The 33rd ISHR European Section (ISHR-ES) Annual Meeting was special for the European Section as we again experimented with holding the ISHR-ES meeting in collaboration with the Frontiers of Cardiovascular Biology (FCVB) meeting organized by the Council of Basic Sciences (CBCS) of the European Society for Cardiology (ESC). In order to respond to the challenges of organizing successful basic science meetings, basic cardiovascular science societies have been trying to find ways to collaborate whilst maintaining their own identity and traditional meeting formats. In keeping with this goal, the 33rd ISHR European Section Annual Meeting was held in...
the beautiful Catalan capital city, Barcelona, Spain, as a one day focused meeting the day before the FCVB meeting at the same venue, the Palau de Congressos de Barcelona.

The main focus of the ISHR-ES meeting was on novel aspects of cardioprotection and the role of mitochondria in cardiac diseases. The plenary sessions started with a joint symposium between the ISHR-ES and the South African Society for Cardiovascular Research keeping with the strategic goal of the ISHR-ES to increase its collaboration with Africa. Throughout the day, speakers (mainly from Europe) presented excellent talks in front of audiences of more than 200 completely filling up the meeting room even after the delivery of extra chairs to the lecture hall. Importantly, junior speakers had the chance to present their data and to compete for the Young Investigator Award in separate sessions. At the conclusion of the scientific part of the ISHR-ES meeting, posters were also presented near the main hall together with wine and cheese. At the end of the day, participants had a small party on the Barcelona beach to celebrate the successful meeting and to network with each other in a relaxing environment. ISHR-ES gratefully acknowledges the perfect organization of the one-day focused meeting by the local organizers, David Garcia Dorado and Marisol Ruiz-Meana, former members of the council of ISHR-ES.

The ISHR-ES meeting was followed by the joint FCVB meeting of the ESC and several sister societies, including ISHR-ES, for 3 more days. The ISHR award lecture and ceremony session were integrated into the main FCVB meeting on the 5th of July. This session was a real celebration of science. The 2014 Servier-ISHR-ES Award was given to Alicia D’Souza, Manchester, UK and the 2013 winner, Alessandra Ghigo, Torino, gave a summary of the work she had carried out. Both presentations convinced the audience that the Servier-ISHR-ES awards...
had been made to excellent candidates. Next the Distinguished Leader Award was presented to Prof. Gerd Heusch (Essen, Germany) after a laudation given by Prof. Peter Ferdinandy. The session was concluded with the Janice Pfeffer Distinguished Lecture by Prof. Joan Heller-Brown (San Diego, CA, USA). During the award lecture and ceremony, a unique constellation of 7 current, future and past ISHR-ES presidents was seen in the room. Six of them gathered later for a photograph (see page 1, Gerd Heusch is missing from the photo).

Based on the success of the Barcelona meeting, this joint meeting format may be a useful model for organizing similar joint meetings at those times when the annual meeting of ISHR-ES and FCVB occur in the same year. We thank the CBCS and the meeting organizing team of ESC for their helpful co-operation with ISHR-ES.

Peter Ferdinandy
Past-President of the ISHR-ES

---

We were saddened by the passing of Dr Guro Valen (Professor of Physiology at the Institute of Basic Medical Sciences, University of Oslo) in September at the age of 54.

Her important research contributions focused on the role of inflammation, remote preconditioning, stem cells and gene transfer in ischemia-reperfusion.

Dr Valen served as a council member of the ISHR-ES from 2007-2011 where she stood out as a person with high scientific standards, absolute integrity and a clear voice with regard to the management and strategic decisions of the society. She served on the editorial board of the Journal of Molecular and Cellular Cardiology since 2007.

A full obituary has been published in the JMCC:
Dear colleagues,

There is no shortage of associations, societies and scientific conferences with a cardiovascular focus (basic, clinical or both) and, indeed, many ISHR members also participate in the activities of other organizations. So what makes the ISHR unique and allows it to prosper, despite the challenges associated with being a federation of multiple regional sections spread across the world, with little direct subscription income and no full-time employees, in a sphere that is occupied by much wealthier, and perhaps more “professional”, organizations? I believe the answer lies in the nature and scope of our meetings, at section level as well as the triennial World Congress. It is the latter that I wish to focus on in this article.

The World Congress is undoubtedly the ISHR’s premier event and is hosted by local organizers belonging to different ISHR sections, in keeping with the global and inclusive nature of our Society. The diverse locations of recent and forthcoming World Congresses include Rhodes (European Section) in 1998, Winnipeg (North American Section) in 2001, Brisbane (Australasian Section) in 2004, Bologna (European Section) in 2007, Kyoto (Japanese Section) in 2010, San Diego (North American Section) in 2013, Buenos Aires (Latin American Section) in 2016, and Beijing (Chinese Section) in 2019 (for interested members, the full programs of the 2004, 2007, 2010 and 2013 World Congresses are available, in PDF format, on the ISHR web pages at www.ishrworld.org). How many other organizations can claim a comparable geographical coverage, which recognizes and showcases the international cardiovascular research effort? Of course, what distinguishes the ISHR is not just the varied (and some might say exotic!) locations of its World Congress, but also the unique nature of each meeting, with strong cultural elements and local flavour (often literally) complementing outstanding science, in a relaxed and friendly environment. Remarkably, all this is achieved through the volunteer efforts of the local organizers, with support from the ISHR Officers and Council, who invariably put their hearts and souls into creating an event that is truly memorable for both the science and the setting.

