been on natriuretic peptide signaling and the effect on contractility in normal and failing hearts. She has especially been interested in how compartmentation of the cGMP signal can cause different effects on contractility dependent on source of cGMP both through the PKG pathway and trough cGMP-cAMP crosstalk.
Peter Sandner	**Wuppertal, Germany**
	Chief Scientist at the Bayer AG Drug Discovery unit in Cardiology Research. Sandner is a pharmacist by training, holds a PhD in physiology (univ. of Regensburg, 1997), did a Post-Doc in cardio-renal physiology and joint Bayer in 2001 as research scientist. He is an expert for the Nitric Oxide/sGC/cGMP, PDE signaling pathway and its impact on cardiovascular diseases. He is identifying potential new applications for pharmacological modulators of the NO pathway, namely PDE5 inhibitors, sGC stimulators and sGC activators. He is supporting these compounds from early research to late stage development and in post-approval life-cycle management. He is also responsible for the non-clinical profiling of the sGC stimulator vericiguat which is currently developed in a Phase III clinical trial for patients with heart failure with reduced EF.

NOTES

SESSION 15. O2. NEW MEDIATORS OF INTER-ORGAN CROSSTALK IN CARDIOVASCULAR DISEASES

CHAIRS: Derek Hausenloy & **xxx**

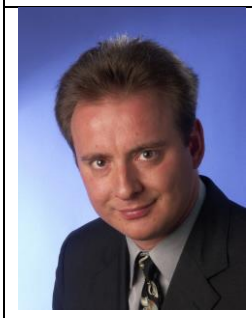
11.00-11.22 Peter Ferdinandy - Circulating Signals Modulating Remote Ischemic Preconditioning

11.22-11.44 Gabriele Schiattarella - Gut Microbe-Generated Metabolites and Cardiovascular Risk

11.44-12.06 Matthias Blueher - Adipocytokines: at a crossroad betwen inflammation and cardiovascular disease

12.06-12.18 Saveria Femminò - Human platelets exert cardioprotective effects via Sphingosine-1 phosphate receptor activation (abstract 105)

12.18-12.30 Attila Kiss - Characterization of left ventricle function in chronic TNF-mediated experimental arthritis (abstract 101)

Péter Ferdinandy	**Budapest, Hungary**
	Ferdinandy is a professor of pharmacology and clinical pharmacology, director of the Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest (www.semmelweis.hu/pharmacology) and the CEO of Pharmahungary Group (www.pharmahungary.com). He was a postdoctoral fellow of MRC Canada for 2 years at the Dept of Pharmacology, University of Alberta, Edmonton, Canada. He completed MBA studies in Finance and Quality Management in 2004 at the Budapest University of Technology and Economics. He was the founder of Pharmahungary Group, a group of R&D companies (www.pharmahungary.com) and consulted hundreds of industrial drug development projects in cardiovascular and metabolic diseases. He was the president of the ISHR-ES, and currently the past chair of the Working Group of Cellular Biology of the Heart, ESC.
G. Schiattarella	**Dallas, USA**
	Gabriele Schiattarella received his MD from the Univ. Federico II of Naples in 2009. After completing the Fellowship in Cardiology and starting a PhD program in Experimental Medicine, he moved to the UT Southwestern Medical Center (Dallas, Texas) under the supervision of Joseph A. Hill. Gabriele's background is in medicine, experimental cardiology and cellular/molecular biology, with specific training and expertise in murine models of cardiovascular diseases and preclinical assessment of cardiovascular function. His research interests include metabolic regulation of cardiac remodeling and failure, mitochondrial dysfunction and autophagy. He is currently active in several clinical and research projects. His research awards include the travel award of the ESC, the Research Award for Young Investigator of the Italian Society of Cardiology and the STAR Award, Young Researcher Mobility of the University Federico II of Naples.
Matthias Blüher	**Leipzig, Germany**
	Blüher is Prof. in Molecular Endocrinology and Speaker of the Collaborative Research Center "Obesity mechanisms" at the Univ. of Leipzig. From 2000-2003, he worked as a postdoctoral fellow at Harvard Medical School in Boston. Blüher´s research is focused on the role of adipose tissue function and distribution in insulin resistance, the development of type 2 diabetes and other metabolic and cardiovascular diseases. He established a large adipose tissue bank from well-phenotyped individuals which supported the functional characterization and translation of association signals for type 2 diabetes and obesity traits into molecular, cellular and physiological mechanisms. His group demonstrated that normal adipose tissue function and protection against adipose tissue inflammation may underly the insulin sensitive "metabolically healthy" obese phenotype. Matthias´ work has been recognized both nationally and internationally.

NOTES

WEDNESDAY 18 JULY

12.30-14.00 POSTER SESSION 4

	Abstract #	Name
1	93	Ľubomír Lonek
2	94	Vadim Fedorovich Sagach
3	95	Hadeel.Khalaf.Mohammed Alboaklah
4	96	Jessica Gambardella
5	97	Elisa Dal Canto
6	98	David Charles Hutchings
7	99	Maria Rita Assenza
9	101	Attila Kiss
10	102	Amber van Broekhoven
11	103	Kirstie Anne De Jong
12	104	Kirstie Anne De Jong
13	105	Saveria Femminò
14	106	Diederik Kuster
15	107	Axel E. Kraft
16	108	Nadja Irene Bork
17	109	Ashay Shah
18	110	Alexander Froese
19	111	Delphine Mika
20	112	Orhan Erkan
21	113	Roman Medvedev
22	115	Marie-Louise Bang
23	116	Larissa M. Dorsch
24	117	Urszula Tyrankiewicz
25	118	Sally Badawi
26	119	Shigemiki Omiya
27	120	Lara Ottaviani
28	121	Michael Khetsuriani
29	122	Carolyn Carr
30	123	Marjolein Droog
31	124	Piotr Berkowicz
32	125	Monique Woelfer
33	152	Valentina Prando (replaces Zaglia)

34	160	Mehroz Ehsan

SESSION 16. AMSTEL. MICRODOMAINS IN CELLULAR SIGNALING

CHAIRS: Rodolphe Fischmeister & Diederik Kuster

14.00-14.22 Slava Nicolaev - FRET Microscopy for Real-Time Visualization of Second Messengers in Living Cells

14.22-14.44 Manuela Zaccolo - FRET biosensor to uncover cAMP nano-domains

14.44-15.06 Julia Gorelik - Micro-domain specific regulation of L-type Ca channels and arrhythmias

15.06-15.18 Axel Kraft - Phosphodiesterases 4B and 4D differentially regulate cAMP signaling in calcium handling microdomains of adult mouse cardiomyocytes (abstract 107)

15.18-15.30 Delphine Mika - PDE4 controls the ß-Adrenergic stimulation of the cardiac excitation-contraction coupling in right ventricular cardiomyocytes isolated from healthy and heart failure pigs (abstract 111)

Slava Nicolaev	**Hamburg, Germany**
	Slava Nikolaev received his PhD in 2005 and his Habilitation in 2012 from the University of Würzburg. From 2009 to 2010 he served as a research associated at the National Heart and Lung Institute, Imperial College London and subsequently became a group leader (funded by the Emmy Noether Program of the German Research Council) at the Heart Center Göttingen, Germany. Since 2014 he is a Director of the Institute for Experimental Cardiovascular Research at the University Medical Center Hamburg-Eppendorf, Germany. He is best known for his work on visualization of functionally relevant cAMP and cGMP signals in cardiomyocyte subcellular microdomains and their impact on cardiac function and disease.
Manuela Zaccolo	**Oxford, United Kingdom**
	Zaccolo graduated in medicine at the Univ. of Torino. She is Professor of Cell Biology in the Dept. of Physiology, Anatomy and Genetics and Director of the Burdon Sanderson Cardiac Science Centre, Univ. Oxford. Her research focuses on how cardiac myocytes sense external stimuli and how these are processed to produce a functional outcome. She is interested in the architectural and regulatory principles by which intracellular signalling networks achieve the plasticity and context-sensitivity necessary for the myocyte to function. Her work has focused on cyclic nucleotide signalling and on the role of local regulation by PDEs. Central is the use of FRET-based reporters and real-time imaging to dissect the topography and function of subcellular cyclic nucleotide nanodomains. Her goal is to understand how alteration of compartmentalised cyclic nucleotides leads to disease and to apply this knowledge to the development of novel therapeutic strategies.
Julia Gorelik	**London, United Kingdom**
	Julia works in the interface between biophysics and cardiovascular Research. She obtained her PhD in Cell Biology from St-Petersburg's Institute of Cytology, Russian Academy of Science. She is Prof. of Cellular Biophysics at Imperial College London. She was at the forefront in developing a high resolution microscopic technique that is suitable for studying living cells, Scanning Ion Conductance Microscopy (SICM). By combining SICM and FRET microscopy Julia found that in cardiomyocytes β2ARs are confined exclusively to the deep transverse tubules, whereas β1ARs are distributed across the entire cell surface. Using SICM in combination with patch-clamp Julia was able to study ion channels localized on the T-tubule opening area in myocytes. This enabled her to study the functional localization of Ca and chloride channels in the cardiac myocyte sarcolemma and to define the link between myoctye structure, ion channel distribution and cell function.

