Report on North American Section Meeting: Novel Strategies to Combat Heart Failure

The 35th ISHR North American Section meeting was held in Miami, Florida this year, amidst the world’s most gorgeous beaches, beautiful sun-filled weather, and renowned South Beach night-life and culture. Of course, attendees were most enthusiastic about the outstanding meeting program organized by Drs Josh Hare and Michael Kapiloff. The meeting was hosted by the Interdisciplinary Stem Cell Institute of the University of Miami Miller School of Medicine. The venue was the Miami Beach Resort Hotel just north of South Beach, which provided attendees with ambiance, great food, and collaborative discussions throughout the meeting. Over 250 scientists and physicians representing thirteen countries, from Japan to Canada, attended the meeting.

The meeting launched with a fabulous welcome reception for meeting Faculty on Sunday evening aboard the Venetian Lady yacht. Organizers Josh Hare and Michael
Meeting organizers, Michael Kapiloff (left) and Joshua Hare welcome delegates to the 2014 ISHR-NAS meeting in Miami Beach, FL.

Kapiloff welcomed everyone to the meeting and organized an amazing evening filled with dining, music and entertainment. A wonderful time was had by all and the evening set a collegial tone of collaboration, networking and tantalizing scientific discussion.

The meeting schedule was packed with morning and afternoon plenary sessions, posters, and networking lunches encompassing the central theme of “Novel Strategies to Combat Heart Disease.” As a result, the program encompassed a variety of topics ranging from basic to clinical research, stem cells to signal transduction. Participants in the sessions discussed extensively the contribution of aberrant cardiac signaling, ion channels and arrhythmias, stem cells and gene therapy, ischemia and cardioprotection, calcium microdomains, contractile protein mutations, impaired metabolism and autophagy. Importantly, sessions gave vital insights into possible therapeutics, including the future of stem cell-, cellular- and ionotropic-based therapies. Excellent new approaches to enhancing our understanding of heart disease were presented, which led to great discussions and enthusiasm for the treatment of heart disease among attendees. The presenters and attendees enjoyed delicious hors d’oeuvres and beverages and the atmosphere throughout the meeting was friendly and relaxed, providing the opportunity for investigators to freely discuss their findings and possible future research directions.

Plenary speakers kicked off the daily sessions with talks from Dr Andrew Schally, Nobel Prize winner in Medicine in 1977, “Hypothalamic Hormones: From Neuro-endocrinology to Therapy of Cancer and Other Diseases,” and Dr Pascal Goldschmidt, Senior Vice President for Medical Affairs and Dean of the University of Miami Miller School of Medicine, “Of Aging, Inflammation, Frailty, and Stem Cells.” Talks were consistent with this year’s main thematic interest: conquering heart disease and finding new therapies for treatment. Some of the field’s most distinguished scientists were formally recognized at the meeting and awarded for their extensive contributions to science. First, Dr Evangelia Kranias, the Hanna Professor and Director of Cardiovascular Biology and Distinguished University Professor and Co-Director of the Cardiovascular Center of Excellence in the Department of Pharmacology and Cell Biophysics at the University of Cincinnati College of Medicine, was recognized as this year’s Peter Harris Research Achievement Award recipient. The Peter Harris Research Achievement Award recognizes a prominent investigator with a sustained and distinguished record of major scientific achievement in the field of cardiovascular research, and whose research has had major impact on our understanding of treatment of cardiovascular disease. Chaired by Drs Matt Hori and Elizabeth Murphy, Dr Kranias spoke on “Calcium Circuits in the Heart: A Matter of Life or Death,” which focused on the role of calcium cycling in cardiac contractility and cell survival. Dr Kranias’ internationally recognized research program has provided fundamental insights into these regulatory mechanisms, particularly as they pertain to phospholamban and its regulation of calcium cycling through the sarcoplasmic reticulum. Indeed, she was the first to identify human
mutations in calcium cycling genes and to show that these predispose individuals to arrhythmias and heart failure. Second, Dr Asa Gustafsson, Associate Professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of San Diego, was this year’s recipient of the Outstanding Investigator Award. Chaired by Drs Richard Moss and David Eisner, Dr Gustafsson’s talk on the “Role of Mitochondrial Autophagy in Cardio–protection” focused on the contributions she has made in the areas of mitochondrial function and the molecular pathways that regulate autophagy, particularly with regard to how BCL-2 proteins and the PINK1/Parkin pathway recognize and mark dysfunctional mitochondria for degradation. Lastly, the meeting closed with the President’s Distinguished Lecture, given by Dr Keiichi Fukuda, President of the ISHR-Japanese Section and Professor and Chief of the Department of Regenerative Medicine and Advanced Cardiac Therapeutics at Keio University School of Medicine. Chaired by Dr Metin Avkiran, Dr Fukuda talked about “Regenerative Medicine of the Heart using iPS cells,” which focused discussions on the field of cardiac regeneration and the importance of stem cells. Dr Fukuda was the first to report that bone marrow mesenchymal stem cells could differentiate into cardiomyocytes in vitro and that these cells could then be transplanted into the heart in vivo. He also reported that neural crest stem cells exist in the heart and bone marrow and that they could differentiate into multiple lineages, including cardiomyocytes. More recently, his work has focused on regeneration of human cardiomyocytes from stem cells for clinical use.

