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Cardiomyocyte Demise

Over the last decade much has been learnt about how and why cardiomyocytes die. In particular understanding of the triggers and pathways involved in apoptotic myocyte death has been enormously advanced and our insight into how this relatively orderly and dignified death compares with the necrotic death of traumatized myocytes has developed. Seminal work in these fields has been contributed by a number of our ISHR colleagues.

Tracking the events of necrosis and apoptosis

In the setting of acute stress associated with myocardial ischemia-reperfusion the necrotic demise of myocytes can be quantified histologically and biochemically. As myocyte permeability is compromised through loss of oncotic control or through mechanical disintegration conferred by hypercontracture strain, the extrusion of intracellular contents can be tracked by measurement of myoplasmic markers (commonly LDH, CK and TnI). The extracellular release of lysosomal enzymes can expand the damage field, and instigates an inflammatory response, prompting macrophage infiltration and involvement in cleaning up the cellular debris. In other less acute settings, there is emerging evidence that necrotic cardiomyocyte death can proceed in a more controlled and regulated manner with some programmed elements similar to apoptosis (see below). Regulated necrosis where membrane permeabilization may be limited, is
understood to produce a less severe inflammation response. Whether passive or controlled, the outcome of focal necrosis is inevitably focal fibrosis.

In contrast to permeabilized necrotic myocytes, those making their exit by apoptosis go relatively quietly. Although often characterized as a ‘physiologic’ form of death in the general cell literature, the loss of a functional working cardiomyocyte from a mature heart is unlikely to be a good thing. Nevertheless a stressed cell which exits by implosion through a programmed death event is definitely less of a liability than one which generates an inflammatory exit response. Many questions still remain about the molecular details of apoptotic signalling in the intrinsically stressed myocyte, but the orderly sequence of events associated with apoptosis induction and execution has been well delineated and to some extent time mapped. Tools to track the loss of mitochondrial integrity, surface membrane annexin V presentation, caspase activation, elevation in the Bax-1/Bcl-2 ratio and DNA fragmentation have been developed and refined and are widely employed to characterise apoptotic activity. The myocardial legacy of apoptosis, depending on the circumstances, involves both focal and diffuse fibrosis.

**There is emerging evidence that necrotic cardiomyocyte death can proceed in a more controlled and regulated manner with some programmed elements similar to apoptosis**

Autophagy - a route to death by increment?

More recently, the concept of another form of cardiomyocyte death has been the focus of considerable research industry - death by autophagic excess. Physiologically, autophagy involves intracellular vacuolar destruction of long-lived macromolecules and organelles - an essential cell degradation and recycling function to support energy homeostasis and/or to eliminate defective cell components. An autophagic breakdown process specific for mitochondria has been characterized (‘mitophagy’) and is a vital component of the ‘quality control’ management of these organelles, to ensure that the cell is equipped with the most efficient respiratory machinery. More generally, the term autophagy is used to describe the common degradation pathway for a range of cell constituents, sometimes referred to as ‘macroautophagy’.

Autophagy is upregulated in stress states, and in the heart was first identified three decades ago as prominent in the neonatal cardiac tissues during postnatal transition - a period of temporary nutrient deprivation. More than 20 mammalian autophagy proteins have been identified so far, and several are used as key measurable markers. Very briefly, Beclin-1, an autophagy initiator, interacts with a class III phosphoinositide 3-kinase (PI3K) to form a membrane. The membrane is expanded through the LC3B mediated transfer of lipidated moieties, with involvement of the adaptor protein p62, to engulf the target material within a phagosome. The phagosome fuses with a lysosome, and the contents are degraded and liberated.

Once triggered, the apoptotic process is apparently inexorable, whereas the road to death by autophagy is perceived to be travelled by increment.

Acute induction of autophagy

There is a body of elegant work providing evidence that autophagy has a role in determining favourable acute outcomes for the ischemia-reperfusion stressed
myocardium. Experimental studies show that if autophagy is inhibited, post-ischemic recovery and myocardial viability is compromised. 

A key signalling pathway generally recognized to operate in this context is the ‘Reperfusion Injury Survival Kinase’ pathway, involving activation of the class I PI3K as a pro-survival signal. 

These studies have provided the impetus for the development of pharmacological agents which show cardiprotection promise through autophagy induction. But not all studies report a positive role for autophagy in determining post-ischemia outcomes. Infarct size is reduced in Beclin-1 transgenic mice and Beclin RNAi treatment in vitro improves myocyte survival after simulated ischemia. 