This leads me to look ahead to 2016 and the XXII ISHR World Congress in Buenos Aires, Argentina (18-21 April 2016), which will be hosted by Martin Vila Petroff and colleagues from Centro de Investigaciones Cardiovasculares, La Plata. This dedicated team of loyal ISHR members has been working hard on their preparations for hosting the ISHR World Congress under the auspices of the Latin American Section for the very first time, ever since their proposal was formally selected by the ISHR Council in 2010. An exceptional venue has been identified and reserved, at a preferential rate, and the ISHR Scientific Program Committee is now hard at work, under the chairmanship of our Secretary General, Richard Moss, to review and consolidate the numerous exciting symposium proposals that have been submitted by the global ISHR membership. I have no doubt that the XXII World Congress will maintain the tradition of scientific excellence, cultural enrichment and outstanding hospitality that has been established by so many previous Congresses and encourage you to put the dates in your diaries and begin making travel plans. Buenos Aires is often referred to as the “Paris of South America” for its architecture and rich heritage, and the city and its people are said to combine European sensibilities with Latin American passion – add to that heady mixture the enthusiasm and energy of Martin and his local organizing team and the assured quality of the scientific program, then I think we are onto another winner!

I leave you with a panoramic view of the Puerto Madero district of Buenos Aires, the location of the Congress venue (one of the red-brick buildings on the right, which was converted from a dockside warehouse into a modern conference center by Universidad Católica Argentina in 2009).
The previous article in this series describes the counterintuitive finding that although myocardial contractility is depressed in chronically failing hearts, treatment which strengthens these hearts often does more harm than good. This article describes another counterintuitive finding: that drugs which weaken these hearts can do more good than harm.

The underlying science has its origins in the 19th century, when Helmholtz’ demonstration that working muscles generate heat led to a focus on energetics that dominated muscle research until the late 20th century. A key discovery, made in 1923 by Fenn, overthrew the established view that activation adds a fixed amount of energy to a muscle by showing that when a skeletal muscle does more work, total energy liberation (work + heat) also increases.

It is noteworthy that this effect had been described in the heart a decade earlier by Evans and Matsuoka, who found that cardiac oxygen consumption increases when the heart does more work.

The link between muscle energetics and contractile mechanics was established in 1938 when Hill postulated that “active points” responsible for energy liberation can exist in two states: one in which they are not attached and so develop no tension, but cycle at their maximal velocity, and another in which they remain attached and develop maximum tension. Described when virtually nothing was known of contractile protein biochemistry, Hill’s “active points” are now recognized to be interactions between myosin cross-bridges on the thick filaments and actin in the thin filaments.

The Failing Heart is Energy-Starved
Efforts to explain experimental heart failure during the first half of the 20th century centered on whether the decreased cardiac work is due to reduced mechanical efficiency or a fall in total energy utilization.

The role of high energy phosphates in energizing muscle contraction, which had been suggested by early observations that the phosphocreatine (PC) content of skeletal muscle falls during contraction and that myosin is an ATPase enzyme, stimulated measurements which showed that because PC and ATP levels are decreased, failing hearts are energy-starved.

More recently, molecular abnormalities involving metabolic enzymes have also been found to reduce high energy phosphate regeneration in failing hearts.

Molecular Changes in Failing Hearts
In 1965 Alpert and Gordon reported that myofibrils prepared from failing human hearts have a low ATPase activity. A decade later Hoh et al. reported that changes in cardiac myosin ATPase activity are associated with heavy chain isoform shifts that were subsequently found by Lompré et al. to explain the decreased myosin ATPase activity in chronically overloaded hearts.

These discoveries made it apparent that two distinct mechanisms regulate cardiac muscle performance: short-term functional responses, such as altered calcium fluxes, that modify the interactions of preexisting structures, and long-term proliferative responses that alter the molecular composition of the heart.

The negative inotropic effect of the decreased myosin ATPase activity in failing hearts was initially viewed as a deleterious change that contributes to the hemodynamic abnormality. However, the fact that these hearts are energy-starved raised another possibility: that the energy-sparing effect of decreased ATP utilization might also have some beneficial consequences. These issues became clinically relevant when β-adrenergic blocker therapy was introduced in the 1960s.

Beta Adrenergic Blockers
Because the negative inotropic and chronotropic effects of β-blockers reduce myocardial energy demand these drugs proved to be effective in alleviating exertional angina pectoris. However, potential side effects of these responses were also recognized: “The most important group of unwanted effects relate to those due to the pharmacologic action of the drug, e.g., hypotension and heart failure.” and “In patients with cardiogenic shock and latent or overt congestive heart failure [β-blockers] should not be used…” Because β-blockers lower blood
pressure, they were also viewed initially as contraindicated after an acute myocardial infarction, however experience showed that the energy-sparing and antiarrhythmic effects of these drugs reduce mortality in these patients (18-19).