The meeting program not only included excellent presentations by accomplished and well-established scientists, but also paid special tribute to the achievements of young scientists. Indeed, the conference was well attended by graduate students, post-doctoral fellows and junior faculty. The early career symposium, consisting of invited talks by early investigators, an early career discussion on alternative career paths, lunch with senior investigators, and an evening social, were lively and well-attended. In addition, one of the highlights of the meeting was the Young Investigator competitions. Annual Young Investigator Awards recognize outstanding research in the field of cardiovascular research by junior investigators. The applicants for these awards fall into one of two categories: graduate students/early postdoctoral fellows and senior postdocs/early assistant professors. Two committees selects finalists to present their work at the meeting, where a panel of judges then make the final award based on the scientific merit of a submitted unpublished manuscript, the quality of the oral presentation, and the responses to questions asked during the discussion. This year, the Junior Young Investigator Award was received by Catherine Makarewich, “Transient receptor potential channels contribute to pathological structural and functional remodeling after myocardial infarction,” mentored by Dr Steve Houser. Finalists were Nirmala Hariharan, “Nucleostemin antagonizes...
senescence of cardiac progenitor cells,” mentored by Dr Mark Sussman; Maggie Lam, “Protein kinetic signatures of the remodeling heart following isoproterenol stimulation,” mentored by Dr Peipei Ping; and Sarah Schumacher-Bass, “Paroxetine-mediated GRK2 inhibition reverses cardiac dysfunction and remodeling post-myocardial infarction,” mentored by Dr Wally Koch. The Senior Young Investigator Award was presented to Stephen Lange, “Defining the role of the stress sensors MLP and CARP in signaling pathways that lead to dilated cardiomyopathy,” mentored by Dr Ju Chen. Finalists for this award were Paul Burridge, “Human induced pluripotent stem cells predicts breast cancer patient’s predilection to doxorubicin-induced cardiotoxicity,” mentored by Dr Joseph Wu; Chad Grueter, “MED14 dependent signaling from the heart enhances metabolism in adipose tissue and liver and confers leanness,” mentored by Dr Eric Olson; and Mark Kohr, “Glyceraldehyde-3 phosphate dehydrogenase acts as a mitochondrial trans-S-nitrosylase in the heart,” mentored by Dr Charles Steenbergen. These talks were all exceptional and thought-provoking; these talented young investigators surely have incredibly bright futures ahead.

Other young investigators also had opportunity to shine, presenting their work at one of two poster sessions, where a total of 106 posters were presented. Poster presentations were judged and three winners were chosen and announced at the meeting Banquet. The winners of the ISHR International Poster Awards were Jonathan Hullman, “GRK5 Exacerbates Cardiac Pathology Through Activation of the NFAT Pathway,” mentored by Dr Wally Koch; Rushita Bagchi, “Scleraxis regulates cardiac extracellular matrix composition and fibroblast phenotype,” mentored by Dr Michael Czubryt; and Christopher Murray, “State Dependent Photo-Crosslinking of Iks Using Unnatural Amino Acid Mutagenesis,” mentored by Dr David Fedida.

Reviews of the meeting were very positive and an abundance of praise was bestowed upon the organizers. Indeed, Josh Hare and Michael Kapiloff put together a wonderful program at a beautiful location to make this year’s North American Section meeting memorable. Next year’s annual meeting will be organized by Chuck Murry, Michael Regnier, and Rong Tian and will be held at the Grand Hyatt Hotel in Seattle, Washington on June 7-10th, 2015. The meeting promises to be as informative, interesting and enjoyable as the one in Miami. I am looking forward to seeing you all there!

Maria Irene Kontaridis, Ph.D. Assistant Professor of Medicine Harvard Medical School Department of Cardiology Beth Israel Deaconess Medical Center

Drs Yibin Wang (left), Chair of the Senior YIA competition, and Elizabeth Murphy (far right), President of ISHR-NAS, with (from left) Paul Burridge (finalist), Stephen Lange (winner) and Chad Grueter (finalist).
Dear colleagues,

I write this letter on my return from the 35th Annual Meeting of the ISHR North American Section in Miami Beach (May 12-15, 2014), which was organized under the theme “Novel Strategies to Combat Heart Failure”. From the outset, I wish to congratulate Joshua Hare and Michael Kapiloff, the local hosts of the meeting from the University of Miami, and the Section executive for putting together an outstanding programme. The breadth and quality of the science was exceptional, comprising excellent lectures by invited faculty and cutting-edge poster presentations selected from submitted abstracts, both complemented by lively (and mostly amicable!) debate.