NOTES

SESSION 17. MAAS. PATHOMECHANISMS IN CARDIOMYOPATHIES

CHAIRS: Paul Wijnker & Emma Robinson

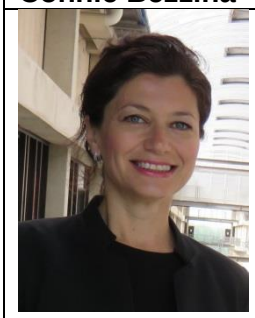
14.00-14.22 Raffaele Coppini - Central role for disturbed Na in pathogenesis of HCM

14.22-14.44 Roddy Walsh - Quantitative approaches improve variant classification in cardiomyopathies

14.44-15.06 Connie Bezzina - Genetic modifiers in inherited cardiac disorders

15.06-15.18 Mehroz Ehsan - RNAseq Reveals Mechanisms of Cardiomyopathy in Mlp-C58G Knock-In Mice (abstract 160)

15.18-15.30 Marie-Louise Bang - Myopalladin is upregulated in dilated cardiomyopathies patients and myopalladin knockout mice develop cardiac dilation and dysfunction following pressure overload (abstract 115)

Raffaele Coppini	**Florence, Italy**
	Coppini received his MD in 2007 and his PhD in pharmacology in 2011 at the University of Florence. He is currently a senior scientist in the lab. of cardiovascular pharmacology and cardiac cell electrophysiology directed by Elisabetta Cerbai in the Dept. NeuroFarBa of the Univ. of Florence. He is best known for his work on the pathophysiology of hypertrophic cardiomyopathy. He first studied the electrophysiological and Ca^{2+}-handling remodeling occurring in human ventricular cardiomyocytes from surgical samples of HCM patients, and identified the increased late sodium current as a possible target for therapy, with direct clinical implications. He also studied the pathological mechanisms of HCM associated with troponin T mutations in transgenic mouse models. In HCM mice, he tested the potential of a long term treatment with the late Na+ current blocker ranolazine.
Roddy Walsh	**London, United Kingdom**
	Roddy Walsh studies the genetics of inherited cardiac conditions, with a particular focus on cardiomyopathies, at Imperial College and the Royal Brompton Hospital in London. His research focuses on investigating the genetic architecture of cardiomyopathies, using large sequencing datasets to evaluate the role of genes implicated in these conditions and to enhance the interpretation of variants detected in cardiomyopathy patients. He also develops novel methods and resources to improve variant interpretation for inherited cardiac disease, including a number of web resources available at http://cardiodb.org.
Connie Bezzina	**Amsterdam, The Netherlands**
	Connie Bezzina obtained her PhD in Genetics from the University of Malta in 1998. In 1997 she joined the Department of Experimental Cardiology at the Academic Medical Center (University of Amsterdam) and was appointed Professor of Molecular Cardiogenetics in 2012. She is recipient of the Established Investigator award of the Netherlands Heart Foundation (2005), the Outstanding Achievement Award of the European Society of Cardiology Council on Basic Cardiovascular Science (2013) and the VICI fellowship of the Netherlands Organisation for Scientific Research (2015). Her research focuses on the identification of genetic factors underlying inherited cardiac disorders with the aim of improving the clinical care of patients and families affected by these disorders. Her work considers the broad spectrum of genetic complexity of these disorders, from monogenic to polygenic. In an integrative approach her group also undertakes functional studies where the identified genetic factors are investigated in model systems to understand the mechanisms of these disorders.

NOTES

SESSION 18. O2. CODING AND NON-CODING RNA IN HEART DISEASE

CHAIRS: Paula da Costa-Martins & Eva van Rooij

14.00-14.22 Leon de Windt - Non coding RNAs in cardiac regeneration

14.22-14.44 Reinier Boon - Non-coding RNA and cardiovascular aging

14.44-15.06 Alicia D'Souza - MicroRNA control of bradyarrhythmias and heart block in the athlete

15.06-15.18 Solenne Paiva - The multiple roles of let-7 family of microRNAs throughout cardiogenesis – from hiPSCs to cardiomyocytes (abstract 48)

15.18-15.30 Lara Ottaviani - Cardiomyocyte-derived exosomes mediate pathological cardiac microvascular remodeling (abstract 120)

Leon de Windt	**Maastricht, The Netherlands**
	Leon de Windt received a PhD in Cardiovascular Physiology and was a postdoctoral fellow at the Howard Hughes Medical Institute of Jeffery Molkentin in Cincinnati. He became group leader at the Hubrecht Institute (Utrecht) in 2002, and was appointed as Prof. of Molecular Cardiovascular Biology at Maastricht Univ. in 2010. In 2018 he became Chair of the inter-faculty Dept. of Molecular Biology at Maastricht Univ. His research aims to understand how programs of cellular differentiation and morphogenesis are affected in the processes leading to heart failure. Chronic heart failure is a progressive disorder of the heart muscle that affects all vital organs, ultimately resulting in loss in quality of life, frequent hospitalizations and a reduced life span. His ultimate goal is to dissect the genomic pathways of heart disease and transform this information to devise the next generation of pharmacological therapies for acquired heart disease in humans.
Reinier Boon	**Amsterdam, The Netherlands**
	Boon received his PhD degree with honors in 2008 from the Academic Medical Center Amsterdam. He then moved to the Institute for Cardiovascular Regeneration in Frankfurt, where he started post-doctoral work in the laboratory of Prof. Dimmeler. From 2011-2016, Boon was a junior group leader in the Institute for CV Regeneration in Frankfurt. Since 2016 Reinier is assoc. prof. at the VUmc Amsterdam and a W2 professor at the Goethe University in Frankfurt. He received multiple awards for his work on the effects of shear stress on endothelial cells and the role of microRNAs in aging of the cardiovascular system, including the prestigious Melvin L Marcus Award from the AHA. Dr. Boon's current research is funded by the German Center for Cardiovascular Research, the European Research Council (Starting grant) and NWO VIDI. Current research is focused on non-coding RNA and aging of the CV system.
Alicia D'Souza	**Manchester, United Kingdom**
	D'Souza is a cardiac physiologist and a Research Fellow at the University of Manchester. She received her PhD in 2011 studying structural remodeling in diabetic cardiomyopathy at the Univ. of Central Lancashire. She then joined Professor Mark Boyett's group in Manchester to investigate electrophysiological remodeling of the cardiac conduction system in athletic training. Alicia's postdoctoral work has been highly recognized, publicized in the popular media (including BBC) and obtained several awards including the ISHR-SERVIER Fellowship, the 2016 inaugural Cairn Electronics 'New and Notable' Prize lecture and the 2016 (inaugural) R Jean Banister Prize Lecture from the Physiological Society. Alicia's current research focuses on the interplay between microRNAs and transcription factors in pacemaker electrophysiology, towards the identification of small molecular therapies for cardiac arrhythmias in the athlete. She is also an elected committee member of the British Society for Cardiovascular Research.

NOTES

AMSTEL Lecture hall

9.00-10.00 Plenary Lecture 4- Meet the editors

John Solaro & Tomasz Kuzic

Session chaired and moderated by: Lucie Carrier

Future President ISHR - European Section

THURSDAY 19 JULY

10.00-11.30 POSTER SESSION 5

	Abstract #	Name
1	3	Diana Bou Teen
2	4	Matteo Sorge
3	5	Eva L. Peters
4	8	Razif Abas
5	9	Filipa Mota
6	11	Michaela Cyprová
7	12	May-Kristin Torp
8	13	Gábor Koncsos
9	14	Lorrie A. Kirshenbaum
10	79	Louise A.M. Nijenkamp
11	126	Paul A.J. Krijnen
12	127	Aida Llucia-Valldeperas
13	128	Francesco Vieceli Dalla Sega
14	129	Leander Stewart
15	130	Andreas Zietzer
16	131	Linghe Wu
17	132	Marit Wiersma
18	133	George Madders
19	134	Luciënne Baks-te Bulte
20	135	Bianca Brundel
21	136	XuHu
22	137	Martina Calore
23	138	Arwa Kohela
24	139	Sebastiaan Johannes van Kampen
25	140	Maria Luisa Barcena de Arellano
26	153	Anika Eike Knaust
27	154	Marco Mongillo
28	155	Mohammed Rabiul Hosen
29	156	Hadar klapper-goldstein
30	157	Denise van Marion
31	158	Alaaeldin Ismail Saleh

SESSION 19. AMSTEL. UNDERSTANDING CARDIAC CELL-TO-CELL COMMUNICATION TO DEVELOP NEW THERAPEUTIC STRATEGIES IN HEART FAILURE

CHAIRS: Mauro Giacca & Francesca Bortolotti

11.30-11.52 Paula da Costa-Martins - Angiomirs as regulators of vascular cardiac remodelling in heart failure

11.52-12.14 Daniele Catalucci - Inhalation of peptide-loaded nanoparticles improves heart failure

12.14-12.36 Diana Nascimento - Neonatal apex resection triggers cardiomyocyte proliferation, neovascularization and functional recovery in spite of local fibrosis.

12.36-12.48 Andreas Zietzer - Heterogeneous nuclear ribonucleoprotein U binds microRNA-30c and negatively regulates the export of microRNA-30c in endothelial microvesicles (abstract 130)

12.48-13.00 Diederik Kuster - PKA's favorite son: prioritizing phosphorylation of phospholamban over cardiac troponin I contributes to diastolic dysfunction in hypertrophic cardiomyopathy (abstract 106)

P da Costa-Martins	**Maastricht, The Netherlands**
	Paula received her PhD (2005) at the Univ. of Amsterdam. After developing her postdoctoral research at the Hubrecht Institute, she engaged in a tenure-track program at Maastricht Univ. She is recognized by her work on deciphering the contribution of non-coding RNAs, specially microRNAs, to the development and progression of cardiac disease, and the identification of specific microRNAs as new therapeutic targets for heart failure. Paula is an Assoc Prof at CARIM School for CV Diseases, Maastricht. She is focusing her research on understanding how different cardiac cell types communicate to influence each other's phenotype and in a concerted manner contribute to pathologic cardiac remodeling. Her main interest is unveiling how cardiomyocytes send "microRNA messages' to endothelial and inflammatory cells via exosomes, to alter their angiogenic and inflammatory properties, respectively. In this way she expects to identify new gene targets or processes where one can intervene to prevent or cure heart disease.
D Catalucci	**Milan, Italy**
	Daniele Catalucci received his PhD (2003) in molecular and cellular biology from the Univ. of Rome. Supported by a Marie Curie Outgoing International Fellowship, he performed his postdoctoral studies at the Dept. of Medicine, Univ. of California San Diego. In 2007, he moved back to Italy (Milan) where he started up his own group at the National Research Council (CNR). In 2009, he became a tenured scientist at CNR and from 2012 he is a PI at the Humanitas Research Hospital. Particular research interest is on three major aspects: 1) Molecular mechanisms underlying cardiomyocyte contractility/relaxation and identification and design of new molecules with inotropic or lusitropic positive properties; 2) Biomimetic nanoparticle formulations for cardiac-specific drug delivery; 3) The role of microRNAs in the regulation of myocardial function.
D Nascimento	**Porto, Portugal**
	Diana Nascimento got her PhD in Zoology by the Univ. of Aberdeen (2008). In the same year she became a PostDoc fellow at INEB, where she is an Assistant Researcher from 2015. The present hypothesis of Nascimento is that cardiac fibroblasts play instructive roles in myocardial regeneration/repair. In the next years she will be devoted to identify new cues on the activation, role and heterogeneity of cardiac fibroblasts and to identify fibroblast–associated signals/subsets of translational relevance. Incorporation of this knowledge in efficient therapies is her long-term goal. She has been appointed member staff of the Bioimaging Centre for Biomaterials and Regenerative Therapies of INEB and she is an Invited Assist Prof. at Instituto de Ciências Biomédicas Abel Salazar (ICBAS) of the University of Porto.