The explanation for these differences is not clear - but certainly these findings suggest that the cell survival influence of autophagy activation depends on the extent activated and the temporal context.

**Chronic activation of autophagy**

Alongside the evidence that short-term autophagy upregulation can confer benefit, G-protein coupled receptor (GPCR) signalling is implicated in many chronic myocardial disease states, and much more work is required to understand the role of these pathways in regulating autophagy.

Recently evidence has emerged that the state of myocardial insulin resistance induced by fructose-feeding in mice (suppression of signalling through the class I PI3K pathway), is observed in association with upregulation of autophagy markers and myocyte attrition, without indication of apoptosis induction. This finding thus produces an interesting anomaly - in the type 2 diabetic/insulin resistance situation down regulation of the PI3K/Akt pathway is associated with elevated autophagy (as is consistent with withdrawal of mammalian target of rapamycin complex 1 (mTORC1) negative regulation), yet in the different situation of acute ischemia (described above), protection is conferred by autophagy induction which would be expected to be linked with PI3K/Akt activation through the RISK pathway. At present, it is not clear how to interpret these contrasting findings.

**How much autophagy is too much autophagy?**

Notwithstanding signaling anomalies, the general consensus is that autophagy can be beneficial and pro-survival as a short term strategy to deal with acute stress, but when chronically elevated or constitutive, excess autophagic activity has potential to be lethal.

Some important new insight into this relationship has been revealed recently through work tracking autophagy response to pressure overload. It has been demonstrated that autophagy is an obligatory element of the cardiac remodelling which occurs in response to pressure overload, and that this response is amplified in Beclin-1 transgenic mice and involves HDAC mediation. Most interestingly, afterload stress was seen to trigger a transient increase in myocyte autophagic activity, which settled to a new, elevated level when the cardiac growth response stabilized. The inference from this and other work, is that autophagy may be ‘titrated’ within an effective operational range - but when pushed beyond the boundary of adaptation, becomes pathological.

The current challenge is to demonstrate how much autophagy is too much - and what are the factors that shift the balance in the stressed cardiomyocyte from metabolic expediency to irretrievable catabolism. The well tuned coordinated operation of all the components of the autophagic flux pathway appears to be crucial, and autophagy becomes a pathological process when flux is impeded. Specifically the term ‘frustrated’ autophagy has been used to describe the situation where autophagosome and
In various situations a reciprocal relationship between apoptosis and autophagy has been observed.

...imposed on a background of constitutive activation. Like apoptotic myocytes, those which die through autophagic excess also go quietly - but the tools are yet to be developed which enable us to determine exactly when these cells have reached the point of no return and exit is imminent. And finally a light 'hearted' note on which to conclude this discussion of death and dying. How do we say it - this thing called autophagy? Does it go 'ort-off-ogy' or "auto-fay-gee"? Syllabic prediction apparently depends on geographic persuasion - but by recourse to the derivation (Greek, 'self-eating'), it would seem that the case for pronunciation is self evident!

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Old disease, old drug and a new paradigm

Atrial fibrillation (AF) is an old disease, however, AF has been recently reevaluated as an emerging abnormality in older patients. There seems to be two reasons for the renaissance of this old arrhythmia: First, prevalence of AF increases with age and AF is a common disease among the elderly. Second, although AF itself is not lethal, thromboembolic stroke (5 ~ 6% per year) causes severe ADL (Activities of Daily Living) insult and thus, the quality of life of the patients is often markedly impaired. The widely used Vitamin K antagonist (VKA), warfarin, is an old drug for anti-coagulant therapy. Unfortunately, practical use of warfarin is limited for a variety of reasons; these include the narrow therapeutic range (INR 2.0 – 3.0), the risk for lethal or critical bleeding, the inevitable drug-drug and drug-food interactions and the large individual variation of the effect. Recently, a novel anti-coagulant, a direct thrombin inhibitor, was developed and is becoming available for clinical use in many countries worldwide. This new drug, dabigatran, was used in more than 400,000 patients with AF within the first year of availability. Since that time, other new anti-coagulants, rivaroxaban, apixaban and edoxaban, have followed dabigatran. These new drugs are now being tested in large clinical trials and will be on the market in a few months or years, expanding the new paradigm of AF treatment.

Regardless, prophylactic use of these new anticoagulants is not a direct treatment of AF. Since AF is a rhythm disorder due to electrical abnormalities in the atrial chambers of the heart, direct restoration of normal sinus rhythm would appear to be a better treatment for AF. Unfortunately, pharmacological or electrical defibrillation and prophylactic use of antiarrhythmic drugs are not effective, and rhythm control is not superior to the rate control obtained using β-blockers and/or digitalis. More direct treatment of AF, electrical ablation around the PV (pulmonary vein) ostium, provides a fairly high restoration rate; however, maintenance of sinus rhythm is rather difficult (only 30 ~ 40%) and thus, the long-term outcome of electrical ablation is still to be elucidated.