What also impressed me enormously at the meeting was the range of initiatives undertaken by the North American Section to embrace and nurture young investigators, and the enthusiasm and dedication of the young investigators themselves. I was particularly struck by the statistic that around 120 emerging cardiovascular researchers participated in the Early Career Investigator (ECI) events held on the first day, which were superbly organised by an ECI committee chaired by Sarah Franklin (University of Utah). The Section recognised and rewarded the work of these investigators in multiple ways, including two Young Investigator Award competitions targeted at individuals at different stages of their evolving careers, a Poster Award competition (supported by ISHR International), and the inclusion of ECIs as invited speakers and co-chairs in the symposia. Notably, Litsa Kranias (University of Cincinnati), the dedicated Treasurer of the North American Section who received the 2014 ISHR International Peter Harris Research Achievement Award at the meeting, chose to donate the honorarium associated with that award to the Section, specifically to support ECI activities. This was a very meaningful gesture by Litsa and an exemplary illustration of the commitment of the Section leadership to supporting young investigators. The future of cardiovascular science and indeed of the ISHR is reliant upon the success of the emerging researchers within our Sections and I applaud the North American Section for undertaking these ECI initiatives, whose value in sustaining the spirit and morale of young investigators is undoubtedly even greater in the current funding environment. I am sure that other ISHR Sections will follow suit with comparable initiatives at their meetings later in the year, with the full endorsement of ISHR International.

The North American Section meeting was also the setting of a new venture by ISHR International, namely to hold its annual Council meeting at ISHR Section meetings rather than at the Scientific Sessions of the American Heart Association as in the past. The Council met in two sessions on Wednesday, May 14, where much discussion centred on how ISHR International may be able to provide further support to Section activities, to complement existing initiatives (e.g. sponsorship of plenary Award lectures and ECI poster awards), as well as on preparations for our next World Congress in Buenos Aires, on April 18-21, 2016. I plan to give details of relevant new developments in my next letter, but suffice to say for now that the ISHR International leadership is acutely aware of the financial challenges faced by our Sections in sustaining their annual scientific activities and is fully committed to helping them overcome these.

Another recent venture undertaken by the ISHR International leadership, in line with my objectives on taking office, is holding regular, web-based meetings of the Executive Committee in-between the annual Council meetings, to maintain greater contiguity and liaison in managing the affairs of our Society. These present something of a logistical challenge for our truly global Society, with the seven members of the Executive Committee located in five different time zones spanning from San Diego (UTC-7) to Osaka (UTC+9). Nevertheless, two such meetings have been held between the Council meetings in July 2013 (at the San Diego World Congress) and May 2014 (at the North American Section meeting) and, looking forward, a timetable for virtual meetings of the Executive Committee on a quarterly basis is being finalised through the good offices of the ISHR Secretary General, Richard Moss (University of Wisconsin). The occasional disruption to the regular sleep patterns of some participants in these meetings is unlikely to have a long-term cardiovascular impact, and is for a very good cause!

Until next time.

Metin Avkiran, PhD DSc
President, ISHR
In 1707, less than 80 years after Harvey described the circulation, Lancisi postulated that the “hidden oppression and... heaviness of the precordium” in patients with heart failure occurred when “weakened texture” reduced the ability of a dilated left ventricle to eject blood (1). The ability of digitalis to reduce the suffering of these patients, first described by Withering in 1783 (2), suggested that the drug could alleviate this weakness. For the next two centuries physicians attributed the benefits of cardiac glycosides to their positive inotropic effect, which was shown clearly in the late 19th century (3), along with their well-known ability to slow the heart in patients with atrial fibrillation (see below).

Evidence that cardiac contraction is weakened in patients with heart failure, which continued to accumulate throughout the 20th century, was confirmed by clarification of the concept of myocardial contractility (4) and the experimental demonstration that contractility, which is reduced by overload-induced hypertrophy, decreases markedly when the heart fails (5).

In addition to cardiac glycosides, inotropic drugs used 60 years ago included epi-nephrine and norepinephrine, which are β-adrenergic agonists now known to increase cyclic AMP synthesis, and caffeine, a phosphodiesterase (PDE) inhibitor that decreases cyclic AMP breakdown. Calcium salts, strychnine and camphor had also been used to strengthen the heart, but were abandoned when it became clear that their toxicity far exceeds their efficacy.