The negative inotropic effect of β-blockers was initially thought to preclude their use in chronic heart failure. However the improvement seen after β-blockers were given to patients with heart failure caused by recent myocardial infarction encouraged Waagstein et al. (20) to administer these drugs to 7 patients with congestive cardiomyopathy, all of whom improved clinically. After several small trials confirmed this improvement a multicenter controlled trial was initiated to examine the effect of a β-blocker on prognosis, but the findings were equivocal in part because of difficulty recruiting patients (21).

The role of β-blockers in treating heart failure remained controversial until 1996, when clinical trials using carvedilol, a new β-blocker, in patients with heart failure and low ejection fraction (EF) (“systolic heart failure”) were stopped prematurely because of an unexpected 65% decrease in mortality in patients receiving the drug (22). This finding did not resolve the controversy because symptomatic improvement and not mortality had been the endpoint of these trials, and because the data safety monitoring board that stopped the trials had been charged to monitor these patients mainly for adverse effects of the new drug. Faced with the large apparent reduction in mortality the trials were stopped not because a benefit of the β-blocker had been established, but instead because it was judged to be unethical to withhold publication of this unexpected finding and so delay the needed mortality trials. Within 3 years, appropriately designed trials documented that other β-blockers also reduced mortality in patients with systolic heart failure (23-24).

The Right Answer for the Wrong Reason

The benefits of β-blockers in patients with systolic heart failure, which are now well established (25), can be attributed in part to the energy-sparing effects of reduced heart rate, contractility and blood pressure (26). In addition to these short term functional responses, β-blockers inhibit the long-term proliferative responses that lead to the progressive ventricular dilatation and molecular remodeling generally seen in systolic heart failure (27). Evidence that these drugs are of much less benefit in patients with heart failure and normal EF (“diastolic heart failure”) (28), where progressive dilatation is uncommon, suggests that inhibition of maladaptive proliferative responses plays a major role in the beneficial effects of β-blockers in systolic heart failure.

REFERENCES

2. Fenn WO. The relation between the work performed and the energy liberated in muscular contraction. J Physiol (Lond) 1923; 58: 373-395.
The annual meeting of the Australasian Section of the ISHR, usually held in conjunction with the Cardiac Society of Australia and New Zealand (CSANZ), took a hiatus in 2014 as Australia was hosting the World Congress of Cardiology (WCC) Scientific Sessions, held in Melbourne on May 4-7. As a prelude to WCC, the ISHR held a Research Workshop at the University of Melbourne on May 3, where students and Early Career Researchers had an opportunity to showcase their research. The Research Workshop, as well as the WCC meeting, was a great success with a large attendance. A comprehensive WCC program and open roundtable discussions at the workshop were some highlights of these meetings.

WCC Melbourne was only the second time in its 64-year history that this international meeting had been held in Australia. The National Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ) were co-hosts and contributed to the scientific programme. The traditional prestigious lectures (RT Hall Lecture, Kempson Maddox Lecture, Basic Science Lecture and Gaston Bauer Lecture) were given by internationally recognised experts in the field of cardiology. This year, the RT Hall Lecture was delivered by Professor Marc Pfeffer (Brigham and Women’s Hospital Boston, USA) and his lecture was titled “Left Ventricular Remodelling: A Personal Journey with Australian Influence”. The Kempson Maddox Lecture was given by Professor Philip Aylward (Southern Adelaide Local Health Network, Australia) where he spoke about “Acute Coronary Syndromes, Past, Present and Future”. Professor Dale Abel (University of Iowa, USA) spoke about the Cardiovascular actions of insulin for his Gaston Bauer Lecture. The Basic Science Lecture was delivered by Professor Nadia Rosenthal (Australian Regenerative Medicine Institute, Australia). Her lecture titled “Emerging concepts in cardiovascular regenerative medicine” where she spoke about the role of growth factors, in particular insulin-like growth factor 1, in tissue regeneration. The Basic Science Sessions at WCC were enriched with talks from Australasian ISHR Scientists covering various aspects of cardiovascular biology including cardiac ischaemia/reperfusion interventions, metabolic remodelling of the heart, translating regenerative intervention approaches, diabetic cardio-myopathy, vascular remodelling and hypertrophic cardiomyopathies.

ISHR Australasian section has long been a proud supporter of research students and early postdoctoral fellows. Numerous opportunities are given to young researchers to present their work and compete for prizes. The ISHR Student Investigator Oral Presentation finalists were Padmapriya Muralidharan (The University of Western Australia), Laura Bienvenu (The University of Melbourne and Prince Henry’s Institute), and Nikia Gupta (The University of Melbourne and Murdoch Childrens Research Institute). Well done to all students for their excellent presentations and responses to questions from a supportive and inquisitive audience. Congratulations to the winner of the prize, Laura Bienvenu, for her presentation titled “Cardiomyocyte mineralocorticoid receptor signalling contributes to sex specific ischemic injury responses and reduces functional recovery post-ischemia”. The poster presentations are always a popular session to discuss cardiovascular research in an informal setting. Congratulations to this year’s winner, Ramona Krauss (The University of Melbourne and Murdoch Childrens Research Institute) for her poster