Since AF is a common disease among elderly people, primary prevention may be the best approach to reduce the disabling and cognition disorders due to thromboembolic stroke. In the Framingham Study and other cohort studies, aging, hypertension, diabetes mellitus, chronic heart failure and valvular heart diseases were determined to be risk factors for AF. Obesity and chronic kidney disease also turned out to be risk factors for AF, consistent with a life-style related disease. Many investigations suggest that supraventricular arrhythmia (SVPC) may trigger AF, and that remodeling of the atrial muscle could be a substrate promoting SVPC and AF. If so, the underlying mechanisms of atrial remodeling should be elucidated.

Recent reports indicate that the inflammatory response may be a key factor which could induce apoptosis of the myocyte, myocardial hypertrophy and fibrotic changes in ECM, leading to remodeling. Several reports further suggest that mechanical overload of the atrial chamber triggers the activation of inflammatory lymphocytes, stimulating immigration of T cells and macrophages. The inflammatory response and activation of adhesion molecules triggers activation of the coagulation cascade through tissue factor activation which may enhance thrombus formation. If this hypothesis proves true, anti-inflammatory interventions could be effective in preventing the onset and maintenance of AF. A recent report supports this hypothesis: colchicine prevents postoperative AF. Colchicine is an old anti-inflammatory drug for gout; microtubules of the lymphocytes are blocked and thus, immigration of these cells is inhibited. It is surprising that an old drug, colchicine, which has been in use for 3,000 years, may play a new role and create another paradigm-shift in AF treatment from a downstream to an upstream approach.

The progress of medical science never pauses and our science map is always redrawn for new paradigms.

Masatsugu Hori, M.D., Ph.D.
President ISHR
Report on the xxxv Meeting of the Australasian Section
August 11-14, 2011; Perth, Australia

This year’s Annual Scientific Meeting of the Australasian Section of the ISHR was held in Perth - the west coast capital city - known for great sailing winds, as the gateway to wonderful vineyard valleys, and now for fabulous cardiovascular research!

The meeting was held in conjunction with the 59th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand (CSANZ). The conference was opened by award-winning science communicator and journalist, Dr Norman Swan, who challenged us to consider the question: “Are we doing medical research the wrong way?” Dr Swan reflected on James Surowiecki’s book, “The Wisdom of Crowds“, and called for a different kind of collaboration between scientists, medical practitioners, patients and other stakeholders to solve medical problems.

Prof. Jeroen Bax of Leiden University (Netherlands) delivered the prestigious RT Hall Lecture, in which he emphasised the value of multimodality imaging in the prognosis of heart failure. Prof. Richard Harvey from the Victor Chang Cardiac Research Institute (Sydney) took the podium to give the prestigious Basic Science Lecture. Prof. Harvey’s expertise is in developmental cardiology, and his insightful talk on “Linking development to regeneration in the mammalian heart,” explored the biology of adult cardiac stem cells and cardiac regeneration.

The Australasian Section was delighted to host two ISHR Fellows, Prof. Leslie Leinwand (University of Colorado, USA) and Prof. Metin Avkiran (King’s College London, UK), at this year’s meeting. Prof. Leinwand intrigued us with her pioneering work in two fields: postprandial cardiac hypertrophy in the Burmese python and dietary phytoestrogen influence on hypertrophic cardiomyopathy rodent phenotypes. Prof. Avkiran provided a comprehensive overview of the role of protein kinase D in the regulation of cardiac function and shared some insights into the challenges of cardiovascular drug development and pre-clinical biology. Profs Avkiran and Leinwand also fielded questions from enthusiastic students and post-docs at the career development workshop organised by Early Career Investigator (ECI) representatives Dr James Bell and Dr Helena Viola.

Once again this conference was a wonderful opportunity to showcase the work of the Society’s Early Career Investigators. Student presentations comprised three different formats: posters, 3 minute mini- orals, and 10 minute maxi-oral presentations. This year’s student investigator maxi-oral finalists were Ms Rhian Shephard (Centenary Institute, Sydney), Mr Matthew Jenkins (Monash University, Melbourne), Ms Rebecca Vella (CQ University, Rockhampton), and Ms Kate Weeks (Baker IDI Heart and Diabetes Institute, Melbourne). Congratulations to the winner, Kate, for her talk “Phosphoinositide 3-kinase p110α is a master regulator of exercise-induced cardiac protection, acting independently of heat shock protein 70” and also to the other finalists for very polished presentations.