**Paired Pulse Stimulation**

A report in 1963 that electrical stimulation of the heart in early diastole caused a marked increase in contractility in the subsequent beat (6) was greeted with great excitement (7). This powerful inotropic effect, which had been observed by Bowditch in 1871 (8), suggested that heart failure could be treated by electrical stimulation of the failing ventricle immediately after each spontaneous beat, or by closely timed pairs of stimuli. Called “paired pulse stimulation” (and sometimes “electrodigitalization”), this method was tried in only a handful of patients before it became apparent that it led to little or no clinical improvement and could initiate dangerous arrhythmias.

**“Powerful” Inotropic Drugs**

Efforts to increase contractility in failing hearts were again stimulated in 1978 when acute administration of the bipyridine derivative amrinone was reported to cause marked hemodynamic improvement in patients with severe heart failure (9). However an accompanying editorial noted that positive inotropes could be deleterious because increasing contractility also increases cardiac energy demand (10). The subsequent finding that amrinone is a PDE inhibitor that increases calcium entry into cardiac myocytes raised the possibility that this class of drugs could initiate arrhythmias, exacerbate relaxation abnormalities and cause myocardial cell death (11). These and other concerns led Packer to observe “whenever we read initial enthusiastic reports of a new ‘breakthrough’ [the benefits] are commonly expressed with great passion and enthusiasm, and this enthusiasm is almost always subsequently tempered by reports of drug failure or adverse reactions” (12).

These different views led to a fierce controversy regarding the safety of inotropic drugs, especially those whose effects are mediated by cyclic AMP. The lethal effects of β-adrenergic agonists in chronic heart failure were quickly documented (13), but a number of small trials suggested that PDE inhibitors could relieve symptoms in these patients without causing adverse effects. As this question had not been examined in controlled trials designed to identify a significant effect on survival, Packer and Leier (14) compared mortality in several small studies of PDE inhibitor and vasodilator treatment of heart failure. This showed one year mortality to be 45% in patients taking vasodilators and 74% in those treated with inotropic drugs. The controversy continued until 1991 when the first large placebo-controlled trial of a PDE inhibitor (milrinone) was stopped prematurely because of excess mortality in patients receiving the drug (15). A subsequent analysis of trials using PDE...
in heart failure supported the view that the major problem in this syndrome is not decreased contractility, but instead is progressive deterioration of the failing heart (20). This issue is discussed in the next article in this series, which describes the responses to β-adrenergic blocking drugs.

References


Digitalis

As already noted, clinical observations made it clear that digitalis can provide dramatic symptomatic relief in patients with heart failure. Until the 1950s, however, the most common cause of this syndrome was rheumatic valvular disease (17), which often leads to atrial fibrillation. This raised the possibility that the benefits of cardiac glycosides were due mainly to their ability to slow the rapid ventricular rate caused by this arrhythmia rather than their inotropic effect. By increasing the likelihood that today’s heart failure patient will be in sinus rhythm, the decreased prevalence of atrial fibrillation reduced the potential benefits of cardiac glycosides. Along with the demonstration that other less toxic drugs improve symptoms and prolong survival in heart failure, this change led many to question the value of digitalis for treating this syndrome as it presents today.

In 1990 a meta-analysis of trials that included 645 heart failure patients who were in sinus rhythm found a 72% greater benefit from treatment with cardiac glycosides than placebo (18); however, the key measurement in this study was clinical deterioration and not mortality. A different conclusion was reached 7 years later when a large (3397 patients) randomized placebo-controlled trial showed that digoxin had no effect on survival (19). Although fewer patients randomized to digoxin died from worsening heart failure, there were more deaths in this group from arrhythmias, coronary disease and other cardiac causes. This failure of digoxin to improve survival in heart failure patients who were in sinus rhythm discouraged the clinical use of the cardiac glycosides.

The finding that the inotropic effect of cardiac glycosides did not improve survival in heart failure confirmed that this class of inotropes causes a significant (17%) reduction in survival (16).
The International Society for Heart Research is dedicated to promoting and supporting its young investigators, who represent the future of cardiovascular research and this society. The ISHR-NAS Early Career Investigator (NAS-ECI) committee, chaired by Dr Sarah Franklin (Univ of Utah; 2012 Senior ISHR-NAS YIA winner), organized an extremely successful series of events at this year’s Section meeting designed by and for young ISHR investigators. More than half the meeting delegates signed up to participate in one or more of the following events:

ECI Symposium (May 12, 9:00 – 10:30 am): Abstracts submitted by ECIs were evaluated by the NAS-ECI committee, and 9 abstracts were chosen for presentation in this symposium chaired by Randi Parks and Samarjit Das.

Alternate Career Paths Workshop (May 12, 10:45-11:45 am): Panelists included Dr Lisa Schwartz-Longacre, Program Officer at NHLBI/NIH, Wayne Bowden, Lead Program Manager at BioRASI, and Dr Grant Budas, Scientist at Gilead Sciences. Brief presentations by each panelist were followed by a question and answer period. The workshop was chaired by Drs Mark Kohr and Sakthivel Sadayappan.