Ramona Krauss, winner of the Best Student Poster, with Julie McMullen (left) and Laura Bienvenu (centre)
titled “Identification of key microRNAs involved in regulation of ovine fetal heart development”. The student publication award went to David White (Baker IDI Heart and Diabetes Institute, Australia) for his original article on “Differential roles of cardiac and leukocyte derived macrophage migration inhibitory factor in inflammatory responses and cardiac remodelling post myocardial infarction” published in the *J Mol Cell Cardiol* 2014; *69*: 32–42. David demonstrated that deletion of migration inhibitory factor in mice exerts cardiac protection against cardiac wall rupture, chamber dilatation and dysfunction following myocardial infarction, actions attributable to attenuated inflammatory responses with decreased extracellular matrix degradation. Congratulations to all of our student prize winners and to all presenting students for their hard work towards scientific excellence.

The postdoctoral publication prize for the best original research paper published during the first six postdoctoral years was awarded to Dr Xiaowei Wang (Baker IDI Heart and Diabetes Institute, Australia). Her publication “Towards Effective and Safe Thrombolysis and Thromboprophylaxis: Preclinical Testing of a Novel Antibody-Targeted Recombinant Plasminogen Activator Directed Against Activated Platelets” was published in *Circ Res* 2014; *114*: 1083-1093, with a feature cover page and editorial letter. Xiaowei has shown that systemic administration of an activation-specific platelet antibody to mice subjected to arterial thrombosis leads to effective thrombolysis without negative effects on hemostasis.

Our Annual General Meeting (AGM) was held on Monday 5 May 2014 at the Melbourne Exhibition and Convection Centre at which Professor Livia Hool (President), Dr Salvatore Pepe (Finance Secretary), Dr Colleen Thomas (Member Secretary), A/Prof Julie McMullen (ECR Development) and Dr Jim Bell (ECR Development) gave a summary of the Australasian section’s activities over the past year.

The Australasian Section of the ISHR held a research workshop on Saturday, May 3rd in the Kenneth Myer Building Auditorium, University of Melbourne preceding the World Congress Cardiology (in lieu of the traditional meeting). The workshop was a great success with attendance from both senior and junior scientists, where Early Career Researchers and students had the opportunity to present their research. The talks after each session was followed by a wider discussion lead by a chair and a panel of senior scientists who facilitated discussion between the audience and the speakers. A special focus of the workshop was a symposium on the Cardiovascular Actions of Seralaxin led by Professor Simon Stewart and Associate Professor Xiao-Jun Du (both from Baker IDI Heart & Diabetes Institute, Melbourne). This symposium covered different aspects of seleraxin biology, from basic mechanism and signalling pathways of the drug, its cardioprotective effects in preclinical models of heart disease to insights from the RELAX-AHF clinical trial. Overall, workshop attendees thoroughly enjoyed the interactive discussion that took place after every session, commenting that the relaxed and informal setting encouraged participation. The ISHR research workshop was followed with a dinner held at Cafe Italia on Lygon Street in Carlton (one of the great food precincts of Melbourne with an Italian flavour). The ISHR dinner made for a wonderful opportunity to network with fellow ISHR members all while celebrating a highly successful and informative (continued on page 13)
MicroRNAs Reloaded: How noncoding RNA species trembled the cardiovascular world

Thomas Thum¹,²,³,⁴,*

¹Institute of Molecular and Translational Therapeutic Strategies (IMTTS); ²Integrated Research and Treatment Center Transplantation; ³REBIRTH Excellence Cluster, Hannover Medical School, Hannover, Germany; ⁴National Heart and Lung Institute, Imperial College London, London, U.K. Tel.: +49 (511) 532-5272; Fax: +49 (511) 532-5274; e-mail: thum.thomas@mh-hannover.de; Homepage: http://www.mh-hannover.de/imtts.html

Abstract
Within the last decade, the role of noncoding RNA species, mainly microRNAs (miRNAs), in cardiovascular development and disease have been studied. New therapeutic approaches based on oligonucleotide therapy have been developed to “treat” specific cardiovascular diseases. Likewise, diagnostic approaches based on measuring miRNA pattern in body fluids have been proposed, as well as findings that circulating miRNAs have paracrine potential as cell-cell communicators. Other noncoding RNA species, such as long noncoding RNAs (lncRNAs), are currently under intense investigation. Seminal work in these fields has been and will be contributed by a number of our ISHR colleagues.

Introduction to noncoding RNA species
Derailed gene expression is the basis of pathological cardiac hypertrophy, cardiac remodelling and heart failure (HF). Well known examples are the upregulation of certain fetal genes during pathological cardiac hypertrophy, causing the often inevitable deterioration in heart function (27). For quite some time, proteins such as transcription factors were thought to be the only and main players in gene expression regulation, but with the recent development of new, high-resolution technologies for RNA research, such as next generation sequencing, this paradigm changed. A great surprise was the fact that although only about 80-90% of the mammalian genome is transcribed, less than two per cent is ultimately translated into protein (7), leaving an unknown biological role for the non-translated RNA species. These non-protein coding transcripts form a vast non-protein-coding RNA (ncRNA) world that we have only recently started to study. Many ncRNAs identified act at various steps along the protein biosynthetic process, including transcription, RNA maturation, translation, and protein degradation. This discovery is fueling a new era in cardiovascular science.