To wind up the scientific program each evening, delegates were treated to local wines and cheeses while enjoying the mini-oral presentations and poster sessions.
Congratulations to the winner of the student investigator mini-oral presentations, Ms Laura Bienvenu (The University of Melbourne/Prince Henry’s Institute), for her talk, “Macrophage mineralocorticoid receptor mediated inflammation and fibrosis in the heart.” The top poster prize was awarded to Mr David White (Baker IDI Heart and Diabetes Institute, Melbourne) for his poster entitled, “Macrophage migration inhibitory factor is a novel biomarker and promotes cardiac inflammation following acute myocardial infarction.”

As is tradition, the Annual General Meeting ‘lite’ was held on Friday evening with glass-in-hand as segue to the collegial Society dinner at the Parmelia Hilton Perth. Between courses, Prof. Lea Delbridge (AUS Section President) announced the winners and awarded the ISHR Student Investigator Prizes. Congratulations to Dr James Bell who received the Postdoctoral Publication Prize for his paper titled, “Ca2+/calmodulin-dependent protein kinase inhibition suppresses post-ischemic arrhythmogenesis and mediates sinus bradycardic recovery in reperfusion.” Every year our Early Career Investigators bring bigger and better science to our meeting and congratulations to all for their important contribution to the program and to the Society.

A vote of appreciation to the ISHR and CSANZ members of the Scientific Programming and Local Organising Committee for all their hard work leading up the conference. The quality of the Basic Mechanisms stream is apparent to all, and the breadth and depth of content contributed by our local and international speakers is remarkable. In particular, the efforts of A/Prof. Livia Hool and Prof. Lea Delbridge are recognized - they put in many long teleconferencing hours to ensure the meeting’s success. After such a fantastic gathering, we look forward to reconvening in Brisbane in 2012 with much anticipation!

Kate Weeks
David White
Helen Kiriazis

You are welcome to join us at the 2012 ISHR AUS-Section Meeting (joint meeting with CSANZ)

August 16-19, 2012
Brisbane Convention & Exhibition Centre
Brisbane, Australia

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MEET THE FUTURE OF THE ISHR-AUSTRALASIAN SECTION

James R. Bell, Ph.D.: Winner of the 2011 ISHR - AUS
Post-doctoral Publication Award
XXXV Australasian Section Meeting (Aug 11-14, 2011), Perth, Australia

Dr Bell is a Heart Foundation (Australia) post-doctoral Fellow in the Department of Physiology at the University of Melbourne. His research utilizes a range of in vitro and in vivo approaches to investigate the cellular mechanisms responsible for cardiac Ca$^{2+}$ mis-management, dysfunction and injury in ischemia/reperfusion. Recently, he has focused on the influence of sex steroids on the heart, questioning the conventional view of the dichotomy of estrogenic-androgenic roles in ischemic cardioprotection.

Kate Weeks: Winner of the 2011 ISHR - AUS
Student Investigator Prize for Best Oral Presentation
XXXV Australasian Section Meeting (Aug 11-14, 2011), Perth, Australia

Kate is a final year PhD student supervised by Dr Julie McMullen from the Cardiac Hypertrophy Laboratory at Baker IDI Heart and Diabetes Institute, Melbourne, Australia. Kate’s dissertation focuses on the cardioprotective effects of physiological cardiac hypertrophy and PI3K signaling in mouse models of cardiovascular disease.

David White: Winner of the 2011 ISHR - AUS
Student Investigator Poster Prize
XXXV Australasian Section Meeting (Aug 11-14, 2011), Perth, Australia

David is a second year PhD Candidate from Experimental Cardiology at the Baker IDI Heart and Diabetes Institute in Melbourne. His research interests include post myocardial infarction cardiac remodelling with an emphasis on acute inflammatory responses with therapeutic interventions and diagnostic potentials.