ECI Lunch with Senior Investigators (May 12, 12:00-1:00 pm): ECIs gathered around the table with invited senior cardiovascular researchers for an informal lunch discussion. More than 60 ECIs and 20 senior investigators participated in this popular event.

ECI Social (May 13, 7:00–10:00 pm): An unexpected downpour did not dampen the spirits of participants in this social networking event! Drinks and finger food accompanied the meet and greet.

In addition to these ECI-organized events, the meeting included several other opportunities to showcase ISHR-NAS’s young investigators:

NAS-ECIs were invited by meeting organizers to co-chair the majority of the meeting symposia along with a senior investigator. This opportunity provided invaluable experience and visibility for young investigators.

ISHR-NAS sponsors an annual Young Investigator Competition, in which candidates in each of two experience categories (Junior (graduate students, early postdoctoral fellows) and Senior (late postdoctoral fellows, early Assistant Professors) submit an application that consists of an unpublished manuscript, CV and recommendation letter. Four Finalists in each category were chosen by committees of senior investigators (chaired

Early career investigators listen attentively to talks presented by their peers at the ECI Symposium.
by Drs Howard Rockman (Senior) and Jeffrey Robbins (Junior)) to give a brief oral presentation of their work followed by questions from the judges. This year’s winners were Stephan Lange (Senior) and Catherine Makarewich (Junior). The Senior YIA winner becomes a member of the ISHR-NAS Council (2-year term), co-chair of the ISHR-NASECI committee for one year (July, 2014 to June, 2015), and chair of the committee the following year.

ISHR-Intl sponsors the ISHR-International Poster Competition at the World Congress and each ISHR Section meeting that chooses to participate. The awards recognize outstanding young investigators whose posters demonstrate both excellence in research and clarity of presentation. Posters were evaluated by a small panel of senior investigators, co-chaired by Drs Federica del Monte and Mark Sussman (representatives of the ISHR-Intl Council). This year’s winners were Rushita Bagchi, Jonathan Hullman and Christopher Murray.

More ECI events are being planned by the NAS-ECI committee led by incoming chairman, Dr Chen Gao (UCLA, winner of the 2013 ISHR Richard J Bing Award for Young Investigators) for the 2015 ISHR-NAS Section meeting in Seattle, WA. Make plans now to attend! In the meantime, network with your fellow ISHR-NASECIs on Facebook and LinkedIn.
In May 2012 I had the great honour to receive the ISHR-ES/SERVIER Research Fellowship at the meeting of the ISHR European Section in Belgrade. Every year a basic scientist gets awarded with this prestigious fellowship to support research in the cardiovascular field. During my fellowship I worked as a postdoctoral researcher in the Department of Medicine at the University of Cambridge under the mentorship of Dr Thomas Krieg and Dr Michael Murphy. My research project involved investigating protective mechanisms against myocardial ischaemia reperfusion injury (IRI) with a focus on S-nitrosation of mitochondrial proteins by a novel S-nitrosating agent, MitoSNO. It is a privilege to present the results of my fellowship research project.

Timely reperfusion of acute ischaemic myocardium is essential for myocardial salvage but also results in a unique form of myocardial damage. Over the last two decades, it has become increasingly clear that reactive oxygen species (ROS) production is greatly increased in the post-ischaemic heart and serves as a critical central mechanism of post-ischaemic injury. The mechanism behind the ROS increase and how it can be prevented are unknown. Nitric oxide (NO) has been shown to be protective against IRI in the heart and NO’s ability to S-nitrosate cysteine residues is correlated with protection. In order to test the mechanism involved in cardioprotection by S-nitrosation we determined the ability of a novel mitochondria-targeted S-nitrosothiol to protect against cardiac damage. The lipophilic triphenylphosphonium (TPP) cation can be used to selectively target mitochondria rapidly in vivo and deliver compounds to the mitochondrial matrix at very high concentrations, effectively protecting the mitochondria from oxidative damage. Recently, the mitochondria-targeted S-nitrosothiol (MitoSNO) has been developed by attaching an SNO moiety to TPP (Fig 1A). MitoSNO selectively accumulates several-hundred fold in mitochondria thereby selectively S-nitrosating mitochondrial proteins and protecting mitochondria from IRI.

In order to test MitoSNO’s cardioprotective effect, mice were subjected to 30 min regional ischaemia followed by 2 h reperfusion. Application of MitoSNO at reperfusion led to a profound infarct size reduction (Fig 1B). Neither the untargeted NO donor SNAP, nor MitoNAP, the mitochondria-targeting moiety alone, was effective when applied at the same concentration as MitoSNO. We next sought to identify the

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**Figure 1**

A. MitoSNO accumulates several hundred-fold within mitochondria and thereby S-nitrosates mitochondrial proteins; in contrast, the untargeted NO donor SNAP modifies non-mitochondrial proteins.