NOTES

SESSION 20. MAAS. UNCOVERING NOVEL MECHANISMS OF ATRIAL FUNCTION IN HEALTH AND DISEASE

CHAIR: Lea Delbridge & Yael Yaniv

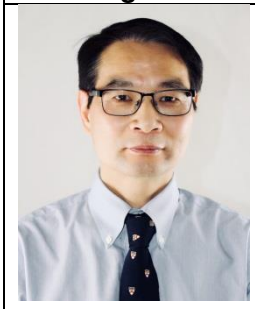
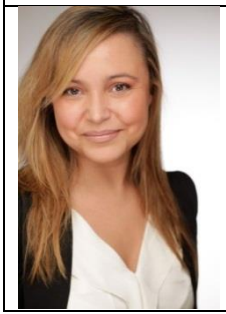
11.30-11.52 Ulrich Schotten - Linking pathophysiological mechanisms of AF to patients phenotype

11.52-12.14 Lei Ming - The role of PMCA1 in atrial Ca2+ handling

12.14-12.36 Christina Molina - cAMP signaling in AF

12.36-12.48 George Madders - Susceptibility to atrial alternans; a role for transverse (t)-tubule loss in heart failure (HF)? (abstract 133)

12.48-13.00 Xu Hu - Heat shock protein inducer reverses the contractile and structural remodeling of HL-1 cardiomyocytes in experimental model of Atrial Fibrillation (abstract 136)

Ulrich Schotten	**Maastricht, The Netherlands**
	Schotten studied medicine at the universities of Aachen, Glasgow and Valetta. After 4 years of training in cardiology at the Univ. Hospital of Aachen, he defended his thesis “Mechanisms of Atrial Paralysis in Atrial Fibrillation” at Maastricht Univ. In 2011, he was appointed professor of cardiac electrophysiology at the Dept. of Physiology in Maastricht. His research programme ranges from the molecular and cellular investigations to studies on the organ and systemic level. He currently works on cellular and integrated actions of antiarrhythmic drugs, the development of substrates for the perpetuation of atrial fibrillation, invasive and non-invasive quantification of the substrate of atrial fibrillation, interaction between atrial fibrillation and activation of the coagulation system, and three-dimensional computer models. Prof. Schotten has been member of the task force for the development of the ESC guidelines for management of AF in 2010 and 2016.
Lei Ming	**Oxford, United Kingdom**
	Ming Lei received a D.Phil in 1997 at Univ. of Oxford and became a group leader in 2001. He is Group Leader, Assoc. Professor and Reader in Cardiovascular Pharmacology since 2013 in the Dept. of Pharmacology at Univ. of Oxford. He is best known for his work on cardiac ion channel function and its regulation under both physiological and pathophysiological conditions, and the development of effective new therapeutic modalities. His team has made fundamental contributions for identification of the novel roles of a multifunctional enzyme-p21 activated kinase in the heart, demonstrating that Pak1 is a critical signalling hub. More recently, his team discovered a new population of cardiomyocytes named as Pnmt+ cell derived cardiomyocytes, PdCMs, opening new frontiers of exploration into the physiological roles of these cells in normal heart function, and pointing the way to their potential application for selective cardiac repair and regeneration strategies.
Christina Molina	**Göttingen, Germany**
	Cristina E Molina is a senior scientist at the Institute of Pharmacology and Toxicology, Univ. Medical Center Göttingen. She received her PhD (2009) at Univ. Autonoma de Barcelona and she did her first post-doc at Paris 11 Univ. After her IEF Marie Curie fellowship at the Cardiovascular Research Center in Barcelona, she moved to Germany. She investigates pathophysiological aspects of cardiac EC coupling and arrhythmogenesis in human atrial myocytes. She is best known for her work on the role of receptor-mediated modulation of ionic currents, intracellular Ca^{2+}-handling and second messengers in AF, including the contribution of different PDEs into the pathophysiological mechanisms underlying this arrhythmia.

NOTES

SESSION 21. O2. MOLECULAR MECHANISMS UNDERLYING ARVC

CHAIRS: Larissa Fabritz & Frederik Flenner

11.30-11.52 Farah Sheikh - Policing Cell-Cell Connections: A Novel Role for the COP9 Signalosome in Arrhythmogenic Heart Disease

11.52-12.14 Eva van Rooij - Using novel sequencing technologies to identify molecular mechanisms underlying ARVC

12.14-12.36 Lior Gepstein - Lessons learned from iPSC models of ARVC

12.36-12.48 Alaaeldin Ismail Saleh - Biochemical and biophysical characterization of the arrhythmogenic E105A calmodulin mutation (abstract 158)

12.48-13.00 Lucie Carrier - Disease modelling and molecular characterization of the PLN p.Arg14del mutation in hiPSC-derived cardiomyocytes (abstract 153)

Farah Sheikh	**San Diego, USA**
	Sheikh obtained her PhD in Cardiovascular Physiology at the Univ of Manitoba, Canada. She is currently an Assoc. Prof. in the Dept of Medicine at the Univ of California San Diego. Her laboratory is focused on uncovering mechanisms underlying biomechanical stress responses in the heart, which play a central role in human heart disease. She has exploited genetic mouse models to uncover novel signaling and cytoskeletal components associated with the cardiomyocyte sarcomere and fascia adherens cell-cell junction that drive the pathogenesis of DCM, HCM and heart failure progression. Her most recent work is focused on exploiting yeast-two-hybrid approaches, genetic mouse models and human induced pluripotent stem cell based models to better understand stress responses associated with the desmosomal cell-cell junction and the associated underlying etiology of arrhythmogenic right ventricular cardiomyopathy. Her lab is supported by the AHA, Tobacco Related Disease Research Program and NIH.
Eva van Rooij	**Utrecht, The Netherlands**
	Eva van Rooij received her PhD. at the department of Cardiology at the University Maastricht. She then went on to complete her postdoctoral training in Molecular Biology at UT Southwestern Medical Center in the lab of Dr. Eric Olson where she served as lead scientist in the studies that linked microRNAs to cardiovascular disease. She currently runs an academic lab at the Hubrecht Institute to further unveil the molecular signaling pathways that underlie ischemic heart disease or genetic forms of heart disease. Using mouse genetics, relevant in vitro and in vivo models of heart disease (like iPS-derived cardiomyocytes or mouse models), state of the art sequencing technologies (such as single-cell sequencing and Tomo-seq) and high-end molecular biology techniques her team aims to identify key players and pathways relevant for the disease.
Lior Gepstein	**Haifa, Israel**
	Lior Gepstein conducted his PhD thesis at the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa. He was involved in the development of a 3-dimensional electroanatomical mapping technique, which became the state-of-the-art technology for the treatment of complex cardiac arrhythmias. Dr. Gepstein completed his residency in internal medicine and Cardiology fellowship at Rambam Health Care Campus and fellowship in Cardiac Electrophysiology at the Univ of California San Francisco. He is Professor of Physiology and Medicine (Cardiology) at the Technion's Faculty of Medicine and holds the Edna and Jonathan Sohnis Chair in Tissue Engineering and Regenerative Medicine. More recently, he was appointed as the Director of the Cardiology Department at Rambam Health Care Campus, Haifa. Prof. Gepstein's research activities focus on the areas of basic and clinical cardiac electrophysiology, stem cell biology, studying of inherited cardiac disorders, and establishment of novel gene and cell-based strategies for the treatment of different cardiac disorders.

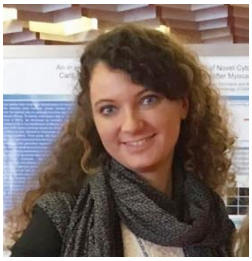
NOTES

AMSTEL Lecture hall

13.30-14.00 Servier awards

Session chaired by: Lucie Carrier
Future President ISHR-European Section

13.30-13.50 Servier award 2017 - Vasco Sequeira
Energy insufficiency-mediated ADP elevations as cause of diastolic dysfunction in hypertrophic cardiomypathy.



13.50-14.00 Servier award 2018 - Francesca Bortolotti
AAV-based, in vivo functional selection to identify factors involved in human ES-derived cardiomyocytes engraftment in vivo.

14.00-14.20 Medal of Merit, Sian Harding

Session chaired by: Rodolphe Fischmeister
President ISHR-European Section

Sian Harding is Acting Head of the national Heart and Lung Institute, Imperial College London and Director of the Imperial British Heart Foundation Cardiovascular Regenerative Medicine Centre. Her work has centered on the myocardium in heart failure, especially beta-adrenergic mechanisms. She was Scientific PI on the first UK Gene therapy Trial in LVAD patients, aimed at improving cardiac contractility. She is now studying the pluripotent stem cell-derived cardiomyocyte, both for disease modelling and cardiac repair. Professor Harding is former President of the European Section of the International Society for Heart Research. She has been elected Fellow of the ISHR, the American Heart Association, European Society of Cardiology, British Society of Pharmacology and Society of Biology. She is on the Board of the British Society of Gene and Cell Therapy.