Laura Bienvenu: Winner of the 2011 ISHR - AUS
Student Mini-Oral Presentation Award
XXXV Australasian Section Meeting (Aug 11-14, 2011), Perth, Australia

Laura Bienvenu is a PhD student of the University of Melbourne, undertaking a project jointly supervised by Dr Morag Young (Prince Henrys Medical Research Institute) and Prof. Lea Delbridge (Cardiac Phenomics Lab, University of Melbourne). Her research is directed towards understanding how mineralocorticoid receptors in different cell types (macrophages and cardiomyocytes) have a role in mediating cardiac inflammation and modulating function in settings where mineralocorticoids levels are both normal and elevated. The goal of her work is to identify cell-specific therapies for heart failure.
The meeting was organized by Professor Mitsuaki Isobe from Tokyo Medical and Dental University. The theme of “Inflammation and Immunity in Cardiovascular Research” was an attractive topic for many cardiovascular researchers. The meeting was well attended by registrants, and young scientists were represented especially well.

Although the weather was unfavorable on both days of the meeting, the meeting attracted over 200 participants. The venue, the National Centre of Science Building, was an ideal place for scientific discourse. One goal of this conference was to promote the exchange of ideas on a worldwide basis between scientists and clinicians interested in all aspects of cardiovascular biology and medicine. Indeed, many professionals involved in delivering cardiovascular care, including physicians and scientists, made contributions to the meeting. There were two award lectures, two special lectures, four symposia, one mini symposium, four luncheon seminars, two evening seminars, the YIA session and the poster sessions.

The two award lectures were, of course, not to be missed. Dr Masao Endoh (Yamagata University) was awarded the 2011 ISHR Distinguished Leader Award. He has dedicated his entire career to research on the physiological and pharmacological regulation of cardiac contractile function and the regulatory mechanisms of Ca2+ signaling, and talked about “Recent advances in cardiac Ca2+ signaling research” in the award lecture chaired by Dr Ryozo Nagai (Tokyo University) and Dr Richard L. Moss (University of Wisconsin). In the second award lecture, the 2011 ISHR Janice Pfeffer Distinguished Lecture chaired by Dr Keichi Fukuda (Keio University) and Dr Richard L. Moss, Dr Thomas L. Force (Thomas Jefferson University) gave a talk on the role of protein kinases (especially GSK-3, Troponin I kinase and Tnnk3k) regulating pathways of injury and repair in the heart.

One of the highlights of the first day was a special lecture on next generation sequencing and cardiovascular genetics by Dr Christine Seidman (Harvard Medical School). The lecture, chaired by Dr Issei Komuro (Osaka University), outlined the utility of next generation sequencing for cardiomyopathy research. In the two symposia of the first day, “New Pharmacological Agents for Cardiovascular Diseases” and “Roles of Inflammation and Immunity in Cardiovascular Diseases”, 11 cardiovascular scientists participated in discussion and debate. These talks included novel insight into the inflammatory and immune mechanism of cardiovascular disease. These new ideas will produce fruitful outcomes in both basic and translational research. Moreover, in the mini symposium, three experts offered their thoughts on the three major pathways of
pathogenesis in pulmonary arterial hypertension, including the NO, endothelin and prostacyclin pathways.

The evening social banquet was held at Josui Hall next to the meeting venue. All of the guests enjoyed delicious appetizers, cocktails and conversation in a friendly atmosphere, with dinner accompanied by a delightful mini-concert performed by a quartet of medical students from Tokyo Medical and Dental University.

The second day also featured one special lecture and two symposia. In the special lecture, which was chaired by Dr Mistuaki Isobe, Dr Shizuo Akira (Osaka University) offered his perspective on regulation of the immune response by the zinc finger domain containing nuclease, Regnase-1/Zc3h12a. Zc3h12a is one gene induced in response to Toll-like receptor stimulation by LPS (lipopolysaccharide). The conclusion of this special lecture was that Zc3h12a is a nuclease involved in destabilization of IL-6 and IL-12 mRNA.

enthusiastically discussed various new mechanisms of cardiac hypertrophy and various aspects of cardiovascular regeneration from basic science to clinical applications.

Another highlight of the meeting was the YIA competition, which has attracted the interest of many participants every year. Fifteen candidates presented their distinguished work in three separate sessions. All the presentations were outstanding and three winners were announced at the closing ceremony. The winners were: Dr Katsuhito Fujiu (Tokyo University) with the gold medal and Dr Yasutomi Higashikuni (Tokyo University) and Satoshi Somekawa (Nara Medical University) with silver medals. There was also a poster session in which 56 investigators presented their data. Three participants were selected for Poster Awards: Dr Ken Shinmura (Keio University), Yosuke Omori (Osaka University) and Susumu Hosokawa (Tokyo Medical and Dental University).

The ISHR2011-Japanese Section meeting was extremely successful thanks to the enthusiasm of all of the participants and the hard work of the organizers. This meeting surely encouraged all of the cardiovascular scientists and clinicians in attendance, and the many new insights presented at the meeting will contribute to further scientific progress in cardiovascular research.