B. Application of MitoSNO at reperfusion reduced infarct size in an acute myocardial infarction model in mice. The targeted control compound MitoNAP and SNAP had no effect on infarct size.
S-nitrosated targets, which mediated the cardioprotection seen with MitoSNO treatment. Tail vein injection of MitoSNO just prior to reperfusion lead to selective S-nitrosation of mitochondrial proteins in the heart while SNAP only modifies non-mitochondrial proteins in the cytoplasm and blood plasma. In particular, S-nitrosated proteins of respiratory complex I seem to be relevant \textit{in vivo}. Complex I activity was found decreased at onset of reperfusion in MitoSNO-treated mice compared to untreated mice and returned to initial values after 30 min reperfusion, indicating that inhibition of complex I activity by S-nitrosation is reversible.

Finally, we identified the ND3 subunit of complex I as being the critical protein modified by MitoSNO-mediated S-nitrosation with a half life of about 5 min. Interestingly, the ND3 S-nitrosation only occurred after the cysteine was exposed through an ischaemia-induced conformational change of complex I.

In the next step we tested whether there is a causal relationship between the MitoSNO-induced ND3 S-nitrosation and the production of damaging ROS. Mitochondrial ROS production occurs predominantly at complex I and this production seems to be a major contributor to reperfusion injury, as well as the redox signalling responsible for remodelling and chronic heart failure development. In order to test mitochondrial ROS production \textit{in vivo}, we used the recently developed mass spectrometric probe, MitoB, which reflects mitochondrial ROS production via its conversion by hydrogen peroxide to MitoP selectively within mitochondria. We could show that IRI increased the MitoP/MitoB ratio, indicating an increase in mitochondrial ROS. MitoSNO treatment abolished this increase. Furthermore, MitoSNO decreased mitochondrial oxidative damage, as determined by measuring the oxidative damage marker protein carbonyls, as well as apoptosis.

In summary, we propose the mechanism drawn in Figure 2 by which S-nitrosation of complex I ND3 Cys39 protects against myocardial IRI. The crucial cysteine is occluded during normal complex I activity, but during ischaemia this cysteine becomes exposed due to low complex I activity. Reperfusion of the ischaemic tissue causes rapid reactivation of complex I and thereby production of hydrogen peroxide, which in turn causes oxidative damage and cell death underlying IRI. When MitoSNO is present during reperfusion, the exposed ND3 Cys39 becomes S-nitrosated and complex I locked in a low activity state, decreasing ROS production upon reperfusion. Subsequently reduction of S-nitrosothiol by glutathione gradually reactivate complex I.

While we could show that MitoSNO selectively S-nitrosated mitochondrial proteins and had profound infarct reducing properties in the acute phase, it was not clear whether this mechanism could prevent long-term changes post-MI.

In the next set of experiments mice were subjected to 30 min left coronary artery occlusion followed by a prolonged reperfusion period of 28 days. One day after surgery late-gadolinium enhanced magnetic resonance imaging (MRI) was performed which confirmed the previous histopathological findings of marked infarct size reduction in the MitoSNO-treated mice. Furthermore, increased LV function was observed. After 28 days this protective effect was still present and we saw preserved cardiac function and decreased tissue fibrosis in MitoSNO-treated animals compared to controls (Fig 3). Since the release of free NO is known to cause changes in blood pressure and haemodynamics that can limit use in patients, we also tested MitoSNO’s effect on blood pressure and haemodynamics and found that MitoSNO did not alter any of those parameters.
Taken together, we could show that (1) mitochondrial protein S-nitrosation is cardioprotective, (2) Complex I ND3 Cys39 S-nitrosation is crucial in the protective mechanism of MitoSNO, (3) MitoSNO, when applied acutely post-MI protects against acute and long-term injury. With these data we demonstrate the cardio-protective properties of MitoSNO against ischaemia reperfusion injury in the heart as well as the underlying mechanism. Therefore MitoSNO is a potential treatment candidate for patients with acute myocardial infarction.

References


Carmen Methner PhD was the winner of the ISHR-ES/SERVIER Research Fellowship 2012 at the XXXI European Section Meeting (Belgrade, Serbia: May 2012).
Eric Olson is professor and chair of the Dept of Molecular Biology at the University of Texas Southern Medical Center in Dallas, where he also holds the Robert A. Welch Distinguished Chair in Science, the Pogue Distinguished Chair in Research on Cardiac Birth Defects, and the Annie and Willie Nelson Professorship in Stem Cell Research.

Dr Olson attended Wake Forest University, receiving a B.A. in Chemistry and Biology and a Ph.D. in Biochemistry. He later also received an honorary doctorate from his alma mater. After postdoctoral training at Washington University School of Medicine, Dr Olson assumed his first faculty position at MD Anderson Cancer Center in 1984, where he became Professor and Chair of Biochemistry and Molecular Biology in 1991. In 1995, he founded the Department of Molecular Biology at UT Southwestern.