Based on size, ncRNAs can be subdivided into two major groups: 1) small ncRNAs (<200 nucleotides short) including micro–RNAs (miRNA), PIWI-interacting RNAs (piRNA), and endogenous short interfering RNAs (siRNA); and 2) long ncRNAs (lncRNA), which have a length between 0.2–2Kb (31).

Examples of how microRNAs can serve as therapeutic “drugable” targets
Around 1500 to 2000 human miRNAs have been identified and a few have been tested as therapeutic targets in cardiovascular disease in small and large animal models. Our group has shown the first potential therapeutic use of manipulating miRNAs in vivo. We demonstrated that miR-21 can silence the ERK–MAP kinase inhibitor sprouty-1, which is mechanistically involved in fibrosis development (28). As miRNAs usually have dozens of targets, it is interesting that miR-21 has also been found to promote cardiac fibrosis by regulating other targets, such as transforming growth factor beta 1 (TGF-β), receptor III and matrix metalloprotease-2. Surprisingly, miR-21 knockout (KO) mice developed cardiac fibrosis under cardiac stress (24), whereas pharmacologic
Inhibition of miR-21 inhibited fibrosis in the heart (26,27) and other organs, such as lung (19) and kidney (5). Pathological stress activates several signaling pathways triggering cardiomyocyte hypertrophy. A well-known example is the activation of the calcineurin–nuclear factor of activated T-cells (NFAT), whereby the calcium-dependent phosphatase calcineurin dephosphorylates the transcription factor NFAT3, enabling it to translocate to the nucleus to activate multiple hypertrophy-related genes (22). One of the first studies that mechanistically investigated the importance of a miRNA in cardiac hypertrophy was from the Olson laboratory, showing miR-208 to be crucially involved in hypertrophic signaling (30). Another early report demonstrated that pressure-overloaded mice had low cardiac miR-133 levels; likewise, inhibition of miR-133 with an anti-miR-133 oligonucleotide generated cardiac hypertrophy in vivo (4). De Windt’s group showed that miR-199b is a direct calcineurin/NFAT target gene that increases in expression in mouse and human heart failure, and targets the nuclear NFAT kinase dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a (Dyrk1a), constituting a pathogenic feed-forward mechanism that affects calcineurin-responsive gene expression (6).

Compared to abundant cardiac miRNAs, many others are expressed at relatively low levels under basal conditions but can be significantly altered during pathological stress. An example is the miR-212/132 family, which becomes activated during HF in humans (27) and animal models (29). This miRNA family regulates cardiac hypertrophy and autophagy in cardiomyocytes by targeting the anti-hypertrophic and pro-autophagic transcription factor forkhead box O3 (FoxO3), leading to hyperactivation of the pro-hypertrophic calcineurin/NFAT signaling pathway. Both genetic and pharmacologic inhibition of miR-132 rescued cardiac hypertrophy and HF in mice, offering a possible therapeutic approach to this pathology (29). In addition to miRNAs enriched in cardiac fibroblasts or cardiomyocytes, endothelial miRNAs have been found to serve as valuable treatment targets. Dimmeler’s group has elegantly shown how inhibition of miR-92 can improve cardiac outcome after myocardial infarction both in mice (3) and large animals (pigs) (13). Our group used inhibition of miR-24 to increase capillary density after myocardial infarction, resulting in smaller infarct sizes and improved cardiac function (8).

These are initial examples how modulation of small RNA species in vivo can result in powerful therapeutic outcome in pre-clinical studies paving the way for future clinical trials in cardiovascular medicine. Indeed, such miRNA modulation therapies have already entered the clinical arena in other disease pathologies, such as hepatitis. Antisense sequences chemically modified to improve stability and tissue distribution of the underlying nucleotide structure have been developed and currently anti-miR-122 has made it through to a phase-II clinical trial for the treatment of hepatitis C virus infection (15). In contrast, the use of anti-miRNA in cardiovascular diseases is still in the pre-clinical phase.