Satoshi Somekawa
Yoshihiko Saito
First Department of Internal Medicine,
Nara Medical University

The poster sessions were well attended and encouraged discussion.

The two symposia of the second day, “New Frontiers in Cardiac Hypertrophy and Heart Failure” and “Current Status and Future Perspective in Cardiovascular Regenerative Medicine”, featured talks by 10 cardiovascular scientists. Speakers
Dr ENDOH is Emeritus Professor of Yamagata University School of Medicine, Department of Pharmacology. Before retirement, he acted as the Dean of the School of Medicine, and vice-President of the University.

Dr Endoh associated with the ISHR in the early 1970’s. Until retiring in the early 2000’s, he served as an International Council member of the ISHR and played an important role in the collaboration of the Japanese Section with the International Society. He organized the 19th Annual Meeting of the ISHR Japanese Section as the chairman of the organizing committee in Yamagata in 2002.

Dr Endoh has attended a number of international meetings, often as an invited speaker and/or to chair a session, including The ISHR World Congresses in Kobe (1992), Prague (1995), Rhodes (1998), Brisbane (2004), and Kyoto (2010); North American Section Meetings in Mobile and Wisconsin; Chinese Section Meetings in Harbin, Yangchow, and Weihai; the European Section Meeting in Dresden; and he has been a regular participant at Japanese Section Meetings.

His research interest has been the regulation of cardiac contractility induced by physiological, pathophysiological and pharmacological interventions in intact myocardium and myocardial cells. Research topics include: (i) receptor-mediated regulatory mechanisms; (ii) mechanisms of novel inotropic agents; and (iii) physiological interventions including force-frequency relationship and acidosis, which have been summarized in several review articles in international journals of pharmacology.

Dr Endoh was the first in the world to demonstrate that myocardial α-adrenergic receptor stimulation increases myofilament Ca\textsuperscript{2+} sensitivity in association with a small increase in Ca\textsuperscript{2+} transients in aequorin-loaded rabbit papillary muscle. Later, he elucidated that angiotensin II and endothelin-1 share a similar mode of inotropic action in aequorin- and/or indo-1-loaded ventricular myocardium and/or cardiomyocytes. Furthermore, he clarified that the GPCR crosstalk, namely endothelin-1 and norepinephrine, plays a crucial role in contractile regulation due to Ca\textsuperscript{2+} transients and myofilament Ca\textsuperscript{2+} sensitivity via PKA, PKC andPKG activation in canine ventricular myocardium.

Dr Endoh also determined that novel cardiotonic agents such as dobutamine, amrinone, milrinone, olprinone, enoximone, Org-9731, UK-1745, UD-CG 212 and OR-1896 act by increasing cellular cyclic AMP by activation of adenyl cyclase or inhibition of PDE 3. By contrast, he showed that Ca\textsuperscript{2+} sensitizers, such as sulmazole, MCI-154, theophylline, Org 30029, levosimendan, SCH00013 and EMD 57033 act, in addition to causing a moderate increase in Ca\textsuperscript{2+} transients, by an increase in myofilament Ca\textsuperscript{2+} sensitivity, effectively eliciting a positive inotropic effect even under acidic conditions, in which Ca\textsuperscript{2+} mobilizers lose their effectiveness as cardiotonic agents.

The role of muscarinic cholinergic receptor activation in the regulation of ventricular contractility has long been a major focus of Dr Endoh’s research interest. He showed that muscarinic receptor activation can be employed as an excellent pharmacological tool to differentiate cyclic AMP-mediated and cyclic AMP-independent mechanisms, in which the positive inotropic effect of β-adrenoceptor agonists, PDE 3 inhibitors and levosimendan is inhibitable, but cyclic AMP-independent effects, induced by α-adrenoceptor agonists and Ca\textsuperscript{2+} sensitizers such as Org30029, EMD 57033 etc, are unaffected by muscarinic stimulation. Activation of PKA, PKC, andPKG play key roles in the crosstalk between muscarinic stimulation and positive inotropic interventions.

Dr Endoh is recognized internationally as an expert in receptor-mediated cardiac signaling in contractile regulation, namely the role of Ca\textsuperscript{2+} in this regulation. He has published more than 200 peer reviewed manuscripts in the field of cardiac excitation-contraction coupling in intact myocardium and cardiomyocytes. He received the prestigious ISHR Keith Reimer Distinguished Lecture Award in 2005.