Dr Olson was an early pioneer in the discovery of the major cardiac transcription factors and showed how these factors function within an evolutionarily conserved gene regulatory network to orchestrate heart formation in organisms ranging from fruit flies to mammals. Dr Olson discovered the MEF2 transcription factor, which activates the genes required for sarcomere formation and cardiac contractility. He and his colleagues discovered the first chamber-restricted cardiac transcription factors, Hand1 and Hand2, and demonstrated that they control growth of the left and right ventricles, respectively, and recently showed that four cardiac transcription factors (Gata4, Hand2, Mef2C and Tbx5) can reprogram cardiac fibroblasts into beating cardiomyocytes within the intact heart following myocardial infarction, diminishing scar formation and enhancing cardiac function. These findings offer a promising new strategy for heart repair, bypassing many of the obstacles associated with other approaches.

Dr Olson discovered the myocardin family of transcriptional coactivators, which function as master regulators of cardiovascular gene expression. Other important cardiac transcription factors discovered by Dr Olson include the homeodomain-only protein (HOP), which regulates cardiomyocyte cell number during development; the HRT family of transcription factors, which mediate Notch signaling in early heart formation; and CAMTA, which functions as a calcium-dependent regulator of heart growth.

In recent studies, Dr Olson and colleagues found that the hearts of neonatal mice can fully regenerate after partial surgical resection, but this capacity is lost early in life due to irreversible suppression of cardiomyocyte proliferation. These findings demonstrate a previously unrecognized regenerative capacity of the mammalian heart and have provided a powerful new model for uncovering the molecular basis of heart regeneration.

In earlier studies, Dr Olson was the first to recognize the importance of the calcium-dependent protein, calcineurin, in cardiac hypertrophy and failure, opening a new direction for the field of molecular cardiology. He also showed calcium-dependent protein kinases control the molecular interaction between MEF2 and class II histone deacetylases (HDACs), providing a trigger for stress-dependent remodeling of the heart. Olson’s discovery that HDACs function as key regulators of cardiac gene expression led to the advancement of HDAC and HDAC kinase inhibitors as new classes of cardioprotective drugs, currently in clinical development.

Most recently, Dr Olson discovered signature patterns of microRNAs associated with cardiovascular development and disease and showed how microRNAs regulate numerous facets of cardiovascular biology, including myocyte growth and survival, contractility, energy metabolism, fibrosis, and angiogenesis. He discovered that myosin heavy chain genes encode microRNAs in their introns and that these microRNAs control cardiac gene expression and contractility. Thus, myosin genes not only encode the major contractile proteins of muscle but act more broadly to control the gene expression programs and func-
Dr Alicia Mattiazzi

2013 Recipient of the ISHR Distinguished Leader Award (2013; San Diego, CA)

Dr Mattiazzi is Consultant Professor of Physiology and Biophysics at the Faculty of Medicine of the University of La Plata and Superior Investigator of the National Research Council of Argentina (CONICET). Previously she was professor and chairman of the Department of Physiology and Biophysics at the Faculty of Medicine of La Plata University and Director of the Cardiovascular Research Center in La Plata, Argentina. After retiring from these positions, she continues to perform active research at the Cardiovascular Research Center and postgraduate teaching activities. She was the founder and is the present Director of the Master of Biomedical Research at the Faculty of Medicine, University of La Plata.

Dr Alicia Mattiazzi is not only regarded as an outstanding leader of South American cardiovascular research but is also widely recognised by her peers for her continuous efforts to promote cardiovascular and physiological research throughout the Latin American Scientific community. She has been an active member of the ISHR, contributing to most of the ISHR World Congresses and, in 2001, serving on the scientific program committee of the XVII World Congress of the ISHR in Winnipeg, Canada.

Closer to home, Dr Mattiazzi served the Latin American Section of the ISHR (LAISHR) for many years, acting in different positions, including President and Past-President. During this time, she worked to attract new members. Dr Mattiazzi organized five annual LAISHR meetings, including a satellite meeting to the XVIII ISHR World Congress in Brisbane, Australia (2004). She was deeply involved in the other four meetings as a member of the organizing or scientific program committee. In all these meetings, Dr Mattiazzi has upheld the highest standards, putting together solid scientific programs and encouraging the participation of young investigators and students. These meetings set a new standard for scientific reporting of cardiovascular research in Latin America and through them, Dr Mattiazzi successfully promoted the integration of heart research groups within Latin America and around the world.

Dr Mattiazzi worked most of the time in La Plata, but spent extensive periods of time working in different outstanding laboratories outside Argentina, mainly in Sweden and the USA. She published more than 100 papers in high profile journals throughout her career and her main research interests have been cardiac mechanics and the regulation of cardiac contractility and relaxation induced by physiological, pathophysiological and pharmacological interventions in intact myocardial preparations and isolated cells, including stimulation frequency, α and β adrenergic agents, Angiotensin II, acidosis, and ischemia-reperfusion injury.