14.20-15.00 Oral & poster awards

Young Investigatior awards
Chaired by: Zoltan Papp & Sandrine Lecour
Future secretary & treasurer of the ISHR-ES
Poster awards
Chaired by: Derek Hausenloy, Secretary ISHR-ES

Abstracts (no permission was given for publication in the special issue of JMCC)

Oral session 1

Poster session5

Abstract # 140

Name of presenter: Maria Luisa Barcena de Arellano

Sex differences in age-related AMPK-Sirt1 axis alteration in human heart

M.L. Barcena de Arellano, S. Pozdniakova, P. Karkacas, A. Kühl, I. Baczko, Y. Ladilov, V. Regitz-Zagrosek

Gender in Medicine, Charité Universitätsmedizin Berlin

Background: Aging is related with declined physiological function, leading to inflammation and mitochondrial dysfunction, promoting development of cardiovascular diseases. Sex differences in aging-related cardiovascular diseases have been postulated. In the current study we aimed to investigate the sex difference in the age-related alteration in Sirt1-AMPK signaling and its relation to the mitochondrial biogenesis and inflammation.

Methods and results: Male and female human non-disease left ventricular tissue (young and old) was used. Western blot was performed for expression analyses of Sirt1, AMPK/pAMPK, ac-Ku70, T0M40, Sirt3, SOD2, catalase. CD68 was used as marker for macrophages and the ratio of IL-12:IL10 was used to examine the inflammatory stage in the heart. Sirt1 expression was significantly higher in young females, whereas in aged hearts Sirt1 expression was significantly downregulated in females. Acetylation of nuclear Ku70, a direct target of Sirt1, was significantly elevated in aged female hearts. AMPK activity was significantly decreased in aged individuals. Expression of mitochondrial proteins TOM40, SOD2 and Sirt3 was significantly higher in young female, while in aged female hearts SOD2 and TOM40 were downregulated. The expression of catalase, an anti-oxidative enzyme was significantly higher in young females and this female sex benefit was lost in aged hearts. The number of cardiac macrophages was significantly increased in old female. The pro-inflammatory shift in old females was confirmed by differences in the IL12/IL10 ratio in young female cardiac tissue in favour of IL-10. The anti-inflammatory environment in the heart was lost in aged females.

Conclusion: Aging leads to significant downregulation of Sirt1 expression and elevated acetylation of Ku70 in female, but not in male hearts. A beneficial upregulation of mitochondrial and anti-oxidative proteins in young females is lost with aging. Malfunctions in the expression of Sirt1 and mitochondrial proteins in aged female hearts is accompanied by a significant pro-inflammatory shift. The study provides a molecular basis for the increased incidence of cardiovascular diseases in old women.

Poster session 1

Abstract # 141

Name of presenter: Sophie Moulin

Chronic intermittent hypoxia, the deleterious feature of obstructive sleep apnea, induces HIF-1-dependent mitochondrial dysfunction

S. Moulin, M. Pauly, A. Thomas, M. Détrait, G. Vial, F. Lamarche, H. Dubouchaud, C. Arnaud, J-L Pépin, D. Godin-Ribuot, E. Belaidi-Corsat

Laboratoire HP2 (Hypoxie PhysioPathologies), University Grenoble Alpes

Background: Chronic intermittent hypoxia (IH) is the major detrimental factor of obstructive sleep apnea (OSA), leading to myocardial alterations (myocardial infarction occurrence and worse recovery). Mitochondrial metabolism is highly sensitive to oxygen fluctuations. Moreover, the oxygen-regulated transcription factor, hypoxia inducible factor-1 (HIF-1), is activated by IH in rodents and in OSA patients with high cardiovascular risk.
Thus, we aimed to assess the impact of IH and consecutive HIF-1 activation on myocardial mitochondrial function, dynamics and turnover.

Methods and results: Wild type and HIF-1α+/- mice were exposed to 21 days of IH (21-5% FiO2, 60s-cycles, 8h/day), or normoxia (N). After isolation of cardiac mitochondria, oxygen consumption, ROS production, membrane potential and calcium retention capacity (CRC) were measured using a Clark electrode and spectrofluorimetry. Mitochondrial dynamics and turnover were assessed by Western blot.
Compared to N, IH decreased mitochondrial respiration by 30%, ROS production by 50%, CRC by 25% and increased time to membrane repolarization by 30%. Although mitochondrial biogenesis and fission were not modified, IH decreased fusion protein (Mfn2: 0.85±0.04 fold increase vs. N, $p<0.05$) and increased autophagy and mitophagy markers (Bnip3: 1.32±0.09 and Parkin: 1.36±0.09 fold increase vs. N, $p<0.05$). All these IH-induced modifications were abolished in mice with partial HIF-1α deletion.

Conclusion: These results demonstrate that HIF-1 is involved in IH-induced myocardial mitochondrial dysfunction, prone to explain deleterious myocardial consequences of IH. Further studies are needed to determine specifically how mitochondria could be considered as a potential therapeutic target in OSA patients with high cardiovascular risk.

Poster session 1

Abstract # 142

Name of presenter: Aurélia Bourcier

GENE THERAPY OF HEART FAILURE WITH PHOSPHODIESTERASE 4B IN TWO MOUSE MODELS

A. Bourcier, J.P. Margaria, C. Coquard, S. Gomez, A. Varin, A. Ghigo, V. Algalarrondo, G. Vandecasteele, E. Hirsch, R. Fischmeister, J. Leroy

INSERM UMR-S 1180, Univ. Paris-Sud, Université Paris-Saclay, Châtenay-Malabry, France

Background: Heart failure (HF) is associated with a compensatory chronic ß-AR activation in an effort to maintain cardiac output, which participates in cardiac remodeling. Multiple cyclic nucleotide phosphodiesterases (PDEs) finely tune ß-AR responses by degrading and compartmentalizing cAMP. Since chronic treatment with PDE inhibitors increases mortality in HF, we postulated that decreasing cAMP levels may have therapeutic effects.

Methods and results: To test this hypothesis, we explored whether AAV9-mediated cardiac overexpression of PDE4B (10^12 viral particles) could prevent maladaptive hypertrophy in mice subjected to transverse aortic constriction (TAC) or 2 weeks isoproterenol (Iso) infusion (60µg/g/day). Echocardiography allowed assessment of cardiac function and of the severity of the constriction by measuring the maximal flow velocity across the ligature. In the two models, PDE4B protein level was increased ~4 to 5-fold. In control mice injected with a Luciferase-AAV9 (LUC), TAC decreased ejection fraction (EF, -10±3%, N=10, $p<0.01$), increased left ventricular weight/body weight ratio (LVW/BW, +38±7,3%, N=10, $p<0.0001$). PDE4B overexpression did not ameliorate EF but prevented LV hypertrophy (N=7, $p<0.05$). A positive correlation between the severity of constriction and the LVW/BW ratio was found in the TAC LUC animals (N=10, $R2=0.5057$, $p=0.02$), but not in mice overexpressing PDE4B (N=7). Chronic Iso treatment induced hypertrophy (N=10, $p<0.0001$), fibrosis (N=9, $p<0.001$) and decreased EF (-31,6±3,5%, N=10, $p<0.0001$). While PDE4B overexpression did not prevent cardiac hypertrophy (N=10) in this model, it decreased fibrosis (N=9, $p<0.01$) and preserved EF (N=10, $p<0.0001$).

Conclusion: Altogether, these results suggest that gene therapy with PDE4B is a potential therapeutic approach for cardiac maladaptive hypertrophy.

Poster session 1

Abstract # 144

Name of presenter: Umber Saleem

Functional relevance of PDE3 and 4 isoforms in human induced pluripotent stem cell-derived cardiomyocytes in engineered heart tissue format

U. Saleem, I. Mannhardt, H. Sadran, T. Schulze, T. Christ, T. Eschenhagen, A. Hansen

Experimental Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf

Background: Phosphodiesterases (PDE) break down cAMP and thereby restrict beta-adrenergic stimulation. Accordingly, PDE inhibitors increase the sensitivity to beta adrenergic stimulation. PDE4 is the most important isoform for regulation of catecholamine response in rodent cardiomyocytes, while the dominating isoform in human adult CM is PDE3. Assuming the potential of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) for biomedical research, we aimed at determining the relevance of different PDE isoforms in hiPSC-CM in an engineered heart tissue model (EHT).

Methods and results: Three-dimensional, force-generating fibrin-based EHT were prepared from hiPSC-CM and contractile force was analysed by video-optical recording. PDE4 inhibitors resulted in a greater increase in sensitivity of EHTs to isoprenaline than PDE3 inhibitors. The EC50 of isoprenaline shifted from 12.4 nM (isoprenaline alone, n=45) to 0.93 nM or 1.38 nM in the presence of the PDE4 inhibitors rolipram (10 µM, n=11) or roflumilast (10 nM, n=22, $P < 0.05$), respectively, to 2.9 nM in the presence of the mixed PDE3/4 inhibitor milrinone (10 µM, n=13) and to 6.0 nM in the presence of the selective PDE3 inhibitor cilostamide (300 nM, n=16). None of the PDE inhibitors produced a significant increase in contraction force when applied alone, except rolipram. RT-PCR indicated PDE4 mRNA levels to be similar and PDE3 lower in hiPSC-EHTs than in non-failing human heart.

Conclusion: The data show that hiPSC-EHT respond qualitatively normal to beta-adrenergic stimulation, but that control of this signalling pathway by PDE4 is more pronounced than that by PDE3 which is likely an indicator of hiPSC-CM immaturity.

Funding: German Centre for Cardiovascular Research

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Poster session 1

Abstract # 145

Name of presenter: Annie TURKIEH

Clusterin: expression and implication in left ventricle remodeling post myocardial infarction

A. Turkieh, M. Fertin, P. Mulder, O. Beseme, M. Chwastyniak, P. Amouyel, V. Richard, C. Bauters, F. Pinet

Institut Pasteur de Lille/INSERM U1167, Universite de Lille

Background: Left ventricular remodeling (LVR) following myocardial infarction (MI) is associated with an increased risk of HF and death. It remains a frequent event despite the modern therapeutic approach and difficult to predict in clinical practice. Our aim was to identify new biomarkers of LVR post-MI and understand their involvement in this process.