Dr Endoh has also contributed to the development of cardiovascular science by serving as an editor and/or reviewer for a number of international journals. He is (continued on page 15)
Dr OM FORCE grew up in rural Illinois. He graduated from Harvard College where he was inducted into the Phi Beta Kappa Society. After taking a year off to be stage manager for rock concerts at Boston Garden and other venues in and around Boston, he went to Harvard Medical School. He did his residency at the University of Vermont and then his cardiology fellowship at West Roxbury VA Medical Center in Boston. In addition to his clinical responsibilities, he was one of the first of a small handful of investigators who helped develop the field of contrast echocardiography in the early 1980’s. He moved to Massachusetts General Hospital in 1985 to run the Preventive Cardiology Program as well as being Director of the Stress Testing Laboratories, and it was at MGH that he met three scientists who radically changed his direction-John Kyriakis who was working in the Diabetes Unit under Joseph Avruch, and Joseph Bonventre. These three introduced him to basic science, specifically protein kinases, and this quickly became the focus of his work. After Kyriakis and Avruch cloned the JNKs, Force and Kyriakis set out to identify kinase pathways, initially focusing on Raf-1. They showed that Raf-1 was activated by various mitogens, and that it signaled to ERKs via a MAPKK (MEK1/2) which they purified and characterized, thus completing the first mammalian protein kinase cascade (JBC 1993; PNAS 1994). Then, working with Celia Pombo (Dr Force’s post-doctoral fellow) they identified and characterized mammalian members of the Sterile20-like kinase family (Mst family/MAP4Ks) including Germinal Center Kinase, which is a key regulator of JNKs and p38 activation in systemic inflammation (Nature 1995), and SOK-1/STK25 (EMBO J 1996; JBC 1997), which is a cell death kinase activated by oxidant stress and ischemia. This kinase is mutated in patients with cerebral cavernous malformations, the most common cause of cerebral hemorrhage, and mechanisms potentially underlying this phenotype were later defined (J Cell Sci. 2010). Furthermore, this group was the first to report activation of JNKs by ischemia (JBC 1994).

Around this time, Force began to collaborate with a group of investigators at the Cardiovascular Research Center at MGH, including Tony Rosenzweig and Roger Hajjar, who helped change his direction toward more translational research focusing on the heart, specifically the role of kinases in ischemic injury and pathologic hypertrophy. Force was greatly aided by what would become a long-standing collaboration with James Woodgett at the University of Toronto. Woodgett had initially purified and cloned GSK-3 in Philip Cohen’s lab, and Force and Woodgett began to actively collaborate. They reported the role of GSK-3 in regulating pathologic hypertrophy in The Journal of Cell Biology (2000) and implicated NF-ATs in the process. Force and Woodgett would go on to publish numerous papers exploring the role of GSK-3s in the adult and developing heart. These studies identified central roles of this family of kinases in everything from proliferation/differentiation of embryonic stem cells to cardiac development (deletion leading to double outlet right ventricle, VSD, and a hyperplastic myopathy that led to near obliteration of the LV cavity), post-MI and post-TAC remodeling, ventricular rupture, β-adrenergic responsiveness, and proliferation of cardiac stem/progenitor cells and immature cardiomyocytes (JCI 2008; Circ Res 2010; JCI 2010). During this period, Force also explored the role of Wnt signaling in the heart in the setting of TAC (Mol Cell Biol 2006) and first reported activation of Wnt pathways downstream of traditional GPCRs (PNAS 2003).

Most recently he has played a key role in highlighting the issue of cardiotoxicity of the so-called “targeted therapeutics” which largely inhibit various protein kinases that drive cancer progression. These agents had been predicted to be relatively free of...
Rise With The Tide
ISHR World Congress XXI
San Diego, California
June 30 - July 4, 2013

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Unifying Invigorating Advancing
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http://www.ishrworld.org
The Latin American Section of the International Society for Heart Research held its 19th meeting at Favaloro University in Buenos Aires. The primary goal of this meeting was to gather research scientists, clinical cardiologists, fellows, and students to discuss the recent advances in diverse cardiovascular topics.

As this year’s meeting was organized as a one-day event, it was certainly a very busy day. We had three symposia, each one with four speakers, which covered a diversity of topics, including *Mechanisms of cardiomyocyte death*, *Signalling pathways in the cardiovascular pathology* and the new/old topic of *Inflammatory mediators as major effectors of cardiac damage*. The meeting was crowded with participants from different regions of Argentina and also from other Latin American countries.