Examples how circulating microRNAs can serve as diagnostic/prognostic tools

The initial detection of circulating miRNAs in serum/plasma several years ago suggests that miRNAs may fulfill biological functions outside the cell and serve as potential biomarkers for diseases. Circulating miRNAs and potentially other noncoding RNA species are protected from RNase-dependent degradation by several mechanisms, including their inclusion in microvesicles, exosomes, and apoptotic bodies as well as through the formation of protein-miRNA complexes resistant to degradation (10). Circulating miRNAs are quite stable even after multiple freeze-thaw cycles making them ideal candidates for diagnostic studies (32). Despite the current knowledge about the existence of circulating miRNAs and the intercellular transfer of miRNAs from donor cells to recipient cells, the underlying mechanisms of the cellular secretion of miRNAs are not fully understood. MiRNA loading into exosomes or other vesicles depends on the association of the RNA-induced silencing complex with multivesicular bodies and/or autophagosomes. Notably, different patterns of circulating miRNAs have been identified in blood of patients with cardiovascular diseases. For instance, we have shown that a panel of different cardiomyocyte-derived miRNAs are increased after myocardial infarction of patients and are able to predict future mortality (32). However, these miRNA biomarkers were not superior to the diagnostic and prognostic power of high sensitive troponin T. Another example is the stratification of different patient groups showing up in the hospital with similar clinical phenotypes, such as angina pectoris. We showed that a panel of miRNAs in the blood was able to discriminate patients with myocardial infarction from those with onset of Tako-Tsubo cardiomyopathy (14). Moreover, miRNA subsets may predict future risk to develop myocardial infarction and thus are of high clinical value (35). Finally, miRNA signatures may be useful to predict future success of treatment strategies in cardiovascular patients; an example could be implantation of left ventricular assist devices where currently no good biomarkers are available to predict their future success. In an miRNA array screen and subsequent validation analyses circulating miR-483-3p showed early and sustained up-regulation with LVAD support, whilst baseline plasma miR-1202 levels identified good vs poor LVAD responders. Both miRs are enriched in ventricular myocardium, suggesting the heart as the possible source of the plasma fraction (23). These examples show the potential for circulating miRNAs to develop into useful tools for improved diagnosis and prognosis evaluation of cardiovascular patients.
Paracrine potential of circulating microRNAs

A next emerging question was whether circulating miRNAs are “only” biomarkers or would also have a biological role, i.e., function as intercellular communicators. It is well known that multiple cell types in the cardiovascular system are able to generate various kinds of vesicles that vehiculate paracrine signals (20). Such secreted vesicles include apoptotic bodies, microvesicles, and exosomes. Exosomes are membrane vesicles with a diameter of 30–100 nm and, thus, can only be visualized by electron microscopy or fluorescent-labeling strategies. Exosomes are formed by fusion of multivesicular bodies with the plasma membrane, leading to a release of exosomes into the extracellular space. For instance, apoptotic bodies enriched in miR-126 have been reported to limit atherosclerosis development (36). Further evidence for the crucial role of miR-126 as an important protector of the endothelial system was recently obtained with miR-126 KO mice, which have impaired endothelial proliferation (25). A further example of atheroprotective actions based on miRNA trafficking was shown for shear-stress stimulated human endothelial cells that produced vesicles enriched in miR-143/145 that led to reduced atherosclerotic lesion formation in aortae of ApoE KO mice (12). Our group was interested in whether cardiac fibroblasts also secrete exosomes and whether they would contribute to intercellular communication. Surprisingly, we found cardiac fibroblast-secreted exosomes to be enriched in passenger strand miRNAs, such as miR-21*, which could be taken up by recipient cardiomyocytes, provoking hypertrophy (1). These early studies provide evidence that many cardiovascular cell types secrete various vesicles filled with genetic information, such as microRNAs, thus enabling intercellular exchange of information.

Long Non-Coding RNAs (lncRNAs)

lncRNAs are transcripts more than 200 nucleotides long that have no known protein-coding function (2), although some lncRNAs have been recently reported to encode short peptides (micropeptides) in human tissues (33). The mechanisms of the various functions of lncRNAs are the subject of intense investigation. lncRNAs can interact with other RNA species, proteins, and DNA. One difference from many messenger RNAs is the fact that lncRNAs have a high folding energy enabling formation of stable tertiary structures that interact with other (endogenous) molecules. Many eukaryotic lncRNAs have been identified, with most of them being species-specific but less conserved than protein-coding genes, although the formed tertiary structures can be better conserved. Recently identified lncRNAs with proven importance in the heart include Bvht (Braveheart) and Fendrr (Foxf1 adjacent non-coding developmental regulatory RNA) (9;16). Bvht is required for cardiomyocyte differentiation and maintenance of cardiomyocyte phenotype in the mouse by regulating the expression of core gene regulatory networks involved in defining cardiovascular cell fate. Fendrr-deficient mice present with thin ventricular walls due to hypoplasia linked to altered cardiomyocyte proliferation, and die at the embryonic stage. Deep sequencing studies revealed that the profile of myocardial lncRNAs is altered upon HF in humans, and that left ventricular assist devices normalized a subset of differentially expressed lncRNAs; moreover, the lncRNA expression signature was more effective at distinguishing non-ischemic from ischemic failing myocardium than were the miRNA or mRNA profiles (34). In the vascular system, MALAT1 is enriched in endothelial cells and regulates the angiogenic features of vascular cells (21). The locus of the cardioid-specific gene myosin heavy chain 7 (Myh7) was demonstrated to harbor a cluster of antisense lncRNAs, which were named myosin heavy-chain-associated RNA transcripts (Mhrt); inhibition of Mhrt expression was found to be an essential step for the induction of cardiomyopathy subsequent to pressure overload (11). As for miRNAs, lncRNAs are also highly stable in biological fluids and recently, the lncRNA LIPCAR (long intergenic noncoding RNA predicting cardiac remodeling), was reported to be detectable in plasma of post-MI patients, and was determined to have a potential to predict onset of future cardiac remodeling processes and survival (18).