Methods and results: Using a proteomic approache without a priori on plasma obtained from REVE-2 study which included 246 patients after a first anterior MI allowed us to identify Clusterin (CLU) that was increased in plasma of patients with high LVR compared to patients who didn't develop LVR one-year post-MI. To verify if increased plasma CLU levels has in part a cardiac origin, we quantified CLU in LV of MI rats and showed that CLU mRNA and its intracellular levels are increased in rat LV at 7 days and 2 months post-MI and are correlated with LVR parameters. The increased of CLU levels is also validated in the LV biopsies obtained from HF patients with ischemic dilated cardiomyopathy. Furthermore, CLU expression and secretion are increased by the hypertrophied NCM treated by isoproterenol. However, CLU silencing in the hypertrophied NCM decreased cell size, ANP and BNP expression associated with decreased ERK1/2 activity suggesting a pro-hypertrophic role of CLU in this model.

Conclusion: Our results show for the first time that plasma CLU levels are associated with the LVR post-MI, have a part a cardiac origin and are involved on compensatory hypertrophy.

Oral Session 5

Poster session 1

Abstract # 146

Name of presenter: Roberto Pane

The histone methyltransferase MLL3 controls the development of cardiomyocyte hypertrophy

R. Pane, L. Laib, M. Laudette, S. Paula-Gomes, Y. Sainte-Marie, F. Tortosa, F. Lezoualc'h, C. Conte

I2MC, University of Toulouse

Background: Epigenetic marks allow cells to respond to environmental cues through altered gene expression patterns. They have emerged recently as key players in the development of cardiovascular diseases, suggesting that epigenetic enzymes may represent promising targets for the development of new treatments. Cardiac hypertrophy, an early hallmark during the clinical course of heart failure, is regulated by various signalling pathways which activate a specific gene program characterized by re-expression of some fetal genes and repression of certain adult cardiomyocyte-specific genes. Recently, histone H3 lysine 4 (H3K4) methylation patterns have been shown to be altered in hypertrophic hearts.

Methods and results: Interestingly, we observed that MLL3 (Mixed-Lineage Leukemia Protein 3), one of the specific H3K4 methyltransferases, and its enzymatic product H3K4Me1 are strongly upregulated in human failing hearts. Moreover, our data show that MLL3 knockdown by short interfering RNA (siRNA) prevents hypertrophy onset in vitro by blunting fetal gene re-expression and blocking H3K4Me1 increase. We, thus, addressed the implication of this epigenetic enzyme in hypertrophic gene reprograming using in vitro and in vivo mouse models.

Conclusion: We will present you our most recent data showing that MLL3 is a key molecular actor for the setting of the hypertrophic epigenome.

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Poster session 1

Abstract # 147

Name of presenter: Loubna Laib

Epigenetic role of the histone demethylase JARID1B in cardiac hypertrophy

L. Laib, R. Pane, Y. Sainte-Marie, F. Tortosa, F. Lezoualc'h, C. Conte

Cardiovascular and Metabolic Diseases, INSERM, University of Toulouse

Background: Heart failure (HF), which is the end-consequence of stress-induced cardiac hypertrophy and remodelling is characterized by the re-expression of fetal genes. Dysregulation of epigenetic posttranscriptional modifications of histones in chromatin have been shown to play a key role in the progression of the pathology. In particular, the histone H3 lysine 4 methylation (H3K4Me) patterns have been shown to be strongly altered in failing hearts. Among the H3K4-targeted histone demethylase, a member of the JARID1 (Jumonji, AT Rich Interactive Domain 1) family, known as a transcriptional repressor drew our attention.

Aim: To determine the role of JARID1B in the development of cardiac hypertrophy and HF.

Methods and results: JARID1B is overexpressed in the heart of transverse aortic constriction-induced pressure overload mice as well in the myocardium of patients with dilated cardiomyopathy. In primary neonatal rat ventricular myocytes, siRNA-mediated knockdown of JARID1B expression prevents the phenylephrin-induced cardiomyocyte hypertrophic response. To study the role of JARID1B in vivo, we constructed an adeno-associated virus serotype 9 encoding a specific short hairpin RNA against JARID1B (AAV9-shJARID1B). Injection of AAV9.shJARID1B induces a 41% decrease of JARID1B expression in mice hearts. Echocardiography analysis shows that cardiac function was unmodified in AAV9.shJARID1B injected mice compared with AAV9.shScramble injected mice in basal condition. The in vivo effect of JARID1B knock down on cardiac remodeling is currently under investigation using an experimental model for pressure overload-induced cardiac hypertrophy and heart failure.

Conclusion: We demonstrate that JARID1B is upregulated in cardiac stress conditions in mice and human. In addition, it promotes cardiomyocyte hypertrophy.

Oral Session 6

Poster session 1

Abstract # 148

Name of presenter: Luc Bertrand

O-GlcNAcylation inhibition by the AMP-activated protein kinase (AMPK), a new duet to prevent cardiac hypertrophy development

R. Gélinas, F. Mailleux, L. Bultot, A. Ginion, E.P. Daskalopoulos, J.-L. Balligand, C. Beauloye, S. Horman, L. Bertrand

Cardiovascular research (CARD), Université Catholique de Louvain

Background: Activation of AMPK is known to prevent cardiac hypertrophy. We recently confirmed this paradigm using the direct and specific activator A769662. Our study also demonstrated that none of the molecular mechanisms previously proposed to explain the anti-hypertrophic action of AMPK was involved. To identify the mechanism by which AMPK blocks cardiac hypertrophy, we evaluated its action on O-GlcNAcylation (O-GlcNAc), a post-translational protein modification discovered to be increased in cardiac hypertrophy.

Methods and results: In vitro hypertrophy is induced in neonatal rat cardiomyocytes (NRVMs) using phenylephrine (PE). In vivo cardiac hypertrophy is induced by angiotensin II (AngII). AMPK is activated by A769662 in vitro and metformin in vivo.
NRVM hypertrophy is accompanied by an increase in O-GlcNAc levels. Hypertrophy and O-GlcNAc are prevented by A769662-mediated AMPK activation, such inhibition disappearing when AMPK is knocked down by siRNA. O-GlcNAc stimulators increase O-GlcNAc levels and reverse the anti-hypertrophic effect of A769662. In vivo experiments confirm these results. Metformin-mediated AMPK activation reduces AngII-mediated cardiac in WT mice. This correlates with the inhibition of the AngII-mediated increase in O-GlcNAc levels. Treatment of WT mice with O-GlcNAc inducers blocks the anti-hypertrophic effect of metformin. By contrast, metformin is unable to prevent Ang-II-induced hypertrophy and does not modify O-GlcNAc in AMPK deficient mice. At the molecular level, AMPK inhibits GFAT and reduces the expression of OGT, the two enzymes responsible for O-GlcNAc process.

Conclusion: Our results demonstrate that AMPK controls cardiac hypertrophy through O-GlcNAcylation inhibition. This new paradigm brings novel putative therapeutic targets to treat cardiac hypertrophy.

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Poster session 1

Abstract # 149

Name of presenter: Justine Dontaine

Inhibiting O-GlcNAcylation by AMP-activated protein kinase, a new way to reverse cardiac hypertrophy development?

J. Dontaine*, F. Mailleux, R. Gélinas, A. Ginion, L. Bultot, C. Beauloye, S. Horman, L. Bertrand

Cardiovascular research (CARD), Université Catholique de Louvain

Background: We have previously shown that AMPK activation prevents cardiac hypertrophy by decreasing protein O-GlcNAcylation (O-GlcNAc) levels. In order to better fit with physio-pathological conditions encountered in patients and reach therapeutic aim, we were interested to check if AMPK activation can also reverse a cardiac hypertrophic phenotype when already developed.

Methods and results: Neonatal rat cardiomyocytes (NRVMs) are treated with the prohypertrophic agent phenylephrine (PE) for 24h, a time necessary to develop significant hypertrophy. NRVMs are then treated with or without the specific AMPK activator A769662 for an additional 24h period. O-GlcNAcylation is stimulated by the pharmacological O-GlcNAc inducer PUGNAc or reduced by the inhibitor DON. NRVM hypertrophy is evaluated by measurement of cell surface area and O-GlcNAc levels by western-blotting.

PE-induced cardiomyocyte hypertrophy is accompanied by an increase in protein O-GlcNAc levels. A769662-mediated AMPK activation is able to reverse this PE-mediated O-GlcNAc increase, reaching levels similar to those found in control cells. This is nicely accompanied by a reduction in cell size. Moreover, siRNA-mediated knockdown of AMPK prevents A769662 action on cell size and O-GlcNAc levels. We next evaluated the key role of O-GlcNAc by co-treating NRVMs with the O-GlcNAc inducer PUGNAc and showed that PUGNAc contracts the anti-hypertrophic action of A769662. Inversely, inhibition of O-GlcNAcylation by DON mimics A769662, reducing cell size

Conclusion: Our results reveal that AMPK activation by A769662 can reverse cardiomyocyte hypertrophy development by reducing O-GlcNAcylation levels.

Poster session 2

Abstract # 150

Name of presenter: Laudette Marion

Role of Epac1 in diabetic cardiomyopathy

M. Laudette, S. Brun, C. Moro, A. Lucas, O. Lairez, Y. Sainte-Marie, F. Lezoualc'h

I2MC, Toulouse

Background: Diabetic cardiomyopathy occurs in a context of metabolic and neurohumoral dysregulation including an excess of circulating fatty acids and an overactivation of the sympathetic nervous system that dysregulate cardiac β-adrenergic receptor-cAMP signaling. However, the role of Epac1, a cAMP-binding protein, in the development of diabetic cardiomyopathy has never been explored.