A particular highlight at this meeting was the presence of Dr Wayne Chen from Calgary University. We had the pleasure of enjoying his wonderful lecture on “Cardiac ryanodine receptor as a target of arrhythmias fired by calcium” and also his sense of humour and kind personality. The day before the meeting, Dr Chen travelled to La Plata, 60 km south of Buenos Aires, where Dr Jorge Martínez, Dean of the School of Medicine, honoured him with the degree of Distinguished Guest. Within the context of the Annual Scientific Conference of this Faculty, Dr Chen gave another enlightened talk on “Ryanodine receptor’s luminal calcium sensor responsible for calcium waves and cardiac arrhythmias”. At lunch he had the opportunity to taste our worldwide renowned beef and our delicate Malbec red wine.

Another very important event that took place during the ISHR meeting was the Section Assembly where Dr Paulina Donoso from Chile was elected President of the LA ISHR for the next period.

Finally, but not less importantly, it is worthwhile to mention the social activities. During the lunch break all of the attendants gathered to enjoy enriching interaction. After the meeting, the outgoing and incoming ISHR officers, together with Dr Chen, celebrated the transition in a typical turn-of-the-19th-century bar in San Telmo, the historical district of Buenos Aires. During their stay in the capital, the foreign guests enjoyed the unique experience of a Ballet Gala at the famous Colon Theatre.

We are very pleased with the result of this meeting. We tried to create an environment where a high level of academic discussion and warm personal interrelationships were blended. This friendly atmosphere encouraged attendants to become new members of the Society.
ISHR MEETINGS CALENDAR

- **May 19-22, 2012.** XXXI Annual Meeting of the European Section (will be held jointly with the ESC HFA). Belgrade, Serbia. 
  Website: www.escardio.org/congresses/hf2012/Pages/welcome.aspx

- **May 28-31, 2012.** XXXIII Annual Meeting of the North American Section. Banff, AB, Canada. Organizer: Dr Gary Lopaschuk (gary.lopaschuk@ualberta.ca). Website: www.american.ishrworld.org

- **August 16-19, 2012.** XXXVI Annual Meeting of the Australasian Section. Brisbane Convention Center, Brisbane, Australia. Website: www.csanz2012.com

- **October 26-27, 2012.** XXIX Annual Meeting of the Japanese Section. Fukuoka, Japan. Organizer: Dr Kenji Sunagawa (sunagawa@cardiol.med.kyushu-u.ac.jp)

- **June 30 - July 4, 2013.** XXI World Congress of the ISHR. San Diego, California. See page 13

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Dr Wayne Chen delighted the audience during his conference, showing not only great knowledge but also a fine sense of humour.

Finally, we would like to remind all ISHR members that in 2016 the World Congress of the ISHR will be held in Buenos Aires. Let us be your host and help you experience the Latin touch in another wonderful and welcoming meeting.

Dr Margarita Ana Salas  
La Plata, Argentina

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cardioxicity, but Force dispelled that myth with the first report of cardiotoxicity with one of these agents (*Nat Med* 2006), and went on to identify the mechanism. This work increased scrutiny of these agents and culminated in the identification by Ming Hui Chen and Force of very significant cardiotoxicity with sunitinib, an agent widely used in various solid tumors (*Lancet* 2007). This, and work by a small group of others in 2006-2007 helped launch the concept of a medical sub-speciality called Cardio-Oncology, and also led to the development of guidelines for treating patients with these agents from the Heart Failure Association of the ESC and the U.S. National Cancer Institute, committees on which Force sat. Clearly, identifying potentially problematic agents before they are used in patients is a critical issue and most recently, Force has explored the use of zebrafish as a pre-clinical tool to attempt to do just that (*Circ Res* 2011).

Recently, Force was named incoming President of the Heart Failure Society of America. He also serves on numerous committees for the American Heart Association. Finally, Force would like to thank all the other collaborators and friends who have supported him, and most of all to thank the students, post-doctoral fellows, and technicians who actually performed the work. Without them, none of this work would have been possible. Force would also like to thank his wife and children for their support and encouragement.

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currently acting as Consulting Editor of *Journal of Molecular and Cellular Cardiology, Circulation Research*, and *Cardiovascular Research*; Associate Editor of *Pharmacology and Therapeutics*; Section Editor of *Journal of Cardiovascular Drugs and Therapy*; and Editorial Board Member of *European Journal of Pharmacology, Naunyn-Schmiedeberg’s Archiv of Pharmacology*, and the *Journal of Cardiovascular Pharmacology*. He also receives manuscripts for reviewing from a number of other cardiovascular journals, including *Circulation, Journal of Pharmacology and Experimental Therapeutics*, and the *British Journal of Pharmacology*. 

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