Non-coding RNA therapeutics: Chances and challenges

There have been a variety of studies using chemically modified antisense oligonucleotides stabilized by use of phosphorothioate backbone linkages or conjugation with 2’-O-methyl-cholesterol to facilitates cellular uptake (17). Locked nucleic acids (LNAs) are antisense molecules with 2′ sugar modifications (2′-fluoro and 2′-O-methoxyethyl groups) creating very high affinity for the target. Long RNA gapmeRs are antisense oligonucleotides containing a central stretch (gap) of DNA monomers flanked by blocks of LNA-modified nucleotides; these produce increased target affinity and nuclease resistance of the oligo. The DNA gap activates RNase H cleavage of the target RNA upon binding. Usually, gapmers are 14–16 nucleotides in length and fully phosphorothioated. A first approach to silence the lncRNA Malat1 in vivo has recently been made in a cardiovascular disease model (21).

To date, use of the antisense approach in the cardiovascular field has been highly successful experimentally. However, the efficacy of the drugs must be titrated against their off-target effects — such as interference with the complement cascade and activation of innate immunity — and toxicity. While the use of anti-miRNA in the cardiovascular arena is still in the pre-clinical phase, we look forward to future clinical trials in various cardiovascular disease entities. This is a major and important challenge for the future.
Sources of Funding
The support of the Foundation Leducq (Project MIRVAD) to T.T. is kindly acknowledged.

Disclosures
TT filed and licensed several miRNA/LncRNA patents.

References
I would like to begin my letter by extending thanks to our previous ECI chair, Dr Sarah Franklin, who organized an extremely successful early career investigator event in Miami (2014). This event attracted more than one hundred early career scientists from North America and provided a great environment for the attendees to discuss both science and career development.

As you know, the ISHR-NAS ECI committee is dedicated to providing opportunities for early career investigators to communicate with fellow researchers (both fellow ECIs and senior investigators) and develop their careers. In keeping with these goals, here are some of the ECI events to be included at the 2015 ISHR-NAS Meeting in Seattle (Jun 7-10, 2015):

**Early Career Symposium**: We will hold a scientific symposium by inviting early career investigators to present their cutting edge science. Every talk will be followed by an open discussion to facilitate communication and feedback.

As a key component for early career development, our **career development workshop** in Seattle will focus on grant review and writing. Senior investigators who are experienced in grant application and review will be invited to join the early career investigators to share their experience and suggestions.

An **Early Career Luncheon** will provide another great environment where the ECIs can join senior investigators at lunch and receive career development advice. This year, the luncheon will focus on three different topics including: 1) How to find the right career mentor 2) How to prepare a manuscript for publication, and 3) How to overcome rejection.

As we continue our event planning, more details will be announced. So stay tuned and I hope to see you in our next ISHR-NAS ECI event in Seattle!

Chen Gao, PhD  
Chair, ISHR-NAS ECI 2014-2015  
University of California, Los Angeles

(continued from page 8)

workshop. The conveners and organising committee [Salvatore Pepe (Murdoch Childrens Research institute, Melbourne), Livia Hool (The University of Western Australia, Perth), Lea Delbridge (University of Melbourne, Melbourne) and Colleen Thomas (La Trobe University, Melbourne)] are to be congratulated for putting together a very successful program and a highly collegial workshop.

Overall, WCC Melbourne, ISHR Workshop and the ISHR dinner made for a wonderful opportunity to network with fellow ISHR members, begin new collaborations, listen to presentations on the latest developments in fields such as basic science, clinical cardiology and epidemiology whilst celebrating the achievements of the section thus far.

Dr Bianca Bernardo  
Dr Jenny Ooi
Deepak Srivastava, MD

Winner of the 2013 Outstanding Investigator Award

(2013 ISHR World Congress, San Diego, CA)

Dr Deepak Srivastava is the Younger Family Director and a Senior Investigator at the Gladstone Institute of Cardiovascular Disease and Director of the Roddenberry Stem Cell Center at Gladstone. At the University of California, San Francisco (UCSF), Dr Srivastava is also a Professor in the Departments of Pediatrics, and Biochemistry & Biophysics, and is the Wilma and Adeline Pirag Distinguished Professor in Pediatric Developmental Cardiology.

Dr Srivastava’s laboratory revealed how chamber-specific gene networks are established at the transcriptional level and are integrated with signaling pathways. His laboratory used human genetics to demonstrate that a decrease in dosage of some of these cardiac developmental regulators can cause human cardiac septal defects and valve disease, and is now using induced pluripotent stem cells to discover the mechanisms of disease in these patients. In studying the regulation of gene dosage, his lab described the first known biological role of a microRNA in the mammalian system, ultimately revealing a network of microRNAs that titrate the dose of key cardiac gene networks that dictate cell fate and differentiation. Dr Srivastava’s lab has leveraged the body of knowledge from cardiac developmental biology to reprogram non-muscle cells in the mouse heart directly into cells that function like heart muscle cells, effectively regenerating heart muscle after damage. This new paradigm of harnessing endogenous cells to regenerate organs may be broadly applicable.

Such approaches to understand human disease promise to yield new therapies. Dr Srivastava has co-founded a biotechnology company to help find new cures for many human diseases and one of the developmental genes whose role he discovered, Thymosin β4, is currently in clinical trials for patients suffering ischemic damage to the heart.