Methods and results: Epac1 expression was increased in the hearts of mice subjected to a high-fat diet (60% lipid, HFD) for 9 months and in atrial samples of obese patients. Treatment of primary cardiomyocytes with 500µM palmitate (a lipotoxic fatty acid) promoted mitochondrial ROS production (assayed using the superoxide-sensitive probe MitoSOX Red) leading to depolarization of ΔΨm and apoptosis measured by JC-1 fluorescence dye, LDH release and cleaved caspase 3 activity, respectively. In contrast, Epac1 inhibition with 20µM CE3F4 prevented palmitate-induced cardiomyocyte death. Interestingly, cardiomyocytes transfected with a mutant form of Epac1 deleted for its mitochondrial-targeting sequence exhibited a decrease in mitochondrial ROS content and cell viability as compared to those transfected with the wild-type form of Epac1 when treated with palmitate. Together, these data strongly suggest that mitochondrial Epac1 participates in cardiomyocyte death during a lipotoxic stress.

Conclusion: Our data show that Epac1 expression is upregulated during a prolonged metabolic stress and promotes the lipotoxicity of palmitate in primary cardiomyocytes.

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Oral Session 12

Poster session 3

Abstract # 151

Name of presenter: Gomez

New role of Epac1 in Doxorubicin-induced cardiotoxicity

M.Ribeiro, A.Belhadef, M.Mazevet, M.Laudette, B.Crozatier, F.Lezoualc'h, J-P.Benitah, A-M Gomez, E.Morel , C.Lemaire

Laboratoire signalisation et physiopathology cardiovasculaire, Université Paris

Background: Doxorubicin (Dox) is an anthracycline commonly used to treat many types of cancer; unfortunately this chemotherapeutic agent often induces side effects such as cardiotoxicity leading to cardiomyocyte death and dilated cardiomyopathy (DCM). This cardiotoxicity has been related to reactive oxygen species generation, DNA intercalation, topoisomerase II inhibition and bioenergetics alterations resulting in DNA damage and ultimately in cardiomyocyte death. Therefore, there is a need for new treatment options and strategies aiming at reducing Dox side effects in the heart. Among these mechanisms Epac (exchange protein directly activated by cAMP) signaling could be worth investigating.

Methods and results: In vivo, Dox-treated mice (C57BL/6 vs Epac1 KO mice, iv injections, 12mg/kg) developed a DCM associated with Ca2+ homeostasis dysfunction. In vitro (primary culture of neonatal rat cardiomyocytes, Dox 1µM), as measured by flow cytometry and western blot, Dox induced DNA damage and cell death. This cell death is associated with apoptotic features including mitochondrial membrane permeabilization, caspase activation, cell size reduction and relative plasma membrane integrity. We also observed that Dox led to a modification of the protein level of Epac1 and Epac2 isoforms. The inhibition of Epac1 (ESI09, CE3F4), but not of Epac2 (ESI05), prevented DNA/TopIIβ complexes, decreased Dox-induced DNA damage, loss of mitochondrial membrane potential, apoptosis and finally cardiomyocyte death. These results were confirmed in vivo since Dox-induced cardiotoxicity was prevented in Epac1 KO mice as evidenced by unaltered cardiac function (no DCM) at 15 weeks post-treatment.

Conclusion: Inhibition of Epac1 could be a valuable therapeutic strategy to limit Dox-induced cardiomyopathy during cancer chemotherapy.

Poster session 4

Abstract # 152

Name of presenter: Tania Zaglia, PhD

CIRCULATING MUSCLE-DERIVED miR-206 LINKS 'SKELETAL MUSCLE DYSFUNCTION'-TO-'HEART AUTONOMIC DENERVATION'

V. Prando*, S. Bertoli*, G. Favaro, V. Di Mauro, F. Lo Verso, P. Pesce, D. Catalucci, M. Mongillo, M. Sandri, T. Zaglia

Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy

Background: Recent work and our data demonstrate that muscle-specific ablation of the autophagy-related protein, Atg7, leads to block of autophagy, sarcopenia and destabilization of the neuro-muscular junction (NMJ). In addition, Atg7 knock-out muscle fibers secrete high levels of exosomes containing the muscle-specific miR-206, which stabilizes the NMJ. Consistently, the increased circulating levels of miR-206 cause muscle denervation and, interestingly, increased miR-206 expression in the myocardium.
On these bases, we aim to define the effects of miR-206 in heart homeostasis and determine its role in the 'skeletal muscle-to-heart' communication.

Methods and results: Our results demonstrate that circulating exosomes containing miR-206 are taken up by the heart leading to atrophy and sympathetic dysinnervation, accompanied to reduction in the neurogenic control of cardiac rhythm and increased arrhythmogenesis. In vitro assays demonstrate that exosomes-carried miR-206 targets both CMs and SNs, compromising cellular structure and function, by affecting specific molecular pathways. In CMs, miR-206 over-expression leads to atrophy, sarcomeric and mitochondrial disorganization, impaired Ca2+ handling and altered β-adrenergic responses. Conversely, in SNs miR-206 increase causes atrophy and irregular axonal distribution of the active neurotransmitter release sites, and reduction in axonal sprouting. These effects are likely attributed to the miR-206-mediated downregulation of the NGF receptor p75, as demonstrated by bioinformatics, luciferase assay, molecular and biochemical analyses in vitro and ex vivo.

Conclusion: Thus, we identify miR-206 as a key regulator of skeletal muscle-to-heart communication. These results are relevant to understand the pathogenesis of muscular/neuro-muscular disorders, associated to cardiomyopathies, and characterized by increased circulating levels of miR-206 (i.e. DMD; Amyotrophic Lateral Scerosis).

Funding: ARISLA

Oral Session 21

Poster session 5

Abstract # 153

Name of presenter: Anika Eike Knaust

Disease modelling and molecular characterization of the PLN p.Arg14del mutation in hiPSC-derived cardiomyocytes

A.E. Knaust, B. Klampe, I. Mannhardt, M. Prondzynski, F. Flenner, A.T.L. Zech, U. Saleem, S. Laufer, A. Shibamiya, I. Braren, I. van Rijsingen, Y. Pinto, S. Harding, T. Eschenhagen, A. Hansen

Institute of Experimental Pharmacology and Toxicology, University Medical Centre Hamburg-Eppendorf

Background: Mutations in phospholamban (PLN) are associated with the development of dilated cardiomyopathy (DCM). To investigate molecular mechanisms we established a human in vitro PLN p.Arg14del disease model and investigated whether any phenotype could be rescued by CRISPR/Cas9 gene correction.

Methods and results: Human induced pluripotent stem cells (hiPSC) were generated from PLN p.Arg14del patient fibroblasts. Isogenic controls (PLNic) were generated by CRISPR/Cas9 technology. PLNic and mutant hiPSC were differentiated into cardiomyocytes (CM) in vitro. Monolayer hiPSC-CM were analysed for calcium transients (Fura 2-AM). Engineered heart tissue (EHT) served as a three-dimensional disease modelling platform to analyse contractility by video-optical recording. Histological and molecular investigations of EHTs were performed after culture. Isogenic controls revealed seamless gene-correction. Electrically paced PLN p.Arg14del-EHTs generated significantly lower forces (0.08±0.03 mN, n=27) than PLNic (0.21±0.03 mN, n=9) and unrelated controls (0.22±0.02 mN, n=10). PLN p.Arg14del-EHTs showed a time- and concentration-dependent increase in arrhythmias with increasing extracellular calcium concentration (1.0, 1.8, 3.0 mM). In PLN p.Arg14del hiPSC-CM, the ratio of PLN wildtype to mutated mRNA was 1:1, indicating allelic balance. PLN protein levels were reduced by 50% in mutated EHTs compared to PLNic despite similar total PLN transcript levels. PLN p.Arg14del EHTs showed histological evidence for disorganization of dystrophin. Calcium transient (caffeine puff) analysis revealed no significant differences between mutated and PLNic hiPSC-CM (n=24-25).

Conclusion: PLN p.Arg14del EHT revealed a robust contractile and arrhythmic phenotype which was rescued in isogenic controls. This disease model will be valuable to further study pathological pathways in PLN p.Arg14del cardiomyocytes.

Funding: British Heart Foundation (BHF), German Centre for Cardiovascular Research (DZHK)

Poster session 5

Abstract # 154

Name of presenter: Marco Mongillo

Role of the neuro-cardiac sympathetic synapse in retrograde neurotrophic signalling from heart to neurons.

M. Franzoso, V. Prando, A. Di Bona, N. Pianca, L. Vitiello, C. Basso, T. Zaglia*, M. Mongillo*

Biomedical Sciences, University of Padova

Background: We have previously demonstrated that communication between SN and CM occurs through direct intercellular coupling at cardiac synapses. This study aims i) to determine whether specific cellular structures are present at the SN/cardiomyocyte (CM) contact site, ii) to investigate the role of SN/CM interaction in NGF-mediated signaling.

Methods and results: Electron microscopy and immunofluorescence on mouse heart slices and rat SN/CM co-cultures showed close association between SNs and CMs and enrichment of the NGF receptor (TrkA) at the contact site. This data supports that neuro-cardiac neurotrophin signaling uses specialized signaling domains at the intercellular junction. Silencing of NGF expression by CMs in co-cultures led to 66% decrease of neuronal density, supporting that SN viability depends on NGF released by CMs. SNs cultured on NGF-silenced CMs showed 20% decrease in the NCJ area when compared to those on wild type CMs of the same culture. Consistently, cultured SNs in contact with CMs survived NGF withdrawal, whereas neurons alone treated with CM-conditioned medium did not survive because of the very low NGF concentration (1.61 pg/mL). Conversely, NGF concentration at the contact site was estimated by using the TrkA inhibitor K252a and resulted about 1000-fold higher (1.75 ng/mL), supporting that the NCJ allows amplification of intercellular NGF signaling.
Dystrophin accumulation on CM membrane contacted by SNs was observed in mouse cardiac slices. Consistently, hearts from mdx mice showed 74.36% decrease of innervation, with no significant changes of NGF expression, supporting that ablation of dystrophin impairs cardiac SNs.

Conclusion: Taken together, our results suggest that NGF-dependent signaling to the neurons requires a direct and specialized interaction with myocytes.