A major contribution of Dr Mattiazzi and her colleagues was to demonstrate the relevance of the phosphorylation of the Thr17 residue of phospholamban (PLN), the Ca2+-calmodulin-dependent protein kinase II (CaMKII) site, in the modulation of myocardial relaxation and contractility under β-adrenoceptor stimulation. These results were described in a series of papers, the first of which appeared in the early 1990s (Vittone et al., Am J Physiol, 1990). By the use of phosphorylation site-specific antibodies combined with the quantification of 32P incorporation into PLN and the simultaneous measurement of mechanical activity, she and her group further demonstrated that cAMP (Ser16)- and Ca2+-calmodulin (Thr17)-dependent pathways of PLN phosphorylation can occur independently of each other in the intact heart. The most representative of this series of papers were those published in J Biol Chem (Mundiña-Weilenmann et al., 1996, Vittone et al., 1998).

In subsequent work, she envisaged the role of CaMKII-dependent phosphorylations in different pathophysiological conditions, including ischemia/reperfusion, acidosis and arrhythmias. In a series of publications, she demonstrated the dual effect of CaMKII-dependent phosphorylations (beneficial or detrimental), in the reversible and irreversible ischemia/reperfusion injury, respectively (For example, Said et al., Am J Physiol, 2003), as.

Dr Alicia Mattiazzi 2013 recipient of the ISHR Distinguished Leader Award (2013; San Diego, CA)
well as the necessary and determinant role played by the phosphorylation of Thr17 of PLN in the contractile and intracellular Ca\(^{2+}\) recovery of the stunned heart (Valverde et al., Cardiovasc Res, 2006). She also showed the importance of CaMKII-dependent phosphorylations at the sarcoplasmic reticulum level, as main players in the cascade of events that leads to apoptosis and necrosis in ischemia/reperfusion (Vila-Petroff et al., Cardiovasc Res, 2007; Salas et al., J Mol Cell Cardiol, 2010) and in acidosis, ischemia/reperfusion and digitalis-induced arrhythmias (Said et al., Am J Physiol, 2008, and J Mol Cell Cardiol, 2011, Gonano et al., Circulation: Arrhythmias and Electrophysiology, 2011).

Dr Mattiauzzi and her colleagues also showed for the first time, how oxidative stress resets the Ca\(^{2+}\)-dependence of CaMKII to extremely low (sub-physiological) Ca\(^{2+}\) levels, to promote myocyte death across different species (Palomeque et al., Circ Res, 2009). This novel and previously unrecognized mode of CaMKII activation constitutes a new paradigm in the intracellular signalling pathways mediated by CaMKII which may be relevant to a large number of diseases in which reactive oxygen species are increased.

Based on her accomplishments, Dr Mattiauzzi has been invited to give numerous national and international lectures and seminars. She is a fellow of the AHA and the ISHR and has received numerous awards, among which are the Guggenheim Fellowship, the Bernardo Houssay Award for outstanding scientific career and the International Women Association Award.

(continued from page 13)

tions of striated muscles through the expression of a family of intronic micro-RNAs. The dual functions of myosin genes, encoding both protein and microRNA, serve as a paradigm for the integration of microRNAs with complex cellular processes. In the course of these studies, Dr Olson uncovered a central role for the heart in the control of systemic energy homeostasis and metabolism via a microRNA regulatory circuit, providing a new entry point into the pathways of obesity and metabolic syndrome.

The many genes and regulatory mechanisms discovered by Dr Olson have established new principles of gene regulation and have provided novel therapeutic targets for normalizing cardiac function in the settings of congenital and acquired heart disease. Toward that end, Dr Olson has cofounded several biotechnology companies to advance studies from his lab toward clinical applications.

Dr Olson is a member of the American Academy of Arts and Sciences, the U.S. National Academy of Sciences, and the Institute of Medicine. His awards include the Pasarow Award in Cardiovascular Medicine, the Pollin Prize in Pediatric Research, and the Passano Prize. In 2009, the French Academy of Science awarded Dr Olson the Fondation Lefoulon-Delahande Grand Prize for Science. He is also a recipient of the Basic Research Prize, the Research Achievement Award and the Inaugural Distinguished Scientist Award from the American Heart Association. In 2013, Dr Olson received the March of Dimes Prize in Developmental Biology.

Dr Olson has trained successive generations of students and postdoctoral fellows, many of whom are emerging as leaders in cardiovascular medicine. In his spare time, Dr Olson plays guitar and harmonica with the Transactivators, a rock ‘n’ roll band inspired by the Texas icon, Willie Nelson, who established the Professorship that Olson holds.
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