Before joining Gladstone in 2005, Dr Srivastava was a Professor in the Department of Pediatrics and Molecular Biology at the University of Texas Southwestern (UTSW) Medical Center in Dallas. He has received numerous honors and awards, including endowed chairs at both UTSW and UCSF, as well as election to the American Society for Clinical Investigation, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science. Dr Srivastava’s laboratory has trained more than 45 postdoctoral fellows and graduate students.

Dr Srivastava completed his undergraduate degree at Rice University, medical training at the University of Texas Medical Branch in Galveston and his residency in the Department of Pediatrics at UCSF. He also did a fellowship in pediatric cardiology at the Children’s Hospital of Harvard Medical School and a postdoctoral fellowship at the M.D. Anderson Cancer Center, before joining the faculty at UTSW in 1996.
ISHR MEETINGS CALENDAR

- **June 7-10, 2015.** XXXV Annual Meeting of the North American Section. Seattle, WA. Inquiries: Charles Murry, murry@u.washington.edu
- **July 2-5, 2015.** XXXIII Annual Meeting of the European Section. Bordeaux, France. Inquiries: Pierre Dos Santos, pierre.dossantos@wanadoo.fr
- **August 13-16, 2015.** XXXVIII Annual Meeting of the Australasian Section. Melbourne Convention and Exhibition Centre, Melbourne, Australia. Website: www.csanz2015.com
- **December 11-12, 2015.** XXXII Annual Meeting of the Japanese Section. Kobe, Japan.
- **April 18-21, 2016.** XXII World Congress of the ISHR. Buenos Aires, Argentina.

(continued from page 4)

“Puerto Madero Panorama” by Luis Argerich (Flickr). Licensed under Creative Commons Attribution 2.0 via Wikimedia Commons: http://commons.wikimedia.org/wiki/File:Puerto_Madero_Panorama.jpg

Until next time.

**Metin Avkiran, PhD DSc**  
President, ISHR

(continued from page 6)


Arnold M. Katz, M.D.  
Professor of Medicine Emeritus,  
Univ. of Connecticut School of Medicine,  
Honorary Professor of Med. and Physiol.,  
Geisel Medical School at Dartmouth  
arnold.m.katz@dartmouth.edu
HEART NEWS AND VIEWS

is published thanks to an unrestricted
grant from Servier Research Group -
Institut la Conférence Hippocrate

A private French pharmaceutical group committed
to therapeutic advances in cardiovascular medicine as
well as other key therapeutic areas. We have successfully
developed products in the field of cardiovascular diseases
(ischemic heart disease, hypertension, and heart failure),
as well as in other major therapeutic fields. A number
of landmark studies like PROGRESS, EUROPA,
PREAMI, ADVANCE, HYVET, BEAUTIFUL,
and SHIFT have been conducted with our support.

The dynamism of our research is ensured by
consistent allocation of at least 25% of the annual
turnover of the Group to search for new molecules
and develop their therapeutic applications.

Servier Research Group - Institut
la Conférence Hippocrate is
also the founder of Dialogues
in Cardiovascular Medicine,
a quarterly publication with
a worldwide circulation edited
by Roberto PERRARI
and Kim FOX.
Dialogues discusses, in a
comprehensive way, issues
from the cutting edge
of basic research and
clinical cardiology.

Visit the Web version at
www.dialogues-cvm.org

The forthcoming issue, devoted to
REMOTE ISCHEMIC CONDITIONING
will feature articles by:
R. K. Kharbanda and A. N. Redington;
H. E. Botker et al; D. J. Hausenloy;
D. H. J. Thijssen; H. Contractor

For further information on
Dialogues in Cardiovascular Medicine please contact:
Servier Research Group - Institut la Conférence Hippocrate
50 rue Carnot - 92284 Suresnes Cedex - France
or webmaster@servier.com

Heart News and Views

is the official News Bulletin of the
International Society for Heart
Research and is published every
fourth month.

Editor
L. Anderson Lobaugh
Durham, NC, USA
E-mail llobaugh@nc.rr.com

Founding Editor
T.J.C. Ruigrok
Wijk bij Duurstede, The Netherlands
E-mail t.j.c.ruigrok@xs4all.nl

Editorial Board
R.A. Altschuld
Columbus, OH, USA
M. Avkiran
London, UK
President
R. Bolli
Louisville, KY, USA
T. Izumi
Kanagawa, Japan
Japanese Section
B. Bernardo
Melbourne, Australia
Australasian Section
X.Y. Li
Beijing, China
Chinese Section
A. Mattiazzi
La Plata, Argentina
Latin American Section
B. McDermott
Belfast, UK
European Section
E. Murphy
Bethesda, MD, USA
President-Elect
T. Ravingerova
Bratislava, Slovak Republic
A.-M.L. Seymour
Hull, UK
N. Takeda
Tokyo, Japan
K.K. Talwar
Chandigarh, India
Indian Section
D. Elsner
Manchester, UK
Editor-in-Chief, JMCC
B.J. Ward
London, UK
K.T. Weber
Memphis, TN, USA

Editorial Office
3711 Lochn’ora Parkway
Durham, NC 27705
USA.
Phone/Fax: +1 919 493 4418