Funding: EUTrigTreat

Poster session 5

Abstract # 156

Name of presenter: Hadar klapper-goldstein

Atrial fibrillation substrate analysis in conscious freely moving rats with hyperaldosteronism

Hadar klapper-goldstein, Sigal Elyagon, Michael Murninkas, Roni Gillis, Wesam Mulla and Etzion Yoram

Physiology and Cell Biology, Ben-Gurion University of the Negev, Israel

Background: Atrial fibrillation (AF) is a complex arrhythmia with suboptimal therapeutic strategies. While large mammals were exclusively used in the past, there is a rapidly emerging interest in the utility of rats in AF research. However, atrial pacing is challenging in these species and is mainly performed ex-vivo or under deep anesthesia. Our laboratory developed the first, and currently the only available tool for long-term implantation of atrial electrodes in rodents.

Objectives: In the present work we calibrated a system for repetitive AF substrate quantification in conscious freely moving rats subjected to hyperaldosteronism, an established trigger of atrial structural remodeling and increased AF substrate.

Methods: SD rats were co-implanted with atrial pacing & recording devices and osmotic mini-pumps delivering Aldosterone (Aldo). AF substrate was evaluated 2 and 4 weeks post implantation using a protocol of 20 induction bursts (100 Hz, 20 sec at double diastolic threshold). AF inducibility (percentage of bursts leading to AF > 1s) as well as total and maximal AF duration were calculated. At the endpoint, left atrial histology was evaluated for fibrosis and cellular apoptosis.

Results: Control rats had extremely low AF substrate. AF susceptibility parameters were all significantly increased following 4 weeks of ALDO treatment ($p<0.05$). The increased AF susceptibility at 4 weeks was associated with increased atrial fibrosis and cellular apoptosis.

Conclusions: We demonstrate a novel system for repetitive AF substrate evaluation in freely moving rats. The presented model of ALDO-induced AF may be an attractive system for AF drug testing.

Poster session 5

Abstract # 155

Name of presenter: Mohammed Rabiul Hosen

Elucidation of role of extracellular vesicles (EVs)-transmitted lncRNA PUNISHER in cardiovascular biology

M. R. Hosen

Molecular Cardiology, University Hospital Bonn

Background: Augmenting evidence indicates that long noncoding RNAs (lncRNAs) are playing a crucial role in diverse cellular/pathological processes, including angiogenesis, apoptosis and different types of cardiovascular disease (CVD) as myocardial infarction (MI), ischemia, coronary artery disease (CAD) and heart failure. Intercellular transfer of extracellular vesicles (EVs) transmitted lncRNA regulates function of acceptor cells via different mechanisms. Such cell-to-cell communication by exporting biologically important cargoes (proteins, lipids, RNAs etc.) modulates the molecular signature and function of acceptor cells. EV-enriched long coding RNA PUNISHER (also known as AGAP2-AS1) is expressed abundantly in the heart and controls endothelial cells function via regulation of vascular gene regulatory network. However, the specific role in cardiac cells and molecular mechanism of packaging of such lncRNA into EVs still vastly unexplored.

Methods and results: PCR-based lncRNA array was used to identify highly dysregulated lncRNAs in CAD patients compared to healthy patients (n=221). Our data showed that PUNISHER is most upregulated transcript in CAD patients with some other lncRNAs (Gas5, Malat1 etc.). Here, we aimed to elucidate the functions of PUNISHER by using cardiac cells, which constitute the heart: cardiomyocytes (CMs), endothelial cells (ECs) and fibroblasts (FBs), by employing loss-of-function experiments followed by molecular profiling via microarray. To examine the role of PUNISHER in EC phenotypic regulation, siRNA-mediated silencing was performed. In vitro functional experiments of EC revealed that PUNISHER depletion suppresses the migration and proliferation. EC function in PUNISHER depleted cells will be investigated by sprouting capacity by aortic ring and tube formation. To assess whether PUNISHER is important for cell survival and viability, MTT, LDH and Caspase 3/7 assay will be performed. To study whether PUNISHER is incorporated into endothelial microvesicles (EMVs) and promotes the cellular functions of acceptor cells, we induced EC by EMVs, which augmented EC function in vitro. To decipher the mechanistic insights, we aim to perform RNA pull-down by using biotinylated full-length PUNISHER and/or RNA-antisense purification (RAP) to identify RBPs. A comparative proteomic analysis via mass spectrometry (MS) to quantify statistically significant enriched candidates will be performed.

Conclusion: Our studies aim to provide an avenue for the better understanding of vesicle-enriched lncRNA-dependent regulation and their effects on recipient cardiac cells. Together, our study will enrich poor understanding of EV-transmitted influence of PUNISHER to acceptor cells, which might be beneficial in cardiovascular pathologies. These approaches can be translated to develop targeted therapeutic interventions for CVDs.

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Poster session 5

Abstract # 156

Name of presenter: Hadar klapper-goldstein

Atrial fibrillation substrate analysis in conscious freely moving rats with hyperaldosteronism

H. Klapper-Goldstein, S. Elyagon, M. Murninkas, R. Gillis, W. Mulla, E. Yoram

Physiology and Cell Biology, Ben-Gurion University of the Negev, Israel

Background: Atrial fibrillation (AF) is a complex arrhythmia with suboptimal therapeutic strategies. While large mammals were exclusively used in the past, there is a rapidly emerging interest in the utility of rats in AF research. However, atrial pacing is challenging in these species and is mainly performed ex-vivo or under deep anesthesia. Our laboratory developed the first, and currently the only available tool for long-term implantation of atrial electrodes in rodents.
Objectives: In the present work we calibrated a system for repetitive AF substrate quantification in conscious freely moving rats subjected to hyperaldosteronism, an established trigger of atrial structural remodeling and increased AF substrate.

Methods and results: SD rats were co-implanted with atrial pacing & recording devices and osmotic mini-pumps delivering Aldosterone (Aldo). AF substrate was evaluated 2 and 4 weeks post implantation using a protocol of 20 induction bursts (100 Hz, 20 sec at double diastolic threshold). AF inducibility (percentage of bursts leading to AF > 1s) as well as total and maximal AF duration were calculated. At the endpoint, left atrial histology was evaluated for fibrosis and cellular apoptosis.
Control rats had extremely low AF substrate. AF susceptibility parameters were all significantly increased following 4 weeks of ALDO treatment ($p<0.05$). The increased AF susceptibility at 4 weeks was associated with increased atrial fibrosis and cellular apoptosis.

Conclusion: We demonstrate a novel system for repetitive AF substrate evaluation in freely moving rats. The presented model of ALDO-induced AF may be an attractive system for AF drug testing.

Poster session 5

Abstract # 157

Name of presenter: Denise van Marion

Heat Shock Proteins 27 and 70 levels in tissue and serum of patients with Atrial Fibrillation: do they correlate and can serum levels predict the stage of AF?

D. van Marion, L. Baks – te Bulte, E. Lanters, N. de Groot, B. Brundel

Physiology, VU University Medical Center

Background: Derailment of proteostasis underlies the progression of Atrial Fibrillation (AF), resulting in structural remodeling, impaired electrical coupling and contractile dysfunction. Previously, we showed that exhaustion of the most important chaperones in the maintenance of proteostasis, the heat shock proteins (HSPs), contribute to remodeling. So far it is unclear whether HSP27 and HSP70 levels in blood and atrial tissue correlate and can predict the stage of AF.

Methods and results: 100 patients (>18y) scheduled for elective cardiothoracic surgery for structural heart disease without (n=47) or with a history of paroxysmal (n=14), persistent (n=23) or long-standing persistent (n=16) AF were included (EMC, Rotterdam, NL). Blood samples were taken before surgery and tissue samples of the atrial appendages were obtained during surgery from the patients for HSP27 and HSP70 measurements, by ELISAs and Western blot analyses. Tissue HSP27 are significantly lower in patients with longstanding persistent AF ($p<0,05$), compared to tissue HSP27 levels in sinus rhythm patients, while tissue HSP70 was unchanged. Tissue HSP27 and HSP70 as well as serum HSP27 and HSP70 levels correlate ($p<0,0001$). Serum HSP27 and HSP70 levels were unchanged for the different stages of AF. Tissue and serum HSP27 or HSP70 levels do not correlate.

Conclusion: Tissue HSP27 is lower in longstanding persistent AF, but serum levels of HSP27 levels are unchanged. Serum HSP27 and HSP70 levels do not predict the stage of AF.

Oral Session 21

Poster session 5

Abstract # 158

Name of presenter: Alaaeldin Ismail Saleh

Biochemical and biophysical characterization of the arrhythmogenic E105A calmodulin mutation

A. Saleh, A. Thanassoulas, B.L. Calver, K. Beck, L. Buntwal, B. Safieh-Garabedian, E. Toft, G. Nounesis, F. Anthony Lai, M. Nomikos

Basic Medical Sciences, College of Mdicine, Qatar University

Background: Calmodulin (CaM) is a multifunctional calcium (Ca2+) sensor ubiquitously expressed in all eukaryotic cells. In cardiomyocytes, CaM directly interacts with the cardiac ryanodine receptor (RyR2), a large transmembrane Ca2+ channel that mediates Ca2+ release from the sarcoplasmic reticulum to activate cardiac muscle contraction. Recent genetic studies have linked mutations in human CaM genes with life-threatening conditions, such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and idiopathic ventricular fibrillation (IVF). A recent clinical report identified a de novo CaM mutation (E105A) with phenotype compatible to LQTS, in a child who experienced an aborted first-episode of cardiac arrest.

Methods and results: Herein, we have investigated the effect of this missense CaM mutation relative to the biophysical and biochemical properties of wild-type CaM (CaMWT) protein. We used CD spectroscopy to examine the overall conformation and thermal stability of CaMWT and CaME105A. Overall confirmation of CaMWT and CaME105A was similar in the absence and presence of Ca2+. In the absence of Ca2+, thermodynamic values of both proteins were similar. In contrast, in the presence of Ca2+, there was a significant decrease in the stability of CaME105A. Furthermore, Ca2+-binding studies revealed that CaME105A significantly reduces the Ca2+-binding affinity of CaMWT. Finally, biochemical analysis revealed that CaME105A displayed a dramatically reduced RyR2 interaction and defective modulation of [3H]ryanodine binding to RyR2.

Conclusion: Our findings suggest that the clinical presentation of LQTS, CPVT or IVF associated with CaM mutations may involve both altered intrinsic Ca2+-binding, as well as dysregulation of RyR2-mediated Ca2+ release via a defective CaM-RyR2 interaction.

Poster session 3

Abstract # 161

Name of presenter: Andria Priyana

Primary Prevention with Statin and Incidence of Malignant Arrhythmia among Acute Coronary Syndrome patients

A. Priyana, A.F. Sunjaya, A.P. Sunjaya

Cardiology, Tarumanagara University

Background: Acute coronary syndrome (ACS) is the greatest single cause of mortality and loss of disability adjusted life years (DALYs) worldwide. Thus, optimal primary prevention is needed to reduce the mortality of ACS. One of the modalities used for prevention is statin due to its various pleiotropic effects. This study therefore aims to evaluate the impact of statin use prior to the onset of ACS and its effects on blood pressure and arrhythmia events after ACS onset in samples from Indonesia.

Methods and results: Medical records of ACS patients are obtained from Cengkareng General Hospital during the period January–December 2016. Diagnosis of ACS was determined based on clinical and laboratory findings obtained from the medical records. Malignant arrhythmia is defined as the incidence of ventricular tachycardia or ventricular fibrillation based on electrocardiographic findings.
One hundred and forty-five patients were found with ACS with a mean age of 56 years old. Seventy-one percent suffered from STEMI while 29% suffered from NSTEMI. Only 16 patients were found to use statin before the onset of ACS. All ACS patients have markedly higher cardiac marker levels. Thirteen mortalities (8.96%) were found. Both mean systolic and diastolic blood pressure was found to be higher in the non-statin group (systolic 137.5±32.8, diastolic 81.9±22.7) compared to the statin group (systolic 116.9±31.1, diastolic 69.5±14.9) although they were not statistically-significant. Incidence of arrhythmia event did not significantly differ between both groups.

Conclusion: The above results showed that there is no significant statistical differences in blood pressure and incidence of malignant arrhythmia events between patients using statin prior to ACS onset and those who do not. Further studies are recommended to confirm these findings.

Poster session 2

Abstract # 162

Name of presenter: Torkia Lalem

Cyclin dependent kinase inhibitor 1 C (CDKN1C) is a female-specific marker of left ventricular function after acute myocardial infarction

Torkia Lalem, Lu Zhang, Markus Scholz, Ralph Burkhardt, Victoria Saccheti, Joachim Thierry, Yvan Devaux On behalf of the Cardiolinc™ network (www.cardiolinc.org).

Cardiovascular Research Unit, Luxembourg Institute of Health, Luxembourg

Background – A significant proportion of patients develop left ventricular (LV) remodelling leading to heart failure after acute myocardial infarction (AMI). Being able to identify these patients would represent a step forward towards personalized medicine. Since men and women with AMI have different clinical profiles, risk factors, pathophysiology and outcome, it is important to find ways to risk stratify patients in a gender-specific manner.
Purpose – To determine the ability of cyclin dependent kinase inhibitor 1C (CDKN1C) to risk stratify AMI patients, in a gender-specific manner.

Methods and results:- CDKN1C expression was measured in blood samples obtained at admission in a test cohort of 447 AMI patients and a validation cohort of 294 patients. The study end-point was LV function assessed by the ejection fraction (EF) at 4-month follow-up. Patients were either classified as having a reduced EF (rEF, <40%), mid-range EF (mrEF, 40-49%) or preserved EF (pEF, >=50%).
In the test cohort, CDKN1C was lower in rEF patients compared to mrEF and pEF patients. This observation was specific to women. Furthermore, CDKN1C was a significant univariate predictor of LV function only in women with an odds ratio (OR) [95% confidence interval (CI)] of 0.56 [0.37-0.83]. In multivariable analyses adjusted for [age, body mass index, white blood cells count, CPK, cTnT, Nt-proBNP, ischemic time (i.e. delay between chest pain onset and reperfusion), gender, history of AMI, diabetes, hypertension, hypercholesterolemia, smoking and infarct type (STEMI vs NSTEMI)], CDKN1C was a strong predictor of LV function in women (OR [95% CI] 0.44 [0.23-0.82]) but not in men (0.90 [0.70-1.16]). On the opposite, Nt-proBNP was associated with LV function in men (1.85 [1.37-2.47]) but not in women (1.06 [0.55-2.0]). CDKN1C increased the predictive value of the clinical model as attested by a decrease of the Akaike information criterion (AIC). This effect was present in women (p=0.006) but not in men (p=0.41). Of note, contrarily to the area under the curve, the AIC is penalized by the number of covariates, thus avoiding model overfitting. A decreased AIC indicates an improvement of prediction. The incremental predictive value of CDKN1C specifically in women was confirmed using bootstrap internal validation. The female-specific association of CDKN1C with LV function after AMI was validated in the independent cohort: OR [95% CI] 0.18 [0.04-0.90] in women and 0.67 [0.29-1.58] in men.

Conclusion - CDKN1C is a novel female-specific biomarker of LV function after AMI. If replicated in additional patient cohorts, this finding may help personalizing healthcare of AMI patients, in a gender-specific manner.

Poster session 3

Abstract # 163

Name of presenter: Inna Rabinovich-Nikitin

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

Inna Rabinovich-Nikitin ‡, Rimpy Dhingra‡, Matthew Guberman ‡, Victoria Margulets‡,Floribeth Aguilar ‡ and Lorrie A. Kirshenbaum‡ †

The Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology‡, Rady College of Medicine, Max Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada R2H 2H6.

Autophagy is a homeostatic process by which damaged organelles such as mitochondria are degraded by an autophagosomal regulated pathway. Accordingly, excessive autophagy can be detrimental and promote cell death. Herein, we provide new compelling evidence that mitophagy and necrotic cell death induced by the chemotherapy drug doxorubicin are obligatorily linked to and mutually dependent upon the Bcl-2 protein Bnip3. In contrast to saline treated mice, a marked increase in mitochondrial targeting of Bnip3 was observed in hearts of mice treated with DOX. This coincided with severe morphological defects, including recruitment of Parkin to mitochondria, increased co-localization of Bnip3 and LC3II and numerous cytoplasmic vesicles containing mitochondria - indicative of increased mitophagy. Interestingly, mitophagy was accompanied by an increase necrosis markers Lactate Dehydrogenase (LDH), Troponin T (cTnT) and loss of nuclear High Mobility Group Box 1 (HMGB1). Further, while mitochondria of wild type mouse embryonic fibroblasts (MEFs) treated with DOX, were severely damaged, resulting in mitophagy and necrotic cell death, Bnip3 - /- MEFs were resistant to the cytotoxic effects of doxorubicin. Conversely, inhibition of autophagy with 3-Methyl Adenine (3-MA), knock-down of Atg 7 or Bnip3 suppressed mitophagy and necrotic cell death of cardiac myocytes treated with DOX. Concordantly, mice deficient for Bnip3 were resistant to mitochondrial injury and mitophagy induced by DOX and exhibited lower mortality than corresponding wild type mice treated with doxorubicin. To our knowledge our data provide the first direct evidence that mitophagy induced by DOX is maladaptive and leads to necrotic cell death by a mechanism that is mutually dependent upon and obligatorily linked to Bnip3. Interventions that mitigate abnormal mitophagy may provide beneficial in suppressing necrotic cell death and cardiac dysfunction in cancer patients treated with doxorubicin.

NOTES

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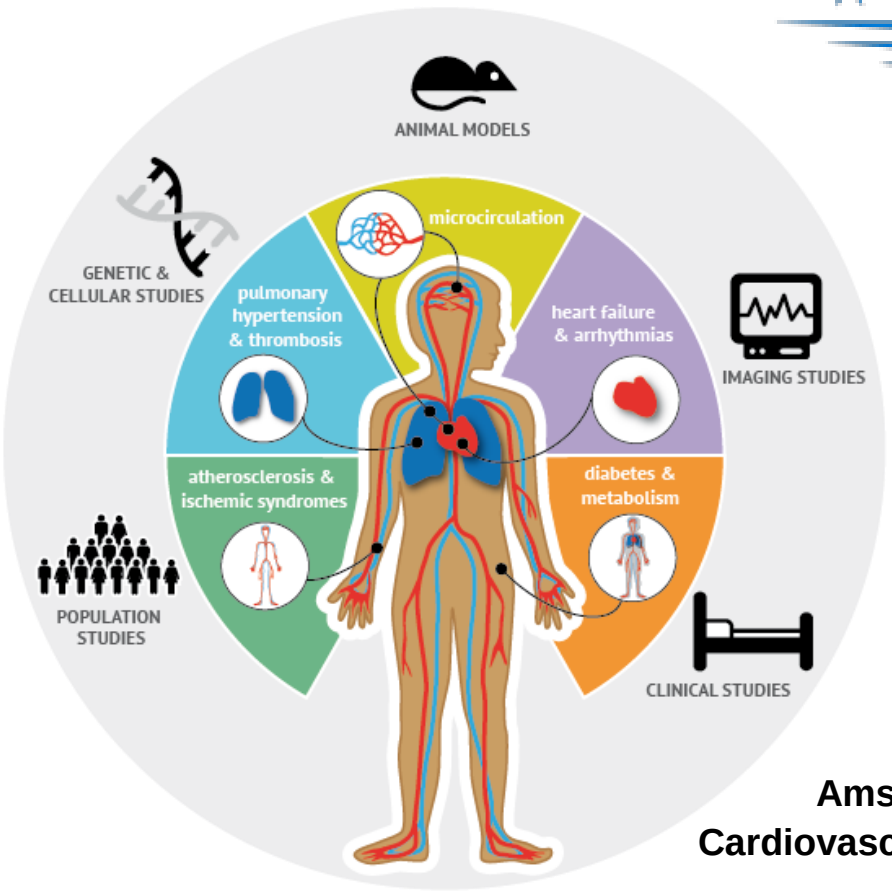

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